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Nonpharmacologic Treatment for Children with Functional Constipation: A Systematic Review and Meta-analysis

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Objective To evaluate the effectiveness and safety of nonpharmacologic interventions for the treatment of childhood functional constipation.

Study design Randomized controlled trials (RCTs) evaluating nonpharmacologic treatments in children with functional constipation which reported at least 1 outcome of the core outcome set for children with functional constipation.

Results We included 52 RCTs with 4668 children, aged between 2 weeks and 18 years, of whom 47% were females. Studied interventions included gut microbiome-directed interventions, other dietary interventions, oral supplements, pelvic floor-directed interventions, electrical stimulation, dry cupping, and massage therapy. An overall high risk of bias was found across the majority of studies. Meta-analyses for treatment success and/or defecation frequency, including 20 RCTs, showed abdominal electrical stimulation (n = 3), *Cassia Fistula* emulsion (n = 2), and a cow's milk exclusion diet (n = 2 in a subpopulation with constipation as a possible manifestation of cow's milk allergy) may be effective. Evidence from RCTs not included in the meta-analyses, indicated that some prebiotic and fiber mixtures, Chinese herbal medicine (Xiao'er Biantong granules), and abdominal massage are promising therapies. In contrast, studies showed no benefit for the use of probiotics, synbiotics, an increase in water intake, dry cupping, or additional biofeedback or behavioral therapy. We found no RCTs on physical movement or acupuncture.

Conclusions More well-designed high quality RCTs concerning nonpharmacologic treatments for children with functional constipation are needed before changes in current guidelines are indicated. *(J Pediatr 2022;240:136-49).*

Functional constipation is a common disorder in children and adolescents worldwide.[1] It is characterized by infrequent, painful, and hard stools and may be accompanied by fecal incontinence and abdominal pain.[2] Functional constipation is a clinical diagnosis based on history and physical examination, and is defined according to the Rome IV criteria (**Table I**; available at www.jpeds.com).[3,4] According to international guidelines, the first steps in the treatment of children with functional constipation include demystification, education, toilet training, and laxative treatment with polyethylene glycol (PEG).[5,6] In addition, guidelines advise a normal fiber and fluid intake, and regular physical activity, but do not recommend the use of probiotics, prebiotics, or behavioral therapy owing to a lack of evidence.[5,6] Laxatives are safe, but adherence to laxatives is low, and except for the use of PEG, little is known about long-term effects of chronic laxative use.[7,8] This factor may explain why 36.4% of parents of children with functional constipation seek help in the form of complementary or alternative medicine.[9]

A systematic review on the nonpharmacologic treatment of childhood functional constipation reported that fiber supplements were more effective than placebo, but no evidence was found regarding the effect of fluid supplements, probiotics, prebiotics, physical movement, or behavioral interventions.[10] Our objective was to review currently available evidence on the effectiveness and safety outcomes of the core outcome set (COS)[11] of nonpharmacologic treatments for children with functional constipation compared with any other, or no treatment, as studied in randomized controlled trials (RCTs).

Methods

This systematic review, including protocol, was registered at the international prospective register of systematic reviews, with registration number CRD42020193119 and is reported in accordance with the PRISMA Statement.[12]

Search Strategy and Study Selection

The Cochrane Library, PubMed, and EMBASE databases were searched by a clinical librarian from inception to August 2020. The search protocol with the full search strategy can be obtained from the authors. Key words used were, including synonyms, "constipation," "child" combined with nonpharmacologic treat-

COS	Core outcome set
PEG	Polyethylene glycol
RCT	Randomized controlled trial

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The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2021.09.010

ments such as, but not limited to, "probiotics," "prebiotics," "nutrition therapy," "physical therapy," "alternative medicine," and "biofeedback." To identify additional studies, reference lists of included studies and (systematic) review articles were searched manually. No language restrictions were applied. Studies were eligible for inclusion if they met the following criteria: (1) The study was a (systematic review of) RCT(s) in which a nonpharmacologic treatment was compared with any other treatment, placebo, or no treatment; (2) the study population consisted of children 0-18 years old with functional constipation; (3) the diagnosis of functional constipation was clearly defined by the authors or by the use of internationally recognized criteria, such as the Rome III[13,14] or Rome IV criteria[3,4]; (4) the study used at least 1 outcome of the COS for clinical trials in constipation, namely, defecation frequency, stool consistency, painful defecation, quality of life of parents and patients, side effects of treatment, fecal incontinence, abdominal pain, and school attendance.[11] Studies were excluded if they included children with an organic cause of constipation (eg, Hirschsprung disease, anorectal malformations, or cerebral palsy) or if the study was a pilot study. Titles and abstracts of the papers identified by the initial search were independently screened by 2 reviewers for eligibility with the use of Rayyan, a web application for systematic reviews.[15] Full-text manuscripts were obtained of all potentially relevant articles and evaluated more in detail. Foreign language articles were translated if necessary with the help of native speakers.

Outcome Assessment

The primary outcome measures for this systematic review and meta-analysis were treatment success and defecation frequency. Treatment success and defecation frequency were chosen because they are recommended outcomes for clinical trials in children with functional constipation.[16] Treatment success was collected as dichotomous outcome as defined by authors when it consisted of at least 2 outcomes, of which at least 1 was part of the COS. If treatment success was categorized, the highest level of treatment success was used as a cutoff point (eg, if subcategories included patients who were not cured, 50% cured, and 90% cured; the latter was collected as dichotomous outcome). Defecation frequency was collected as continuous outcome: number of bowel movements per week after treatment completion, or if not available, at first follow-up. Secondary outcomes included all other outcomes of the COS: stool consistency, painful defecation, quality of life of parents and patients, side effects of treatment, fecal incontinence, abdominal pain, and school attendance.[11]

Data Extraction

Data were extracted from each selected study by 2 authors, including general information of the study (author, year, country), study design, criteria for functional constipation diagnosis, population information (age, sex distribution, previous treatment), intervention (comparison[s] and duration), and reported outcomes of the COS including results. When extraction was completed, data were checked by the other author and the disputes were solved by consensus. Data were extracted according to the intention-to-treat principle, where all dropouts were assumed to be treatment failures. When studies had a cross-over design, only the first period was taken into account owing to insufficient run-out periods, especially for microbiome-directed interventions. Fibers and prebiotics were labeled as 1 type of intervention, because the term prebiotic is strictly spoken a health claim, so not all substrates that possess prebiotic properties might be labeled as such, and some studies used a mixture of fibers and prebiotics.[17-19]

Risk of Bias Assessment

The risk of bias of each included study was measured independently by 2 authors according to the Cochrane risk of bias tool version 2.[20] Assessment of the domain "bias owing to deviations from intended interventions" was based on the intention-to-treat principle and evaluated the outcome of treatment success after treatment or at first follow-up of the study, or if not available defecation frequency, or if not available the primary outcome of the study. Any disagreement between reviewers was resolved by consensus.

Data Synthesis and Statistical Analyses

If possible, data were pooled using a random effects model. Data that could not be pooled were reported per type of intervention. The effect of the interventions of interest on treatment success was expressed as risk difference accompanied by 95% CI by the Mantel-Haenszel method.[21] The effect of interventions of interest on defecation frequency was examined using a standardized mean difference with a 95% CI.[21] If medians were provided, we estimated the mean and SD from the median, range, and sample size with the aid of the formula as proposed by Hozo et al.[22] Moreover, in case defecation frequencies were given per day, data per week were estimated by $Mean_{week} = Mean_{day} \times 7$ and $SD_{week} = SD_{day} \times \sqrt{7}$ or $SD_{week} = \sqrt{(Var_{week} = Var_{day1} + Var_{day2} + \ldots + Var_{day7})}$.[22,23] Heterogeneity across individual trials included in our meta-analysis was assessed with I^2 ranging from 0% to 100%, with higher values indicating higher levels of heterogeneity. An I^2 of less than 25% was arbitrarily chosen to correspond with low levels of heterogeneity.[24] The "meta," "metafor," "robvis," and "dmetar" packages, a hands-on guide, and RevMan5 (The Cochrane Collaboration) were used to generate Forest plots of pooled standardized mean differences for outcomes with 95% CIs.[25-29]

Results

A total of 4240 studies were identified, of which 52 studies were eligible for inclusion, 49 were RCTs and 3 were long-term follow-ups of already included RCTs. **Figure 1** (available at www.jpeds.com) depicts the PRISMA flow chart, including reasons for exclusion. These studies included 4668 children aged between 2 weeks and 18 years, of whom 47% were female. The included RCTs were carried out in Asia (n = 21; 43%), Europe (n = 19; 39%), South America (n = 5; 10%), North America (n = 4; 8%), and Oceania (n = 1; 2%); 37 studies (71%) were conducted in tertiary care, 11 (21%) in secondary care, 3 (6%) in primary care, and 2 (4%) did not report on the setting. Thirty-seven studies (71%) used the Rome criteria for functional constipation and 15 (29%) used author-defined criteria. Besides the interventions of interest, 28 (57%) studies reported to give advice on toilet training, and 19 (39%) gave dietary advice to all their participants.

