

Systematic review and meta-analysis of the effect of probiotic supplementation on functional constipation in children

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Abstract

Background: To evaluate the effect of probiotic supplementation on functional constipation in children.

Methods: We performed electronic searches in PubMed, Embase, and Cochrane Library without language restriction to identify relevant studies from the time of inception of these databases to March 2018. The relative risk or weighted mean difference was calculated to evaluate the treatment effect of probiotics using random-effects model.

Results: We included 4 trials reporting data on 382 children with functional constipation. Overall, there were no significant differences in treatment success ($P = .697$), spontaneous bowel movements per week ($P = .571$), fecal soiling episodes per week ($P = .642$), straining at defecation ($P = .408$), use of lactulose ($P = .238$), use of laxatives ($P = .190$), fecal incontinence ($P = .139$), pain during defecation ($P = .410$), flatulence ($P = .109$), and adverse events ($P = .979$) between probiotics and placebo. Further, the use of probiotics was associated with lower frequency of glycerin enema use (weighted mean difference -2.40 , $P = .004$) and abdominal pain (weighted mean difference -4.80 , $P < .001$).

Conclusion: The findings of this study suggested that the use of probiotics was associated with significant improvement in glycerin enema use and abdominal pain but did not affect the treatment success and other function indices.

Abbreviations: CIs = confidence intervals, RCTs = randomized controlled trials, RRs = relative risks, sBMs = spontaneous bowel movements, WMDs = weighted mean differences.

Keywords: childhood, functional constipation, meta-analysis, probiotics, systematic review

1. Introduction

Chronic constipation is a common problem in the pediatric population and is characterized by infrequent painful defecation, fecal incontinence, and abdominal pain. The reported prevalence rate of chronic constipation in the Western world is 3% but is 10% to 25% in children referred to pediatric gastroenterologists.^[1–3] Chronic constipation is associated with pain and no

identifiable organic cause in more than 90% of children and is usually of functional origin.^[4,5] The goals of treatment for chronic constipation are to achieve remission in fecal impaction, improve bowel habits, and promote passing of soft stools without discomfort.

Lactulose, an osmotic laxative, is currently widely used to manage constipation in children, although it does not significantly relieve symptoms and requires additional treatment strategy in children with functional constipation.^[6] Previous studies have suggested that probiotic supplementation could treat or prevent multiple gastrointestinal disorders.^[7,8] Potential mechanisms of probiotics are as follows: probiotics could adhere to the intestinal epithelia, inhibiting pathogenic organisms;^[9] they could exert immunomodulatory and anti-inflammatory effects in the gastrointestinal lumen;^[10] and they could convert undigested carbohydrates into short-chain fatty acids, improving gut function.

Several studies have reported the effect of probiotics on childhood functional gastrointestinal disorders and showed that probiotic use was associated with a significant improvement in symptoms in patients with abdominal pain-related functional gastrointestinal disorders, especially in patients with irritable bowel syndrome.^[11–20] However, data on the effect of probiotics on functional constipation in children are both limited and inconclusive. Therefore, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the effect of probiotic supplementation on functional constipation in children.

2. Methods

2.1. Data sources, search strategy, and selection criteria

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and

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Meta-Analyses statement issued in 2009 (Appendix 1, <http://links.lww.com/MD/C494>).^[21]

We performed a systematic review and meta-analysis to identify trials on probiotics for children with functional constipation that were published until March 2018. For literature review, we searched PubMed, Embase, and Cochrane Library using the following core terms: “probiotic” AND “constipation.” The details of search strategy for each database are presented in Appendix 2, <http://links.lww.com/MD/C494>. The inclusion criteria were limited to RCTs. We also conducted manual searches of the reference lists from all relevant original and review articles to identify additional eligible studies. No language restriction was applied. Unpublished trials were excluded. The medical subject heading, methods, participants’ status, study design, intervention, and outcome variables were used to identify relevant studies.

The literature search was independently performed by 2 reviewers using a standardized approach. Any inconsistencies were settled by group discussion until a consensus was reached. The following studies were included in the analysis: RCTs; studies that included patients with functional constipation, which was defined based on clinical symptoms, physician’s opinion, or the Rome I, II, or III criteria; studies that included patients with a mean age of <16.0 years; studies in which the intervention group received probiotics, whereas the control group received placebo; and studies in which the primary outcome was treatment success, which was defined as ≥ 3 spontaneous bowel movements (sBMs) per week with no fecal soiling, and the secondary outcomes were sBMs per week, fecal soiling episodes per week, straining and pain during defecation, use of lactulose, glycerin enema, and laxatives, abdominal pain, fecal incontinence, flatulence, and adverse events.

