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Probiotics for treatment of chronic constipation in children (Review)

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[Intervention Review]

Probiotics for treatment of chronic constipation in children

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A B S T R A C T

Background

Functional constipation is defined as chronic constipation with no identifiable underlying cause. It is a significant cause of morbidity in children, accounting for up to 25% of visits to paediatric gastroenterologists. Probiotic preparations may sufficiently alter the gut microbiome and promote normal gut physiology in a way that helps relieve functional constipation. Several studies have sought to address this hypothesis, as well as the role of probiotics in other functional gut disorders. Therefore, it is important to have a focused review to assess the evidence to date.

Objectives

To evaluate the efficacy and safety of probiotics for the management of chronic constipation without a physical explanation in children.

Search methods

On 28 June 2021, we searched CENTRAL, MEDLINE, Embase, CINAHL, AMED, WHO ICTR, and ClinicalTrials.gov, with no language, date, publication status, or document type limitations.

Selection criteria

We included randomised controlled trials (RCTs) that assessed probiotic preparations (including synbiotics) compared to placebo, no treatment or any other interventional preparation in people aged between 0 and 18 years old with a diagnosis of functional constipation according to consensus criteria (such as Rome IV).

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

We included 14 studies (1127 randomised participants): 12 studies assessed probiotics in the treatment of functional constipation, whilst two studies investigated synbiotic preparations.

Three studies compared probiotics to placebo in relation to the frequency of defecation at study end, but we did not pool them as there was very significant unexplained heterogeneity. Four studies compared probiotics to placebo in relation to treatment success. There may be no difference in global improvement/treatment success (RR 1.29, 95% CI 0.73 to 2.26; 313 participants; low-certainty evidence). Five

studies compared probiotics to placebo in relation to withdrawals due to adverse events, with the pooled effect suggesting there may be no difference (RR 0.64, 95% CI 0.21 to 1.95; 357 participants; low-certainty evidence).

The pooled estimate from three studies that compared probiotics plus an osmotic laxative to osmotic laxative alone found there may be no difference in frequency of defecation (MD -0.01, 95% CI -0.57 to 0.56; 268 participants; low-certainty evidence). Two studies compared probiotics plus an osmotic laxative to osmotic laxative alone in relation to global improvement/treatment success, and found there may be no difference between the treatments (RR 0.95, 95% CI 0.79 to 1.15; 139 participants; low-certainty evidence). Three studies compared probiotics plus osmotic laxative to osmotic laxative alone in relation to withdrawals due to adverse events, but it is unclear if there is a difference between them (RR 2.86, 95% CI 0.12 to 68.35; 268 participants; very low-certainty evidence).

Two studies compared probiotics versus magnesium oxide. It is unclear if there is a difference in frequency of defecation (MD 0.28, 95% CI -0.58 to 1.14; 36 participants), treatment success (RR 1.08, 95% CI 0.74 to 1.57; 36 participants) or withdrawals due to adverse events (RR 0.50, 95% CI 0.05 to 5.04; 77 participants). The certainty of the evidence is very low for these outcomes.

One study assessed the role of a synbiotic preparation in comparison to placebo. There may be higher treatment success in favour of synbiotics compared to placebo (RR 2.32, 95% CI 1.54 to 3.47; 155 participants; low-certainty evidence). The study reported that there were no withdrawals due to adverse effects in either group.

One study assessed a synbiotic plus paraffin compared to paraffin alone. It is uncertain if there is a difference in frequency of defecation (MD 0.74, 95% CI -0.96, 2.44; 66 participants; very low-certainty evidence), or treatment success (RR 0.91, 95% CI 0.71 to 1.17; 66 participants; very low-certainty evidence). The study reported that there were no withdrawals due to adverse effects in either group.

One study compared a synbiotic preparation to paraffin. It is uncertain if there is a difference in frequency of defecation (MD -1.53, 95% CI -3.00, -0.06; 60 participants; very low-certainty evidence) or in treatment success (RR 0.86, 95% CI 0.65, 1.13; 60 participants; very low-certainty evidence). The study reported that there were no withdrawals due to adverse effects in either group.

All secondary outcomes were either not reported or reported in a way that did not allow for analysis.

Authors' conclusions

There is insufficient evidence to conclude whether probiotics are efficacious in successfully treating chronic constipation without a physical explanation in children or changing the frequency of defecation, or whether there is a difference in withdrawals due to adverse events when compared with placebo. There is limited evidence from one study to suggest a synbiotic preparation may be more likely than placebo to lead to treatment success, with no difference in withdrawals due to adverse events.

There is insufficient evidence to draw efficacy or safety conclusions about the use of probiotics in combination with or in comparison to any of the other interventions reported. The majority of the studies that presented data on serious adverse events reported that no events occurred. Two studies did not report this outcome.

Future studies are needed to confirm efficacy, but the research community requires guidance on the best context for probiotics in such studies, considering where they should be best considered in a potential treatment hierarchy and should align with core outcome sets to support future interpretation of findings.

PLAIN LANGUAGE SUMMARY

Probiotics for treatment of chronic constipation in children

What is the aim of this review?

The aim of this Cochrane Review was to find out whether probiotics can be used to treat chronic constipation without a physical explanation in children (aged 0 to 18 years).

We analysed data from 14 studies to answer this question.

Key messages

We were unable to draw conclusions when comparing probiotics to placebo for frequency of defecation in children treated for chronic constipation without a physical explanation. There may be no difference in treatment success between the two groups.

There may not be a difference in frequency of defecation or treatment success when comparing probiotics and laxatives to using laxatives alone.

We were unable to draw conclusions when comparing probiotics to magnesium oxide for frequency of defecation or treatment success.

There may be a higher frequency of defecation in children treated with synbiotic preparations compared to placebo.

There may not be a difference in participants withdrawing from the studies due to adverse events when comparing probiotic preparations to placebo.

We were unable to draw conclusions on the safety of any of the other comparisons due to the low number of people who withdrew from the studies.

What was studied in the review?

Children often suffer from constipation for long periods of time, and when there is no underlying physical cause that can be found we call it 'functional constipation'.

It has been suggested that probiotic and synbiotic preparations might help improve symptoms in these children. Probiotics are preparations that contain living bacteria that have been proposed to be beneficial to the digestive system. Synbiotics also include food substances that support the growth of these bacteria.

There is currently no consensus about whether this is the case, or how these preparations are best used.

What are the main results of the review?

We searched for randomised controlled trials (studies in which participants are assigned to one of two or more treatment groups using a random method) comparing any probiotic or synbiotic treatment with any other treatment (such as dummy/placebo treatments) in children with chronic constipation without a physical explanation. We found 14 trials including a total of 1127 participants who were aged under 18. We made the following conclusions.
• There may be no difference in treatment success when comparing probiotics to placebo.
• We were unable to draw conclusions on whether there is a difference in the frequency of defecation.
• There may be no difference in treatment success when comparing probiotics and laxatives to laxatives alone.
• We were unable to draw conclusions on frequency of defecation or treatment success when comparing probiotics to magnesium oxide.
• Synbiotics may be better than placebo in improving the frequency of defection.
• There may be no difference in how many people withdrew from the trials because of side effects when comparing probiotics to placebo, or probiotics and laxative to laxative alone.
• We have limited confidence in the evidence because the studies only included a small number of children, and due to lack of detail on some of the methods used.

All analyses were limited due to differences in the specific probiotics or the treatments they were compared with, low numbers of children included in the studies and, most importantly, the use of a range of different measures of success. This meant that combining studies was difficult, so the overall ability of this review to answer its core questions was limited.

What next?

Future studies are needed to find out how helpful probiotics are for childhood constipation. Researchers need to agree whether probiotics should be a first option therapy, an add-on to other therapies, a second option after other therapies have failed, or a combination of all the above.

Future research should measure the same items (known as a core outcome set) to ensure these results can support future reviews.

How up-to-date is this review?

This review is current to June 2021.

SUMMARY OF FINDINGS

Summary of findings 1.   Probiotic compared to placebo for treatment of chronic constipation in children

Probiotic compared to placebo for treatment of chronic constipation in children

Patient or population: children with chronic constipation without a physical explanation
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 probiotic**				
Frequency of defecation, stools/week	-	-	Not estimable	280 (3 studies)	-	Very significant inconsistency due to unexplained heterogeneity, so no analysis performed.
Global improvement/treatment success as defined by primary study Follow-up: 3 to 12 weeks	Study population		RR 1.29 (0.73 to 2.26	313 (4 studies)	⊕⊕⊝⊝ Low[a,b]	-
	342 per 1000	441 per 1000 (250 to 773)				
Withdrawals due to adverse events Follow-up: 3 to 12 weeks	Study population		RR 0.64 (0.21 to 1.95)	357 (5 studies)	⊕⊕⊝⊝ Low [c]	-
	40 per 1000	26 per 1000 (8 to 78)				
Serious adverse events	-	-	Not estimable	198 (4 studies)	-	All studies reported 0 serious adverse events

*__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; **RR:** risk ratio

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.

Trusted evidence.
Informed decisions.
Better health.

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 imprecision from low participant numbers.
[b]Downgraded one level due to inconsistency (I^2 = 71%).
[c]Downgraded two levels due to serious imprecision from very low event numbers.

Summary of findings 2.   Probiotics and osmotic laxative compared to osmotic laxative for treatment of chronic constipation in children

Probiotics and osmotic laxative compared to osmotic laxative for treatment of chronic constipation in children

Patient or population: children with chronic constipation without a physical explanation
Setting: outpatient
Intervention: probiotics and osmotic laxative
Comparison: osmotic laxative

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Osmotic laxative	Risk with Probiotics and osmotic laxative				
Frequency of defecation (number of stools/week) Follow-up: 8 to 12 weeks	Mean number of stools per week ranged from 6.3 to 6.9	MD 0.01 lower (0.57 lower to 0.56 higher)	-	268 (3 studies)	⊕⊕⊖⊖ Low [a],[b]	-
Global improvement or treatment success, as defined by primary studies Follow-up: 8 to 12 weeks	Study population		RR 0.95 (0.79 to 1.15)	139 (2 studies)	⊕⊕⊖⊖ Low [a],[b]	-
	739 per 1000	702 per 1000 (584 to 850)				
Withdrawal due to adverse events Follow-up: 8 to 12 weeks	Study population		RR 2.86 (0.12 to 68.35)	268 (3 studies)	⊕⊖⊖⊖ Very low [a],[c]	-
	0 per 1000	0 per 1000 (0 to 0)				
Serious adverse events Follow-up: 8 to 12 weeks	Study population		-	308 (4 studies)	-	All studies reported 0 serious adverse events.
	0 per 1000	0 per 1000 (0 to 0)				

*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

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 risk of bias for allocation concealment and blinding.
[b]Downgraded one level due to imprecision from low participant numbers.
[c]Downgraded two levels due to serious imprecision from low event numbers.

Summary of findings 3.   Probiotics compared to magnesium oxide for treatment of chronic constipation in children

Probiotics compared to magnesium oxide for treatment of chronic constipation in children

Patient or population: children with chronic constipation without a physical explanation
Setting: outpatients
Intervention: probiotics
Comparison: magnesium oxide

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of partici-pants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with magnesium oxide	Risk with probiotics				
Frequency of defecation (number of stools/week) Follow-up: 4 weeks	The mean number of stools per week was 4.75	MD 0.28 higher (0.58 lower to 1.14 higher)	-	36 (1 study)	⊕⊖⊖⊖ Very low [a]	
Global improvement/treatment success, as defined by the primary study Follow-up: 4 weeks	Study population		RR 1.08 (0.74 to 1.57)	36 (1 study)	⊕⊖⊖⊖ Very low [a]	
	722 per 1000	780 per 1000 (534 to 1000)				
Withdrawals due to adverse events Follow-up: 4 weeks	Study population		RR 0.50 (0.05 to 5.04)	77 (2 studies)	⊕⊖⊖⊖ Very low [a]	
	51 per 1000	26 per 1000				

	(3 to 257)				
Serious adverse events	Study population		not estimable	77	-	The studies reported 0 serious adverse events.
Follow-up: 4 weeks	0 per 1000	0 per 1000 (0 to 0)		(2 studies)	

***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; **RR:** risk ratio

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 twice due to high imprecision from very low participant numbers and once more due to risk of bias for allocation concealment

Summary of findings 4. Synbiotics compared to placebo for treatment of chronic constipation in children

Synbiotics compared to placebo for treatment of chronic constipation in children

Patient or population: children with chronic constipation without a physical explanation
Setting: outpatient
Intervention: synbiotics
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 synbiotics				
Frequency of defecation (number of stools/week at end of study)	-	-	-	-	-	-
Global improvement or treatment success, as defined by primary study	Study population		RR 2.32 (1.54 to 3.47)	155 (1 study)	⊕⊕⊝⊝ Low [a]	
Follow-up: 4 weeks	269 per 1000	633 per 1000 (414 to 933)				

Withdrawals due to adverse events Follow-up: 4 weeks	**Study population**		Not estimable	155 (1 study)	-	The study reported 0 withdrawals due to adverse events.
	0 per 1000	0 per 1000 (0 to 0)				
Serious adverse events Follow-up: 4 weeks	**Study population**		Not estimable	155 (1 study)	-	The study reported 0 serious adverse events.
	0 per 1000	0 per 1000 (0 to 0)				

*__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; **RR:** risk ratio

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 two levels due to serious imprecision from low participant numbers

Summary of findings 5.   Synbiotics and paraffin compared to paraffin for treatment of chronic constipation in children

Synbiotics and paraffin compared to paraffin for treatment of chronic constipation in children

Patient or population: children with chronic constipation without a physical explanation
Setting: outpatient
Intervention: synbiotics and paraffin
Comparison: paraffin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with paraffin	**Risk with synbiotics and paraffin**				
Frequency of defecation (number of stools/week) Follow-up: 4 weeks	The mean number of stools per week was 6.75.	MD 0.74 higher (0.96 lower to 2.44 higher)	-	66 (1 study)	⊕⊖⊖⊖ Very low [a, b]	

Global improvement or treatment success, as defined by primary studies	Study population		RR 0.91 (0.71 to 1.17)	66 (1 study)	⊕⊖⊖⊖ Very low [a, b]	
Follow-up: 4 weeks	774 per 1000	705 per 1000 (580 to 983)				
Withdrawals due to adverse events	Study population		not estimable	66 (1 study)	-	The study reported 0 withdrawals due to adverse events.
Follow-up: 4 weeks	0 per 1000	0 per 1000 (0 to 0)				
Serious adverse events	Study population		not estimable	66 (1 study)	-	The study reported 0 serious adverse events.
Follow-up: 4 weeks	0 per 1000	0 per 1000 (0 to 0)				

*****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; **RR:** risk ratio

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 two levels due to serious imprecision from very low participant numbers.
[b]Downgraded one level due to risk of bias for randomisation method.

Summary of findings 6. Synbiotics compared to paraffin for treatment of chronic constipation in children

Synbiotics compared to paraffin for treatment of chronic constipation in children

Patient or population: children with chronic constipation without a physical explanation
Setting: outpatient
Intervention: synbiotics
Comparison: paraffin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with paraffin	Risk with synbiotics				

Frequency of defecation (number of stools/week) Follow-up: 4 weeks	The mean number of stools per week was 6.75.	MD 1.53 lower (3.00 lower to 0.06 lower)	-	60 (1 study)	⊕⊖⊖⊖ Very low [a, b]	
Global improvement or treatment success, as defined by primary studies Follow-up: 4 weeks	Study population		RR 0.86 (0.65 to 1.13)	60 (1 study)	⊕⊖⊖⊖ Very low [a, b]	
	774 per 1000	967 per 1000 (789 to 1000)				
Withdrawals due to adverse events Follow-up: 4 weeks	Study population		not estimable	60 (1 study)	-	The study reported 0 withdrawals due to adverse events
	0 per 1000	0 per 1000 (0 to 0)				
Serious adverse events Follow-up: 4 weeks	Study population		not estimable	60 (1 study)	-	The study reported 0 serious adverse events
	0 per 1000	0 per 1000 (0 to 0)				

***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; **RR:** risk ratio

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 two levels due to serious imprecision from low participant numbers.
[b]Downgraded one level due to risk of bias for randomisation method.

BACKGROUND

Description of the condition

Childhood constipation is a very common problem in paediatrics (Kubota 2020), with a reported pooled prevalence of 9.5% in a recent study (Koppen 2018). It accounts for 3% of all visits to general paediatric clinics and up to 25% of visits to paediatric gastroenterologists (Banaszkiewicz 2005). The Rome criteria III for functional gastrointestinal disorders were published in 2006 (Hyman 2006; Rasquin 2006). They were updated to Rome IV in 2016, to include definitions for functional constipation and other functional disorders (Hyams 2016). According to the Rome IV criteria, functional constipation, which is chronic constipation without physical causation, is diagnosed when the symptoms below are met (and no other pathological cause exists) (Hyams 2016). Criteria do vary, but are mostly based on key symptoms, including decreased frequency of defecations, hard or painful bowel movements, faecal incontinence, and large diameter stools (Hyams 2016).

To diagnose constipation in children over four years old, using the Rome IV criteria, at least two of these symptoms must be present at least once per week for one month, with insufficient criteria for the diagnosis of irritable bowel syndrome (Hyams 2016):

- two or fewer defecations in the toilet per week;
- history of painful or hard bowel movements;
- history of retentive posturing (standing or sitting with legs straight or stiff), or excessive volitional stool retention (withholding from passing stool);
- history of large diameter stools that can obstruct the toilet;
- presence of a large faecal mass in the rectum;
- one or more episodes of faecal incontinence per week.

These criteria were amended for infants and toddlers in Rome IV, excluding reference to incontinence or large diameter stools until the child is toilet trained (Zeevenhooven 2017).

Effective management of childhood functional constipation requires a partnership between clinicians and parents, particularly for younger children who cannot accurately report symptoms. The North American and European societies for Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN and ESPGHAN) published a consensus international guideline to support these decisions (Tabbers 2014). Informed by parents' reports and interpretations, since they know their child best, clinicians use their training and experience to differentiate between health and illness (Hyams 2016). To successfully treat functional constipation, clinicians must manage the constipation and its causes, and also the psychological impact that functional childhood constipation can have on children and their families.

Description of the intervention

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

How the intervention might work

Experimental studies have shown that constipation is often associated with gut microbiota dysbiosis, which consists of the modified abundance of certain taxa of the colonic microbiome, i.e. the natural balance of gut bacteria has been lost (Attaluri 2010). The use of micro-organisms might change the composition of bacterial colonies in the bowel, reduce inflammation, and promote normal gut physiology, thereby reducing functional symptoms. Some probiotics may influence colonic motility by softening the stool; changing secretion or absorption of water and electrolytes, or both; modifying smooth muscle cell contractions; increasing the production of lactate and short-chain fatty acids; and lowering intraluminal pH (Waller 2011). In addition, since they are essentially a food supplement, probiotics are generally perceived as having a good safety profile, particularly compared with other treatments.

Why it is important to do this review

The management of functional childhood constipation varies internationally, and also between centres within the same region. This reflects the lack of a good evidence base for many current treatment strategies (Gordon 2016; Tabbers 2014).

Until recently, there had only been minimal research on the use of these agents (Tabbers 2010), with published studies showing conflicting results (Banaszkewicz 2005; Sadeghzadeh 2014).

A number of recent systematic reviews in the wider fields of probiotics and childhood constipation have demonstrated a rapid rise in published trials in this context (Horvath 2013; Tabbers 2010; Tabbers 2015). To date, there is not a Cochrane Review that examines the role of probiotics for chronic constipation in children. Therefore, it is important to synthesise the evidence, using Cochrane methodology.

International guidelines do not list probiotics as therapy; however, it is clear they are of interest to researchers (Tabbers 2014). In addition, as many probiotics are available without a prescription, clear evidence-based guidelines are key for policymakers and parents, to empower them to make appropriate choices for their children.

OBJECTIVES

To evaluate the efficacy and safety of probiotics for the management of chronic constipation without a physical explanation in children.

METHODS

Criteria for considering studies for this review

Types of studies

A protocol for this review has been previously published (Wallace 2021).

We included randomised controlled trials (RCTs) that compared probiotics to no intervention, placebo, or any other intervention. If identified, we planned to include cross-over trials and cluster-RCTs.

Types of participants

We included trials with children and adolescents between the ages of 0 and 18 years, who have been diagnosed with functional constipation, with or without incontinence. The diagnosis of constipation was based on consensus criteria (e.g. Rome IV). We excluded studies with children suffering from any underlying pathology, such as thyroid abnormalities, Hirschsprung's disease, or those who underwent previous bowel surgery at study entry.

Types of interventions

Eligible interventions were probiotics administered in any form (powder, liquid, capsule), through any route (oral or rectal), as a single species or as a cocktail of multiple species (including combination with other agents, e.g. synbiotics), compared to no treatment, placebo, or any other intervention. Studies could use probiotics at any dosage, and for any duration deemed appropriate by the primary study. We planned to consider studies that used probiotics as adjunct therapy, and meta-analyse their results where they could be appropriately grouped per main therapy.

Types of outcome measures

The outcome measures are noted below. We included the primary outcomes in summary of findings tables.

Primary outcomes

1. The frequency of defecation (number of stools per week), measured at end of study
2. Global improvement or treatment success, as defined by primary studies, measured at end of study
3. Withdrawal due to adverse events

Secondary outcomes

1. Faecal incontinence, or encopresis, measured at end of study
2. Successful disimpaction, as defined by study, measured at end of study
3. Need for additional therapies during the study period
4. Serious adverse events
5. Adverse events

Search methods for identification of studies

Electronic searches

On 28 June 2021, the Information Specialist searched the following sources:

- CENTRAL via the Cochrane Library (Cochrane Central Register of Controlled Trials; until 28 June 2021; Appendix 1);
- MEDLINE via Ovid SP (1946 to 28 June 2021; Appendix 2);
- Embase via Ovid SP (1974 to 2021, Week 25; Appendix 3);
- CINAHL via EBSCOhost (Cumulative Index to Nursing and Allied Health Literature; 1937 until 28 June 2021; Appendix 4);
- AMED via Ovid SP (Allied and Complementary Medicine; 1985 to 28 June 2021; Appendix 5);
- World Health Organization's International Clinical Trials Registry Platform (ICTRP) (until search date; Appendix 6);
- ClinicalTrials.gov (28 June 2021; Appendix 7).

We adapted the MEDLINE search strategy for the other sources. We also used Cochrane's sensitivity-maximising RCT filter for Ovid MEDLINE (Lefebvre 2019), Cochrane's RCT filter for Embase (Glanville 2019a), and RCT filter for CINAHL (Glanville 2019b).

For studies published in a non-English language we planned to have them professionally translated in full. We collated references and removed any duplicates. We did not impose any date, language, publication status, or document type restrictions on the searches.

Searching other resources

Reference Searching

We inspected the references of all identified studies for more trials.

Personal contacts

We contacted leaders in the field to try to identify other studies.

Manufacturers

We contacted manufacturers of probiotic agents to try to identify other studies.

Grey Literature

We searched Google, Google Scholar, and OpenGrey, using the main search terms. To identify other potentially relevant studies that may not have been published in full, we handsearched conference proceedings from the Digestive Disease Week (DDW), United European Gastroenterology Week (UEGW), and European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) annual scientific meetings from 2019 to 2021. We only included studies from the grey literature if they presented sufficient data to enable an inclusion decision.

Concerns have been raised previously regarding the accuracy of data presented in abstract publications (Pitkin 1999). Therefore, we planned that if we identified references for relevant unpublished or ongoing studies, we would attempt to collect sufficient information to incorporate them in this review. If data were incomplete, we planned to contact the authors to verify the eligibility of the study, and only include it if they provided suitable data to enable us to assess quality and outcomes.

Data collection and analysis

We carried out data collection and analysis according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020).

Selection of studies

Two review authors (CW and VS) independently screened titles, abstracts, and full reports for eligibility against the inclusion criteria. The authors discussed and resolved disagreement by consensus, or with resolution by a third review author (MG).

At the stage of screening abstracts and titles, the two review authors identified reports that appeared to be potentially relevant. We obtained the full-text reports of those that appeared to be potentially relevant. After reading the full texts, the two review authors independently assessed the eligibility of trials, based on the inclusion criteria above, and develop a PRISMA flowchart (Page 2021).

Data extraction and management

We developed data extraction forms a priori, as per the recommendations in the *Cochrane Handbook for Systematic Reviews* (Higgins 2020), to extract information on relevant features and results of included studies. Eight review authors extracted and recorded data on the data extraction form (two authors extracted data independently and a third author checked the exactions). We extracted the following data:

- characteristics of children: age, sex, duration of symptoms;
- inclusion and exclusion criteria;
- study methods;
- total number of children originally assigned to each treatment group;
- intervention: preparations, dose, administration regimen;
- control: placebo, other drugs;
- concurrent medications;
- outcomes (time of assessment, length of follow-up, frequency of defecation, pain or straining on defecation, faecal incontinence, stool consistency, need for additional therapies, number and type of adverse events associated with treatment, adverse events); and
- withdrawals and reasons for withdrawals.

After data extraction, the review authors compared the extracted data and discussed and resolved discrepancies before the data were transferred into the 'Characteristics of included studies' table.

Assessment of risk of bias in included studies

Eight review authors independently assessed all studies meeting the inclusion criteria for their risk of bias, using criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* (Higgins 2011). The domains were:

- sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective reporting (reporting bias);
- other bias, such as imbalance in participants' baseline characteristics.

We judged the studies to be at low, high, or unclear risk of bias for each domain assessed, based on the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* (Higgins 2011).

For cluster-RCTs, we intended to judge risk of bias as prescribed in Section 16.3.2 of the *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* (Higgins 2011)

Measures of treatment effect

Dichotomous outcomes

We assessed all dichotomous outcomes by calculating the risk ratio (RR) and 95% confidence interval (CI).

Continuous outcomes

We assessed all continuous outcomes by calculating the mean difference (MD) and 95% CI, when using the same units. When studies had used different scales to evaluate the same outcome, we calculated the standardised mean difference (SMD) and 95% CI.

