Functional defecation disorders in children
Koppen, I.J.N.

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CHAPTER 12
IS THERE A ROLE FOR PRE-, PRO- AND SYNBIOTICS IN THE TREATMENT OF FUNCTIONAL CONSTIPATION IN CHILDREN? A SYSTEMATIC REVIEW

Ilan J.N. Koppen, Marc A. Benninga, Merit M. Tabbers

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ABSTRACT

Purpose of review: To investigate the efficacy and safety of pre-, pro- and synbiotics in the treatment of pediatric functional constipation (FC).

Recent findings: A recent study reported that the gut microbiota in obese children with FC differs from that of obese children without FC. The gut microbiota may be involved in the pathophysiology of FC. Pre- and probiotics have been suggested as potential treatment modalities for FC in children.

Summary: PubMed and Cochrane databases were searched from inception to February 2016. We found six RCTs on prebiotics, six RCTs on probiotics and one RCT concerning synbiotics. Overall, most studies were at high risk of bias. The majority of studies were unable to demonstrate a significant effect of pre-, pro- or synbiotics on predefined outcome measures such as defecation frequency, fecal incontinence and painful or difficult defecation. Pre-, pro- and synbiotics were not associated with significant adverse effects. In conclusion, there is insufficient evidence to recommend pre-, pro- or synbiotics in the treatment of children with FC. High-quality randomized controlled trials are warranted to further explore these treatment modalities.
INTRODUCTION

As a result of the development of culture-independent techniques, we are starting to understand the human microbiome and its role in health and disease. We now know that the vast majority of our resident microbes are contained in the gut and that gut microbiota changes are associated with a wide variety of diseases and disorders. Unfortunately, in most cases it remains unclear whether these microbiota changes are cause, effect or innocent bystander effect of these illnesses. One of the disorders in which the gut microbiota may be involved is functional constipation (FC). FC is a common and bothersome problem in pediatric healthcare. The prevalence ranges between 0.7% and 29.6%. This functional gastrointestinal disorder is defined according to the Rome III criteria (Table 1). Symptoms include infrequent defecation, hard, painful stools that are difficult to pass, fecal incontinence and abdominal pain. These symptoms are known to have a significant impact on the quality of life of children and on healthcare costs. The conventional approach towards FC encompasses education including dietary advice, a toilet program and laxatives. However, conventional treatment turns out to be insufficient in a substantial amount of children. Also, most laxatives have adverse effects such as abdominal pain or flatulence. More importantly, although laxatives are generally considered to be safe, little is known about the long-term adverse effects of chronic laxative usage, such as efficacy, potential electrolyte disturbances or mucosal damage. Therefore, it remains important to develop and evaluate new treatment strategies for FC in children.

Pre- and probiotics have been suggested as potential treatment modalities for FC in children. In this systematic review we provide an update on current literature describing the potential role of pre-, pro- and synbiotics in the treatment of FC in children.

<table>
<thead>
<tr>
<th>Rome III criteria</th>
<th>Developmental age of ≥4 years</th>
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<tbody>
<tr>
<td>Age</td>
<td>&lt;4 years</td>
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<tr>
<td>1. &lt;3 defecations per week</td>
<td>1. &lt;3 defecations in the toilet per week</td>
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<td>2. ≥1 episode of fecal incontinence per week after the acquisition of toileting skills</td>
<td>2. ≥1 episode of fecal incontinence per week</td>
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<tr>
<td>3. History of excessive stool retention</td>
<td>3. History of retentive posturing or excessive volitioanl stool retention</td>
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<tr>
<td>4. History of painful or hard bowel movements</td>
<td>4. History of painful or hard bowel movements</td>
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<tr>
<td>5. Presence of a large fecal mass in the rectum</td>
<td>5. Presence of a large fecal mass in the rectum</td>
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<td>6. History of large diameter stools which may obstruct the toilet</td>
<td>6. History of large diameter stools which may obstruct the toilet</td>
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<tr>
<td>- Must fulfill ≥2 criteria for ≥1 month prior to diagnosis.</td>
<td>- Must fulfill ≥2 criteria at least once per week for ≥2 months prior to diagnosis</td>
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<tr>
<td>- Insufficient criteria for diagnosis of IBS</td>
<td>- Insufficient criteria for diagnosis of IBS</td>
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</table>
METHODS