2.2. Data collection and quality assessment

The collected data included the first author’s name, publication year, country, sample size, sex ratio, mean age, duration of constipation, diagnostic criteria, intervention, control, reported endpoints, and study design variables. The reviewers independently scanned the titles and abstracts of the studies for eligibility and relevance. Potentially relevant articles were retrieved and reviewed for selection based on the inclusion and exclusion criteria. Any discrepancies were resolved by discussion. Two reviewers independently assessed the quality of studies using the Jadad scale, which assesses the reporting of essential points in an RCT (i.e., randomization, blinding, withdrawals, and drop-outs).^[22] The 3-point questionnaire produces a total score ranging from 0 to 5. In case of a disagreement, a consensus was reached through discussion.

2.3. Statistical analysis

Relative risks (RRs) and weighted mean differences (WMDs) with 95% confidence intervals (CIs) were calculated using the outcomes extracted from each study before data pooling. We used a random-effects model for pooled RRs or WMDs with 95% CI to evaluate the treatment effect of probiotics.^[23,24] We also performed a sensitivity analysis for treatment success by removing each individual study from the meta-analysis.^[25] Subgroup analyses were planned to explore potential sources of heterogeneity but were not performed because of the small number of trials finally identified. Heterogeneity among trials was investigated using the Q statistic and P values <.10 were

indicative of significant heterogeneity.^[26,27] We evaluated potential publication bias using funnel plots. The Egger^[28] and Begg tests^[29] were also used to statistically assess publication bias for treatment success. All reported P values were 2-sided, and P values <.05 were considered statistically significant. Statistical analyses were performed using Stata 10 software (StataCorp, College Station, TX).

3. Results

The results of the study selection process are shown in Fig. 1. A total of 980 potentially relevant articles were identified after a systematic search in electronic databases, professional journals, and other sources. After reviewing the titles or abstracts, 919 articles were excluded as they did not meet the inclusion criteria, leaving 61 articles for further full-text review. After full-text review, 57 studies were discarded, and 4 trials were finally identified and included in the analysis of efficacy and safety of probiotics in children with functional constipation.^[30] The remaining studies were excluded because they were reported as conference abstracts without full text, were performed on similar populations, evaluated adult patients, had non-RCT study designs, or included patients with other diseases. A manual search of the reference lists from the articles of these trials did not yield any new eligible studies. The general characteristics of the included trials are presented in Table 1.

The sample sizes of the trials varied from 45 to 159 children with functional constipation. Of the trials, 2 were conducted in Poland,^[30–33] 1 in the Netherlands and Poland,^[32] and the remaining one in China.^[31] The mean age of the included children ranged from 34.6 to 81.0 months, and the duration of constipation ranged from 14.3 to 40.8 months. Two of the included trials defined constipation as <3 sBMs per week for at least 2 months or 12 weeks,^[30,31] whereas the remaining 2 trials defined it according to the Rome III criteria.^[32,33] All included trials were of high study quality, as assessed using the Jadad scale. Overall, 3 trials had a score of 5,^[30,32,33] whereas the remaining one trial had a score of 4.^[31]

After pooling all included trials, we noted that probiotics have no significant effect on treatment success rate compared with placebo (RR 1.05, 95% CI 0.81–1.38, $P=.697$; Fig. 2), but potential evidence of significant heterogeneity was observed. A sensitivity analysis for treatment success was consequently performed, and after each study was sequentially excluded from the pooled analysis, the conclusion was not affected by the exclusion of any specific study (Table 2). Finally, we examined the funnel plots, which indicated no significant publication bias for treatment success (Fig. 3).