Unit of analysis issues

The participant was the unit of analysis. For studies comparing more than two intervention groups, we made multiple pair-wise comparisons between all possible pairs of intervention groups. To avoid double-counting if it had been necessary to include multiple arms within the same forest plot, we planned to divide shared intervention groups evenly among the comparisons. For dichotomous outcomes, we planned to divide both the number of events and the total number of participants. For continuous outcomes, we planned to only divide the total number of participants and leave the means and standard deviations unchanged.

We planned to include cross-over studies, but only pool data if they were separately reported before and after the cross over; we planned to only use data from the pre-cross-over phase.

Dealing with missing data

We contacted authors when there were missing data, or where studies did not report data in sufficient detail. We planned to estimate missing standard deviations using relevant statistical tools and calculators available in Review Manager 5 if studies reported standard errors (Review Manager 2020). We judged studies that failed to report measures of variance to be at high risk of selective reporting bias.

Assessment of heterogeneity

We scrutinised studies to ensure that they were clinically homogeneous in terms of participants, interventions, comparators, and outcomes. To test for statistical heterogeneity, we used a Chi^2 test and interpreted a P value of less than 0.1 to give an indication of the presence of heterogeneity. We quantified consistency as represented by the I^2 statistic. We interpreted the thresholds as follows (Higgins 2020):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%; may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We planned to examine possible explanations for heterogeneity when sufficient data were available, exploring factors such as participant characteristics (e.g. age, sex), condition severity, healthcare system, and country.

We planned to avoid pooling data in a meta-analysis if we detected a considerable degree of statistical heterogeneity ($I^2 > 75\%$). In cases of considerable statistical heterogeneity, we planned to investigate whether this could be explained on clinical, methodological, or risk of bias grounds, in which case, we planned to perform sensitivity analyses excluding identified studies, with reasons. If we could not find any such reasons for the considerable statistical heterogeneity, we planned to present the results narratively, in detail.

Assessment of reporting biases

An inclusive search strategy minimised most reporting biases. We planned to investigate publication bias using a funnel plot if there were 10 or more studies. We planned to determine the magnitude of publication bias by visual inspection of the asymmetry of the funnel plot. In addition, we planned to test funnel plot asymmetry by conducting a linear regression of intervention effect estimate against its standard error, weighted by the inverse of the variance of the intervention effect estimate (Egger 1997).

Data synthesis

We combined data from individual trials into a meta-analysis if the interventions, participant groups, and outcomes were sufficiently similar (determined by consensus). We calculated the pooled RR and corresponding 95% CI for dichotomous outcomes, and MD or SMD and corresponding 95% CI for continuous outcomes. We used a random-effects model for meta-analysis. We did not pool data in meta-analysis if we detected considerable heterogeneity (i.e. $I^2 > 75\%$).

We used RevMan Web 2022 for data analysis. We analysed data according to the intention-to-treat principle. We assumed that participants with missing final outcomes had failed treatment.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analyses to study the effects of a number of variables on the outcomes, including:

- specific probiotic preparation;
- the effect of length of therapy and follow-up;
- what, if anything, was initially allowed in the protocol to clear any impaction (such as enemas);|
- age of participants (infants, non-toilet trained toddlers, older children and adolescents, as per Rome IV criteria (Hyams 2016)).

Sensitivity analysis

Where possible, we planned to undertake a sensitivity analysis on the primary outcomes to assess whether the findings of the review are robust, based on the decisions made during the review process. In particular, we planned to exclude studies at high or unclear risk of selection bias due to allocation bias and performance bias, from analyses that include studies with different risk of bias judgements.

Where data analyses included studies with reported and estimated standard deviations, we planned to exclude those with estimated standard deviations, to assess whether this affected the findings of the review. We planned to investigate whether the choice of model (fixed-effect versus random-effects) affected results, as well as studies published in full versus abstract format.

Summary of findings and assessment of the certainty of the evidence

We presented the main results in summary of findings tables. We exported data for each comparison and primary outcome from RevMan Web (RevMan Web 2022) to GRADEpro GDT software to assess the certainty of the evidence (GRADEpro GDT).

We planned to present two summary of findings tables in the following hierarchy:

1. probiotics versus placebo;
2. probiotics and osmotic laxative versus osmotic laxative.

We added summary of findings tables for other comparisons identified during the review, including comparisons with magnesium oxide (Summary of findings 3), synbiotics compared with placebo (Summary of findings 4), synbiotics and paraffin compared with paraffin (Summary of findings 5), and synbiotics compared with paraffin (Summary of findings 6).

We planned to include all three primary outcomes and the secondary outcome 'serious adverse events'.

We did not conduct GRADE assessments for outcomes for which meta-analysis was not conducted.

Based on risk of bias, inconsistency, imprecision, indirectness, and publication bias, we graded the certainty of the evidence for each outcome as high, moderate, low, or very low (described below). We justified all decisions to downgrade the certainty of studies using footnotes, and we made comments to aid the reader's understanding of the review where necessary.

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.

R E S U L T S

Description of studies

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

Results of the search

The search conducted on 28 June 2021 identified 941 records. After duplicates were removed, a total of 618 records entered the title and abstracts screening stage. Two authors independently reviewed titles and abstracts, and identified 29 reports full-text review (Figure 1). Of those, we excluded four records, classified two under awaiting classification, and included 23 records.

Figure 1. Study flow diagram.

Figure 1. Study flow diagram.

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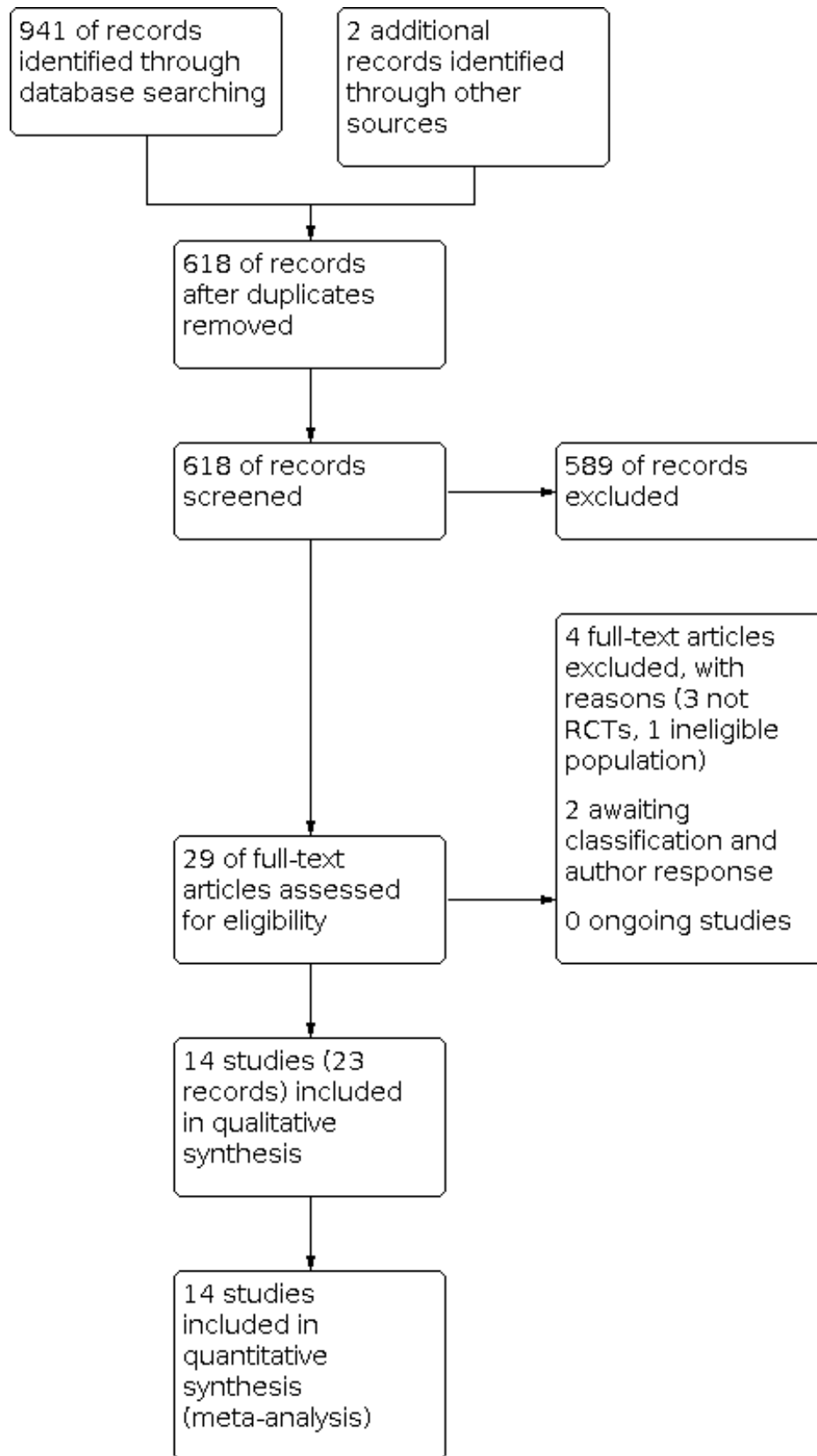
Included studies

We included 14 RCTs (in 23 reports) involving a total of 1127 participants (Banaszkiewicz 2005; Basturk 2017; Bu 2007; Chao 2016; Coccorullo 2010; Guerra 2011; Jadresin 2018; Khodadad 2010; Kubota 2020; Russo 2017; Tabbers 2011; Wegner 2018; Wojtyniak 2017; Zaja 2021).

Participants

Age

In the studies that reported age ranges, participants were between the ages of six months and 18 years old. Bu 2007 and Wojtyniak 2017 did not specify a lower age limit for the children randomised in their studies. However, the inclusion criteria for the Wojtyniak 2017 study required children to be under five years old, and the mean age of children in the Bu 2007 study was approximately three years old.

Diagnosis/definition of chronic constipation

Twelve studies based diagnosis of chronic constipation on Rome criteria, 11 of them on Rome III (Basturk 2017; Chao 2016; Coccorullo 2010; Guerra 2011; Jadresin 2018; Khodadad 2010; Russo 2017; Tabbers 2011; Wegner 2018; Wojtyniak 2017; Zaja 2021), and one on Rome IV (Kubota 2020). Banaszkiewicz 2005 defined chronic constipation as three or fewer bowel movement per week for at least three months, and Bu 2007 as three or fewer bowel movement per week for at least two months.

The participants in the Zaja 2021 RCT were children and adolescents with anorexia nervosa who also had chronic constipation.

Interventions

Length of the interventions and time points of outcome measurements

The interventions of the included RCTs lasted from three weeks (Tabbers 2011), up to 12 weeks (Banaszkiewicz 2005; Chao 2016; Jadresin 2018; Zaja 2021).

Four studies measured their outcomes only at the end of the intervention (Basturk 2017; Bu 2007; Kubota 2020 Zaja 2021). Eight studies measured outcomes at both the end of the intervention and various time points in between (Chao 2016; Coccorullo 2010; Guerra 2011; Khodadad 2010; Russo 2017; Tabbers 2011; Wegner 2018; Wojtyniak 2017). Banaszkiewicz 2005 measured outcomes at the end of the intervention, at various time points in between, and followed up their participants 12 weeks after the end of the intervention. Jadresin 2018 measured their outcomes four weeks after the end of their 12-week intervention.

Interventions

Intervention arms

Three studies had three intervention arms (Bu 2007; Khodadad 2010; Kubota 2020), and the others had two intervention arms. Guerra 2011 was a cross-over RCT.

Intervention and placebo agents

1. Seven studies compared probiotics to placebo (Bu 2007; Coccorullo 2010; Guerra 2011; Jadresin 2018; Tabbers 2011; Wojtyniak 2017; Zaja 2021).

2. Five studies compared probiotics and osmotic laxatives to osmotic laxatives (Banaszkiewicz 2005; Chao 2016; Kubota 2020; Russo 2017; Wegner 2018).

3. Two studies compared probiotics to magnesium oxide (Bu 2007; Kubota 2020).

4. One study compared synbiotics to placebo (Basturk 2017).

5. One study compared synbiotics and paraffin to paraffin (Khodadad 2010).

6. One study compared synbiotics to paraffin (Khodadad 2010).

All agents were taken orally. Information on the interventional agents, strains and dosages can be found in Table 2.

Reporting of outcomes

Primary outcomes

Six studies reported our primary continuous outcome of frequency of defecation (Banaszkiewicz 2005; Bu 2007; Khodadad 2010; Russo 2017; Wegner 2018; Wojtyniak 2017). In the other studies, the outcome was either unclear or not reported.

Nine studies reported our primary dichotomous outcome of global improvement/treatment success (Banaszkiewicz 2005; Basturk 2017; Bu 2007; Jadresin 2018; Khodadad 2010; Russo 2017; Tabbers 2011; Wojtyniak 2017; Zaja 2021). In the other studies, the outcome was either unclear or not reported.

Twelve studies reported out primary dichotomous outcome of withdrawals due to adverse events (Banaszkiewicz 2005; Basturk 2017; Bu 2007; Coccorullo 2010; Jadresin 2018; Khodadad 2010; Kubota 2020; Russo 2017; Tabbers 2011; Wegner 2018; Wojtyniak 2017; Zaja 2021). The remaining two studies did not report this outcome.

Reporting of secondary outcomes

Four studies reported faecal incontinence/encopresis as a continuous outcome (Banaszkiewicz 2005; Bu 2007; Khodadad 2010; Wojtyniak 2017), and four reported it as a dichotomous outcome (Basturk 2017; Russo 2017; Tabbers 2011; Wegner 2018). The other studies either did not report the outcome or reported it unclearly.

None of the studies reported our secondary outcome of successful disimpaction.

Eight studies reported our secondary outcome of need for additional therapies (Banaszkiewicz 2005; Basturk 2017; Bu 2007; Jadresin 2018; Russo 2017; Tabbers 2011; Wegner 2018; Wojtyniak 2017).

Eleven studies reported serious adverse events as an outcome (Banaszkiewicz 2005; Basturk 2017; Bu 2007; Jadresin 2018; Khodadad 2010; Kubota 2020; Russo 2017; Tabbers 2011; Wegner 2018; Wojtyniak 2017; Zaja 2021). The remaining three studies did not report this outcome.

Twelve studies reported total adverse events as an outcome (Banaszkiewicz 2005; Basturk 2017; Bu 2007; Coccorullo 2010; Jadresin 2018; Khodadad 2010; Kubota 2020; Russo 2017; Tabbers 2011; Wegner 2018; Wojtyniak 2017; Zaja 2021).

Excluded studies

We excluded four records (Figure 1). Three studies were not RCTs (Bekkali 2007; Olgac 2013; Szajewska 2011), and one had an ineligible study population (Magro 2014).

Figure 2. Risk of bias graph

Risk of bias in included studies

Figure 2 and Figure 3 provide a graph and a summary for the risk of bias of the included studies.

Figure 2. Risk of bias graph

Figure 3. Risk of bias summary

Allocation

Random sequence generation

All included studies were described as randomised trials.

Twelve of the fourteen studies adequately described their method of random sequence generation, so we deemed these to be at low risk of bias (Banaszkiewicz 2005; Basturk 2017; Bu 2007; Coccorullo 2010; Guerra 2011; Jadresin 2018; Kubota 2020; Russo 2017; Tabbers 2011; Wegner 2018; Wojtyniak 2017; Zaja 2021).

Chao 2016 and Khodadad 2010 described participants as being randomised into intervention or control groups, but did not give information on how this random sequence was obtained, so we deemed these to be at unclear risk of bias.

Allocation concealment

We rated five studies as having a low risk of bias, as they adequately described a method of allocation concealment (Basturk 2017; Jadresin 2018; Khodadad 2010; Tabbers 2011; Wojtyniak 2017).

The remaining nine studies either did not mention allocation concealment, or had a description of allocation concealment that did not adequately describe the process in order to be deemed low risk of bias. We contacted these authors for clarification but they did not provide further details, so we rated these with an unclear risk of bias for allocation concealment (Banaszkiewicz 2005; Bu 2007; Chao 2016; Coccorullo 2010; Guerra 2011; Kubota 2020; Russo 2017; Wegner 2018; Zaja 2021).

Blinding

Blinding of participants and personnel

Twelve of the fourteen studies adequately described their methods of blinding of study participants and personnel - including the matching of placebo in taste, look and packaging - in order to be rated as low risk of bias (Banaszkiewicz 2005; Basturk 2017; Bu 2007; Coccorullo 2010; Guerra 2011; Jadresin 2018; Khodadad 2010; Kubota 2020; Tabbers 2011; Wegner 2018; Wojtyniak 2017; Zaja 2021). Chao 2016 was described as being a controlled trial, but did not describe the method or means of blinding of participants and personnel, so we deemed it to be at unclear risk of bias. Russo 2017 was an open-label trial, and as such we deemed it to be at high risk for blinding of participants and personnel.

Blinding of outcome assessors

Twelve of the fourteen studies adequately described their methods of blinding for those assessing the study outcomes in order to be rated as low risk of bias (Banaszkiewicz 2005; Basturk 2017; Bu 2007; Coccorullo 2010; Guerra 2011; Jadresin 2018; Khodadad 2010; Kubota 2020; Tabbers 2011; Wegner 2018; Wojtyniak 2017; Zaja 2021). Chao 2016 did not describe the method or means of blinding of those assessing the outcomes, so we deemed it to be at unclear risk of bias. Russo 2017 was an open-label trial, so we considered it to be at high risk for blinding of outcome assessors.

Incomplete outcome data

Thirteen of the fourteen studies described their study flow in sufficient detail and with balanced withdrawals in order to be deemed at low risk for attrition bias (Banaszkiewicz 2005; Basturk 2017; Bu 2007; Coccorullo 2010; Guerra 2011; Jadresin 2018; Khodadad 2010; Kubota 2020; Russo 2017; Tabbers 2011; Wegner 2018; Wojtyniak 2017; Zaja 2021). It was not possible to assess the study flow or withdrawals from the Chao 2016 study based on the information provided, so we deemed this to be at unclear risk of attrition bias.

Selective reporting

Twelve of the fourteen studies reported all the outcomes described in their methods in sufficient detail to be deemed at low risk of reporting bias (Banaszkiewicz 2005; Basturk 2017; Bu 2007; Coccorullo 2010; Jadresin 2018; Khodadad 2010; Kubota 2020; Russo 2017; Tabbers 2011; Wegner 2018; Wojtyniak 2017; Zaja 2021).

Chao 2016 did not provide sufficient detail in the methods or results section for us to assess against this domain, and so we rated it as having an unclear risk of bias. Guerra 2011 reported their primary outcomes, but only in graphical form with insufficient detail on the graphs to extract data from them. We contacted the authors for further clarification, but having received no response we deemed this study to be at high risk of reporting bias.

Other potential sources of bias

Thirteen of the fourteen studies had no other sources of bias of note that we could see, and had balanced baseline characteristics for the intervention and control groups. As such, we rated them at low risk for other sources of bias (Banaszkiewicz 2005; Basturk 2017; Bu 2007; Coccorullo 2010; Guerra 2011; Jadresin 2018; Khodadad 2010; Kubota 2020; Russo 2017; Tabbers 2011; Wegner 2018; Wojtyniak 2017; Zaja 2021). As Chao 2016 was presented in abstract form, without information on baseline characteristics, we were unable to assess this study and so rated it as having an unclear risk of bias.

Effects of interventions

See: **Summary of findings 1** Probiotic compared to placebo for treatment of chronic constipation in children; **Summary of findings 2** Probiotics and osmotic laxative compared to osmotic laxative for treatment of chronic constipation in children; **Summary of findings 3** Probiotics compared to magnesium oxide for treatment of chronic constipation in children; **Summary of findings 4** Synbiotics compared to placebo for treatment of chronic constipation in children; **Summary of findings 5** Synbiotics and paraffin compared to paraffin for treatment of chronic constipation in children; **Summary of findings 6** Synbiotics compared to paraffin for treatment of chronic constipation in children

Details on the outcome data can be found in Table 3.

Probiotics vs placebo

Key outcomes for this comparison are summarised in Summary of findings 1.

Of the seven studies that looked at this comparison, one study with 31 participants was conducted in a population of people with chronic constipation who had anorexia nervosa (Zaja 2021). We have reported the available results from their study separately below, and not as part of our meta-analyses on the general population of children with chronic constipation.

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Primary outcomes

Frequency of defecation

Three studies with 280 participants provided data for a meta-analysis of this outcome (Bu 2007; Tabbers 2011; Wojtyniak 2017). We performed meta-analysis, but this had very serious inconsistency with two studies not overlapping visually on opposing sides of the forest plot and an I² of 95%. Exploration of this was not possible due to there only being three studies; therefore, in line with the planned methods, we have not presented this analysis. One study found a mean frequency of defecation at study end greater in the probiotic group (Bu 2007 probiotics mean 5.03 stools per week, SD 1.5; placebo mean 2.6 stools per week, SD 0.71), one found no difference between groups on change scores (Tabbers 2011 probiotics mean 2.9 stools per week, SD 3.2; placebo mean 2.6 stools per week, SD 2.6), and in the other (Wojtyniak 2017), the placebo group had greater frequency of defecation at study end (probiotics mean 4 stools per week, SD 1.48; placebo mean 6 stools per week, SD 3.7).

Global improvement/treatment success

Four studies with 313 participants provided data for a meta-analysis of this outcome (Bu 2007; Jadresin 2018; Tabbers 2011; Wojtyniak 2017). There may be no difference in global improvement/treatment success in childhood chronic constipation (RR 1.29, 95% CI 0.73 to 2.26; Analysis 1.1) when probiotics (72/161) are compared to placebo (52/152). The certainty of the results is low due to imprecision and inconsistency (I² = 63%). A sensitivity analysis using a fixed-effect model did not change the result (Analysis 1.2).

Zaja 2021 reported global improvement/treatment success in 13/15 patients in their probiotics group and 10/16 patients in their placebo group.

Withdrawals due to adverse events

Five studies with 357 participants provided data for a meta-analysis of this outcome (Bu 2007; Coccorullo 2010; Jadresin 2018; Tabbers 2011; Wojtyniak 2017). There may be no difference in withdrawals due to adverse events (RR 0.64, 95% CI 0.21 to 1.95; Analysis 1.3) when probiotics (5/183) are compared to placebo (7/174). Three of the studies in the meta-analysis reported zero withdrawals due to adverse events; therefore, the analysis is only based on data from two studies (Bu 2007; Tabbers 2011). The certainty of the results is low due to serious imprecision (Summary of findings 1). A sensitivity analysis using the fixed effect model found no difference in this result (Analysis 1.4).

Zaja 2021 reported zero withdrawals due to adverse events in their study.

Secondary outcomes

Faecal incontinence/encopresis

Two studies with 121 participants provided continuous data for a meta-analysis of this outcome (Bu 2007; Wojtyniak 2017). There may be no difference in faecal incontinence/encopresis episodes per week (MD -0.60, 95% CI -2.58 to 1.38; Analysis 1.5) when probiotics (n = 64) are compared to placebo (n = 57). The certainty of the results is low due to serious imprecision.

One study with 159 participants provided dichotomous data for this outcome (Tabbers 2011). It is uncertain if there is a difference in faecal incontinence/encopresis (RR 0.76, 95% CI 0.51 to 1.12; Analysis 1.6) when probiotics (27/79) are compared to placebo (36/80). The certainty of the results is low due to serious imprecision.

Successful disimpaction

No studies reported this outcome.

Need for additional therapies

Four studies with 380 participants provided data for a meta-analysis of this outcome (Banaszkiewicz 2005; Jadresin 2018; Tabbers 2011; Wojtyniak 2017). There probably is no difference in need for additional therapies (RR 1.04, 95% CI 0.78 to 1.39; Analysis 1.7) when probiotics (70/186) are compared to placebo (64/184). The certainty of the results is moderate due to imprecision.

Serious adverse events

Four studies with 198 participants provided data for a meta-analysis of this outcome (Bu 2007; Coccorullo 2010; Jadresin 2018; Wegner 2018; Wojtyniak 2017). There was no estimable effect for this meta-analysis as all studies reported zero serious adverse events for their participants.

Zaja 2021 reported zero serious adverse events in their study.

Total adverse events

Five studies with 357 participants provided data for a meta-analysis of this outcome (Bu 2007; Coccorullo 2010; Jadresin 2018; Tabbers 2011; Wojtyniak 2017). There may be no difference in total adverse events (RR 0.54, 95% CI 0.17 to 1.67; Analysis 1.8) when probiotics (4/183) are compared to placebo (9/174). The certainty of the results is low due to serious imprecision.

Zaja 2021 reported zero total adverse events in their study.

Probiotics and osmotic laxative vs osmotic laxative

Primary outcomes

Frequency of defecation

Three studies with 268 participants provided data for a meta-analysis of this outcome (Banaszkiewicz 2005; Russo 2017; Wegner 2018). There may be no difference in frequency of defecation, measured in stools per week (MD -0.01, 95% CI -0.57 to 0.56; Analysis 2.1) when probiotics and osmotic laxative (n = 135) are compared to osmotic laxative (n = 133). The certainty of the results is low due to risk of bias and imprecision (Summary of findings 2). A sensitivity analysis using a fixed-effect model led to no change in the result (Analysis 2.2).

Global improvement/treatment success

Two studies with 139 participants provided data for a meta-analysis of this outcome (Banaszkiewicz 2005; Russo 2017). There may be no difference in global improvement/treatment success in childhood chronic constipation (RR 0.95, 95% CI 0.79 to 1.15; Analysis 2.3) when probiotics and osmotic laxative (49/70) are compared to osmotic laxative (51/69). The certainty of the results is low due to risk of bias and imprecision (Summary of findings 2). A sensitivity

analysis using a fixed-effect model led to no change in the result (Analysis 2.4).

Withdrawals due to adverse events

Three studies with 268 participants provided data for a meta-analysis of this outcome (Banaszkiewicz 2005; Russo 2017; Wegner 2018). There may be no difference in withdrawals due to adverse events (RR 2.86, 95% CI 0.12 to 68.35) when probiotics and osmotic laxative (1/135) are compared to osmotic laxative (0/133). Two of the studies in the meta-analysis reported zero withdrawals due to adverse events; this analysis is only based on data from one study (Banaszkiewicz 2005). The certainty of the results is very low due to risk of bias and serious imprecision (Analysis 2.5; Summary of findings 2). A sensitivity analysis using a fixed-effect model led to no change in the result (Analysis 2.6).

