Efficacy and safety of probiotics and synbiotics for functional constipation in children: A systematic review and meta-analysis of randomized clinical trials

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BACKGROUND

- Functional constipation is a common disorder among children and adolescents.
- Approximately one-quarter of children continue to experience symptoms into adulthood.
- Laxatives remain the first-line pharmacological treatment for children with functional constipation.
- The adherence to medications was suboptimal due to treatment inconvenience and dissatisfaction.
- The role of probiotics and synbiotics for the treatment of functional constipation is unclear.

OBJECTIVES

- To assess the efficacy and safety of probiotics and synbiotics in children diagnosed with functional constipation using Rome III or IV criteria based on evidence from randomized controlled trials (RCTs).

MATERIAL AND METHODS

- This systematic review and meta-analysis were reported to be consistent with PRISMA Statement.
- It was previously registered as a protocol on PROSPERO (CRD42022376671).

Table 1: Study design, participants, interventions, comparators, and outcomes

Characteristics	
Study design	Randomized controlled trials
Participants	Inclusion criteria: 1. Aged < 18 years. 2. Diagnosed with functional constipation with Rome III/IV criteria Exclusion criteria: 1. Individuals with metabolic and gastrointestinal diseases 2. Individuals with neuropathic diseases 3. Individuals with intestinal nervous and muscle diseases 4. Individuals with abnormal abdominal muscle morphology
Interventions	Probiotics: any species, strains, and dose of live microorganisms, administered individually or as mixtures. Synbiotics: any probiotic in conjunction with a prebiotic fiber administered together.
Comparators	Placebo or other active treatment
Outcomes	Any data on treatment success, defecation frequency, stool consistency, fecal incontinence, painful defecation, abdominal pain, and adverse effects.

Search strategy

- Database:
  - PubMed, Embase, and Cochrane Library were searched up to November 2022.
- Key terms included:
  - ("functional constipation" OR "chronic constipation") and (Probiotics OR Lactobacillus OR probiotic* OR Bifidobacterium) and (Child OR children or pediatric) and ("Randomized controlled trial*" OR RCT OR randomiz* OR "clinical trial" OR randomis*).
- No limitations on language or publication date were applied.

Data synthesis

- R 4.1.2 'meta" package was used for all statistical tests.
- Dichotomous outcomes
  - Odds ratio (OR) with 95% confidence interval (CI)
- Continuous variable
  - Standard mean difference (SMD) with 95% CI
- Heterogeneity was evaluated through the I^2 test.
- P< 0.05 indicated statistical significance.

RESULTS

- 17 RCTs were eligible for this review and meta-analysis.
  - 12 double-blind, 1 single-blind, and 3 open-label RCTs.
- These studies included 1504 patients.
- Patient age ranged from 6 months to 18 years.
- The sample size was from 33 to 187 patients,
- Duration of therapy varied from 3 weeks to 12 weeks.
- Probiotics included Lactobacillus reuteri, L. rhamnosus, Lcr35, B. longum, S. boulardii, and mixture of probiotics.
- Probiotics were used as an intervention in 14 studies.
  - 7 studies investigated the effect of probiotics versus placebo.
  - 6 trials compared probiotics plus laxatives versus laxatives alone.
  - 1 follow-up study of above RCT
  - Adverse events were reported in 10 of 13 RCTs, and 5 of them did not observe any treatment-related adverse events.
  - The most common adverse events were gastroenteritis, nasopharyngitis, nausea/vomiting, diarrhea, abdominal pain, abdominal distention, and anal bleeding during defecation
- Synbiotics were used in 3 studies.
  - 1 trial compared synbiotics with placebo.
  - 2 studies compared synbiotics plus mineral oil with mineral oil alone.
  - None of RCTs observed any adverse events in the synbiotics group.

Figure 1: Flow diagram of the study selection process based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRASMA) statements.

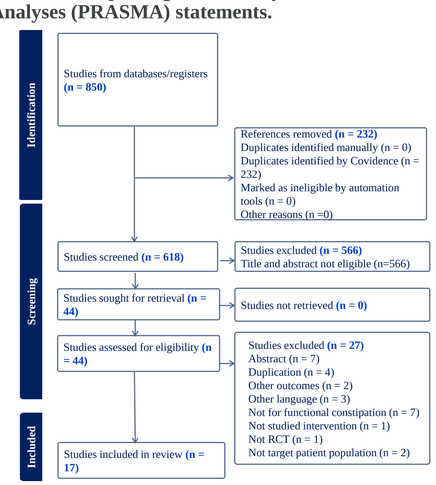


Table 2: Summary of findings on probiotics vs. placebo

Outcomes	No. of studies	Estimates of effects	95% CI
Treatment success	3	OR 1.54	0.90 to 2.61
Defecation frequency	2	SMD 0.40	0.10 to 0.70
Fecal incontinence	2	OR 0.53	0.29 to 0.96
Painful defecation	3	OR 0.91	0.29 to 2.89
Abdominal pain	2	OR 1.05	0.57 to 1.92

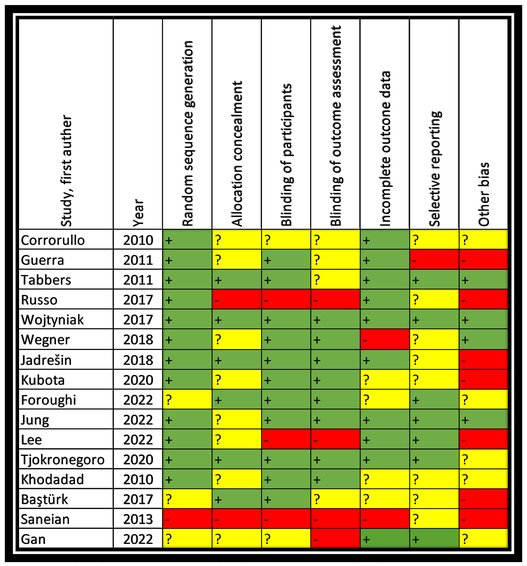
Table 3: Summary of findings on probiotics + laxatives vs. laxatives monotherapy

Outcomes	No. of studies	Estimates of effects	95% CI
Treatment success	2	OR 1.23	0.22 to 6.72
Defecation frequency	3	SMD 0.13	−0.13 to 0.39
Defecation consistency	2	SMD -0.01	−0.40 to 0.38
Fecal incontinence	2	OR 0.95	0.48 to 1.90
Abdominal pain	2	OR 0.6	0.24 to 1.53

Table 4: Summary of findings on synbiotics + laxatives vs. laxatives monotherapy

Outcomes	No. of studies	Estimates of effects	95% CI
Defecation Frequency	2	SMD −0.57	−1.29 to 0.14
Painful defecation	2	OR 3.39	0.74 to 15.55

Figure 2: Risk of bias summary



STRENGTHS AND LIMITATIONS

- This meta-analysis provided the most up-to-date and comprehensive summary of current evidence.
- A detailed assessment of the risk of bias was evaluated.
- The strict Rome III/IV criteria for diagnosis of functional constipation was used as a strength.
- Studies in other languages were excluded.
- The high risk of bias of the included RCTs should be considered when interpreting the results.
- Poor methodological quality were identified in most RCTs.
- Standard definitions of diagnosis and outcomes, and validated instruments to measure the outcomes should be advocated.
- Multicenter randomized controlled trials are needed to further investigate the efficacy of probiotics and synbiotics.

CONCLUSIONS

- Current evidence did not advocate using probiotics and synbiotics in treating functional constipation in children, in part due to lack of data about the specificity of various strains, the optimal dose, and treatment duration of the probiotics and synbiotics.

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