The summary results for other outcomes are presented in Table 3. The pooled analysis showed that children who received probiotics had lower frequency of glycerin enema use (WMD -2.40 , 95% CI -4.03 to -0.77 , $P=.004$) and abdominal pain (WMD -4.80 , 95% CI -7.08 to -2.52 , $P<.001$). However, probiotics had no significant effect on sBMs per week (WMD 0.89 , 95% CI -2.18 to 3.95 , $P=.571$), fecal soiling episodes per week (WMD 0.15 , 95% CI -0.48 to 0.79 , $P=.642$), straining during defecation (WMD -0.30 , 95% CI -1.01 to 0.41 , $P=.408$), use of lactulose (WMD -1.80 , 95% CI -4.79 to 1.19 , $P=.238$), use of laxatives (RR 0.72 , 95% CI 0.44 – 1.18 , $P=.190$), fecal incontinence (RR 0.75 , 95% CI 0.51 – 1.10 , $P=.139$), pain during defecation (RR 1.16 , 95% CI 0.81 – 1.66 , $P=.410$), flatulence (RR 0.65 , 95% CI 0.39 – 1.10 , $P=.109$), and adverse events (RR 1.01 , 95% CI 0.62 – 1.63 , $P=.979$).

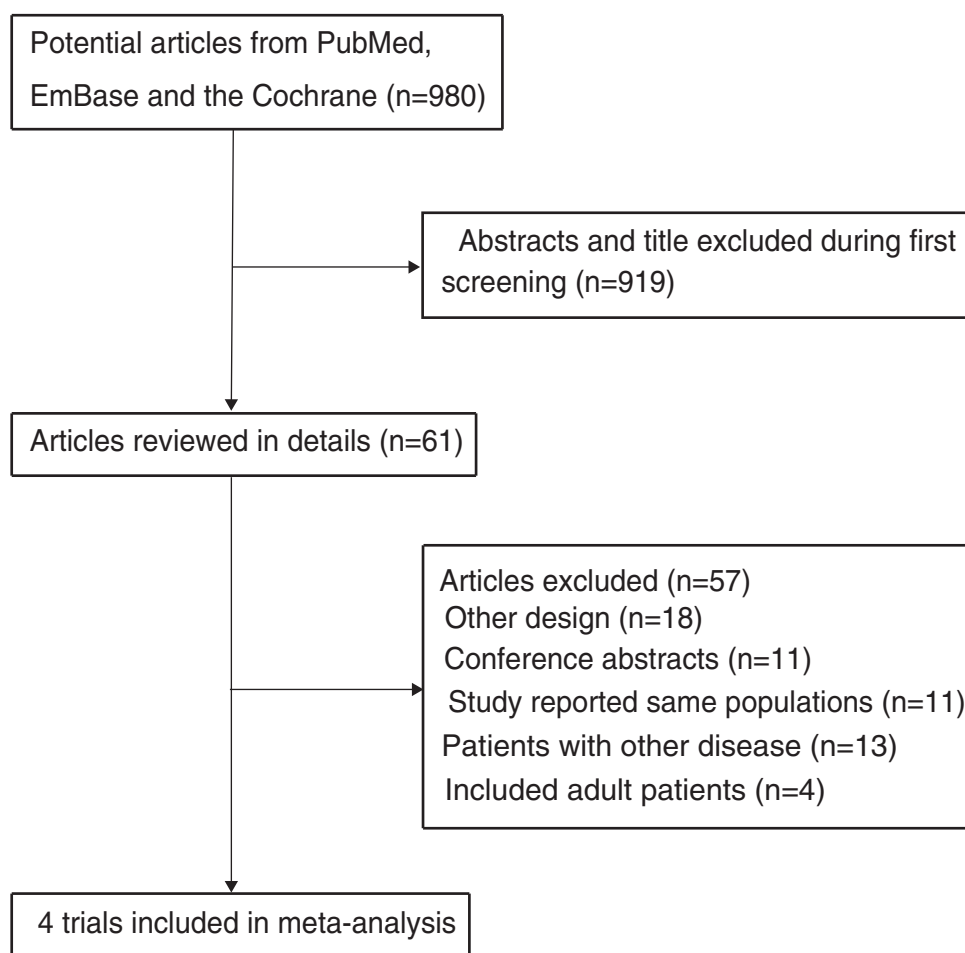


Figure 1. Flow diagram of the literature search and trial selection process.

Table 1

Demographic characteristics of included studies.