Secondary outcomes

Faecal incontinence/encopresis

One study with 84 participants provided continuous data for this outcome (Banaszkiewicz 2005). There may be no difference in faecal incontinence/encopresis episodes per week (MD 0.50, 95% CI -0.10 to 1.10; Analysis 2.7) when probiotics and osmotic laxative (n = 43) are compared to osmotic laxative (n = 41). The certainty of the results is low due to serious imprecision.

Two studies with 184 participants provided dichotomous data for a meta-analysis of this outcome (Russo 2017; Wegner 2018). There may be no difference in faecal incontinence/encopresis (RR 1.40, 95% CI 0.73 to 2.68; Analysis 2.8) when probiotics and osmotic laxative (18/92) are compared to osmotic laxative (13/92). The certainty of the results is very low due to imprecision and risk of bias.

Successful disimpaction

No studies reported this outcome.

Need for additional therapies

Three studies with 268 participants provided data for a meta-analysis of this outcome (Banaszkiewicz 2005; Russo 2017; Wegner 2018). There may be no difference in need for additional therapies (RR 0.98, 95% CI 0.63 to 1.50; Analysis 2.9) when probiotics and osmotic laxative (26/135) are compared to osmotic laxative (26/133). The certainty of the results is low due to imprecision and risk of bias.

Serious adverse events

Four studies with 308 participants provided data for a meta-analysis of this outcome (Banaszkiewicz 2005; Coccorullo 2010; Russo 2017; Wegner 2018). There was no estimable effect for this meta-analysis as all studies reported zero serious adverse events for their participants.

Total adverse events

Four studies with 308 participants provided data for a meta-analysis of this outcome (Banaszkiewicz 2005; Coccorullo 2010; Russo 2017; Wegner 2018). There may be no difference in total adverse events (RR 1.11, 95% CI 0.18 to 6.79; Analysis 2.10) when probiotics and osmotic laxative (6/154) are compared to

osmotic laxative (6/154). The certainty of the results is low due to imprecision and risk of bias.

Probiotic vs magnesium oxide

Primary outcomes

Frequency of defecation

One study with 36 participants reported this outcome (Bu 2007). It is not clear if there is a difference in frequency of defecation, measured in stools per week (MD 0.28, 95% CI -0.58 to 1.14; Analysis 3.1) when probiotics (n = 18) are compared to magnesium oxide (n = 18). The certainty of the results is very low due to high imprecision and risk of bias (Summary of findings 3).

Global improvement/treatment success

One study with 36 participants reported this outcome (Bu 2007). It is not clear if there is a difference in global improvement/treatment success in childhood chronic constipation (RR 1.08, 95% CI 0.74 to 1.57; Analysis 3.2) when probiotics (14/18) are compared to magnesium oxide (13/18). The certainty of the results is very low due to high imprecision and risk of bias (Summary of findings 3).

Withdrawals due to adverse events

Two studies with 77 participants provided data for a meta-analysis of this outcome (Bu 2007; Kubota 2020). It is not clear if there is a difference in withdrawals due to adverse events in childhood chronic constipation (RR 0.50, 95% CI 0.05 to 5.04; Analysis 3.3) when probiotics (1/38) are compared to magnesium oxide (2/39). The certainty of the results is very low due to high imprecision and risk of bias (Summary of findings 3).

Secondary outcomes

Faecal incontinence/encopresis

One study with 36 participants reported this outcome (Bu 2007). It is not clear if there is a difference in faecal incontinence/encopresis episodes per week in childhood chronic constipation (MD -0.60, 95% CI -3.54 to 2.34; Analysis 3.4) when probiotics (n = 18) are compared to magnesium oxide (n = 18). The certainty of the results is very low due to high imprecision and risk of bias.

Successful disimpaction

No studies reported this outcome.

Need for additional therapies

One study with 36 participants reported this outcome (Bu 2007). It is not clear if there is a difference in need for additional therapies (measured as number of times glycerin enema was used) in childhood chronic constipation (MD 0.30, 95% CI -0.94 to 1.54; Analysis 3.5) when probiotics (n = 18) are compared to magnesium oxide (n = 18). The certainty of the results is very low due to high imprecision and risk of bias.

Serious adverse events

Two studies with 77 participants provided data for a meta-analysis of this outcome (Bu 2007; Kubota 2020). There was no estimable effect for this meta-analysis as both studies reported zero serious adverse events for their participants (Summary of findings 3).

Total adverse events

Two studies with 77 participants provided data for a meta-analysis of this outcome (Bu 2007; Kubota 2020). It is not clear if there is a difference in total adverse events in childhood chronic constipation (RR 0.33, 95% CI 0.01 to 7.68) when probiotics (0/38) are compared to magnesium oxide (1/39). The certainty of the results is very low due to high imprecision and risk of bias (Analysis 3.6)

Synbiotics vs placebo

Primary outcomes

Frequency of defecation

No studies reported this outcome.

Global improvement/treatment success

One study with 155 participants provided data for this outcome (Basturk 2017). There may be higher global improvement/ treatment success in childhood chronic constipation in favour of synbiotics (RR 2.32, 95% CI 1.54 to 3.47; Analysis 4.1) when synbiotics (48/77) are compared to placebo (21/78). The certainty of the results is low due to serious imprecision (Summary of findings 4). A sensitivity analysis using a fixed-effect model led to no change in the result (Analysis 4.2).

Withdrawals due to adverse events

One study with 155 participants provided data for this outcome (Basturk 2017). There was no estimable effect for this analysis as the study reported zero withdrawals due to adverse events for their participants (Summary of findings 4).

Secondary outcomes

Faecal incontinence/encopresis

One study with 155 participants provided dichotomous data for this outcome (Basturk 2017). There may be no difference in faecal incontinence/encopresis (RR 0.91, 95% CI 0.51 to 1.61; Analysis 4.3) when synbiotics (17/77) are compared to placebo (19/78). The certainty of the results is very low due to serious imprecision.

Successful disimpaction

The study did not report this outcome.

Need for additional therapies

One study with 155 participants provided data for this outcome (Basturk 2017). There probably is no difference in need for additional therapies (RR 1.27, 95% CI 0.35 to 4.54; Analysis 4.4) when synbiotics (5/77) are compared to placebo (4/78). The certainty of the results is low due to serious imprecision.

Serious adverse events

One study with 155 participants provided data for this outcome (Basturk 2017). There was no estimable effect for this analysis as the study reported zero serious adverse events for their participants.

Total adverse events

One study with 155 participants provided data for this outcome (Basturk 2017). There may be no difference in total adverse events (RR 1.27, 95% CI 0.35 to 4.54; Analysis 4.5) when synbiotics (5/77) are compared to placebo (4/78). The certainty of the results is low due to serious imprecision.

Synbiotics and paraffin vs paraffin

Primary outcomes

Frequency of defecation

One study with 66 participants provided data for this outcome (Khodadad 2010). It is uncertain if there is a difference in frequency of defecation, measured in stools per week (MD 0.74, 95% CI -0.96, 2.44; Analysis 5.1) when synbiotics and paraffin (n = 37) are compared to paraffin (n = 29). The certainty of the results is very low due to serious imprecision and risk of bias (Summary of findings 5). A sensitivity analysis using a fixed-effect model led to no change in the result (Analysis 5.2).

Global improvement/treatment success

One study with 66 participants provided data for this outcome (Khodadad 2010). It is uncertain if there is a difference in global improvement/treatment success in childhood chronic constipation (RR 0.91, 95% CI 0.71 to 1.17; Analysis 5.3) when synbiotics and paraffin (28/37) are compared to paraffin (24/29). The certainty of the results is very low due to serious imprecision and risk of bias (Summary of findings 5). A sensitivity analysis using a fixed-effect model led to no change in the result (Analysis 5.4).

Withdrawals due to adverse events

One study with 66 participants provided data for a meta-analysis of this outcome (Khodadad 2010). There was no estimable effect for this meta-analysis as the study reported zero withdrawals due to adverse events for their participants (Summary of findings 5).

Secondary outcomes

Faecal incontinence/encopresis

One study with 66 participants provided continuous data for this outcome (Khodadad 2010). It is uncertain if there is a difference in faecal incontinence/encopresis episodes per week (MD -0.23, 95% CI -0.70 to 0.24; Analysis 5.5) when synbiotics and paraffin (n = 37) are compared to paraffin (n = 29). The certainty of the results is very low due to serious imprecision and risk of bias.

Successful disimpaction

The study did not report this outcome.

Need for additional therapies

The study did not report this outcome.

Serious adverse events

One study with 66 participants provided data for this outcome (Khodadad 2010). There was no estimable effect for this meta-analysis as the study reported zero serious adverse events for their participants.

Total adverse events

One study with 68 participants provided data for this outcome (Khodadad 2010). It is uncertain if there is a difference in total adverse events (RR 0.91, 95% CI 0.61 to 1.36; Analysis 5.6) when synbiotics and paraffin (21/37) are compared to paraffin (18/29). The certainty of the results is very low due to serious imprecision and risk of bias.

Synbiotics vs paraffin

Primary outcomes

Frequency of defecation

One study with 60 participants provided data for this outcome (Khodadad 2010). It is uncertain if there is a difference in frequency of defecation in stools per week in childhood chronic constipation (MD -1.53, 95% CI -3.00 to -0.06; Analysis 6.1) when synbiotics (n = 31) are compared to paraffin (n = 29). The certainty of the results is very low due to serious imprecision and risk of bias (Summary of findings 6). A sensitivity analysis using a fixed-effect model led to no change in the result (Analysis 6.2).

Global improvement/treatment success

One study with 60 participants provided data for this outcome (Khodadad 2010). It is uncertain if there is a difference in global improvement/treatment success in childhood chronic constipation (RR 0.86, 95% CI 0.65 to 1.13; Analysis 6.3) when synbiotics (22/31) are compared to paraffin (24/29). The certainty of the results is very low due to serious imprecision and risk of bias (Summary of findings 6). A sensitivity analysis using a fixed-effect model led to no change in the result (Analysis 6.4).

Withdrawals due to adverse events

One study with 60 participants provided data for this outcome (Khodadad 2010). There was no estimable effect for this meta-analysis as the study reported zero withdrawals due to adverse events for their participants (Summary of findings 6).

Secondary outcomes

Faecal incontinence/encopresis

One study with 60 participants provided continuous data for this outcome (Khodadad 2010). It is uncertain if there is a difference in faecal incontinence/encopresis episodes per week (MD -0.18, 95% CI -0.66 to 0.30; Analysis 6.5) when synbiotics (n = 31) are compared to paraffin (n = 29). The certainty of the results is very low due to serious imprecision and risk of bias.

Successful disimpaction

The study did not report this outcome.

Need for additional therapies

The study did not report this outcome.

Serious adverse events

One study with 60 participants provided data for this outcome (Khodadad 2010). There was no estimable effect as the study reported zero serious adverse events for their participants.

Total adverse events

One study with 60 participants provided data for this outcome (Khodadad 2010). It is uncertain if there is a difference in total adverse events (RR 0.03, 95% CI 0.0 to 0.40; Analysis 6.6) when synbiotics (0/31) are compared to paraffin (18/29). The certainty of the results is very low due to serious imprecision and risk of bias.

DISCUSSION

Summary of main results

This review included 14 parallel group randomised controlled trials (three of which were multi-arm studies that included two different comparisons): seven studies compared probiotics to placebo, five compared probiotics and osmotic laxatives to osmotic laxatives, two studies compared probiotics to magnesium oxide, one compared synbiotics to placebo, one synbiotics and paraffin to paraffin alone, and a final study compared synbiotics to paraffin for the treatment of functional constipation of childhood.

The results did not allow any conclusions to be drawn as to the effect of probiotics for functional constipation in children versus placebo on frequency of defecation at study end. There may be no difference in occurrence of treatment success or adverse events when compared with placebo (low-certainty evidence).

Probiotics combined with osmotic laxatives may lead to no difference in frequency of defecation, occurrence of treatment success or adverse events at study end when compared with osmotic laxatives for functional constipation in children (low-certainty evidence).

No conclusions could be drawn when probiotics were compared to magnesium oxide (very low-certainty evidence) for frequency of defecation, treatment success, faecal incontinence, need for additional therapies or about any adverse events (leading to withdrawals, serious or total).

Synbiotics may result in increased occurrence of treatment success when compared with placebo (low-certainty evidence), with no withdrawals due to adverse events observed in either group (low-certainty evidence).

Synbiotics combined with paraffin may result in no difference in treatment success when compared with paraffin (low-certainty evidence). No conclusions can be drawn for frequency of defecation (very low-certainty evidence) and no withdrawals due to adverse events occurred in either group (low-certainty evidence).

No conclusions can be drawn for treatment success or frequency of defecation (very low-certainty evidence) when comparing synbiotics to paraffin, and no withdrawals due to adverse events occurred in either group (very low-certainty evidence).

There were insufficient data to allow analysis of faecal incontinence, successful disimpaction, need for additional therapies, or total adverse events. There were insufficient data for subgroup analysis of treatment success, frequency of defecation or withdrawals due to adverse events by specific probiotic preparation, length of follow-up, initial disimpaction or age of participants.

Overall completeness and applicability of evidence

The evidence is incomplete in a number of ways. Whilst using consensus diagnostic criteria in all studies (as a required inclusion criteria) has helped clinical homogeneity and applicability of the findings, within the context of functional constipation there is still much scope for variations in patient characteristics. The most prominent issue is the chronic nature of the constipation and previous use of therapies. It is conceivable that these trials could

be considering treatment-naive children together with those who have had years of failed interventions, and the studies do little to differentiate between the two. This is not a component of current consensus diagnostic definitions and so it is difficult to suggest this is just an issue with research design, but it remains a way in which the applicability of the evidence to individual children is limited.

The severity of the participants' constipation was not evaluated in the primary studies, which further limits interpretation of findings. There was also no assessment and relevant classification of the type of functional constipation, such as cases related to slow transit or rectal outlet dysfunction.

Multiple probiotics and synbiotics were used in the studies, therefore little can be said regarding such specific preparations; instead, the evidence can only consider the broad class of these interventions.

Additionally, the majority of studies had short follow-up. Given the chronic nature of the condition, this raises questions about the completeness of the studies' evidence for children and their clinicians. The impact of cessation of therapy or long-term continuation by children or young people has not been addressed at all. This must also be considered when interpreting evidence. The capricious selection of outcome measures was a major contributor to this issue, a factor limiting the completeness of the evidence, and is not in line with a recently published core outcome set (Kuizenga-Wessel 2017).

The issues of clinical heterogeneity above have limited meta-analysis to small groups of studies with smaller sample sizes. This may impact a number of other factors. Clearly, it impacts and reduces certainty due to imprecision and may be contributing to inconsistency. Whilst these judgements are objective and in line with guidance, it is possible that further studies could impact the results.

Finally, the reporting of adverse events is another area of concern with the evidence. It is not uncommon to experience problems related to heterogeneity of thresholds of defining serious or severe events, and as such withdrawals due to adverse events is often the most available measure for review teams. This is not necessarily the most important outcome for clinicians or children with chronic constipation, and represents a gap in the evidence that must be considered.

Quality of the evidence

We reviewed the studies' quality and assessed their risk of bias. The evidence-base was generally at low risk of bias, as shown in Figure 2. The overall risk of bias was low for most studies, with very few items at high risk in all the studies and just one study with unclear risk of bias in all items (Chao 2016). However, allocation concealment was the most poorly-reported risk of bias item, resulting in nine of the 14 studies to be judged at unclear risk of bias for allocation concealment, as well as two cases of unclear description of the randomisation method.

Due to an insufficient number of studies, we could not examine publication bias with a funnel plot.

In GRADE analysis, imprecision due to low participant and event numbers was pervasive in the judgements made. Additionally, there was inconsistency seen in statistical heterogeneity testing

and visual inspection of forest plots, which may be related to the insufficient number of studies and low participant and event numbers.

We did not conduct GRADE assessments for outcomes for which meta-analysis was not carried out.

Potential biases in the review process

The definition of the Rome process has changed in small ways over time. The bulk of studies used Rome III and only one used the latest Rome IV, so this must be considered when interpreting the findings.

We had fewer than the recommended number of studies required to carry out some subgroup analyses, particularly by specific probiotic preparation. The lack of data available by specific probiotic preparation is a significant issue in the primary literature, and future studies should take this into account.

The certainty of the evidence across all primary outcomes was impacted by significant imprecision as a result of the small sample sizes and event numbers.

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

Agreements and disagreements with other studies or reviews

The North American and European Societies for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN and ESPGHAN) published a consensus international guideline (Tabbers 2014). They concluded that the evidence does not support the use of probiotics in the treatment of childhood constipation, which is aligned with this review.

A recent systematic review also found no evidence for benefit from the use of probiotics (Wegh 2021).

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to draw conclusions as to whether probiotics are effective in changing the frequency of defecation or achieving global treatment success, or whether there is any difference in withdrawals due to adverse events compared with placebo. Limited evidence from one study suggests synbiotics may be efficacious in enhancing global treatment success when compared to placebo, with no difference in withdrawals due to adverse events.

There is insufficient evidence to make efficacy or safety conclusions about the use of probiotics in combination with osmotic laxatives compared with laxatives alone, probiotics compared with magnesium oxide, synbiotics and paraffin compared with paraffin alone or synbiotics compared with paraffin.

The majority of the studies that presented data on serious adverse events reported that no events occurred. Two studies did not report this outcome.

Implications for research

Research is still needed to confirm efficacy, but key issues must be considered by the research community prior to such trials. It is important for a consensus to be reached as to the potential practical role for probiotics. It is not clear whether this is as a primary first-line therapy, an add-on therapy to enhance efficacy, a second-line therapy after primary treatment failure, or a combination. It is important for the research community to get a clear position view from stakeholders in the international community, as this will directly impact the design of future trials.

Consistent alignment with the Rome criteria is key moving forward, but as this does not address chronicity or resistance to treatment of the condition, future studies need to consider, report or even stratify for such characteristics. Additionally, the role for these medications in more than just the short term is of interest, given the chronic nature of the underlying condition.

The use of outcome measures consistently through studies is also key to support the completeness of the evidence base. The use of a recently published core outcome set should be considered (Kuizenga-Wessel 2017).

Safety will always be a real priority in paediatric populations when considering any interventions. Reporting of total adverse events, events needing treatment withdrawal, serious adverse events and particularly long-term safety follow-up are vital to move the evidence base forward.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Banaszkiewicz 2005

Study characteristics	
Methods	Type: double-blind, randomised, placebo-controlled clinical trial.
	Setting: Department of Paediatric Gastroenterology and Nutrition, The Medical University of Warsaw, Poland.
	Study period: October 2002 to December 2003
Participants	**Establishment of diagnosis**
	Rome criteria
	< 3 BMs per week for at least 12 weeks
	Would have aligned with Rome I criteria. Authors do not specify
	Other elements of diagnostic work-up: diary to record the frequency of their BMs for 14 days before study inclusion
	Inclusion criteria
	Children 2 to 16 years of age presenting with constipation, defined as < 3 BMs per week for at least 12 weeks.
	Exclusion criteria
	Constipation caused by enteric neuromuscular, anatomic, or metabolic diseases (as established by medical history, an abnormal thyroid hormone level, or prior anorectal manometry, barium, or sono-gram examination).
	Baseline characteristics
	Age (mean ± SD)
	IG: 79 ± 47 months
	CG: 65 ± 36 months
	Toilet trained or not: not specified
	Presence of soiling/incontinence at baseline: not defined
	Presence of impaction at baseline: not defined
	Concomitant diagnosis/symptoms: soiling, straining, stool consistency, as well as any symptoms participants considered important (e.g. abdominal pain, bloating, diarrhoea).

Banaszkiewicz 2005 *(Continued)*

Sex (M/F): not specified

Use of concurrent medication

- Both groups had rectal disimpaction with phosphate and saline enemas before starting the study.
- Not defined during intervention phase.
- Lactulose or other laxatives (not specified) between weeks 13 and 24 as needed.

Disease duration/chronicity (mean ± SD)

IG: 24 ± 21 months

CG: 23 ± 16 months

Number of participants

Number randomised: total 84; IG: 43; CG: 41

Number reaching end of study: total: 76; IG: 38; CG: 38

Number analysed: IG: 43; CG: 41

Postrandomisation exclusion: none

Interventions	Both groups had rectal disimpaction with phosphate and saline enemas before starting the study.
	IG: 1 mL/kg/day of 70% lactulose (in two divided doses) plus 10^9 colony-forming units (CFU) of *Lactobacillusrhamnosus* GG (LGG), twice daily orally for 12 weeks.
	CG: 1 mL/kg/day of 70% lactulose (in two divided doses) plus comparable placebo, twice daily orally for 12 weeks.
Outcomes	**Primary outcome**
	The primary outcome measure was treatment success, defined as ≥ spontaneous BMs per week with no episodes of faecal soiling. This primary outcome measure was assessed 12 and 24 weeks after enrolment.
	Secondary outcomes
	The secondary outcome measures were the number of BMs per week, number of episodes of faecal soiling per week, stool consistency, and straining frequency per week. These secondary outcome measures were assessed at baseline and at 4, 8, and 12 weeks after study entry. In addition, the percentage of patients using laxatives was assessed at 24 weeks.
Notes	Funding source: Medical University of Warsaw
	Conflict of interest: Not reported
	Author contact details: hania@ipgate.pl.
	* Author emailed on 14 June 21; she replied on 22 June 21

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The allocation sequence and randomisation list were computer-generated by investigators at the Medical University of Warsaw.
Allocation concealment (selection bias)	Unclear risk	Method of concealment not adequately described in the text, "Allocation concealment was achieved by the use of study products with similar appearances

Banaszkiewicz 2005 *(Continued)*

and tastes" does not describe allocation concealment. Authors were contacted but no response received.

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Study products with similar appearances and tastes, which were packed identically and which were indistinguishable from each other", "Throughout the duration of the study, all investigators, participants, outcome assessors, and data analysts were blinded to the assigned treatment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Throughout the duration of the study, all investigators, participants, outcome assessors, and data analysts were blinded to the assigned treatment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed, including those who discontinued interventions.
Selective reporting (reporting bias)	Low risk	Results reported as per predefined outcomes
Other bias	Low risk	No concerns and no imbalance in the baseline populations

Basturk 2017

Study characteristics	
Methods	Type: randomised double-blind placebo-controlled study Setting: outpatient clinics of paediatric gastroenterology of the University of Akdeniz. Study period: December 2015 to May 2016
Participants	**Establishment of diagnosis** Rome criteria. Individuals with weekly number of defecations < 3 and individuals with at least one of the symptoms stated below: • weekly encopresis > 1 painful defecation; • individuals who defecate thick and large amounts of stools; • those who defecate in large amounts that obstruct the toilet; • individuals with the behaviour of stopping defecation during defecation; • individuals who were found to have hard stool during abdominal or rectal examination. Other elements of diagnostic work up: not specified Used BSS to describe stool consistency. At the end of the 1st month, the participants were questioned about initial symptoms, such as weekly number of defecations, abdominal pain, painful defecation, rectal bleeding, behaviour of avoiding defecation, stool incontinence (encopresis), and changes in the paediatric Bristol stool scale. **Inclusion criteria** Paediatric patients aged between 4 and 18 years. Patients diagnosed with functional constipation according to the Roma III diagnostic criteria. Children who were diagnosed to have functional constipation according to Rome III criteria in the last 2 months.

Exclusion criteria

Pediatric patients younger than 4 years.

Individuals with one of the following

- Metabolic and gastrointestinal diseases (such as hypothyroidism and celiac disease)
- Neuropathic diseases (such as spinal cord abnormalities and cerebral palsy)
- Intestinal nervous and muscle diseases (such as Hirschsprung disease, intestinal neuronal dysplasia, intestinal pseudo-obstruction, visceral myopathies, and visceral neuropathy)
- Abnormal abdominal muscle morphology (such as prune belly syndrome, gastroschisis, and Down syndrome)
- Connective tissue disorders (such as scleroderma, systemic lupus erythematosus, Ehlers-Danlos syndrome) chronic drug use (such as opioids, phenobarbital, sucralfate, antacids, antihypertensives, anticholinergics, antidepressants, and sympathomimetics)
- Conditions such as heavy-metal poisoning (lead), vitamin D poisoning, botulism, and intolerance to cow's milk protein
- Individuals with constipation due to any of the following organic causes and those who used antibiotics for a period close to enrolment, any drug treatment for constipation prior to enrolment, use of drugs affecting gastrointestinal motility, and children fitting criteria for irritable bowel syndrome (IBS) were excluded from this study.

Baseline characteristics

Age (mean ± SD) (years)

IG: 9.31 ± 3.47

CG: 9.06 ± 3.49

Whole group mean age: 9.18 ± 3.48

Toilet trained or not: toilet education was given to participants in both groups in addition to synbiotic or placebo treatment (ages 4 to 18).

Presence of soiling/incontinence at baseline: yes

CG: 23/74 (31.1%)

IG: 24/72 (33.3%)

Presence of impaction at baseline: not specified

Concomitant diagnosis/symptoms: none

Sex (M/F)

IG: 34 M; 40 F (n = 74)

CG: 32 M; 4 0F (n = 72)

Use of concurrent medication

Fleet enema (paraffin oil 15 mL/y to 30 mL/y) was performed on participants who presented with complaints of progressive abdominal distention and pain while receiving synbiotic or placebo treatment.

Evaluation of response

Disease duration/chronicity (mean ± SD): not specified

Number of participants

Number randomised: 155

- IG: n = 77

Basturk 2017 *(Continued)*

- CG: n= 78

Number reaching end of study: 146

- IG: n = 72
- CG: n= 74

Number analysed: total: 146

IG: n = 72

CG: n= 74

Postrandomisation exclusion: 9

Five patients in the synbiotic group and four in the placebo group were excluded from the study because they did not complete the study.

