



Probiotics in pediatric functional abdominal pain disorders: a systematic review and meta-analysis

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Abstract

Functional abdominal pain disorders (FAPDs), currently referred to as abdominal pain-related disorders of gut–brain interaction (AP-DGBIs), are characterized by recurrent abdominal discomfort in children that cannot be fully explained by an identifiable organic disorder. Probiotics are increasingly used as microbiota-targeted treatments, although their true clinical benefit remains uncertain. The objective of this study is to evaluate the efficacy and safety of probiotic supplementation compared with placebo in children with AP-DGBIs. PubMed, Embase, Web of Science and Scopus were searched from the start of each database to April 2026; the review followed PRISMA guidelines. Randomized controlled trials in patients < 18 years with FAPDs (IBS, FAP-NOS, functional dyspepsia, abdominal migraine) diagnosed by Rome II–IV, in which probiotic supplementation was evaluated. Two reviewers independently extracted data and assessed risk of bias using RoB2 tool. Meta-analyses and network meta-analyses were used to synthesize the data; the certainty of the evidence was evaluated using GRADE and CINeMA. This review covers 21 trials (2005–2025) with 1899 patients treatments completed. Probiotics modestly reduced pain intensity and weekly pain episodes, and modestly increased the rate of complete symptom resolution compared with placebo. Treatment with probiotics was associated with complete symptom resolution in 35.3% versus 22.8% of placebo-treated patients, corresponding to a number needed to treat (NNT) of 7 (95%CI=3.97–29.04). However, the certainty of evidence was rated as low to moderate across outcomes. Moreover, from a clinical perspective, when success was defined as an improvement in symptoms according to an author-defined threshold, probiotic supplementation was not associated with different response rates compared with placebo.

Conclusion: Probiotics provide modest symptom relief in pediatric FAPDs and may be considered a safe adjunctive therapy rather than a stand-alone treatment. While these findings are in line with the ESPGHAN/NASPGHAN 2025 guidelines, larger standardized trials are required to define optimal strain selection, dosage and treatment duration.

Trial registration: <https://www.crd.york.ac.uk/PROSPERO/view/CRD420251149947>, identifier CRD420251149947.

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Key points

Question: Is probiotic supplementation effective and safe for reducing symptoms in children with functional abdominal pain disorders (FAPDs/AP-DGBIs)?

Findings: This updated systematic review of 21 randomized controlled trials (RCTs) demonstrated that probiotic supplementation produced a statistically significant but clinically modest reduction in abdominal pain intensity and the number of weekly pain episodes, and increased symptom resolution compared with placebo. However, effect sizes were small, heterogeneity was high and overall certainty of evidence was low to moderate.

Meaning: This work supports a modest role for probiotics in managing pediatric AP-DGBIs; however, expected benefits are limited and should be integrated into a multimodal management strategy given the high placebo response and the role of psychosocial factors.

Extended author information available on the last page of the article

What is Known:

- AP-DGBIs (formerly FAPDs) are common childhood disorders characterized by recurrent abdominal pain without identifiable organic disease.
- Probiotics are increasingly used to restore gut microbial balance, but their clinical benefit remains uncertain.

What is New:

- Our meta-analysis showed that probiotic supplementation reduced pain intensity and weekly pain episodes and increased symptom resolution versus placebo.
- Benefits were modest, with substantial heterogeneity across studies and low-to-moderate certainty of evidence.

Keywords Functional abdominal pain disorders · Pediatric · FAPDs · AP-DGBIs · Probiotics · Synbiotics · Irritable bowel syndrome · Functional dyspepsia · Meta-analysis · Gut–brain axis · *L. rhamnosus* GG · *L. reuteri* DSM 17938

Introduction

Functional abdominal pain disorders (FAPDs) are highly prevalent and burdensome conditions. They are characterized by chronic or recurrent pain with no clear organic cause. The term FAPDs is being replaced by ‘abdominal pain–related disorders of gut–brain interaction’ (AP-DGBIs) according to Rome IV criteria (2016). This definition reflects a deeper understanding of bidirectional communication dysfunction between the central and enteric nervous systems [1]. FAPDs are categorized into four subtypes: irritable bowel syndrome (IBS), functional abdominal pain not otherwise specified (FAP-NOS), functional dyspepsia (FD) and abdominal migraine (AM) [2]. FAPDs affect roughly 13.5% of children worldwide. IBS is the most frequently reported subtype [3], collectively accounting for most children presenting with chronic abdominal pain [4], impairing quality of life, school attendance and psychosocial well-being [5].

The possible role of the gut–brain axis has emerged in understanding these disorders, and several studies have postulated the role of dysbiosis in the intestinal microbiome in the pathogenicity of FAPDs [6, 7]. Alterations in the gut microbiome may provide a rationale for therapies targeting the microbiota, such as probiotic formulations containing live microorganisms that can exert a beneficial effect by restoring a healthy microbial balance [8].

In practice, no single probiotic regimen has been established. Pediatricians usually choose probiotics that are known to be safe, such as *L. reuteri* DSM 17938, *L. rhamnosus* GG, *L. acidophilus*, *L. paracasei* and various *Bifidobacterium* species, either as single strains or in multi-strain products like VSL#3 [9].

In a Cochrane review of interventions by Gordon et al. [10], it was reported that probiotic therapy may alleviate abdominal pain compared to placebo in pediatric FAPDs. The same review showed that synbiotic formulations (probiotics combined with prebiotic fibres) had the same effect on stomach pain in children with FAPDs over placebo, although

the evidence was limited. However, the current European and North American Societies for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN/NASPGHAN 2025) consensus statements on pediatric FAP/IBS only gave a conditional recommendation with low certainty for probiotics or synbiotics. For IBS, soluble fibre and *L. rhamnosus* GG were also recommended [11]. A recent expert consensus panel advised using probiotics for FAPDs as part of a comprehensive approach with dietary changes, psychological interventions and other tailored therapies. The panel also noted that probiotics should be administered for 6–8 weeks and can be reintroduced if symptoms recur [12]. Notably, in previous reviews effect size measurements were lacking, and new randomized clinical trials were released after the Cochrane review, so we decided in our current review to give an update about the latest findings including the new trials.

This systematic review and meta-analysis aimed to synthesize and critically evaluate the evidence from clinical trials investigating the efficacy and safety of probiotic formulations for managing AP-DGBIs.

Methods

This work followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered with PROSPERO (n. CRD420251149947).

Search strategy

A comprehensive literature search was conducted across PubMed, Embase, Web of Science and Scopus from database inception to April 2026. The following search terms were used: abdominal pain, functional abdominal pain, irritable bowel syndrome, abdominal migraine, functional dyspepsia, Rome criteria and probiotics, lactobacilli, bacillus, saccharomyces, bifidobacteria. The full search strategy is presented in the supplementary Methods.

Only randomized clinical trials (RCTs) conducted on pediatric patients (under 18 years) diagnosed with functional dyspepsia, irritable bowel syndrome, abdominal migraine or functional abdominal pain not otherwise specified (all by Rome II, III and IV criteria [1]) in which probiotic or synbiotic supplementation was investigated were included. Only studies comparing probiotics or synbiotics with placebo were included in the meta-analysis, whereas the network meta-analysis additionally included trials with placebo, prebiotic or other probiotic as comparator arms. Only articles written in English were considered. Studies conducted on adults; studies of patients with other functional gastrointestinal disorders (e.g. functional constipation); observational studies; retrospective chart reviews; and case series studies were excluded.