Cochrane Library and Medline databases were searched from inception to February 2016. Search terms related to pediatric FC, fiber, pre-, pro- and synbiotics were used. The full search strategy is available from the authors. Studies were eligible for inclusion if they were; 1) systematic reviews of randomized controlled trials (RCTs); 2) written in English; 3) comparing pre-, pro- or synbiotics with placebo, no treatment or any pharmacological therapy for the treatment of FC in children from 0–18 years of age; 4) functional constipation was clearly defined by the authors; 5) reported outcome measures were defecation frequency, fecal incontinence, painful defecation, difficulty with defecation, abdominal pain, quality of life or possible harm from treatment (tolerance, adverse effects). Two authors (I.J.N.K. and M.M.T.) independently assessed the eligibility of all abstracts. In cases of disagreement, consensus was reached through discussion. Additionally, reference lists of included articles were searched. Reasons for exclusion were: 1) treatment arms with < 10 patients; 2) evaluation of a mixture of pre-, pro- or synbiotics with other potentially therapeutic components in the intervention group, to assure that we evaluated the effect of pre- and probiotics only. Quality of evidence was assessed using the Cochrane Collaboration’s tool for assessing risk of bias.

FIGURE 1. Flowchart of article selection process
RESULTS

Figure 1 shows the article selection process. Study characteristics of all included studies are summarized in Tables 2–4. Table 5 depicts the risk of bias assessment for all studies.

Prebiotics

Prebiotics are non-digestible food ingredients that beneficially affect the host by selectively stimulating growth and/or activity of one or a limited number of bacteria in the colon. By this definition, many dietary fibers are prebiotics. Insufficient dietary fiber intake has been reported to be associated with FC. This has led to the hypothesis that a lack of intake of prebiotics may be involved in the pathogenesis of constipation. Prebiotics may be beneficial for children with FC due to: 1) increase in water content (bulking effect and softening of stools); 2) increase in microbial mass and gas from fiber fermentation; 3) modification of colonic metabolite absorption, including secondary bile acids; 4) influencing gut microbes that affect motility.

We identified four systematic reviews describing a total of six RCTs.

In their crossover trial, Loening-Baucke et al. evaluated the effect of glucomannan (a fiber gel polysaccharide) compared to placebo in 31 children with FC >4 years of age. Children continued using their laxatives and were instructed to conduct toilet training throughout the study. Both groups received either placebo or glucomannan for 4 weeks. No significant difference was found in defecation frequency or fecal incontinence frequency between both groups after 4 weeks. There were however significant differences in the percentages of children with <3 bowel movements per week (glucomannan: 19% vs placebo: 52%, P < .05) and abdominal pain (glucomannan: 10% vs placebo: 42%, P < .05). It is important to note that the initial daily fiber intake was low in 71% of children.

Castillejo et al. performed a study where 48 children with FC received either a cocoa husk supplement or placebo, in addition to toilet training. No significant differences in defecation frequency or parental report of pain during defecation were observed. In both study groups, the mean basal dietary fiber intake was near the recommended daily allowance.

In a larger RCT by Kokke et al., the effect of a fiber mixture was compared with lactulose in 97 children with FC. There were no significant differences between both groups with respect to defecation frequency, presence of ≥1 fecal incontinence episode(s) per week or abdominal pain. Baseline fiber intake was not reported.

Üstündag et al. investigated partially hydrolyzed guar gum (PHGG) and compared this with lactulose in 61 children. The authors found a significant improvement in defecation frequency in both groups, but children receiving lactulose had significantly more bowel
movements after treatment (mean defecation frequency: PHGG: 5.0 ± 1.7 vs lactulose: 6.0 ± 1.1, *P* < .05). The authors reported that baseline daily fiber intake and diet were similar in both groups.

In succession to the study by Loening-Baucke *et al.*, glucomannan was evaluated in a placebo-controlled 4-week RCT in 72 children by Chmielewska *et al.* The authors found no significant difference between both groups with respect to therapeutic success at the end of the study. Abdominal pain occurred significantly less in the glucomannan group at the end of the study. Median number of episodes of abdominal pain per week (interquartile range): glucomannan: 0 (0–2) vs placebo: 0 (0–1), *P* < .01.