Interventions	**IG**: The first group received a mixture including 4x10^9 colony-forming units of *Lactobacillus casei, L rhamnosus, L plantarum, Bifidobacterium lactis* and prebiotics at a dose of 1996.57 mg (fibre, polydextrose, fructo-oligosaccharides, and galacto-oligosaccharides) as a sachet once a day.
	CG: The second group received a sachet once a day placebo treatment which had the same properties of colour, odour, taste, and packaging as the synbiotic treatment.
	Both: recommendations of a fibrous diet (20 to 25 g/d for children aged 4 to 8 years and 30 to 35 g/d for children aged 8 to 16 years) and toilet education were given to participants in both groups in addition to synbiotic or placebo treatment.
Outcomes	**Primary outcome**
	Complete benefit by resolution of all complaints of the participant with the 4-week synbiotic treatment.
	Secondary outcomes
	Frequency of complaints, such as weekly number of defecations, consistency of stools, number of weekly faecal incontinence episodes, presence of abdominal pain, painful defecation, rectal bleeding, behaviour of avoiding defecation, and incidence of side effects, such as vomiting and diarrhoea, at the end of the 4-week treatment.
Notes	Funding source: this study was supported by the Scientific Research Fund of Akdeniz University (Project No: 2015/323).
	Conflict of interest: No conflict of interest was declared by the authors.
	Authors contact details: drahmetbasturk@hotmail.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Directed to the pediatric gastroenterology nurse, and drug boxes that were labeled with code numbers only and whose package ingredients were unknown were randomly administered to patients and randomization was ensured."
		The author did not reply to confirm. However, as they have been centrally randomised prior to recruitment, pseudorandomisation does not appear conceivable.
Allocation concealment (selection bias)	Low risk	"Directed to the pediatric gastroenterology nurse, and drug boxes that were labeled with code numbers only and whose package ingredients were un-

Basturk 2017 *(Continued)*

		known were randomly administered to patients and randomization was ensured." Code numbers known only to manufacturer.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Drugs that were completely the same in colour, smell, taste and packaging properties, but had one of the two different code numbers on them were used. The ingredients of the drugs were unknown to the doctor, nurse, and the participant, and which code number included which ingredient was known to the manufacturer only.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unblinding occurred after data collection and analysis complete.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Balanced withdrawals
Selective reporting (reporting bias)	Low risk	Outcomes reported as predefined in methods
Other bias	Low risk	Balanced groups and no other concerns

Bu 2007

Study characteristics

Methods	Type: randomised double-blind placebo-controlled study
	Setting: Department of Pediatrics, National Taiwan University Hospital and Keelung Hospital, Department of Health, Executive Yuan, Taiwan
	Study period: December 2004 to March 2005
Participants	**Establishment of diagnosis**
	Rome criteria: not specified
	Other elements of diagnostic work up: not specified
	Inclusion criteria
	Children under 10 years old, with chronic constipation defined as stool frequency of < 3 times per week for > 2 months and at least one of the following minor criteria: anal fissures with bleeding due to constipation, faecal soiling, or passage of large and hard stool
	Exclusion criteria
	Children with organic causes of constipation such as Hirschsprung's disease, spinal bifida (occulta), hypothyroidism or other metabolic or renal abnormalities, mental retardation, and children using drugs (e.g. calcium channel blockers, antidysrhythmic agents, anticonvulsants, antidepressants, anticholinergic agents) influencing gastrointestinal function other than laxatives were excluded.
	Age (mean ± SD) (in months)
	MgO (n = 18) 32.4 ± 13.9
	Probiotic (n = 18) 36.7 ± 14.5
	Placebo (n = 9) 35 ± 14.7

Bu 2007 *(Continued)*

Toilet trained or not: not specified - numbers queried with authors, but no response received

Presence of soiling/incontinence at baseline: yes

MgO (n = 18): 5.4/18? 30%

Probiotic (n = 18): 7.7/18? 42.9%

Placebo (n = 9): 3.6/9? 40%

Numbers queried with authors, but no response received.

Presence of impaction at baseline: not specified.

Concomitant diagnosis/symptoms: none

Sex (M/F):

MgO (n = 18): 9 M; 9 F

Probiotic (n = 18): 10 M; 8 F

Placebo (n = 9): 4 M; 5 F

Use of concurrent medication

Lactulose use (1 mL /kg per day) was allowed when no stool passage was noted for 3 days. Glycerin enema was used only when there was no defecation for > 5 days or abdominal pain was suffered due to stool impaction. All participants were asked to discontinue any laxatives previously prescribed 3 days before entering the protocol. The participants were also asked to avoid any other probiotics, yogurt or beverage containing probiotics for at least 2 weeks before treatment and during therapy.

Evaluation of Response

The parents received a stool diary to record the frequency of daily bowel movements, stool consistency, abdominal pain, faecal soiling and the use of lactulose or enema of their children. Bacterial cultures of stool were performed before and after treatment to evaluate the change of intestinal flora. Treatment success was defined as 3 spontaneous defecations per week with no episodes of faecal soiling in the fourth week.

Disease duration/chronicity (mean ± SD)

MgO (n = 18) 20.9 ± 15.6

Probiotic (n = 18) 21.9 ± 16.9

Placebo (n = 9) 22.8 ± 16.6

Number of participants

Number randomised: 45

MgO (n = 18)

Probiotic (n = 18)

Placebo (n = 9)

Number reaching end of study: 41

MgO (n = 16)

Probiotic (n = 17)

Placebo (n = 8)

Number analysed: total: 45

Bu 2007 *(Continued)*

MgO (n = 18)

Probiotic (n = 18)

Placebo (n = 9)

Postrandomisation exclusion: 4

Four participants discontinued the medication during the study period: two in the MgO group, one in the probiotic group and one in the placebo group (two participants suffered from acute gastroenteritis and two participants were lost to follow-up).

Interventions	**MgO** (n = 18) with MgO (50 mg/kg per day, b.i.d.)
	Probiotic: (n = 18) with Lcr35, 8 × 10 8 CFU/day (antibiophilus 250 mg, two capsules, b.i.d., Laboratoires Lyocentre, Aurillac, France)
	Placebo: (n = 9) (starch in content)
Outcomes	Treatment success was defined as >=3 spontaneous defecations per week with no episodes of faecal soiling in the fourth week.
	Comparisons of the frequency of defecation, consistency of stool, episodes of soiling or abdominal pain and the use of lactulose or enema were made among the 3 groups. Change in the intestinal flora was also evaluated.
Notes	Funding source: not specified
	Conflict of interest: not specified
	Authors contact details: Ling-Nan Bu, MD, Department of Pediatrics, Keelung Hospital, Department of Health, Executive Yuan, No. 268, Shin 2nd Road, Keelung City 201, Taiwan. Email: b05992@ya-hoo.com.tw

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The 45 children were assigned randomly into three groups according to a computer-generated randomisation list.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described, method of concealment described in text refers to blinding not concealment. Authors were contacted but no response received.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Throughout the duration of the study all investigators, participants, and data analysts were blinded to the assigned treatment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Throughout the duration of the study all investigators, participants, and data analysts were blinded to the assigned treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Balanced withdrawals
Selective reporting (reporting bias)	Low risk	Authors report findings based on predefined outcomes.

Bu 2007 *(Continued)*

Other bias	Low risk	Balanced groups and no other concerns

Chao 2016

Study characteristics

Methods	Type: prospective, randomised, placebo-controlled clinical trial
	Setting: not defined
	Study period: not defined
Participants	**Establishment of diagnosis**
	Based on Rome III criteria
	Other elements of diagnostic work up: none
	Inclusion criteria
	Children 6 months to 10 years of age presenting with functional constipation.
	No information on specific criteria.
	Exclusion criteria
	No data
	Baseline characteristics
	Age (mean ± SD)
	IG (Group A): 3.7 ± 1.5 years
	CG (Group B): 4.0 ± 1.8 years
	Toilet trained or not: not specified
	Presence of soiling/incontinence at baseline: not defined
	Presence of impaction at baseline: not defined
	Concomitant diagnosis / symptoms: not defined
	Sex (M/F)
	IG (Group A): 17 males, 24 females
	CG (Group B): 19 males, 21 females
	Use of concurrent medication: no data
	Disease duration / chronicity (mean ± SD): no data
	Number of participants
	Number randomised: IG: 41; CG: 40
	Number reaching end of study: no data
	Number analysed: IG: 41; CG: 40
	Postrandomisation exclusion: no data

Chao 2016 *(Continued)*

Interventions	No information about disimpaction before study intervention
	IG: Magnesium oxide and probiotics (*Clostridium butyricum Miyairi*) for 12 weeks.
	CG: Magnesium oxide for 12 weeks.
Outcomes	Severity of constipation
	Quantification of microflora
Notes	Funding source: not reported
	Conflict of interest: not reported
	Author contact details: not reported
	Author emailed on 14 June 2021 to request further details about risk of bias domains. Emailed again on 15 September 2021, no response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Mentions it was randomised but did not mention means of randomisation.
Allocation concealment (selection bias)	Unclear risk	No stated method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo controlled but does not mention blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information about blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers of participants randomised, withdrawn and that completed the study, are unclear.
Selective reporting (reporting bias)	Unclear risk	Only defecation frequency and constipation score are reported, but this study is only available as an abstract.
Other bias	Unclear risk	Unable to assess balance of groups.

Coccorullo 2010

Study characteristics

Methods	Type: double-blind, randomised, placebo-controlled clinical trial.
	Setting: Gastrointestinal Endoscopy and Motility Unit of the Department of Pediatrics, University ''Federico II'' of Naples, Italy.
	Study period: January 2008 to December 2008

Coccorullo 2010 *(Continued)*

Participants	**Establishment of diagnosis**

Establishment of diagnosis

Per Rome III Criteria, at least two of these symptoms: #2 defecations per week; history of excessive stool retention and painful or hard bowel movements; presence of a large faecal mass in the rectum; history of large-diameter stools.

Other elements of diagnostic work up

Used BSS to describe stool consistency.

Weaning started in a standard fashion at 5 months of age with fruit followed by weaning purees with a dose of 0.5 g/Kg/day of fibre, according to guideline proposed by the American Academy of Pediatrics Committee on Nutrition.

Inclusion criteria

Formula-fed infants > 6 months of age with functional constipation per Rome III criteria.

Exclusion criteria

Infants with organic causes of constipation such as Hirschsprung's disease, spinal bifida (occulta), hypothyroidism or other metabolic or renal abnormalities, and mental retardation, infants taking oral laxatives or antibiotics, and infants who were fed breast milk and formula with the addition of probiotics, prebiotics, or both.

Baseline characteristics

Age (mean ± SD)

IG: 8.2 ± 2.4 months

CG: 8.8 ± 2.1 months

Toilet trained or not: not specified, but assumed not based on age.

Presence of soiling/incontinence at baseline: not applicable

Presence of impaction at baseline

Provided as percentages only, and the percentage for CG does not add up

IG: 16/22 (72.7%)

CG: 11.5/22 (52.4%)

Concomitant diagnosis / symptoms: none

Sex (M/F)

IG: 8 males; 14 females

CG: 16 males; 6 females

Use of concurrent medication

Glycerin suppository was used only when there was no defecation for > 5 days.

Disease duration / chronicity (mean ± SD): no data

Number of participants

Number randomised: total 44

IG: 22; CG: 22

Number reaching end of study: total: 44

Coccorullo 2010 *(Continued)*

	IG: 22; CG: 22
	Number analysed: IG: 22; CG: 22
	Postrandomisation exclusion: none
Interventions	**IG**: *Lactobacillus reuteri* (DSM 17938) was administered at a dose of 10^8 colony-forming units in 5 drops of a commercially available oil suspension (Reuterin, Noos S.r.l.; BioGaia AB, Stockholm, Sweden), 30 minutes after feeding, once per day for 8 weeks.
	CG: Comparable placebo, once daily for 8 weeks.
Outcomes	**Primary outcome**
	Frequency of bowel movements per week, stool consistency, and presence of inconsolable crying episodes.
	Secondary outcome was comparison of the frequency of defecation, stool consistency, and presence of inconsolable crying episodes in the two groups.
Notes	Funding source: Noos (Italy)
	Conflict of interest: none
	Author contact details: staiano@unina.it
	Author emailed on 14 June 2021 to request further details about allocation concealment. Emailed again on 15 September 2021, no response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Automatically generated randomisation list"
Allocation concealment (selection bias)	Unclear risk	No stated method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants received identical placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome data gathered by parents in a diary, parents remained blinded during study period.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	No apparent concerns. No imbalance in baseline population.

Guerra 2011

Study characteristics

Methods	Type: cross-over, double-blind, formula-controlled clinical trial with 2 parallel groups
	Setting: Public school in the central area of the city of Belo Horizonte, Minas Gerais, Brazil
	Study period: Not mentioned
Participants	**Establishment of diagnosis**
	Per Rome III Criteria, at least two out of six of the following symptoms for two or more months: two or fewer defecations per week;
	at least one episode of faecal incontinence per week; history of retentive posturing or excessive volitional stool retention; history of painful or hard bowel movements; presence of a large faecal mass in the rectum; history of wide diameter stools that may obstruct the toilet.
	Other elements of diagnostic work up: used BSS to describe stool consistency
	Inclusion criteria
	Children aged 5 to 15 years and with functional chronic intestinal constipation (FC per Rome III).
	Exclusion criteria
	Use of any oral laxative < 4 wk before intake, metabolic disease, a history of gastrointestinal surgery and faecal incontinence.
	Children with faecal incontinence were excluded in order to make the sample more homogeneous in relation to disease severity.
	Baseline characteristics
	Age
	IG: 5 to 7 y: 12; 8 to 9 y: 5; 10 to 12 y: 11; 13 to 15 y: 2
	CG: 5 to 7 y: 6; 8 to 9 y: 7; 10 to 12 y: 12; 13 to 15 y: 4
	Toilet trained or not: not defined but children with faecal incontinence were excluded
	Presence of soiling/incontinence at baseline: no
	Presence of impaction at baseline: not defined
	Concomitant diagnosis/symptoms: abdominal pain and defecation pain
	Sex (M/F)
	IG: 6 males; 24 females
	CG: 6 males; 23 females
	Use of concurrent medication: none
	Disease duration/chronicity (mean ± SD): no data
	Number of participants
	Number randomised
	total: 60; IG: 30; CG: 30
	Number reaching end of study
	total: 59; IG: 30; CG: 29

Guerra 2011 *(Continued)*

	Number analysed
	total: 59; IG: 30; CG: 29
	Postrandomisation exclusion: not mentioned
Interventions	**IG**: *bifidobacterium longum* concentrate (1 mL) added to 9 mL of a commercial goat yogurt (Capril Jacomé, Contagem, Brazil) to obtain a final concentration of 109 colony forming unit (CFU)/mL.
	CG: students randomised to 2 groups to receive intervention or placebo once daily for 5 weeks, and then crossed over to alternate intervention for another 5 weeks, once per day.
	The goat yogurt contained the two classical yogurt starters, *Lactobacillus delbrueckii* subspecies bulgaricus and *Streptococcus thermophilus* from the YF-L812 commercial culture (DVS - Christian Hansen Laboratory, Horsholm, Denmark).
	Both yogurts were maintained at 4 ℃ until use and for a maximum of one week.
	During this period, the bifidobacterium cells remained viable at 109 CFU/mL levels.
Outcomes	Defecation frequency, stool consistency and abdominal or defecation pain were assessed at the first (A1), third (A2) and fifth week (A3) before crossing over, and the first (B1), third (B2) and fifth week (B3) after crossing over.
Notes	Funding source: grants from Conselho Nacional de Desenvolvimento Cientifico e Tecnológico and Fundação de Amparo à Pesquisa do Estado de Minas Gerais
	Conflict of interest: not reported
	Author contact details: jnicoli@icb.ufmg.br

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The allocation sequence and randomisation list were computer-generated using the Epi Info Program.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not adequately described, methods describe blinding not concealment. Authors were contacted but no response received.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The two products, goat yogurt with or without *B longum* were identical in weight, colour, smell, taste and package. All doctors and children involved were unaware of the treatment administered.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The two products, goat yogurt with or without *B longum* were identical in weight, colour, smell, taste and package. All doctors and children involved were unaware of the treatment administered.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participant flow described - only one dropped out due to not wanting to take part.
Selective reporting (reporting bias)	High risk	All outcomes reported but only in graphical format, and we were unable to extract any primary numerical data. Authors did not respond.
Other bias	Low risk	Balanced groups and no other concerns.

Jadresin 2018

Study characteristics

Methods	Type: randomised double-blind placebo-controlled study
	Setting: Referral Centre for Pediatric Gastroenterology, Children's Hospital Zagreb
	Study period: May 2012 to December 2014
Participants	**Establishment of diagnosis**
	According to the Rome III criteria: Individuals with weekly number of defecations < 3 and individuals with at least one of the symptoms stated below:
	• weekly encopresis > 1 painful defecation
	• individuals who defecate thick and large amounts of stools
	• those who defecate in large amounts that obstruct the toilet.
	• individuals with the behaviour of stopping defecation during defecation.
	• individuals who were found to have hard stool during abdominal or rectal examination.
	Other elements of diagnostic work up: not specified
	Inclusion criteria
	All children referred to a paediatric gastroenterologist for functional chronic constipation (age 2 to 18 years) at the Referral Centre for Pediatric Gastroenterology, Children's Hospital Zagreb from May 2012 to December 2014 were eligible for the study. Diagnosis was based on Rome III criteria.
	Exclusion criteria
	Criteria were presence of red flags and use of probiotic 7 days before the inclusion in the study.
	Baseline characteristics
	Age (mean ± SD): (years)
	IG: 4.4 ± (range 3 to 15)
	CG: 4.7 ± (range 2 to 16)
	Toilet trained or not: not specified
	Presence of soiling/incontinence at baseline: not specified
	Presence of impaction at baseline: not specified
	Concomitant diagnosis / symptoms: none
	Sex (M/F)
	IG: 6 M; 12 F (n = 18)
	CG: 4 M; 11 F (n = 15)
	Use of concurrent medication: none
	Evaluation of response
	Disease duration/chronicity (mean ± SD): not specified
	Number randomised
	Number randomised: 33
	• IG: n = 18

Jadresin 2018 *(Continued)*

- CG: n = 15

Number reaching end of study: 27

- IG: n = 16
- CG: n= 11

Number analysed: total: 33

- IG: n = 18
- CG: n= 15

Postrandomisation exclusion: 9

Five children in the synbiotic group and four in the placebo group were excluded from the study because they did not complete the study.

Interventions	**IG**: the active study product containing freeze-dried *L reuteri* DSM 17938, isomalt, xylitol, sucrose distearate, hydrogenated palm oil, lemon-lime flavouring, and anhydrous citric acid. The total viable count of *L reuteri* was 1 # 108 CFU (colony forming units)/tablet. **CG**: the placebo study product consisted of an identical formulation as in the active study product in all respects but live bacteria. Both: both groups received lactulose treatment in a dose of 1 to 3 mL/kg per day.
Outcomes	**Primary outcomes** were frequency of bowel movements, change of the frequency of bowel movements, and presence of symptoms at the end of the study. **Secondary outcomes** were need for lactulose at the end of the treatment, dose of the lactulose used, number of days with soiling, and stool consistency using a Bristol Stool Chart.
Notes	Funding source: not reported Conflict of interest: I.H. in the last 2 years received speakers grants from BioGaia, Nutricia, Medis Adria, Pharmas. O.J. received speakers grants from BioGaia. Z.M. has in the last 2 years received speakers grants from Pharmas. S.K. participated as a clinical investigator, and/or speaker for Abbott, Arla, Biogaia, Chr. Hansen, Danone, Dukat, Nestle, Nutricia, and MSD. S.S. has no conflict of interest. I.T. has no conflict of interest. Authors contact details: Iva Hojsak, MD, PhD, Referral Center for Pediatric Gastroenterology and Nutrition, Children's Hospital Zagreb, Klaiceva 16, 10000 Zagreb, Croatia (e-mail: ivahojsak@gmail.com)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using Random Allocation Software in which every participant got a number and received the preparation successively.
Allocation concealment (selection bias)	Low risk	To ensure allocation concealment, sequentially numbered, opaque, sealed envelopes were used, and an independent person prepared the randomisation schedule.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both products, active and placebo, were of the same taste, same colour and the same smell.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unblinding procedure was performed only after the statistical analyses were accomplished and the results finalised

Jadresin 2018 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Balanced withdrawals
Selective reporting (reporting bias)	Low risk	All endpoints are reported. The primary endpoints have been reported with a measure that is out of keeping with other studies in this review, however, it is transparent and does match their goals.
Other bias	Low risk	Balanced groups and no other concerns.

Khodadad 2010

Study characteristics

Methods	Type: double-blind, randomised, placebo-controlled clinical trial.
	Setting: Children's Medical Center in Tehran, Iran referred to paediatric GI clinic for constipation
	Study period: January 2008 to December 2009
Participants	**Establishment of diagnosis**
	Rome criteria: childhood functional constipation defined by Rome III criteria.
	Other elements of diagnostic work up: from seven days prior to study all children were requested to record frequency of BMs, number of faecal incontinence episodes, stool consistency, abdominal pain, painful defecation and effects such as vomiting, diarrhoea and oil seepage in a bowel diary.
	Inclusion criteria
	Children 4 to 12 years with functional constipation per Rome III criteria.
	Exclusion criteria
	Organic causes for constipation such as Hirschsprung's disease, spina bifida occulta, hypothyroidism, cystic fibrosis, neurologic abnormalities and intestinal pseudo-obstruction.
	Baseline characteristics
	Age (mean ± SD): group A (paraffin + placebo): 6.9 ± 2.4 years; group B (synbiotics + placebo): 6.2 ± 1.9 years; group C (paraffin + synbiotics): 5.9 ± 2.2 years
	Toilet trained or not: not specified
	Presence of soiling/incontinence at baseline
	Group A (paraffin + placebo): 10/29 (34.5%)
	Group B (synbiotics + placebo): 13/31 (41.9%)
	Group C (paraffin + synbiotics): 9 /37(24.3%)
	Presence of impaction at baseline: evaluated by physician exam. If present, disimpaction was indicated (see below).
	Concomitant diagnosis/symptoms: abdominal pain, painful defecation vomiting, diarrhoea and oil seepage.
	Sex (M/F)
	Group A (paraffin + placebo): 13 males; 16 females

Khodadad 2010 *(Continued)*

	Group B (synbiotics + placebo): 15 males; 16 females
	Group C (paraffin + synbiotics): 18 males; 19 females
	Use of concurrent medication: none
	Disease duration / chronicity (mean ± SD): no data
	Number of participants
	Number randomised: total 102
	Group A: 29;
	Group B: 31;
	Group C: 37
	Number reaching end of study: total: 97
	Group A: 26;
	Group B: 29;
	Group C: 37
	Number analysed: total: 97;
	Group A: 29;
	Group B: 31;
	Group C: 37
	Postrandomisation exclusion: not mentioned
Interventions	Disimpaction prior to start of study: rectal enema (paraffin oil 15 to 30ml/year) once daily for three days in order to accomplish rectal disimpaction.
	Group A: 1.5 ml/kg/day oral liquid paraffin plus placebo
	Group B: 1 sachet synbiotic per day (restore* 1 x 109 CFU/1 sachet, Protexin Co, UK). Synbiotic combination consisted of probiotic strains containing *L casei, L rhamnosus, S thermophilus, B breve, L acidophilus, B infantis*, fructo-oligosaccharide as prebiotic, and placebo.
	Group C: 1.5 ml/kg/day oral liquid paraffin and 1 sachet synbiotic per day.
	All patients in the 3 groups received drugs in bottles and sachets with similar shape, taste and colour.
	Dietary and toilet training advice was given to all participants similarly.
Outcomes	**Primary outcome**
	Frequency of BMs per week, stool consistency, faecal incontinence episodes per week, presence of abdominal pain, and painful defecation
	Secondary outcomes
	Successful treatment and incidence of adverse effects such as vomiting, diarrhoea and seepage. Stool consistency was rated by the participants as hard, normal or watery.
Notes	Funding source: not reported
	Conflict of interest: none

Khodadad 2010 *(Continued)*

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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The randomisation and allocation sequence was generated before study began by our biostatistics consultant. Patients assigned to each group were selected randomly." Does not describe means of randomisation. Authors were contacted but no response received.
Allocation concealment (selection bias)	Low risk	"The randomisation and allocation sequence was generated before study began by our biostatistics consultant. Patients assigned to each group were selected randomly." Authors do not describe means of allocation concealment explicitly, but with the use of an external staff member to generate this, on balance, we rated it as low risk.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Label of drugs was replaced by a new label indicating drug A or B. Contents of sachets or bottles were not known to the physicians or nurses involved in the study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Label of drugs was replaced by a new label indicating drug A or B. Contents of sachets or bottles were not known to the physicians or nurses involved in the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Five participants were stated to be "lost to follow-up" postrandomisation, but there was no large imbalance.
Selective reporting (reporting bias)	Low risk	The outcomes outlined in the study design section were presented in the results.
Other bias	Low risk	Balanced groups and no other concerns.

Kubota 2020

Study characteristics

Methods	Type: prospective, double-blind, placebo-controlled, randomised, and parallel-group trial
	Setting: five paediatric outpatient clinics in Japan
	Study period: January 2017 to December 2017
Participants	**Establishment of diagnosis**
	Rome IV criteria
	Constipation for at least one month and including at least two of the following criteria: two or fewer defecations per week, a history of excessive stool retention, a history of painful or hard bowel movements, a history of large-diameter stools, presence of a large faecal mass in the rectum, and incontinence after the acquisition of toileting skills.
	Other elements of diagnostic work up
	• Before patients were included in the study, their baseline condition of constipation was evaluated over a period of two weeks using a defecation diary.

Kubota 2020 *(Continued)*

- Changes in the gut microbiome profiles using high-throughput sequencing of the V3–V4 region of the bacterial 16S ribosomal RNA gene before and after treatment.
- Defecation frequency was assessed with a defecation diary.
- Stool consistency was scored according to the Bristol stool form scale.

Inclusion criteria

More than six months old or under six years of age, diagnosis of functional constipation according to the Rome IV criteria

Exclusion criteria

Children with known organic causes of constipation, such as Hirschsprung's disease, spina bifida, cow's milk allergy, and metabolic disease.

Baseline characteristics

Age (mean ± SD) (months)

IGA: 32.7 ± 15.9

IGB: 40.3 ± 17.4

CG: 34.2 ± 15.2

Toilet trained or not: not specified

Presence of soiling/incontinence at baseline: no

Additionally, other symptoms related to constipation, such as abdominal pain, withholding behavior, and faecal soiling, were not collected in this study.