Two authors (F.K. and L.Z.) independently screened the studies, and any disagreements were resolved by involving a third author (N.B.). For the risk of bias, two authors (N.B. and L.Z.) independently conducted the assessment using Version 2 of the Cochrane Risk of Bias Tool for Randomised Trials (RoB 2) [13]. Discrepancies were resolved by consensus. This sequence ensured that screening preceded risk-of-bias assessment.

The quality of evidence for the meta-analysis was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework (guidelinedevelopment.org/handbook), which considers risk of bias, inconsistency, indirectness and imprecision. Results were presented in the appropriate tables. The quality of evidence for network meta-analysis was assessed using the Confidence in Network Meta-Analysis Framework (CINeMA), which evaluates within-study bias, reporting bias, indirectness, imprecision, heterogeneity and incoherence. Outcomes were shown in the appropriate tables and as a network plot of the eligible comparisons [14].

Data collection and analysis

The primary outcome was the change in abdominal pain severity. Secondary outcomes included frequency of pain episodes, treatment success and complete resolution or improvement of symptoms. Patients receiving probiotic or synbiotic supplementation were compared with those treated with a placebo. Placebo was defined as a control that did not contain any probiotic microorganisms, including inert carriers or excipients (such as prebiotic, inulin, xylitol or similar substances).

Data extraction was performed independently by two authors (N.B. and L.Z.) and subsequently verified by a third author (F.K.). Collected data included demographic characteristics of patients enrolled; diagnosis; probiotic and placebo supplementation (dosage and duration); treatment

outcome (level of abdominal pain and symptoms resolution or improvement); and publication information.

Statistical analysis was conducted using R software (version 4.5.1) in RStudio environment. Pairwise meta-analysis was performed using the ‘meta’ package [15], and network meta-analysis (NMA) was conducted using the ‘netmeta’ package [16]. The Meta-Analysis Accelerator online tool was also used for data conversion [17]. Risk ratios (RRs) were employed for binary outcomes, and mean differences (MDs) for continuous outcomes. Effect estimates were reported with 95% confidence intervals (CIs) and pooled using a random effect model. Results were presented as a forest plot. A subgroup analysis was planned based on the type of microorganism used. Heterogeneity was assessed using I^2 statistics and τ^2 . Influence diagnostics were also performed, and a funnel plot was inspected to assess publication bias. In the NMA, relative risk (RR) and mean difference (MD) were used for the comparison, and the results were presented as forest plots. Heterogeneity was assessed using the Cochrane’s Q test. In addition, network graphs and league tables were presented.

The results of the pairwise meta-analysis were presented as the primary analysis in the main text. The NMA was conducted as an exploratory analysis to estimate the relative ranking of probiotic formulations.

Results

The literature search identified 1564 records. After removing duplicates and screening the titles and abstracts of the remaining 1129 articles, 86 were selected for full-text review. The reason for exclusion of 62 articles is reported in Supplementary Table 1. Ultimately, 24 studies met the inclusion criteria. However, two articles—the cross-over trials by Giannetti 2017 [18] and Guandalini 2010 [19]—were subsequently excluded because they did not report data that could be used in a meta-analysis. The study by Ratna Sudha 2018 [20] was excluded due to potential bias and conflict of interest within the research team, as well as positive data. Finally, 21 RCTs were included in the systematic review (Fig. 1), involving 2054 participants who met inclusion criteria and 1899 completed the treatment (see references of included RCTs [21–41]). The details of the studies are reported in Table 1.

Participants’ age

Most participants in the included studies were aged 4–18 years. Five studies had an age range of less than 10 years [21, 22, 26, 41]. Bausserman 2005 et al. [24] specified an age range of 5–21 years.

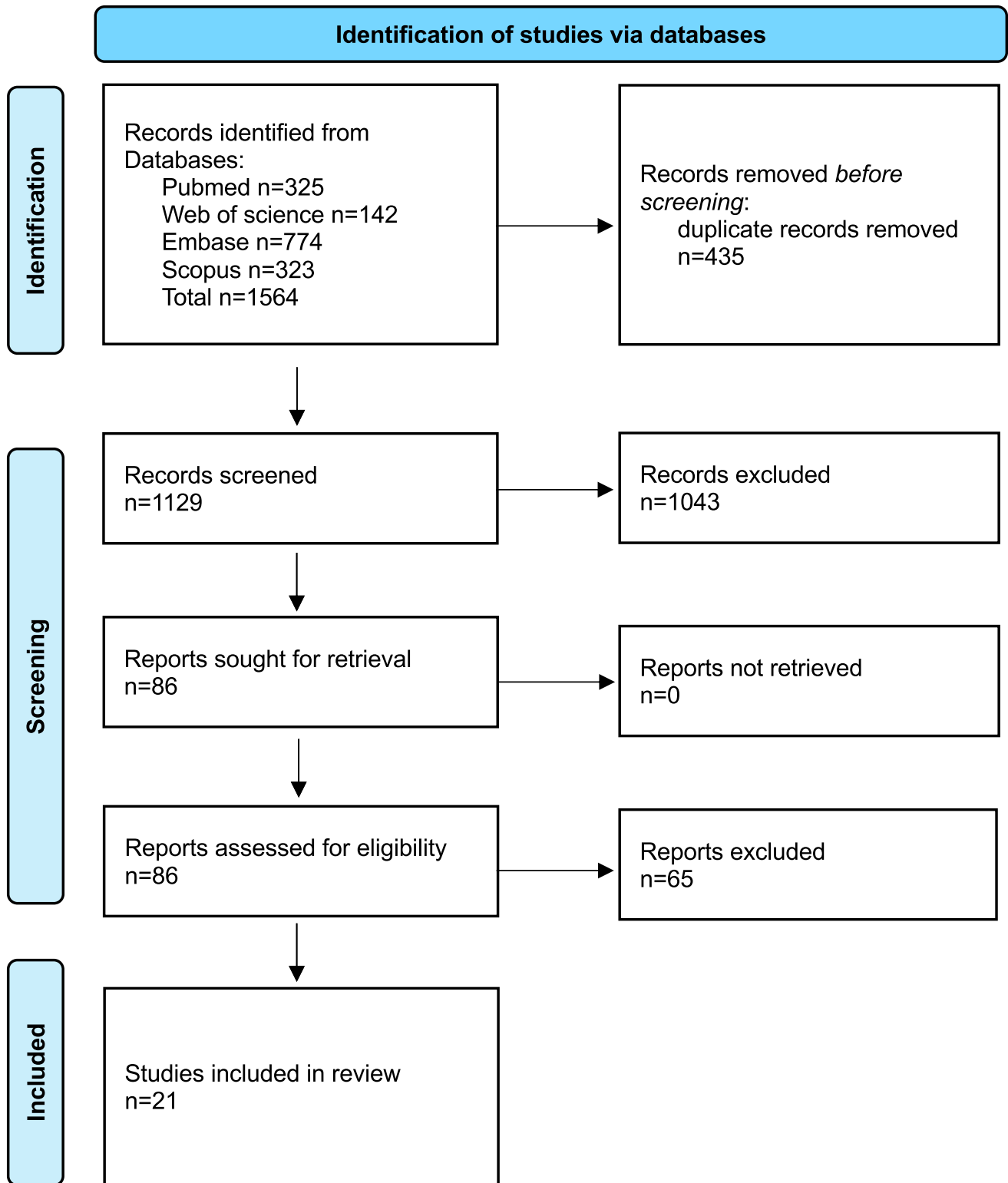


Fig. 1 Flowchart of the study

Table 1 Description of the characteristics of the 21 included RCTs: interventions and trial registration