Weber *et al.* described the use of a dietary fiber mixture in comparison to placebo in 54 children. Although the defecation frequency did not differ between groups at the end of treatment (fiber: 1.1 ± 0.5 vs placebo: 0.9 ± 0.3), there was a significantly larger improvement in daily bowel movements compared to baseline in the fiber group. The mean increase in defecation frequency per day in the fiber mixture group was 0.5 ± 0.4 versus 0.2 ± 0.4 in the placebo group (*P* = .01). The median dietary fiber intake was similar in both groups before the start of the clinical trial.

**Probiotics**

Probiotics contain viable microorganisms which alter the microflora of the host and exert beneficial health effects in this host. It has been suggested that certain microorganisms affect colonic motility by softening the stools and by influencing secretion and/or absorption of water and electrolytes. Also, they may influence smooth muscle cell contractions, directly manipulating peristalsis. Probiotics can also influence intraluminal pH; by lowering the pH they can affect intestinal motility. Furthermore, it is likely that metabolic processes play a role; substances involved in microbiota metabolism that may influence colonic motility include methane and butyrate. We identified four systematic reviews describing five RCTs and one subsequent RCT which was not described in any of the previous systematic reviews.

**Lactobacillus rhamnosus GG**

Banaskwiecz *et al.* assessed the effectiveness of *Lactobacillus rhamnosus* GG (ATCC 53103) as an adjunct to lactulose, comparing this with placebo added to lactulose treatment in 84 children. The authors found no significant difference in defecation frequency, fecal incontinence episodes or straining at defecation between the two groups. The side effect profile was similar in both groups; with abdominal being the most commonly reported adverse effect.
### TABLE 2. Study characteristics of RCTs on prebiotics. Significant results are bold.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>n (age)</th>
<th>Diagnosis</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Duration</th>
<th>Outcome</th>
<th>Effect</th>
<th>Adverse effects</th>
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</thead>
</table>
| Loening-Baucke, 2004 | 31 (4-11 yrs) | chronic FC (defined as a delay or difficulty in defecation, present for >2 weeks, and sufficient to cause significant distress to the child, for ≥6 months) | glucomannan<sup>a</sup> + laxatives + toilet training | placebo + laxatives + toilet training | 8 weeks: crossover after 4 weeks | 1. defecation frequency/week (mean±SD)  
2. % <3 bowel movements/week  
3. fecal incontinence/week (mean±SD)  
4. % fecal incontinence  
5. % abdominal pain  
6. % treatment success (≥3 bowel movements per week and ≤1 fecal incontinence episode in the last 3 weeks with no abdominal pain) | I: 4.5±2.3 vs C: 3.8±2.2  
I: 19% vs C: 52%  
I: 4.0±6.3 vs C: 4.2±4.8  
I: 42% vs C: 48%  
I: 42% vs C: 10%  
I: 45% vs C: 13% | -no serious adverse effects |
| Castillejo, 2006  | 48 (3-10 yrs) | adult Rome II criteria | cocoa husk<sup>b</sup> + toilet training | placebo + toilet training | 4 weeks | 1. defecation frequency/week (mean±SD)  
2. % improvement painful defecation | I: 6.1±3.4 vs C: 5.1±3.1  
I: 67% vs C: 46% | -no difference adverse effects |
| Kokke, 2008 | 97 (1-12 yrs) | ≥2 out of the following 4 criteria: stool frequency <3 times per week, fecal incontinence ≥2 times per week, periodic passage of large amounts of stool ≥ once every 7-30 days, or a palpable abdominal or rectal mass. | fiber mixture<sup>c</sup> | lactulose | 13 weeks (8 weeks treatment) | 1. defecation frequency (median)  
2. % fecal incontinence  
3. % abdominal pain (mean) | I: 7 vs C: 6  
I: 16% vs C: 10%  
I: 1.5 vs C: 1.4 | -no serious adverse effects |
| Üstündag, 2010  | 61 (4-16 yrs) | Rome III criteria | PHGG<sup>d</sup> | lactulose | 4 weeks | 1. defecation frequency (mean±SD)  
2. % abdominal pain | I: 15.0±1.7 vs C: 6.0±1.1  
I: 18% vs C: 10% | -no serious adverse effects |
<table>
<thead>
<tr>
<th>Author, year</th>
<th>n (age)</th>
<th>Diagnosis</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Duration</th>
<th>Outcome</th>
<th>Effect</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chmielewska, 2011</td>
<td>72 (3-16 yrs)</td>
<td>Rome III criteria</td>
<td>glucomannan(^a) + toilet training</td>
<td>placebo + toilet training</td>
<td>4 weeks</td>
<td>1. defecation frequency (median, IQR) 2. fecal incontinence (median, IQR) 3. painful defecation (median, IQR) 4. abdominal pain (median, IQR) 5. % treatment success (≥3 stools per week with no soiling)</td>
<td>I: 6 (3-8) vs C: 4 (2-6.25) I: 0 (0-1) vs C: 0 (0-0) I: 0 (0-2) vs C: 0 (0-1)</td>
<td>16% vs C: 58%</td>
</tr>
<tr>
<td>Weber, 2014</td>
<td>54 (4-12 yrs)</td>
<td>Rome III criteria; at inclusion all patients were asymptomatic (defecation frequency ≥ once every 2 days and no fecal incontinence or fecal impaction for ≥ 1 month). They were on low doses of laxatives.</td>
<td>fiber mixture(^b) + toilet training</td>
<td>placebo + toilet training</td>
<td>4 weeks</td>
<td>1. defecation frequency/day (mean±SD) 2. defecation frequency improvement/day (mean±SD) 2. % treatment failure (hardened stools, defecation with pain or difficulty, a greater interval between evacuations compared with the previous day, the appearance of fecal incontinence and fecal impaction, or when the patient required an enema or a stool softener during the study period. Hardened stools were defined as Bristol Stool Scale 1-3)</td>
<td>I: 1.1±0.5 vs C: 0.9±0.3 I: 0±0.4 vs C: 0.2±0.4</td>
<td>13.5% vs C: 36%</td>
</tr>
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</table>