Interventions of the studies included probiotics (n = 15), prebiotics/fiber/infant formulas (n = 11), synbiotics (n = 2), a cow's milk exclusion diet (n = 2), (additional) water (n = 1), oral supplements (*Cassia fistula* emulsion, Sophia seeds, Xia'er Biantong granules, green banana biomass, or black strap molasses) (n = 6), biofeedback (n = 4), electrical therapy (1 with cryotherapy) (n = 4), massage therapy (n = 3), pelvic physiotherapy (n = 1), behavioral therapy (n = 1), dry cupping (n = 1), and a combination of abdominal muscle training, breathing exercises, and abdominal massage (n = 1). The hypotheses on the mode of action of the interventions, accompanied by a summary of the evidence found in this review, are shown in **Table II**. A summary of study characteristics of all included studies (including results of outcomes not discussed in this section) is available in the **Appendix** (available at www.jpeds.com). An overview of which COS outcomes are reported by which studies is available in **Table III** (available at www.jpeds.com). A summary of risk of bias of all included studies can be found in **Figure 2** (available at www.jpeds.com), and more details on the risk of bias judgement per domain can be found in **Figure 3**, A-D (available at www.jpeds.com).

Probiotics

Thirteen studies, including 965 children[34-43,92-94] and 2 follow-up studies, including 166 children,[95,96] investigated the effect of (or the addition of) probiotics versus placebo or laxative treatment (**Appendix**). A low risk of bias was found in 2 of 13, some concerns of bias in 4 of 13, and a high risk of bias in 7 of 13 studies and some concerns of bias for both follow-ups (**Figure 3**, A).

Meta-analysis. The meta-analysis of 2 studies evaluating *Lacticaseibacillus rhamnosus* (previously *Lactobacillus rhamnosus*) (Lcr 35) versus placebo, with considerable levels of heterogeneity, showed no significant effect on treatment success or defecation frequency (**Figures 4** and **5**).[36,41]

Treatment Success. Treatment success was reported in 5 of 15 studies, of which 1 (with 3 *Bifidobacterium* spp. strains) was found to be as effective as laxative treatment,[34] 1 more effective than placebo,[36] and 3 (*L rhamnosus* GG, *B lactis* DN-173 010, *L rhamnosus* Lcr35) not more effective than placebo or control.[39-41] Both follow-up studies reported no difference in treatment success rates between groups.[95,96] The authors who did not define treatment success, concluded that their probiotic was more effective than placebo on stool consistency (goat yoghurt with *Bifidobacterium longum*)[37] or on fecal incontinence and abdominal pain (7-strain multispecies mix),[38] and 2 concluded that probiotics were not successful as additional treatment on any reported outcomes (both *Limosilactobacillus* [previously *Lactobacillus*] *reuteri* DSM 17938).[42,43] Authors of 1 study did not compare outcomes between treatment groups (*L reuteri* DSM 17938).[35]

Defecation Frequency. Defecation frequency was reported in 10 of 15 studies and was comparable with laxative treatment in 2 studies (*L rhamnosus* Lcr35 and a 3-strain *Bifidobacterium* spp. mix),[34,36] higher than placebo or control in 3 studies (*L rhamnosus* Lcr35, *L reuteri* DSM 17938, and a 7-strain multispecies mix),[36,38,92] and similar to placebo or control in 6 studies (*L rhamnosus* GG, *B lactis* DN-173 010, *L rhamnosus* Lcr35, and 3 studies with *L reuteri* DSM 17938).[35,39-43] The follow-up studies (*L rhamnosus* GG and *B lactis* DN-173 010) found no significant difference in defecation frequency between groups, after 2 years[96] and 3 years of follow-up,[95] respectively.

Adverse Events. Adverse events were reported in 12 of 15 studies. Of these studies, 6 of 12 (50%) observed no adverse events. One study observed abdominal pain (n = 3) and vomiting (n = 1) in children receiving treatment with *L rhamnosus* GG.[39] One study reported gastroenteritis (n = 1) and nausea/vomiting (n = 3) in children receiving *B lactis* DN-173 010.[40] One study reported transient diarrhea, which disappeared after dose reduction (3-strain *Bifidobacterium* spp. mix and PEG[34]), and another study reported abdominal pain (n = 2) (*L reuteri* DSM 17938).[42]

(Mixtures of) Fibers and/or Prebiotics

Ten studies, including 728 children,[45-49,97-101] and 1 follow-up study including 80 children[95] investigated the effect of (or the addition of) 7 different (mixtures of) fibers and/or prebiotics and/or infant formulas (designed to support bowel habit problems) compared with placebo or control treatment (**Appendix**). Some concerns of bias were found in 4 of 10 studies, a high risk of bias in 6 of 10 studies, and some concerns of bias in the follow-up study (**Figure 3**, B).

Meta-analysis. The meta-analysis of the 2 studies evaluating glucomannan vs placebo showed no significant effect on treatment success or defecation frequency (**Figures 4** and **5**).[45,97] The meta-analysis of the 2 studies evaluating an infant formula with added β-palmitate, prebiotics, and hydrolysed whey protein (Omneo/Conformil) vs regular formula showed no evidence for an effect on defecation frequency (**Figure 5**).[46,98]

Treatment Success. A definition of treatment success was reported in 5 of 10 studies, of which 1 (a mixture of acacia fiber, psyllium fiber, and fructose) was as effective as laxative treatment,[47] 1 (glucomannan) was more effective than placebo,[45] and 3 (glucomannan, fiber/prebiotic mixture [fructo-oligosaccharides [FOS], inulin, gum Arabic, resistant starch, soy polysaccharide, and cellulose], FOS) were not more effective than placebo.[97,99,100] The authors of 3

Table II. Summary of interventions with their potential mode of action on FC and findings of this systematic review

