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Probiotics for management of functional abdominal pain disorders in children (Review)

Gordon M, Wallace C, Sinopoulou V, Akobeng AK

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[Intervention Review]

Probiotics for management of functional abdominal pain disorders in children

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ABSTRACT

Background

Functional abdominal pain is pain occurring in the abdomen that cannot be fully explained by another medical condition and is common in children. It has been hypothesised that the use of micro-organisms, such as probiotics and synbiotics (a mixture of probiotics and prebiotics), might change the composition of bacterial colonies in the bowel and reduce inflammation, as well as promote normal gut physiology and reduce functional symptoms.

Objectives

To assess the efficacy and safety of probiotics in the treatment of functional abdominal pain disorders in children.

Search methods

We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and two clinical trials registers from inception to October 2021.

Selection criteria

Randomised controlled trials (RCTs) that compare probiotic preparations (including synbiotics) to placebo, no treatment or any other interventional preparation in patients aged between 4 and 18 years of age with a diagnosis of functional abdominal pain disorder according to the Rome II, Rome III or Rome IV criteria.

Data collection and analysis

The primary outcomes were treatment success as defined by the primary studies, complete resolution of pain, improvement in the severity of pain and improvement in the frequency of pain. Secondary outcomes included serious adverse events, withdrawal due to adverse events, adverse events, school performance or change in school performance or attendance, social and psychological functioning or change in social and psychological functioning, and quality of life or change in quality life measured using any validated scoring tool. For dichotomous outcomes, we calculated the risk ratio (RR) and corresponding 95% confidence interval (95% CI). For continuous outcomes, we calculated the mean difference (MD) and corresponding 95% CI.

Main results

We included 18 RCTs assessing the effectiveness of probiotics and synbiotics in reducing the severity and frequency of pain, involving a total of 1309 patients.

Probiotics may achieve more treatment success when compared with placebo at the end of the treatment, with 50% success in the probiotic group versus 33% success in the placebo group (RR 1.57, 95% CI 1.05 to 2.36; 554 participants; 6 studies; I^2 = 70%; low-certainty evidence).

It is not clear whether probiotics are more effective than placebo for complete resolution of pain, with 42% success in the probiotic group versus 27% success in the placebo group (RR 1.55, 95% CI 0.94 to 2.56; 460 participants; 6 studies; I^2 = 70%; very low-certainty evidence). We judged the evidence to be of very low certainty due to high inconsistency and risk of bias.

We were unable to draw meaningful conclusions from our meta-analyses of the pain severity and pain frequency outcomes due to very high unexplained heterogeneity leading to very low-certainty evidence.

None of the included studies reported serious adverse events. Meta-analysis showed no difference in withdrawals due to adverse events between probiotics (1/275) and placebo (1/269) (RR 1.00, 95% CI 0.07 to 15.12). The results were identical for the total patients with any reported adverse event outcome. However, these results are of very low certainty due to imprecision from the very low numbers of events and risk of bias.

Synbiotics may result in more treatment success at study end when compared with placebo, with 47% success in the probiotic group versus 35% success in the placebo group (RR 1.34, 95% CI 1.03 to 1.74; 310 participants; 4 studies; I^2 = 0%; low certainty). One study used *Bifidobacterium coagulans*/fructo-oligosaccharide, one used *Bifidobacterium lactis*/inulin, one used *Lactobacillus rhamnosus* GG/inulin and in one study this was not stated).

Synbiotics may result in little difference in complete resolution of pain at study end when compared with placebo, with 52% success in the probiotic group versus 32% success in the placebo group (RR 1.65, 95% CI 0.97 to 2.81; 131 participants; 2 studies; I^2 = 18%; low-certainty evidence).

We were unable to draw meaningful conclusions from our meta-analyses of pain severity or frequency of pain due to very high unexplained heterogeneity leading to very low-certainty evidence.

None of the included studies reported serious adverse events. Meta-analysis showed little to no difference in withdrawals due to adverse events between synbiotics (8/155) and placebo (1/147) (RR 4.58, 95% CI 0.80 to 26.19), or in any reported adverse events (3/96 versus 1/93, RR 2.88, 95% CI 0.32 to 25.92). These results are of very low certainty due to imprecision from the very low numbers of events and risk of bias.

There were insufficient data to analyse by subgroups of specific functional abdominal pain syndrome (irritable bowel syndrome, functional dyspepsia, abdominal migraine, functional abdominal pain - not otherwise specified) or by specific strain of probiotic.

There was insufficient evidence on school performance or change in school performance/attendance, social and psychological functioning, or quality of life to draw conclusions about the effects of probiotics or synbiotics on these outcomes.

Authors' conclusions

The results from this review demonstrate that probiotics and synbiotics may be more efficacious than placebo in achieving treatment success, but the evidence is of low certainty. The evidence demonstrates little to no difference between probiotics or synbiotics and placebo in complete resolution of pain. We were unable to draw meaningful conclusions about the impact of probiotics or synbiotics on the frequency and severity of pain as the evidence was all of very low certainty due to significant unexplained heterogeneity or imprecision.

There were no reported cases of serious adverse events when using probiotics or synbiotics amongst the included studies, although a review of RCTs may not be the best context to assess long-term safety. The available evidence on adverse effects was of very low certainty and no conclusions could be made in this review. Safety will always be a priority in paediatric populations when considering any treatment. Reporting of all adverse events, adverse events needing withdrawal, serious adverse events and, particularly, long-term safety outcomes are vital to meaningfully move forward the evidence base in this field.

Further targeted and appropriately designed RCTs are needed to address the gaps in the evidence base. In particular, appropriate powering of studies to confirm the safety of specific strains not yet investigated and studies to investigate long-term follow-up of patients are both warranted.

PLAIN LANGUAGE SUMMARY

Probiotics for the management of functional abdominal pain disorders in children

Probiotics for stomach pain in children

Key messages

Probiotics may be better than placebo (dummy treatment) at improving stomach pain for children with functional abdominal pain.

Synbiotics may be better than placebo (dummy treatment) at improving stomach pain for children with functional abdominal pain.

What is functional abdominal pain?

Functional abdominal pain is a common problem in children. The term functional abdominal pain is used when no cause can be found for the symptoms. These symptoms include frequent stomach pain that has lasted for at least six months, which causes problems in daily life.

What are probiotics?

Probiotics are live bacteria and yeasts, promoted as having various health benefits. They are often referred to as 'good bacteria'. It is thought that these probiotics may help the natural balance of bacteria in the gut and may improve symptoms in certain illnesses. They can also be added to agents called prebiotics (foods that support the growth of these bacteria and yeasts) and when these are put together in a single preparation, this is a called a synbiotic.

What did we want to find out?

We wanted to find out if probiotics and synbiotics can be used for the treatment of functional abdominal pain in children and whether they are safe to use.

What did we do?

We searched for studies that looked at probiotics or synbiotics compared with placebo, no treatment or another intervention in children aged between 4 and 18 years with a diagnosis of functional abdominal pain disorder. We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 18 studies with a total of 1309 children, which compared probiotics or synbiotics with placebo.

We found that probiotics may provide better pain relief and relief from other stomach problems than placebo for children with functional abdominal pain. In particular, in children taking probiotics, treatment was judged a success more often than in those taking a placebo. Synbiotics also showed a difference from placebo but this was based on a smaller number of studies. There was not enough information to consider changes in the frequency of pain when comparing synbiotics to placebo.

We cannot reach any conclusions about safety as the evidence we found on any unwanted or harmful effects was of very low certainty.

What are the limitations of the evidence?

The evidence for synbiotics in this review is limited by the fact that the results are from fewer studies. In terms of safety, there were not enough cases of unwanted or harmful effects to give a clear picture about the safety of probiotics and synbiotics.

How up to date is this evidence?

This evidence is up to date to October 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Probiotic compared to placebo for management of functional abdominal pain disorders in children

Probiotic compared to placebo for management of functional abdominal pain disorders in children

Patient or population: children (4 to 18 years) with functional abdominal pain disorders
Setting: outpatient
Intervention: probiotic
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with probiotics				
Treatment success (at study end, as reported by study authors)	Study population		RR 1.57 (1.05 to 2.36)	554 (6 studies)	⊕⊕⊖⊖ Low [a]	—
	339 per 1000	532 per 1000 (374 to 675)				
Complete resolution of pain (at study end, as reported by study authors)	Study population		RR 1.55 (0.94 to 2.56)	460 (6 studies)	⊕⊖⊖⊖ Very low [b]	—
	272 per 1000	422 per 1000 (256 to 696)				
Severity of pain (at study end, using the Faces Pain Scale)	Severity of pain using the Faces Pain Scale when comparing probiotics versus placebo: SMD -0.28 (95% CI -0.67 to 0.12)			665 participants (7 studies)	⊕⊖⊖⊖ Very low[b]	—
Frequency of pain (at study end, episodes per week)	Frequency of pain episodes (per week) when comparing probiotics versus placebo: MD -0.43 (95% CI -0.92 to 0.07)			605 participants (6 studies)	⊕⊖⊖⊖ Very low[c]	—
Withdrawals due to adverse events	Study population		RR 1.00 (0.07 to 15.12)	544 (8 studies)	⊕⊖⊖⊖ Very low [e]	—
	4 per 1000	4 per 1000 (0 to 60)				
Serious adverse events	There were no SAEs reported within these studies in either group.			685 (9 studies)	⊕⊖⊖⊖ Very low [e]	—
Adverse events (any)	Study population		RR 1.00	489	⊕⊖⊖⊖	—

	4 per 1000	4 per 1000 (0 to 60)	(0.07 to 15.12)	(7 studies)	Very low [e]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SAE:** serious adverse event; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded one level due to inconsistency (I^2 = 59% for both outcomes) and one level for risk of bias.
[b]Downgraded three levels due to very high inconsistency (I^2 = 70%) and risk of bias (allocation concealment, attrition and reporting bias).
[c]Downgraded three levels due to very high inconsistency (I^2 = 70%) and risk of bias (reporting bias).
[d]Downgraded one level due to risk of bias.
[e]Downgraded two levels due to imprecision because of very low numbers of adverse event cases and one level due to risk of bias.

Summary of findings 2. Synbiotic compared to placebo for management of functional abdominal pain disorders in children

Synbiotic compared to placebo for management of functional abdominal pain disorders in children

Patient or population: children (4 to 18 years) with functional abdominal pain disorders
Setting: outpatient
Intervention: synbiotic
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with synbiotic				
Treatment success (at study end, as reported by study authors)	Study population		RR 1.34 (1.03 to 1.74)	310 (4 studies)	⊕⊕⊖⊖ LOW [a,b]	—
	350 per 1000	469 per 1000 (360 to 609)				
Complete resolution of pain (at study end, as reported by study authors)	Study population		RR 1.65 (0.97 to 2.81)	131 (2 studies)	⊕⊕⊖⊖ LOW [a,b]	—
	319 per 1000	405 per 1000				

		(309 to 896)				
Severity of pain (at study end, using the Faces Pain Scale)	Severity of pain measured using the Faces Pain Scale for synbiotics versus placebo: MD -0.21 (95% CI -0.78 to 0.37)			319 (4 studies)	⊕⊖⊖⊖ Very low[c]	—
Frequency of pain (at study end, episodes per week)	The mean in the placebo group was 3.4	MD 1.26 lower (1.77 lower to 0.75 lower)	—	80 (1 study)	⊕⊖⊖⊖ Very low[a,d]	—
Withdrawals due to adverse events	Study population		RR 4.58 (0.80 to 26.19)	302 (4 studies)	⊕⊖⊖⊖ Very low[e]	—
	7 per 1000	31 per 1000 (6 to 183)				
Serious adverse events	There were no SAEs reported within these studies in either group			302 (4 studies)	⊕⊖⊖⊖ Very low[e]	—
Adverse events (any)	Study population		RR 2.88 (0.32 to 25.92)	189 (3 studies)	⊕⊖⊖⊖ Very low[e]	—
	11 per 1000	30 per 1000 (3 to 285)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SAE:** serious adverse event; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded one level for imprecision due to low participant numbers.
[b]Downgraded one level due to risk of bias.
[c]Downgraded two levels due to very serious unexplained heterogeneity, and one level due to risk of bias.
[d]Downgraded two levels for severe risk of bias, due to unclear/high risk of bias for the single study that provided data for this outcome.
[e]Downgraded two levels due to very serious imprecision from very low event numbers, and one level due to risk of bias.

BACKGROUND

Description of the condition

The term 'recurrent abdominal pain' was introduced by Apley 1958 and describes clinically apparent, non-organic, chronic or recurrent abdominal pain in children, with three or more episodes within three months that are severe enough to interfere with daily activities. Drossman 2006 replaced recurrent abdominal pain with the term "abdominal functional gastrointestinal disorders" (AP-FGIDs) in the Rome III system, and described AP-FGIDs as "chronic or recurrent abdominal pain without evidence of an organic cause". In 2016, the Rome III criteria were replaced with the more recent Rome IV criteria (Drossman 2016; Drossman 2017), updating the nomenclature to "functional abdominal pain disorders" (FAPDs) (Hyams 2016).

The Rome IV criteria divide FAPDs into the following subcategories (Hyams 2016):

- Functional dyspepsia
- Irritable bowel syndrome (IBS)
- Abdominal migraine (AM)
- Functional abdominal pain - not otherwise specified (FAP-NOS)

The diagnosis of functional dyspepsia must include one or more of the following for at least four days per month (Hyams 2016):

- Bothersome postprandial fullness
- Bothersome early satiation
- Bothersome epigastric pain not associated with defecation
- Bothersome epigastric burning not associated with defecation
- After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

These criteria should be fulfilled for the last two months before diagnosis.

The diagnosis of irritable bowel syndrome must include all of the following (Hyams 2016):

- Abdominal pain at least four days per month associated with one or more of the following:
  - related to defecation;
  - a change in frequency of stool; and
  - a change in form (appearance) of stool.
- In children with constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not irritable bowel syndrome).
- After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

These criteria should be fulfilled for the last three months with symptom onset at least six months before diagnosis of irritable bowel syndrome.

The diagnosis of abdominal migraine must include all of the following (Hyams 2016):

- Paroxysmal episodes of intense, acute periumbilical, midline or diffuse abdominal pain lasting one hour or more (should be the most severe and distressing symptom).
- Episodes are separated by periods of usual health lasting weeks to months.
- The pain is incapacitating and interferes with normal activities.
- Stereotypical pattern and symptoms in the individual patient.
- The pain is associated with two or more of the following:
  - anorexia;
  - nausea;
  - vomiting;
  - headache;
  - photophobia;
  - pallor.
- After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

These criteria should be fulfilled two or more times in the past 12 months.

The diagnosis of functional abdominal pain - not otherwise specified (FAP-NOS) must be fulfilled at least four times per month and include all of the following (Hyams 2016):

- Episodic or continuous abdominal pain that does not occur solely during physiologic events (e.g. eating, menses).
- Insufficient criteria for irritable bowel syndrome, functional dyspepsia or abdominal migraine.
- After appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition.

These criteria should be fulfilled at least two months before diagnosis.

Functional abdominal pain disorders (FAPDs) are common in children and adolescents with a worldwide pooled prevalence of 13.5% (Korterink 2015). Paediatric FAPDs have a major impact on daily life, resulting in a significantly lower quality of life and higher rates of school absenteeism (Assa 2015; Varni 2015). Moreover, patients are at higher risk for developing anxiety or depressive disorders compared to healthy school-aged children (Newton 2019). The pathophysiological mechanisms underlying FAPDs are poorly understood and are thought to be multifactorial. Psychosocial, genetic and physiological factors, such as inflammation, poor gastric emptying, increased rectal sensitivity and altered gut microbiota, have been suggested to contribute to the development of functional abdominal pain by influencing the visceral sensitivity, gastrointestinal motility and gut-brain axis (Korterink 2015). Paediatric FAPDs are now labelled as 'disorders of gut-brain interaction' given that their bio-psychosocial basis encompasses complex interactions within the gut-brain axis (Drossman 2016). More recently, the latter is entitled as the 'microbiota-gut-brain axis' to reflect an increase in our understanding of the magnitude, complexity, role and interactions of the microbial populations hosted within the lumen of the gastrointestinal tract.

The management of paediatric FAPDs consists of non-pharmacological and pharmacological interventions. The first step of treatment includes 'standard medical treatment', which contains explanation, reassurance, and simple dietary and behavioural

advice (Schurman 2010). Non-pharmacological interventions consist of dietary interventions and psychosocial interventions such as cognitive behavioural therapy (CBT) and hypnotherapy.

Description of the intervention

Probiotics are micro-organisms which, when ingested, are thought to have beneficial effects on a person's health. Research is ongoing into the use of probiotics for the treatment of various gastrointestinal illnesses including inflammatory pathological disorders, functional disorders and chronic non-pathological disorders. In infants, it has been proposed that supplying probiotic bacteria can redress the balance of intestinal bacteria and provide a healthier intestinal microbiota landscape with resulting impact on transit through the gut (Savino 2013). In the context of constipation, these mechanisms have been proposed to enhance colonic peristalsis and shorten whole gut transit time (Waller 2011).

How the intervention might work

The use of micro-organisms might change the composition of bacterial colonies in the bowel and reduce inflammation, as well as promoting normal gut physiology and thereby reducing functional symptoms. Some probiotics may influence colonic motility by softening the stool, changing secretion and absorption of water and electrolytes, modifying smooth muscle cell contractions, increasing the production of lactate and short-chain fatty acids, and lowering intraluminal pH (Waller 2011). Additionally, as essentially a food supplement, probiotics are generally perceived as having a good safety profile, particularly when compared with other treatments.

Why it is important to do this review

As interest in probiotics for the treatment of gastrointestinal disorders is relatively new, until recently there has been a general paucity of research on the use of these agents. In adults, the evidence has been synthesised previously (Moayyedi 2010). This systematic review found that probiotics appear to be efficacious in irritable bowel syndrome, but the magnitude of benefit and the most effective species and strain remained uncertain.

A previous Cochrane Review in children found only three studies examining probiotics (Huertas-Ceballos 2009). This review was updated in 2017 with a total of 13 probiotic studies identified, although it focused not only on probiotics but also other dietary interventions (Newlove-Delgado 2017). This review found moderate- to low-quality evidence to suggest that probiotics may be effective in improving pain in children, with issues around risk of bias, imprecision and inconsistency impacting the certainty of evidence. Additionally, the new Rome IV criteria have simplified and clarified the nomenclature and diagnostic categories in such conditions (Drossman 2017). A number of new trials have also been published.

A new review is indicated, to align with the new classifications within children and update the evidence.

OBJECTIVES

To assess the efficacy and safety of probiotics in the treatment of functional abdominal pain disorders in children.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs).

Types of participants

Participants were children between 4 and 18 years of age with a diagnosis of functional abdominal pain disorder. This is in line with the Rome IV criteria, which do not cover infants or toddlers: there is a separate set of diagnostic criteria that address this age group (Hyams 2016). Participants could include children with irritable bowel syndrome, abdominal migraine or functional abdominal pain as defined by the Rome IV criteria (Hyams 2016). We also included participants who met earlier Rome criteria. Studies including children with Hirschsprung's disease, previous bowel surgery or complex congenital disorders were not included.

Types of interventions

We considered for inclusion studies that assessed probiotic preparations in any form (powder, liquid, capsule) through any route (either oral or rectal) as a single species or as a cocktail of multiple species or treatments (for example, symbiotic) compared to placebo, no treatment or any other interventional preparation. We also considered studies with probiotics as adjunct therapy for inclusion. Studies involving prebiotics alone were not included, as they fall into the more broad scope of dietary interventions, which is covered by another review (Newlove-Delgado 2017).

Types of outcome measures

Primary outcomes

- Global improvement or treatment success as defined by the primary studies.
- Complete resolution of pain.
- Severity of pain or change in the severity of pain.
- Frequency of pain or change in the frequency of pain.

Secondary outcomes

- Serious adverse events.
- Withdrawal due to adverse events.
- Adverse events.
- School performance, or change in school performance or attendance.
- Social and psychological functioning, or change in social and psychological functioning.
- Quality of life, or change in quality life, measured using any validated measurement tool.

Search methods for identification of studies

Electronic searches

We identified relevant trials by searching the following electronic sources, from the inception of each database to 1 October 2021 (Appendix 1):

- Cochrane Central Register of Controlled Trials (CENTRAL 2021, Issue 9) (from inception to 1 October 2021) (via Ovid);

- MEDLINE (from 1946 to 1 October 2021) (via Ovid);
- Embase (from 1974 to 1 October 2021) (via Ovid).

We did not restrict the searches by date or language. Studies published in a non-English language were professionally translated in full.

Searching other resources

Reference checking

We searched the references of all included studies and relevant systematic reviews to identify studies missed by the search strategies.

Personal contacts

We contacted leaders in the field to try and identify other relevant studies. We also contacted manufacturers of probiotic agents to try and identify other studies.

Trials registries

We searched ClinicalTrials.gov (www.clinicaltrials.gov) (Appendix 1) and the World Health Organization International Clinical Trials Registry Platform (ICTRP; https://trialsearch.who.int/) (Appendix 1) to identify ongoing studies, by combining terms related to probiotics and functional abdominal pain in children.

Grey literature

We searched Google, Google Scholar and the OpenGrey Repository using the main search terms. We handsearched conference proceedings from Digestive Disease Week, United European Gastroenterology Week and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition annual scientific meeting (from 2019 to 2021) to identify other potentially relevant studies that may not have been published in full. Concerns have been raised regarding the accuracy of data reported in abstract publications (Pitkin 1999). Therefore, where references to relevant unpublished or ongoing studies were identified, we made attempts to collect sufficient extra information to allow inclusion in this systematic review. Studies from the grey literature were included if sufficient data were reported to judge eligibility for inclusion. If data were incomplete, we contacted the study authors in order to verify the eligibility of the study, and we only included the study if suitable data to assess quality and outcomes were supplied.

Data collection and analysis

Selection of studies

Two authors independently screened titles, abstracts and full reports for eligibility against the inclusion criteria.

Specifically, they:

- collated the search results using reference management software and removed any duplicate records;
- examined titles and abstracts to remove results that were not relevant;
- retrieved the full texts of potentially relevant reports;
- linked together multiple reports that were found for the same study;
- examined full-text reports for studies that met the inclusion criteria;
- corresponded with primary study investigators to clarify study eligibility when needed; and
- at all stages, the authors recorded the reasons for inclusion and exclusion of studies, resolving any disagreements through reaching consensus. When consensus could not be reached, we consulted with a third author (AA).

Data extraction and management

We developed data extraction forms a priori to extract information on the relevant features and results of the included studies. Two authors independently extracted and recorded data on a predefined checklist. Extracted data included the following items:

- characteristics of patients (age, gender, disease distribution, disease duration, activity index);
- inclusion and exclusion criteria of studies;
- total number of patients originally assigned to each intervention group;
- intervention: type and amount of probiotics;
- control: no intervention, placebo or other interventions;
- concurrent medications; and
- outcomes: time of assessment, length of follow-up, type of symptom score used and adverse events.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias in the included studies using the Cochrane risk of bias tool (Higgins 2011). We assessed the following items: sequence generation; allocation concealment; blinding of participants, parents and health professionals; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; and other potential threats to validity. We judged each domain as being at 'low', 'high' or 'unclear' risk of bias. We compared the judgements, and discussed and resolved any inconsistencies in the assessments. A third review author resolved any disagreements.

Sequence generation for randomisation

We only considered RCTs for inclusion in the review. We assessed randomisation as being at low risk of bias where the procedure for random sequence generation was explicitly described. Examples include computer-generated random numbers, a random numbers table or coin-tossing. Where no description was given, we contacted the authors for further information.

Allocation concealment

We assessed concealment of treatment allocation as being at low risk of bias if the procedure was explicitly described and adequate efforts were made to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment. Examples include centralised randomisation, numbered or coded containers, or sealed envelopes. Procedures considered to have a high risk of bias include alternation or reference to case record numbers or dates of birth. Where no description was given of the method of allocation concealment, we contacted the study authors and, where we did not receive a response, we assigned a judgement of unclear risk of bias.

Blinding of participants, parents and health professionals

In this context, the intervention is administered by parents as well as directly by children so, in effect, we considered them both the targets of the blinding procedures. We primarily assessed the risk of bias associated with the blinding of participants based on the likelihood that such blinding is sufficient to ensure they had no knowledge of which intervention they received. We noted the blinding of health professionals, if reported.

Blinding of outcome assessment

For each included study, we described the methods used, if any, to blind the outcome assessors from knowledge of which intervention a participant received. We judged studies to be at low risk of bias if outcome assessors were blinded, or where we considered that the lack of blinding could not have affected the results. If blinding was not done or was not possible because of the nature of the intervention, we judged the study to be at high risk of bias because it was possible that the lack of blinding influenced the results. If no description was given, we contacted the study authors for more information and if we did not receive a response we assigned a judgement of unclear risk of bias.

Incomplete outcome data

Incomplete outcome data essentially included attrition, exclusions and missing data.

We assigned a judgement of low risk of bias in the following instances:

- If participants included in the analysis were exactly those who were randomised into the trial; missing outcome data were balanced in terms of numbers across intervention groups, with similar reasons for missing data across groups; or if there were no missing outcome data.
- If, for dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk was not sufficient to have a clinically relevant impact on the intervention effect estimate.
- If, for continuous outcome data, the plausible effect size (mean difference) among the missing outcomes was not sufficient to have a clinically relevant impact on observed effect size.
- If missing data have been imputed using appropriate methods.

We assigned a judgement of high risk of bias in the following instances:

- When reasons for missing outcome data were likely to be related to the true outcome, with either an imbalance in numbers or reasons for missing data across intervention groups.
- When, for dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk was sufficient to induce clinically relevant bias in the intervention effect estimate.
- When, for continuous outcome data, the plausible effect size (mean difference) among missing outcomes was sufficient to induce clinically relevant bias in the observed effect size.
- When an 'as-treated' analysis was carried out in cases where there is a substantial departure of the intervention received from that assigned at randomisation.
- When there was a potentially inappropriate application of simple imputation.

We will assign a judgement of unclear risk of bias in the following instances:

- When there was insufficient reporting of attrition or exclusions, or both, to permit a judgement of low or high risk of bias.
- When the study reported incomplete outcome data.
- When the trial did not clearly report the numbers randomised to intervention and control groups.

Selective outcome reporting

We assessed the reporting of outcomes as being at low risk of bias if all outcomes pre-specified in the study protocol were reported in the study manuscript or secondary publications. If no protocol existed or if trial registration was retrospective, we assigned a rating of unclear risk of bias if the authors report on the outcomes described in the methods section of the study manuscript. We evaluated all study publications (primary and secondary) to ensure that there was no evidence of selective outcome reporting. If no description was given, we contacted the authors for more information and, if we did not receive a response, we assigned a judgement of unclear risk of bias. If there was evidence of selective reporting (deviation from protocol, key planned outcomes not reported), we assigned a judgement of high risk of bias.

Other potential threats to validity

We considered other potential sources of bias including early trial termination (e.g. if a study was stopped early due to a data-dependent process) and baseline imbalance between treatment groups. We assessed the study as being at low risk of bias if it appeared to be free from such threats to validity. When the risk of bias was unclear from the published information, we attempted to contact the study authors for clarification. If this was not forthcoming, we assessed these studies as being at unclear risk of bias.

Measures of treatment effect

Dichotomous outcomes

For dichotomous outcomes, we calculated the risk ratio (RR) and corresponding 95% confidence interval (CI).

Continuous outcomes

For continuous outcomes, we calculated the mean difference (MD) and corresponding 95% CI.