Study	Publication year	Country	Sample size	Sex ratio (M/F)	Mean age (mo)	Duration of constipation (mo)	Diagnostic criteria	Intervention	Control	Jadad score
Banaszkiewicz and Szajewska ^[30]	2005	Poland	84	NA	72.2	23.5	Defined as: stools <3 sBM/wk for at least 12 wk	1 mL/kg/d of 70% lactulose plus 10 ⁹ CFU of LGG	1 mL/kg/d of 70% lactulose plus placebo	5
Bu et al ^[31]	2007	China	45	23/22	34.6	21.7	Defined as: stools <3 sBM/wk for at least 2 mo, and anal fissures or soiling or hard/large stools	Lcr35 (8 × 10 ⁸) CFU/d	MgO (50 mg/kg/d) or placebo	4
Tabbers et al ^[32]	2011	Netherlands and Poland	159	83/76	81.0	40.8	Rome III criteria	Bifidobacterium lactis strain DN-173 010 4.25 × 10 ⁹ CFU	Nonfermented dairy product (125-g pot) without probiotics and with a low content of lactose (<2.5 g per pot)	5
Wojtyniak et al ^[33]	2017	Poland	94	42/52	38.0	14.3	Rome III criteria	Lcr35 (8 × 10 ⁸) CFU/d	Placebo	5

CFU=colony-forming units, Lcr35=Lactobacillus casei rhamnosus, LGG=Lactobacillus rhamnosus GG, MgO=magnesium oxide, sBM=spontaneous bowel movements.

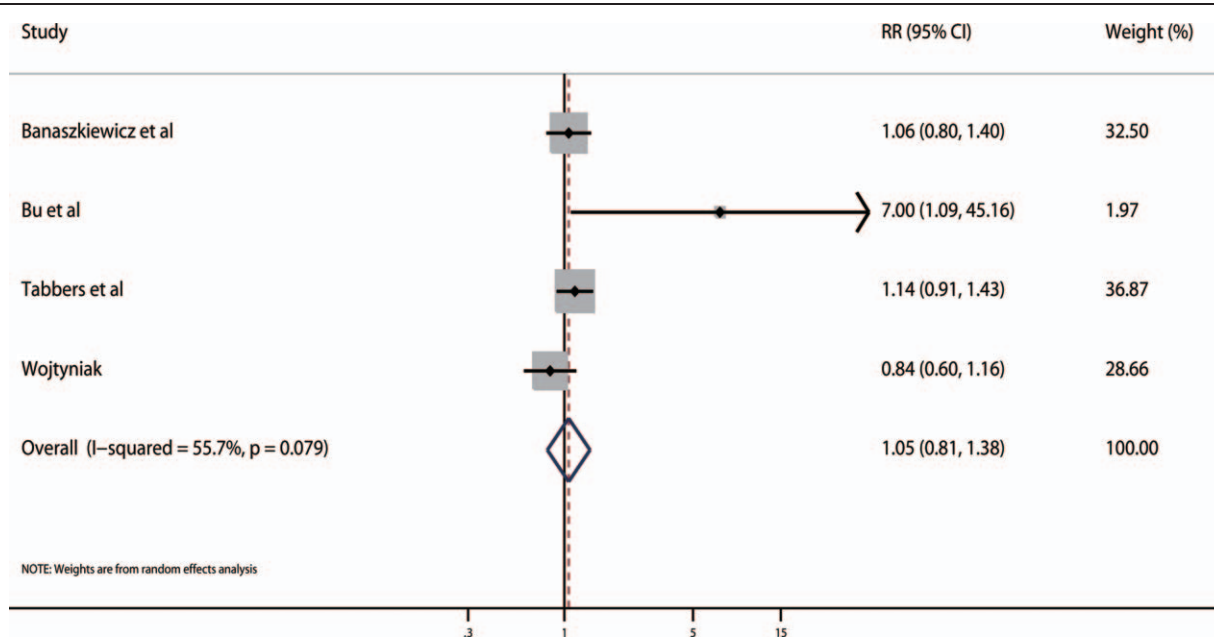


Figure 2. Effect of probiotics on treatment success.

4. Discussion

The present meta-analysis aimed to evaluate the efficacy of probiotics in children with functional constipation. Four trials that included 382 patients were identified. The results showed that probiotic supplementation resulted in lower frequency of glycerin enema use and abdominal pain but had no significant effect on other outcomes. These results may help better clarify the efficacy of probiotics in children with functional constipation and can aid physicians in selecting appropriate treatment strategies.