Interventions	Mode of action	Findings
Probiotics	Probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host."[30] Associations have been found between gut motility and several probiotic strains.[31] Moreover, several genera and community compositions have been associated with a harder stool consistency and others with softer stool consistencies.[32] *Bifidobacteria* and *Lactobacilli* are well-known for the production of acetate and lactate, which might increase gut motility.[33] Therefore, directing the gut microbiota composition towards compositions associated with softer stools may be obtained with the use of probiotics.	RoB: low/some concerns/high Two studies were found to be as effective as laxative treatment[34,35] and 3 were more effective than placebo[36-38]; in contrast, several studies reported not to be effective in the treatment of FC.[39-43]
Fiber	Fibers can be divided in several ways, one of which by properties of solubility, viscosity and fermentation. Those that are fermentable are often but not exclusively regarded as prebiotics.[44] The mode of action for soluble viscous fibers is by forming a gel-like consistency with water resulting in an improvement consistency of stools (both hard and loose stools). Insoluble fibers can exert a laxative effect by stool bulking, irritation, and stimulation of the gut mucosa to increase peristalsis.	RoB: Some concerns/high Some evidence that specific fibers or prebiotic supplements may be more effective than placebo,[45,46] or as effective as laxative treatment.[47-49]
Prebiotics	In addition to the effect of soluble, fermentable fibers as mentioned, prebiotics are defined as "a substrate that is selectively utilized by host microorganisms conferring a health benefit."[17] Mode of action of prebiotics in FC may include increasing microbial biomass and SCFA production which may increase stool consistency and gastrointestinal motility,[50] and several specific bacterial species have been reported to promote gastro-intestinal motility including genera that are stimulated by prebiotics such as *Lactobacilli* and *Bifidobacteria*.[31]	
Synbiotics	Synbiotics are defined as "a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host"[51] and are thought to have a synergetic effect of both prebiotics and probiotics.	RoB: Some concerns/high Minimal evidence was found for the use of synbiotics.[52,53]
Water	Sufficient water intake is of importance for normal defecation patterns and is therefore often advised.[54] It is based on the assumption that additional oral intake of fluid leads to an increase in colonic fluid, which would promote increased stool output or a softer consistency. However, this seems contrary to physiologic expectation given the large adaptive absorptive capacity of the gut in response to acute or chronic challenges.[55]	RoB: High. No evidence was found for the increase of water or hyperosmolar liquid intake.[56]
Cow's milk-free diet	Symptoms of cow's milk allergy might be very unspecific and resemble symptoms of FC.[57] Therefore, it has been suggested that in children, whose onset of constipation symptoms occurred with the introduction of dairy, a cow's milk-free diet challenge can be considered to evaluate if these children may have an underlying cow's milk allergy.[58,59] The hypothetic pathogenic mechanism lies in increased anal pressure at rest, probably caused by allergic inflammation of the internal sphincter area owing to mucosal eosinophil and mast cell infiltration.[59]	RoB: High. Some evidence that suggests it may be useful in children with constipation as manifestation of an underlying cow's milk allergy. [60,61]
Cassia Fistula	*Cassia Fistula* emulsion is an extract from the plant *Cassia Fistula leguminosae*, which belongs to the same Genus (*Cassia*) as *Cassia Officinalis*, more known as *Senna alexandrina*, from which the laxative senna is made. The precise mechanism of action of senna is unknown, but both senna and *Cassia Fistula* seem to act as stimulant laxatives via anthraquinone type derivates that are naturally occurring in plants as glycosides.[62,63]	RoB: High. Minimal evidence that suggests it may be more effective than treatment with mineral oil,[64] and just as effective as PEG.[65]
Flixweed seeds	The exact working mechanism of flixweed seeds (*Descurainia Sophia*) is unknown. The seeds may produce a mucilage that can absorb water from bowel lumen thereby softening stools. One of the compounds in the seeds, allyl disulfide, may have a relaxing effect on smooth muscles and facilitate defecation.[66]	RoB: High. Minimal evidence that suggests it may be just as effective as PEG treatment, but with worse taste.[67]
Xiao'er Biantong granules	Xiao'er Biantong granules are a Chinese patent medicine composed of 7 herbs. Traditional Chinese medicine considers the spleen and stomach as the most important organs for digestion. Improper feeding increases the burden of the stomach and intestine, leading to food stagnation. This disturbs qi movement so that the weakened qi cannot push the chime to move powerfully and quickly in the intestine. Based on these mechanisms, the principle of treatment is to remove food retention (Houpo, LaiFuZi), promote defecation (XingRen, LuHui, and JueMingZi,), regulate qi movement (HouPo, ZhiQiao), and strengthen and nourish the spleen and stomach (BaiZhu).[68]	RoB: High. Minimal evidence that suggests it may be more effective than placebo treatment.[68]

(*continued*)

Table II. Continued

Interventions	Mode of action	Findings
Green banana biomass	Green banana biomass has a high content of dietary fiber and resistant starch, which may result in the effects describes in the fiber section.[69] Important to note is that resistant starch is a wide category of substances that differ in their effects on gut microbiota and thereby in their effect on constipation symptoms.[44,70]	RoB: High. Inconclusive evidence to use on its own, may be effective as addition to PEG or sodium phosphate treatment.[69]
Black strap molasses	Black strap molasses syrup is a black and viscous product resulting from sugarcane after 3 stages of sugar extraction. It contains several minerals and a small amount of polysaccharides and other compounds, including polyphenols.[58] The exact mechanism of action in unknown, but several types of polysaccharides and polyphenols might exhibit laxative effects.[71]	RoB: some concerns Minimal evidence that suggests it may be just as effective as PEG treatment.[58]
Biofeedback	Biofeedback training entails teaching children how to coordinate muscle relaxation with the use of anorectal monitoring instruments to make physiological information accessible to the child's consciousness. It is thought to improve the dyssynergic defecation often seen during anorectal manometry in children with FC. Dyssynergic defecation refers to dysfunction of the pelvic floor muscles which contract instead of relax during a bowel movement. It is thought to be secondary to, or the manometric equivalent of, stool withholding which is considered the major cause for the development and persistence of childhood constipation.[72,73]	RoB: High. Evidence suggests no additional benefit for the use of biofeedback over conventional treatment in all children with FC, inconclusive evidence for its use in children with dyssynergic defecation.[74-76]
Transabdominal interferential electrical therapy	Transabdominal (interferential) electrical stimulation involves the generation of 2 sinusoidal currents that cross within the body with the use of 4 electrode pads applied on the skin of the abdomen and lower back. The exact mechanism of action is not yet understood, the current may result in an alteration of neuronal function, and increase colonic motility by stimulating the interstitial cells of Cajal, the pacemaker cells of the gut, and/or enteric or extrinsic autonomic nerves.[77]	RoB: High. Minimal evidence that suggests benefit as addition to conventional treatment when combined with pelvic floor muscles exercises.[78-81]
Cryotherapy	Scientific evidence for the use of cryotherapy and its role in pathophysiology of FC is lacking. It is thought that cryotherapy might influence local blood circulation and normalize vascular tone and motility.[81]	RoB: High. Minimal evidence suggests it may be beneficial as addition to therapy with electrical stimulation and pelvic floor muscles exercises.[81]
Abdominal massage	The mechanisms behind abdominal massage's constipation-reducing are most likely a combination of local stimulation and relaxation, and by stimulation of the parasympathetic nervous system. Direct pressure over the abdominal wall alternately compresses and then releases sections of the digestive tract, briefly distorting lumen size and activating stretch receptors that can reinforce the gastrocolic reflex and trigger intestinal and rectal contraction.[82,83]	RoB: High. Minimal evidence that suggests benefit as additional to Chinese herbal treatment,[84,85] or as part of a combination therapy.[86]
Foot reflexology	The science of reflexology is based on the premise that there are zones and reflex areas (eg, the feet) that correspond with all glands, organs, parts, and systems of the body. Pressure applied to these specific areas by applying specific techniques assists in potentiating the normal function of the corresponding body part and activates the body's innate healing power, reduces stress, and promotes physiologic changes in the body.	RoB: High. Minimal evidence that suggests no additional benefit over regular advice.[87]
Pelvic physiotherapy	Pelvic physiotherapy consists of exercises, practicing a stabilized posture on the toilet, teaching effective straining to defecate, increasing awareness of sensations, and exercising adequate pelvic floor muscle functions.	RoB: High/low. Minimal evidence that suggests benefit as addition to conventional treatment.[88]
Behavioral therapy	Withholding behavior may be the result of fear and avoidance of defecation. The phobic reactions related to withholding defecation may be decreased and adequate toileting behavior and appropriate defecation straining may be (re)acquired by teaching parents behavioral procedures and by behavioral play therapy with the child.	RoB: High. Minimal evidence that suggests no benefit as additional to conventional treatment.[89]
Dry cupping	Cupping therapy is based on applying negative pressure suction on the skin. During dry cupping, a glass cup is placed on the skin and a vacuum is created inside it for a few minutes to congest the skin. The underlying treatment mechanism is not yet understood, it possibly induces muscle relaxation, and may decrease pain.[90]	RoB: High. Minimal evidence that suggests it may be less effective as PEG treatment.[91]

FC, functional constipation; *RoB*, risk of bias.

of the remaining 5 studies did not define treatment success. However, they reported that the studied treatment was as effective as lactulose on defecation frequency, fecal incontinence, and abdominal pain (yogurt drink with dietary fiber/prebiotic mixtures of transgalacto-oligosaccharides, inulin, soy fiber, and resistant starch),[48] or on defecation frequency, consistency of stools, and abdominal pain (partially hydrolyzed guar gum).[49] The third remaining study reported that an infant formula containing modified vegetable oil with β-palmitate, prebiotics and hydrolyzed whey