Unit of analysis issues

Where cross-over trials were included, we extracted data from the first phase of the study, if they were reported (i.e. before the cross-over occurred). We conducted separate analyses for comparisons between probiotics versus placebo, and probiotics versus active comparator (e.g. lactulose). To deal with repeated observations on participants, we determined appropriate fixed intervals for follow-up for each outcome. To deal with events that may re-occur (e.g. adverse events), we reported on the proportion of participants who experienced at least one event. If we encountered multiple treatment groups (e.g. different probiotic dose groups or different probiotic species), we divided the placebo group across

the treatment groups or we combined probiotic groups to create a single pair-wise comparison as appropriate.

Dealing with missing data

Where data were missing, we contacted the corresponding authors of included studies to supply any unreported data. For all outcomes in all studies, we carried out analyses as far as possible on an intention-to-treat (ITT) basis; that is, we attempted to include all participants randomised to each group in the analyses, and we analysed all participants in the group to which they were allocated regardless of whether or not they received the allocated intervention. For missing continuous data, we estimated standard deviations from other available data, such as standard errors, or we imputed them using the methods suggested in Higgins 2021. We conducted analyses for continuous outcomes based on participants completing the trial, in line with available case analysis; this assumes that data were missing at random. If there was a discrepancy between the number randomised and the number analysed in each treatment group, we calculated and reported the percentage lost to follow-up in each group. When it was not possible to obtain missing data, we recorded this on the data collection form, reported it in the risk of bias table, and discussed the extent to which the missing data could alter the results and hence the conclusions of the review. We conducted sensitivity analyses to explore the impact of including studies with high levels of missing data on the overall estimate of treatment effect.

Assessment of heterogeneity

We assessed heterogeneity among trial results by visual inspection of forest plots and by calculating the Chi^2 test (a P value of 0.10 is regarded as statistically significant heterogeneity). We also used the I^2 statistic to quantify the effect of heterogeneity (Higgins 2021). We conducted sensitivity analyses as appropriate to investigate heterogeneity. For example, if a pooled analysis showed statistically significant heterogeneity and a visual inspection of the forest plot identified studies that may have contributed to this heterogeneity, the analysis was repeated excluding these studies to see if this could be explained.

Assessment of reporting biases

If an appropriate number of studies were pooled for meta-analysis (≥ 10 studies), we planned to investigate the possibility of publication bias through the construction of funnel plots (trial effects versus trial size).

Data synthesis

We combined data from individual trials for meta-analysis when the interventions, patient groups and outcomes were deemed to be sufficiently similar (determined by consensus). We calculated the pooled RR and corresponding 95% CI for dichotomous outcomes. We calculated the pooled MD and corresponding 95% CI for continuous outcomes that were measured using the same units or when combining change-from-baseline and post-intervention value scores (Higgins 2021). We calculated the pooled standardised mean difference (SMD) and 95% CI when different scales were used to measure the same underlying construct. We carried out meta-analysis using a random-effects model. We used Review Manager software for data analysis (RevMan 2020). We analysed data according to the ITT principle. We assumed patients with final missing outcomes to be treatment failures. We grouped analyses by length of follow-up. We did not pool data for meta-analysis if we detected a high degree of statistical heterogeneity (I^2 > 75%) that was unexplained. In case of a high degree of statistical heterogeneity we investigated whether this could be explained based on clinical grounds or risk of bias, in which case we performed sensitivity analyses. If we could not find any such reasons for the high statistical heterogeneity we presented the results narratively, in detail.

Subgroup analysis and investigation of heterogeneity

We carried out subgroup analyses to further study the effects of a number of variables on the outcomes including:

- specific probiotic preparation or species;
- probiotic dose;
- length of therapy, follow-up;
- whether the probiotic was sole therapy or adjunct therapy; and
- type of functional pain disorder (i.e. irritable bowel syndrome, abdominal migraine or functional abdominal pain, in line with the Rome IV criteria (Hyams 2016)).

Sensitivity analysis

We conducted sensitivity analyses based on the following:

- random-effects versus fixed-effect models (this is based on the approach in the *Cochrane Handbook for Systematic Reviews of Interventions* Section 13.3.5.6 on sensitivity analysis; Page 2021);
- studies published in full versus abstract;
- removing studies judged to be at high risk of bias.

For future updates, if we identify studies of adequate duration we will also explore a sensitivity analysis of dropouts and exclusions by conducting worst-case versus best-case scenario analyses, as pre-specified in our protocol.

Summary of findings and assessment of the certainty of the evidence

We assessed the overall certainty of evidence supporting the primary outcomes (i.e. global improvement or treatment success, complete resolution of pain, severity of pain and frequency of pain) and selected secondary outcomes (serious adverse events, withdrawal due to adverse events, adverse events) using the GRADE approach (GRADEpro GDT; Schünemann 2013), and presented these findings in summary of findings tables for each comparison.

The GRADE approach appraises the certainty of a body of evidence based on the extent to which one can be confident that an estimate of effect, or association, reflects the item being assessed. RCTs start as high-certainty evidence, but may be downgraded due to overall risk of bias (methodological quality), indirectness of evidence, inconsistency of effect, imprecision (sparse data) and publication bias. Reasons for downgrading are presented in footnotes in the summary of findings tables, with justification. Two review authors independently assessed the overall certainty of the evidence for each outcome after considering each of these factors and graded them as follows:

- high certainty: further research is very unlikely to change confidence in the estimate of effect;

- moderate certainty: further research is likely to have an important impact on confidence in the estimate of effect, and may change the estimate;
- low certainty: further research is very likely to have an important impact on confidence in the estimate of effect, and is likely to change the estimate; or
- very low certainty: any estimate of effect is very uncertain.

RESULTS

Description of studies

Key characteristics of the included studies can be found in Table 1 and Table 2.

Results of the search

A literature search conducted on 1 October 2021 identified 1712 records. After duplicates were removed a total of 757 records remained for review of titles and abstracts. Two authors independently reviewed these titles and abstracts, and discarded 687 records. We selected 70 potentially relevant reports on the use of probiotics for the management of functional abdominal pain disorders in children for full-text review (see Figure 1). We excluded 29 studies (30 records), with reasons (see Excluded studies). Five studies (six records) are awaiting classification (see below and Characteristics of studies awaiting classification). We identified two ongoing studies (see Characteristics of ongoing studies).

Figure 1.

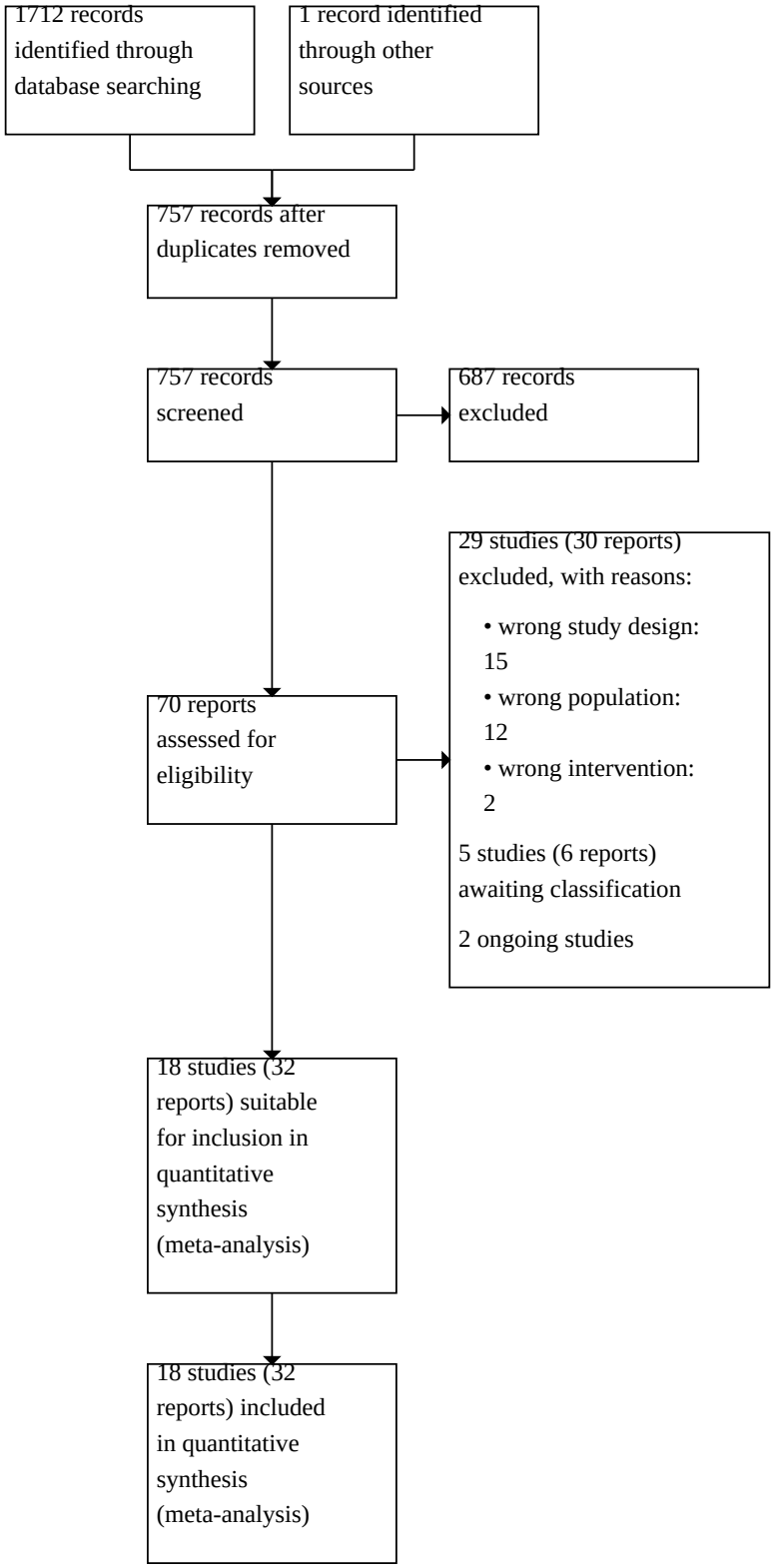


Figure 1. (Continued)

Included studies

We selected a total of 18 studies (32 records) involving 1309 patients for inclusion (Asgarshirazi 2015; Baştürk 2016; Bauserman 2005; Eftekhari 2015; Francavilla 2010; Gawrońska 2007; Giannetti 2017; Guandalini 2010; Jadrešin 2017; Jadrešin 2020; Kianifar 2015; Maragkoudaki 2017; Otuzbir 2016; Rahmani 2020; Romano 2014; Sabbi 2012; Saneian 2015; Weizman 2016).

Age of participants

Participants in all included studies were between the ages of 4 and 18 years. Six of the studies had a more restrictive age range than this (Asgarshirazi 2015; Baştürk 2016; Eftekhari 2015; Francavilla 2010; Gawrońska 2007; Giannetti 2017). Bauserman 2005 specified an age range of 5 to 21 years old for participants, but no included participants were above the age of 17 based on the tables provided. Otuzbir 2016 and Sabbi 2012 did not provide age information.

Diagnosis

Four of the studies based the diagnosis of functional abdominal pain on the Rome II criteria (Bauserman 2005; Francavilla 2010; Gawrońska 2007; Guandalini 2010), whilst all others based the diagnosis on the Rome III criteria, except for Sabbi 2012, which did not provide this information.

Eight studies included more than one diagnosis within the definition of functional abdominal pain disorders (Asgarshirazi 2015; Francavilla 2010; Gawrońska 2007; Giannetti 2017; Jadrešin 2017; Jadrešin 2020; Otuzbir 2016; Rahmani 2020). Four of them provided separate data per diagnosis assessed (Francavilla 2010; Gawrońska 2007; Giannetti 2017; Rahmani 2020).

Functional abdominal pain was studied in 13 studies (Asgarshirazi 2015; Eftekhari 2015; Francavilla 2010; Gawrońska 2007; Jadrešin 2017; Jadrešin 2020; Maragkoudaki 2017; Otuzbir 2016; Rahmani 2020; Romano 2014; Sabbi 2012; Saneian 2015; Weizman 2016). Irritable bowel syndrome was studied in 11 studies (Asgarshirazi 2015; Baştürk 2016; Bauserman 2005; Francavilla 2010; Gawrońska 2007; Giannetti 2017; Guandalini 2010; Jadrešin 2017; Jadrešin 2020; Kianifar 2015; Rahmani 2020). Functional dyspepsia was studies in five studies (Asgarshirazi 2015; Gawrońska 2007; Giannetti 2017; Otuzbir 2016; Rahmani 2020). Abdominal migraine was studied in one study (Rahmani 2020).

Length of the interventions and time points of outcome measurements

Five studies measured outcomes solely at the end of the length of their given interventions: Asgarshirazi 2015, Baştürk 2016 and Gawrońska 2007 at four weeks, Bauserman 2005 at six weeks and Otuzbir 2016 at eight weeks.

In Eftekhari 2015, Romano 2014 and Weizman 2016, interventions lasted four weeks and the outcomes were measured at the end of the intervention and four weeks after the end.

In Kianifar 2015, the intervention lasted four weeks and outcomes were measured at the end of every week until the end of the intervention.

In Maragkoudaki 2017 and Rahmani 2020, the interventions lasted four weeks; outcomes were measured at the end of the second week and at the end of the intervention.

The intervention in Saneian 2015 lasted four weeks and outcomes were measured at the end of the intervention and eight weeks after the end.

In Sabbi 2012, the intervention lasted six weeks and outcomes were measured at the end of the intervention and four weeks after the end.

The intervention in Francavilla 2010 lasted eight weeks and the outcomes were measured at the end of the intervention and eight weeks after the end.

In Jadrešin 2017 and Jadrešin 2020, interventions lasted 12 weeks and outcomes were measured at four weeks into the interventions, at the end of the interventions (12 weeks) and four weeks after the end of the intervention.

Giannetti 2017 had a cross-over design that included a two-week run-in period, six intervention weeks for the pre-cross-over phase, followed by a two-week washout period, and six intervention weeks for the post-cross-over phase. Outcomes were measured at the end of each period/phase of the study.

Guandalini 2010 had the same design and length for their intervention and measured outcome data every two weeks until the end of the intervention.

Intervention arms

All studies had two intervention arms except for two, which had three intervention arms (Asgarshirazi 2015; Baştürk 2016). Baştürk 2016 had a synbiotic, a probiotic and a prebiotic (placebo) group; Asgarshirazi 2015 had a synbiotic, a peppermint and a placebo group. We did not use the data for the peppermint group in our analysis as this is beyond the scope of this review.

Intervention and placebo agents

All studies compared probiotics or synbiotics to a placebo (including prebiotics).

Thirteen studies compared probiotics to placebo (Baştürk 2016; Eftekhari 2015; Francavilla 2010; Gawrońska 2007; Giannetti 2017; Guandalini 2010; Jadrešin 2017; Jadrešin 2020; Maragkoudaki 2017; Rahmani 2020; Romano 2014; Sabbi 2012; Weizman 2016). Seven studies used *Lactobacillus reuteri* (Eftekhari 2015; Jadrešin 2017; Jadrešin 2020; Rahmani 2020; Romano 2014; Maragkoudaki 2017; Weizman 2016). Three studies used *Lactobacillus rhamnosus* GG (Francavilla 2010; Gawrońska 2007; Sabbi 2012). Baştürk 2016 used *Bifidobacterium lactis* B94. Giannetti 2017 used a combination of

three stains of bifidobacteria. Guandalini 2010 used a combination of eight strains of bifidobacteria, lactobacilli and *Streptococcus*.

Six studies compared synbiotics to placebo (Asgarshirazi 2015; Baştürk 2016; Bauserman 2005; Kianifar 2015; Otuzbir 2016; Saneian 2015). Asgarshirazi 2015 and Saneian 2015 used *Bifidobacterium coagulans* combined with fructo-oligosaccharide. Bauserman 2005 and Kianifar 2015 used *Lactobacillus rhamnosus* GG combined with inulin. Baştürk 2016 used *Bifidobacterium lactis* B94 combined with inulin. Otuzbir 2016 did not provide any information.

Eleven studies used unidentified placebos (Eftekhari 2015; Francavilla 2010; Gawrońska 2007; Giannetti 2017; Guandalini 2010; Maragkoudaki 2017; Otuzbir 2016; Rahmani 2020; Sabbi 2012; Saneian 2015; Weizman 2016). Two of them described the placebo as an inert powder (Francavilla 2010; Gawrońska 2007). Jadrešin 2017 and Jadrešin 2020 used a tablet containing isomalt, xylitol, sucrose distearate, hydrogenated palm oil, lemon-lime flavouring and citric acid as placebo. Romano 2014 used a product containing sunflower oil and medium-chain triglyceride oil from coconut oil as placebo. Asgarshirazi 2015 used folic acid as placebo. Baştürk 2016, Bauserman 2005 and Kianifar 2015 used the prebiotic inulin as placebo. For the purposes of our analysis we decided to group inulin together with the other placebos, despite its theoretically potential active role as a prebiotic, because its role in the improvement of functional abdominal pain disorder symptoms is unknown.

All agents were taken orally. Information on dosages can be found in Table 1.

Reporting of primary outcomes

Global improvement or treatment success as defined by the primary studies

Our primary dichotomous outcome of patient global improvement or treatment success as defined by the primary studies was reported in 11 studies (Baştürk 2016; Bauserman 2005; Eftekhari 2015; Francavilla 2010; Gawrońska 2007; Jadrešin 2017; Jadrešin 2020; Maragkoudaki 2017; Otuzbir 2016; Rahmani 2020 ; Saneian 2015). In the other seven studies, the outcome was either unclear or not reported (Asgarshirazi 2015; Giannetti 2017; Guandalini 2010; Kianifar 2015; Romano 2014; Sabbi 2012; Weizman 2016).

Complete resolution of pain

Our primary dichotomous outcome of complete resolution of pain was reported in five studies (Baştürk 2016; Gawrońska 2007; Jadrešin 2017; Jadrešin 2020; Otuzbir 2016).

Severity of pain or change in the severity of pain

Our primary continuous outcome of severity of pain/change in the severity of pain was reported in 13 studies (Asgarshirazi 2015; Bauserman 2005; Eftekhari 2015; Francavilla 2010; Gawrońska 2007; Jadrešin 2017; Jadrešin 2020; Kianifar 2015; Maragkoudaki 2017; Rahmani 2020; Romano 2014; Saneian 2015; Weizman 2016).

Asgarshirazi 2015 measured pain on 0 to 10 numerical rating scale. Bauserman 2005 used a four-point Likert scale (0 to 3). Eftekhari 2015 and Saneian 2015 measured pain according to the Wong-Baker six-point scale (0 to 5). Francavilla 2010 used a combination of 0 to 10 visual analogue scale (VAS) and the 1- to 6-point Faces Pain Scale (FPS). Gawrońska 2007 and Romano 2014 used the Faces seven-point (0 to 6) pain scale. Jadrešin 2017 and Jadrešin 2020 used the 0 (no hurt) to 10 (hurts worst) Wong-Baker FACES Pain Rating Scale. Kianifar 2015 measured pain on a (0 to 4) five-point Likert scale. Maragkoudaki 2017 used an unspecified Wong-Baker FACES Pain Rating Scale. Weizman 2016 used the face scoring system by Hicks (each of the six faces in the scoring system ranked 0, 2, 4, 6, 8 or 10, where 0 = no pain (relaxed face) and 10 = very severe pain (miserable face)).

Frequency of pain or change in the frequency of pain

Our primary continuous outcome of frequency of pain/change in the frequency of pain was reported in nine studies (Asgarshirazi 2015; Eftekhari 2015; Francavilla 2010; Gawrońska 2007; Jadrešin 2017; Jadrešin 2020; Maragkoudaki 2017; Rahmani 2020; Romano 2014; Weizman 2016).

Asgarshirazi 2015, Eftekhari 2015, Francavilla 2010, Gawrońska 2007, Maragkoudaki 2017 and Weizman 2016 measured this as pain episodes per week. Jadrešin 2017 and Jadrešin 2020 measured this as days without pain. Rahmani 2020 measured it as frequency of repetitive pain per day. Romano 2014 measured pain as episodes per day.

Reporting of secondary outcomes

Serious adverse events

Our secondary outcome of serious adverse events was reported in 12 studies (Asgarshirazi 2015; Bauserman 2005; Eftekhari 2015; Gawrońska 2007; Giannetti 2017; Guandalini 2010; Jadrešin 2020; Kianifar 2015; Maragkoudaki 2017; Romano 2014; Saneian 2015; Weizman 2016).

Withdrawals due to adverse events

Withdrawals due to adverse events were reported in 14 studies (Asgarshirazi 2015; Baştürk 2016; Bauserman 2005; Eftekhari 2015; Gawrońska 2007; Giannetti 2017; Guandalini 2010; Jadrešin 2017; Jadrešin 2020; Kianifar 2015; Maragkoudaki 2017; Romano 2014; Saneian 2015; Weizman 2016).

Adverse events

Adverse events were reported in 12 studies (Asgarshirazi 2015; Baştürk 2016; Bauserman 2005; Eftekhari 2015; Gawrońska 2007; Giannetti 2017; Guandalini 2010; Jadrešin 2020; Kianifar 2015; Maragkoudaki 2017; Romano 2014; Weizman 2016).

School performance

Our secondary outcome of school performance was reported in three studies (Gawrońska 2007; Maragkoudaki 2017; Weizman 2016).

Social and psychological functioning

Social and psychological functioning was reported in one study (Kianifar 2015).

Quality of life

Quality of life was reported in one study (Guandalini 2010).

Notes on data availability

We noted during data extraction that there were a number of studies with concerning data that could not be interpreted:

In Rahmani 2020, the outcome data were inversed between the text and the tables for several outcomes, with no consistent pattern. It was therefore not possible to confirm which were the appropriate figures and we received no response from the contact author or the editor of the journal after numerous attempts at contact (this is a pre-publication manuscript that has not been copy-edited and so we also attempted to contact the journal with no response received). In the end, as some of the data made no mathematical sense if they were taken from the table (negative standard deviation (SD)), we elected to use the data that were reported in the text.

Eftekhari 2015 provided many conflicting results for their complete resolution outcome, with "no hurt" referring to pain intensity and "no pain" referring to no pain episodes. We did not receive any clarification from the authors after contacting them and we decided to use the figures of no pain episodes per week for our dichotomous outcome as this appeared to be the most homogeneous item.

Jadrešin 2017 and Jadrešin 2020 reported a pooled analysis for the outcomes of days without pain, pain intensity and complete resolution of pain in both their studies at the end of their 2020 paper, which seemingly used different results than those reported in the 'Results' section of both papers. We did not receive any response from the authors after contacting them. We could not use the misreported data for the outcomes of pain frequency and pain severity in our analysis because they did not provide SDs or other variance data to calculate SDs.

Maragkoudaki 2017 also had some concerns with regard to the severity of pain outcome, as the baseline mean for one group was 17, which is greater than the pain scale they reported. They may have used a different scale but as this is not specified it was unclear how this could be accommodated within the rest of the data set. We did not receive any response from the authors after contacting them.

Baştürk 2016 and Kianifar 2015 reported randomised patients discontinuing the study and not being included in the results without mentioning the group to which these patients had been randomised. The authors of Baştürk 2016 responded to our email and informed us about the correct randomisation numbers. The authors of Kianifar 2015 did not respond.

Otuzbir 2016 and Sabbi 2012 were available as abstracts only with extremely limited information provided. The authors did not respond to our emails asking for more information.

Giannetti 2017 and Guandalini 2010 were cross-over studies and did not provide separate data per intervention and control groups for pre- and post-cross-over; instead results were analysed in one unique analysis combining pre- and post-cross-over treatments. The authors did not respond to our emails asking for more information.

Information on the primary and secondary outcome data is illustrated in Table 3 and Table 4.

Excluded studies

We excluded a total of 29 studies (see Characteristics of excluded studies). We excluded10 studies because they were conducted in adult patients (Cha 2012; Choi 2015; Enck 2009; Han 2016; Le Neve 2016; Mezzasalma 2016; Sen 2002; Spiller 2016; Yoon 2014; Yoon 2015). We excluded four studies because they were letters to journals or letters to authors (Anonymous 2010; Chassany 2008; Faber 2003; Pélerin 2016). We excluded one record because it was a comment on an included study (Abu-Salih 2011). We excluded nine studies because they were review articles and not randomised controlled trials (Anuradha 2005; Berger 2007; Cash 2011; Charrois 2006; Enck 2007; Ford 2012; Kajander 2008; Rose 2011; Schmulson 2011). We excluded one study because it studied antibiotics rather than probiotics (Drossman 2011). We excluded one study because it studied the effect of guar gum rather than probiotics (Comito 2011). We excluded two studies because they looked at the effect of probiotics on functional constipation rather than functional abdominal pain disorders (Baştürk 2017; Wegner 2018). We excluded one study as it was not randomised (NCT04922476).

Studies awaiting classification

A total of five studies are categorised as awaiting classification (Characteristics of studies awaiting classification). We were unable to confirm whether Chao 2011 met our inclusion criteria from the information presented, and we were unable to contact the authors to clarify. Gholizadeh 2021 was found in a pre-publication update search and will be included in future reviews. Initially, Sudha 2018 was included, but we noted concerns with the outlying data as these were highly positive, as well as significant conflicts from the team. We sought advice from the Cochrane research integrity unit and the Cochrane Gut team and, based on this, we attempted to contact the authors on numerous occasions, as well as the editors of the journal for clarification. No response has been received (two named authors were directly employed by the manufacturer of their interventional agent, and the study was funded by the same manufacturer). This is in line with the Cochrane policy for managing potentially problematic studies. Given the concerns and lack of response from the authoring team or journal, we have moved this study to awaiting classification. NCT00793494 is a trial registration with no corresponding published results, which states that recruitment was terminated due to inability to recruit. NCT02613078 is a trial registration with no corresponding published results and insufficient details for us to be confident that it meets our inclusion criteria.

Ongoing studies

We also identified two ongoing studies (see Characteristics of ongoing studies).

Risk of bias in included studies

The risk of bias analysis for the included studies is summarised in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

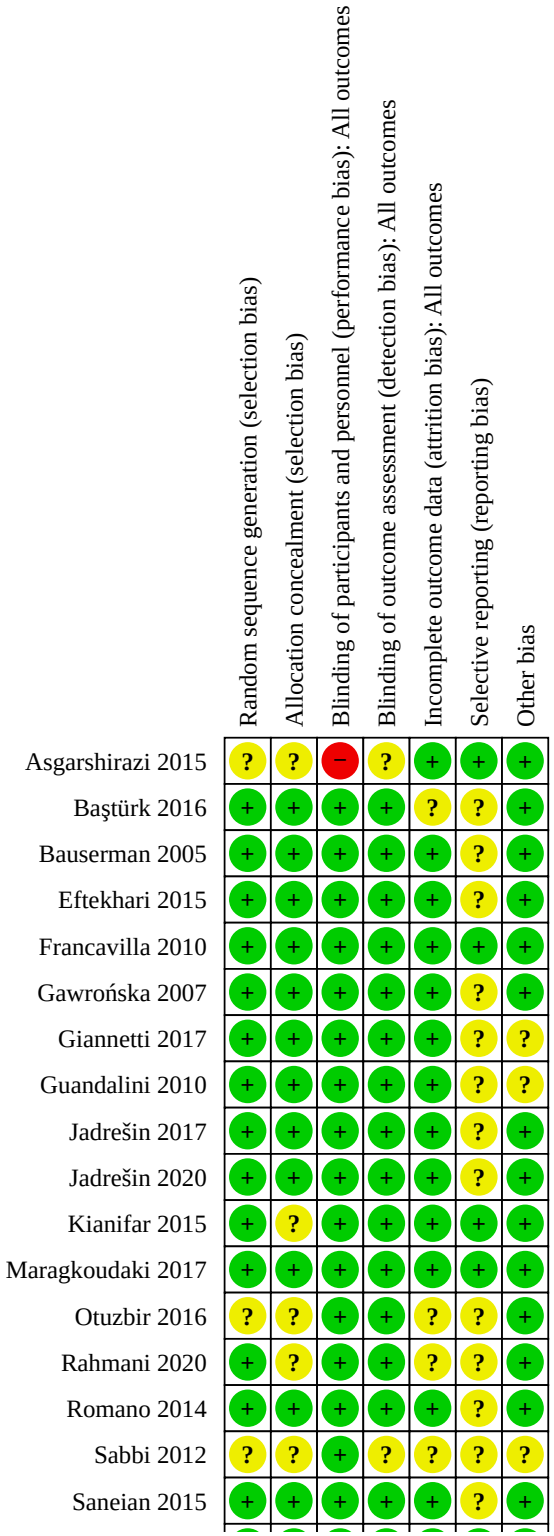
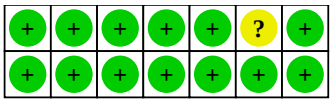


Figure 2. (Continued)



In addition, we reviewed each included study for potential conflicts of interest as well as the source of their funding, summarising our findings in Table 1. Fifteen of the18 studies declared no conflict of interest, or did not make a statement on conflicts of interest.