Presence of impaction at baseline: not specified

Concomitant diagnosis / symptoms: none

Sex (M/F)

IGA: 11 M; 9 F (n = 20)

IGB: 10 M; 9 F (n = 19)

CG: 12 M; 9 F (n = 21)

Use of concurrent medication

The use of other laxatives, antibiotics, probiotics, fermented dairy products, and yogurt were not allowed a month before inclusion and during the study period, and a glycerin suppository was used only when there was no defecation for more than three days.

Disease duration/chronicity (mean ± SD): not specified

Number of participants

Number randomised: total: 63 (3 then excluded)

IGA: n = 20

IGB: n = 19

CG: n = 21

Number reaching end of study: total: 60

IGA: n = 20

IGB: n = 19

Kubota 2020 *(Continued)*

	CG: n = 21
	Number analysed: total: 60
	IGA: n = 20
	IGB: n = 19
	CG: n = 21
	Postrandomisation exclusion: 3 (2 for using antibiotics for otitis media and 1 who developed Kawasaki disease during study period)
Interventions	**IGA**: *L rueteri* DSM 17938 and lactose hydrate as a placebo of MgO.
	IGB: *L rueteri* DSM 17938 and MgO and lactose hydrate.
	CG: Placebo of *L rueteri* DSM 17938 and MgO and lactose hydrate.
Outcomes	**Primary outcome**: defecation frequency at the fourth week after starting treatment compared with the baseline condition.
	Secondary outcomes: change in the stool consistency score at the fourth week compared with the baseline condition; changes in the gut microbiome profiles using high-throughput sequencing of the V3–V4 region of the bacterial 16S ribosomal RNA gene before and after treatment.
	A cross-section analysis of defecation frequency was performed with the taxonomy data.
Notes	Funding source: this study was funded through scholarships. Additionally, BioGaia AB Sweden supplied products of *L reuteri* DSM 17938 and KENEI Pharmaceutical Co., Ltd., supplied the placebo and magnesium oxide.
	Conflict of interest: funders had no role in the design of the study; collection, analyses, or interpretation of data; writing of the manuscript; or in the decision to publish the results.
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly divided into three groups according to an automatically generated randomisation list.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated. Authors were contacted but no response received.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All caregivers of participants, research staff, and physicians were blinded to which treatment group the participants belonged.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded throughout.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Balanced withdrawals

Kubota 2020 *(Continued)*

Selective reporting (reporting bias)	Low risk	Author replied and confirmed it was completed as per their study plan, and all data were reported.
Other bias	Low risk	No concerns with baseline data or other risks

Russo 2017

Study characteristics	
Methods	Type: open label randomised, placebo-controlled clinical trial.
	Setting: outpatient setting. Gastrointestinal Endoscopy and Motility Unit of the Department of Translational Medical Science, Section of Pediatrics, University of Naples "Federico II", Italy
	Study period: January 2014 to December 2014
Participants	**Establishment of diagnosis**
	Rome III criteria: < 3 defecations per week; history of excessive stool retention and painful or hard bowel movements; faecal incontinence > 2 times/week; withholding behaviour; presence of a large faecal mass in the rectum; history of large diameter stools.
	Other elements of diagnostic work up
	At enrolment, frequency of bowel movements, stool consistency according to the Bristol stool form scale (BSFS), presence of faecal incontinence, abdominal pain, painful defecation, and rectal bleeding were accurately recorded. A thorough medical history was collected by one of the authors and all participants underwent a clinical evaluation, including anorectum digital examination, in order to evaluate whether an abdominal or rectal faecal mass was present.
	Inclusion criteria
	Rome III criteria, as described above
	Exclusion criteria
	Children with suspected or proved organic causes of constipation, such as Hirschsprung's disease, spinal bifida, hypothyroidism or other metabolic or renal abnormalities, and mental retardation were excluded from the study.
	Baseline characteristics
	Age (mean ± SD) (years)
	IG: 7.4 ± 2.8
	CG: 7.1 ± 2.5
	Whole group: 7.2 ± 2.3
	Toilet trained or not
	A proper toilet training, with regular stool sittings for 5 to 10 min after each meal, was required.
	Presence of soiling/incontinence at baseline: specified
	IG: 5/27(18.5%)
	CG: 4/28 (14%)
	Presence of impaction at baseline: yes, rectal enema

Russo 2017 *(Continued)*

Concomitant diagnosis/symptoms: none

Sex (M/F)

IG: 13 M (48.1%); 14 F (n = 27)

CG: 13M (46.4%); 15 F (n = 28)

Use of concurrent medication

Other laxatives were not allowed during the study period, whereas enemas were permitted only when there was no defecation for > 3 days, as a rescue therapy. (PEG was increased if not improving after 3 days)

Disease duration / chronicity (mean ± SD): 2 months (8 weeks)

Number of participants

Number randomised: total: 55

IG: 27

CG: 28

Number reaching end of study: total: 50

IG: 25

CG: 25

Number analysed: total: 50

IG: 25

CG: 25

Postrandomisation exclusion: 5 children dropped out from the study due to different reasons.

Interventions	**IG**: Oral combination of PEG 4000 (Pergidal® sachets 3.6 g) plus a PM including *Bifidobacteria breve* M-16 V®, infantis M-63®, and longum BB536® (Tribif® sachets 3 g) (Valeas®Spa, Milan, Italy) **CG**: Oral PEG only (Pergidal® sachets 3.6 g) Both groups: children in both groups underwent rectal disimpaction by rectal enema (120 mL sodium-dioctyl sulfosuccinate and sorbitol) on three consecutive days to achieve an empty rectum before starting the treatment trial.
Outcomes	**Primary outcome** measures were frequency of bowel movements per week, stool consistency, presence of abdominal pain, faecal incontinence, painful defecation, and rectal bleeding. Treatment success was defined as ≥ 3 defecation per week, stool consistency ≥ grade 3 on BSFS, and no episodes of abdominal pain, faecal incontinence, painful defecation, and rectal bleeding. **Secondary outcome** measures were safety and tolerability of the study products evaluated through the incidence of adverse effects such as vomiting, nausea or meteorism, flatulence, and diarrhoea
Notes	Funding source: Valeas S.p.A. (Italy) provided a grant for data analysis. Conflict of interest: the authors declare that they have no competing interests. Authors contact details: staiano@unina.it

Risk of bias

Bias	Authors' judgement	Support for judgement

Russo 2017 *(Continued)*

Random sequence generation (selection bias)	Low risk	All the enrolled children were randomly assigned into two groups according to an automatically generated randomisation list.
Allocation concealment (selection bias)	Unclear risk	Method not stated. Authors were contacted but no response received.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Balanced withdrawals
Selective reporting (reporting bias)	Low risk	Reported as per study plan.
Other bias	Low risk	No baseline imbalance

Tabbers 2011

Study characteristics	
Methods	Type: prospective randomised, double-blind, controlled trial.
	Setting: outpatient setting (Academic Medical Centre Amsterdam, University Hospital Groningen, The Netherlands and the Medical University of Warsaw, Poland), 12 Dutch non-academic hospitals and general practitioners (region of Rotterdam) in The Netherlands.
	Study period: February 2008 to November 2008
Participants	**Establishment of diagnosis**
	Rome III criteria
	Inclusion criteria
	Children were eligible to be randomly assigned if they had been suffering from functional constipation according to Rome III criteria for the last 2 months.
	They had a defecation frequency of < 3 times per week and 1 or more of the following criteria.
	• Faecal incontinence >1 episode per week • A large amount of stools that clog the toilet • Painful defecation • Withholding behaviour • Abdominal or rectal faecal impaction on physical examination • Children had to be familiar with consumption of dairy products
	Exclusion criteria
	• Treatment for constipation 2 weeks before the start of the study

Tabbers 2011 *(Continued)*

- A diagnosis of either IBS or functional nonretentive faecal incontinence according to Rome III criteria
- A diagnosis of mental retardation or metabolic disease (hypothyroidism)
- Hirschsprung disease, spinal anomalies, anorectal pathology
- Previous gastrointestinal surgery, lactose intolerance or known allergy to a product component
- Treatment with antibiotics in the previous month
- Treatment with medication that influences gastrointestinal motility (e.g. cisapride)

Baseline characteristics

Age (mean ± SD) (years)

IG: 7.0 ± 3.4

CG: 6.5 ± 3.1

Toilet trained or not: yes

Presence of soiling / incontinence at baseline: yes

Presence of impaction at baseline: yes

Concomitant diagnosis/symptoms: none

Sex (M/F)

IG: 42 M (53%); 37 F (n = 79)

CG: 41M (51%); 39 F (n = 80)

Use of concurrent medication

During the product consumption period, participants were instructed to take 5 mg bisacodyl if they did not defecate for 3 consecutive days.

Disease duration/chronicity (mean ± SD): 2 months

Number of participants

Number randomised: 160

IG: 79

CG: 80

Number reaching end of study: 159

IG: 79

CG: 80

Number analysed: 148

IG: 74

CG: 74

Postrandomisation exclusion: 11

Interventions	**IG**: The probiotic product consisted of the fermented milk Activia (125-g pot containing 5 g of lactose) manufactured with lactic cultures including *B lactis* DN-173 010 (strain number I-2494 in French National Collection of Cultures of micro-organisms (CNCM, Paris, France) at least 4.25x10^9 colony-forming U (CFU) per pot), yogurt starter cultures (*Lactobacillus delbrueckii* ssp. *Bulgaricus* CNCM strain numbers

Tabbers 2011 *(Continued)*

I-1632 and I-1519, and *Streptococcus thermophilus* CNCM strain number I-1630, at least 1.2×10^9 CFU per pot) and *Lactococcus cremoris* (CNCM strain number I-1631).

CG: The control product consisted of a milk-based, nonfermented dairy product (125-g pot) without probiotics and with a low content of lactose (2.5g per pot). Both the probiotic and control preparations were checked according to national regulations for any contamination with known pathogens and macronutrient composition including lactose.

Both groups: during the study, all children were instructed to try to defecate on the toilet for 5 to 10 minutes after each meal and to complete daily a standardised bowel diary. Intake of any other fermented dairy product or yogurt was not allowed. Names of these products were pointed out in the diary

Outcomes	**Primary outcome:** change in stool frequency from baseline (the week before randomisation) to after 3 weeks of product consumption. **Secondary outcomes:** rate of success (defined as 3 or more bowel movements per week and < 1 faecal incontinence episode in 2 weeks over the last 2 weeks of product consumption) and the rate of responders (with a responder defined as a subject who reports a stool frequency >= 3 episodes during the last week of product consumption). Other secondary end points were calculated over the 3-week product consumption period: stool frequency; stool consistency; frequency of episodes of faecal incontinence; frequency of pain during defecation; frequency of digestive symptoms (abdominal pain and flatulence); frequency of adverse effects (nausea, diarrhoea, and bad taste); and frequency of intake of bisacodyl.
Notes	Funding source: Danone Research is the sponsor of this study. Conflict of interest: authors declare that they have no competing interests. Authors contact details: m.m.tabbers@amc.nl

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers were generated by a computer program with an allocation ratio of 1:1 and with well-balanced blocks.
Allocation concealment (selection bias)	Low risk	The randomisation lists were kept confidential by the person responsible for the preparation of the study products and their labelling (unblinded pharmacist)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The 2 study products were identical in weight, colour, smell, taste, and packaging. All doctors, research staff, and participants with their caregivers remained unaware of the product administered to the participant.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All outcome assessors blinded throughout.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Balanced withdrawals
Selective reporting (reporting bias)	Low risk	Reported as per predefined outcomes.
Other bias	Low risk	Balanced groups and no other concerns.

Wegner 2018

Study characteristics

Methods	Type: double-blind, placebo-controlled, randomised, multicentre trial
	Setting: six paediatric gastroenterology departments in Poland: the Department of Gastroenterology, Hepatology, Nutritional Disorders and Paediatrics at the Children's Memorial Health Institute in Warsaw, the Department of Paediatric, Gastroenterology and Nutrition at the Medical University of Warsaw, the Department of Paediatrics, Gastroenterology and Eating Disorders at the Medical University of Gdansk, the Department of Paediatrics, Gastroenterology and Rheumatology at the Children's Hospital in Szczecin, the Department of Paediatrics, the Gastroenterology Unit, at the Medical University of Silesia in Katowice, and the Department of Gastroenterology and Hepatology of Children at the Medical University of Silesia in Zabrze.
	Study period: 2011 to 2014
Participants	**Establishment of diagnosis**
	Rome III Criteria: constipation for at least 2 months, < 3 bowel movements per week
	Inclusion criteria: 3 to 7-year-olds with a history of constipation for at least two months, with less than 3 bowel movements per week who had been treated with poor results for at least two months prior to the study
	Exclusion criteria: hypothyroidism, Hirschsprung disease, cystic fibrosis, anatomic defects of the gastrointestinal tract, a history of abdominal surgery, or antibiotic or probiotic treatment during two weeks prior to the study
	Baseline characteristics
	Age (mean ± SD) (years)
	IG: 4.66 ± 1.34
	CG: 4.69 ± 1.33
	Toilet trained or not: not specified
	Presence of soiling/incontinence at baseline
	• IG: 36/65 (55%) • CG: 39/64 (60%)
	Presence of impaction at baseline: not reported. However, 34 (26%) of participants received enemas as a monotherapy prior to enrolling into trial.
	Concomitant diagnosis/symptoms: not reported
	Sex (M/F)
	57 girls, 72 boys
	IG: 29 girls
	CG: 28 girls
	Use of concurrent medication: all of the children were treated pharmacologically before the inclusion to the trial (for at least 2 months) with poor results, described as no signs of improvement after therapy.
	Medicament
	Number of participants

Wegner 2018 *(Continued)*

Lactulose

43 (33%)

Macrogol

7 (5%)

Lactulose and macrogol

24 (19%)

Magnesium sulphate

3 (2%)

Paraffin

24 (18%) – 2 (1.5%) as monotherapy

Enemas

34 (26%) – 4 (3%) as monotherapy

Disease duration / chronicity (mean ± SD) (months)

IG: 23.23 ± 17.09

CG: 23.05 ± 17

Number of participants

Number randomised: total: 129

IG: 65 CG: 64

Number reaching end of study: total:

IG: 59 CG: 62

Number analysed: IG: 59 CG: 62

Postrandomisation exclusion:

IG: 5 (lack of compliance), 1 (lost to follow-up)

CG: 1 (lack of compliance), 1 (lost to follow-up)

Interventions	**IG**: *L. reuteri* DSM 17938 (1 tablet containing 10^8 CFU – colony forming units) and macrogol therapy (10 g per day) x 8 weeks
	CG: matching placebo and macrogol (10 g per day) x 8 weeks
	Enemas were administered for disimpaction to participants with a large faecal mass in the rectum, detected during abdominal or rectal examination before inclusion into the trial.
Outcomes	**Primary outcome:** number of participants with ≥ 3 bowel movements per week.
	Secondary outcomes: frequency of defecation; stool consistency; number of participants with painful defecation or faecal incontinence episodes at least once a week
Notes	Funding source: sponsored by BioGaia (Sweden). The sponsor had no involvement in: study design, the collection, analysis, and interpretation of data, the writing of the report; and the decision to submit the paper for publication.
	Conflict of interest: authors declare that they have no competing interest.

Wegner 2018 *(Continued)*

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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Automatically generated list by computer
Allocation concealment (selection bias)	Unclear risk	Method not stated. Authors were contacted but no response received.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical product, indistinguishable, and all parties blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded throughout
Incomplete outcome data (attrition bias) All outcomes	Low risk	Balanced withdrawals
Selective reporting (reporting bias)	Low risk	Reported as per predefined outcomes
Other bias	Low risk	Balanced groups and no other concerns

Wojtyniak 2017

Study characteristics

Methods	Type: randomised, double-blind, placebo-controlled trial
	Setting: Department of Pediatrics, the Medical University of Warsaw
	Study period: November 2013 to October 2016
Participants	**Establishment of diagnosis**
	Rome III criteria
	Other elements of diagnostic work up: stool consistency according to Bristol Stool Form Scale
	Inclusion criteria: < 5 years of age with functional constipation according to the Rome III criteria. Must include 2 or more of the following criteria: (1) ≤ 2 defecations per week, (2) at least 1 episode per week of incontinence after the acquisition of toileting skills, (3) history of retentive posturing or excessive volitional stool retention, (4) history of painful or hard bowel movements, (5) presence of a large faecal mass in the rectum, and (6) history of large-diameter stools that may obstruct the toilet. Those criteria must have been fulfilled for at least 1 month in infants up to 4 years and 2 months in children > 4 years.
	Exclusion criteria: irritable bowel syndrome, intellectual disability, metabolic disease (hypothyroidism), Hirschsprung disease, spinal anomalies, anorectal pathology, previous gastrointestinal surgery, functional nonretentive faecal incontinence, or treatment with medication that influences gastrointestinal motility

Wojtyniak 2017 *(Continued)*

Baseline characteristics

Age (mean ± SD) (months)

IG: 38.7(12.1)

CG: 37.3(14.2)

Toilet trained or not: not specified

Presence of soiling/incontinence at baseline: n (%)

IG: 21 (43.8)

CG: 21 (45.7)

Presence of impaction at baseline:

IG: 35(72.9)

CG: 35(76.1)

Concomitant diagnosis/symptoms: not mentioned

Sex (F/M)

IG: 26/22

CG: 26/20

Use of concurrent medication: no (laxatives were discontinued)

Disease duration/chronicity (mean ± SD)

IG: 14.7(9.1)

CG: 13.8(11.1)

Number of participants

Number randomised: total: 94

IG: 48

CG: 46

Number reaching end of study: 81

IG: 40

CG: 41

Number analysed:

IG: 40

CG: 41

Postrandomisation exclusion:

IG: 6 lost to follow-up

CG: 7 lost to follow-up

Interventions	**IG**: Lcr35 8×10^8 CFU, twice daily orally, for 4 weeks.

Wojtyniak 2017 *(Continued)*

	CG: comparable placebo (containing 99% milk powder and 1% magnesium stearate), twice daily orally, for 4 weeks. When there was no defecation for 3 consecutive days, PEG 3350 was allowed at a single dose of 1.5 mg/kg/d until the child passed a stool.
Outcomes	**Primary outcome:** treatment success, defined as ≥ 3 spontaneous stools per week, without episodes of faecal soiling (in toilet-trained children), in the last week of the intervention (week 4). **Secondary outcomes:** stool consistency (according to the Bristol Stool Form Scale), frequency of defecation, frequency of faecal soiling, frequency of pain during defecation, frequency of abdominal pain or flatulence, need for intake of additional laxative treatment, and adverse events.
Notes	Funding source: funded by the Medical University of Warsaw, which received a donation from Sequoia, the distributor of Lcr35. Conflict of interest: none Author contact details: szpital@litewska.edu.pl

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Sequentially numbered, white, opaque, sealed, and stapled envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Products identical and explicitly states all personnel and outcome assessors were blinded throughout.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	States outcome assessors blinded throughout.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition of less than 20%, balanced between both groups, all reasons given and all reasons balanced.
Selective reporting (reporting bias)	Low risk	Reported as per predefined outcomes.
Other bias	Low risk	Balanced groups and no other concerns

Zaja 2021

Study characteristics

Methods	Type: Randomised, double blind, placebo-controlled study Setting: Department of Pediatric Gastroenterology, Hepatology and Nutrition, University Hospital Sestre Milosrdnice Zagreb

Zaja 2021 *(Continued)*

	Study period: not reported

Participants	**Establishment of diagnosis**
	Rome III criteria
	Other elements of diagnostic work up: The diagnosis of anorexia nervosa (AN) was defined according to the APA's DSM-V diagnostic criteria
	Inclusion criteria: anorexia and constipation according to APA DSM-V and Rome III criteria, referred to gastroenterologist
	Exclusion criteria: AN and constipation present for less than 3 months; any disease other than AN or constipation, including Crohn's disease, food allergy, coeliac, hypothyroidism, any severe chronic illness including neoplasm or immunodeficiency; receiving probiotics, prebiotics, or antibiotics 14 days prior to enrolment, constipation prior to AN, receiving laxatives as a therapy for constipation or laxatives abuse, extraintestinal symptoms, such as fever and rash.
	Baseline characteristics
	Age range (years) (± SD)
	IG: L retueri, n = 15: 10 to 18 (15.06 ± 2.31)
	CG: placebo, n=16: 13 to 18 (15.13 ± 1.70)
	Toilet trained or not: not reported
	Presence of soiling/incontinence at baseline: not reported
	Presence of impaction at baseline: not reported
	Concomitant diagnosis/symptoms: anorexia
	Sex (M/F): all females (31)
	Use of concurrent medication: not reported
	Disease duration / chronicity (mean ± SD): not reported
	Number of participants
	Number randomised: total: 31
	IG: CG: not reported
	Number reaching end of study: total: not reported
	IG: CG: not reported
	Number analysed: IG: CG: not reported
	Postrandomisation exclusion: not reported

Interventions	**IG**: *Lactobacillus reuteri* DSM 17938
	CG: placebo

Outcomes	**Primary outcome:** relief of constipation, defined as dropping out from Rome-III criteria. It was assessed at the end of the 3-month therapy period.
	Secondary outcomes: normalisation of stool frequency, stool consistency and relief of dyspepsia, weight normalisation and recovery from malnutrition in respect of BMD and vitamin D3 serum levels. They were assessed at the end of the study, after the 6-month period. Achieving the Z-score for BMI less

Zaja 2021 *(Continued)*

	than -1.5 (CDC BMI-growth charts) or menstrual cycle normalisation, was considered weight normalisation. Stool frequency normalisation was defined as having 3 stools/week
Notes	Funding source: the study products (L reuteri DSM 17938 and placebo) were manufactured and supplied by BioGaia (Sweden) free of charge. The manufacturer had no role in the conception, protocol developments, design or conduct of the study, or in the analysis or interpretation of the data. Conflict of interest: none Author contact details: matea.crnkovic@kbcsm.hr (M.C. Cuk).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Automatically generated randomisation list
Allocation concealment (selection bias)	Unclear risk	"The study personnel, healthcare providers, patients and parents were blinded to the study group allocation." Paper did not specify how this was done. Authors were contacted but no response received.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study personnel, healthcare providers, patients and parents were blinded to the study group allocation. The unblinding procedure was performed after the study terminated and statistical analysis was finalised.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study personnel, healthcare providers, patients and parents were blinded to the study group allocation. The unblinding procedure was performed after the study terminated and statistical analysis was finalised.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts appear to have occurred.
Selective reporting (reporting bias)	Low risk	All appropriate outcomes reported.
Other bias	Low risk	No concerns

AN: Anorexia Nervosa; APA: American Psychological Association; BM: bowel movement; BMD: Body Mass Density; BSFS: Bristol Stool Form Scale; BSS: Bristol stool scale; CFU: colony-forming units; CG: control group; DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; IG: intervention group; PEG: polyethylene glycol; PM: probiotic mixture

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

Study	Reason for exclusion
Bekkali 2007	Not an RCT
Magro 2014	Ineligible population
Olgac 2013	Not an RCT: we contacted the authors and they stated that they used alternate entry based on the order in which patients attended the outpatients clinic.
Szajewska 2011	Not an RCT

RCT: randomised controlled trial

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

Abediny 2016

Methods	RCT
Participants	90
Interventions	IG: routine treatment of constipation in addition to probiotics
	CG: routine treatment of constipation (0.7 to 1.5 gr/kg Pidrolax powder daily) for 4 weeks
Outcomes	"Initial assessment included the frequency of bowel movements per week, stool consistency, number of fecal incontinence per week, and abdominal pain and painful defecation. The secondary assessment consisted of successful treatment, and side effects such as diarrhoea and vomiting."
Notes	No further information, authors unresponsive to contact

Saneian 2013

Methods	"Controlled Trial"
Participants	60
Interventions	IG: Synbiotic (Lactol®, composed of *lactobacillus sporogenes*, 1 tab/20 kg/d) plus mineral oil (paraffin 1 ml/kg/d) for two months
	CG: the mineral oil alone for two months
Outcomes	Symptoms of constipation (defecation frequency, stool consistency, stool retention, painful defecation, urgency, straining, passing mucus, and feeling of incomplete evacuation, soiling), compliance, side effects, and global improvement
Notes	Not clear if an RCT, no response from authors after contact.