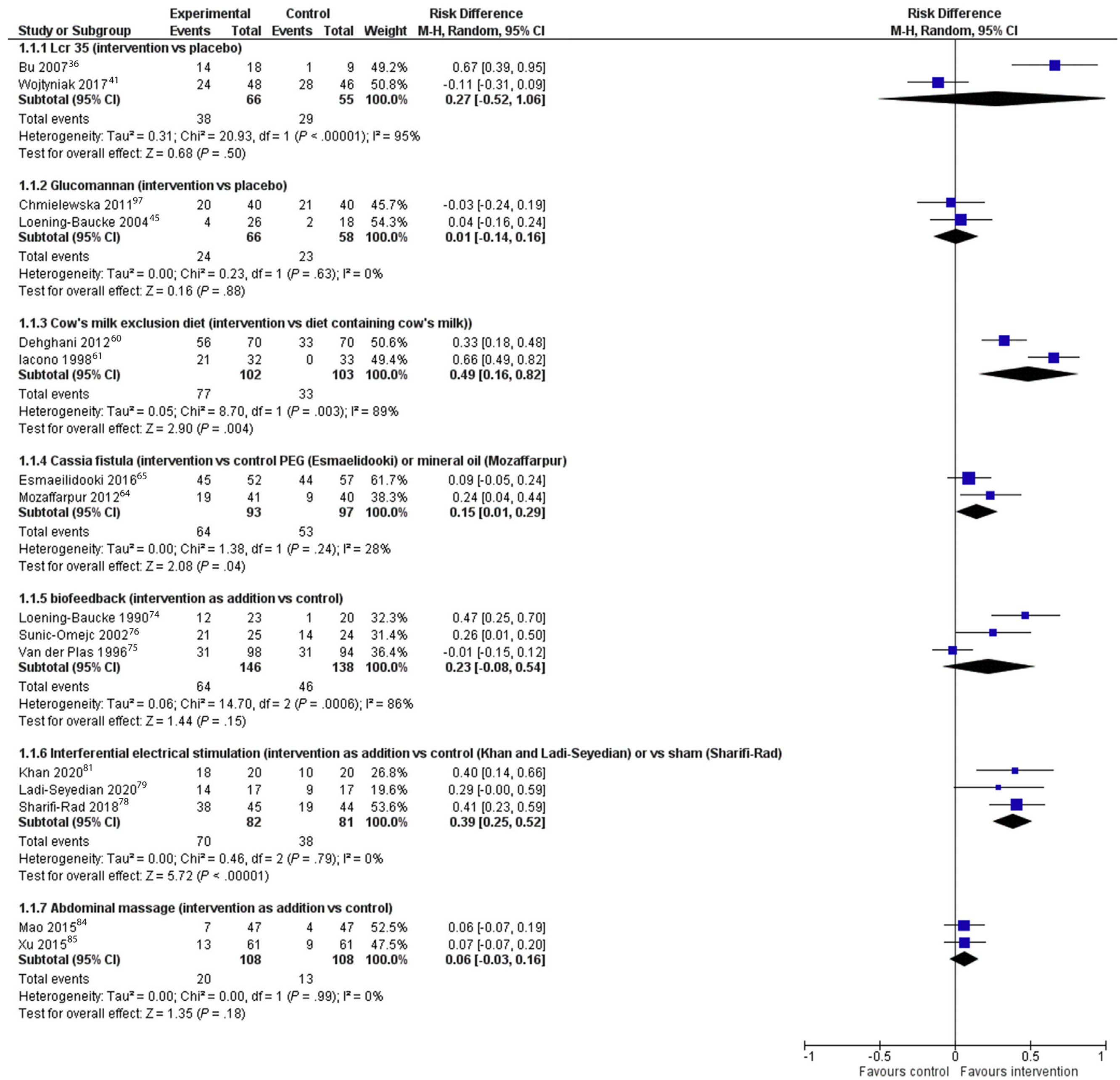

Figure 4. Forest plot of trials on treatment success.

protein (Omneo/Conformil) was not more effective than standard infant formula on any outcomes at end point (day 14), although an increase in stool frequency was seen at day 7.[46]

Defecation Frequency. Defecation frequency was reported in all 10 studies, of which 3 found no difference in improvement of defecation compared with laxative treatment[47-49] and 7 found no difference in improvement of defecation compared with placebo or control treatment.[45,46,97-101]

Adverse Events. Adverse events were reported by 8 of the 10 studies; 4 observed mild side effects in the experimental group, such as diarrhea, abdominal distention, flatulence, and vomiting.[47,48,97,100]

Synbiotics

Two studies, including 252 children, investigated the effect of 2 different synbiotics on constipation symptoms (a combination *of L casei, L rhamnosus, Streptococcus thermophilus, B breve, Lacidophilus, B infantis*, and FOS), and the other study a combination of *L casei, L rhamnosus, L plantarum, B lactis*, fiber, polydextrose, FOS, and GOS, respectively.[52,53] A high risk of bias was found in both studies (Figure 3, C). A meta-analysis was not possible owing to the use of different intervention products.

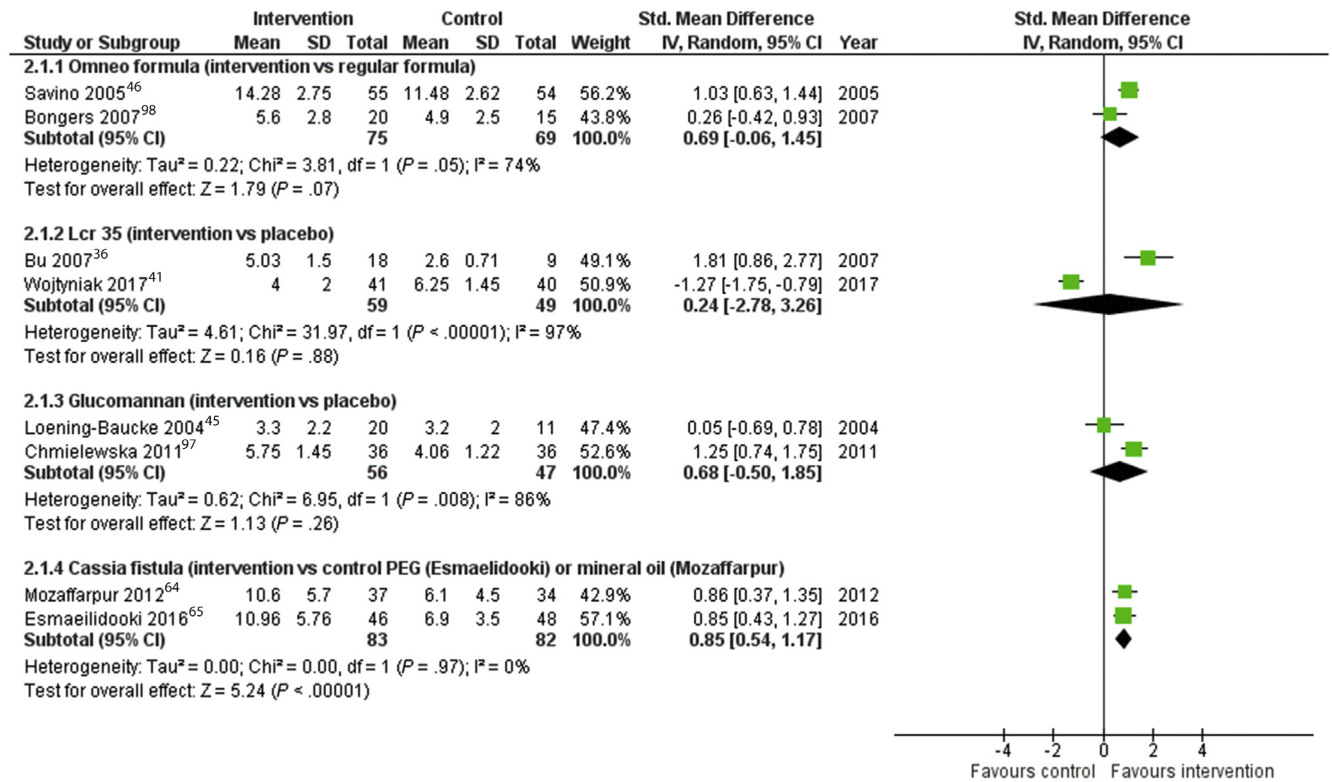

Figure 5. Forest plot of trials for defecation frequency per week.