Jadrešin 2020 declared that three named authors had received payment or honoraria in the past for lectures or consultation from industry sources.

Maragkoudaki 2017 declared that three named authors had received research grants from the manufacturer of their interventional agent, and a further two authors had been speakers for the same manufacturer.

Weizman 2016 declared that one author had previously been a speaker for the manufacturer of their interventional agent.

Allocation

Random sequence generation

In 15 of the 18 included studies the method of random allocation of participants to intervention groups (selection bias) was described and judged to be adequate (Baştürk 2016; Bauserman 2005; Eftekhari 2015; Francavilla 2010; Gawrońska 2007; Giannetti 2017; Guandalini 2010; Jadrešin 2017; Jadrešin 2020; Kianifar 2015; Maragkoudaki 2017; Rahmani 2020; Romano 2014; Saneian 2015; Weizman 2016). We rated these studies as having a low risk of selection bias for random sequence generation.

Two studies stated that they randomly allocated participants, but did not describe how they achieved this, and did not respond to requests for clarification. Therefore, we rated them as having an unclear risk of selection bias (Asgarshirazi 2015; Sabbi 2012).

One study randomised participants according to time of admission into the trial, with no further details on randomisation, and no response to requests for further information. Therefore, we rated this study as having an unclear risk of selection bias (Otuzbir 2016).

Allocation concealment

Allocation concealment was adequately described in 13 of the 18 included studies and we rated them as having a low risk of bias (Baştürk 2016; Bauserman 2005; Eftekhari 2015; Francavilla 2010; Gawrońska 2007; Giannetti 2017; Guandalini 2010; Jadrešin 2017; Jadrešin 2020; Maragkoudaki 2017; Romano 2014; Saneian 2015; Weizman 2016). The code revealing participant allocation was only revealed by the vendor on completion of the statistical analysis, and those involved in enrolment were unaware of the allocation sequence.

In the remaining five included studies allocation sequence concealment was inadequately described and we thus rated them as having an unclear risk of bias (Asgarshirazi 2015; Kianifar 2015; Otuzbir 2016; Rahmani 2020; Sabbi 2012). In each case we sought further information from the authors but did not receive a reply.

Blinding

Methods for blinding of participants and personnel were described and judged to be low risk of bias for 17 of the 18 included studies (Baştürk 2016; Bauserman 2005; Eftekhari 2015; Francavilla 2010; Gawrońska 2007; Giannetti 2017; Guandalini 2010; Jadrešin 2017; Jadrešin 2020; Kianifar 2015; Maragkoudaki 2017; Otuzbir 2016; Rahmani 2020; Romano 2014; Sabbi 2012; Saneian 2015; Weizman 2016).

Asgarshirazi 2015 described their study as placebo-controlled and single-blinded, and stated that the nurse involved in administering the questionnaire was blinded. The authors did not respond to requests for clarification and we therefore rated this study as being at high risk of performance bias.

The method for blinding of outcomes was well described and judged to be at low risk of detection bias in 16 of the 18 studies (Baştürk 2016; Bauserman 2005; Eftekhari 2015; Francavilla 2010; Gawrońska 2007; Giannetti 2017; Guandalini 2010; Jadrešin 2017; Jadrešin 2020; Kianifar 2015; Maragkoudaki 2017; Otuzbir 2016; Rahmani 2020; Romano 2014; Saneian 2015; Weizman 2016).

Two studies did not adequately describe the methods for preventing detection bias, and did not reply to requests for clarification. We subsequently rated them as having an unclear risk of bias (Asgarshirazi 2015; Sabbi 2012).

Incomplete outcome data

We judged 15 of the 18 included studies to be at low risk of attrition bias given the balanced nature of withdrawals for similar reasons and adequately described study flow (Asgarshirazi 2015; Baştürk 2016; Bauserman 2005; Eftekhari 2015; Francavilla 2010; Gawrońska 2007; Giannetti 2017; Guandalini 2010; Jadrešin 2017; Jadrešin 2020; Kianifar 2015; Maragkoudaki 2017; Romano 2014; Saneian 2015; Weizman 2016).

Two studies gave inadequate information on patient flow through the study and did not respond to requests for clarification. We therefore rated them as having an unclear risk of bias for incomplete outcome data (Otuzbir 2016; Sabbi 2012)

One study did not clarify how many participants were excluded post-randomisation based on exclusion criteria versus how many were excluded because of poor compliance with treatment. The authors did not respond to our requests for clarification and we therefore rated the study as having an unclear risk of bias for incomplete outcome data (Rahmani 2020).

Selective reporting

We rated five of the 18 included studies as low risk for reporting bias due to the complete reporting of outcomes as per a prospectively registration of the trial, and a full description of adverse events (Asgarshirazi 2015; Francavilla 2010; Kianifar 2015; Maragkoudaki 2017; Weizman 2016).

One study did not provide information on the randomisation and adverse effects for five patients who withdrew from the study post-randomisation, and did not respond to our requests for clarification. This study also did not have a trial registration. We therefore rated it as having an unclear risk of bias for selective reporting (Baştürk 2016)

One study included conflicting reports for the primary outcomes and had a trial protocol that was registered retrospectively (IRCT2014083018971N1). The authors did not respond to a request for clarification regarding the primary outcome data and we therefore rated the study as having an unclear risk of bias (Eftekhari 2015).

Two studies from the same team included outcomes in their prospective trial registration (NCT01587846) that were not reported in the final study (Jadrešin 2017; Jadrešin 2020). In addition, Jadrešin 2020 included a pooled analysis that does not tally with the data from the individual reports. The authors did not respond to requests for clarification and we therefore rated the studies as having an unclear risk of bias for selective reporting.

One study reported all outcomes appropriately but the methodology was inadequately described, and there was no full text or protocol available to clarify this. In addition, the authors did not respond to our requests for clarification and we therefore rated this study as having an unclear risk of bias for selective reporting (Otuzbir 2016).

One study did not provide data for their outcomes and simply stated that the differences between intervention and control groups were 'significant'. We were unable to contact the authors to request further information, so we rated this study as having an unclear risk of bias for selective reporting (Sabbi 2012).

Other potential sources of bias

There were no concerns about other potential sources of bias for 15 of the 18 included studies and we rated these as low risk of bias (Asgarshirazi 2015; Baştürk 2016; Bauserman 2005; Eftekhari 2015; Francavilla 2010; Gawrońska 2007; Jadrešin 2017; Jadrešin 2020; Kianifar 2015; Maragkoudaki 2017; Otuzbir 2016; Rahmani 2020; Romano 2014; Saneian 2015; Weizman 2016).

Two studies presented results in an unclear fashion by combining pre- and post-cross-over data and presenting their results in a per condition manner rather than per intervention and control group (Giannetti 2017; Guandalini 2010). They also did not provide randomisation numbers for each therapy. The authors did not respond to our requests for clarification and we therefore rated these studies as having an unclear risk of bias.

There was insufficient information to judge one of the studies and the author did not respond to requests for further information, so we judged it to be at unclear risk of other bias (Sabbi 2012).

Effects of interventions

See: **Summary of findings 1** Probiotic compared to placebo for management of functional abdominal pain disorders in children; **Summary of findings 2** Synbiotic compared to placebo for management of functional abdominal pain disorders in children

Information on the primary and secondary outcome data we used can be found in Table 3 and Table 4. We planned to conduct several subgroup analyses in our protocol, including probiotic dose and length of therapy, as well as sensitivity analyses (e.g. random-effects versus fixed-effect models), but these were not pursued in this review due to a lack of data.

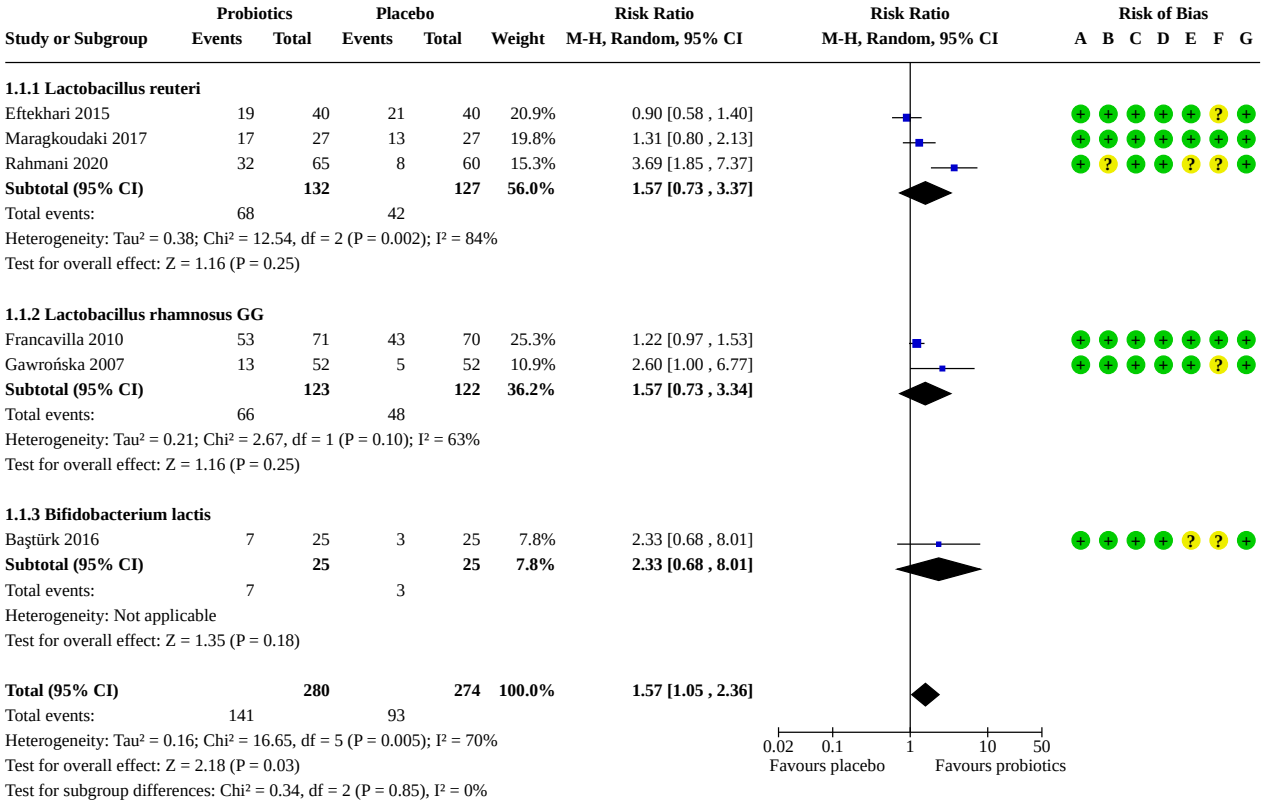
Probiotics versus placebo

Primary outcomes

Treatment success

Six studies with 554 participants provided data for this outcome (Baştürk 2016; Eftekhari 2015; Francavilla 2010; Gawrońska 2007; Maragkoudaki 2017; Rahmani 2020). Meta-analysis of six studies with 554 participants showed that patients with functional abdominal pain disorders may respond more to probiotics (167/330) than placebo (118/325) (risk ratio (RR) 1.57, 95% confidence interval (CI) 1.05 to 2.36, I^2 = 70%) (Analysis 1.1; Figure 3). The evidence is of low certainty due to inconsistency and risk of bias (Summary of findings 1). After repeating this analysis with a fixed-effect model, the significant result remained unchanged (RR 1.49, 95% CI 1.23 to 1.80, I^2 = 70%).

Figure 3.



Subgroup analysis for specific strains revealed low-certainty evidence for *Lactobacillus reuteri*, *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis*, indicating that there may be no difference to placebo (Analysis 1.1). None of these analyses were statistically significant, but the results were homogenous on visual inspection and the confidence intervals tight. The certainty of the evidence was low for all of these analyses due to serious or very serious imprecision and significant inconsistency. The results of sensitivity analyses using a fixed-effect model for the probiotics strains *Lactobacillus reuteri* and *Lactobacillus rhamnosus* GG were different from the random-effects analysis, now showing both of these strains as superior to placebo; however, these findings were still of low certainty as described above (Analysis 1.2).

The remaining probiotics studies did not report this outcome.

Complete resolution of pain

Complete resolution of pain was reported in six studies (Başţürk 2016; Eftekhari 2015; Gawrońska 2007; Jadrešin 2017; Jadrešin 2020; Rahmani 2020). Meta-analysis of the results of these studies did not show a clear difference between probiotics (97/232) and placebo (62/228) (RR 1.55, 95% CI 0.94 to 2.56, I^2 = 70%) (Analysis 1.3). The evidence is of very low certainty due to very high inconsistency and risk of bias (Summary of findings 1).

A sensitivity analysis, removing Rahmani 2020 due to risk of bias for this outcome, again did not show a clear difference between probiotics (65/167) and placebo (54/168) (RR 1.18, 95% CI 0.84 to 1.67, I^2 = 30%) (Analysis 1.4).

Severity of pain on completion

This outcome was reported in seven studies with 655 participants (Eftekhari 2015; Francavilla 2010; Gawrońska 2007; Maragkoudaki 2017; Rahmani 2020; Romano 2014; Weizman 2016). We conducted a meta-analysis; however, we were unable to draw meaningful conclusions due to very high unexplained heterogeneity (Analysis 1.5). The evidence is of very low certainty. In line with our pre-planned methodology for managing heterogeneity, a narrative synthesis is presented in Summary of findings 1.

Jadrešin 2017 and Jadrešin 2020 did not provide standard deviations (SDs) for their severity of pain results, and we did not receive a response from the study authors when we requested these. Jadrešin 2017 reported a mean score of 0.21

for the probiotics group and 0.6 for the placebo group at study end. Jadrešin 2020 reported a median score of 0.035 (interquartile range (IQR) 0 to 1) for the probiotics group and 0.81 (IQR 0.2 to 1.48) for the placebo group at study end. We decided not to use the latter for our analysis due to uncertainty as to whether data were skewed in this study, which would make statistical transformation to a mean and SD inappropriate. As stated above, the authors did not respond to our requests for confirmation.

Frequency of pain on completion

Frequency of pain was measured in episodes per week in six studies with 605 patients (Eftekhari 2015; Francavilla 2010; Gawrońska 2007; Maragkoudaki 2017; Rahmani 2020; Weizman 2016). We conducted a meta-analysis; however, we were unable to draw meaningful conclusions due to very high unexplained heterogeneity (Analysis 1.6). The evidence was of very low certainty. In line with our pre-planned methodology for managing heterogeneity, a narrative synthesis is presented in Summary of findings 1.

We conducted a sensitivity analysis, removing Eftekhari 2015 from the analysis due to risk of bias. The results showed that probiotics reduce pain frequency per week when compared to placebo (mean difference (MD) -0.58, 95% CI -0.81 to -0.35, I^2 = 0%) (Analysis 1.7).

Romano 2014 measured pain frequency in episodes per day. The mean (SD) on completion for the probiotics group was 1 (0.7) and for the placebo group was 2 (0.8).

Jadrešin 2017 reported the median number of days without pain in the probiotics group at four months as 89.5 (range 5 to 108) and the number of days without pain in the placebo group at four months as 51 (range 0 to 107). Jadrešin 2020 reported the median number of days without pain in the probiotics group at four months as 90 (IQR 54 to 99) and the median number of days without pain in the placebo group at four months as 59.5 (IQR 21.5 to 89.25). We decided not to use the latter for our analysis due to the uncertainty as to whether data were skewed in this study, which would make statistical transformation to a mean and SD inappropriate. As stated above, the authors did not answer our requests for confirmation.

Secondary outcomes

Serious adverse events

There were no recorded serious adverse events in any of the included studies within either the probiotics or placebo groups.

Withdrawal due to adverse events

Meta-analysis of eight studies with 544 participants showed no difference in withdrawals due to adverse events between probiotics (1/275) and placebo (1/269) (RR 1.00, 95% CI 0.07 to 15.12) (Analysis 1.8). The evidence is of very low certainty because of imprecision due to the very low numbers of events and risk of bias (Summary of findings 1).

Baştürk 2016 reported five post-randomisation withdrawals from the study, but it was not stated whether these withdrawals came from the intervention or placebo group. However, the author responded to a request to clarification regarding these withdrawals, so these data have now been included in this analysis.

It was not possible to include figures for Giannetti 2017 in this analysis as although the primary study stated that some participants were lost post-randomisation, the study was a cross-over trial and did not break down withdrawals by group at randomisation.

It was also not possible to include figures for Guandalini 2010 as the primary study did not specify which groups the withdrawals came from.

Rahmani 2020 did not present any data on either adverse events or withdrawals from the study, and did not respond to our attempts at contact either via the corresponding author or via the journal in which the paper was published. As such, no data from this study are included in this analysis.

Adverse events

We analysed the number of participants experiencing any adverse events if this was explicitly stated in the primary studies or supplied on request from authors. If the total number of events was reported, but it was not clear how many participants experienced these events, we did not include these data for this outcome.

A meta-analysis of seven studies with 489 participants showed no difference in adverse events between probiotics (1/249) and placebo (1/240) (RR 1.00, 95% CI 0.07 to 15.12) (Analysis 1.9). The evidence is of very low certainty due to imprecision from the very low numbers of events and risk of bias (Summary of findings 1). These results are identical to the analysis above as all studies reported the same participant numbers for occurrence of adverse events and withdrawals due to adverse events. As reported above, Baştürk 2016 reported five post-randomisation withdrawals from the study due to adverse events, but it was not stated whether these events occurred in the intervention or placebo group. Following a response to our request for clarification regarding these adverse events, we have now included the data in this analysis.

It was not possible to include figures for Giannetti 2017 in this analysis as although the primary study stated that some participants were lost post-randomisation, the study was a cross-over trial and did not break down withdrawals by group at randomisation.

It was also not possible to include figures for Guandalini 2010 as the primary study did not specify which groups the withdrawals came from.

Rahmani 2020 did not present any data on adverse events, and did not respond to our attempts at contact either via the corresponding author or via the journal in which the paper was published. As such, no data are included in this analysis.

School performance or change in school performance or attendance

Due to the different outcomes reported and measures used by the primary studies, it was not possible to perform a meta-analysis for this outcome.

Gawrońska 2007 reported on school absenteeism at four weeks after the start of intervention, and found one participant absent at four weeks in the placebo group and no children absent in the placebo group.

Maragkoudaki 2017 reported on the average number of school absences per week at both the end of four weeks of intervention and at the end of follow-up. At the end of four weeks of intervention the average number of days per week absent from school in the probiotics group was 0.07 ± 0.29 and the average number of days absent from school per week in the placebo group was 0.03 ± 0.15 (MD 0.04, 95% CI -0.10 to 0.17). At the end of follow-up the average number of days per week absent from school in the probiotics group was 0.0 ± 0.0 and the average number of days absent from school per week in the placebo group was 0.11 ± 0.52 (MD 0.11, 95% CI -0.32 to 0.10). At neither time point were the results statistically significant.

Weizman 2016 reported on the number of days of school missed over the four-week period of intervention. The average number of days missed in the probiotics group was 1.9 ± 1.1 and the average number of days missed in the placebo group was 2.7 ± 0.9 (P = 0.08).

Social and psychological functioning or change in social and psychological functioning

None of the included studies reported on this outcome.

Quality of life or change in quality life

None of the included studies reported on this outcome. Of note, Guandalini 2010 reported on a measure of quality of life, but did not use a validated measurement tool and so was not included in our review.

Synbiotic versus placebo

Primary outcomes

Treatment success

Meta-analysis of four studies with 310 participants showed that patients with functional abdominal pain disorders may respond better to synbiotics (74/156) than placebo (54/154) (RR 1.34, 95% CI 1.03 to 1.74, I^2 = 0%) (Analysis 2.1) (Baştürk 2016; Bauserman 2005; Otuzbir 2016; Saneian 2015). The evidence is of low certainty due to imprecision and risk of bias (Summary of findings 2).

The results were consistent when we ran the analysis with a fixed-effect model (RR 1.36, 95% CI 1.04 to 1.77, I^2 = 0%) (Analysis 2.2). We conducted a sensitivity analysis, removing Otuzbir 2016 due to risk of bias, which showed no clear difference between synbiotics (49/117) and placebo (36/113) (RR 1.27, 95% CI 0.88 to 1.82, I^2 = 6%) (Analysis 2.3). The evidence remains of low certainty due to serious imprecision.

The remaining synbiotics studies did not report this outcome.

Complete resolution of pain

Complete resolution of pain was reported in two studies with 131 participants (Baştürk 2016; Otuzbir 2016). The results showed no clear difference between synbiotics (34/65) and placebo (21/66) (RR 1.65, 95% CI 0.97 to 2.81) (Analysis 2.4). The evidence is of low certainty due to imprecision and risk of bias (Summary of findings 2).

We conducted a sensitivity analysis, removing Otuzbir 2016 due to risk of bias. The results showed no clear difference between synbiotics (9/26) and placebo (3/25) (RR 2.88, 95% CI 0.88 to 9.44) (Analysis 2.5).

Severity of pain on completion

Severity of pain was reported in four studies with 319 participants (Asgarshirazi 2015; Bauserman 2005; Kianifar 2015; Saneian 2015). We conducted a meta-analysis; however, we were unable to draw meaningful conclusions due to very high unexplained heterogeneity (Analysis 2.6). The evidence was of very low certainty. In line with our pre-planned methodology for managing heterogeneity, a narrative synthesis is presented in Summary of findings 2). No further conclusions could be drawn after inspection for risk of bias, and visual and clinical heterogeneity.

The remaining studies did not report this outcome or provided unclear results.

Frequency of pain on completion

Only one study with 80 participants reported results for frequency of pain on completion (Asgarshirazi 2015). This study measured frequency in episodes per week (MD -1.26, 95% CI -1.77 to -0.75, I^2 = 0%) (Analysis 2.7). The certainty of the evidence is very low due to very high imprecision and risk of bias (Summary of findings 2).

The remaining synbiotics studies did not report this outcome or presented results in a manner unsuitable for meta-analysis.

Secondary outcomes

Serious adverse events

There were no recorded serious adverse events in any of the included studies within either the synbiotic or placebo groups.

Withdrawal due to adverse events

Meta-analysis of four studies with 302 participants showed no difference in withdrawals due to adverse events between synbiotics (8/155) and placebo (1/147) (RR 4.58, 95% CI 0.80 to 26.19) (Analysis 2.8). The evidence is of very low certainty because of risk of bias and imprecision due to the very low numbers of events (Summary of findings 2).

Baştürk 2016 reported five post-randomisation withdrawals from the study, but it was not stated whether these withdrawals came from the intervention or placebo group. The author responded to a request to clarification regarding these withdrawals, so we have now included the data in this analysis.

Similarly, Kianifar 2015 reported five post-randomisation withdrawals from the study, but again it was not stated whether these were from the intervention or placebo groups.

Otuzbir 2016 made no comment on adverse events or post-randomisation withdrawals within the abstract we were able to review, and did not respond to our requests for further information.

Adverse events

Meta-analysis of three studies with 189 participants showed no difference in adverse events between synbiotics (3/96) and placebo (1/93) (RR 2.88, 95% CI 0.32 to 25.92) (Analysis 2.9). The evidence is of very low certainty because of risk of bias and imprecision due to the very low numbers of events (Summary of findings 2).

Baştürk 2016 reported five post-randomisation withdrawals from the study, but it was not stated whether these withdrawals due to adverse events came from the intervention or placebo group.

The author responded to a request to clarification regarding these withdrawals, so we have now included the data in this analysis.

Similarly, Kianifar 2015 reported five post-randomisation withdrawals from the study due to adverse events (stated as "lack of follow up"), but again it was not stated whether these were from the intervention or placebo groups.

Otuzbir 2016 made no comment on adverse events within the abstract we were able to review, and did not respond to our requests for further information.

Saneian 2015 included a table showing adverse events broken down by symptom. Due to the possibility that some patients fell in to more than one of these categories, and that the data were not broken down by the number of patients suffering adverse events, we could not use these data for meta-analysis.

School performance or change in school performance or attendance

None of the included studies reported on this outcome.

Social and psychological functioning or change in social and psychological functioning

None of the included studies reported on this outcome. Of note, Kianifar 2015 included disruption of social activities as an outcome in their methods, but did not report on this outcome in their results.

Quality of life or change in quality life

None of the included studies reported on this outcome.

DISCUSSION

Summary of main results

This review includes 18 parallel-group randomised controlled trials (RCTs). Twelve assessed the effectiveness of probiotics, five assessed the effectiveness of synbiotics, and one assessed the effectiveness of both probiotics and synbiotics in treating functional abdominal pain in childhood.

Probiotics

The results demonstrate that probiotics may achieve greater *treatment success* at study end than placebo in children with functional abdominal pain (low-certainty evidence). Subgroup analysis for specific strains revealed low-certainty evidence for *Lactobacillus reuteri*, *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* that there may be no difference to placebo. On sensitivity analysis using a fixed-effect model, *Lactobacillus reuteri* showed a small increase in treatment success (number needed to treat for an additional beneficial outcome (NNTB) = 7) and *Lactobacillus rhamnosus* GG a large increase in treatment success (NNTB = 3) when compared to placebo, but this evidence was also of low certainty.

It is not clear whether probiotics are more effective than placebo for complete resolution of pain when compared with placebo (very low-certainty evidence).

We were unable to draw meaningful conclusions from our meta-analyses of the *pain severity* and *pain frequency* outcomes due to very high unexplained heterogeneity leading to very low-certainty evidence.

There were insufficient data for subgroup analysis of treatment success or severity of pain on completion of treatment by specific diagnosis of either functional abdominal pain or irritable bowel syndrome.

No studies recorded *serious adverse events*. Very few *withdrawals due to adverse events* or *adverse events* (patient totals) were reported. No conclusions can be made regarding the comparison of probiotics and placebo for any of the adverse event outcomes due to the very low certainty of the evidence.

Synbiotics

Synbiotics may result in more treatment success at study end when compared with placebo for children with functional abdominal pain (low-certainty evidence).

There may be no difference between synbiotics and placebo for complete resolution of pain.

We were unable to draw meaningful conclusions from our meta-analyses of pain severity or frequency of pain due to very high unexplained heterogeneity leading to very low-certainty evidence.

No studies recorded serious adverse events. Very few withdrawals due to adverse events or adverse events (patient totals) were reported. No conclusions can be made in the comparison of synbiotics and placebo for any of the adverse event outcomes due to the very low certainty of the evidence.

There were insufficient data on school performance or change in school performance or attendance, social and psychological functioning, or quality of life.