Study ID	Country setting	Methods of diagnosis	FAPD diagnosis	Age range	Randomized/analyzed (n)	Received treatment (n)	Probiotics/synbiotics dose (CFU)	Comparison	Time points of outcome measurements
Ahyani 2016 [21]	Indonesia	Rome III	FD	7 to 14	124/116	58 probiotic/58 placebo	<i>L. rhamnosus</i> Dose: 1.9×10^9 CFU + <i>Lactobacillus acidophilus</i> Dose: 0.1×10^9 CFU (once daily for 2 weeks)	Placebo (saccharum lactis)	End of intervention
Asgarshirazi 2015 [22]	Iran Gastroenterology clinic	Rome III	FAP/IBS/FD	4 to 13	120/88 (45 FAP/30 IBS/5 FD/8 APS)	34 colpermin/29 synbiotic/25 placebo	Group A: peppermint oil (Colpermin) capsule Dose: 187 mg three times a day, before meals (for patients over 45 kg weight, two caps per dose) Group B: Lactol tablet (150 million spores of <i>B. coagulans</i> + Fructooligosaccharide) after meals Group C as a placebo: folic acid tablet 1 mg (daily, before breakfast or lunch). The treatment for groups A, B and C for 1 month	Placebo (folic acid)	End of intervention
Baştürk 2020 [23]	Turkey Gastroenterology outpatient clinic	Rome III	IBS	4 to 16	83/71	24 probiotic/23 synbiotic/24 prebiotic	Synbiotic group: <i>Bifidobacterium lactis</i> B94 Dose: 5×10^9 CFU + 900 mg inulin Prebiotic group: <i>Bifidobacterium lactis</i> B94 Dose: 5×10^9 CFU (twice daily for 4 weeks)	Prebiotic (900 mg inulin)	End of intervention

Table 1 (continued)

Study ID	Country setting	Methods of diagnosis	FAPD diagnosis	Age range	Randomized/analyzed (n)	Received treatment (n)	Probiotics/synbiotics dose (CFU)	Comparison	Time points of outcome measurements
Bausserman 2005 [24]	United States, Dayton, Ohio Pediatric gastroenterology outpatient clinic	Rome II	IBS	6 to 17	64/50	25 probiotic/25 placebo	<i>L. rhamnosus GG</i> Dose: 10^{10} CFU (1 capsule twice daily for 6 weeks)	Placebo (Inulin)	End of intervention
Eftekhari 2015 [25]	Iran Gastroenterology clinic	Rome III	FAP	4 to 16	80/80	40 probiotic/40 placebo	<i>L. reuteri</i> Dose: 10^8 CFU (5 drops per day for 4 weeks)	Placebo (not stated)	End of intervention (4 weeks) and 4 weeks after end of intervention
Francavilla 2010 [26]	Italy 9 primary care pediatricians chosen by random selection	Rome II	FAP/IBS	5 to 14	141/136 (56 FAP/80 IBS)	67 probiotic/69 placebo	<i>L. rhamnosus GG</i> Dose: 3×10^9 CFU (twice daily for 8 weeks)	Placebo (not stated)	End of intervention (8 weeks) and 8 weeks after end of intervention
Gawrońska 2007 [27]	Poland Tertiary care level	Rome II	FAP/IBS/FD	6 to 16	112/104 (47 FAP/37 IBS/20 FD)	52 probiotic/52 placebo	<i>L. rhamnosus GG</i> Dose: 3×10^9 CFU (twice daily for 4 weeks)	Placebo (inulin)	End of intervention
Gholizadeh 2021 [28]	Iran Pediatric gastroenterology clinic	Rome III	FAP	4 to 14	70/65	33 synbiotic/32 placebo	Synbiotic sachets: fructo-oligosaccharides (FOS) and seven types of bacteria, including <i>Lactobacillus casei</i> , <i>Streptococcus thermophilus</i> , <i>L. acidophilus</i> , <i>L. bulgaricus</i> , <i>L. rhamnosus</i> , <i>Bifidobacterium breve</i> and <i>Bifidobacterium infantis</i> (twice daily for 4 weeks)	Placebo (not stated)	End of intervention
Giorgio 2025 [29]	Italy Three centres outpatients pediatric gastrointestinal unite	Rome IV	IBS	4 to 17	72/72	36 probiotic/36 placebo	<i>Bifidobacterium adolescentis</i> PRL2019 Dose: 20×10^9 CFU (once daily for 12 weeks)	Placebo (not stated)	4 weeks, 8 weeks during the intervention period, and 12 weeks at the end of intervention

Table 1 (continued)

Study ID	Country setting	Methods of diagnosis	FAPD diagnosis	Age range	Randomized/analyzed (n)	Received treatment (n)	Probiotics/synbiotics dose (CFU)	Comparison	Time points of outcome measurements
Jadrešin 2017 [30]	Croatia Tertiary care level	Rome III	FAP/IBS	4 to 18	55/55 (not stated)	26 probiotic/29 placebo	<i>L. reuteri</i> DSM 17938 Dose: 10 ⁸ CFU (450 mg chewable tablet, once daily for 12 weeks)	Placebo (mix of isomalt, xylitol, sucrose distearate, hydrogenated palm oil, lemon-lime flavoring and anhydrous citric acid)	4 weeks during intervention; end of intervention (12 weeks); 1 month after end of intervention
Jadrešin 2020 [31]	Croatia Tertiary care level	Rome III	FAP/IBS	4 to 18	46/46 (not stated)	24 probiotic/22 placebo	<i>L. reuteri</i> DSM 17938 Dose: 10 ⁸ CFU (450 mg chewable tablet, once daily for 12 weeks)	Placebo (mix of isomalt, xylitol, sucrose distearate, hydrogenated palm oil, lemon-lime flavoring and anhydrous citric acid)	4 weeks during intervention; end of intervention (12 weeks); 1 month after end of intervention
Kalvandi 2021 [32]	Iran One centre	Rome IV	FAP	5 to 15	115/104	52 probiotic/52 placebo	250 mg oral supplementation of <i>Saccharomyces boulardii</i> (twice daily for 3 weeks)	Placebo (not stated)	Weekly until 6 weeks
Kesharani 2023 [33]	India One centre	Rome IV	FAP	5 to 18	82/77	38 probiotic/39 placebo	<i>L. rhamnosus</i> GG (ATCC 53103) Dose: 10 ¹⁰ CFU (one sachet daily for 4 weeks)	Placebo (sugar powder)	2 weeks into intervention; end of intervention; 4 weeks after end on intervention
Kianifar 2015 [34]	Iran One centre	Rome III	IBS	4 to 18	60/52	26 probiotic/26 placebo	<i>L. rhamnosus</i> GG Dose: 10 ¹⁰ CFU (capsule twice daily for 4 weeks)	Placebo (Inulin)	Weekly until end of intervention
Maragkoudaki 2017 [35]	Greece, Slovenia, Poland Multi-centred	Rome III	FAP	5 to 16	54/52	26 probiotic/26 placebo	<i>L. reuteri</i> DSM 17938 Dose: 10 ⁸ CFU (two chewable tablets once daily for 4 weeks)	Placebo (not stated)	2 weeks during intervention and end of intervention
Rahmani 2020 [36]	Iran Gastroenterology clinic	Rome III	FAP/IBS/FD/abdominal migraine	6 to 16	125/125 (57 FAP/29 FD/30 IBS/9 AM)	65 probiotic/60 placebo	<i>L. reuteri</i> Dose: 10 ⁸ CFU (twice daily for 4 weeks)	Placebo (not stated)	2 weeks during intervention and end of intervention