A previous meta-analysis suggested that the use of probiotics was associated with increased treatment success rate but had no significant effect on the frequency of abdominal pain. Further, the summary results did not indicate a significant improvement in stool patterns. The inherent limitation of the previous meta-analysis is that the effect of probiotics on functional constipation was not evaluated. Moreover, many other outcomes were not reported.^[34] Dimidi et al^[35] conducted a meta-analysis of RCTs on the effect of probiotics on functional constipation in adults and found that probiotics could improve whole gut transit time, stool frequency, and stool consistency. However, the treatment effect of probiotics in children remains unclear.^[35] Therefore, we conducted a comprehensive systematic review and meta-analysis to evaluate the efficacy and safety of probiotics in children with functional constipation.

There was no significant difference in treatment success rate between probiotics and placebo. Majority of the included studies reported the nonsignificant effect of probiotics on treatment

success, except for the trial performed by Bu et al.^[31] They reported that *Lactobacillus casei rhamnosus* was associated with a reduced treatment success rate compared with placebo, with no significant difference between *Lactobacillus casei rhamnosus* and magnesium oxide. Further, they suggested that *Lactobacillus casei rhamnosus* was associated with a reduced frequency of abdominal pain. Banasziewicz and Szajewska^[30] reported that the treatment success rate was 68% and 65% in the *Lactobacillus GG* group and 72% and 64% in the placebo group at 12 and 24 weeks, respectively, and that there were no significant differences in sBMs per week, fecal soiling episodes per week, adverse events, and overall tolerance between both groups at 4, 8, and 12 weeks.^[30] Tabbers et al^[32] indicated that both fermented dairy product containing *Bifidobacterium lactis* DN-173010 and control product could improve stool frequency from baseline to after 3 weeks, with no significant difference between both, and that no serious adverse events were observed in constipated children.^[32] Finally, Wojtyniak et al^[33] suggested that *Lactobacillus casei rhamnosus* was not associated with significant improvement in symptoms in children with functional constipation aged less than 5 years and did not recommend the use of probiotics in children with functional constipation.^[33]

The findings of this study suggested that probiotic supplementation led to significant persistent improvement in glycerin enema use and abdominal pain. However, probiotics were not associated with several important indices. This could be because most trials were designed with other outcomes as the primary

Table 2

Sensitivity analysis for treatment success.

Excluding study	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
Banaszkiewicz and Szajewska	1.10 (0.69–1.75)	.688	71.1	.032
Bu et al	1.03 (0.87–1.22)	.707	14.3	.311
Tabbers et al	1.06 (0.66–1.70)	.811	68.3	.043
Wojtyniak et al	1.16 (0.83–1.62)	.374	56.6	.100