Treatment Success. Treatment success was reported in both studies, 1 of which found similar success rates in all groups (multispecies probiotic with FOS, multispecies probiotic with FOS plus oral liquid paraffin, or oral liquid paraffin only).[52] The other study found a significantly higher success rate in the synbiotic group compared with the placebo group.[53]

Defecation Frequency. Defecation frequency was reported in both studies and was significantly higher in the group receiving both liquid paraffin and the synbiotic[52] and a significant improvement in the synbiotic but not placebo group after treatment. No between-group comparison was executed.[53]

Adverse Events. Adverse events were reported by both studies, none were observed in the synbiotic-only treatment groups. In contrast, 39 children receiving liquid paraffin as control or in addition to a synbiotic reported seepage.[52]

Dietary Interventions

Three studies, including 295 children, investigated the effect of a dietary intervention.[56,60,61] Two studies investigated the effect of a cow's milk elimination diet versus a diet containing dairy (in a subpopulation with constipation as a possible manifestation of cow's milk allergy),[60,61] and 1 investigated the effect of an increase in water intake, or the consumption of hyperosmolar liquids, versus normal liquid intake.[56] A high risk of bias was found in all 3 studies.

Meta-analysis. The meta-analysis of the 2 studies evaluating a cow's milk-free diet to a diet containing dairy, with considerable heterogeneity, showed a significant effect of the cow's milk-free diet on treatment success (**Figure 4**).

Treatment Success. Treatment success was reported as a combination of outcomes in 1 study, which reported a significantly higher treatment success rate in the cow's milk elimination diet group.[60] The authors of the other study concluded that constipation can be a manifestation of intolerance of, or a allergic reaction to, cow's milk.[61] The authors of the study investigating higher water intake and hyperosmolar liquids found no significant effect of fluid intake on constipation symptoms.[56]

Defecation Frequency. Defecation frequency was reported in all studies. Children receiving a cow's milk-free diet had a significantly higher defecation frequency compared with those receiving a diet containing cow's milk.[60,61] An increase in water intake or hyperosmolar liquid had no significant effect on defecation frequency.[56]

Adverse Events. The 2 studies including a cow's milk diet reported that none of the children receiving a cow's milk diet had an acute allergic reaction.[60,61]

Oral Supplements

***Cassia Fistula* Emulsion.** Two studies, including a total of 190 children, investigated the effect of *Cassia Fistula* emulsion compared with laxative treatment (mineral oil[64] and PEG[65]), with a high risk of bias in both studies. Meta-analyses showed evidence for a higher treatment success rate and increased defecation frequency in the *Cassia Fistula* emulsion group compared with control treatment (**Figures 4** and **5**). Treatment success was defined in both studies, and *Cassia Fistula* emulsion was found to be more effective than treatment with mineral oil[64] and as effective as treatment with PEG.[65] Defecation frequency was reported in both studies and was significantly higher in the *Cassia Fistula* emulsion groups. Both studies reported adverse events. In children using *Cassia Fistula* emulsion, diarrhea was the most common side effect reported in 25%-32% of children, all in whom the diarrhea resolved after a 25% dose decrease. Medication refusal because of taste was similar in both treatment groups in both studies.

Descurainia Sophia Seeds (Flixweed)

One study, including 120 children, investigated the effect of flixweed compared with PEG, with a high risk of bias.[67] Treatment success rates and defecation frequency were not significantly different between the groups. Adverse events were not clearly reported, except that in the flixweed group fewer children required rescue medication and more children (30%) disliked the taste.

Xiao'er Biantong Granules

One study, including 480 children, investigating the effect of Chinese patent medicine Xiao'er Biantong granules compared with placebo.[68] A high risk of bias was found. Treatment success rates and defecation frequency were significantly higher in the Xiao'er Biantong granules group. There were no differences in observed adverse events between groups, all of which were mild with favorable prognosis.

Green Banana Biomass

One study, including 80 children, investigated the effect of green banana biomass and included 5 different treatment groups, with a high risk of bias (**Appendix**).[69] Treatment success was not defined by authors. No between-group comparisons were made. Adverse events were reported, none were observed.

Black Strap Molasses (Sugar Cane Extract)

One study, including 92 children, investigated the effect of black strap molasses compared with PEG, with some concerns for bias.[58] Treatment success and the proportion of children with at least 3 bowel movements per week did not significantly differ between groups. Adverse events were reported and included transient abdominal pain which disappeared over time in both treatment groups (I, n = 4; PEG, n = 7).

Biofeedback

Four studies, including 320 children, investigated the effect of biofeedback, of which 3 studied the effect of the addition of biofeedback to laxative treatment[74-76] and 1 studied the effect of the addition of home biofeedback to biofeedback in the laboratory.[102] A high risks of bias was found in all studies.

Meta-analysis. A meta-analysis on treatment success, including the 3 studies, which investigated the additional effect of biofeedback to laxative treatment,[74-76] showed considerable levels of heterogeneity and no evidence for benefit of the addition of biofeedback (**Figure 4**).

Treatment Success. Treatment success was defined by authors and reported in all studies. Treatment success rates were higher in the biofeedback group in 2 studies,[74,76] were not different between groups in 1 study,[75] and were higher in the group receiving additional home biofeedback in 1 study.[102]

Defecation Frequency. Defecation frequency was reported in 1 study, which found no benefit of the addition of biofeedback training at home compared with biofeedback in the laboratory.[102]

Adverse Events. Adverse events were not reported in any of the studies.

Electrical Stimulation and Cryotherapy

Four studies, including 237 children, investigated the use of electrical stimulation and/or cryotherapy.[78-81] Two studies investigated the effect of abdominal interferential electrical stimulation (versus sham[78] or no stimulation[79]) as addition to treatment with pelvic floor muscle exercises and laxatives when necessary. One study investigated the effect of abdominal interferential electrical stimulation versus sham stimulation.[80] One study investigated not only the effect of percutaneous abdominal electrical stimulation but also looked at the effect of local cryotherapy and the combination of the 2 (cryoelectroneurostimulation).[81] A high risk of bias was found for all studies.

Meta-analysis. The meta-analysis on treatment success including 3 of the studies which defined treatment success[78,79,81] showed a significant effect of the addition of abdominal electrical stimulation to conventional treatment (**Figure 4**).

Treatment Success. Treatment success was reported in 3 of the 4 studies, and all studies showed benefit of the addition of electrical stimulation to conventional treatment.[78,79,81] The addition of cryotherapy also significantly increased treatment success rates compared with conventional treatment alone.[81] Cryoelectroneurostimulation significantly increased treatment success rates compared with the other 3 treatment groups.[81] The authors of 1 study did not define treatment success, nor did they compare outcomes between groups.[80]

Defecation Frequency. Defecation frequency was reported in 3 of the 4 studies, of which 2 found a significantly higher defecation frequency in the group receiving additional electrical stimulation compared with those receiving conventional treatment.[78,79] The addition of cryotherapy alone significantly increased defecation frequency compared with conventional treatment, and cryoelectroneurostimulation significantly increased defecation frequency compared with the other 3 treatment groups.[81]

Adverse Events. Adverse events were reported in 3 of the 4 studies; none were observed.

Massage Therapy

Three studies, including 256 children, investigated the effect of massage therapy.[84,85,87] Two studies investigated the effect of the addition of daily sessions of Chinese abdominal massage (Tui Na) to treatment with Chinese herbal medicine.[84,85] The other study investigated the effect of a 10-minute foot reflexology massage for 5 days a week as addition to regular advice including dietary advice and toilet training.[87] A high risk of bias was found in all studies (**Figure 3**, D).

Meta-analysis. A meta-analysis on treatment success using the proportions of children whom were completely cured in the 2 studies investigating the effect of the addition of Chinese abdominal massage[84,85] showed low levels of heterogeneity, and no significant effect of the addition of Chinese abdominal massage (**Figure 4**).

Treatment Success. Treatment success was reported in the 2 studies investigating the effect of Chinese abdominal massage. Authors reported that a higher number of the children receiving Chinese abdominal massage were cured, although not completely cured, see meta-analysis. The authors of the study investigating the effect of foot reflexology found no differences between groups after 4 weeks of treatment.[87]

Defecation Frequency. Defecation frequency was only reported in the study investigating the effect of foot reflexology, which did not show any significant difference between the groups.[87]

Adverse Events. Adverse events were not reported in any of the studies.