CG: control group; IG: intervention group

DATA AND ANALYSES

Comparison 1. Probiotics vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Global improvement or treatment success, as defined by primary studies	4	313	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.73, 2.26]
1.2 Global improvement or treatment success, as defined by primary studies (sensitivity analysis fixed-effect model)	4	313	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.97, 1.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Withdrawals due to adverse events	5	357	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.21, 1.95]
1.4 Withdrawals due to adverse events (sensitivity analysis fixed-effect model)	5	357	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.21, 1.96]
1.5 Faecal incontinence, or encopresis, measured at end of study (continuous data)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.6 Faecal incontinence, or encopresis, measured at end of study (dichotomous data)	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.7 Need for additional therapies during the study period	4	370	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.78, 1.39]
1.8 Total adverse events	5	357	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.17, 1.67]

Analysis 1.1. Comparison 1: Probiotics vs placebo, Outcome 1: Global improvement or treatment success, as defined by primary studies

Study or Subgroup	Probiotics Events	Probiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Bu 2007	14	18	1	9	7.6%	7.00 [1.09 , 45.16]	
Jadresin 2018	7	18	6	15	22.2%	0.97 [0.42 , 2.27]	
Tabbers 2011	27	79	17	80	32.4%	1.61 [0.96 , 2.71]	
Wojtyniak 2017	24	46	28	48	37.7%	0.89 [0.62 , 1.29]	
Total (95% CI)		**161**		**152**	**100.0%**	**1.29 [0.73 , 2.26]**	
Total events:	72		52				

Heterogeneity: Tau² = 0.18; Chi² = 8.14, df = 3 (P = 0.04); I² = 63%
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable

0.02 0.1 1 10 50
Favours placebo   Favours probiotics

Analysis 1.2. Comparison 1: Probiotics vs placebo, Outcome 2: Global improvement or treatment success, as defined by primary studies (sensitivity analysis fixed-effect model)

Study or Subgroup	Probiotics Events	Probiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bu 2007	14	18	1	9	2.6%	7.00 [1.09 , 45.16]	
Jadresin 2018	7	18	6	15	12.5%	0.97 [0.42 , 2.27]	
Tabbers 2011	27	79	17	80	32.4%	1.61 [0.96 , 2.71]	
Wojtyniak 2017	24	46	28	48	52.5%	0.89 [0.62 , 1.29]	
Total (95% CI)		**161**		**152**	**100.0%**	**1.29 [0.97 , 1.72]**	
Total events:	72		52				

Heterogeneity: Chi² = 8.14, df = 3 (P = 0.04); I² = 63%
Test for overall effect: Z = 1.75 (P = 0.08)
Test for subgroup differences: Not applicable

0.02 0.1 1 10 50
Favours placebo   Favours probiotics
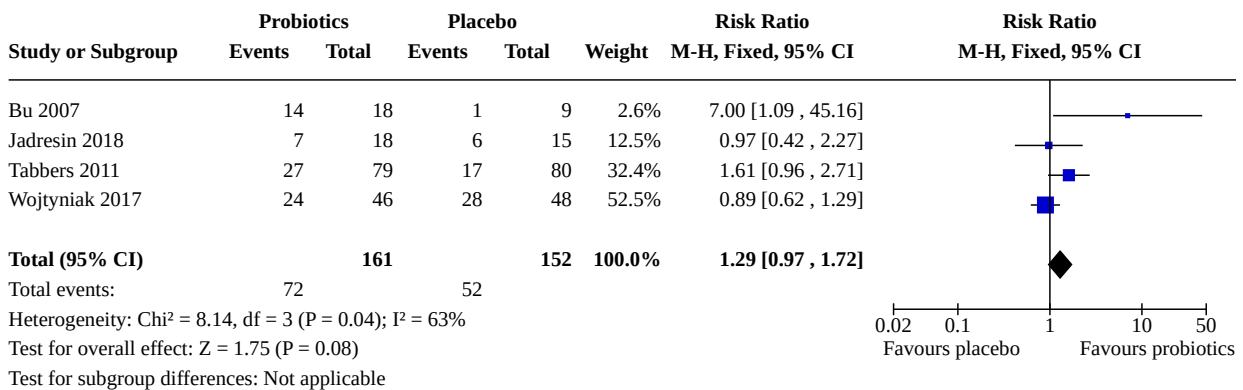
Analysis 1.3. Comparison 1: Probiotics vs placebo, Outcome 3: Withdrawals due to adverse events

Study or Subgroup	Probiotics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Bu 2007	1	18	1	9	17.6%	0.50 [0.04 , 7.10]	
Coccorullo 2010	0	22	0	22		Not estimable	
Jadresin 2018	0	18	0	15		Not estimable	
Tabbers 2011	4	79	6	80	82.4%	0.68 [0.20 , 2.30]	
Wojtyniak 2017	0	46	0	48		Not estimable	
Total (95% CI)		**183**		**174**	**100.0%**	**0.64 [0.21 , 1.95]**	
Total events:	5		7				

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.78 (P = 0.43)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours placebo   Favours probiotics

Analysis 1.4. Comparison 1: Probiotics vs placebo, Outcome 4: Withdrawals due to adverse events (sensitivity analysis fixed-effect model)

Study or Subgroup	Probiotics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bu 2007	1	18	1	9	18.3%	0.50 [0.04 , 7.10]	
Coccorullo 2010	0	22	0	22		Not estimable	
Jadresin 2018	0	18	0	15		Not estimable	
Tabbers 2011	4	79	6	80	81.7%	0.68 [0.20 , 2.30]	
Wojtyniak 2017	0	46	0	48		Not estimable	
Total (95% CI)		**183**		**174**	**100.0%**	**0.64 [0.21 , 1.96]**	
Total events:	5		7				

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.78 (P = 0.44)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours placebo   Favours probiotics

Analysis 1.5. Comparison 1: Probiotics vs placebo, Outcome 5: Faecal incontinence, or encopresis, measured at end of study (continuous data)

Study or Subgroup	Probiotics Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Bu 2007	2.1	3.8	18	2.7	1.4	9	-0.60 [-2.58 , 1.38]	
Wojtyniak 2017	0	0	46	0	0	48	Not estimable	

Test for subgroup differences: Not applicable

-10 -5 0 5 10
Favours probiotics   Favours placebo
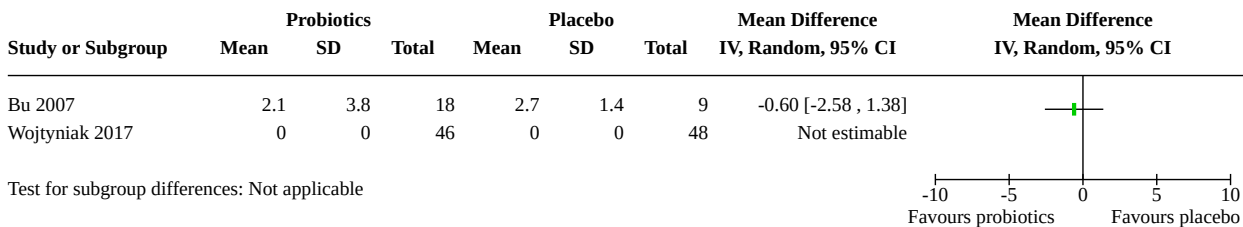
Analysis 1.6. Comparison 1: Probiotics vs placebo, Outcome 6: Faecal incontinence, or encopresis, measured at end of study (dichotomous data)

Study or Subgroup	Probiotics Events	Total	Placebo Events	Total	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Tabbers 2011	27	79	36	80	0.76 [0.51 , 1.12]	

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours probiotics   Favours placebo
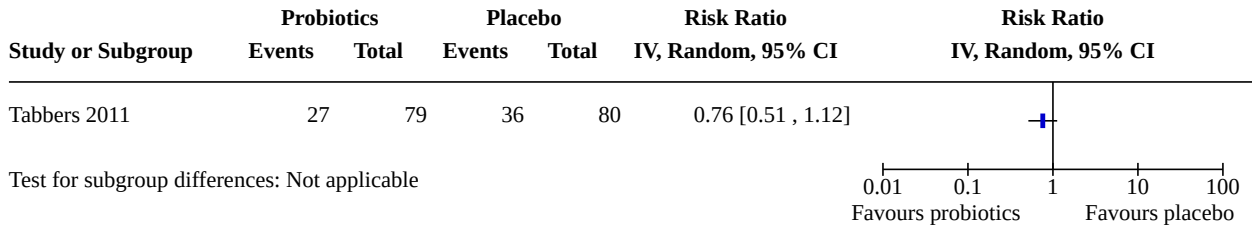
Analysis 1.7. Comparison 1: Probiotics vs placebo, Outcome 7: Need for additional therapies during the study period

Study or Subgroup	Probiotics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Banaszkiewicz 2005	19	43	18	41	24.9%	1.01 [0.62 , 1.63]	
Jadresin 2018	14	18	12	15	36.9%	0.97 [0.68 , 1.38]	
Tabbers 2011	19	79	24	80	22.7%	0.80 [0.48 , 1.34]	
Wojtyniak 2017	18	46	10	48	15.5%	1.88 [0.97 , 3.63]	
Total (95% CI)		**186**		**184**	**100.0%**	**1.04 [0.78 , 1.39]**	
Total events:	70		64				

Heterogeneity: Tau² = 0.03; Chi² = 4.28, df = 3 (P = 0.23); I² = 30%
Test for overall effect: Z = 0.27 (P = 0.79)
Test for subgroup differences: Not applicable

0.02 0.1 1 10 50
Favours probiotics   Favours placebo

Analysis 1.8. Comparison 1: Probiotics vs placebo, Outcome 8: Total adverse events

Study or Subgroup	Probiotic Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Bu 2007	0	18	0	9		Not estimable	
Coccorullo 2010	0	22	0	22		Not estimable	
Jadresin 2018	0	18	0	15		Not estimable	
Tabbers 2011	4	79	6	80	85.1%	0.68 [0.20 , 2.30]	
Wojtyniak 2017	0	46	3	48	14.9%	0.15 [0.01 , 2.81]	
Total (95% CI)		**183**		**174**	**100.0%**	**0.54 [0.17 , 1.67]**	
Total events:	4		9				

Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 1.07 (P = 0.28)
Test for subgroup differences: Not applicable

0.002 0.1 1 10 500
Favours probiotics   Favours placebo

Comparison 2. Probiotics and osmotic laxative vs osmotic laxative

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Frequency of defecation (number of stools/week at end of study)	3	268	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.57, 0.56]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.2 Frequency of defecation (number of stools/week at end of study) (sensitivity analysis fixed-effect model)	3	263	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.43, 0.43]
2.3 Global improvement or treatment success, as defined by primary studies	2	139	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.79, 1.15]
2.4 Global improvement or treatment success, as defined by primary studies (sensitivity analysis fixed-effect model)	2	139	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.78, 1.17]
2.5 Withdrawal due to adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.6 Withdrawal due to adverse events (sensitivity analysis fixed-effect model)	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.7 Faecal incontinence, or encopresis, measured at end of study (continuous)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.8 Faecal incontinence, or encopresis, measured at end of study (dichotomous)	2	184	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.73, 2.68]
2.9 Need for additional therapies during the study period	3	268	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.63, 1.50]
2.10 Total adverse events	4	308	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.18, 6.79]

Analysis 2.1. Comparison 2: Probiotics and osmotic laxative vs osmotic laxative, Outcome 1: Frequency of defecation (number of stools/week at end of study)

Study or Subgroup	Probiotics and osmotic laxative			Osmotic laxative			Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Banaszkiewicz 2005	6.1	1.8	43	6.8	3.1	41	21.2%	-0.70 [-1.79 , 0.39]	
Russo 2017	6.3	1	27	6.3	0.9	28	54.9%	0.00 [-0.50 , 0.50]	
Wegner 2018	7.5	3.3	65	6.9	2.5	64	23.9%	0.60 [-0.41 , 1.61]	
Total (95% CI)			**135**			**133**	**100.0%**	**-0.01 [-0.57 , 0.56]**	

Heterogeneity: Tau² = 0.09; Chi² = 2.94, df = 2 (P = 0.23); I² = 32%
Test for overall effect: Z = 0.02 (P = 0.99)
Test for subgroup differences: Not applicable

Favours osmotic laxative   Favours probiotics and osmotic laxative

Analysis 2.2. Comparison 2: Probiotics and osmotic laxative vs osmotic laxative, Outcome 2: Frequency of defecation (number of stools/week at end of study) (sensitivity analysis fixed-effect model)

Study or Subgroup	Probiotics and osmotic laxative			Osmotic laxative			Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Banaszkiewicz 2005	6.1	1.8	43	6.8	3.1	41	15.5%	-0.70 [-1.79 , 0.39]	
Russo 2017	6.3	1	25	6.3	0.9	25	66.4%	0.00 [-0.53 , 0.53]	
Wegner 2018	7.5	3.3	65	6.9	2.5	64	18.1%	0.60 [-0.41 , 1.61]	
Total (95% CI)			**133**			**130**	**100.0%**	**0.00 [-0.43 , 0.43]**	

Heterogeneity: Chi² = 2.94, df = 2 (P = 0.23); I² = 32%
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable

Favours osmotic laxative ⟷ Favours probiotics and osmotic laxative

Analysis 2.3. Comparison 2: Probiotics and osmotic laxative vs osmotic laxative, Outcome 3: Global improvement or treatment success, as defined by primary studies

Study or Subgroup	Probiotics and osmotic laxative		Osmotic laxative		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
Banaszkiewicz 2005	27	43	27	41	35.2%	0.95 [0.69 , 1.31]	
Russo 2017	22	27	24	28	64.8%	0.95 [0.75 , 1.20]	
Total (95% CI)		**70**		**69**	**100.0%**	**0.95 [0.79 , 1.15]**	
Total events:	49		51				

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.51 (P = 0.61)
Test for subgroup differences: Not applicable

Favours osmotic laxative ⟷ Favours probiotics and osmotic laxative

Analysis 2.4. Comparison 2: Probiotics and osmotic laxative vs osmotic laxative, Outcome 4: Global improvement or treatment success, as defined by primary studies (sensitivity analysis fixed-effect model)

Study or Subgroup	Probiotics and osmotic laxative		Osmotic laxative		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Banaszkiewicz 2005	27	43	27	41	54.0%	0.95 [0.69 , 1.31]	
Russo 2017	22	27	24	28	46.0%	0.95 [0.75 , 1.20]	
Total (95% CI)		**70**		**69**	**100.0%**	**0.95 [0.78 , 1.17]**	
Total events:	49		51				

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.47 (P = 0.64)
Test for subgroup differences: Not applicable

Favours osmotic laxative ⟷ Favours probiotics and osmotic laxative
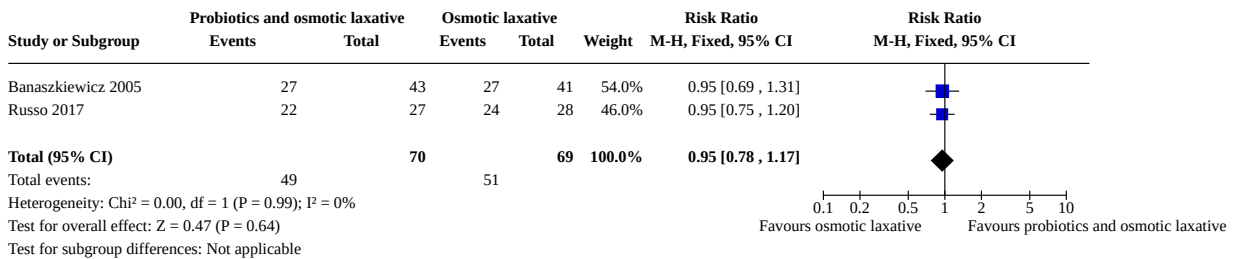
Analysis 2.5. Comparison 2: Probiotics and osmotic laxative vs osmotic laxative, Outcome 5: Withdrawal due to adverse events

Study or Subgroup	Probiotics and osmotic laxative		Osmotic laxative		Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Banaszkiewicz 2005	1	43	0	41	2.86 [0.12 , 68.35]	
Russo 2017	0	27	0	28	Not estimable	
Wegner 2018	0	65	0	64	Not estimable	

Favours probiotics and osmotic laxative ⟷ Favours osmotic laxative
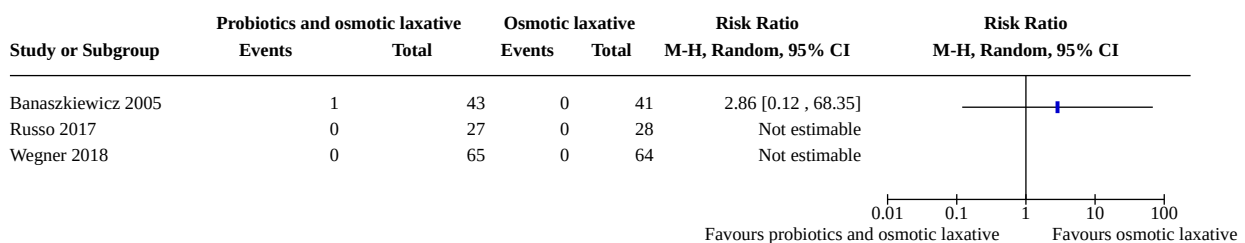
Analysis 2.6. Comparison 2: Probiotics and osmotic laxative vs osmotic laxative, Outcome 6: Withdrawal due to adverse events (sensitivity analysis fixed-effect model)

Study or Subgroup	Probiotics and osmotic laxative Events	Total	Osmotic laxative Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Banaszkiewicz 2005	1	43	0	41	2.86 [0.12 , 68.35]	
Russo 2017	0	27	0	28	Not estimable	
Wegner 2018	0	65	0	64	Not estimable	

0.01 0.1 1 10 100
Favours probiotics and osmotic laxative   Favours osmotic laxative
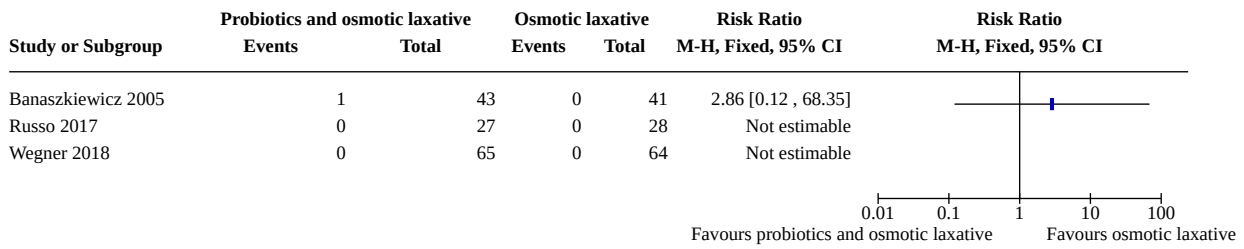
Analysis 2.7. Comparison 2: Probiotics and osmotic laxative vs osmotic laxative, Outcome 7: Faecal incontinence, or encopresis, measured at end of study (continuous)

Study or Subgroup	Probiotics and osmotic laxative Mean	SD	Total	Osmotic laxative Mean	SD	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Banaszkiewicz 2005	0.8	1.8	43	0.3	0.9	41	0.50 [-0.10 , 1.10]		+ ? + + + + +

Test for subgroup differences: Not applicable

-4 -2 0 2 4
Favours probiotics and osmotic laxative   Favours osmotic laxative

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 2.8. Comparison 2: Probiotics and osmotic laxative vs osmotic laxative, Outcome 8: Faecal incontinence, or encopresis, measured at end of study (dichotomous)
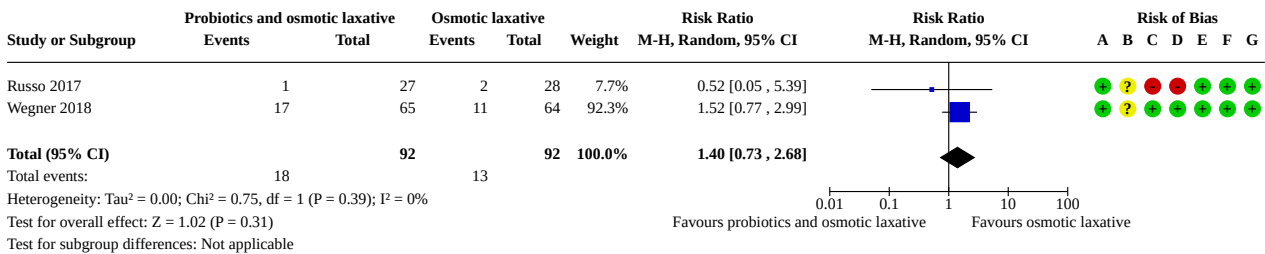
Study or Subgroup	Probiotics and osmotic laxative Events	Total	Osmotic laxative Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Russo 2017	1	27	2	28	7.7%	0.52 [0.05 , 5.39]		+ ? + + + + +
Wegner 2018	17	65	11	64	92.3%	1.52 [0.77 , 2.99]		+ ? + + + + +
Total (95% CI)		**92**		**92**	**100.0%**	**1.40 [0.73 , 2.68]**		
Total events:	18		13					

Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 1.02 (P = 0.31)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours probiotics and osmotic laxative   Favours osmotic laxative

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: Probiotics and osmotic laxative vs osmotic laxative, Outcome 9: Need for additional therapies during the study period

Study or Subgroup	Probiotics and osmotic laxative Events	Total	Osmotic laxative Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Banaszkiewicz 2005	19	43	18	41	79.6%	1.01 [0.62 , 1.63]		
Russo 2017	0	27	0	28		Not estimable		
Wegner 2018	7	65	8	64	20.4%	0.86 [0.33 , 2.24]		
Total (95% CI)		**135**		**133**	**100.0%**	**0.98 [0.63 , 1.50]**		
Total events:	26		26					

Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.91)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours probiotics and osmotic laxative   Favours osmotic laxative

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 2.10. Comparison 2: Probiotics and osmotic laxative vs osmotic laxative, Outcome 10: Total adverse events

Study or Subgroup	Probiotic and osmotic laxative Events	Total	Osmotic laxative Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Banaszkiewicz 2005	4	43	6	41	73.0%	0.64 [0.19 , 2.09]		
Kubota 2020	0	19	0	21		Not estimable		
Russo 2017	0	27	0	28		Not estimable		
Wegner 2018	2	65	0	64	27.0%	4.92 [0.24 , 100.60]		
Total (95% CI)		**154**		**154**	**100.0%**	**1.11 [0.18 , 6.79]**		
Total events:	6		6					

Heterogeneity: Tau² = 0.81; Chi² = 1.59, df = 1 (P = 0.21); I² = 37%
Test for overall effect: Z = 0.11 (P = 0.91)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours probiotic and osmotic laxative   Favours osmotic laxative

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 3. Probiotics vs magnesium oxide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Frequency of defecation (number of stools/week at end of study)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.2 Global improvement or treatment success, as defined by primary studies	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.3 Withdrawals due to adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.4 Faecal incontinence, or encopresis, measured at end of study (continuous)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.5 Need for additional therapies during the study period (continuous data)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.6 Total adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 3.1. Comparison 3: Probiotics vs magnesium oxide, Outcome 1: Frequency of defecation (number of stools/week at end of study)

Study or Subgroup	Probiotics			Magnesium oxide			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Bu 2007	5.03	1.5	18	4.75	1.11	18	0.28 [-0.58 , 1.14]	

Test for subgroup differences: Not applicable

-4 -2 0 2 4
Favours magnesium oxide   Favours probiotics

Analysis 3.2. Comparison 3: Probiotics vs magnesium oxide, Outcome 2: Global improvement or treatment success, as defined by primary studies

Study or Subgroup	Probiotics		Magnesium oxide		Risk Ratio	Risk Ratio
	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Bu 2007	14	18	13	18	1.08 [0.74 , 1.57]	

Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Favours magnesium oxide   Favours probiotics

Analysis 3.3. Comparison 3: Probiotics vs magnesium oxide, Outcome 3: Withdrawals due to adverse events

Study or Subgroup	Probiotics		Magnesium oxide		Risk Ratio	Risk Ratio
	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Bu 2007	1	18	2	18	0.50 [0.05 , 5.04]	
Kubota 2020	0	20	0	21	Not estimable	

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours probiotics   Favours magnesium oxide

Analysis 3.4.   Comparison 3: Probiotics vs magnesium oxide, Outcome 4: Faecal incontinence, or encopresis, measured at end of study (continuous)

| Study or Subgroup | Probiotics | | | Magnesium oxide | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Bu 2007	2.1	3.8	18	2.7	5.1	18	-0.60 [-3.54 , 2.34]	

Test for subgroup differences: Not applicable

-4 -2 0 2 4
Favours probiotics   Favours magnesium oxide
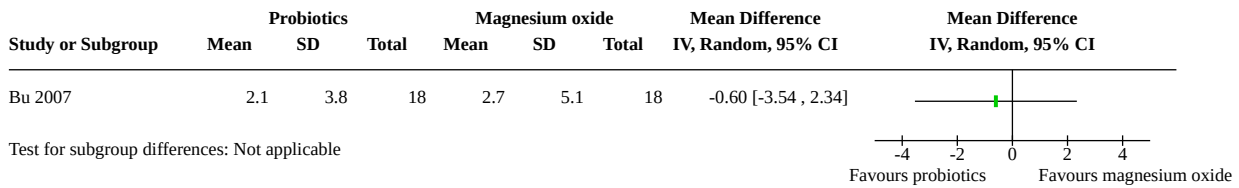
Analysis 3.5.   Comparison 3: Probiotics vs magnesium oxide, Outcome 5: Need for additional therapies during the study period (continuous data)
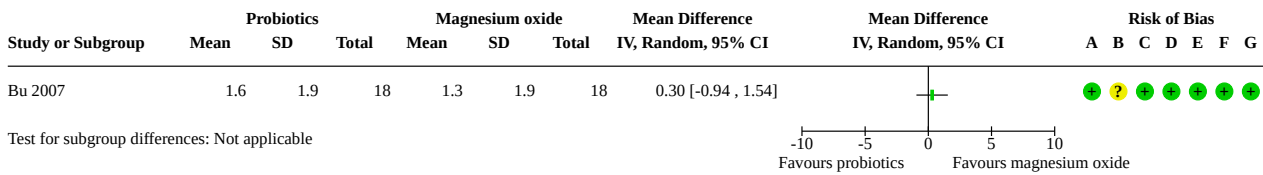
| Study or Subgroup | Probiotics | | | Magnesium oxide | | | Mean Difference | Mean Difference | Risk of Bias |
	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI	A B C D E F G
Bu 2007	1.6	1.9	18	1.3	1.9	18	0.30 [-0.94 , 1.54]		+ ? + + + + +

Test for subgroup differences: Not applicable

-10 -5 0 5 10
Favours probiotics   Favours magnesium oxide

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 3.6.   Comparison 3: Probiotics vs magnesium oxide, Outcome 6: Total adverse events
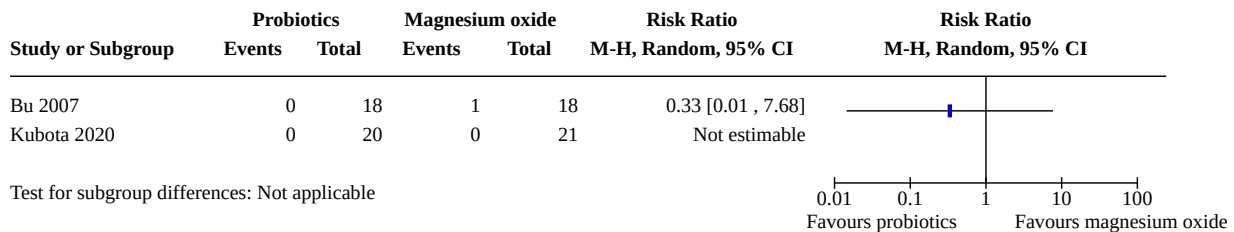
| Study or Subgroup | Probiotics | | Magnesium oxide | | Risk Ratio | Risk Ratio |
	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Bu 2007	0	18	1	18	0.33 [0.01 , 7.68]	
Kubota 2020	0	20	0	21	Not estimable	