Overall completeness and applicability of evidence

The evidence is complete in a number of ways. Certainly the use of Rome diagnostic criteria in all studies (as required inclusion criteria) has ensured clinical homogeneity and applicability of the findings (Drossman 2006; Hyams 2016). Additionally, two probiotics in particular have been used in multiple studies, considering safety and efficacy. A range of ages of patients are included in the primary studies and the numbers of participants in the meta-analyses are appropriate to support the findings. Finally, the range of primary outcomes expected were reported, with reasonable heterogeneity.

However, there are some areas of incomplete evidence. When considering the separate entities of irritable bowel syndrome or functional abdominal pain (Hyams 2016), there are insufficient studies to run these as separate analyses. Many studies considered these sub-diagnostic categories as one and this is reflected in the analysis. However, this must be considered when applying the findings of this review in clinical practice. Additionally, whilst two particular preparations are the most commonly found, subgroup analysis is still impacted by imprecision due to low event and patient numbers, which reduces the certainty of the evidence. The number of studies is simply smaller when subgrouped by specific strain. The evidence for probiotics allowed meta-analysis for two specific strains, *Lactobacillus reuteri* and *Lactobacillus rhamnosus* GG, but due to the low numbers the certainty of the results was impacted. In this area, the evidence is more complete than in previous reviews (Martin 2017), but further work may be indicated to enhance certainty.

Additionally, the majority of studies had short follow-up (all less than 20 weeks). Given the chronic nature of these conditions and the length of symptoms needed to qualify for a Rome criteria diagnosis, this evidence does not consider the impact of cessation of therapy or long-term continuation. This must also be considered when interpreting the evidence.

Finally, the reporting of harms is another area of concern. It is not uncommon to experience difficulties in reporting related to heterogeneity of thresholds of defining serious or severe adverse events, and as such withdrawals due to adverse events is often the most available measure. This is not necessarily the most important outcome for clinicians or patients and represents a gap in the completeness of the evidence that must be considered. This is further compounded by the findings in this review, which found in most cases that the number of withdrawals was identical or very close to the reported number of adverse events. This suggests that very few events occurred that were not at a level of severity that warranted withdrawal. This is of course possible, but it does raise a question about thresholds of reporting in these studies, which may be of interest to patients who may want to know of mild side effects, even if researchers deem them of minimal interest.

The other concern with randomised trial data is this is not necessarily the best method to comprehensively identify all safety issues, particularly rare issues. It has previously been noted that prophylactic use of probiotics in certain conditions has been associated with bowel ischaemia and increased mortality (Besselink 2008), as well as reports of sepsis secondary to *Lactobacillus* use (Boyle 2006), and other gastrointestinal side effects (Dore 2019). Such rare events are unlikely to be identified in the context of a randomised study, but are nonetheless of interest to prescribers and patients.

Quality of the evidence

We thoroughly assessed the included studies for quality and risk of bias. The evidence is overall at low risk of bias, as shown in Figure 2.

Publication bias could not be examined as there were insufficient studies in each analysis to create funnel plots.

One issue that was apparent was statistical heterogeneity in some of the analyses. Whilst in some analyses this could be explained via sensitivity analyses, for others, despite significant exploration, no reason could be found and therefore we could not pool the data in meta-analysis. This means that the evidence in the analyses that could be run and that is presented in the summary of findings tables is predominantly of low or very low certainty, but a large proportion of planned analyses were not completed due to heterogeneity and this must be taken into account by readers.

Probiotics versus placebo

The certainty of the evidence for the treatment success outcome in the probiotics versus placebo comparison was compromised due to heterogeneity (I^2 = 59%) and risk of bias (predominantly selective reporting) and for this reason we rated the evidence as low certainty. We conducted a sensitivity analysis with a fixed-effect model, which showed statistical significance for the strains *Lactobacillus rhamnosus* GG and *Lactobacillus reuteri* in contrast with the original analysis, indicating further issues with heterogeneity. Given the clinical and methodological context of these studies, it is arguable that they are from subgroups in which a fixed-effect model would be appropriate, but we did not believe that there was enough patient-specific detail available to make such a judgement to present this single analysis.

The certainty of the evidence for the complete resolution of pain outcome in the probiotics versus placebo comparison was also severely compromised due to high inconsistency (I^2 = 70%) which, when explored in a sensitivity analysis for clinical heterogeneity, was greatly reduced (I^2 = 30%).

The severity of pain outcome in the same comparison was also severely impacted by heterogeneity (I^2 > 75%). Sensitivity analyses based on clinical heterogeneity, risk of bias, random-effects versus fixed-effect models and abstract versus full-text studies had the same issue, so we were unable to present data for this outcome, as per our pre-planned methodology for managing very high heterogeneity.

The frequency of pain outcome presented the same issue in this comparison. A sensitivity analysis based on risk of bias showed no inconsistency and we were able to present the results.

We rated the certainty of the evidence for withdrawals due to adverse events and total adverse events for this comparison as very low because of imprecision due to the very low numbers of adverse event cases and risk of bias associated with selective reporting.

Synbiotics versus placebo

The certainty of the evidence for the treatment success outcome in the synbiotics versus placebo comparison was of low certainty due to imprecision and risk of bias from a study for which we only had abstract data (Otuzbir 2016). We rated the results of the risk of bias sensitivity analysis as low certainty because of imprecision due to the low numbers of participants.

We rated the evidence for complete resolution of pain in the synbiotics versus placebo comparison as low certainty because of issues with imprecision due to low participant numbers and risk of bias from a study for which we only had abstract data (Otuzbir 2016).

The severity of pain outcome in the same comparison was also severely impacted by heterogeneity (I^2 > 75%), which we could not explain via sensitivity analyses and therefore we could not present the results, in line with the reasoning outlined above.

We rated the evidence for frequency of pain as of very low certainty because of imprecision due to low participant numbers and severe risk of bias from a single open-label study that did not properly describe randomisation and allocation (Asgarshirazi 2015).

We rated the certainty of the evidence for withdrawals due to adverse events and total adverse events for this comparison as very low because of imprecision due to very low numbers of adverse event cases and risk of bias mainly from a single open-label study that did not properly describe randomisation and allocation (Asgarshirazi 2015).

The primary evidence for all other secondary outcomes was poorly reported and no conclusions could be reached about them.

Finally, the reporting of adverse events was sparse and so this was also reflected in the GRADE analysis.

Potential biases in the review process

The definitions of the Rome process have changed in small ways over time. The bulk of the included studies used Rome III, with some using Rome II. None used the latest Rome IV criteria, so this must be considered when interpreting the findings of this review.

Some studies reported outcomes as proportions; in order to include the data in the analyses, the numbers of events were calculated by the review authors. We were able to minimise errors by having two independent authors to extract the data. Additionally, some studies reported mean and standard error of the mean (SEM) and thus the standard deviation (SD) had to be calculated. Finally, some studies reported median and range, and again the mean and SD had to be calculated.

We contacted study authors for additional information and clarification; however, some authors failed to reply. We will aim to include any data which become available in future updates.

We identified fewer than the recommended number of studies required to carry out some subgroup analysis, particularly by specific pain disorder. This is a significant issue in the primary literature and future studies should take this into account.

Two studies were only available as abstracts, but we explored their impact in sensitivity analysis when relevant.

Agreements and disagreements with other studies or reviews

A previously published Cochrane Review considered pharmacological treatments for recurrent abdominal pain of childhood (Martin 2017). Whilst this review did not use identical patient groups or disease types, and did not include probiotics as a pharmacological agent, it is worth noting that this review found no evidence to support any of the classes of agents studied (tricyclic antidepressants, antibiotics, 5-HT4 receptor agonists, antispasmodics, antihistamines, H2 receptor antagonists, serotonin antagonists, selective serotonin re-uptake inhibitors, a dopamine receptor antagonist and a hormone).

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) commissioned a review in 2013 (van Tilburg 2013), and at the time there were only two randomised trials included. van Tilburg 2013 concluded that there was promising early evidence regarding probiotics and further research was needed. They in particular requested consideration of specific strains of probiotic and this has been achieved in the current review for both *Lactobacillus reuteri* and *Lactobacillus rhamnosus* GG.

There are currently no clear international guidelines for the use of these agents in children.

AUTHORS' CONCLUSIONS

Implications for practice

There is low-certainty evidence from this review that probiotics may be more efficacious in achieving treatment success than placebo in children with functional abdominal pain disorders. It is not clear whether probiotics are more efficacious than placebo for complete resolution of pain (very low-certainty evidence). We were unable to draw meaningful conclusions as to whether probiotics are effective in changing the frequency or severity of pain when compared with placebo.

There is also low-certainty evidence that synbiotics may be more efficacious in achieving treatment success than placebo, although there was insufficient evidence to judge whether synbiotics reduce the severity or frequency of pain when compared with placebo (very low-certainty evidence).

The evidence demonstrated little to no difference between synbiotics and placebo in the complete resolution of pain.

The evidence on adverse event outcomes was of very low certainty and no conclusions could be made in this review.

There was insufficient evidence to draw conclusions about the efficacy of probiotics or synbiotics in relation to school attendance and/or performance, social and psychological functioning, or on quality of life measures.

Implications for research

Rather than generic research to confirm efficacy, further targeted and appropriately designed randomised controlled trials may be needed to address the gaps in the evidence base. In particular, appropriate powering and design of these studies is needed to solve the issue of imprecision for the outcomes of school performance, social and psychological functioning, and quality of life, and also add more certainty to the evolving evidence base. Consistent alignment with the Rome diagnostic criteria is key, as is appropriate reporting of allocation concealment to address the risk of bias issues that have further impacted the certainty of the conclusions in this review.

Key areas for investigation include studies to confirm the safety of specific probiotic strains not yet investigated and studies with long-term follow-up of patients, including the investigation of the impact of continuing and ceasing therapy. Given that two patient groups have emerged in whom treatment is effective: those in whom treatment is successful and those in whom treatment reduces symptoms, investigators may wish to consider these groups separately in long-term follow-up. It is also worth emphasising that there is currently no consensus as to what constitutes treatment success in this field and thus future research addressing this would be helpful.

Studies that consider the different subgroups of abdominal pain disorders may also be needed to explore whether there is a difference in the efficacy of probiotics, as most included studies in this review presented these groups together or did not offer sufficient data for subgroup analysis.

Safety will always be a real priority in paediatric populations when considering any treatment. Reporting of all adverse events, events needing withdrawal, serious adverse events and particularly long-term harms data is vital to meaningfully move forward the evidence base.

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The following people conducted the editorial process for this review:

- Sign-off Editor (final editorial decision): Robert Boyle, Imperial College London, UK; Co-ordinating Editor of Cochrane Skin.
- Managing Editor (selected peer reviewers, collated peer reviewer comments, provided editorial guidance to authors, edited the article): Joey Kwong, Cochrane Central Editorial Service.
- Editorial Assistant (conducted editorial policy checks and supported editorial team): Leticia Rodrigues, Cochrane Central Editorial Service.
- Copy Editor (copy-editing and production): Jenny Bellorini, c/o Cochrane Central Production Service.
- Peer reviewers (provided comments and recommended an editorial decision): Nuala Livingstone, Cochrane Evidence Production and Methods Directorate (methods review); Robin Featherstone, Cochrane Central Editorial Service (search review).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Asgarshirazi 2015

Study characteristics	
Methods	Study design: single-blinded, placebo-controlled randomised controlled trial Setting: Valiasr Hospital of Imam Khomeini Hospital Complex, Tehran, Iran Study period: September 2012 to August 2014
Participants	Inclusion criteria: abdominal pain at least weekly for past 2 months

Asgarshirazi 2015 *(Continued)*

	Exclusion criteria: right lower quadrant or right upper quadrant pain, weight loss or growth impairment, dysphagia, vomiting, anaemia, diarrhoea (especially nocturnal), fever, arthritis, familial history of inflammatory bowel disease (IBD) or any abnormal finding in physical examination or primary lab tests. Patients with mentioned red flags and probable diagnosis of abdominal migraine were excluded. Condition duration intervention group 1: > 2 months Condition duration intervention group 2: > 2 months Condition duration control group: > 2 months Concurrent therapy intervention group 1: none stated Concurrent therapy intervention group 2: none stated Concurrent therapy control group: none stated Number randomised to intervention group 1: 40 Number randomised to intervention group 2: 40 Number randomised to control group: 40 Number assessed in intervention group 1: 34 Number assessed in intervention group 2: 29 Number assessed in control group: 25 Age at randomisation intervention group 1: mean 7.06 (SD ± 2.38) Age at randomisation intervention group: mean 7.44 (SD ± 2.44) Age at randomisation control group: mean 7.42 (SD ± 2.49) Sex (M/F) intervention group 1: 19/15 Sex (M/F) intervention group 2: 13/16 Sex (M/F) control group: 8/17
Interventions	Intervention group 1: Colpermin Intervention group 2: Lactol tablet (*Bacillus coagulans* + fructo-oligosaccharide) Control group: folic acid tablet
Outcomes	The outcome measure was changes in the severity, duration and frequency of pain after the 1-month intervention in each group and between groups. Pain severity assessment was done based on patients' or their parents' reports with numbers from 0 to 10 (numerical rating scale). Duration of pain as minutes per day and frequency as pain episodes in a week was assessed.
Notes	Funding source: not stated Author contact: Masoumeh Asgarshirazi, Pediatric Department, Valiasr Hospital, Tehran University of Medical Sciences, Tehran, IR Iran. Tel: +98-2166581596, Fax: +98-2166591315, Email: dr.m.asgarshirazi@gmail.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly allocated", but no stated means of randomisation. We emailed the authors about this and received no response.

Asgarshirazi 2015 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No stated method of allocation concealment. We emailed the authors about this and received no response.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Placebo-controlled but unclear language about who was blinded. In their discussion the authors mention that this was a single-blind study and the nurse who administered the questionnaires was blinded. We emailed the authors about this and received no response.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear as above. We emailed the authors about this and received no response.
Incomplete outcome data (attrition bias) All outcomes	Low risk	88/120 patients completed the 1-month trial and periodic visits (32 in Colpermin, 29 in Lactol, 25 in the placebo group). 32 patients were excluded during the trial because they did not complete 1-month drug consumption due to journey or lack of 2-week visit.
Selective reporting (reporting bias)	Low risk	Prospective trial registration with outcomes matching registration.
Other bias	Low risk	None.

Baştürk 2016

Study characteristics	
Methods	Study design: randomised, double-blind, controlled trial Setting: Akdeniz University Pediatric Gastroenterology Outpatient Clinic Study period: September 2014 to May 2015
Participants	Inclusion criteria: ages 4 to 16 Exclusion criteria: none stated Condition duration intervention group 1: not stated Condition duration intervention group 2: not stated Condition duration control group: not stated Concurrent therapy intervention group 1: none stated Concurrent therapy intervention group 2: none stated Concurrent therapy control group: none stated Number randomised to intervention group 1: 26 Number randomised to intervention group 2: 25 Number randomised to control group: 25 Number assessed in intervention group 1: 23 Number assessed in intervention group 2: 24 Number assessed in control group: 24

Baştürk 2016 *(Continued)*

	Age at randomisation intervention group 1: mean 12.33 (SD ± 4.65) Age at randomisation intervention group 2: mean 10.20 (SD ± 3.78) Age at randomisation control group: mean 12.33 (SD ± 4.65) Sex (M/F) intervention group 1: 12/12 Sex (M/F) intervention group 2: 10/14 Sex (M/F) control group: 12/12
Interventions	Intervention group 1: synbiotic: *B. lactis* and inulin Intervention group 2: probiotic: *B. lactis* Control group: prebiotic inulin
Outcomes	The primary endpoint criterion was complete benefit of the patient with resolution of all present complaints with synbiotic or probiotic treatment for 4 weeks The secondary endpoint criterion was resolution at the end of the 4-week treatment of one or more of the symptoms such as postprandial swelling, belching, abdominal distension, mucoid defecation, difficulty in defecation, feeling of incomplete defecation and urgent defecation
Notes	Funding source: the authors declared that this study has received no financial support Author contact: Ahmet Baştürk; email: drahmetbasturk@hotmail.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation process was strange: "Patients... were directed to the paediatric gastroenterology nurse and drug boxes that were labelled with code numbers only. The package ingredients were unknown and were randomly given to the patients, thus randomization was provided". Even though this is an unconventional way to randomise a study we deemed that it was low risk as the contents of the packages were unknown to everyone involved and so this method would be similar to throwing a die, for example.
Allocation concealment (selection bias)	Low risk	Patients received medication from a gastroenterology nurse. The ingredients of the package were unknown to the doctor, nurse and patient but only the manufacturer knew which code number included which drug. As there were no conflicts of interest involving the manufacturer we think allocation concealment was achieved.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Same colour, odour, taste and package properties
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomisation and adverse effects data are not presented for the 5 patients who could not complete their treatment. We emailed the authors and they responded on 10 December 2020, clarifying the groups where the missing pa-

Baştürk 2016 *(Continued)*

		tients had been randomised but did not explain the reasons they discontinued the study.
Selective reporting (reporting bias)	Unclear risk	No trial registration mentioned or found.
Other bias	Low risk	None

Bauserman 2005

Study characteristics	
Methods	Study design: double-blind, randomised, placebo-controlled trial Setting: Children's Medical Centre, Dayton, Ohio Study period: July 2003 to June 2004
Participants	Inclusion criteria: active symptoms of abdominal pain over a period of at least 2 weeks Exclusion criteria: under the age of 5 or over the age of 21; receiving any medication for the treatment of IBS; receiving drugs known to cause abdominal pain Condition duration intervention group: mean (SD) 18.6 (18.4) months range (1 to 72 months) Condition duration control group: mean (SD) 13.4 (10.9) months range (1 to 49 months) Concurrent therapy intervention group: none Concurrent therapy control group: none Number randomised to intervention group: 32 Number randomised to control group: 32 Number assessed in intervention group: 25 Number assessed in control group: 25 Age at randomisation intervention group: mean 11.6 (3.2) (min 6, max 17) Age at randomisation control group: mean 12.4 (2.9) (min 6, max 17) However authors mention an overall age range of 6 to 20 Sex (M/F) intervention group: 6/19 Sex (M/F) control group: 4/21
Interventions	Intervention group: *Lactobacillus* GG Control group: placebo
Outcomes	The primary outcome was the change in abdominal pain severity score from baseline to the end of the treatment period. Secondary outcomes included the number of responders versus non-responders in each group and changes in the remaining symptoms of the GSRS by syndrome. Patients were classified as responders if they experienced a decrease in abdominal pain severity of 1 or more levels (1 point or more) on the 4-point Likert scale from baseline to the end of treatment. Base-

Bauserman 2005 *(Continued)*

	line abdominal pain and other GSRS scores were averaged from the daily scores recorded by the patients/parents during the week preceding treatment. Post-treatment scores were averaged for each week of data collected after baseline measurements.
Notes	Funding source: not stated Author contact: sonia.michail@wright.edu

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random list.
Allocation concealment (selection bias)	Low risk	A pharmacy separate to the study generated the random list, and each patient was assigned by the central pharmacy in order of entry by the study.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical taste, appearance and colour.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The code was revealed by the vendor after recruitment, data collection and statistical analyses were complete, which implies that statistical analysis was performed blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study flow described in detail. 22% of patients withdrew or were lost to follow-up and not included in the analysis, however this was balanced between groups.
Selective reporting (reporting bias)	Unclear risk	All outcomes from the methods were reported, appropriate and complete. No trial registration was mentioned or found.
Other bias	Low risk	Baseline characteristics were balanced between groups.

Eftekhari 2015

Study characteristics

Methods	Study design: randomised, double-blind, placebo-controlled trial Setting: Gastroenterology Clinic of Ayatollah Mousavi Hospital, Zanjan, Iran Study period: 2012 to 2013
Participants	Inclusion criteria: age 4 to 16 Exclusion criteria: abdominal pain with known organic cause; history of abdominal and gastrointestinal surgery; FTT or weight loss more than 5% of body weight; any abnormal paraclinical finding including complete blood count, urinalysis, stool examination for occult blood, biochemistry, abdominal ultrasound, liver function tests, serum amylase and lipase; history of drug use in the past 3 months including antidepressants or laxatives; any kind of chronic illness; history of abdomen blunt trauma Condition duration intervention group: > 2 months Condition duration control group: > 2 months

Eftekhari 2015 *(Continued)*

	Concurrent therapy intervention group: none stated Concurrent therapy control group: none stated Number randomised to intervention group: 40 Number randomised to control group: 40 Number assessed in intervention group: 40 Number assessed in control group: 40 Age at randomisation intervention group: mean 6.26 (SD ± 2.10) Age at randomisation control group: mean 6.26 (SD ± 2.61) Sex (M/F) intervention group: 20/20 Sex (M/F) control group: 21/19
Interventions	Intervention group: *Lactobacillus reuteri* Control group: placebo
Outcomes	During follow-up the researcher assessed intensity pain scores, frequency of pain and ultimately response to treatment
Notes	Funding source: financial support was provided by the Vice Chancellor for Research of Zanjan University of Medical Sciences Author contact: Kambiz Eftekhari, Department of Pediatrics, Bahrami Hospital, Tehran University of Medical Sciences, Tehran, IR Iran. Tel: +98-2173013000, Fax: +98-2177568809, Email: k-eftekhari@sina.tums.ac.ir

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Low risk	Not described adequately. Emailed the author and confirmed on 16 July 2019 that a staff member "not involved in the research" was used and therefore ensured allocation concealment of the computer-generated number list.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The physicians and the patients were unaware of the contents of the medications prescribed (double-blind study).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients completed the study and were included in the analysis.
Selective reporting (reporting bias)	Unclear risk	Conflicting reporting of the results for the primary outcomes. The protocol IRCT2014083018971N1 was retrospectively registered (22 September 2014). We emailed the authors about this and received no response.

Eftekhari 2015 *(Continued)*

Other bias	Low risk	No other concerns.

Francavilla 2010

Study characteristics	
Methods	Study design: double-blind, randomised, placebo-controlled trial Setting: Southern Italy Study period: 2004 to 2008
Participants	Inclusion criteria: aged 5 to 14 Exclusion criteria: any chronic diseases; received treatment with antibiotics/probiotics in the previous 2 months; had a pain history suggestive of functional dyspepsia/aerophagia/abdominal migraine; exhibited growth failure; had gastroparesis; had gastrointestinal obstructions/stricture; displayed alarming signs of organic conditions; had previous abdominal surgery; 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; faecal calprotectin; urinalysis; 13C-urea breath test; and abdominal ultrasound) Condition duration intervention group: mean (SD) 2.1 (1.7) years Condition duration control group: mean (SD) 2.6 (2.5) years Concurrent therapy intervention group: not reported Concurrent therapy control group: not reported Number randomised to intervention group: 71 Number randomised to control group: 70 Number assessed in intervention group: 69 Number assessed in control group: 67 Age at randomisation intervention group: mean 6.5 (SD ± 2.1) Age at randomisation control group: mean 6.3 (SD ± 2.0) Sex (M/F) intervention group: 43/24 Sex (M/F) control group: 35/23
Interventions	Intervention group: oral *Lactobacillus* GG Control group: placebo
Outcomes	The primary outcome was the change in abdominal pain (frequency/severity) according to the VAS score from baseline to the end of the treatment period. We chose pain as the primary outcome measure consistent with the proposed points to consider for IBS trials. Secondary outcomes were (1) a decrease of at least 50% in the number of episodes and intensity of pain (treatment success), (2) a decrease in the perception of children's pain according to their parents, and (3) modification of intestinal permeability.
Notes	Funding source: the authors have indicated they have no financial relationships relevant to this article to disclose.

Francavilla 2010 *(Continued)*

Author contact: Ruggiero Francavilla, MD, PhD, Clinica Pediatrica "B. Trambusti," Piazza Giulio Cesare, 11-Policlinico, Bari, Italy. Email: rfrancavilla@libero.it

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Children were assigned consecutive numbers, starting with the lowest number available, and were randomly assigned, with the use of a computer-generated randomisation list created by using a permuted block design,
Allocation concealment (selection bias)	Low risk	Group assignment was concealed from participants and investigators.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical in size, taste and appearance.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Adequate blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 4% of randomised patients not included in the analysis.
Selective reporting (reporting bias)	Low risk	Prospective trial registration. All outcomes reported appropriately and in line with study plan.
Other bias	Low risk	No other concerns.

Gawrońska 2007

Study characteristics

Methods	Study design: double-blind, randomised, placebo-controlled trial Setting: Department of Pediatric Gastroenterology and Nutrition, The Medical University of Warsaw Study period: October 2003 to May 2006
Participants	Inclusion criteria: aged 6 to 16 Exclusion criteria: 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 Condition duration intervention group: > 12 weeks Condition duration control group: > 12 weeks Concurrent therapy intervention group: 16 use of drug treatment for abdominal pain Concurrent therapy control group: 15 use of drug treatment for abdominal pain Number randomised to intervention group: 52 Number randomised to control group: 52

Gawrońska 2007 *(Continued)*

	Number assessed in intervention group: 52 Number assessed in control group: 52 Age at randomisation intervention group: mean 11.9 (SD ± 3) Age at randomisation control group: mean 11.2 (SD ± 2.7) Sex (M/F) intervention group: 29/23 Sex (M/F) control group: 19/33
Interventions	Intervention group: *Lactobacillus* GG Control group: placebo
Outcomes	The primary outcome measure was treatment success defined as no pain (a relaxed face, score of 0, on the Faces Pain Scale) at the end of the intervention The secondary outcome measures were improvements defined as a change in (1) the Faces Pain Scale by at least 2 faces scores; (2) self-reported severity of pain during the preceding week measured on the Faces Pain Scale; (3) self-reported frequency of pain during the preceding week; (4) use of medication for abdominal pain and (5) school absenteeism because of abdominal pain
Notes	Funding source: grant from the Medical University of Warsaw Author contact: Prof. H. Szajewska, The Second Department of Paediatrics, The Medical University of Warsaw, 01–184 Warsaw, Dzialdowska 1, Poland. Email: hania@ipgate.pl

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list.
Allocation concealment (selection bias)	Low risk	Not specified. Emailed the author and received a response on 27 June 2018 confirming sealed, opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical active and placebo treatments.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants included in the analysis.
Selective reporting (reporting bias)	Unclear risk	No trial registration mentioned or found. All expected outcomes reported.
Other bias	Low risk	There is a gender imbalance between the intervention (29/23) and control (19/33) groups but we did not think it posed a high risk of bias.

Giannetti 2017

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled, cross-over trial Setting: Naples and Foggia, Italy Study period: January 2014 to December 2014
Participants	Inclusion criteria: ages 8 to 17 Exclusion criteria: chronic organic gastrointestinal diseases; previous abdominal surgery, diseases affecting bowel motility, or concomitant psychiatric, neurological, metabolic, renal, hepatic, infectious, haematological, cardiovascular or pulmonary disorders; patients treated with antibiotics, proton-pump inhibitors, H2 antagonists or receiving any commercial preparation of probiotics during the previous 3 months Condition duration intervention group: not stated Condition duration control group: not stated Concurrent therapy intervention group: not stated Concurrent therapy control group: not stated Number randomised to intervention group: 78 total patients randomised (it is a cross-over trial and the authors have combined pre- and post-cross-over data in the presentation of their results) Number randomised to control group: 78 total patients randomised (it is a cross-over trial and the authors have combined pre- and post-cross-over data in the presentation of their results) Number assessed in intervention group: 75 total patients assessed (it is a cross-over trial and the authors have combined pre- and post-cross-over data in the presentation of their results) Number assessed in control group: 75 total patients assessed (it is a cross-over trial and the authors have combined pre- and post-cross-over data in the presentation of their results) Age at randomisation IBS: median 11.2 (range 8 to 17.9) Age at randomisation FD: median 11.6 (range 8 to 16.6) Sex (M/F) IBS: 21/27 Sex (M/F) FD: 11/14
Interventions	Intervention group: bifidobacteria Control group: placebo
Outcomes	The main outcome parameter considered was AP resolution, defined as no episodes of pain during the treatment period, as reported in the questionnaire of symptoms Secondary outcome parameters were reduction in AP frequency, patient-reported quality of life, changes in bowel habit for IBS patients, and improvement in nausea for FD patients
Notes	Funding source: none stated Author contact: Annamaria Staiano, MD, Department of Translational Medical Sciences, Section of Pediatrics, Federico II University, Via S. Pansini, Naples 5-80131, Italy (email: staiano@unina.it)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Giannetti 2017 *(Continued)*

Random sequence generation (selection bias)	Low risk	Described randomisation according to a computer-generated table.
Allocation concealment (selection bias)	Low risk	We contacted the author and received a response from Prof Staiano on 11 November 2020 confirming that each assignment was in sealed opaque envelopes that were opened sequentially.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded and author responded and confirmed this was also the case for those assessing outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/78 patients not included in the analysis; reasons given in the paper.
Selective reporting (reporting bias)	Unclear risk	Trial registered after enrolment complete and posted to NCT after completion of trial period. The outcomes are reported as presented in the methods section.
Other bias	Unclear risk	The results are unclear as the authors have combined pre- and post-cross-over data and present their results per condition (FD and IBS) instead of per intervention and control group. They have not provided randomisation numbers for each therapy. We emailed the authors about this and received no response.