Other and Combined Treatments

Pelvic Physiotherapy. Although multiple studies describe the use of pelvic muscles exercises in the treatment of children with functional constipation,[78,79,86,88] only 1 study, including 53 children, specifically evaluated the effect of the addition of pelvic muscle exercises to laxative treatment, with a low risk of bias.[88] Treatment success rates were significantly higher in the group whom received additional pelvic physiotherapy. Improvement rates of children defecating at least 3 times per week did not differ between groups. Adverse events were not reported.

Behavioral Therapy. One study, including 134 children, evaluated the additional benefit of 12 sessions of behavioral therapy to laxative treatment with toilet training, with a high risk of bias.[89] Both treatment success rates and defecation frequency were not significantly different between groups indicating no evidence for the addition of behavioral therapy. Adverse events were not reported.

Dry Cupping. One study, including 120 children, investigated the effect of dry cupping therapy to conventional treatment with PEG, with a high risk of bias.[91] Treatment success rates were higher in the group receiving conventional treatment. Defecation frequency was not different between groups. Adverse events were not reported.

Combination Therapy. One study, including 72 children, investigated the combined effect of the addition of abdominal muscle training, breathing exercises, and abdominal massage to treatment with magnesium hydroxide, with a high risk of bias.[86] Treatment success was not defined by authors. Defecation frequency was higher in the group receiving the combination therapy. Adverse events were reported; none were observed.

Discussion

A total of 52 RCTs were analyzed, including 4592 children, with a wide variety of interventions. Meta-analyses for treatment success and defecation frequency showed that a cow's milk exclusion diet (n = 2 in a subpopulation with constipation as a possible manifestation of cow's milk allergy), abdominal electrical stimulation (n = 3), and *Cassia Fistula* emulsion (n = 2) may be effective. Evidence from studies not included in the meta-analyses, indicated that some prebiotic and fiber mixtures, Xiao'er Biantong granules, and abdominal massage are promising therapies. In contrast, studies showed no benefit for the use of probiotics, synbiotics, an increase in water intake, dry cupping, or additional biofeedback or behavioral therapy. Studies were heterogeneous with respect to study design, diagnostic criteria for functional constipation, study population, study intervention, duration of treatment and follow-up, and outcome measures. Adverse events were reported by the majority of the studies (33 of 52). Overall, adverse events of studied interventions were uncommon. If adverse events were observed, they were mild and mostly consisted of transient abdominal pain, diarrhea, or other gastrointestinal symptoms. No serious adverse events were reported. Additionally, an overall high risk of bias was found across the majority of studies. Therefore, the evidence found in this systematic review should be interpreted with caution.

We found that some prebiotic and fiber mixtures may be effective treatments, whereas no evidence was found for the use of probiotics or synbiotics. This difference may be explained by the fact that fibers and prebiotics stimulate fecal bulking via their own mass and the ability of insoluble fibers to bind water directly.[50] In accordance with this finding, numerous trials in healthy infants with infant formulas supplemented with prebiotics and/or fibers report stool softening effects.[103] Moreover, associations have been found between childhood constipation and low consumption of fiber,[104,105] fruits and vegetables,[104,106-108] and frequent consumption of fast foods.[108] As with laxatives, a dose-response effect is likely to be present for the effects of fibers and prebiotics. Some of the included studies used a low dose of fibers and prebiotics, which may explain the observed ineffectiveness, besides that some substrates might have no effect on functional constipation symptoms.[46,97,98] Adequate dosing regimens have not yet been established, and studies investigating which fiber and prebiotic mixtures to use, including dose-response effects, are needed. Of the studies included in this systematic review, only 3 evaluated the effects of treatment on microbiota composition. Future studies should take into account the actual differences in gut microbiota composition, working mechanisms, and metabolite profiles before and after intervention to clarify host-microbe interactions and identify possible differences between responders and nonresponders to move towards personalized gut microbiome-directed medicine or nonpharmacologic treatments.

Several studies investigated the effects of oral supplements or dietary changes, other than prebiotics, probiotics, or synbiotics, on constipation symptoms. In addition, 19 studies (37%) gave general dietary advice to all included children, often consisting of frequent consumption of fruits and vegetables and a normal fiber and fluid intake. This systematic review shows a lack of evidence for the benefit of a particular dietary intervention or supplement. Future studies may focus on investigating the effects of *Cassia Fistula* emulsion, Xiao'er Biantong granules, or black strap molasses as alternative laxative treatment. Current adult guidelines on functional constipation consider Chinese herbal medicine, like Xiao'er Biantong granules, effective, but clearly state that it is unknown which formulation and dosage is best to use.[109] Flixweed and green banana biomass seem less attractive options, because approximately one-third of children disliked the taste of flixweed, and green banana biomass alone did not seem to be an effective treatment.[67,69] Evidence from 2 studies with high risk of bias suggested that a cow's milk-free diet may be useful in children with constipation as manifestation of an underlying cow's milk allergy.[60,61] However, the generalizability of these findings is limited, because the authors of both studies described that their study populations represent a select patient population of children not responsive to conventional treatment, and one of the participating centers had considerable experience in the treatment of food allergies.[61]

Another subset of the identified interventions—namely, biofeedback and pelvic physiotherapy—target the act of defecation, because stool withholding is a major contributing factor in the onset and persistence of childhood constipation. By teaching children how to control their pelvic floor, in addition to laxative therapy to soften stools, they may relearn how to defecate. Indeed, after biofeedback training, the majority of constipated children was able to relax their pelvic floor but this was not related to successful outcome.[75] The addition of pelvic physiotherapy with a more extensive approach may contribute to better outcomes.[88] However, this might only be the case in children with symptoms refractory to conventional treatment, because a large study in primary care setting did not find additional benefit of pelvic physiotherapy.[110]

Massage therapy,[86] abdominal electrical stimulation,[78-81] and cryotherapy might directly enhance colonic motility.[81] Although evidence is limited and the mode of action remains incompletely understood, these interventions may have a positive effect on functional constipation in children. More rigorous and uniform studies using a standardized approach should be performed before these interventions can be recommended.

The main limitations of this review arise from the nature of the included studies. The actual therapeutic effect size is uncertain owing to possible publication bias, the majority of studies (71%) were conducted in a tertiary care setting, therefore limiting the generalizability of these findings. Additionally, the risk of bias within studies was overall high, especially in the overall risk of bias and bias in the selection of the reported results. Moreover, a meta-analysis was only possible for a proportion of studies owing to the lack of reported outcomes or differences in investigated treatment. Therefore, heterogeneity was only assessed for studies included in the meta-analysis and was found to be high for many studies. Also, large differences in effectiveness may exist between individual interventions, like probiotic strains or prebiotic substrates, which may differ greatly in their potential therapeutic effect.

Future research should focus on conducting high quality multicenter trials and follow current trial recommendations[16] using outcomes described in the COS.[11] Trials may focus on the most promising interventions found in this review: specific prebiotic and fiber mixtures, abdominal electrical stimulation, *Cassia Fistula* emulsion, and Xiao'er Biantong granules. Future studies may also investigate interventions of interest of which no trials were found like personalized gut-microbiota interventions, chicory inulin,[111] exercise,[112] (electro)acupuncture,[113-115] other noninvasive neuromodulating therapies like posterior tibial nerve stimulation,[116] and virtual and digital interventions.[117] Because education and ongoing toilet training are considered key elements in the treatment of childhood constipation, interventions motivating children to defecate and improving the self-efficacy of children in their constipation treatment are likely to be of great value.[118] Last, more attention should be given to the costs and cost-effectiveness of treatments, because none of the currently included studies reported on costs of the studied interventions.[119,120]

To conclude, more rigorous evidence is needed to confirm the effectivity of nonpharmacologic interventions for children with functional constipation, before strong recommendations can be given to change current guidelines. ■

We thank Faridi S. van Etten-Jamaludin for her help with building the search strategy. We thank Tatiana Degtyareva, Taojun Wang, and Siavash Atashgahi for their help with translating articles in foreign languages. We thank Ploon Defourny and Zoë Borst for their valuable insights in the evaluation of the included studies for their thesis. T.W. is financially supported by the China Scholarship Council (File No. 201600090211), has no industry relation, and no conflicts of interest. The other individuals listed in the acknowledgments declare no conflicts of interest.