Table 1 (continued)

Study ID	Country setting	Methods of diagnosis	FAPD diagnosis	Age range	Randomized/analyzed (n)	Received treatment (n)	Probiotics/synbiotics dose (CFU)	Comparison	Time points of outcome measurements
Romano 2014 [37]	Italy Multi-centred, tertiary-level care	Rome III	FAP	6 to 16	60/56	30 probiotic/26 placebo	<i>L. reuteri</i> DSM 17938 Dose: 10^8 CFU (5 drops, twice daily for 4 weeks)	A mixture of sunflower oil and a medium-chain triglyceride oil (refined from coconut oil)	End of intervention and 4 weeks after end of intervention
Sajad Jafari 2022 [38]	Iran Gastroenterology clinic	Rome IV	FAP/IBS/FD/abdominal migraine	5 to 15	116/116 (84 FAP/14 IBS/8 FD/8 AM)	116 probiotic (58 PMP + 58 MSP)	Polymicrobial probiotic (PMP group) or mono-strain probiotic (MSP group) (once daily for 4 weeks)	No placebo	1 week and 3 weeks into intervention; 1 week and 3 weeks after end of intervention
Saneian 2015 [39]	Iran Outpatient tertiary clinic of pediatric gastroenterology	Rome III	FAP	6 to 18	115/88	45 synbiotic/43 placebo	Synbiotic group: <i>B. coagulans</i> (unique IS-2, 150 million spores) plus FOS (100 mg) (twice daily for 4 weeks)	Placebo (not stated)	End of intervention; 8 weeks after end of intervention
Vázquez-Frias 2023 [40]	Mexico Parallel clinical trial at 15 study sites	Rome IV	IBS (IBS-C, IBS-D, IBS-mix)	6 to 17	259/253	129 probiotic/130 placebo	<i>B. clausii</i> Dose: 4×10^9 CFU (once daily before a meal for 8 weeks)	Placebo (identical formulation without active bacteria)	4 weeks into intervention; end of intervention; 8 weeks after end of intervention
Weizman 2016 [41]	Israel Multi-centred	Rome III	FAP	6 to 15	101/93	47 probiotic/46 placebo	<i>L. reuteri</i> DSM 17938 Dose: 10^8 CFU (chevabale tablets once daily for 4 weeks)	Placebo (identical formulation without active bacteria)	End of intervention; 4 weeks after end of intervention

CFU colony-forming units, FAP functional abdominal pain, FD functional dyspepsia, IBS irritable bowel syndrome, LGG *Lactobacillus rhamnosus* GG, *L. reuteri* *Lactobacillus reuteri*, RCT randomized controlled trial

Diagnosis

In terms of diagnostic criteria, three studies employed the Rome II criteria [24, 26, 27], while the majority utilized Rome III. More recently, five studies have applied the Rome IV framework for diagnosis [29, 32, 33, 38, 40]. A subset of seven studies included more than one diagnosis within their definition of FAPDs [22, 26, 27, 30, 31, 36, 38]. Eight studies focused specifically on FAP within the individual subtypes [25, 28, 32, 33, 35, 37, 39, 41]. IBS was the primary focus in four studies [23, 24, 29, 34]. An additional two studies addressed IBS subgroups (IBS-C, IBS-D, IBS-mix) [40]. Functional dyspepsia was investigated as the main syndrome in one study [21], and as part of a broader group of FAPDs in three others [22, 27, 36]. While abdominal migraine was reported in a group in two studies [36] and [38].

Length of interventions and timing of outcome measurements

The duration of interventions and the timing of outcome assessments varied considerably across the included studies. Treatment duration was 2 weeks in one study [21]; 3 weeks in one study [32]; 4 weeks in thirteen studies [22, 23, 25, 27, 28, 33–39, 41]; 6 weeks in one trial [24]; 8 weeks in two trials [40] and [26]; or 12 weeks in three studies [29–31].

Outcomes were measured during and at the end of the interventions in ten studies [29–36, 38, 40], only at the end of the interventions in six studies [21–24, 27, 28], or after some weeks after the end of the treatments in eight studies [30–32, 37–41].

Types of intervention

Nearly all included studies compared probiotic or synbiotic intervention with a placebo (including prebiotics). The majority of studies evaluated probiotics versus placebo.

Seven studies used *Lactobacillus reuteri*, with five of them employing *L. reuteri* DSM 17938 [30, 31, 35, 37, 41]. Five studies used *L. rhamnosus* GG [24, 26, 27, 33, 34]. *Bifidobacterium adolescentis* PRL2019, *Bacillus clausii*, *Bacillus coagulans* and *Saccharomyces boulardii* were used in individual studies [29, 32, 40].

Baştürk 2020 [23] used *Bifidobacterium lactis* B94 as a probiotic and combined it with inulin as a synbiotic. Four studies used a synbiotic formulation [21, 22, 28, 39].

Finally, Sajad Jafari 2022 [38] evaluated the effects of a polymicrobial probiotic (PMP) versus a mono-strain probiotic (MSP) intervention.

Risk of bias

The risk of bias assessment revealed that 13 studies were judged to be at a low risk of bias, while 8 trials were

considered to be at some risk, and 1 had a high risk. A detailed summary of the individual judgments for each domain is reported in Supplementary Fig. 1.

Abdominal pain levels

Improvement in abdominal pain levels was reported in fifteen studies.

The results of the meta-analysis indicated that, overall, probiotic supplementation led to a modest reduction in pain levels (MD = −0.80, 95%CI = −1.45; −0.15), with *L. rhamnosus* GG showing the greatest efficacy (MD = −1.15, 95%CI = −1.63; −0.68). However, there was high heterogeneity across studies ($I^2=83.4\%$, $\tau^2=0.89$) (Fig. 2). Influence analysis and the funnel plot are reported in Supplementary Results and Supplementary Figs. 2 and 3. The use of a synbiotics formulation also slightly reduced abdominal pain levels (MD = −1.27, 95%CI = −2.53; −0.01), although heterogeneity remained high (Supplementary Fig. 4).

In the NMA, the network of eligible comparisons for efficacy comprised only direct evidence and contained no closed loops, as there was no overlap between direct and indirect comparisons (Supplementary Fig. 5).