Guandalini 2010

Study characteristics	
Methods	Study design: double-blind, randomised, placebo-controlled, cross-over trial Setting: 5 paediatric tertiary care centres located in Italy (4) and in India (1) Study period: April 2006 to October 2007
Participants	Inclusion criteria: ages 4 to 18 Exclusion criteria: any chronic organic gastrointestinal disorders, as assessed by full clinical history and examination, and supported by normal results of initial limited laboratory investigation; any disease that may affect bowel motility such as diabetes mellitus, sarcoidosis, connective tissue disease or poorly controlled hypo-/hyperthyroidism; previous abdominal surgery, as well as significant concomitant psychiatric, neurological, metabolic, renal, hepatic, infectious, haematological, cardiovascular or pulmonary illnesses; patients who had been using any commercial preparation of probiotics during the previous 3 months Condition duration intervention group: > 12 weeks Condition duration control group: > 12 weeks Concurrent therapy intervention group: none allowed Concurrent therapy control group: none allowed

Guandalini 2010 *(Continued)*

	Number randomised to intervention group: 67 total patients randomised (it is a cross-over trial and the authors have combined pre- and post-cross-over data in the presentation of their results) Number randomised to control group: 67 total patients randomised (it is a cross-over trial and the authors have combined pre- and post-cross-over data in the presentation of their results) Number assessed in intervention group: 59 total patients assessed (it is a cross-over trial and the authors have combined pre- and post-cross-over data in the presentation of their results) Number assessed in control group: 59 total patients assessed (it is a cross-over trial and the authors have combined pre- and post-cross-over data in the presentation of their results) Age at randomisation mean 12.5 (range 5 to 18) Sex (M/F): 31/28
Interventions	Intervention group: patented probiotic preparation Control group: placebo
Outcomes	The primary endpoint was improvement in the participant's global assessment of relief (SGARC) The secondary endpoints were improvements in abdominal pain/discomfort, stool pattern, bloating/gassiness and family assessment of the impact of their child's IBS on the family's life. ("SGAR" for Subject's Global Assessment of Relief), modified for children ("SGARC") including frequency and intensity of episodes of abdominal pain/discomfort expressed on a 5-point scale from 0 (normal) to 4 (worst)
Notes	Funding source: locally available grants. There was no industry support except for providing product and placebo. No extramural financial support was provided for this investigator-initiated study. Author contact: Stefano Guandalini, MD, Professor of Pediatrics, University of Chicago Section of Pediatric Gastroenterology, Hepatology and Nutrition, 5839 S. Maryland Ave, MC 4065, Chicago, IL 60637 (email: sguandalini@peds.bsd.uchicago.edu)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list.
Allocation concealment (selection bias)	Low risk	Central pharmacy dispensed medication.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical products and double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 8/67 randomised patients not included in the analysis.
Selective reporting (reporting bias)	Unclear risk	No trial registration mentioned or found. Outcomes are reported as presented in the methods section.

Guandalini 2010 *(Continued)*

Other bias	Unclear risk	The results are unclear as the authors have combined pre- and post- cross-over data. We emailed the authors for clarification and received no response.

Jadrešin 2017

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled trial Setting: referral centre for Paediatric Gastroenterology, Children's Hospital, Zagreb Study period: May 2012 to December 2014
Participants	Inclusion criteria: age 4 to 18 with diagnosis of FAP or IBS according to Rome III criteria Exclusion criteria: known or suspected immunodeficiency, treatment with probiotic and/or prebiotic products 7 days before enrolment, known neoplastic disorder or any chronic disease, and presence of 'red flags' for other organic disease Condition duration intervention group: not stated Condition duration control group: not stated Concurrent therapy intervention group: none stated Concurrent therapy control group: none stated Number randomised to intervention group: 26 Number randomised to control group: 29 Number assessed in intervention group: 26 Number assessed in control group: 29 Age at randomisation intervention group: median 10.5, IQR 5.4 to 17 Age at randomisation control group: median 9.5, IQR 5.5 to 16.5 Sex (M/F) intervention group: 11/15 Sex (M/F) control group: 12/17
Interventions	Intervention group: *L. reuteri* DSM 17938 Control group: placebo
Outcomes	Primary endpoints were number of days without pain and difference in the duration of the pain in minutes between the beginning and end of the study; difference in the severity of the pain assessed by the Faces scale between the beginning and the end of the study Secondary endpoints were severity of the pain assessed by the Faces scale during the first, second, third and fourth month; duration of pain in minutes during the first 2 and the last 2 months
Notes	Funding source: probiotic and placebo provided by Biogaia Author contact: Iva Hojsak, MD, PhD, referral centre for Pediatric Gastroenterology and Nutrition, Children's Hospital Zagreb, Klaic´eva 16, 10000 Zagreb, Croatia (email: ivahojsak@gmail.com)
Risk of bias	

Jadrešin 2017 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation software.
Allocation concealment (selection bias)	Low risk	Opaque, sealed envelopes opened sequentially.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical and packaged.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors not aware of allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients included in the analysis. Because of a low recruitment rate it was decided among the researchers that an interim analysis would be performed after 55 children were recruited.
Selective reporting (reporting bias)	Unclear risk	Baseline data for severity and frequency of pain are not clear. Study protocol prospectively registered (NCT01587846). Protocol presents as an outcome only the intensity of pain and outcomes for chronic constipation, which was not finally included. In a pooled analysis they performed (Jadrešin 2020), the results are different to those presented here.
Other bias	Low risk	More girls than boys in total (32 girls/23 boys) but we did not think this posed a risk of bias.

Jadrešin 2020

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled trial Setting: referral centre for Paediatric Gastroenterology, Children's Hospital, Zagreb Study period: January 2017 to March 2019
Participants	Inclusion criteria: age 4 to 18 with diagnosis of FAP or IBS according to Rome III criteria Exclusion criteria: known or suspected immunodeficiency, treatment with probiotic and/or prebiotic products 7 days before enrolment, known neoplastic disorder or any chronic disease, and presence of 'red flags' for other organic disease Condition duration intervention group: none stated Condition duration control group: none stated Concurrent therapy intervention group: none stated Concurrent therapy control group: none stated Number randomised to intervention group: 24 Number randomised to control group: 22 Number assessed in intervention group: 24

Jadrešin 2020 *(Continued)*

	Number assessed in control group: 22 Age at randomisation intervention group: median age 10.1 years, range 5 to 17 years Age at randomisation control group: median age 10.6 years, range 5 to 17 years Sex (M/F) intervention group: 13/11 Sex (M/F) control group: 9/13
Interventions	Intervention group: *L. reuteri* DSM 17938 Control group: placebo
Outcomes	Primary endpoints were: number of days without pain; difference in the duration of the pain in minutes between beginning and the end of the study; difference in the severity of the pain assessed between beginning and the end of the study Secondary endpoints were: severity of the pain assessed by VAS during the 1st, 2nd, 3rd and 4th month; duration of pain in minutes during first 2 and last 2 months Secondary endpoint was to assess difference in the severity of pain between beginning and end of the study in each group. This seems to have been added retrospectively. Exploratory variables included: number of days without school/activities (absence from school or other activities due to pain); complete resolution of abdominal pain until the end of the study (number of children). This also seems to have been retrospectively added.
Notes	Funding source: probiotic and placebo provided by Biogaia Author contact: not given Other: this is a second analysis after the interim analysis from Jadrešin 2017; the data above are from the second analysis only and not pooled data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation software.
Allocation concealment (selection bias)	Low risk	Opaque, sealed envelopes opened sequentially.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical and packaged.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors not aware of allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients included in the analysis.
Selective reporting (reporting bias)	Unclear risk	Baseline data for severity and frequency of pain are not clear. Study protocol prospectively registered (NCT01587846) is the same as for Jadrešin 2017. Protocol presents as an outcome only the intensity of pain and outcomes for

Jadrešin 2020 *(Continued)*

		chronic constipation, which was not finally included. In a pooled analysis they performed (Jadrešin 2020), the results are different to those presented here.
Other bias	Low risk	No concerns.

Kianifar 2015

Study characteristics	
Methods	Study design: double-blind, randomised, placebo-controlled trial Setting: Dr. Sheikh Hospital, Mashhad University of Medical Sciences, Iran Study period: August 2012 to September 2012
Participants	Inclusion criteria: aged 4 to 18 Exclusion criteria: "Differential diagnoses must have been excluded by laboratory evaluation"; patients taking any drugs or had underlying diseases (cardiac disease, renal disease, asthma, failure to thrive, cystic fibrosis) Condition duration intervention group: > 2 weeks Condition duration control group: > 2 weeks Concurrent therapy intervention group: none stated Concurrent therapy control group: none stated Number randomised (not reported per group): initially 60 patients were randomised but 5 were excluded due to lack of follow-up and 3 because they had to start antibiotics. It is not mentioned to which groups they had been randomised. Number assessed in intervention group: 26 Number assessed in control group: 26 Age at randomisation intervention group: mean 6.8 (SD ± 0.4) Age at randomisation control group: mean 7.3 (SD ± 0.5) Sex (M/F) intervention group: 13/13 Sex (M/F) control group: 14/12
Interventions	Intervention group: *Lactobacillus* GG Control group: placebo (inulin)
Outcomes	The primary outcome was any change in the severity of the patients' pain, on a 5-point Likert scale Secondary outcomes were changes of the functional scale, stool patterns and associated problems
Notes	Funding source: grant from the Vice Chancellor for Research at the Mashhad University of Medical Sciences Author contact: Assistant Professor Dr. Maryam Khalesi, Department of Pediatrics, Ghaem Medical Center, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +98.5138012469, +98.9151037242, Fax: +98.5138417451, Email: khalesim@mums.ac.ir

Kianifar 2015 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list using a block design.
Allocation concealment (selection bias)	Unclear risk	No details given.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical, with blinding of both investigators and patient.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Identical, with blinding of both investigators and patient.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Initially 60 patients were randomised but 5 were excluded due to lack of follow-up and 3 because they had to start antibiotics. It is not mentioned to which groups they had been randomised.
Selective reporting (reporting bias)	Low risk	All reported. Trial registered while recruiting: IRCT201205219825N1. The trial registration outcomes correspond with those outlined in the paper.
Other bias	Low risk	No concerns.

Maragkoudaki 2017

Study characteristics	
Methods	Study design: double-blind, randomised, placebo-controlled trial Setting: university hospitals of Athens in Greece, Ljubljana in Slovenia and Warsaw in Poland Study period: January 2013 to December 2015
Participants	Inclusion criteria: aged 5 to 16, pain of at least 40 mm on a 0 to 100 mm VAS Exclusion criteria: chronic illness; prior surgery of the gastrointestinal tract; a weight loss of 5% or more over the preceding 3 months; exposure to any drugs for FAP in the past 2 weeks; exposure to probiotics or antibiotics in the 4 weeks before the study; participation in other interventional clinical trials in the past 3 months; special dietary needs or any symptoms or signs of organic disease Condition duration intervention group: not stated Condition duration control group: not stated Concurrent therapy intervention group: none stated Concurrent therapy control group: none stated Number randomised to intervention group: 27 Number randomised to control group: 27 Number assessed in intervention group: 26

Maragkoudaki 2017 *(Continued)*

	Number assessed in control group: 26 Age at randomisation intervention group: mean 9.2 (SD ± 4.3) Age at randomisation control group: mean 9.0 (SD ± 3.2) Sex (M/F) intervention group: 14/13 Sex (M/F) control group: 11/16
Interventions	Intervention group: *Lactobacillus reuteri* DSM 17938 Control group: placebo
Outcomes	The primary endpoints were the reduction in pain frequency and pain intensity in the *L. reuteri* group compared with the placebo group over the 4-week treatment period, which were measured by the participants' diaries. There were also a number of secondary endpoints, which were measured and compared in the *L. reuteri* and the placebo groups at the end of treatment and at the end of the follow-up period compared to baseline. These were as follows: (1) any reduction in the frequency and intensity of other gastrointestinal symptoms, as measured by the GSRS; (2) any reduction in the days when the child was absent from school or could not take part in other activities due to abdominal pain; (3) any reduction in the days that parents were absent from work to care for their child; (4) any reduction in need for drugs to relieve pain. In addition, the treatment success rate, defined as a reduction in the pain score of more than 50%, was measured at 4 and at 8 weeks.
Notes	Funding source: the study was funded by a non-restricted grant from BioGaia, Sweden Author contact: email: a.papadopoulou@paidon-agiasofia.gr

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method of randomisation described, using computer software.
Allocation concealment (selection bias)	Low risk	Not specified in methods. Contacted author and reply received on 27 June 2018 confirming appropriate allocation concealment of randomised list.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical active and placebo treatments.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for.
Selective reporting (reporting bias)	Low risk	Outcomes reported. The protocol was prospectively registered (NCT01719107). The protocol outcomes correspond with the stated outcomes in the paper.

Maragkoudaki 2017 *(Continued)*

Other bias	Low risk	No other concerns.

Otuzbir 2016

Study characteristics	
Methods	Study design: double-blind, randomised, placebo-controlled trial Setting: Uludag University Medical Faculty Study period: January 2015 to May 2015
Participants	Inclusion criteria: not stated Exclusion criteria: not stated Condition duration intervention group: not stated Condition duration control group: not stated Concurrent therapy intervention group: none stated Concurrent therapy control group: none stated Number randomised to intervention group: 39 Number randomised to control group: 41 Number assessed in intervention group: 39 Number assessed in control group: 41 Age at randomisation intervention group: not broken down by arm of trial Age at randomisation control group: not broken down by arm of trial Sex (M/F) intervention group: not broken down by arm of trial Sex (M/F) control group: not broken down by arm of trial
Interventions	Intervention group: synbiotic Control group: placebo
Outcomes	Pain intensity and frequency, number of days of school without attendance, limitation of daily activities and serum levels of proinflammatory (TNF alpha, IFN gamma) and anti-inflammatory (IL-10, TGF beta, IL-13) cytokines were evaluated both at the beginning and at the end of the study. Treatment success (resolution of pain) and rate of reduction of complaints were also evaluated following the treatment.
Notes	Funding source: not declared Author contact: T.B. Ozkan, Uludag University, Faculty of Medicine, Pediatric Gastroenterology, Bursa, Turkey
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Otuzbir 2016 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomised by time of admission to trial; no further details provided. We have contacted the author and have not received a response.
Allocation concealment (selection bias)	Unclear risk	Not specified in methods. We have contacted the author and have not received a response.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear: no information on patient flow in the abstract. We have contacted the author and have not received a response.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported as stated but the methodology is not described. No protocol available and no full methods as abstract only.
Other bias	Low risk	No other concerns.

Rahmani 2020

Study characteristics	
Methods	Study design: double-blind, randomised, placebo-controlled trial Setting: Tehran University of Medical Sciences, Tehran, Iran Study period: June 2017 to June 2018
Participants	Inclusion criteria: aged 6 to 16 years with diagnosis of FAP according to the Rome III criteria Exclusion criteria: the presence of any one of the red flag items; use of antibiotics in the last 1 month, organic disorder based on clinical and paraclinical findings; participants or parents who did not co-operate in regards to medications and referrals Condition duration intervention group: not specified Condition duration control group: not specified Concurrent therapy intervention group: none mentioned Concurrent therapy control group: none mentioned Number randomised to intervention group: 65 Number randomised to control group: 60 Number assessed in intervention group: 65 Number assessed in control group: 60 Age at randomisation intervention group: 6 to 16 years (7.3 ± 1.7) Age at randomisation control group: 6 to 16 years (7.7 ± 2.1)

Rahmani 2020 *(Continued)*

	Sex (M/F) intervention group: 27/38 Sex (M/F) control group: 30/30
Interventions	Intervention group: *L. reuteri* Control group: placebo
Outcomes	Pain intensity based on the WBFPRS 2 (Wang-Baker FACES Pain Rating Scale); frequency of pain and recurrence; duration of each episode of pain; pattern of pain (colic cramps or permanent); the number of days that day-to-day activities affected (such as school absenteeism); the need for other medications to relieve pain
Notes	Funding source: Research Funding Centre, Tehran University of Medical Sciences, Iran Author contact: Alireza Moradzadeh, MD, Email: md.moradzadeh.a@gmail.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomly assigned into two groups as quadruple blocks of case and control using Block-Randomization method"
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment given.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Similar in the shape, size and taste.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All patients accounted for; unclear how many patients were excluded on the basis of the exclusion criteria versus how many were excluded for non-compliance.
Selective reporting (reporting bias)	Unclear risk	No trial registration mentioned or found. All expected outcomes reported.
Other bias	Low risk	Well-balanced groups.

Romano 2014

Study characteristics

Methods	Study design: double-blind, randomised, placebo-controlled trial, multi-centre Setting: paediatric departments of the Universities of Messina, Palermo, Catania and the Pediatric Unit of Vittoria (Sicily) Study period: not stated
Participants	Inclusion criteria: aged 6 to 16

Romano 2014 *(Continued)*

	Exclusion criteria: organic disease (established by medical history, complete blood count, urine analysis, stool examination for occult blood and parasites, abdominal ultrasound and screening for celiac disease), other chronic disease and growth failure Condition duration intervention group: not specified Condition duration control group: not specified Concurrent therapy intervention group: none stated Concurrent therapy control group: none stated Number randomised to intervention group: 32 Number randomised to control group: 28 Number assessed in intervention group: 2 were lost due to poor compliance but unclear if included in the analysis Number assessed in control group: 2 were lost due to poor compliance but unclear if included in the analysis Age at randomisation intervention group: mean 10.2 (SD ± 2.5) Age at randomisation control group: mean 9.6 (SD ± 0.4) Sex (M/F) intervention group: 14/16 Sex (M/F) control group: 11/15
Interventions	Intervention group: *L. reuteri* DSM 17938 Control group: placebo
Outcomes	The primary outcome was defined as the reduction of the intensity of FAP and the secondary outcome was the reduction of the frequency of the symptoms.
Notes	Funding source: not stated Author contact: Claudio Romano, Gastroenterology and Endoscopy Section, Genetic and Immunology Unit, Department of Pediatrics, University of Messina, 98122 Messina, Italy. Fax: +390902217005; email: romanoc@unime.it

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list.
Allocation concealment (selection bias)	Low risk	Randomisation list was retained by the dispensing pharmacist at each centre to ensure allocation concealment. This was also confirmed to us by the author.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical active and placebo treatments.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded.

Romano 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Two children from each group were lost to completion due to poor compliance; unclear if they were included in the analysis.
Selective reporting (reporting bias)	Unclear risk	No trial registration mentioned or found. All methods section outcomes reported, but in graph-bars with no data numbers provided. The number of participants the results were based on is also unclear: whether it was the total number randomised or without the children lost due to poor compliance.
Other bias	Low risk	No concerns.

Sabbi 2012

Study characteristics	
Methods	Study design: randomised controlled trial
	Setting: Belcolle Hospital, Italy
	Study period: not stated
Participants	Inclusion criteria: children with functional abdominal pain
	Exclusion criteria: not stated
	Condition duration intervention group: not stated
	Condition duration control group: not stated
	Concurrent therapy intervention group: not stated
	Concurrent therapy control group: not stated
	Number randomised to intervention group: not stated (61 in total)
	Number randomised to control group: not stated (61 in total)
	Number assessed in intervention group: not stated
	Number assessed in control group: not stated
	Age at randomisation intervention group: not stated
	Age at randomisation control group: not stated
	Sex (M/F) intervention group: not stated
	Sex (M/F) control group: not stated
Interventions	Intervention group: *Lactobacillus* GG
	Control group: placebo
Outcomes	Frequency and severity of abdominal pain
Notes	Funding source: not stated
	Author contact: not stated and could not find any
Risk of bias	

Sabbi 2012 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised but no information. We could not contact the author.
Allocation concealment (selection bias)	Unclear risk	No information and we could not contact the author.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study, placebo-controlled.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information and we could not contact the author.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on patient flow and we could not contact the author.
Selective reporting (reporting bias)	Unclear risk	The authors only state that their results were significant and we could not contact the author.
Other bias	Unclear risk	No information to judge and we could not contact the author.

Saneian 2015

Study characteristics	
Methods	Study design: double-blind, randomised, placebo-controlled trial Setting: Isfahan, Iran Study period: February 2013 to December 2013
Participants	Inclusion criteria: aged 6 to 18 Exclusion criteria: those with organic diseases as the cause of abdominal pain, other concomitant gastrointestinal disorders, or immune-compromised conditions, and those with recent history (preceding 2 months) of or current treatment with antibiotics, antidepressants, antispasmodics or probiotics were not included in the study Condition duration intervention group: > 2 months Condition duration control group: > 2 months Concurrent therapy intervention group: none stated Concurrent therapy control group: none stated Number randomised to intervention group: 59 Number randomised to control group: 56 Number assessed in intervention group: 45 Number assessed in control group: 43

Saneian 2015 *(Continued)*

	Age at randomisation intervention group: mean 9.0 (SD ± 2.2) Age at randomisation control group: mean 8.5 (SD ± 2.2) Sex (M/F) intervention group: 25/20 Sex (M/F) control group: 24/19
Interventions	Intervention group: *Bacillus coagulans* Control group: placebo
Outcomes	The primary outcome measure was treatment response, defined as at least a 2-point reduction in the Wong-Baker FACES Pain Rating Scale or “no pain” after medication Secondary outcomes included the physician-rated global severity and improvement using the Clinical Global Impression Severity and Improvement scales (control groupI-S, control groupI-I), scored 1 to 7
Notes	Funding source: Isfahan University of Medical Sciences Author contact: Zahra Pourmoghaddas, MD, Child Growth and Development Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list.
Allocation concealment (selection bias)	Low risk	Dispensed by central pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double-blinded, with confirmation that the bottles and preparations ensured blinding of participant and physician.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	27 (13/14) randomised participants in total not included in the final analysis but all the reasons are explained and the numbers are well balanced between groups.
Selective reporting (reporting bias)	Unclear risk	Prospective trial registration; report appears to be partial results as the trial registration mentions 2 further groups receiving citalopram and mebeverine. Outcomes described in registration do not completely match those described in report, mentions use of Wong-Baker scale but not that reduction of 2 points or 'no pain' would be defined as 'treatment response'.
Other bias	Low risk	No other concerns.

Weizman 2016

Study characteristics

Weizman 2016 *(Continued)*

Methods	Study design: double-blind, randomised, placebo-controlled trial Setting: Soroka Medical Center, Israel and at 3 community childcare centres in the Beer-Sheva area Study period: March 2011 to October 2013
Participants	Inclusion criteria: aged 6 to 15 Exclusion criteria: chronic illness, growth failure, previous abdominal surgery, or any alarming signs of organic conditions (such as vomiting, chronic diarrhoea, bloody stools); 16 participants who were treated with antibiotics, probiotics or prebiotics in the previous 8 weeks were excluded Condition duration intervention group: 1.8 (1.4) mean (SD) years Condition duration control group: 2.2 (1.9) mean (SD) years Concurrent therapy intervention group: only stated that 13/47 were using drugs for abdominal pain Concurrent therapy control group: only stated that 16/46 were using drugs for abdominal pain Number randomised to intervention group: 52 Number randomised to control group: 49 Number assessed in intervention group: 47 Number assessed in control group: 46 Age at randomisation intervention group: mean 12.2 (SD ± 2.8) Age at randomisation control group: mean 11.7 (SD ± 3.2) Sex (M/F) intervention group: 28/19 Sex (M/F) control group: 25/21
Interventions	Intervention group: *Lactobacillus reuteri* DSM 17938 Control group: placebo
Outcomes	The primary outcome measures included frequency and intensity of abdominal pain Secondary measures included school absenteeism because of abdominal pain, additional gastrointestinal symptoms and adverse effects
Notes	Funding source: not stated Author contact: Zvi Weizman, MD, Pediatric Gastroenterology and Nutrition Unit, Soroka Medical Center, Faculty of Health Sciences, Ben-Gurion University, PO Box 151, Beer-Sheva, Israel 84101. Email: wzvi@bgu.ac.il

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Described as computer-generated.
Allocation concealment (selection bias)	Low risk	Details described, performed independently.

Weizman 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical, with procedures described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient flow details confirmed and accounted for. No major differences between groups.
Selective reporting (reporting bias)	Low risk	All outcomes reported. Trial registered prospectively (NCT01180556).
Other bias	Low risk	No other concerns.

AP: abdominal pain
F: female
FAP: functional abdominal pain
FD: functional dyspepsia
FTT: failure to thrive
GSRS: Gastrointestinal Symptom Rating Scale
IBS: irritable bowel syndrome
IFN: interferon
IQR: interquartile range
M: male
NR: not reported
SD: standard deviation
TNF: tumour necrosis factor
VAS: visual analogue scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abu-Salih 2011	Commentary
Anonymous 2010	Letter to journal
Anuradha 2005	Review article
Baştürk 2017	Wrong condition
Berger 2007	Review article
Cash 2011	Review article
Cha 2012	Adult study
Charrois 2006	Review article
Chassany 2008	Letter to journal
Choi 2015	Adult study

Study	Reason for exclusion
Comito 2011	Wrong intervention
Drossman 2011	Studied antibiotics
Enck 2007	Review article
Enck 2009	Adult study
Faber 2003	Letter to journal
Ford 2012	Review article
Han 2016	Adult study
Kajander 2008	Review article
Le Neve 2016	Adult study
Mezzasalma 2016	Adult study
NCT04922476	Not an RCT
Pélerin 2016	Letter to editor
Rose 2011	Review article
Schmulson 2011	Review article
Sen 2002	Adult study
Spiller 2016	Adult study
Wegner 2018	Study in to use of probiotics in functional constipation, not FAPD
Yoon 2014	Adult study
Yoon 2015	Adult study

FAPD: functional abdominal pain disorder
RCT: randomised controlled trial

Characteristics of studies awaiting classification *[ordered by study ID]*

Chao 2011

Methods	RCT
Participants	60 children
Interventions	Probiotics and antidiarrhoeal faecal softener vs antidiarrhoeal faecal softener
Outcomes	Content, release and reuptake of serotonin
Notes	Could not find any author contact information, therefore we were unable to contact the authors

Gholizadeh 2021

Methods	RCT
Participants	Intervention group: 35 Control group: 35
Interventions	Intervention group: synbiotic preparation Control group: placebo
Outcomes	The primary outcome was at least a 50% reduction in the number of pain episodes Secondary outcomes were (1) a decline of at least 2 points in the pain intensity based on FACE scale, (2) a decrease of at least 50% in pain duration, and (3) a decrease of at least 50% in missing school days. Decrease of pain frequency/intensity was considered as response to treatment.
Notes	Identified during pre-publication update search and will be included in an update of the review.