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours probiotics   Favours magnesium oxide

Comparison 4.   Synbiotics vs placebo

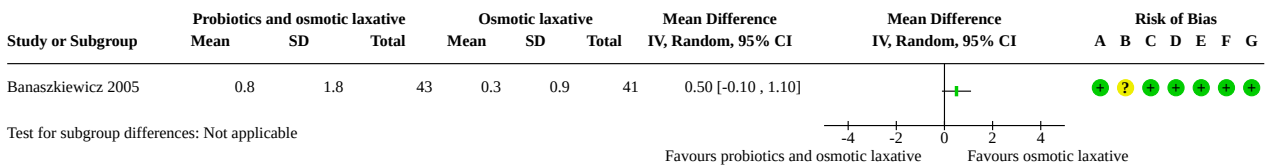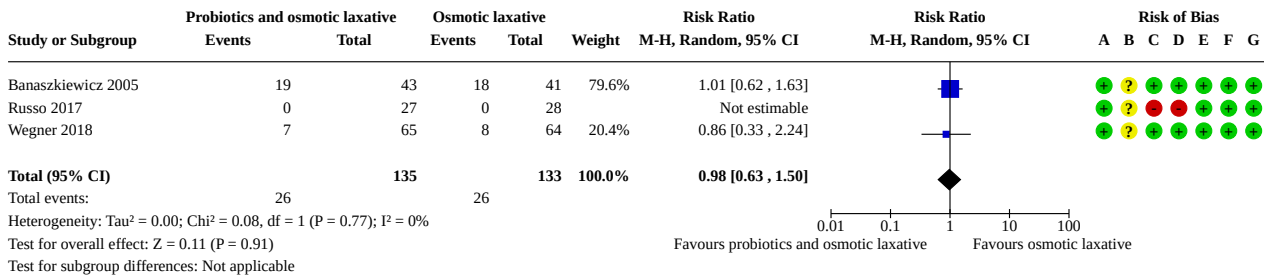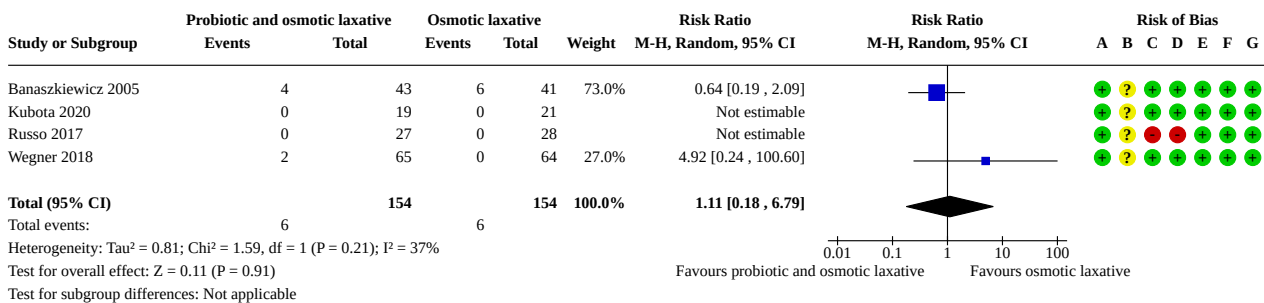| Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Global improvement or treatment success, as defined by primary studies	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.2 Global improvement or treatment success, as defined by primary studies (sensitivity analysis fixed-effect model))	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.3 Faecal incontinence, or encopresis, measured at end of study (dichotomous)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.4 Need for additional therapies during the study period	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.5 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 4.1. Comparison 4: Synbiotics vs placebo, Outcome 1: Global improvement or treatment success, as defined by primary studies

	Synbiotics		Placebo		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI	A B C D E F G
Basturk 2017	48	77	21	78	2.32 [1.54 , 3.47]		+ + + + + + +

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100
Favours placebo   Favours synbiotics
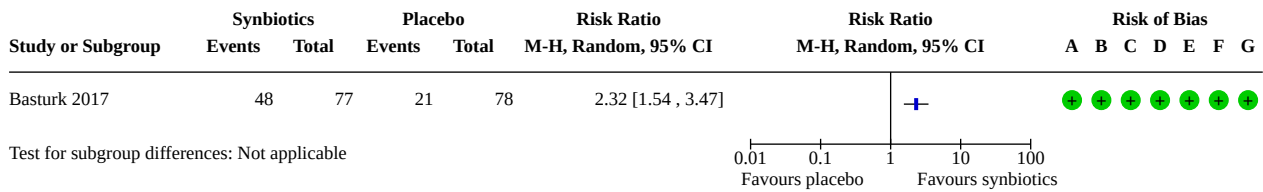
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.2. Comparison 4: Synbiotics vs placebo, Outcome 2: Global improvement or treatment success, as defined by primary studies (sensitivity analysis fixed-effect model))

	Synbiotics		Placebo		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	A B C D E F G
Basturk 2017	48	77	21	78	2.32 [1.54 , 3.47]		+ + + + + + +

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100
Favours placebo   Favours synbiotics
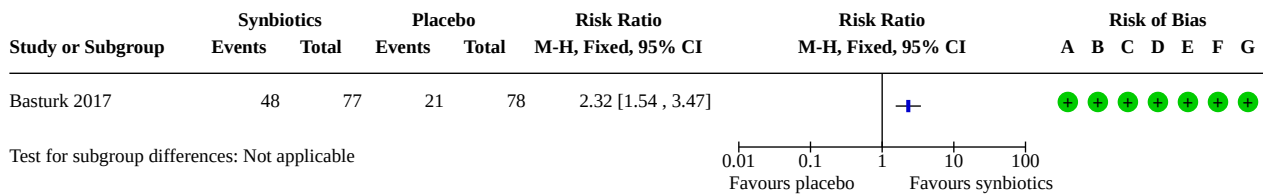
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.3. Comparison 4: Synbiotics vs placebo, Outcome 3: Faecal incontinence, or encopresis, measured at end of study (dichotomous)

Study or Subgroup	Synbiotics Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Basturk 2017	17	77	19	78	0.91 [0.51 , 1.61]		+ + + + + + +

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours synbiotic   Favours placebo

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 4.4. Comparison 4: Synbiotics vs placebo, Outcome 4: Need for additional therapies during the study period

Study or Subgroup	Synbiotics Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Basturk 2017	5	77	4	78	1.27 [0.35 , 4.54]	

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours synbiotics   Favours placebo

Analysis 4.5. Comparison 4: Synbiotics vs placebo, Outcome 5: Total adverse events

Study or Subgroup	Synbiotics Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Basturk 2017	5	77	4	78	1.27 [0.35 , 4.54]		+ + + + + + +

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours synbiotics   Favours placebo

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 5. Synbiotics and paraffin vs paraffin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Frequency of defecation (number of stools/week at end of study)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
5.2 Frequency of defecation (number of stools/week at end of study) (sensitivity analysis fixed-effect model)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.3 Global improvement or treatment success, as defined by primary studies	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.4 Global improvement or treatment success, as defined by primary studies (sensitivity analysis fixed-effect model)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.5 Faecal incontinence, or encopresis, measured at end of study (continuous)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.6 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 5.1. Comparison 5: Synbiotics and paraffin vs paraffin, Outcome 1: Frequency of defecation (number of stools/week at end of study)

	Synbiotics and paraffin			Paraffin			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI	A B C D E F G
Khodadad 2010	7.49	4.4	37	6.75	2.6	29	0.74 [-0.96 , 2.44]		? + + + + + +

Test for subgroup differences: Not applicable

-10 -5 0 5 10
Favours paraffin   Favours synbiotics and paraffin

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 5.2. Comparison 5: Synbiotics and paraffin vs paraffin, Outcome 2: Frequency of defecation (number of stools/week at end of study) (sensitivity analysis fixed-effect model)

	Synbiotics and paraffin			Paraffin			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI	A B C D E F G
Khodadad 2010	7.49	4.4	37	6.75	2.6	29	0.74 [-0.96 , 2.44]		? + + + + + +

Test for subgroup differences: Not applicable

-10 -5 0 5 10
Favours paraffin   Favours synbiotics and paraffin

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)
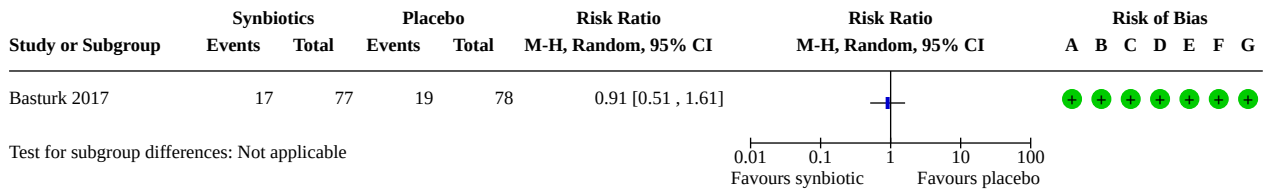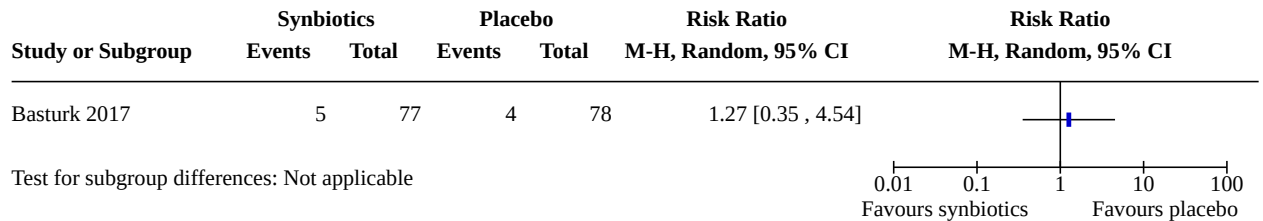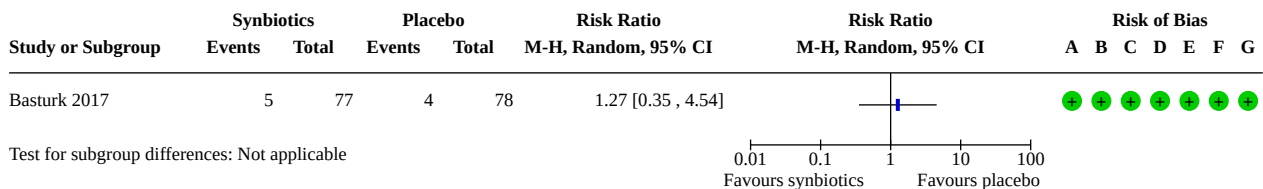(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.3. Comparison 5: Synbiotics and paraffin vs paraffin, Outcome 3: Global improvement or treatment success, as defined by primary studies

Study or Subgroup	Synbiotics and paraffin Events	Total	Paraffin Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Khodadad 2010	28	37	24	29	0.91 [0.71 , 1.17]	

Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Favours paraffin   Favours synbiotics and paraffin

Analysis 5.4. Comparison 5: Synbiotics and paraffin vs paraffin, Outcome 4: Global improvement or treatment success, as defined by primary studies (sensitivity analysis fixed-effect model)

Study or Subgroup	Synbiotics and paraffin Events	Total	Paraffin Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Khodadad 2010	28	37	24	29	0.91 [0.71 , 1.17]	

Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Favours paraffin   Favours synbiotics and paraffin

Analysis 5.5. Comparison 5: Synbiotics and paraffin vs paraffin, Outcome 5: Faecal incontinence, or encopresis, measured at end of study (continuous)

Study or Subgroup	Synbiotics and paraffin Mean	SD	Total	Paraffin Mean	SD	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Khodadad 2010	0.01	0.01	37	0.24	1.3	29	-0.23 [-0.70 , 0.24]		? + + + + + +

Test for subgroup differences: Not applicable

-10 -5 0 5 10
Favours synbiotics and paraffin   Favours paraffin

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 5.6. Comparison 5: Synbiotics and paraffin vs paraffin, Outcome 6: Total adverse events

Study or Subgroup	Synbiotics and paraffin Events	Total	Paraffin Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Khodadad 2010	21	37	18	29	0.91 [0.61 , 1.36]		? + + + + + +

Test for subgroup differences: Not applicable

0.001 0.1 1 10 1000
Favours synbiotics and paraffin   Favours paraffin

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 6.   Synbiotics vs paraffin

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.1 Frequency of defecation (number of stools/week at end of study)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.2 Frequency of defecation (number of stools/week at end of study) (sensitivity analysis fixed-effect model)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.3 Global improvement or treatment success, as defined by primary studies	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.4 Global improvement or treatment success, as defined by primary studies (sensitivity analysis fixed-effect model)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.5 Faecal incontinence, or encopresis, measured at end of study (continuous)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.6 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 6.1.   Comparison 6: Synbiotics vs paraffin, Outcome 1: Frequency of defecation (number of stools/week at end of study)

Study or Subgroup	Synbiotics			Paraffin			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Khodadad 2010	5.22	3.2	31	6.75	2.6	29	-1.53 [-3.00 , -0.06]	

Test for subgroup differences: Not applicable

-10   -5   0   5   10
Favours paraffin   Favours synbiotics
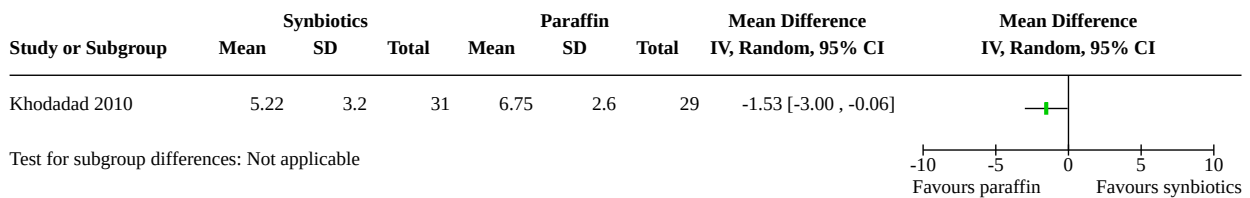
Analysis 6.2.   Comparison 6: Synbiotics vs paraffin, Outcome 2: Frequency of defecation (number of stools/week at end of study) (sensitivity analysis fixed-effect model)
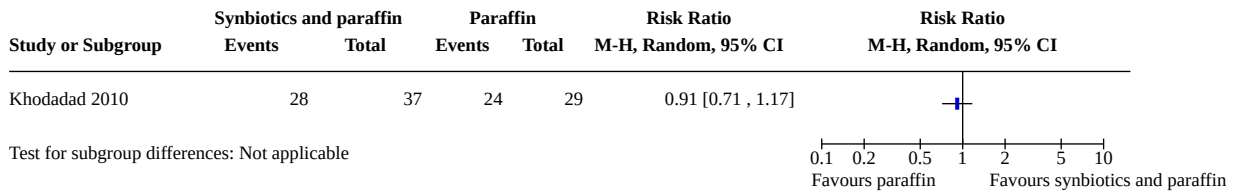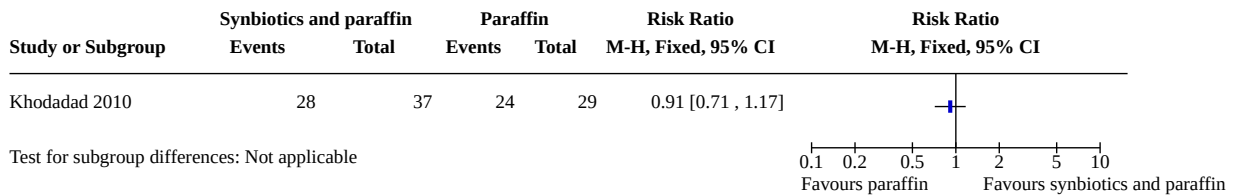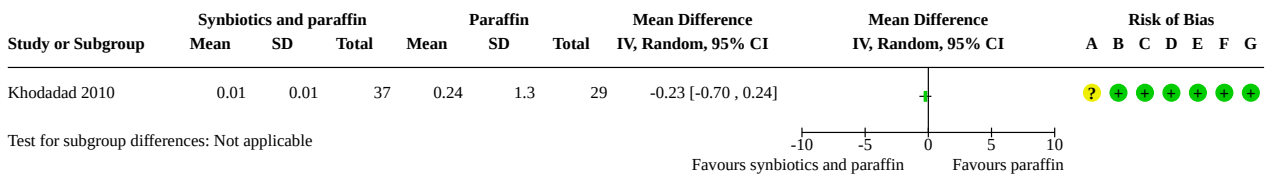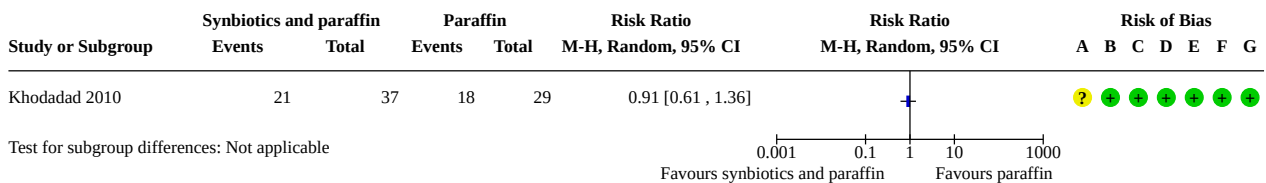
Study or Subgroup	Synbiotics			Paraffin			Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Khodadad 2010	5.22	3.2	31	6.75	2.6	29	-1.53 [-3.00 , -0.06]	

Test for subgroup differences: Not applicable

-10   -5   0   5   10
Favours paraffin   Favours synbiotics
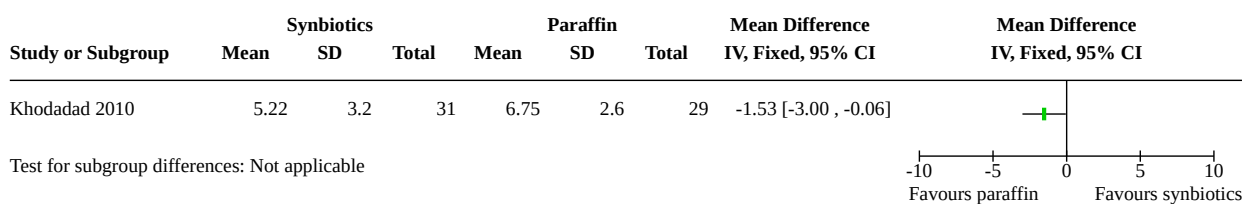
Analysis 6.3. Comparison 6: Synbiotics vs paraffin, Outcome 3: Global improvement or treatment success, as defined by primary studies

Study or Subgroup	Synbiotics Events	Synbiotics Total	Paraffin Events	Paraffin Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Khodadad 2010	22	31	24	29	0.86 [0.65 , 1.13]	

Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Favours paraffin   Favours synbiotics
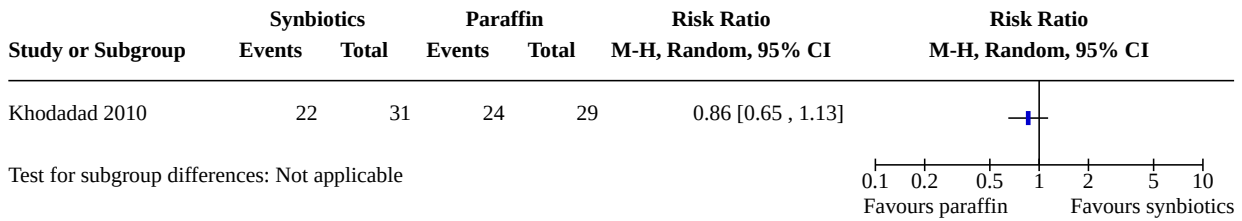
Analysis 6.4. Comparison 6: Synbiotics vs paraffin, Outcome 4: Global improvement or treatment success, as defined by primary studies (sensitivity analysis fixed-effect model)

Study or Subgroup	Synbiotics Events	Synbiotics Total	Paraffin Events	Paraffin Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Khodadad 2010	22	31	24	29	0.86 [0.65 , 1.13]	

Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Favours paraffin   Favours synbiotics
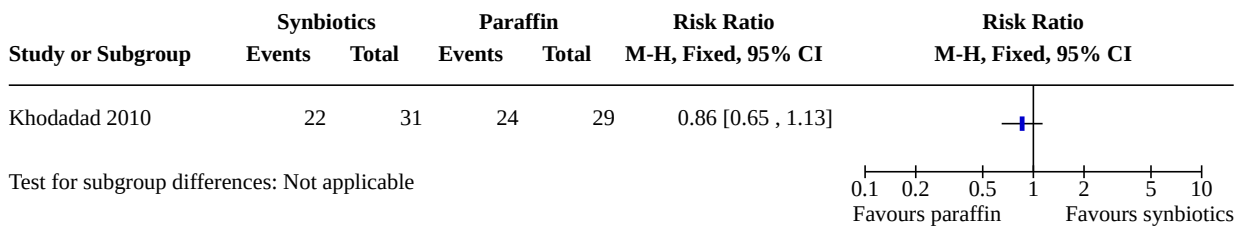
Analysis 6.5. Comparison 6: Synbiotics vs paraffin, Outcome 5: Faecal incontinence, or encopresis, measured at end of study (continuous)

Study or Subgroup	Synbiotics Mean	Synbiotics SD	Synbiotics Total	Paraffin Mean	Paraffin SD	Paraffin Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Khodadad 2010	0.06	0.25	31	0.24	1.3	29	-0.18 [-0.66 , 0.30]	

Test for subgroup differences: Not applicable

-100 -50 0 50 100
Favours synbiotics   Favours paraffin
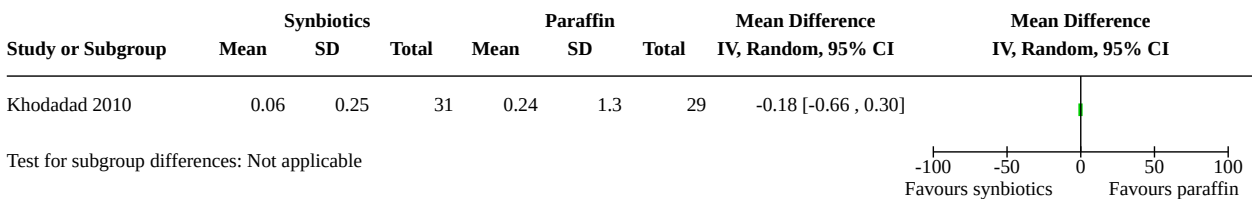
Analysis 6.6. Comparison 6: Synbiotics vs paraffin, Outcome 6: Total adverse events

Study or Subgroup	Synbiotics Events	Synbiotics Total	Paraffin Events	Paraffin Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Khodadad 2010	0	31	18	29	0.03 [0.00 , 0.40]	

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours synbiotics   Favours paraffin
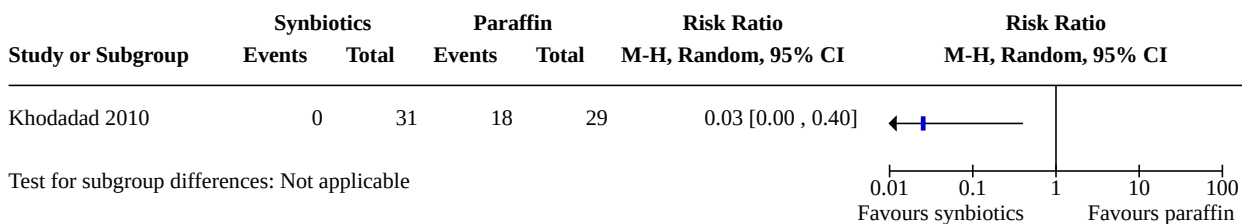
ADDITIONAL TABLES

Table 1. Included studies further details - diagnosis, participants, length of treatment, time point of outcome measurements

Study ID	Methods of diagnosis	Age range	Number randomised (IG/CG)	Number analysed (IG/CG)	Length of intervention	Time points of outcome measurements
Banaszkiewicz 2005	< 3 BMs per week for > 12 weeks	2 to 16 y	43/41	43/41	12 weeks	Weeks 4, 8, 12, 24
Basturk 2017	Rome III	4 to 18 y	77/78	72/74	4 weeks	End of intervention
Bu 2007	< 3 BMs per week for > 2 months	< 10 y	18/18/9	18/18/9	4 weeks	End of intervention
Chao 2016	Rome III	6m to 10 y	41/40	41/40	12 weeks	Weeks 4 and 12
Coccorullo 2010	Rome III	6 to 12 m	22/22	22/22	8 weeks	Weeks 4 and 8
Guerra 2011	Rome III	5 to 15 y	30/30	30/29	5 weeks	Weeks 1, 3, 5
Jadresin 2018	Rome III	2 to 18 y	18/15	18/15	12 weeks	4 weeks after the end of the intervention
Khodadad 2010	Rome III	4 to 12 y	29/31/37	29/31/37	4 weeks	Weekly and at the end
Kubota 2020	Rome IV	6 m to 6 y	20/19/21	20/19/21	4 weeks	End of intervention
Russo 2017	Rome III	4 to 12 y	27/28	25/25	8 weeks	2, 4, 8 weeks
Tabbers 2011	Rome III	3 to 16 y	79/80	74/74	3 weeks	1, 2, 3 weeks
Wegner 2018	Rome III	3 to 7 y	65/64	59/61	8 weeks	Weeks 4 and 8
Wojtyniak 2017	Rome III	< 5 y	46/48	41/40	4 weeks	Weeks 1, 2, 3, 4
Zaja 2021	Rome III	10 to 18 y	15/16	15/16	12 weeks	End of intervention

BM: bowel movement; CG: control group; IG: intervention group

Table 2. Included studies further details - interventions and trial registrations

Study ID	Interventional Agent	Intervention dosage (amount and frequency)	Control	Control dosage (amount and frequency)	Trial registration (prospective/ retrospective/none)	Do the trial registration outcomes match those published?
Banaszkiewicz 2005	*Lactobacillus rhamnosus* GG (LGG) + lactulose	10^9 CFU twice daily orally + 1mL/kg/day of 70% lactulose (in two divided doses)	"comparable" placebo + lactulose	placebo twice daily orally + 1 mL/kg/day of 70% lactulose (in	None	NR