The NMA confirmed the meta-analysis results, showing that *L. rhamnosus* GG (MD = −1.14, 95%CI = −2.02; −0.25, p -score = 0.68) and synbiotics (MD = −1.28, 95%CI = −2.26; −0.29, p -score = 0.72) were significantly associated with improved pain outcomes compared to placebo. Despite being used in only a single study, *Bacillus clausii* also showed higher efficacy in this analysis (MD = −2.60, 95%CI = 4.72; −0.48, p -score = 0.94) (Supplementary Fig. 6 and Supplementary Table 2).

Heterogeneity in the NMA was quite high ($\tau^2=0.81$; $\tau=0.90$; $I^2=85.8\%$ [75.8%; 91.7%]), with significant total heterogeneity (Cochran's Q test $Q=63.59$, $p<0.0001$) and within-design heterogeneity ($Q=63.59$, $p<0.0001$). Inconsistency was not assessed as an indirect comparison was not performed.

Pain episodes per week

Eleven studies reported the number of pain episodes per week before and after treatment.

In the meta-analysis, probiotics performed slightly better than placebo overall (MD = −1.02, 95%CI = −1.88; −0.17), although heterogeneity across studies was high ($I^2=93\%$, $\tau^2=1.22$). In the subgroup analysis, the different probiotic formulations revealed only a non-statistically significant trend towards improvement (Fig. 3). Influence analysis and the funnel plot are reported in Supplementary Results, Supplementary Figs. 7 and 8. Synbiotic supplementation was found to slightly reduce the number of abdominal pain episodes per week (MD = −0.93, 95%CI = −1.46; −0.41),

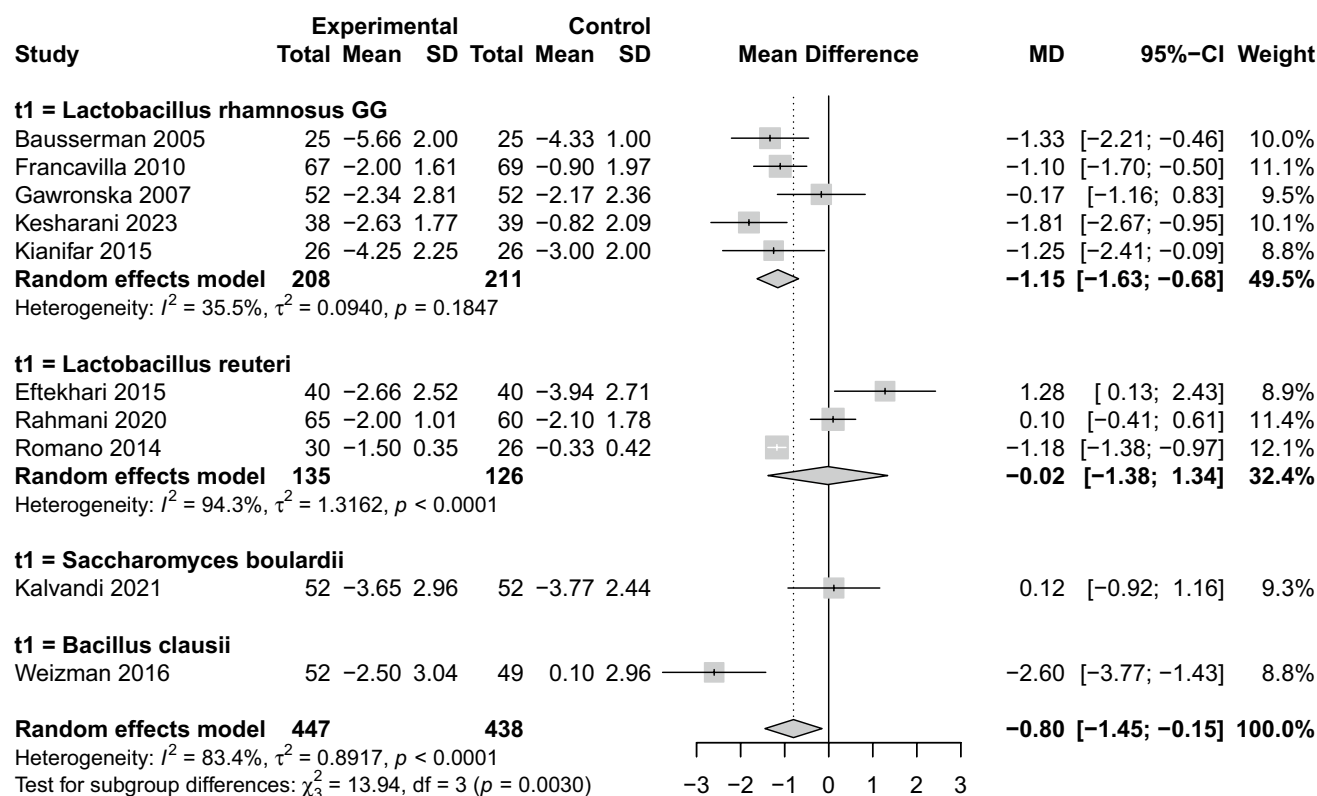


Fig. 2 Forest plot of the meta-analysis evaluating **abdominal pain intensity** as an outcome. The effect of probiotic supplementation ('experimental') on the level of abdominal pain (expressed as mean difference $\pm$ standard deviation (SD) before and after intervention) compared with placebo ('control') is displayed. Results are reported

using random effect model, expressed as mean difference ('MD'), with corresponding 95% confidence interval (CI). Measures of heterogeneity (I^2 and τ^2) are shown. Subgroup analysis according to the specific probiotic formulation is also presented

with moderate heterogeneity observed (Supplementary Fig. 9).

The network of comparisons in the NMA was entirely based on direct evidence, without any closed loops, reflecting the absence of overlap between direct and indirect comparisons (Supplementary Fig. 10).

The NMA confirmed that all treatments significantly reduced the number of pain episodes, *L. reuteri* (MD = -0.83, 95%CI = -1.53; -0.13, p -score = 0.60); *L. rhamnosus GG* (MD = -0.96, 95%CI = -1.75; -0.16, p -score = 0.69); and synbiotics (MD = -0.98, 95%CI = -1.75; -0.20, p -score = 0.70) (Supplementary Fig. 11 and Supplementary Table 3). However, substantial heterogeneity remained, reflecting potential variability across studies ($\tau^2 = 0.40$; $\tau = 0.63$, $I^2 = 89.5\%$ [82.3%; 93.8%]).

Substantial variations among studies were reflected in a high Cochran's Q test p -value ($Q = 76.22$, $p < 0.0001$) and within-design heterogeneity (direct comparison, $Q = 76.22$, $p < 0.0001$).

Treatment success—complete resolution of symptoms

Complete resolution of pain or symptoms was defined as treatment success in 8 studies.

The use of probiotics was associated with raised response rates relative to placebo (RR = 1.56, 95%CI = 1.07; 2.27); however, no clear differences were observed in the subgroup analysis, with high heterogeneity persisting across studies ($I^2 = 61.2\%$, $\tau^2 = 0.16$) (Fig. 4). Influence analysis and funnel plot are reported in Supplementary Results and Supplementary Figs. 12 and 13.