NCT00793494

Methods	RCT, single group assignment
Participants	44
Interventions	Intervention group: Probaclac Control group: placebo
Outcomes	Primary outcome measures: Subjective assessment of improvement of symptoms (time frame: 4 weeks) Secondary outcome measures: Change in severity of symptoms (Likert scale) (time frame: 4 weeks) Presence and intensity of pain episodes (time frame: 4 weeks) Presence or absence of urgency, incomplete evacuation, gas (time frame: 4 weeks) Number and consistency of stools (time frame: 4 weeks) School and social absenteeism (time frame: 4 weeks) Quality of life (time frame: 4 weeks) Adverse events (time frame: 2 months)
Notes	Principal Investigator: Christophe M Faure, MD Ste-Justine Hospital

NCT02613078

Methods	RCT
Participants	60
Interventions	Behavioural: gut-directed hypnotherapy Dietary supplement: nutritional supplement

NCT02613078 *(Continued)*

	Behavioural: self-monitoring
Outcomes	Primary outcome measures: Change in number of days with pain/discomfort (time frame: baseline, at week 10 and at 3 months follow-up) Secondary outcome measures: Change in parental report on gastrointestinal symptoms (Abdominal Pain Index (API)) (time frame: baseline, at week 10 and at 3 months follow-up) Change in pain related disability (Pediatric Pain Disability Index (P-PDI)) (time frame: baseline, at week 10 and at 3 months follow-up) Change in somatic complaints (Children's Somatization Inventory (CSI)) (time frame: baseline, at week 10 and at 3 months follow-up) Change in health-related quality of life (KINDL-R Questionnaire) (time frame: baseline, at week 10 and at 3 months follow-up) The KINDL-R is a generic instrument for assessing health-related quality of life in children and adolescents Change in pain-related coping (Pediatric Pain Coping Inventory (PPCI)) (time frame: baseline, at week 10 and at 3 months follow-up) Change in emotional and behavioural problems (Child Behaviour Checklist (CBCL)) (time frame: baseline, at week 10 and at 3 months follow-up) Change in heart rate variability (time frame: baseline and at week 10) Change in cortisol awakening response (amount of cortisol in saliva, nmol/l) (time frame: baseline and at week 10) Change in self-reported pain intensity (visual analogue scale) (time frame: baseline, at week 10 and at 3 months follow-up) Change in self-reported pain duration (hours per day) (time frame: baseline, at week 10 and at 3 months follow-up)
Notes	Contact: Marco D Gulewitsch, PhD, Tel: 004970712977187, Email: marco-daniel.gulewitsch@uni-tuebingen.de Contact: Paul Enck, PhD, Tel: 004970712989118, Email: paul.enck@uni-tuebingen.de

Sudha 2018

Methods	Study design: double-blind, randomised, placebo-controlled trial, multicentre Setting: Angel Healthcare Paediatric outpatient clinic and Life Veda Treatment and Research Centre in Mumbai, India Study period: February 2014 to October 2016
Participants	Inclusion criteria: age between 4 and 12; IBS as defined by the Rome III criteria Exclusion criteria: structural or metabolic abnormalities to explain the symptoms; other diseases affecting gut motility other than IBS; history of lactose intolerance or other malabsorption; previous abdominal surgery; severe systemic disease; use of commercial probiotic preparation in preceding 3 months; history of digestive disease; symptoms suggestive of rectal bleeding; weight loss of more than 3 kg in last 3 months; acute gastroenteritis in the 4 weeks prior to inclusion; calprotectin assay of > 500 µg/g stool Condition duration intervention group: none stated Condition duration control group: none stated Concurrent therapy intervention group: "rescue medication", not stated Concurrent therapy control group: "rescue medication", not stated

Sudha 2018 *(Continued)*

	Number randomised to intervention group: 77 Number randomised to control group: 77 Number assessed in intervention group: 72 Number assessed in control group: 69 Age at randomisation intervention group: mean 7.86 (min 4, max 11) Age at randomisation control group: mean 7.89 (min 4, max 10) Sex (M/F) intervention group: 43/29 Sex (M/F) control group: 37/32
Interventions	Intervention group: *B. coagulans* Control group: placebo
Outcomes	The intensity of pain was measured with an 11-point Likert scale. For children aged less than 8 years, the parent/caretaker was instructed to fill the patient diary. For children aged between 8 and 12 years, the patient diary was filled by the child and if required they were assisted by the parent/caretaker. Secondary efficacy variables were measured as: (1) change in the severity of symptoms score which consisted of 8 domains (abdominal discomfort, bloating, urgency, incomplete evacuation, straining, passage of gas, bowel habit satisfaction and overall assessment of IBS) with a Likert scale of 1 to 5; (2) stool consistency (relief in stool disturbances or trouble with bowel habits, which is "either going more or less often than normal, diarrhoea or constipation, or having a different kind of stool, thin, hard, or soft and liquid" measured with the Bristol stool scale of 1 to 7 and recorded by the patients in the diary; (3) Subject'sGlobal Assessment of Relief (SGARC), a globally accepted/validated questionnaire, which includes the assessment of overall wellbeing, abdominal pain/discomfort and bowel function (Likert scale 0 to 4). Drug compliance, usage of rescue medications, and adverse events (AE), if any, were monitored throughout the study.
Notes	Funding source: Unique Biotech Ltd. Author contact: sudha@uniquebiotech.com This study was classified under awaiting classification. Initially, it was included, but we noted concerns with the outlying data as these were highly positive, as well as significant conflicts from the team. We sought advice from the Cochrane research integrity unit and the Cochrane Gut team and based on this we attempted to contact the authors on numerous occasions, as well as the editors of the journal for clarification. No response has been received (2 named authors were directly employed by the manufacturer of their interventional agent, and the study was funded by the same manufacturer). This is in line with the Cochrane policy for managing potentially problematic studies.

F: female
IBS: irritable bowel syndrome
M: male
RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

IRCT20150706023084N14

Study name	'Evaluation of the effectiveness of Lactobacillus reuteri probiotics in the treatment of chronic functional abdominal pain in children aged 5 to 15 years'

IRCT20150706023084N14 *(Continued)*

Methods	RCT
Participants	180 children
Interventions	A group of 90 patients will receive a probiotic sachet every day for 28 days A control group of 90 patients will receive a placebo sachet with the same original packaging every day for 28 days
Outcomes	Pain intensity; pain frequency
Starting date	21 January 2022
Contact information	Maryam Shiehmorteza: shiehmorteza@iaups.ac.ir
Notes	End date: 23 August 2022

IRCT20200806048325N1

Study name	'Comparison of the effect of Prokid with Rotflore sachet in reducing functional abdominal pain in children'
Methods	RCT
Participants	116 children
Interventions	One group will receive ProCID capsules and will continue at regular intervals and the other group will be given Reuteflore sachets with the same conditions
Outcomes	Percentage of children with functional abdominal pain
Starting date	1 January 2020
Contact information	Sajad Jafari: sajad.jafari20@gmail.com
Notes	End date: 30 December 2020

RCT: randomised controlled trial

DATA AND ANALYSES

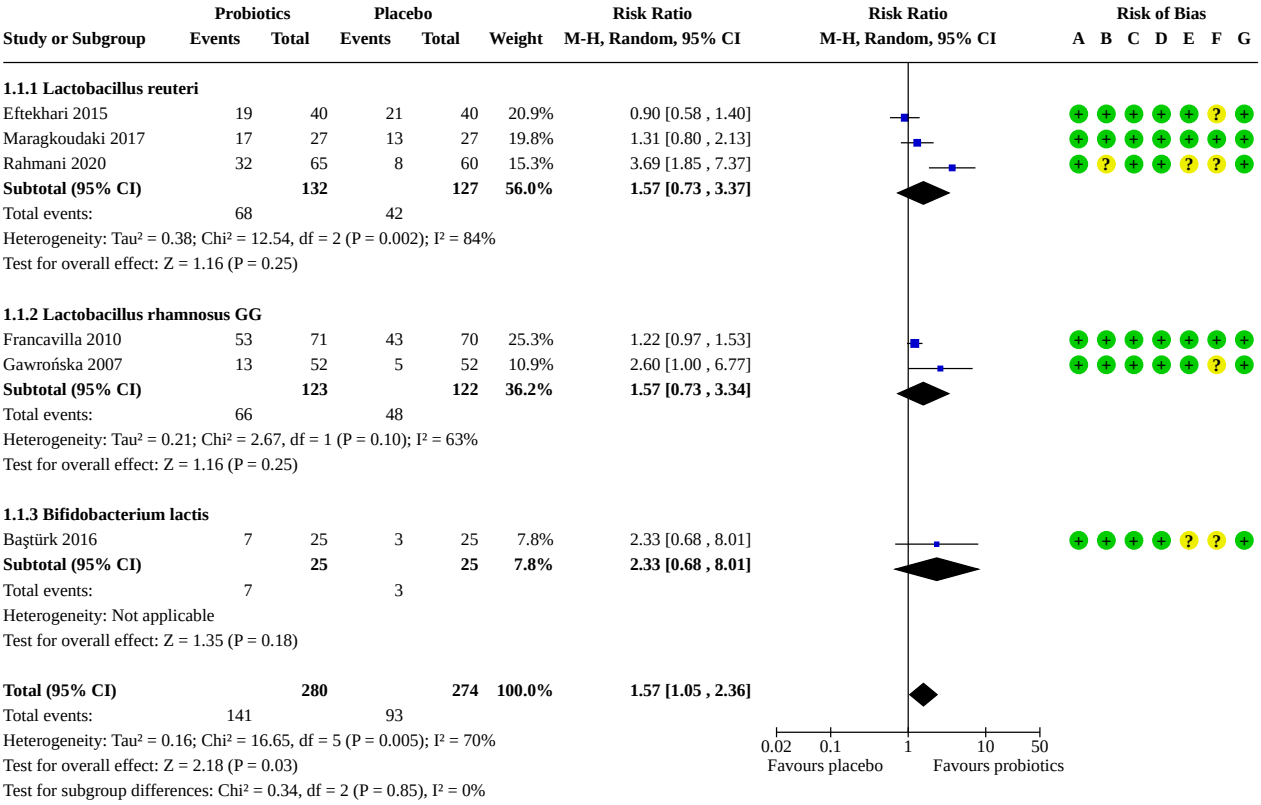
Comparison 1. Probiotic versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Treatment success	6	554	Risk Ratio (M-H, Random, 95% CI)	1.57 [1.05, 2.36]
1.1.1 Lactobacillus reuteri	3	259	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.73, 3.37]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1.2 Lactobacillus rhamnosus GG	2	245	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.73, 3.34]
1.1.3 Bifidobacterium lactis	1	50	Risk Ratio (M-H, Random, 95% CI)	2.33 [0.68, 8.01]
1.2 Treatment success (sensitivity analysis: fixed-effect model)	6	554	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.23, 1.80]
1.2.1 Lactobacillus reuteri	3	259	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.17, 2.12]
1.2.2 Lactobacillus rhamnosus GG	2	245	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.07, 1.72]
1.2.3 Bifidobacterium lactis	1	50	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [0.68, 8.01]
1.3 Complete resolution of pain	6	460	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.94, 2.56]
1.3.1 Lactobacillus reuteri	4	306	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.76, 2.41]
1.3.2 Lactobacillus rhamnosus GG	1	104	Risk Ratio (M-H, Random, 95% CI)	2.60 [1.00, 6.77]
1.3.3 Bifidobacterium lactis	1	50	Risk Ratio (M-H, Random, 95% CI)	2.33 [0.68, 8.01]
1.4 Complete resolution of pain (sensitivity analysis: risk of bias)	5	335	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.84, 1.67]
1.4.1 Lactobacillus reuteri	3	181	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.76, 1.34]
1.4.2 Lactobacillus rhamnosus GG	1	104	Risk Ratio (M-H, Random, 95% CI)	2.60 [1.00, 6.77]
1.4.3 Bifidobacterium lactis	1	50	Risk Ratio (M-H, Random, 95% CI)	2.33 [0.68, 8.01]
1.5 Severity of pain	7	665	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.67, 0.12]
1.5.1 Faces scales	6	524	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-0.61, 0.23]
1.5.2 Combination VAS-Faces scale	1	141	Std. Mean Difference (IV, Random, 95% CI)	-0.76 [-1.10, -0.41]
1.6 Frequency of pain (episodes per week)	6	605	Mean Difference (IV, Random, 95% CI)	-0.43 [-0.92, 0.07]
1.6.1 Lactobacillus reuteri	4	360	Mean Difference (IV, Random, 95% CI)	-0.43 [-1.42, 0.56]
1.6.2 Lactobacillus rhamnosus GG	2	245	Mean Difference (IV, Random, 95% CI)	-0.57 [-0.81, -0.33]
1.7 Frequency of pain (episodes per week) (sensitivity analysis: risk of bias)	4	400	Mean Difference (IV, Random, 95% CI)	-0.58 [-0.81, -0.35]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.1 Lactobacillus reuteri	2	155	Mean Difference (IV, Random, 95% CI)	-0.12 [-2.80, 2.55]
1.7.2 Lactobacillus rhamnosus GG	2	245	Mean Difference (IV, Random, 95% CI)	-0.57 [-0.81, -0.33]
1.8 Withdrawals due to adverse events	8	544	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.07, 15.12]
1.8.1 Lactobacillus reuteri	6	390	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.8.2 Lactobacillus rhamnosus GG	1	104	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.8.3 Bifidobacterium lactis	1	50	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.07, 15.12]
1.9 Adverse events	7	489	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.07, 15.12]
1.9.1 Lactobacillus reuteri	5	335	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.9.2 Lactobacillus rhamnosus GG	1	104	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.9.3 Bifidobacterium lactis	1	50	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.07, 15.12]

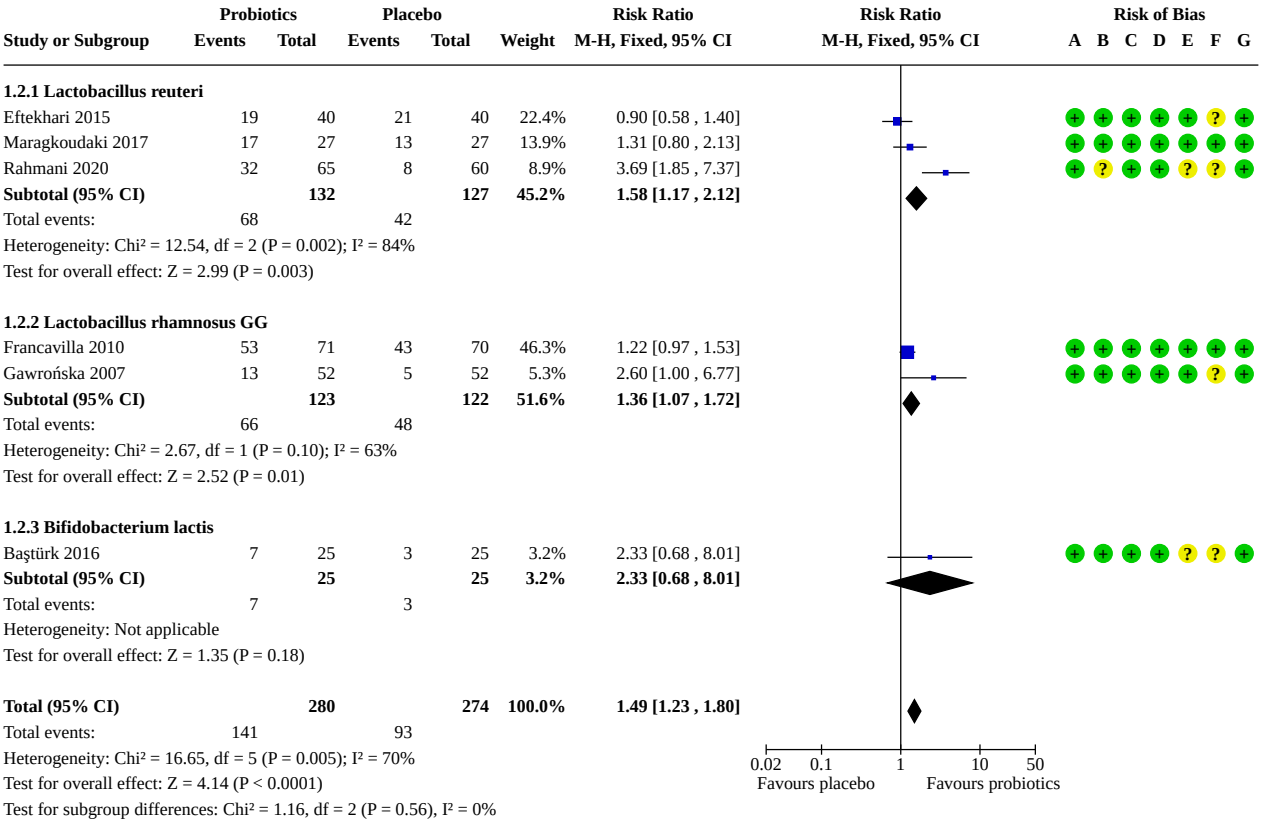
Analysis 1.1. Comparison 1: Probiotic versus placebo, Outcome 1: Treatment success



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

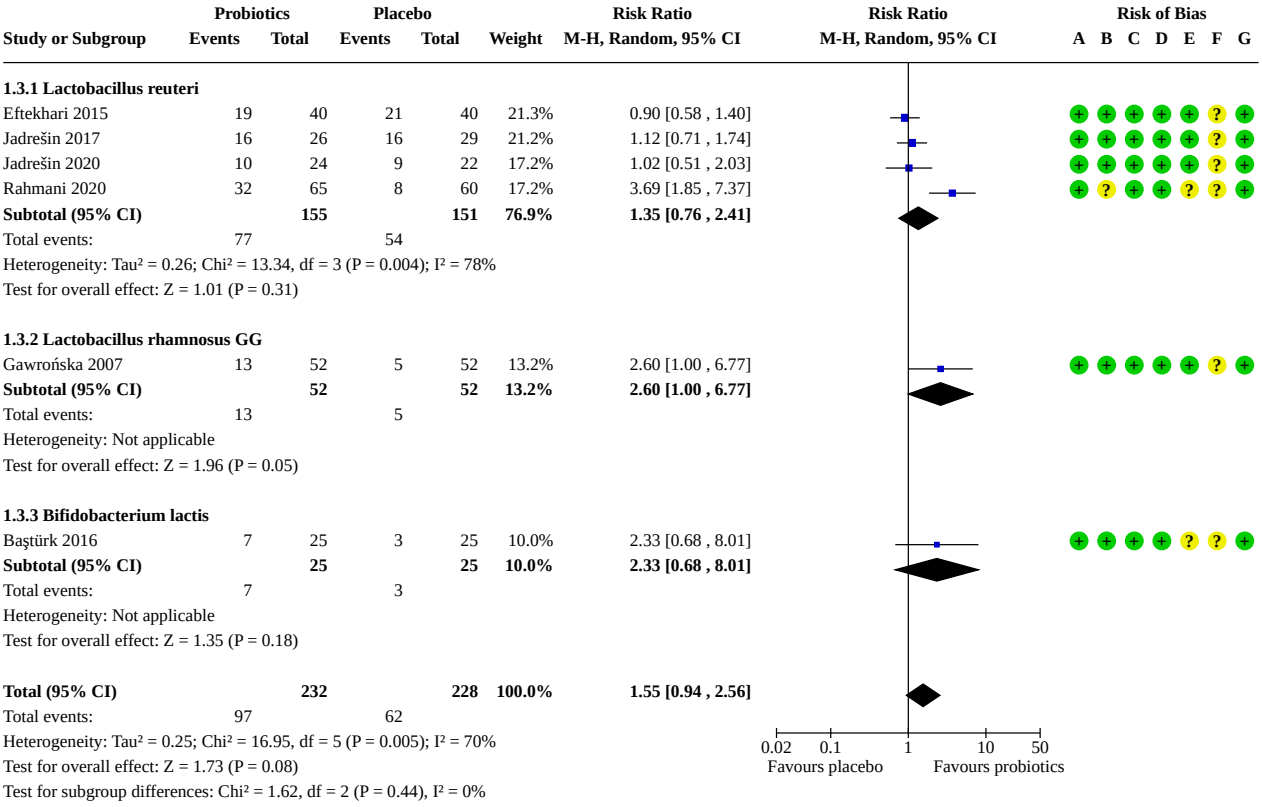
Analysis 1.2. Comparison 1: Probiotic versus placebo, Outcome 2: Treatment success (sensitivity analysis: fixed-effect model)



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

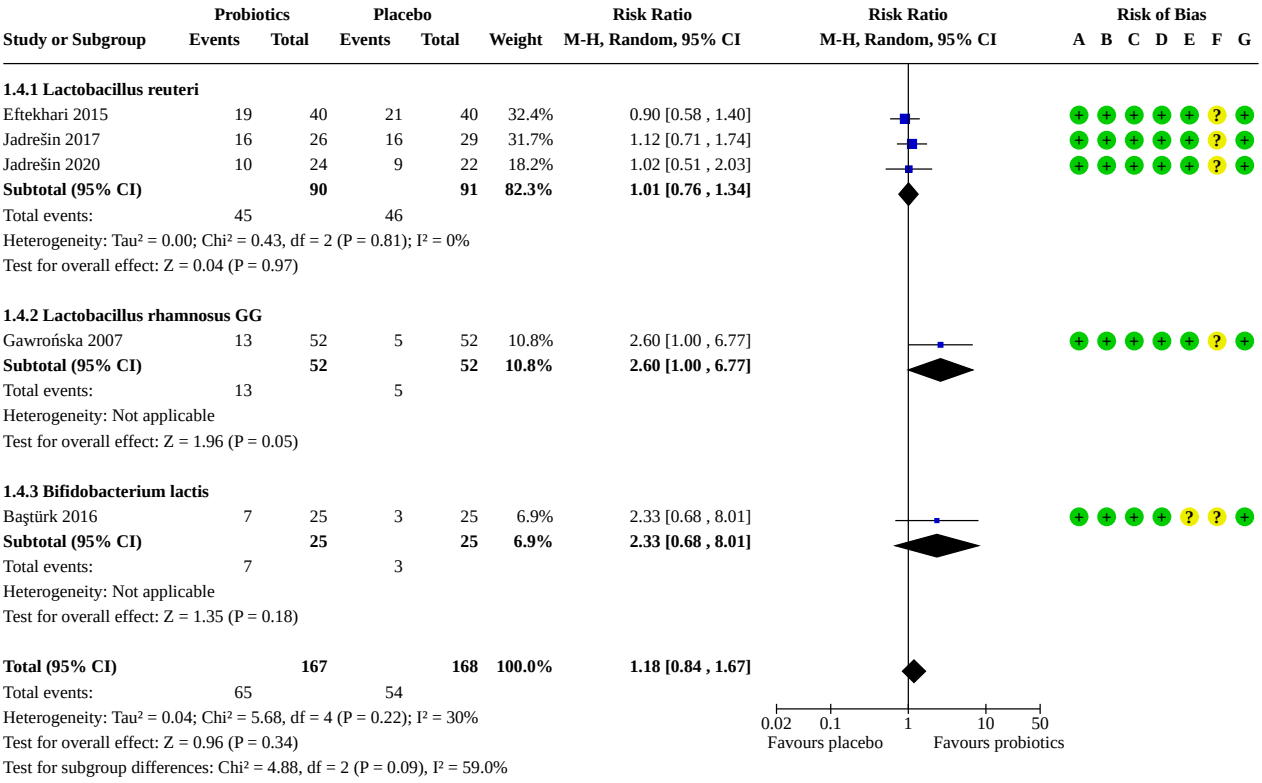
Analysis 1.3. Comparison 1: Probiotic versus placebo, Outcome 3: Complete resolution of pain



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.4. Comparison 1: Probiotic versus placebo, Outcome 4: Complete resolution of pain (sensitivity analysis: risk of bias)

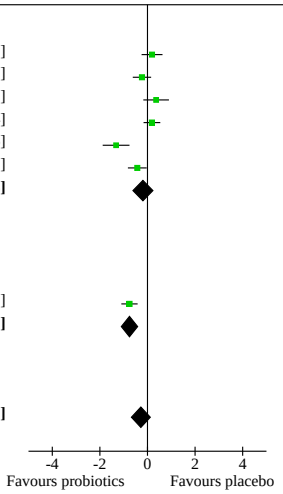


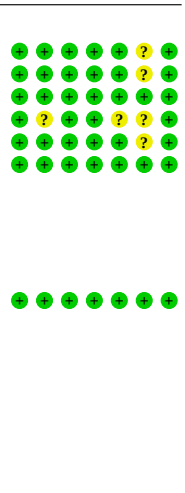
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.5. Comparison 1: Probiotic versus placebo, Outcome 5: Severity of pain

Study or Subgroup	Probiotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.5.1 Faces scales								
Eftekhari 2015	2.53	1.43	40	2.25	1.46	40	14.2%	0.19 [-0.25 , 0.63]
Gawrońska 2007	2.5	1.9	52	2.9	1.5	52	14.8%	-0.23 [-0.62 , 0.15]
Maragkoudaki 2017	7.2	17.7	27	2.5	3.4	27	13.1%	0.36 [-0.17 , 0.90]
Rahmani 2020	1.3	1.1	65	1	2	60	15.2%	0.19 [-0.16 , 0.54]
Romano 2014	1	0.7	32	2	0.8	28	12.8%	-1.32 [-1.88 , -0.76]
Weizman 2016	4.8	3.3	52	6.4	4.1	49	14.7%	-0.43 [-0.82 , -0.03]
Subtotal (95% CI)			**268**			**256**	**84.7%**	**-0.19 [-0.61 , 0.23]**
Heterogeneity: Tau² = 0.22; Chi² = 27.99, df = 5 (P < 0.0001); I² = 82%								
Test for overall effect: Z = 0.90 (P = 0.37)								
1.5.2 Combination VAS-Faces scale								
Francavilla 2010	0.9	0.5	71	1.5	1	70	15.3%	-0.76 [-1.10 , -0.41]
Subtotal (95% CI)			**71**			**70**	**15.3%**	**-0.76 [-1.10 , -0.41]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.33 (P < 0.0001)								
Total (95% CI)			**339**			**326**	**100.0%**	**-0.28 [-0.67 , 0.12]**
Heterogeneity: Tau² = 0.24; Chi² = 37.82, df = 6 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 1.38 (P = 0.17)								
Test for subgroup differences: Chi² = 4.19, df = 1 (P = 0.04), I² = 76.2%								

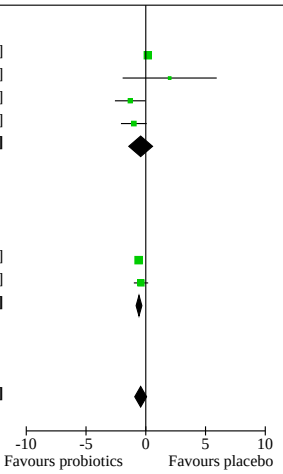


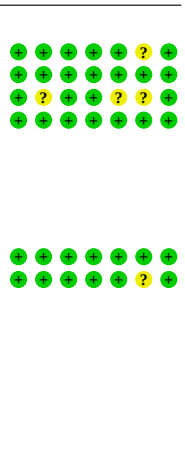


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.6. Comparison 1: Probiotic versus placebo, Outcome 6: Frequency of pain (episodes per week)