Table 2.   Included studies further details - interventions and trial registrations *(Continued)*

				two divided doses)		
Basturk 2017	Probiotic mixture containing: *Lactobacillus casei; L rhamnosus; L plantarum; Bifidobacterium lactis* and prebiotic mixture (fibre, polydextrose, fructo-oligosaccharides, and galacto-oligosaccharides)	4×10^9 CFU of probiotics and prebiotics at a dose of 1996.57 mg as a sachet once a day	Placebo which had the same properties of colour, odour, taste	Sachet once a day	None	NR
Bu 2007	Group 1: *Lactobacillus casei rhamnosus* (Lcr 35) Group 2: magnesium oxide (MgO)	Group 1: 8×10^8 CFU/day, two capsules twice daily Group 2: 50 mg/kg per day, twice daily (both were administered in identical looking capsules)	placebo ("starch in content") similar in appearance and administered in identical capsules	NR	None	NR
Chao 2016	*Clostridium butyricum miyair*i + MgO	NR	MgO	NR	None	NR
Coccorullo 2010	*Lactobacillus reuteri* (DSM 17938)	10^8 CFU in 5 drops of oil suspension	Unidentified placebo	5 drops once daily	None	NR
Guerra 2011	*Bifidobacterium longum* + commercial goat yogurt (The goat yogurt contained the two classical yogurt starters, *Lactobacillus delbrueckii subspecies bulgaricus* and *Streptococcus thermophilus*)	1 ml of 10^9 CFU/mL (1mL) + 9 mL of commercial goat yogurt	Peptoned water + commercial goat yogurt	1 mL of peptoned water + 9 mL of goat yogurt	None	NR
Jadresin 2018	*Lactobacillus reuteri* DSM 17938	1×10^8 CFU in citrus flavoured 450 mg chewable tablet (containing isomalt, xylitol, sucrose distearate, hydrogenated palm oil, lemon-lime flavouring, and anhydrous citric acid), dosage not reported + lactulose treatment in a dose of 1 to 3 mL/kg per day.	Placebo (identical tablets as in the active study product in all respects but live bacteria)	Dosage not reported + lactulose treatment in a dose of 1 to 3 mL/kg per day.	Prospective	Yes

Table 2. Included studies further details - interventions and trial registrations *(Continued)*

Khodadad 2010	Group B: synbiotic (*L casei, L rhamnosus, S hermophilus, B breve, L acidophilus, B infantis* and fructo-oligosaccharide as prebiotic) + placebo (n = 29)	Group B: 1 x 10^9 CFU/ sachet, 1 sachet per day	Group A: paraffin plus placebo (n = 31)	Group A: 1.5 ml/kg/ day oral liquid paraffin plus placebo	Prospective	Yes
	Group C: synbiotic ((*L casei, L rhamnosus, S hermophilus, B breve, L acidophilus, B infantis* and fructo-oligosaccharide as prebiotic) +paraffin (n = 37)	Group C: 1.5ml/kg/ day oral liquid paraffin and 1 sachet synbiotic per day				
Kubota 2020	Group A received *L reuteri* DSM 17938 and lactose hydrate	*L reuteri*i DSM 17938 was administered at a dose of 10^8 CFU in 5 drops, twice daily.	Group C received a placebo and MgO and lactose hydrate	MgO was administered at a dose of 30 mg/kg of body weight per day	None	NR
	Group B received *L reuteri* DSM 17938 and MgO and lactose hydrate	MgO was administered at a dose of 30 mg/kg of body weight per day.		Placebo dosage not reported		
		Placebo dosage not reported				
Russo 2017	Polyethylene glycol (PEG) and probiotic mixture (PM) (including *Bifidobacteria breve, infantis* and *longum*)	1 sachet of PEG (3.6 g) and 1 sachet (3g) of probiotics daily	PEG	1 sachet (3.6 g) daily	None	NR
Tabbers 2011	The intervention product was the milk drink Activia containing *B lactis* and yogurt starter cultures (*Lactobacillus delbrueckii* ssp. *bulgaricus, Streptococcus thermophilus, Lactococcus cremoris*)	4.25 x 10^9 CFU of *B lactis*, and *L bulgaricus* at least 1.2 x 10^9 CFU per pot, twice daily	Placebo which consisted of a milk-based, non-fermented dairy product (125-g pot) without probiotics and with a low content of lactose (2.5 g per pot).	Twice daily	Prospective	Yes
Wegner 2018	*L reuteri* DSM 17938 and macrogol therapy	*L reuteri*: 1 tablet containing 10^8 CFU	Matching placebo and macrogol	Macrogol (10 g per day)	Prospective	Yes
		Macrogol: 10 g per day				

Table 2. Included studies further details - interventions and trial registrations *(Continued)*

Wojtyniak 2017	Lcr35	8×10^8 CFU, twice daily orally	comparable placebo (containing 99% milk powder and 1% magnesium stearate), twice daily orally	99% milk powder and 1% magnesium stearate	Prospective	Yes
Zaja 2021	*L reuteri* DSM 17938 (the tablet also contained isomalt, xylitol, sucrose distearate, hydrogenated palm oil, lemon-lime flavouring and anhydrous citric acid)	1×10^8 CFU/tablet, twice daily	Identical placebo without the probiotic (isomalt, xylitol, sucrose distearate, hydrogenated palm oil, lemon-lime flavouring and anhydrous citric acid)	One tablet, twice daily	Prospective	Yes

CFU: colony forming units; NR: not reported

Table 3. Included studies further details - outcome data

Study ID	Inter-vention grouping	1a. Frequency of defeca-tion	1b. Global improve-ment/treat-ment suc-cess	1c. With-drawals due to adverse events	2a. Faecal inconti-nence/encopresis	2b. Suc-cessful disim-paction	2c. Need for ad-ditional therapies	2d. Seri-ous ad-verse events	2e. Adverse events
Ba-naszkiewicz 2005	Probiotic plus lactu-lose vs lac-tulose	Stools/week 4 weeks • IG: 5.9 ± 2.3 • CG: 7.7 ± 5.4 8 weeks • IG: 6.1 ± 2.3 • CG: 7.2 ± 3.8 12 weeks • IG: 6.1 ± 1.8 • CG: 6.8 ± 3.1	12 weeks • IG: 31/43 • CG: 28/41 24 weeks • IG: 27/43 • CG: 27/41	IG:1 CG: 0	Episodes/week 4 weeks • IG: 0.9 ± 2.1 • CG: 0.7 ± 1.5 8 weeks • IG: 0.8 ± 2.2 • CG: 0.3 ± 0.8 12 weeks • IG: 0.8 ± 1.8 • CG: 0.3 ± 0.9	NR	IG: 19/43 CG: 18/41	IG:0 CG:0	IG: 4/43 (9%) • IG:3/4 (abdomi-nal pain) • IG: 1/4 (vomit-ing) CG: 6/41 (14.68%) • CG:5/6 (abdomi-nal pain) • CG: 1/6 (headache)
Basturk 2017	Synbiotic vs placebo	Not provided as continuous data by study	4 Weeks: • IG: 48/72 • CG: 21/74	IG: 0 CG: 0	Episodes of inconti-nence 4 weeks • IG: 17/72 • CG: 19/74	NR	IG:5/72 CG:4/74	IG:0 CG:0	Fleet en-ema was performed due to com-plaints of abdominal distention and pain. IG: 5/72 CG: 4/74
Bu 2007	MgO vs probiotic vs placebo	Stools/week MgO: 4.75 ± 1.11	MgO = 13/18 (72.2%) Probiot-ic = 14/18 (77.8%)	MgO = 2 Probiotic = 1	Episodes/week MgO = 2.7 ± 5.1	NR	Number of times glyc-erin ene-mas was used, as reported	MgO = 0 Probiotic =0	MgO = 1 Probiotic =0 Placebo =0

Table 3. Included studies further details - outcome data *(Continued)*

		Probiotic: 5.03 ± 1.50 Placebo: 2.60 ± 0.71	Placebo = 1/9 (11.1%)	Placebo = 1	Probiotic = 2.1 ± 3.8 Placebo = 2.7 ± 1.4		in the diary MgO = 1.3 ± 1.9 Probiotic = 1.6 ± 1.9 Placebo = 4.0 ± 2.1	Placebo = 0	
Chao 2016	Probiotic vs placebo	Data presented as change in frequency with no SD	NR	NR	NR	NR	NR	NR	NR
Coccorullo 2010	Probiotic vs placebo	Data not presented in format suitable for meta-analysis	NR	IG: 0 CG: 0	NR	NR	NR	IG: 0 CG: 0	IG: 0 CG: 0
Guerra 2011	Probiotic vs placebo	Data not presented in format suitable for meta-analysis	NR	NR	Excluded if incontinent	NR	NR	NR	NR
Jadresin 2018	Probiotic vs Placebo	NR	Absence of symptoms at the end of study (number of children): • IG: 7/18 • CG: 6/15	IG: 0 CG: 0	Data presented as median and range, unable to convert to suitable format for meta-analysis	NR	IG: 14/18 CG: 12/15	IG: 0 CG: 0	IG: 0 CG: 0
Khodadad 2010	Synbiotics plus paraffin vs Synbiotic vs Paraffin	Stools/week Group A (paraffin + placebo): 6.75 (± 2.6) Group B (synbiotics + placebo): 5.22 (± 3.2) Group C (paraffin + synbiotics): 7.49 (± 4.4)	Group A (paraffin + placebo): 24/29 Group B (synbiotics + placebo): 22/31	Group A: 0 Group B: 0 Group C: 0	Episodes/week Group A (paraffin + placebo): 0.24 (± 1.3) Group B (synbiotics + placebo): 0.06 (± 0.25) Group C (paraffin + synbiotics): 0.0 (± 0.0)	NR	NR	Group A: 0 Group B: 0 Group C: 0	Group A (paraffin + placebo): 18 Group B (synbiotics + placebo): 0 Group C (paraffin +

Table 3. Included studies further details - outcome data *(Continued)*

			Group C (paraffin + synbiotics): 28/37							synbiotics): 21
Kubota 2020	Probiotic vs probiotic + MgO vs MgO	Data presented as change in stool frequency	NR	IGA: 0 IGB: 0 CG: 0	NR	NR	NR	IGA: 0 IGB: 0 CG: 0	IGA: 0 IGB: 0 CG: 0	
Russo 2017	Probiotic plus macrogol vs macrogol	Stools/week 2 weeks IG: 5.4 ± 1.4 CG: 5.9 ± 1.3 4 weeks IG: 6.0 ± 1.2 CG: 6.3 ± 0.9 8 weeks IG: 6.3 ± 1.0 CG: 6.3 ± 0.9	2 weeks IG: 59% (n=16) CG: 72% (n=20) 4 weeks IG: 63.6% (n=17) CG: 80% (n=22) 8 weeks IG: 81.8% (n=22) CG: 88% (n=24)	IG: 0 CG: 0	Episodes of incontinence 2 weeks IG: 8% (n = 2) CG: 12% (n = 2) 4 weeks IG: 4% (n = 1) CG: 8% (n = 2) 8 weeks IG: 4% (n = 1) CG: 6% (n = 2)	NR	IG: 0 CG: 0	IG: 0 CG: 0	IG: 0 CG: 0	
Tabbers 2011	Probiotic vs placebo	Reported as change in stool frequency, and end of follow-up. Data not presented with SD for meta-analysis	IG: 27/71 CG: 17/72	IG: 6/74 CG: 4/74	Episodes of incontinence IG: = 27 (reported as 36.6%; n = 74)	NR	Use of bisacodyl IG: = 23.6% (n = 19)	2 serious adverse events, not specified in which group (the authors conclude	IG: 4 CG: 6	

Table 3. Included studies further details - outcome data *(Continued)*

Cochrane Library

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Cochrane Database of Systematic Reviews

							CG: = 36 (reported as 48.6%; n=74)	CG: = 30.6% (n = 24)	these were probably unrelated to the intervention as one child broke his arm, and one developed gynecological pain, which was caused by a gynecological cyst)
Wegner 2018	Probiotic plus macrogol vs macrogol	Stools/week Week 4 • IG: 7.69 ± 4.3 • CG: 7.74 ± 3.6 Week 8 • IG: 7.5 ± 3.3 • CG: 6.9 ± 2.5	NR	0	Episodes of incontinence Week 4 IG 23/59; CG 26/61 Week 8 IG 17/59; CG 11/61	NR	Rescue enema: Week 4 IG 4; CG 5 Weeks 4 to 8: IG 3; CG 3	0	IG: 2 (abdominal pain – did not cause withdrawal) CG: 0
Wojtyniak 2017	Probiotic vs placebo	Presented as median and IQR, converted to mean and SD for analysis using *Cochrane Handbook* formulae. Stools/week Week 1	IG: 24/41 CG: 28/40	0	Presented as median and IQR, converted to mean and SD for analysis using *Cochrane Handbook* formulae. episodes/week Week 1	NR	IG: 18/41 CG: 10/40	0	IG: 0 CG: 3

Table 3. Included studies further details - outcome data (Continued)

		CG: 6 (5 to 8.2)			CG: 0 (0)				
		IG: 5 (3 to 6)			IG: 0 (1.35)				
		Week 2			Week 2				
		CG: 6 (4 to 7)			CG: 0 (0.27)				
		IG: 4 (3 to 6)			IG: 0 (0)				
		Week 3			Week 3				
		CG: 6 (3 to 8)			CG: 0 (0)				
		IG: 4 (3 to 5)			IG: 0 (1.35)				
		Week 4			Week 4				
		CG: 6 (4 to 9)			CG: 0 (0)				
		IG: 4 (3 to 5)			IG: 0 (0)				
Zaja 2021	Probiotic vs placebo	NR	IG: 13/15 CG: 10/16	0	NR	NR	NR	0	0

CG: control group; IG: intervention group; NR: not reported

APPENDICES

Appendix 1. CENTRAL via Cochrane Library search strategy

Date run: 28 June 2021

#1 ([mh Probiotics] or [mh Saccharomyces] or [mh Lactobacillus] or [mh Bifidobacterium] or [mh "Escherichia coli"] or [mh Streptococcus] or [mh Bacillus] or [mh "Clostridium butyricum"] or [mh Enterococcus] or (probiotic or probiotics or Saccaromyce* or boulardii or lactobacil* or Betabacterium or Lactobacteria or lactic acid bacteria or casei or paracasei or rhamnosus or helveticus or acidophilus or Bifidobacter* or Escherichia coli or "E.Coli" or "E. Coli" or Mutaflor or Colinfant or Streptococcus or Streptococceae or VSL* or Bacillus or clostridium butyricum or enterococcus or faecalis or "Biok+" or Lacidofil or Lactogermine or Pb Probinul or BIfido Triple or Commensal* or yeast or Fung*):ti,ab,kw) and ([mh Constipation] or (constipation or (f?ecal NEAR/3 (impaction or retention or evacuation)) or ((bowel or intestinal) adj3 (delayed or retention or evacuation or function* or habit* or movement* or symptom* or motility)) or obstipation or colon transit or def?ecation):ti,ab,kw) and ([mh Adolescent] or [mh Child] or [mh Infant] or [mh Minors] or [mh Pediatrics] or [mh Puberty] or [mh Schools] or (baby or babies or child or children or p?ediatric* or p?adiatric* or infan* or neonat* or new?born* or kid or kids or adolescen* or pre?school or toddler* or 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* or elementary school* or high?school* or kinder* or Jugend* or nursery school* or primary school* or secondary school* or youth* or young or student* or juvenil* or school age* or underage* or schoolchild* or (under* adj age*) or under 16 or under 18):ti,ab,kw)

in Trials 407

Appendix 2. MEDLINE via Ovid SP search strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to June 28, 2021>

1. exp Probiotics/ or exp Saccharomyces/ or exp Lactobacillus/ or exp Bifidobacterium/ or exp Escherichia coli/ or exp Streptococcus/ or exp Bacillus/ or exp Clostridium butyricum/ or exp Enterococcus/ or (probiotic or probiotics or Saccaromyce* or boulardii or lactobacil* or Betabacterium or Lactobacteria or lactic acid bacteria or casei or paracasei or rhamnosus or helveticus or acidophilus or Bifidobacter* or Escherichia coli or "E.Coli" or "E. Coli" or Mutaflor or Colinfant or Streptococcus or Streptococceae or "VSL#3" or "VSL #3" or Bacillus or clostridium butyricum or enterococcus or faecalis or "Biok+" or Lacidofil or Lactogermine or Pb Probinul or BIfido Triple or Commensal* or yeast or Fung*).tw,kw. (1081466)

2. exp Constipation/ or (constipation or (f?ecal adj3 (impaction or retention or evacuation)) or ((bowel or intestinal) adj3 (delayed or retention or evacuation or function* or habit* or movement* or symptom* or motility)) or obstipation or colon transit or def?ecation).tw,kw. (64276)

3. exp Adolescent/ or exp Child/ or exp Infant/ or exp Minors/ or exp Pediatrics/ or exp Puberty/ or exp Schools/ or (baby or babies or child or children or p?ediatric* or p?adiatric* or infan* or neonat* or new?born* or kid or kids or adolescen* or pre?school or toddler* or 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* or elementary school* or high?school* or kinder* or Jugend* or nursery school* or primary school* or secondary school* or 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. (5081042)

4. ((Randomized Controlled Trial or Controlled Clinical Trial).pt. or (Randomi?ed or Placebo or Randomly or Trial or Groups).ab. or Drug Therapy.fs.) not (exp Animals/ not Humans.sh.) (4399672)

5. 1 and 2 and 3 and 4 (329)

Appendix 3. Embase via Ovid SP search strategy

Database: Embase <1974 to 2021 Week 25>

1. Randomized controlled trial/ or Controlled clinical study/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/ or (random$ or placebo or (open adj label) or ((double or single or doubly or singly) adj (blind or blinded or blindly)) or parallel group$1 or crossover or cross over or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)) or assigned or allocated or (controlled adj7 (study or design or trial)) or volunteer or volunteers).ti,ab. or (compare or compared or comparison or trial).ti. or ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (5428813)

2. (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) (8622)

3. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or (randomi?ed controlled or control group$1).ti,ab.) (273249)

4. (((case adj control$) and random$) not randomi?ed controlled).ti,ab. (18606)

5. (Systematic review not (trial or study)).ti. (178569)

6. (nonrandom$ not random$).ti,ab. (17036)

7. ("Random field$" or (random cluster adj3 sampl$)).ti,ab. (3885)

8. (review.ab. and review.pt.) not trial.ti. (899994)

9. "we searched".ab. and (review.ti. or review.pt.) (37230)

10. ("update review" or (databases adj4 searched)).ab. (43658)

11. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1111708)

12. Animal experiment/ not (human experiment/ or human/) (2333009)

13. or/2-12 (3725272)

14. 1 not 13 (4820770)

15. exp Probiotic Agent/ or exp Saccharomyces/ or exp Lactobacillus/ or exp Bifidobacterium/ or exp Escherichia coli/ or exp Streptococcus/ or exp Bacillus/ or exp Clostridium butyricum/ or exp enterococcus/ or (probiotic or probiotics or Saccaromyce* or boulardii or lactobacil* or Betabacterium or Lactobacteria or lactic acid bacteria or casei or paracasei or rhamnosus or helveticus or acidophilus or Bifidobacter or Escherichia coli or "E.Coli" or "E. Coli" or Mutaflor or Colinfant or Streptococcus or Streptococceae or "VSL#3" or "VSL #3" or Bacillus or clostridium butyricum or enterococcus or faecalis or "Biok+" or Lacidofil or Lactogermine or Pb Probinul or BIfido Triple or Commensal* or yeast or Fung*).tw,kw. (1229722)

16. exp constipation/ or (constipation or (f?ecal adj3 (impaction or retention or evacuation)) or ((bowel or intestinal) adj3 (delayed or retention or evacuation or function* or habit* or movement* or symptom* or motility)) or obstipation or colon transit or def?ecation).tw,kw. (154540)

17. exp adolescence/ or exp adolescent/ or exp child/ or exp newborn/ or exp kindergarten/ or exp pediatrics/ or exp puberty/ or exp nursery school/ or exp primary school/ or exp middle school/ or exp high school/ or exp school/ or (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* or 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* or elementary school* or high school* or highschool* or kinder* or Jugend* or nursery school* or primary school* or secondary school* or youth* or young or student* or juvenil* or school age* or underage* or schoolchild* or (under* adj age*) or under 16 or under 18).kw,kw. (4028681)

18. 14 and 15 and 16 and 17 (342)

Appendix 4. CINAHL via EBSCOhost search strategy

S7 S3 AND S4 AND S5 Limiters - Exclude MEDLINE records; Age Groups: Adolescent: 13-18 years, All Infant, All Child 16

S6 S3 AND S4 AND S5 148

S5 (TX (constipation or ((fecal or faecal) and (impaction or retention or evacuation))) OR TX (((bowel or intestinal) and (delayed or retention or evacuation or function* or habit* or movement* or symptom* or motility))) AND TX (obstipation or colon transit or defecation or defaecation)) OR (MM "Constipation") 11,500

S4 (TX (probiotic or probiotics or Saccaromyce* or boulardii or lactobacil* or Betabacterium or Lactobacteria or lactic acid bacteria or casei or paracasei or rhamnosus or helveticus or acidophilus or Bifidobacter* or Escherichia coli or "E.Coli" or "E. Coli" or Mutaflor or Colinfant or Streptococcus or Streptococceae or "VSL#3" or "VSL #3" or Bacillus or clostridium butyricum) OR TX (enterococcus or faecalis or "Biok+" or Lacidofil or Lactogermine or Pb Probinul or BIfido Triple or Commensal* or yeast or Fung*)) OR (MM "Probiotics") 64,582

S3 S1 NOT S2 823,646

S2 (MH Animals+ OR MH (Animal Studies) OR TI (Animal Model*)) NOT MH (Human) 193,618

S1 MH ("Randomized Controlled Trials" OR "Double-Blind Studies" OR "Single-Blind Studies" OR "Random Assignment" OR "Pretest-Posttest Design" OR "Cluster Sample" OR "Placebos" OR "Crossover Design" OR "Comparative Studies") OR TI (Randomised OR Randomized OR Trial) OR AB (Random* OR (Control W5 Group) OR (Cluster W3 RCT)) OR (MH ("Sample Size") AND AB (Assigned OR Allocated OR Control)) OR PT (Randomized Controlled Trial) 864,607

Appendix 5. AMED via Ovid SP search strategy

Database: AMED (Allied and Complementary Medicine) <1985 to June 2021>

1 (probiotic or probiotics or Saccaromyce* or boulardii or lactobacil* or Betabacterium or Lactobacteria or lactic acid bacteria or casei or paracasei or rhamnosus or helveticus or acidophilus or Bifidobacter* or Escherichia coli or "E.Coli" or "E. Coli" or Mutaflor or Colinfant or Streptococcus or Streptococceae or "VSL#3" or "VSL #3" or Bacillus or clostridium butyricum or enterococcus or faecalis or "Biok+" or Lacidofil or Lactogermine or Pb Probinul or BIfido Triple or Commensal* or yeast or Fung*).tw. and (exp Constipation/ or (constipation or (f?ecal adj3 (impaction or retention or evacuation)) or ((bowel or intestinal) adj3 (delayed or retention or evacuation or function* or habit* or movement* or symptom* or motility)) or obstipation or colon transit or def?ecation or defaecation).tw.) and (exp Pediatrics/ or

exp Puberty/ or exp Schools/ or (baby or babies or child or children or p?ediatric* or p?adiatric* or infan* or neonat* or new?born* or kid or kids or adolescen* or pre?school or toddler* or 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* or elementary school* or high?school* or kinder* or Jugend* or nursery school* or primary school* or secondary school* or 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.) (4)

Appendix 6. WHO ICTRP search strategy

Advanced Search

Constipation *in the Condition*

Probiotic OR Probiotics *in the Intervention*

Search for clinical trials in children

Recruitment Status is: ALL

14 records for 14 trials found

Appendix 7. ClinicalTrials.gov search strategy

Advanced Search

Condition or disease: Constipation

Study type: Interventional Studies (Clinical Trials)

Age Group: Child (birth–17)

Intervention/Treatment: Probiotic OR Probiotics

13 Studies found

H I S T O R Y

Protocol first published: Issue 5, 2021

C O N T R I B U T I O N S   O F   A U T H O R S

CW and VS equally led and contributed to the analysis, GRADE assessment and writing of the review. MG conceived the review, and led the Discussion and Authors' conclusions section of the writing. These three authors provided guidance to the rest of the authoring team and resolved screening, extraction and risk of bias conflicts. MG resolved GRADE conflicts. MG is guarantor of the review.

ALC, LFR, AF, LFV, AL, GH and MS performed the screening, data extraction and risk of bias assessment of the included studies.

MS and AKA made an intellectual contribution and advised on the review.

All authors approved the final version prior to submission.

D E C L A R A T I O N S   O F   I N T E R E S T

KCW has none to declare.

VS has none to declare.

MG - Since January 2019, I have received travel fees to attend international scientific and training meetings from two Pharma companies. These grants included no honoraria, inducement, advisory role or any other relationship and were restricted to the travel and meeting related costs of attending such meetings. This was Digestive Diseases Week May 2019 from companies including Biogaia (2019) and Tillots (2019). Neither of these companies have had any involvement in any works completed by me and I have never had any payments for any other activities for them, as confirmed below. From this date onwards, I have made a personal undertaking to take no further funds from any pharmaceutical or formula company in any form for travel or other related activities. This is to lift the limitations such funding has on my ability to act as a first and corresponding author on reviews, in line with the Cochrane policies on such matters, and is reported in line with these policies. These current declarations will expire in May 2022 and this statement will be updated regularly to reflect this.

AKA has none to declare.

SOURCES OF SUPPORT

Internal sources

External sources

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Due to author team expansions, eight different review authors carried out the extractions and assessment of risk of bias instead of two as preplanned in the protocol.

There were not sufficient data to carry out any of our preplanned subgroup or sensitivity analyses, or publication bias investigation. We planned to group analyses by length of follow-up, preparation, age and method to clear impaction, however there were insufficient data to do so. We did not identify any cluster-randomised trials for inclusion in the review, so did not need to carry out the preplanned analysis.

We planned to use Review Manager 2020 for the analysis and writing of the review but used RevMan Web 2022 instead.