Using probiotics increased the likelihood of achieving treatment success compared to placebo (35.3% versus 22.8%), corresponding to a 56% relative improvement and a 14% absolute increase. The number needed to treat (NNT) was 6.98 (95%CI = 3.97–29.04).

The network of eligible comparisons in the network meta-analysis included one closed loop, allowing assessment of

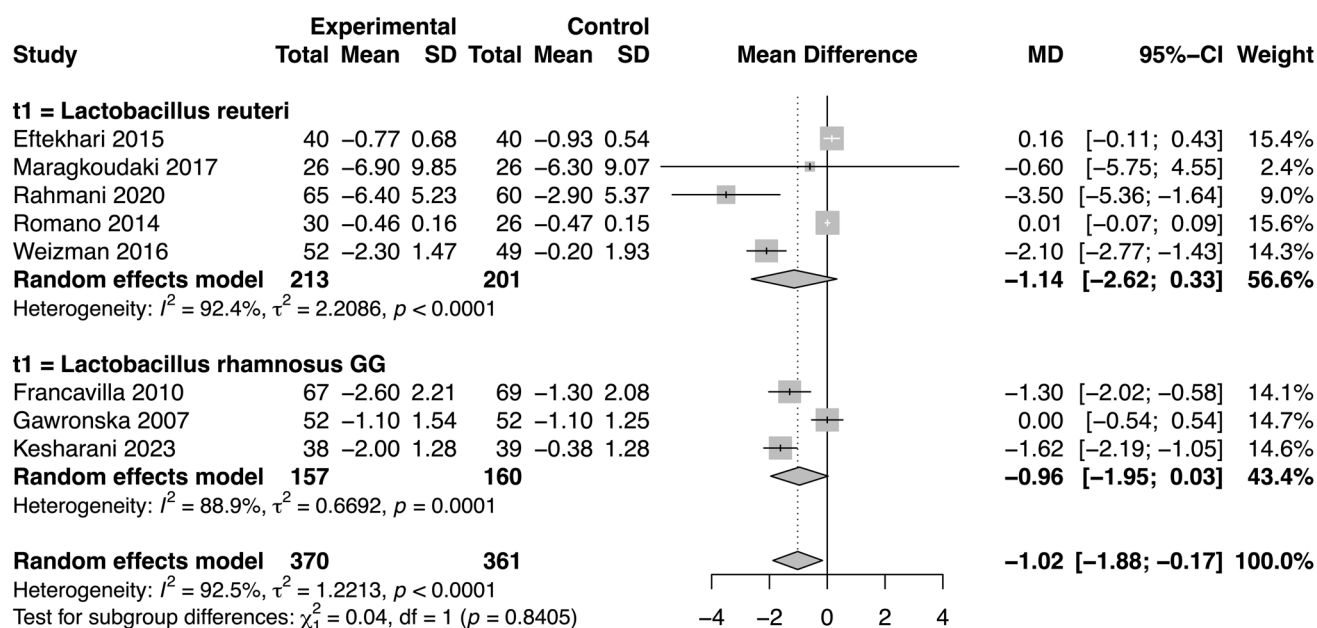


Fig. 3 Forest plot of the meta-analysis evaluating the **number of pain episodes per week** as an outcome. The effect of probiotic supplementation ('experimental') on the number of weekly pain episodes (expressed as mean difference $\pm$ standard deviation (SD) before and after intervention) compared with placebo ('control') is displayed.

Results are reported using random effect model, expressed as mean difference ('MD'), and 95% confidence interval (CI). Measures of heterogeneity (I^2 and τ^2) are shown. Subgroup analysis according to the specific probiotic formulation is also presented

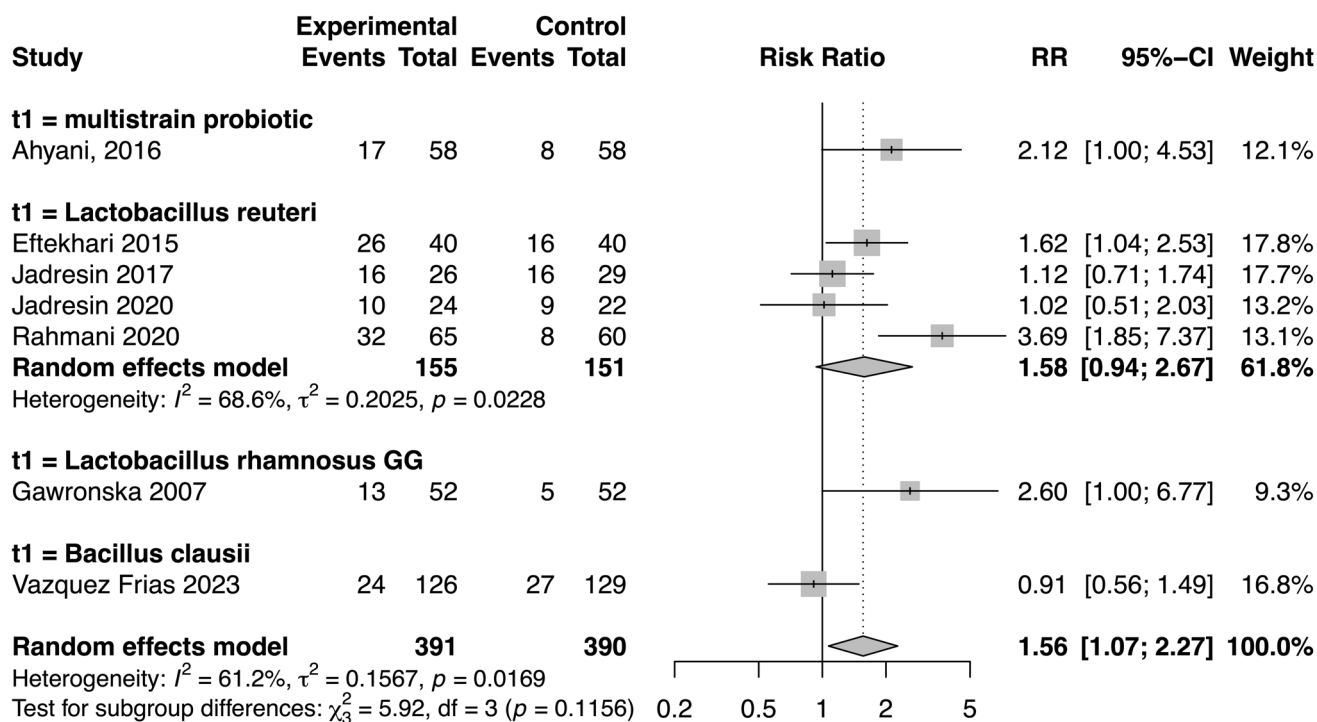


Fig. 4 Forest plot of the meta-analysis evaluating **complete resolution of pain symptoms** as an outcome. The effect of probiotic supplementation ('experimental') on the complete resolution of pain symptoms ('events') compared with placebo ('control') is shown.

Results are reported using a random effect model, expressed as risk ratio ('RR'), with corresponding 95% confidence interval (CI). Measures of heterogeneity (I^2 and τ^2) are shown. Subgroup analysis according to the specific probiotic formulation is also presented

consistency between direct and indirect evidence. All other comparisons were connected exclusively through direct evidence (Supplementary Fig. 14).