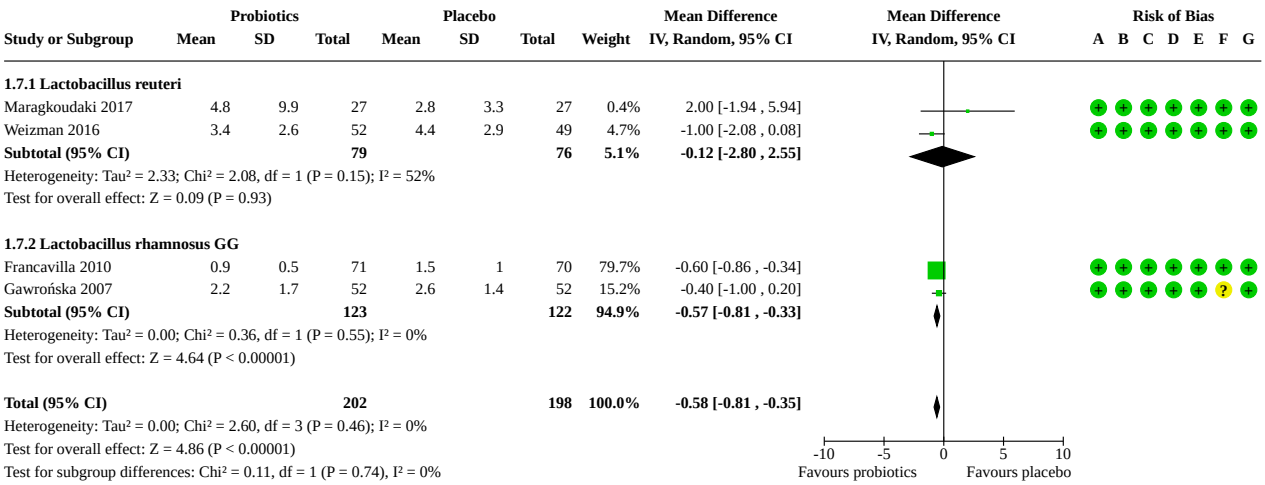
Study or Subgroup	Probiotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.6.1 Lactobacillus reuteri								
Eftekhari 2015	0.7	0.75	40	0.53	0.59	40	27.3%	0.17 [-0.13 , 0.47]
Maragkoudaki 2017	4.8	9.9	27	2.8	3.3	27	1.5%	2.00 [-1.94 , 5.94]
Rahmani 2020	3.6	2.2	65	4.9	4.6	60	10.0%	-1.30 [-2.58 , -0.02]
Weizman 2016	3.4	2.6	52	4.4	2.9	49	12.4%	-1.00 [-2.08 , 0.08]
Subtotal (95% CI)			**184**			**176**	**51.2%**	**-0.43 [-1.42 , 0.56]**
Heterogeneity: Tau² = 0.60; Chi² = 9.48, df = 3 (P = 0.02); I² = 68%								
Test for overall effect: Z = 0.84 (P = 0.40)								
1.6.2 Lactobacillus rhamnosus GG								
Francavilla 2010	0.9	0.5	71	1.5	1	70	27.9%	-0.60 [-0.86 , -0.34]
Gawrońska 2007	2.2	1.7	52	2.6	1.4	52	20.9%	-0.40 [-1.00 , 0.20]
Subtotal (95% CI)			**123**			**122**	**48.8%**	**-0.57 [-0.81 , -0.33]**
Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 1 (P = 0.55); I² = 0%								
Test for overall effect: Z = 4.64 (P < 0.00001)								
Total (95% CI)			**307**			**298**	**100.0%**	**-0.43 [-0.92 , 0.07]**
Heterogeneity: Tau² = 0.21; Chi² = 20.13, df = 5 (P = 0.001); I² = 75%								
Test for overall effect: Z = 1.70 (P = 0.09)								
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%								





Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.7. Comparison 1: Probiotic versus placebo, Outcome 7: Frequency of pain (episodes per week) (sensitivity analysis: risk of bias)

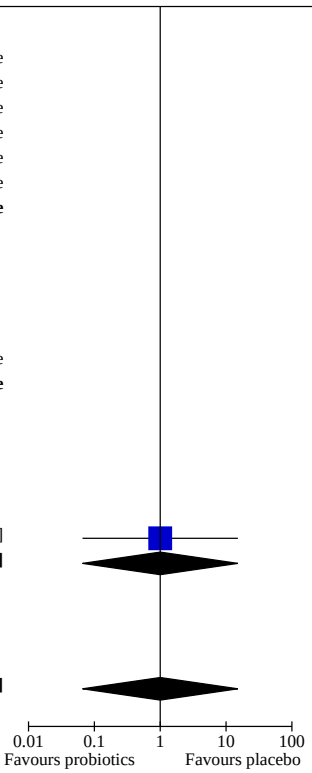


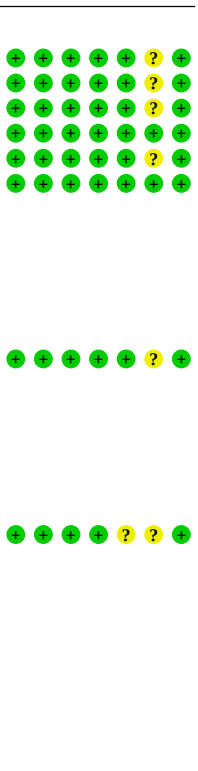
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.8. Comparison 1: Probiotic versus placebo, Outcome 8: Withdrawals due to adverse events

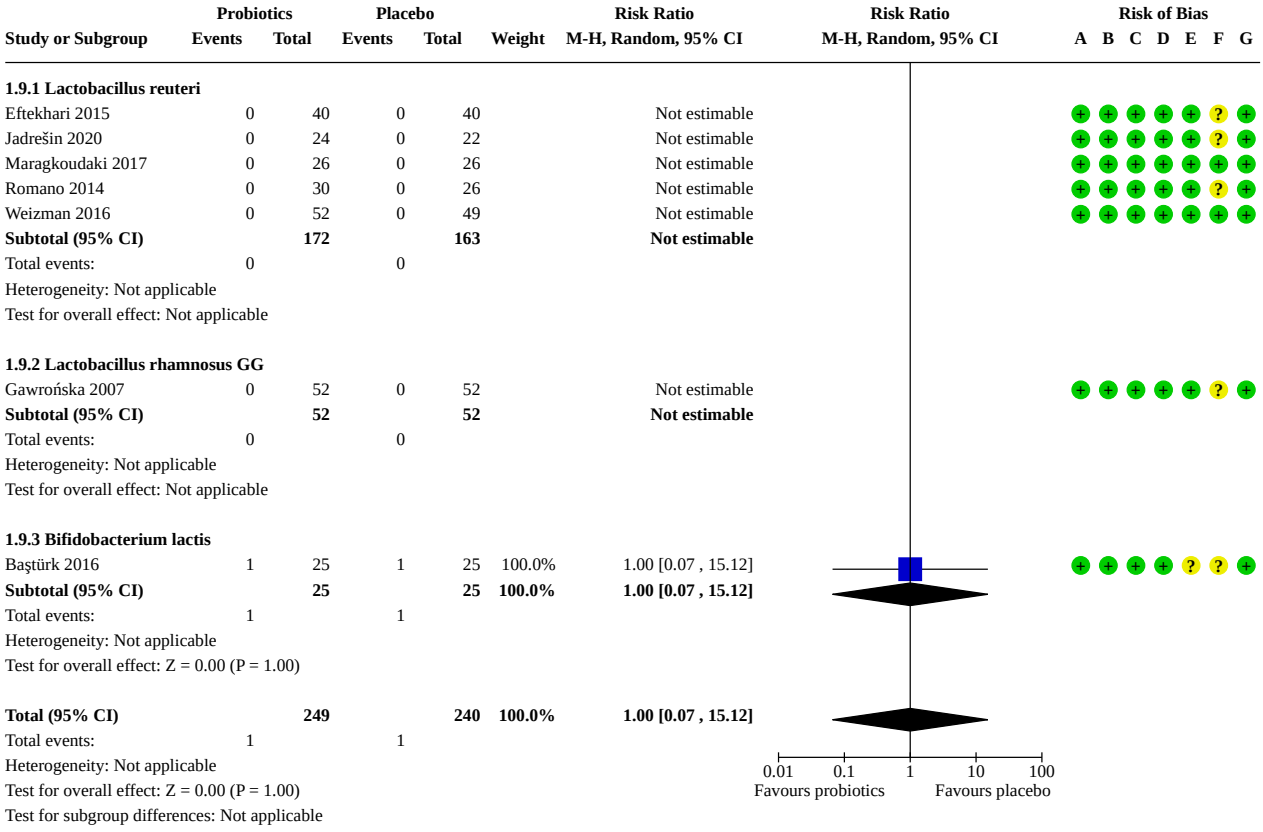
Study or Subgroup	Probiotic Events	Probiotic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Lactobacillus reuteri						
Eftekhari 2015	0	40	0	40		Not estimable
Jadrešin 2017	0	26	0	29		Not estimable
Jadrešin 2020	0	24	0	22		Not estimable
Maragkoudaki 2017	0	26	0	26		Not estimable
Romano 2014	0	30	0	26		Not estimable
Weizman 2016	0	52	0	49		Not estimable
Subtotal (95% CI)		**198**		**192**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.8.2 Lactobacillus rhamnosus GG						
Gawrońska 2007	0	52	0	52		Not estimable
Subtotal (95% CI)		**52**		**52**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.8.3 Bifidobacterium lactis						
Baştürk 2016	1	25	1	25	100.0%	1.00 [0.07 , 15.12]
Subtotal (95% CI)		**25**		**25**	**100.0%**	**1.00 [0.07 , 15.12]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**275**		**269**	**100.0%**	**1.00 [0.07 , 15.12]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Not applicable						





Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.9. Comparison 1: Probiotic versus placebo, Outcome 9: Adverse events



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2. Synbiotics versus placebo

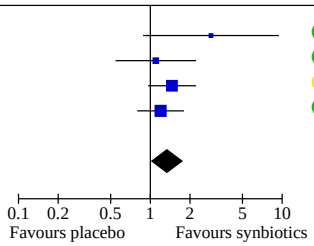
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Treatment success	4	310	Risk Ratio (M-H, Random, 95% CI)	1.34 [1.03, 1.74]
2.2 Treatment success (sensitivity analysis: fixed-effect model)	4	310	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.04, 1.77]
2.3 Treatment success (sensitivity analysis: risk of bias)	3	230	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.88, 1.82]
2.4 Complete resolution of pain	2	131	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.97, 2.81]
2.5 Complete resolution of pain (sensitivity analysis: risk of bias)	1	51	Risk Ratio (M-H, Random, 95% CI)	2.88 [0.88, 9.44]

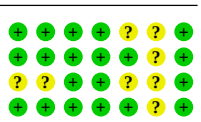
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.6 Severity of pain	4	319	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.78, 0.37]
2.6.1 Likert scales	2	124	Mean Difference (IV, Random, 95% CI)	-0.13 [-1.21, 0.94]
2.6.2 Faces scales	1	115	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.81, 0.21]
2.6.3 Visual analogue scales	1	80	Mean Difference (IV, Random, 95% CI)	-0.31 [-0.84, 0.22]
2.7 Frequency of pain (episodes per week)	1	80	Mean Difference (IV, Random, 95% CI)	-1.26 [-1.77, -0.75]
2.8 Withdrawals due to adverse events	4	302	Risk Ratio (M-H, Random, 95% CI)	4.58 [0.80, 26.19]
2.9 Adverse events	3	189	Risk Ratio (M-H, Random, 95% CI)	2.88 [0.32, 25.92]

Analysis 2.1. Comparison 2: Synbiotics versus placebo, Outcome 1: Treatment success

Study or Subgroup	Synbiotics Events	Synbiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Başţürk 2016	9	26	3	25	4.9%	2.88 [0.88 , 9.44]
Bauserman 2005	11	32	10	32	14.0%	1.10 [0.54 , 2.22]
Otuzbir 2016	25	39	18	41	39.5%	1.46 [0.96 , 2.22]
Saneian 2015	29	59	23	56	41.6%	1.20 [0.80 , 1.80]
Total (95% CI)		**156**		**154**	**100.0%**	**1.34 [1.03 , 1.74]**
Total events:	74		54			

Heterogeneity: Tau² = 0.00; Chi² = 2.38, df = 3 (P = 0.50); I² = 0%
Test for overall effect: Z = 2.16 (P = 0.03)
Test for subgroup differences: Not applicable



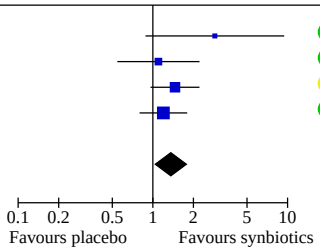


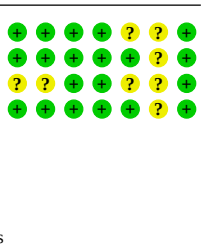
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.2. Comparison 2: Synbiotics versus placebo, Outcome 2: Treatment success (sensitivity analysis: fixed-effect model)

Study or Subgroup	Synbiotics Events	Synbiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Baştürk 2016	9	26	3	25	5.6%	2.88 [0.88 , 9.44]
Bauserman 2005	11	32	10	32	18.4%	1.10 [0.54 , 2.22]
Otuzbir 2016	25	39	18	41	32.4%	1.46 [0.96 , 2.22]
Saneian 2015	29	59	23	56	43.5%	1.20 [0.80 , 1.80]
Total (95% CI)		**156**		**154**	**100.0%**	**1.36 [1.04 , 1.77]**
Total events:	74		54			

Heterogeneity: Chi² = 2.38, df = 3 (P = 0.50); I² = 0%
Test for overall effect: Z = 2.27 (P = 0.02)
Test for subgroup differences: Not applicable



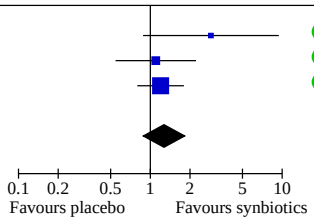


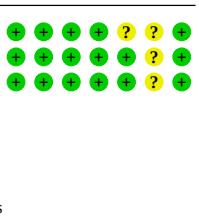
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.3. Comparison 2: Synbiotics versus placebo, Outcome 3: Treatment success (sensitivity analysis: risk of bias)

Study or Subgroup	Synbiotics Events	Synbiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Baştürk 2016	9	26	3	25	9.1%	2.88 [0.88 , 9.44]
Bauserman 2005	11	32	10	32	24.9%	1.10 [0.54 , 2.22]
Saneian 2015	29	59	23	56	66.0%	1.20 [0.80 , 1.80]
Total (95% CI)		**117**		**113**	**100.0%**	**1.27 [0.88 , 1.82]**
Total events:	49		36			

Heterogeneity: Tau² = 0.01; Chi² = 2.13, df = 2 (P = 0.34); I² = 6%
Test for overall effect: Z = 1.29 (P = 0.20)
Test for subgroup differences: Not applicable



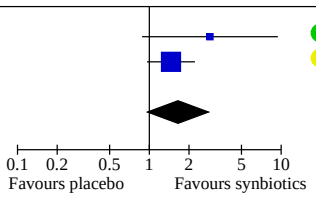


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.4. Comparison 2: Synbiotics versus placebo, Outcome 4: Complete resolution of pain

Study or Subgroup	Synbiotics Events	Synbiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Baştürk 2016	9	26	3	25	18.0%	2.88 [0.88 , 9.44]
Otuzbir 2016	25	39	18	41	82.0%	1.46 [0.96 , 2.22]
Total (95% CI)		**65**		**66**	**100.0%**	**1.65 [0.97 , 2.81]**
Total events:	34		21			

Heterogeneity: Tau² = 0.04; Chi² = 1.22, df = 1 (P = 0.27); I² = 18%
Test for overall effect: Z = 1.84 (P = 0.07)
Test for subgroup differences: Not applicable

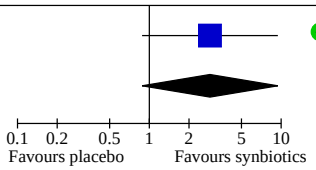


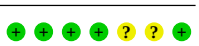
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.5. Comparison 2: Synbiotics versus placebo, Outcome 5: Complete resolution of pain (sensitivity analysis: risk of bias)

Study or Subgroup	Synbiotics Events	Synbiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Baştürk 2016	9	26	3	25	100.0%	2.88 [0.88 , 9.44]
Total (95% CI)		**26**		**25**	**100.0%**	**2.88 [0.88 , 9.44]**
Total events:	9		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.75 (P = 0.08)
Test for subgroup differences: Not applicable

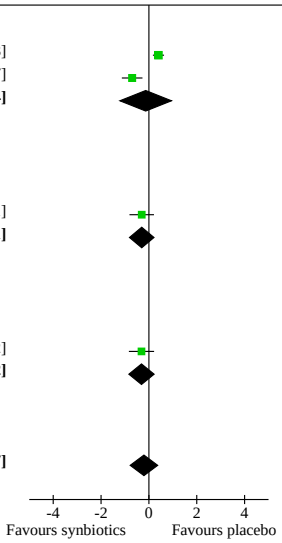


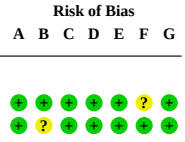


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.6. Comparison 2: Synbiotics versus placebo, Outcome 6: Severity of pain

Study or Subgroup	Synbiotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.6.1 Likert scales								
Bauserman 2005	-1.3	0.3	32	-1.7	0.6	32	27.8%	0.40 [0.17 , 0.63]
Kianifar 2015	0.8	0.9	30	1.5	0.8	30	25.1%	-0.70 [-1.13 , -0.27]
Subtotal (95% CI)			**62**			**62**	**52.9%**	**-0.13 [-1.21 , 0.94]**
Heterogeneity: Tau² = 0.57; Chi² = 19.39, df = 1 (P < 0.0001); I² = 95%								
Test for overall effect: Z = 0.24 (P = 0.81)								
2.6.2 Faces scales								
Saneian 2015	-2.1	1.4	59	-1.8	1.4	56	23.7%	-0.30 [-0.81 , 0.21]
Subtotal (95% CI)			**59**			**56**	**23.7%**	**-0.30 [-0.81 , 0.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.15 (P = 0.25)								
2.6.3 Visual analogue scales								
Asgarshirazi 2015	3.93	1.06	40	4.24	1.33	40	23.4%	-0.31 [-0.84 , 0.22]
Subtotal (95% CI)			**40**			**40**	**23.4%**	**-0.31 [-0.84 , 0.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.15 (P = 0.25)								
Total (95% CI)			**161**			**158**	**100.0%**	**-0.21 [-0.78 , 0.37]**
Heterogeneity: Tau² = 0.29; Chi² = 23.93, df = 3 (P < 0.0001); I² = 87%								
Test for overall effect: Z = 0.71 (P = 0.48)								
Test for subgroup differences: Chi² = 0.09, df = 2 (P = 0.96), I² = 0%								

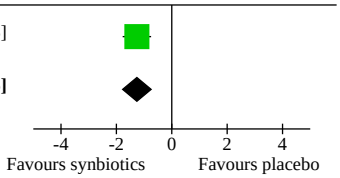




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.7. Comparison 2: Synbiotics versus placebo, Outcome 7: Frequency of pain (episodes per week)

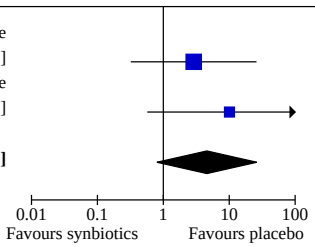
Study or Subgroup	Probiotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Asgarshirazi 2015	2.14	0.87	40	3.4	1.41	40	100.0%	-1.26 [-1.77 , -0.75]
Total (95% CI)			**40**			**40**	**100.0%**	**-1.26 [-1.77 , -0.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.81 (P < 0.00001)								
Test for subgroup differences: Not applicable								



Analysis 2.8. Comparison 2: Synbiotics versus placebo, Outcome 8: Withdrawals due to adverse events

Study or Subgroup	Synbiotics Events	Synbiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Asgarshirazi 2015	0	40	0	40		Not estimable
Baştürk 2016	3	26	1	25	63.1%	2.88 [0.32 , 25.92]
Bauserman 2005	0	30	0	28		Not estimable
Saneian 2015	5	59	0	54	36.9%	10.08 [0.57 , 178.17]
Total (95% CI)		**155**		**147**	**100.0%**	**4.58 [0.80 , 26.19]**
Total events:	8		1			

Heterogeneity: Tau² = 0.00; Chi² = 0.49, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.71 (P = 0.09)
Test for subgroup differences: Not applicable

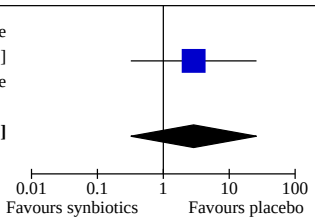


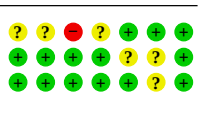
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.9. Comparison 2: Synbiotics versus placebo, Outcome 9: Adverse events

Study or Subgroup	Synbiotics Events	Synbiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Asgarshirazi 2015	0	40	0	40		Not estimable
Baştürk 2016	3	26	1	25	100.0%	2.88 [0.32 , 25.92]
Bauserman 2005	0	30	0	28		Not estimable
Total (95% CI)		**96**		**93**	**100.0%**	**2.88 [0.32 , 25.92]**
Total events:	3		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.95 (P = 0.34)
Test for subgroup differences: Not applicable





Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

ADDITIONAL TABLES

Table 1. Characteristics of included studies: interventions and trial registration

Study ID	Interventional agent	Dosage (amount and frequency)	Control	Dosage (amount and frequency)	Trial registered(prospective/retrospective/none)	Trial registry outcomes published?	Conflicts of interest
Asgarshirazi 2015	Synbiotic group: *Bifidobacterium coagulans* + fructo-oligosaccharide	150 million spores of *Bifidobacterium coagulans* + fructo-oligosaccharide twice daily	Peppermint group: peppermint oil (Colpermin) Placebo group: folic acid	Peppermint group: 187 mg 3 times daily Placebo group: 1 mg once daily	Prospective	Yes	None declared
Baştürk 2016	Synbiotic group: *Bifidobacterium lactis* B94 + inulin	5×10^9 CFU *Bifidobacterium lactis* 900 mg inulin twice daily	Probiotic group: *Bifidobacterium lactis* Prebiotic group: inulin	Probiotic group: 5×10^9 CFU twice daily Prebiotic group: 900 mg twice daily	None	NA	None declared, no financial support received
Bauserman 2005	Synbiotic group: *Lactobacillus* GG + inulin	1×10^{10} bacteria/capsule twice daily	Prebiotic group: inulin	Dose unstated (1 capsule twice daily)	None	NA	None declared
Eftekhari 2015	Probiotic group: *Lactobacillus reuteri*	1×10^8 CFU (5 drops per day)	Placebo group: unidentified placebo	Unstated	Retrospective	Yes	None declared, financial support from Zanjan University of Medical Sciences
Francavilla 2010	Probiotic group: *Lactobacillus rhamnosus* GG	3×10^9 CFU twice daily	Placebo group: inert powder	Unstated dose twice daily	Retrospective	Yes	None declared, no financial support received

Table 1. Characteristics of included studies: interventions and trial registration *(Continued)*

Gawrońska 2007	Probiotic group: *Lactobacillus rhamnosus* GG	3 x 10^9 CFU twice daily	Placebo group: powder	Unstated dose twice daily	None	NA	None declared, financial support from the Medical University of Warsaw
Giannetti 2017 (crossover)	Probiotic group: *Bifidobacterium longum* BB536/ *Bifidobacterium infantis* M-63/*Bifidobacterium breve* M-16V	1 sachet daily (3 billion/1 billion/1 billion per bacterium)	Placebo group: unidentified placebo	Unstated (1 sachet daily)	Retrospective	Yes	None declared
Guandalini 2010 (crossover)	Probiotic group: a patented probiotic preparation, which contains live, freeze-dried lactic acid bacteria, at a total concentration of 450 billion lactic acid bacteria per sachet, comprising 8 different strains: *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus bulgaris* and *Streptococcus thermophilus*	1 sachet once daily if 4 to 11 years old or twice daily if 12 to 18 years old	Placebo group: unidentified placebo	1 sachet once daily if 4 to 11 years old or twice daily if 12 to 18 years old)	None	NA	None declared, funding from locally available grants; no industry support other than providing probiotic and placebo products
Jadrešin 2017	Probiotic group: *Lactobacillus reuteri* DSM 17938 (tablet also containing isomalt, xylitol, sucrose distearate, hydrogenated palm oil, lemon-lime flavouring and citric acid)	1 x 10^8 CFU once daily (1 x 450 mg chewable tablet)	Placebo group: tablet containing isomalt, xylitol, sucrose distearate, hydrogenated palm oil, lemon-lime flavouring and citric acid	Once daily (1 x 450 mg chewable tablet)	Prospective	Yes	None declared, no industry support other than providing probiotic and placebo products
Jadrešin 2020	Probiotic group: *Lactobacillus reuteri* DSM 17938 (tablet also containing isomalt, xylitol, sucrose distearate, hydrogenated palm oil, lemon-lime flavouring and citric acid)	1 x 10^8 CFU once daily (1 x 450 mg chewable tablet)	Placebo group: tablet containing isomalt, xylitol, sucrose distearate, hydrogenated palm oil, lemon-lime flavouring and citric acid	Once daily (one x 450 mg chewable tablet)	Prospective	Yes	Three contributing authors (Iva Hojsak, Sanja Kolacek, Zrinjka Misak) received either payment/honoraria for lectures or consultation, travel grants or lecture fees from several industry sources. All other au-

Table 1. Characteristics of included studies: interventions and trial registration *(Continued)*

							thors declare no conflict of interest.
Kianifar 2015	Synbiotic group: *Lactobacillus* GG + inulin	1 x 10^{10} CFU capsule twice daily	Prebiotic group: inulin	Unstated dose (1 capsule twice daily)	Prospective	Yes	None declared, funding received from Mashhad University of Medical Sciences, Iran
Maragkoudaki 2017	Probiotic group: *Lactobacillus reuteri* DSM 17938	2 x 10^{8} CFU (in the form of 2 chewable tablets once daily)	Placebo group: unidentified placebo	Unstated (2 chewable tablets once daily)	Prospective	Yes	Three contributing authors received research grants from BioGaia, 2 authors have been speakers for Biogaia and the remaining author had no conflicts to declare
Otuzbir 2016	Synbiotic group	Not stated	Placebo group: unidentified	Not stated	None	NA	Abstract only, none declared
Rahmani 2020	Probiotic group: *Lactobacillus reuteri*	1 x 10^{8} CFU twice daily in the form of chewable tables	Placebo group: unidentified	Unstated dose (twice daily in the form of chewable tablets)	None	NA	None declared, funding from research centre
Romano 2014	Probiotic group: *Lactobacillus reuteri* DSM 17938 (product also containing sunflower oil, medium-chain triglyceride oil from coconut oil)	1 x 10^{8} CFU twice daily in the form of a 10 mL bottle	Placebo group: product containing sunflower oil, medium-chain triglyceride oil from coconut oil	10 mL bottle twice daily	None	NA	None declared
Sabbi 2012	Probiotics group: *Lactobacillus* GG	Unstated dose	Placebo group: unidentified placebo	Unstated dose	None	NA	Abstract only, none declared
Saneian 2015	Synbiotic group: *Bacillus coagulans* + fructo-oligosaccharide	150 million spores + fructo-oligosaccharides 100 mg twice daily in the form of tablets	Placebo group: unidentified placebo	1 tablet twice daily	Prospective	Yes	None declared, funding from Isfahan University of Medical Sciences

Table 1. Characteristics of included studies: interventions and trial registration *(Continued)*

Weizman 2016	Probiotic group: *Lactobacillus reuteri* DSM 17938	1 x 10^8 CFU once daily in the form of chewable tablet	Placebo group: unidentified placebo	Once daily in the form of chewable tablet	Prospective	Yes	One author (Zvi Weizman) has been a speaker for Biogaia AB which supplied the probiotic. No other conflicts of interest declared, and statement that Biogaia had no role in 'conception, design, and conduct of the study'.