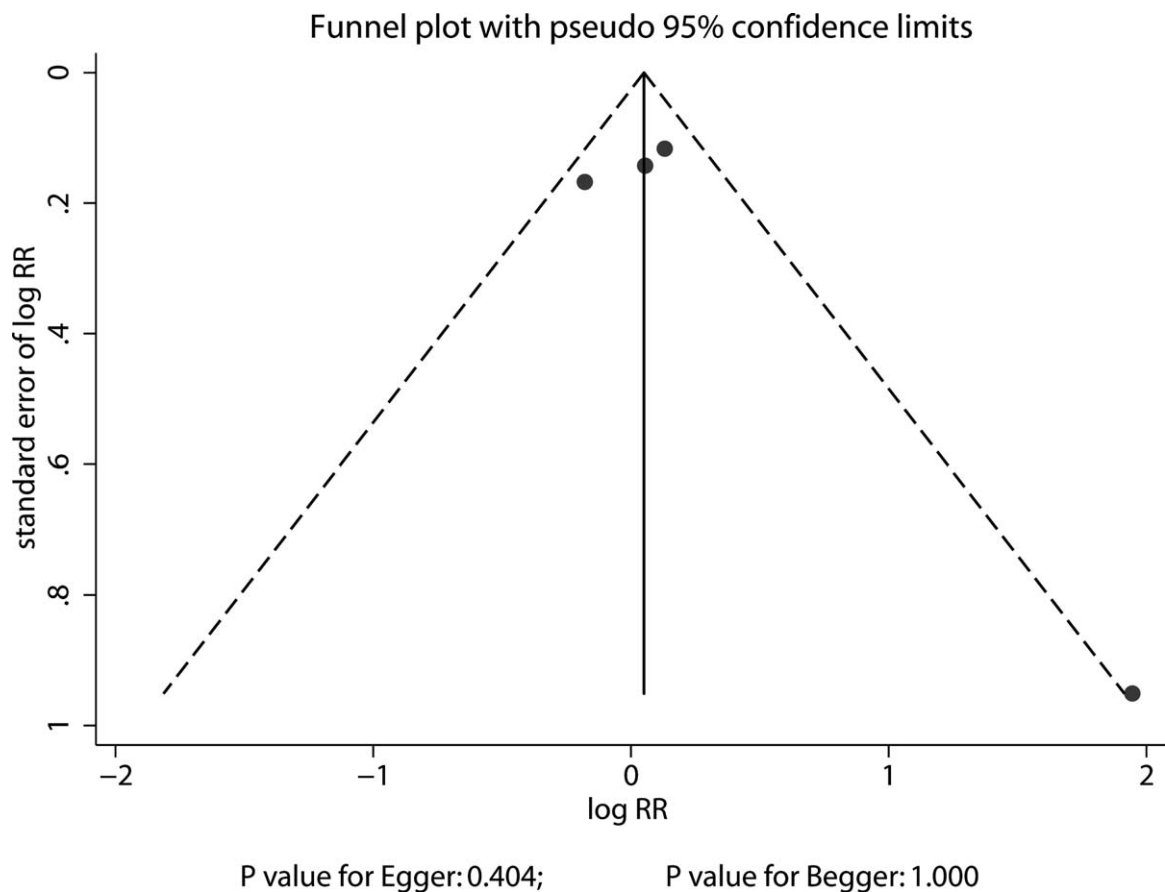


Figure 3. Funnel plots for treatment success.

endpoint and because their sample sizes were too small to detect potentially clinically relevant differences. Further, the few trials that reported these outcomes showed no statistically significant differences. Therefore, we simply reported a relative result and provided a synthetic and comprehensive review.

The strengths of our study should be highlighted. First, the large sample size allowed us to quantitatively assess the efficacy of probiotics in children with functional constipation; thus, our findings are potentially more robust than those of any individual study. Second, the study reported children with functional constipation, and no such meta-analysis has been previously

performed. Third, the summary results for sBMs per week, fecal soiling episodes per week, straining and pain during defecation, use of lactulose, glycerin enema, and laxatives, abdominal pain, fecal incontinence, flatulence, and adverse events were presented.

The limitations of our study are as follows: Publication bias was inevitable because this meta-analysis was based on published studies, which might overestimate the treatment effects of probiotics. Subgroup analysis was not performed as a small number of trials were included. The meta-analysis used pooled data (individual data were not available), which prevented a detailed analysis to obtain more comprehensive results.

Table 3

The summary results of all evaluated outcomes.

Outcomes	RR or WMD and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
sBMs per week	0.89 (-2.18 to 3.95)	.571	95.0	<.001
Fecal soiling episodes per week	0.15 (-0.48 to 0.79)	.642	62.4	.103
Straining at defecation	-0.30 (-1.01 to 0.41)	.408	—	—
Use of lactulose	-1.80 (-4.79 to 1.19)	.238	—	—
Use of glycerin enema	-2.40 (-4.03 to -0.77)	.004	—	—
Abdominal pain	-4.80 (-7.08 to -2.52); or 1.08 (0.81-1.43)	<.001; or.620	—	—
Patients using laxatives	0.72 (0.44-1.18)	.190	0.0	.820
Fecal incontinence	0.75 (0.51-1.10)	.139	—	—
Pain during defecation	1.16 (0.81-1.66)	.410	—	—
Flatulence	0.65 (0.39-1.10)	.109	—	—
Adverse events	1.01 (0.62-1.63)	.979	—	—

5. Conclusion

The results of this study suggested that probiotic supplementation might result in reduced frequency of glycerin enema use and abdominal pain but has no significant effect on treatment success, sBMs per week, fecal soiling episodes per week, straining and pain during defecation, use of lactulose and laxatives, fecal incontinence, flatulence, and adverse events. Future studies should focus on specific types of probiotics and children with specific characteristics.

Author contributions

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Visualization: Wanjin Shao.

Writing – original draft: Lei Jin.

Writing – review & editing: Lei Jin.

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