Probiotic supplementation generally increased patients' response rates; however, individual comparisons did not reach statistical significance (Supplementary Fig. 15 and Supplementary Table 4).

Heterogeneity was high ($\tau^2 = 0.22$; $\tau = 0.47$; $I^2 = 65.8\%$ [10.7%; 86.9%]) as well as total heterogeneity ($Q = 11.70$, $p = 0.02$) and within-design heterogeneity ($Q = 9.55$, $p = 0.02$), while between-design inconsistency was not statistically significant ($Q = 2.15$).

Treatment success—improvement of symptoms

When success was defined as an improvement in symptoms according to an author-defined threshold (eight studies), probiotic or synbiotic supplementations were not associated with different response rates compared with placebo (Fig. 5, Supplementary Fig. 18). Influence analysis and funnel plot are reported in the Supplementary Results and Supplementary Figs. 16 and 17.

In the network meta-analysis, the network plot of eligible comparisons shows that all connections were based on direct evidence, with no closed loops present (Supplementary Fig. 19).

The network meta-analysis combined both direct and indirect evidence and found that *Bifidobacterium adolescentis*

(RR = 2.71, 95%CI = 1.30–5.65, p -score = 0.96) and synbiotic (RR = 1.80, 95%CI = 1.20; 2.68, p -score = 0.80) were associated with a higher response rate. This suggests a potential benefit when considering the entire network of comparisons (Supplementary Fig. 20 and Supplementary Table 5).

The analysis showed low heterogeneity and inconsistency ($\tau^2 < 0.0001$; $I^2 = 28\%$ [0.0%; 73.3%]), indicating that the treatment effects were generally consistent across studies and that the network estimates were reliable. Cochrane Q statistics did not indicate potential heterogeneity within designs or overall ($Q = 4.17$).

Subgroup analysis by disease subtype

A further analysis was performed based on the different AP-DGBIs subtypes, namely, IBS, FAP-NOS, AM and FD. All types of formulations (including synbiotics and probiotics) were considered together due to the small number of studies.

This analysis did not identify statistically significant differences between patients treated with placebo and those treated with probiotics/synbiotics for the outcome of pain episodes, or treatment success defined as complete resolution or improvement of symptoms (data not shown).

However, VAS scores modestly improved both in IBS subgroup (MD = −1.20; 95%CI = −1.61; −0.78, heterogeneity, $I^2 = 0\%$, $\tau^2 = 0$) and FAP-NOS subgroup (MD = −1.08;

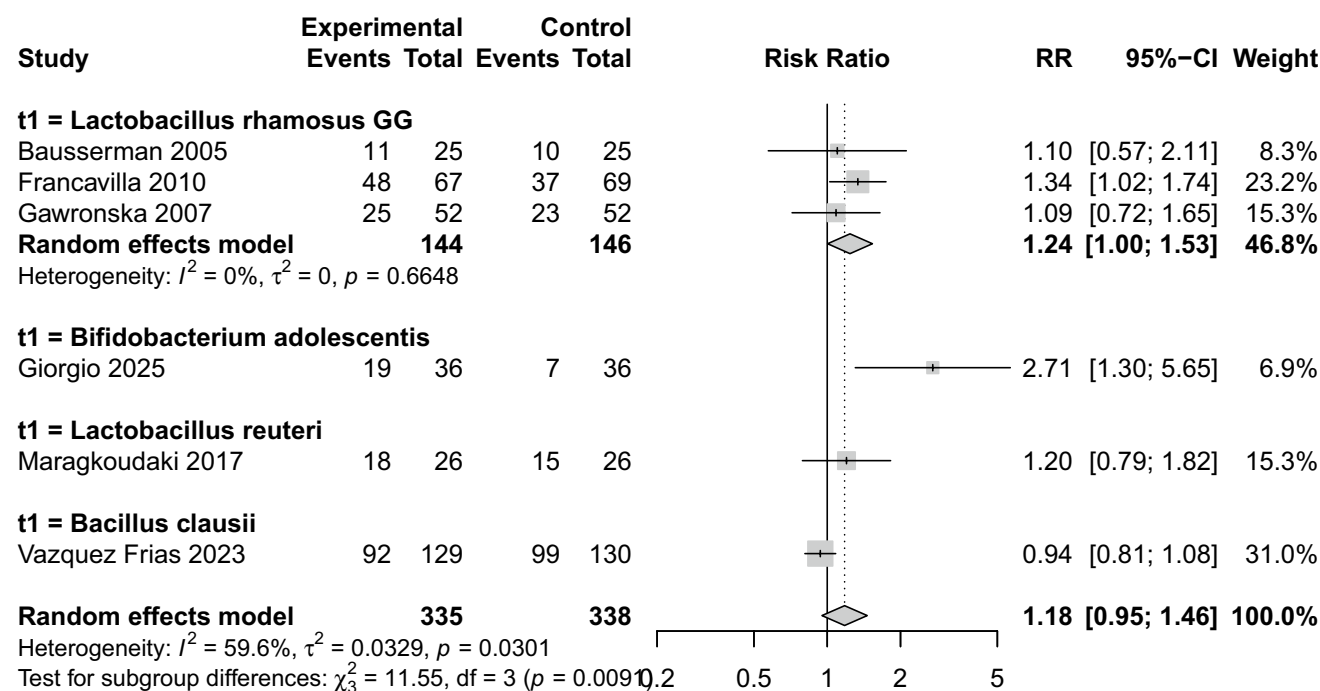


Fig. 5 Forest plot of the meta-analysis evaluating **improvement of pain symptoms** as an outcome. The effect of probiotic supplementation ('experimental') on the improvement of pain symptoms ('events') compared with placebo ('control') is displayed. Results are

reported using a random effect model, expressed as risk ratio ('RR'), with corresponding 95% confidence interval (CI). Measures of heterogeneity (I^2 and τ^2) are shown. Subgroup analysis according to the specific probiotic formulation is also presented

95%CI = $-1.87; -0.29$, $I^2 = 74\%$, $\tau^2 = 0.64$) but not in FD subgroup (MD = -0.42 , 95%CI = $-2.08; 1.24$, $I^2 = 82\%$, $\tau^2 = 1.19$) (Figure supplementary 21).

Adverse effects and safety profile of probiotics

No severe adverse effects were reported in 21 studies. In one study [33], the authors observed some vomiting episodes in the treated group. In another study [39], minor side effects, including vomiting, insomnia, nausea, drowsiness, dry mouth, diarrhoea, fatigue, headache, dizziness and loss of appetite, were reported in both the treated and placebo groups. These findings were consistent with the known safety profile of the tested strains.

In a randomized clinical trial of children with functional dyspepsia, Ahyani et al. [21] reported that probiotic supplementation was well tolerated in their pediatric cohort, with no adverse effects observed during the study period. The authors noted that, in general, probiotic-related side effects tend to be mild and self-limiting, most commonly flatulence or transient abdominal discomfort. Similarly, in the study by Gawrońska [27], *L. rhamnosus* GG was well tolerated and no adverse effects were reported.

Gholizadeh et al. and his colleagues [28] monitored adverse events by scheduled telephone interviews and a predefined checklist of probiotic-related side effects (bloating, diarrhoea, itching and skin rash), with discontinuation planned in the case of severe events, and observed no adverse events or school absenteeism in either group during the trial.