CFU: colony-forming unit
NA: not applicable

Table 2. Characteristics of included studies: participants, outcomes and follow-up

Study ID	Methods of diagnosis	FAPD diagnosis	Separate data per sub-diagnosis reported (yes/no)	Age range	Number of participants	Length of intervention	Time points of outcome measurements
Asgarshirazi 2015	Rome III	FAP/IBS/FD	No	4 to 13	54	1 month	End of intervention
Başẗurk 2016	Rome III	IBS	Not relevant as they only included one	4 to 16	76	4 weeks	End of intervention
Bauserman 2005	Rome II	IBS	Not relevant as they only included one	5 to 17	50	6 weeks	End of intervention
Eftekhari 2015	Rome III	FAP	Not relevant as they only included one	4 to 16	80	4 weeks	End of intervention; 4 weeks after end of intervention
Francavilla 2010	Rome II	FAP/IBS	Yes	5 to 14	136	8 weeks	End of intervention; 8 weeks after end of intervention
Gawrońska 2007	Rome II	FAP/IBS/FD	Yes	6 to 16	104	4 weeks	End of intervention
Giannetti 2017 (cross-over)	Rome III	IBS/FD	Yes	8 to 17	48	2 week run-in period 6 weeks pre-cross-over phase	At the end of each period/phase and data combined at the end per intervention

Table 2. Characteristics of included studies: participants, outcomes and follow-up *(Continued)*

						2 weeks washout 6 weeks post-cross-over phase	
Guandalini 2010 (cross-over)	Rome II	IBS	Not relevant as they only included one	4 to 18	59	2 week run-in period 6 weeks pre-cross-over phase 2 weeks washout 6 weeks post-cross-over phase	Every 2 weeks and data combined at the end per intervention
Jadrešin 2017	Rome III	FAP/IBS	No	4 to 18	55	12 weeks	1 month into intervention; end of intervention; 1 month after end of intervention
Jadrešin 2020	Rome III	FAP/IBS	No	4 to 18	46	12 weeks	1 month into intervention; end of intervention; 1 month after end of intervention
Kianifar 2015	Rome III	IBS	Not relevant as they only included one	4 to 18	52	1 month	Weekly until end of intervention
Maragkoudaki 2017	Rome III	FAP	Not relevant as they only included one	5 to 16	48	4 weeks	At 2 weeks and end of intervention
Otuzbir 2016	Rome III	FAP/FD	No	Not stated	80	8 weeks	End of intervention
Rahmani 2020	Rome III	FAP/IBS/FD/abdominal migraine	Yes	6 to 16	125	4 weeks	At 2 weeks and end of intervention
Romano 2014	Rome III	FAP	Not relevant as they only included one	6 to 16	60	4 weeks	End of intervention; 4 weeks after end of intervention
Sabbi 2012	Unstated	FAP	Not relevant as they only included one	Unstated	61	6 weeks	End of intervention; 4 weeks after end of intervention
Saneian 2015	Rome III	FAP	Not relevant as they only included one	6 to 18	115	4 weeks	End of intervention; 8 weeks after end of intervention

Table 2. Characteristics of included studies: participants, outcomes and follow-up *(Continued)*

Weizman 2016	Rome III	FAP	Not relevant as they only included one	6 to 15	101	4 weeks	End of intervention; 4 weeks after end of intervention

FAP: functional abdominal pain
FAPD: functional abdominal pain disorder
FD: functional dyspepsia
IBS: irritable bowel syndrome

Table 3. Summary of primary outcome data in included studies

Study ID	1a. Global improvement or treatment success	1b. Complete resolution of pain	1c. Severity of pain	1d. Frequency of pain
Asgarshirazi 2015	NR	NR	Intervention group: 3.93 ± 1.06 Control group: 4.24 ± 1.33	Intervention group: 2.14 ± 0.87 Control group: 3.40 ± 1.41
Baştürk 2016	NR	Intervention group 1: 9/26 Intervention group 2: 7/25 Control group: 3/25	NR	NR
Bauserman 2005	Intervention group: 11/32 Control group: 10/32	NR	Change in pain intervention group: -1.3 (± 0.3) Change in pain control group: -1.7 (± 0.6)	NR
Eftekhari 2015	No pain episodes per week, end of first month Intervention group: 20; control group: 26 No pain episodes per week, end of second month Intervention group: 19; control group: 21	NR	End of first month intervention group: mean (SD) 2.50 (1.45); control group: mean (SD) 2.08 (1.56) End of second month intervention group: mean (SD) 2.53 (1.43); control group: mean (SD) 2.25 (1.46)	At first month intervention group: mean (SD) 0.68 (0.76); control group: mean (SD) 0.40 (0.59) At second month intervention group: mean (SD) 0.70 (0.75); control group: mean (SD) 0.53 (0.59)
Francavilla 2010	Decrease of at least 50% in the number of episodes and intensity of pain at 12 weeks Intervention group: 48/69; control group: 37/67 Decrease of at least 50% in the number of episodes and in-	NR	At 12 weeks intervention group: mean (SD) 2.3 (1.3); control group: 3.4 (2.1) At end of follow-up intervention group: mean (SD) 0.9 (0.5); control group: 1.5 (1.0)	Number of episodes per week at 12 weeks intervention group: 1.1 (0.8); control group: 2.2 (1.2) At end of follow-up intervention group: 0.9 (0.5); control group: 1.5 (1.0)

Table 3. Summary of primary outcome data in included studies *(Continued)*

	tensity of pain at end of follow-up Intervention group: 53/69; control group: 43/67			
Gawrońska 2007	NR	Intervention group: 13/52 (FD 1/10, IBS 6/18, FAP 6/24) Control group: 5/52 (FD 2/10, IBS 6/18, FAP 2/23)	At 4 weeks Intervention group: mean 2.5 (SD ± 1.9) (FD 2.9 ± 1.5, IBS 2.2 ± 2.1, FAP 2.6 ± 2.0) Control group: mean 2.9 (SD ± 1.5) (FD 1.9 ± 1.3, IBS 3.2 ± 1.5, FAP 3.0± 1.5)	At 4 weeks Intervention group: mean 2.2 (SD ± 1.7) (FD 2.7 ± 1.3, IBS 1.8 ± 1.7, FAP 2.3 ± 1.8) Control group: mean 2.6 (SD ± 1.4) (FD 2.0 ± 1.6, IBS 3.1 ± 1.1, FAP 2.4 ± 1.4)
Giannetti 2017 (cross-over)	NR	Not clear as the authors have combined pre- and post- cross-over data	Not clear as the authors have combined pre- and post- cross-over data	Not clear as the authors have combined pre- and post- cross-over data
Guandalini 2010 (cross-over)	NR	NR	Not clear as the authors have combined pre- and post- cross-over data	Not clear as the authors have combined pre- and post- cross-over data
Jadrešin 2017	NR	Intervention group: 16/26 Control group: 16/29	End of first month intervention group/ control group: 0.75/0.96 End of second month intervention group/control group: 0.17/0.64 End of third month intervention group/ control group: 0.32/0.71 End of fourth month intervention group/ control group: 0.21/0.6 Difference in the severity of pain between first and fourth month, Wong-Baker FACES/day intervention group: median 0.42 (range 0.31 to 2.9); control group: median 0.23 (range 1.2 to 2.2)	Number of days without pain intervention group at 4 months: 89.5 (range 5 to 108); control group at 4 months: 51 (range 0 to 107)
Jadrešin 2020	NR	Intervention group: 10/24 Control group: 9/22	End of first month intervention group/ control group: 1.35 (IQR 0.64 to 1.98)/1.1 (IQR 0.76 to 2.04) End of second month intervention group/control group: 1.0 (IQR 0.09 to 2.12)/0.8 (IQR 0.37 to 1.68) End of third month intervention group/ control group: 0.83 (IQR 0.025 to 2.26)/0.78 (IQR 0.43 to 2.0)	Number of days without pain intervention group at 4 months: 90 (IQR 54 to 99); control group at 4 months: 59.5 (IQR 21.5 to 89.25)

Table 3. Summary of primary outcome data in included studies *(Continued)*

			End of fourth month intervention group/control group: 0.035 (IQR 0 to 1.0)/0.81 (IQR 0.2 to 1.48) Change in severity of pain from 1st to 4th month intervention group: 0.55 (IQR 0.28 to 0.55); control group: median 0.36 (IQR -0.14 to 0.36)	
Kianifar 2015	NR	NR	1 week: intervention group/control group 1.5 (1.0)/1.8 (0.6) 2 weeks: intervention group/control group 1.2 (1.1)/1.9 (0.8) 3 weeks: intervention group/control group 1.0 (0.9)/1.8 (0.6) 4 weeks: intervention group/control group 0.8 (0.9)/1.5 (0.8)	NR
Maragkoudaki 2017	Reduction in pain score of greater than 50% at 4 weeks intervention group: 19/27 (70.4%); control group: 16/27 (58.3%) Reduction in pain score of greater than 50% at 8 weeks intervention group: 17/25 (65.4%); control group: 13/23 (56.5%)	NR	Intervention group/control group: mean (SD) 2 weeks: 10.4 (18.8)/12.2 (17.3) 4 weeks: 4.3 (8.5)/4.0 (5.6) 8 weeks: 7.2 (17.7)/2.5 (3.4)	Intervention group/control group: mean (SD) 2 weeks: 5.6 (8.1)/8.2 (10.7) 4 weeks: 2.9 (4.5)/3.1 (4.1) 8 weeks: 4.8 (9.9)/2.8 (3.3)
Otuzbir 2016	NR	Intervention group: 25/39 Control group: 18/41	NR	NR
Rahmani 2020	Intervention group = 32/65 (FAP 13/28, FD 11/16, IBS 6/15, AM 2/6) Control group = 8/60 (FAP 8/29, FD 0/13, IBS 0/6, AM, 0/3)	NR (in Rahmani 2020, treatment success was defined as pain intensity = 0)	Text: severity at 4 weeks in intervention group = 1.3 ± 1.1 (Table 1 reports: 1.1 ± 1.3) Text: severity at 4 weeks in control group = 1 ± 2 (Table 1 reports: 2 ± 1) FAP (intervention group/control group): 1.2 ± 1.3; 2 ± 1	Text: frequency of repetitive pain at 4 weeks intervention group 3.6 ± 2.2 (Table 1 reports: intervention group 2.2 ± 3.6) Text: frequency of repetitive pain at 4 weeks control group 4.6 ± 4.9 (Table 1 reports: control group 4.9 ± 4.6)

Table 3. Summary of primary outcome data in included studies *(Continued)*

			FD (intervention group/control group): 0.8 ± 1.5; 2.0 ± 6 IBS (intervention group/control group): 1.4 ± 1.4; 2.8 ± 0.8 AM (intervention group/control group): 1.3 ± 1.5; 2.3 ± 0.5	FAP (intervention group/control group): 2.1 ± 2.7; 4.1 ± 4.4 FD (intervention group/control group): 1.6 ± 3.0; 6.0 ± 5.0 IBS (intervention group/control group): 3.7 ± 5.5; 6.3 ± 0.8 AM (intervention group/control group): 1.1 ± 0.9; 1.3 ± 0.5
Romano 2014	NR	NR	Mean (SD) as we interpreted it from the figures: Week 4 intervention group/control group: 1.25 (0.9)/2 (0.8) Week 8 intervention group/control group: 1 (0.7)/2 (0.8)	Mean (SD) as we interpreted it from the figures: Week 4 intervention group/control group: 1.4 (1.1)/2.2 (0.5) per day Week 8 intervention group/control group: 2.1 (0.6)/2 (0.5) per day
Sabbi 2012	NR	NR	NR	NR
Saneian 2015	Response at week 4 intervention group: 27/45; control group: 17/43 Response at week 12 intervention group: 29/45; control group: 23/43	NR	Change in pain scale from start of intervention to week 4 intervention group: mean -1.7 (SD ± 1.5); control group: mean -1.6 (SD ± 1.5) Change in pain scale from start of intervention to week 12 intervention group: mean -2.1 (SD ± 1.4); control group: mean -1.8 (SD ± 1.4)	NR
Weizman 2016	NR	NR	Improvement in intensity of abdominal pain at 4 weeks intervention group: mean 4.3 (SD ± 2.7); control group: mean 7.2 (SD ± 3.1) Improvement in intensity of abdominal pain at end 8 weeks intervention group: mean 4.8 (SD ± 3.3); control group: mean 6.4 (SD ± 4.1)	Number of episodes of pain per week at 4 weeks intervention group: mean 1.9 (SD ± 0.8); control group: mean 3.6 (SD ± 1.7) Number of episodes of pain per week at 8 weeks intervention group: mean 3.4 (SD ± 2.6); control group: mean 4.4 (SD ± 2.9)

AM: abdominal migraine
FAP: functional abdominal pain
FD: functional dyspepsia
IBS: irritable bowel syndrome
IQR: interquartile range
NR: not reported
SD: standard deviation

Table 4. Summary of secondary outcome data in included studies

Study ID	2a. Serious adverse events	2b. Withdrawal due to adverse events	2c. Adverse events	2d. School performance	2e. Social and psychological functioning	2f. Quality of life
Asgarshirazi 2015	0	0	0	NR	NR	NR
Baştürk 2016	NR	Intervention group 1: 3 Intervention group 2: 1 Control group: 1	Intervention group 1: 3 Intervention group 2: 1 Control group: 1	NR	NR	NR
Bauserman 2005	0	0	0	NR	NR	NR
Eftekhari 2015	0	0	0	NR	NR	NR
Francavilla 2010	NR	NR	NR	NR	NR	NR
Gawrońska 2007	0	0	0	School absenteeism at end of intervention Intervention group: 5/52; control group: 0/52	NR	NR
Giannetti 2017 (cross-over)	0	0	0	NR	NR	NR
Guandalini 2010 (cross-over)	0	0	0	NR	NR	Questionnaire of disruption to family life (change in score) Intervention group: mean -0.9 (SD ± 0.2); control group: mean -0.51 (SD ± 0.3)
Jadrešin 2017	NR	0	NR	NR	NR	NR
Jadrešin 2020	0	0	0	NR	NR	NR
Kianifar 2015	0	0	0	NR	Functional changes on a	NR

Table 4. Summary of secondary outcome data in included studies *(Continued)*

					3 point Likert scale at end of intervention Intervention group: mean 2.4 (SD ± 0.5); control group: mean 1.9 (SD ± 0.4)	
Maragkoudaki 2017	0	0	0	Average number of school absences per week at end of follow-up Intervention group: mean 0.0 (SD ± 0.0); control group: mean 0.11 (SD ± 0.52)	NR	NR
Otuzbir 2016	NR	NR	NR	NR	NR	NR
Rahmani 2020	NR	NR	NR	NR	NR	NR
Romano 2014	0	0	0	NR	NR	NR
Sabbi 2012	NR	NR	NR	NR	NR	NR
Saneian 2015	0	Intervention group: 5; control group:0	NR as numbers of people with adverse events Total number of adverse events intervention group: 45; control group: 43	NR	NR	NR
Weizman 2016	0	0	0	Days of school absenteeism over 4 weeks Intervention group: mean 2.7 (SD ± 0.9); control group: mean 1.9 (SD ± 1.1)	NR	NR

Numbers presented as per the original study reports.
NR: not reported
SD: standard deviation

APPENDICES

Appendix 1. Search strategies

I. CENTRAL (via Ovid)

1. exp Probiotics/
2. (probiotic or probiotics).tw,kw.
3. exp Saccharomyces/
4. (Saccaromyce* or boulardii).tw,kw.
5. exp Lactobacillus/
6. (lactobacil* or Betabacterium or Lactobacteria or lactic acid bacteria or casei or paracasei or rhamnosus or helveticus or acidophilus).tw,kw.
7. exp Bifidobacterium/
8. Bifidobacter*.tw,kw.
9. exp Escherichia coli/
10. (Escherichia coli or "E.Coli" or "E. Coli" or Mutaflor or Colinfant).tw,kw.
11. exp Streptococcus/
12. (Streptococcus or Streptococceae or "VSL#3" or "VSL #3").tw,kw.
13. exp Bacillus/
14. Bacillus.tw,kw.
15. exp Clostridium butyricum/
16. clostridium butyricum.tw,kw.
17. exp Enterococcus/
18. (enterococcus or faecalis).tw,kw.
19. ("Biok+" or Lacidofil or Lactogermine or Pb Probinul or BIfido Triple).tw,kw.
20. (Commensal* or yeast or Fung*).tw,kw.
21. or/1-20
22. (functional gastrointestinal disorder* or FGIDs).tw,kw.
23. exp Irritable Bowel Syndrome/
24. (irritable bowel or irritable colon* or IBS).tw,kw.
25. exp Dyspepsia/
26. (dyspepsia or dyspeptic or indigestive or indigestion or NUD or FD).tw,kw.
27. ((abdominal or abdomen or bowel or stomach or epigastric) adj2 (pain* or migraine* or colic* or discomfort* or ache* or aching or sorrow or soreness)).tw,kw.
28. exp Abdominal Pain/
29. ((abdominal or abdomen) adj migraine*).tw,kw.
30. (functional abdominal or FAP or FAPs or CFAP or CFAPs).tw,kw.
31. or/22-30
32. 21 and 31
33. exp Adolescent/
34. exp Child/
35. exp Infant/
36. exp Minors/
37. exp Pediatrics/
38. exp Puberty/
39. exp Schools/
40. (baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infan* or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).tw,kw.
41. (postmatur* or prematur* or preterm* or preemie or perinat* or boy* or girl* or teen* or minors or prepubescen* or postpubescen* or prepuberty* or pubescen* or puber*).tw,kw.
42. (elementary school* or high school* or highschool* or kinder* or Jugend* or nursery school* or primary school* or secondary school*).tw,kw.
43. (youth* or young or student* or juvenil* or school age* or underage* or schoolchild* or (under* adj age*) or under 16 or under 18).tw,kw.
44. or/33-43
45. 32 and 44

II. MEDLINE (via Ovid)

1. exp Probiotics/

2. (probiotic or probiotics).tw,kw.
3. exp Saccharomyces/
4. (Saccaromyce* or boulardii).tw,kw.
5. exp Lactobacillus/
6. (lactobacil* or Betabacterium or Lactobacteria or lactic acid bacteria or casei or paracasei or rhamnosus or helveticus or acidophilus).tw,kw.
7. exp Bifidobacterium/
8. Bifidobacter*.tw,kw.
9. exp Escherichia coli/
10. (Escherichia coli or "E.Coli" or "E. Coli" or Mutaflor or Colinfant).tw,kw.
11. exp Streptococcus/
12. (Streptococcus or Streptococceae or "VSL#3" or "VSL #3").tw,kw.
13. exp Bacillus/
14. Bacillus.tw,kw.
15. exp Clostridium butyricum/
16. clostridium butyricum.tw,kw.
17. exp Enterococcus/
18. (enterococcus or faecalis).tw,kw.
19. ("Biok+" or Lacidofil or Lactogermine or Pb Probinul or BIfido Triple).tw,kw.
20. (Commensal* or yeast or Fung*).tw,kw.
21. or/1-20
22. (functional gastrointestinal disorder* or FGIDs).tw,kw.
23. exp Irritable Bowel Syndrome/
24. (irritable bowel or irritable colon* or IBS).tw,kw.
25. exp Dyspepsia/
26. (dyspepsia or dyspeptic or indigestive or indigestion or NUD or FD).tw,kw.
27. ((abdominal or abdomen or bowel or stomach or epigastric) adj2 (pain* or migraine* or colic* or discomfort* or ache* or aching or sorrow or soreness)).tw,kw.
28. exp Abdominal Pain/
29. ((abdominal or abdomen) adj migraine*).tw,kw.
30. (functional abdominal or FAP or FAPs or CFAP or CFAPs).tw,kw.
31. or/22-30
32. 21 and 31
33. exp Adolescent/
34. exp Child/
35. exp Infant/
36. exp Minors/
37. exp Pediatrics/
38. exp Puberty/
39. exp Schools/
40. (baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infan* or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).tw,kw.
41. (postmatur* or prematur* or preterm* or preemie or perinat* or boy* or girl* or teen* or minors or prepubescen* or postpubescen* or prepuberty* or pubescen* or puber*).tw,kw.
42. (elementary school* or high school* or highschool* or kinder* or Jugend* or nursery school* or primary school* or secondary school*).tw,kw.
43. (youth* or young or student* or juvenil* or school age* or underage* or schoolchild* or (under* adj age*) or under 16 or under 18).tw,kw.
44. or/33-43
45. 32 and 44
46. randomized controlled trial.pt.
47. controlled clinical trial.pt.
48. randomized.ab.
49. placebo.ab.

50.drug therapy.fs.
51.randomly.ab.
52.trial.ab.
53.groups.ab.
54.or/46-53
55.exp animals/ not humans.sh.
56.54 not 55
57.45 and 56

Note: Lines 46-56. RCT filter “Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format”

III. Embase (via Ovid)

1. exp probiotic agent/
2. (probiotic or probiotics).tw,kw.
3. exp Saccharomyces/
4. (Saccaromyce* or boulardii).tw,kw.
5. exp Lactobacillus/
6. (lactobacil* or Betabacterium or Lactobacteria or lactic acid bacteria or casei or paracasei or rhamnosus or helveticus or acidophilus).tw,kw.
7. exp Bifidobacterium/
8. Bifidobacter*.tw,kw.
9. exp Escherichia coli/
10. (Escherichia coli or "E.Coli" or "E. Coli" or Mutaflor or Colinfant).tw,kw.
11. exp Streptococcus/
12. (Streptococcus or Streptococceae or "VSL#3" or "VSL #3").tw,kw.
13. exp Bacillus/
14. Bacillus.tw,kw.
15. exp Clostridium butyricum/
16. clostridium butyricum.tw,kw.
17. exp enterococcus/
18. (enterococcus or faecalis).tw,kw.
19. ("Biok+" or Lacidofil or Lactogermine or Pb Probinul or BIfido Triple).tw,kw.
20. (Commensal* or yeast or Fung*).tw,kw.
21. or/1-20
22. (functional gastrointestinal disorder* or FGIDs).tw,kw.
23. exp irritable colon/
24. (irritable bowel or irritable colon* or IBS).tw,kw.
25. exp dyspepsia/
26. (dyspepsia or dyspeptic or indigestive or indigestion or NUD or FD).tw,kw.
27. ((abdominal or abdomen or bowel or stomach or epigastric) adj2 (pain* or migraine* or colic* or discomfort* or ache* or aching or sorrow or soreness)).tw,kw.
28. exp abdominal pain/
29. ((abdominal or abdomen) adj migraine*).tw,kw.
30. (functional abdominal or FAP or FAPs or CFAP or CFAPs).tw,kw.
31. or/22-30
32. 21 and 27
33. exp adolescence/ or exp adolescent/
34. exp child/
35. exp newborn/
36. exp kindergarten/
37. exp pediatrics/
38. exp puberty/

39.exp nursery school/ or exp primary school/ or exp middle school/ or exp high school/ or exp school/
40.(baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infan* or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).tw,kw.
41.(postmatur* or prematur* or preterm* or preemie or perinat* or boy* or girl* or teen* or minors or prepubescen* or postpubescen* or prepuberty* or pubescen* or puber*).tw,kw.
42.(elementary school* or high school* or highschool* or kinder* or Jugend* or nursery school* or primary school* or secondary school*).tw,kw.
43.(youth* or young or student* or juvenil* or school age* or underage* or schoolchild* or (under* adj age*) or under 16 or under 18).tw,kw.
44.or/33-43
45.32 and 44
46.random:.tw.
47.placebo:.mp.
48.double-blind:.tw.
49.or/46-48
50.exp animal/ not human.sh.
51.49 not 50
52.45 and 51

Lines 46-49. RCT filter. Hedge Best balance of sensitivity and specificity filter for identifying randomized trials in Embase. https://hiru.mcmaster.ca/hiru/HIRU_Hedges_EMBASE_Strategies.aspx

IV. ClinicalTrials.gov

Advance search:

Condition or disease: functional dyspepsia OR IBS OR Irritable Bowel Syndrome OR abdominal pain OR functional gastrointestinal disease*

Study type: interventional studies (clinical trials)

Age: Child (birth- 17)

Intervention: probiotic OR probiotics

V. WHO ICTRP (https://trialsearch.who.int/)

Advanced search:

Status: All

Condition: (functional dyspepsia OR IBS OR Irritable Bowel Syndrome OR abdominal pain OR functional gastrointestinal disease*) AND (child OR children OR paediatric OR pediatric)

Intervention:probiotic OR probiotics

WHAT'S NEW

Date	Event	Description
22 February 2023	Amended	Author order amended.

HISTORY

Protocol first published: Issue 11, 2017
Review first published: Issue 2, 2023

CONTRIBUTIONS OF AUTHORS

Chris Wallace took the lead in writing the review; performed screening of titles and abstracts, and full-text articles; extracted data and contacted authors; checked the quality of data extraction; analysed and interpreted data; undertook and checked risk of bias assessment;

performed statistical analysis; checked the quality of the statistical analysis; produced the first draft of the review; contributed to writing and editing the review; made an intellectual contribution to the review; approved the final review prior to submission.

Morris Gordon performed screening of titles and abstracts, and full-text articles; extracted data and contacted authors; analysed and interpreted data; checked risk of bias assessment; checked the quality of statistical analysis; contributed to writing and editing the review; made an intellectual contribution to the review; approved the final review prior to submission.

Vassiliki Sinopoulou performed screening of titles and abstracts, and full-text articles; extracted data and contacted authors; checked the quality of data extraction; analysed and interpreted data; undertook and checked risk of bias assessment; performed statistical analysis; checked the quality of the statistical analysis; contributed to writing and editing the review; made an intellectual contribution to the review; approved the final review prior to submission.

Anthony Akobeng initiated and conceptualised the review; supported the analysis; approved the final review prior to submission.

DECLARATIONS OF INTEREST

Chris Wallace: none known.

Morris Gordon: no relevant interests; Co-ordinating Editor, Cochrane Gut.

Vassiliki Sinopoulou: none known.

Anthony K Akobeng: no relevant interests; Physician, Sidra Medicine; Co-ordinating Editor, Cochrane Gut.

SOURCES OF SUPPORT

Internal sources

- None, UK

  There was no internal funding for this review, however three of the authors (CW, MG and VS) are employed by the University of Central Lancashire and part of their post is to carry out Cochrane systematic reviews.

External sources

- None, Other

  None

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the original protocol, we had not specified how we would analyse our data in case of high statistical heterogeneity. We have now clarified that data were not pooled for meta-analysis if a high degree of statistical heterogeneity was detected (I^2 > 75%). In case of a high degree of statistical heterogeneity, we investigated whether this could be explained based on clinical grounds or risk of bias, in which case we planned sensitivity analyses. If we could not find any such reasons for the high statistical heterogeneity we planned to present the results narratively, in detail.

The protocol was written seven years ago, meaning that many parts of it were outdated when work started on this review. Therefore, several updates to the protocol were made a priori, and in accordance with current Cochrane standards. The changes include updating the methodology sections to meet modern Cochrane standards, amending texts for clarity and comprehensiveness, and an updated search strategy.

Another difference is the addition of complete resolution of pain as a primary outcome. Originally, we had considered this would be presented under the outcome global improvement/treatment success, however as it is a clinically relevant outcome with huge importance for patients and their families, we decided to add it as a separate outcome when we found out a number of studies were reporting it as such.

INDEX TERMS

Medical Subject Headings (MeSH)

Abdominal Pain [therapy]; Inulin; *Irritable Bowel Syndrome; *Probiotics [adverse effects]; Treatment Outcome

MeSH check words

Adolescent; Child; Child, Preschool; Humans