Submitted for publication May 25, 2021; last revision received Sep 2, 2021; accepted Sep 8, 2021.

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50 Years Ago in *The Journal of Pediatrics*

Steel to Teflon and Vialon: Evolution of Intravenous Devices

Peter G, Lloyd JD-Still JD, Lovejoy FH. Local infection and bacteremia from scalp vein needles and polyethylene catheters in children. J Peds 1972;80:78-83.

Fifty years ago, Peter et al concluded that scalp vein needles are a better alternative to indwelling polyethylene catheters for intravenous infusions, because the latter are associated with higher rates of hospital-acquired infections (8.5% vs 24%). It is important to note that the then-customary technique of introducing polyethylene catheters was by surgical venostomy (cut-down).

The middle of 20th century proved to be a golden era for development of disposable medical devices. From steel reusable needles with a stylet in the 1950s to the Angiocath (the first disposable device) in 1964 to polyethylene, polyurethane (plastics) in the 1970s and 1980s, to modern-day catheters made of Teflon and Vialon, peripheral intravascular catheters have evolved.[1,2] Today, with the availability of superior technology, obtaining an intravascular access has become much easy. Catheters made of Vialon and Teflon have the advantages of longer dwell times and a decreased incidence of phlebitis.[3] Intravenous catheters are now inserted percutaneously in peripheral veins, obviating the need for the venostomy (cut-down) procedure used 50 years ago.

Peripheral intravenous cannulas can be inserted blindly by identifying the most prominent veins and then puncturing the overlying skin after applying strict aseptic precautions. In difficult venous access, ultrasound guidance has proved to be a blessing. Vessel purchase methodology is used to access deep-seated veins.[4] With the advent of superior quality and less invasive modes of intravascular access, we have reverted to intravenous catheters as the most common method of peripheral vascular access. They have replaced scalp vein needles universally. Scalp vein needles can also dislodge easily. The role of scalp vein needles in the current era is limited to an occasional scalp vein cannulation in young infants in emergency until a peripheral line can is secured. Owing to the availability of superior quality intravascular catheters with ease of insertion, retention, and a decreased rate of phlebitis, scalp vein needles for securing intravenous access in children have become a part of history.

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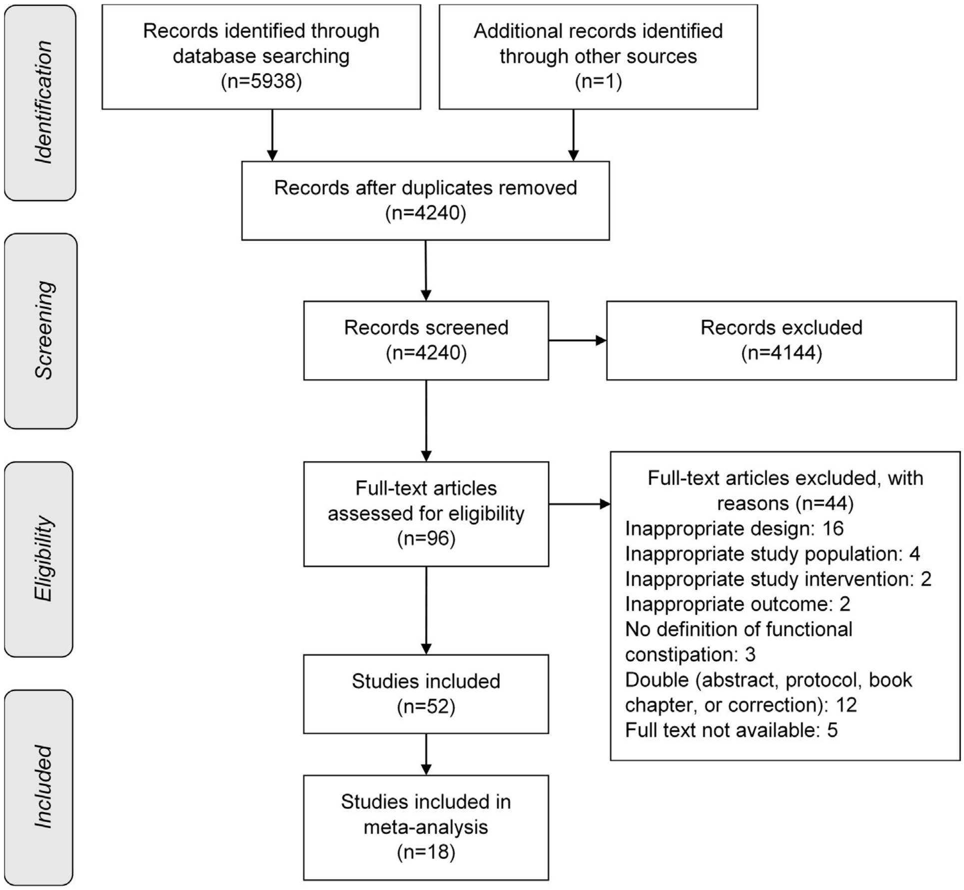

Figure 1. PRISMA Flow chart.[12]

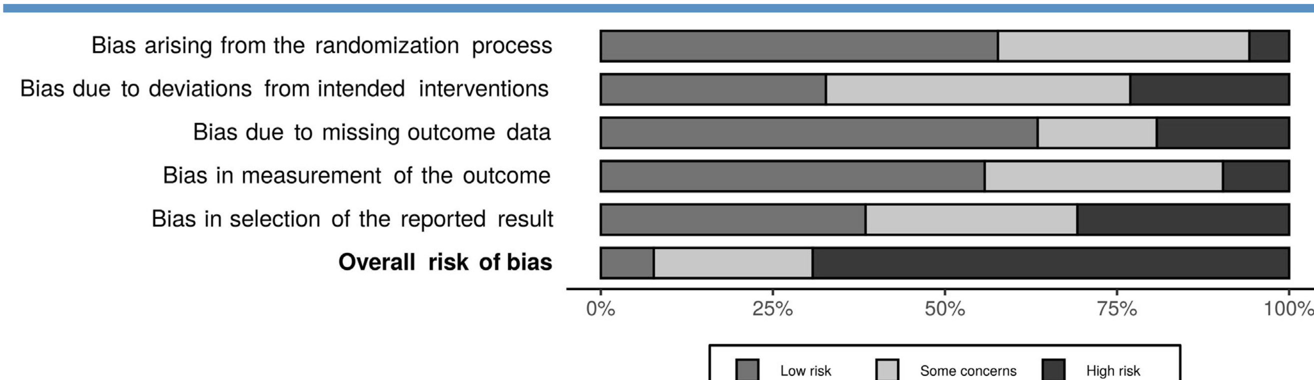

Figure 2. Risk of bias summary of all included studies.