In the trial by Kianifar et al. [34], no complications leading to discontinuation of the study medication were reported, while Maragkoudaki et al. [35] found that *L. reuteri* DSM 17938 was well tolerated without adverse side effects, and Weizman et al. [41] likewise reported that no adverse effects were observed among participants. Taken together, these data support a favourable safety profile of the probiotic strains used in pediatric AP-DGBIs.

Quality of evidence

The quality of evidence in the meta-analysis was rated as low for outcomes assessing pain intensity and the frequency of pain episodes. It was rated as moderate for the outcome of complete resolution of symptoms. The most critical limitation was the presence of moderate to high heterogeneity across studies (Supplementary Table 6).

The certainty of the network meta-analysis evidence for the two binary outcomes (resolution and improvement of abdominal pain symptoms) was evaluated using the CINeMA framework. Overall, confidence in the estimates was rated as low across all comparisons. Substantial heterogeneity and inconsistency were observed in most

comparisons (Supplementary Tables 7 and 8 and Supplementary Figs. 22 and 23).

Discussion

This systematic review and meta-analysis evaluated the efficacy of probiotic and synbiotic formulations for the management of AP-DGBIs in pediatric patients, updating and extending the findings of previous syntheses with newly available trials.

The statistically significant, albeit modest, reductions in pain intensity and pain episode frequency observed with probiotic supplementation could be clinically plausible given their proposed mechanisms of action. Probiotics are thought to alleviate FAPDs through several non-mutually exclusive pathways, including restoration of microbial diversity, reinforcement of intestinal barrier integrity, modulation of mucosal immune activation and attenuation of visceral hypersensitivity via the gut–brain axis [42, 43]. The finding that *L. rhamnosus* GG strain showed the most consistent effect on pain intensity in both pairwise and network meta-analyses (NMA) is mechanistically coherent: LGG is among the best-characterized strains in terms of strengthening the gut barrier, immune modulation and production of bioactive metabolites [10, 44]. In contrast, *L. reuteri* DSM 17938 has exhibited anti-nociceptive properties partly mediated by serotonin signalling and partly by modulation of colonic motility [30, 31]. This difference in mechanism may explain the variation in results between strains. The network meta-analysis positive findings for *Bacillus clausii* (pain intensity) and *Bifidobacterium adolescentis* (symptom improvement) were intriguing, but both were based on a single trial and should be considered preliminary hypotheses until confirmed.

Beyond statistical results, and the possible pathophysiological speculations, in a strictly clinical pragmatic perspective the impact of treatment appears questionable. As a matter of fact, when success was defined as an improvement in symptoms according to an author-defined threshold, probiotic supplementation was not associated with different response rates compared with placebo. The treatment effect (complete resolution in 35.3% versus 22.8% with placebo), corresponding to an NNT of 7, suggests that probiotics may be an adjunctive therapy with modest benefit. Interpretation of the NNT requires caution, as the 95% confidence interval of 3.97 to 29.04 encompasses a very wide range of potential clinical effects, indicating substantial imprecision. Although the direction of the effect consistently favoured probiotics, the magnitude of the clinical benefit remains uncertain. Accordingly, the true NNT may range from a substantially low value (indicating meaningful clinical relevance) to a considerable high value (suggesting limited clinical impact), reflecting overall uncertainty in the strength of the effect.

The high response rate to placebo is not a methodological inconvenience but a clinically meaningful signal [45]. This finding reflects the well-established contribution of the gut–brain axis, as well as expectation, therapeutic attention and parental reassurance to symptom perception in AP-DGBIs, as further demonstrated by the observation that even open-label placebo treatment significantly reduces pain in this population [46]. Probiotics may partly act through the effect of regular therapeutic expectations rather than through exclusive microbiological action [47].

The predominance of subjective patient-reported outcomes across the included trials is a fundamental interpretive challenge that the field has yet to resolve. Indeed, when objective measures were incorporated, such as stool characteristics, school absenteeism, analgesic use or validated functional scales, the results were generally neutral, with beneficial stool differences reported in only one study [29] but failed to demonstrate changes in four others [30, 31, 34, 40]. This discrepancy between subjective relief and objective measurements may reflect the limitations of pain-focused instruments in conditions where visceral hypersensitivity and central sensitization dominate the symptom profile. The Core Outcome Set (COS) developed by Zeevenhooven et al. [48] measurements of eight domains, including pain intensity, pain frequency, quality of life and school attendance, and the standardized responder definition of a $\geq 30\%$ reduction in pain intensity, as proposed by Saps et al. on behalf of the Rome Foundation [49], offers the most direct path to resolving this uncertainty and should be adopted as mandatory minimum standards in future probiotic trials.

Building on previous reviews, this analysis confirms and refines the existing evidence base. The Cochrane review by Gordon et al. [10] and the earlier synthesis by Korterink et al. [50] both concluded that probiotics may be more effective to placebo for pain relief in pediatric FAPDs, especially IBS. The added value of this review lies in three aspects: the inclusion of seven additional RCTs published after the Cochrane search cutoff, the explicit quantification of clinical relevance through the calculation of NNT and the use of an NMA to rank individual formulations. The conditional recommendation for *L. rhamnosus* GG in IBS from the ESPGHAN/NASPGHAN 2025 guidelines is directly supported by our strain-specific findings, while the recommendation for probiotics in broader FAPDs, issued with low certainty, aligns with the modest NNT and wide confidence interval we reported [49].

Synbiotic findings demand critical interpretive attention. Modest reductions in pain intensity and pain episode frequency suggest that co-administration of prebiotic substrates may potentiate probiotic colonization and metabolic activity, a biologically plausible mechanism given that prebiotics selectively promote the growth and function of co-administered strains

[51, 52]. However, only four RCTs employing synbiotics were included in our study [22, 23, 28, 39], prebiotic components were heterogeneous across formulations and synbiotics failed to increase complete symptom resolution in the pairwise analysis. Dedicated synbiotic trials with standardized formulations, transparent prebiotic dosing and core outcome endpoints [48] are a clear research priority.

Several methodological limitations constrain the strength of these conclusions. Clinical and methodological heterogeneity was substantial: enrolled populations spanned IBS, FAP, FD and AM; treatment durations ranged from 2 to 12 weeks; probiotic doses and formulations varied widely; and different cutoff criteria were applied to assess improvement of symptoms. Future research should prioritize adequately powered trials stratified by FAPD subtype and baseline psychosocial burden, using standardized core outcomes and pre-specified responder definitions, with follow-up of at least 6 months to assess the durability of benefit.

Conclusion

In summary, this systematic review suggests that probiotics may play a modest role in managing pediatric AP-DGBIs. Probiotic interventions appear to be more effective than a placebo at alleviating AP-DGBIs symptoms. However, the overall effect sizes are small, and evidence certainty is only low to moderate due to heterogeneity and study limitations. It is important to note that probiotics are safe and can be used alongside standard treatments. Larger, well-designed pediatric trials are needed to clarify which intervention parameters (strain, dose, duration) are most effective, and to strengthen confidence in these findings. Until then, probiotics may be recommended as a safe adjunctive therapy, providing realistic expectations of modest benefit.

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Data availability Data are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

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