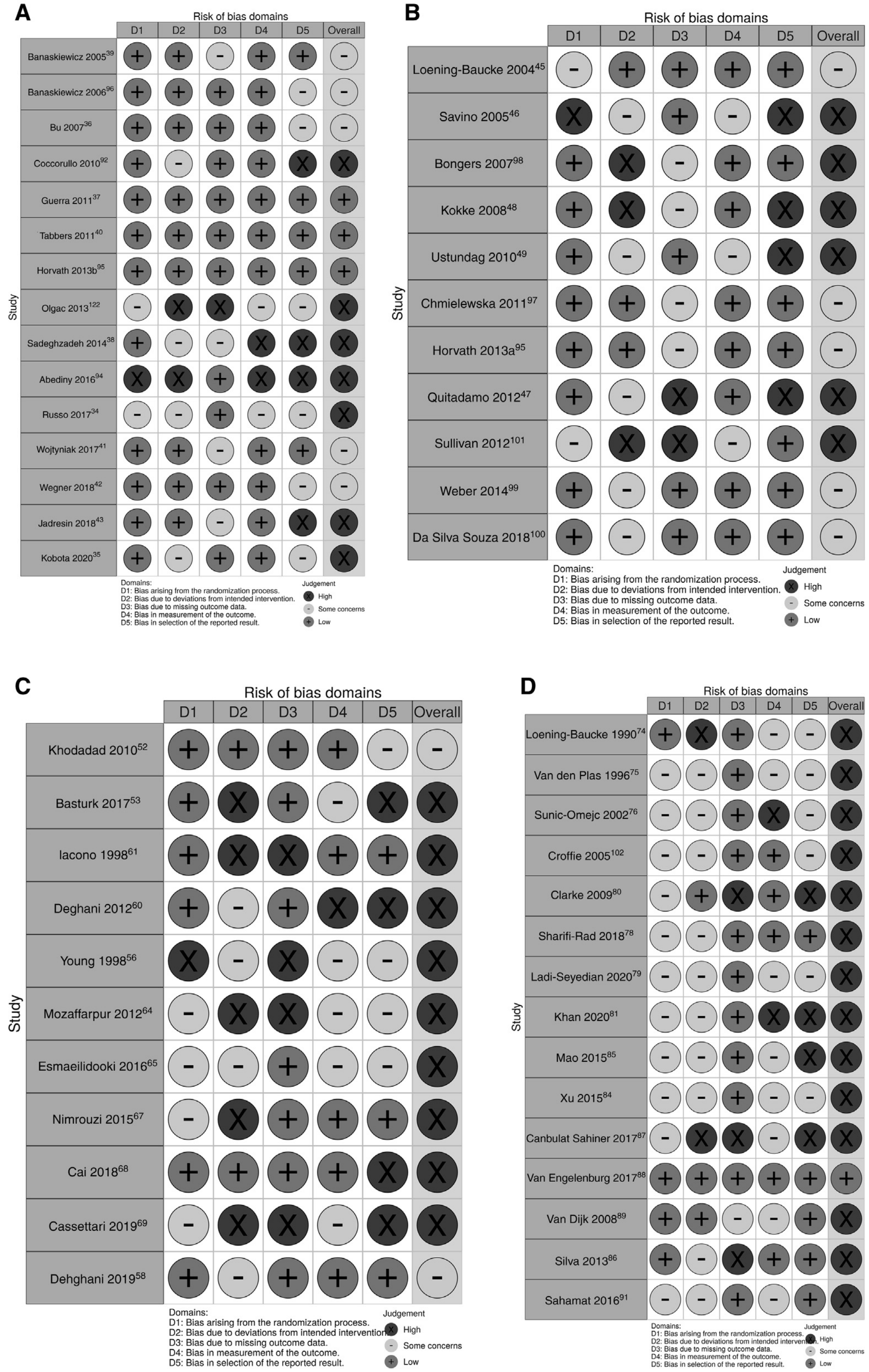

Figure 3. A, Risk of Bias traffic light plot for probiotics. **B,** Risk of bias traffic light plot for prebiotics and/or fiber. **C,** Risk of bias traffic light plot for synbiotics, dietary interventions, and oral supplements. **D,** Risk of bias traffic light plot for biofeedback, electrical stimulation and cryotherapy, massage therapy, and other and combined treatments.

Table I. Rome IV criteria for functional constipation

Patients <4 years of age	Developmental age of >4 years[4]
Must include 1 month of ≥2 of the following in infants ≤4 years of age: 1. ≤2 defecations per week 2. History of excessive stool retention 3. History of painful or hard bowel movements 4. History of large-diameter stools 5. Presence of a large fecal mass in the rectum In toilet-trained children, the following additional criteria may be used: 6. ≥1 episode/week of incontinence after the acquisition of toileting skills 7. History of large-diameter stools that may obstruct the toilet	Must include ≥2 of the following occurring at least once per week for a minimum of 1 month with insufficient criteria for a diagnosis of irritable bowel syndrome 1. ≤2 defecations in the toilet per week in a child of a developmental age of ≥4 years 2. ≥1 episode of fecal incontinence per week 3. History of retentive posturing or excessive volitional stool retention 4. History of painful or hard bowel movements 5. Presence of a large fecal mass in the rectum 6. History of large diameter stools that can obstruct the toilet After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

Table III. COS outcomes

Characteristics	Year	Defecation frequency	Defecation consistency	Painful defecation	Quality of life	Side effects	Fecal incontinence	Abdominal pain	School attendance	Treatment success
Probiotics										
Banaszkiewicz et al[39]	2005	X				X	X			2 items of COS
Banaszkiewicz et al[121] FU	2006									2 item of COS
Bu et al[36]	2007	X	X			X	X	X		2 items of COS
Coccorullo et al[92]	2010	X	X			X				
Guerra et al[37]	2011	X	X	X		X		X		
Tabbers et al[40]	2011	X	X	X		X	X	X		2 items of COS
Horvath et al[95] FU	2013									2 items of COS
Olgaç et al[122]	2013	X	X	X	X	X	X	X		
Sadeghzadeh et al[38]	2014	X	X			X	X	X		
Abediny et al[94]	2016		X	X				X		
Russo et al[34]	2017	X	X	X		X	X	X		5 items of COS
Wojtyniak et al[41]	2017	X	X	X		X	X	X		2 items of COS
Wegner et al[42]	2018	X	X	X		X	X	X		
Jadrešin et al[43]	2018	X	X			X	X	X		
Kubota et al[35]	2020	X	X			X				
Fiber and prebiotics										
Loening-Baucke et al[45]	2004	X	X			X	X	X		3 items of COS
Savino et al[46]	2005	X	X							
Bongers et al[98]	2007	X	X	X		X				
Kokke et al[48]	2008	X	X	X		X	X	X		
Üstündağ et al[123]	2010	X	X			X		X		2 items of COS
Chmielewska et al[97]	2011	X	X	X		X	X	X		2 items of COS
Horvath et al[95] FU	2013									2 items of COS
Quitadamo et al[47]	2012	X	X	X		X	X	X		5 items of COS
Sullivan et al[101]	2012	X								
Weber et al[99]	2014	X	X			X				4 items of COS
Da Silva Souza et al[124]	2018	X	X	X		X				2 items of COS
Synbiotics										
Khodadad et al[99]	2010	X	X	X			X	X		3 items of COS
Baştürk et al[53]	2017	X	X	X		X	X	X		
Cow's milk exclusion diet										
Iacono et al[61]	1998	X	X	X						
Dehghani et al[60]	2012	X	X	X		X			X	Fulfilling Rome III criteria
Water and hyperosmolar fluid										
Young et al[56]	1998									
Other herbs and other oral supplements										
Mozaffarpur et al[64]	2012	X	X	X		X	X			Fulfilling Rome II criteria (1/6 or 0/6)
Esmaeilidooki et al[64]	2016	X	X	X		X	X			Fulfilling Rome II criteria
Nimrouzi et al[67]	2015	X	X	X		X	X	X		Fulfilling Rome III criteria
Cai et al[68]	2018	X	X				X			3 items of COS
Cassettari et al[69]	2019	X	X	X		X	X	X		
Dehghani et al[58]	2019	X								Fulfilling Rome III criteria
Biofeedback										
Loening-Baucke et al[45]	1990						X			2 items of COS
van der Plas et al[75]	1996									2 items of COS
Sunic-Omejc et al[76]	2002									2 items of COS
Croffie et al[102]	2005	X					X			3 items of COS

(continued)

Table III. Continued

Characteristics	Year	Defecation frequency	Defecation consistency	Painful defecation	Quality of life	Side effects	Fecal incontinence	Abdominal pain	School attendance	Treatment success
Electrical therapy										
Clarke et al[80]	2009				X				X	
Sharifi-Rad et al[78]	2018	X	X	X	X	X	X	X		Fulfilling Rome III criteria
Ladi-Seyedian et al[79]	2020	X	X	X			X			Fulfilling Rome IV criteria
Khan et al[81]	2020	X		X			X	X		2 items of COS
Massage therapy										
Mao et al[85]	2015									2 items of COS
Xu et al[84]	2015									1 item of COS
Canbulat Sahiner et al[87]	2017	X	X							
Pelvic floor physiotherapy										
van Engelenburg et al[88]	2017	X	X	X			X			Fulfilling Rome III criteria
Behavioral therapy										
Van Dijk et al[89]	2008	X					X			2 items of COS
Dry cupping										
Shahamat et al[125]	2016	X	X	X			X			Fulfilling Rome III criteria
A combination of abdominal muscle training, breathing exercised and abdominal massage										
Silva et al[86]		X	X	X		X	X			

FU, follow-up.