\(^a\) 33 children after exclusion of the placebo arm (<10 children)
\(^b\) glucomannan was given in capsules containing 500mg, patients received 100 mg/kg body weight daily (max 5 g/day) rounded to the nearest 500 mg.
\(^c\) a sachet of fiber supplement contained 4 g of cocoa husk and 1 g of betafructosans; children aged 3-6 years took 1 sachet before lunch and dinner, older children took 2 sachets before lunch and dinner. Parents were instructed to dissolve the sachet in 200mL of whole milk.
\(^d\) per 100mL the yoghurtdrink contained 3.0 g transgalacto-oligosaccharides, 3.0 g inulin, 1.6 g soy fiber, and 0.33 g resistant starch 3. Patients <15 kg received 125 mL daily, those weighing 15-20 kg 250 mL, and those >20 kg 375 mL.
\(^e\) PHGG was dosed as follows: 4-6 years: 3 g/day; 6-12 years: 4 g/day; and 12-16 years: 5 g/day. Co-intervention not similar in both groups: the group given PHGG was recommended to increase their fluid intake as well.
\(^f\) patients received two sachets of 1.26 g glucomannan a day (2.52 g/day).
\(^g\) fiber mixture contents: 10.5% fructooligosaccharides, 12.5% inulin, 24% gum arabic, 9% resistant starch, 33% soy polysaccharide, and 12% cellulose. Dosage was based on body weight: 3.8 g twice a day in children <18kg and 7.6 g for children >18 kg. Children received medication in chocolate milk. Abbreviations: FC, functional constipation; PHGG, partially hydrolyzed guar gum; ns, not significant; vs, versus.
**Lactobacillus reuteri**
Coccorullo *et al.* evaluated the effect of *Lactobacillus reuteri* (DSM 17938) versus placebo in 44 infants with FC.
The authors stated that *L. reuteri* significantly increased the frequency of bowel movements compared with placebo at 2, 4 and 8 weeks. However, results were graphically presented without reporting absolute numbers.

**Lactobacillus casei rhamnosus**
Another RCT investigated the effect of *Lactobacillus casei rhamnosus* (Lcr35), comparing this with that of magnesium oxide (MgO) and placebo in 41 children. We will not report on the placebo arm, since this arm contained less than 10 children. There was no significant difference in defecation frequency between the Lcr35 group and the MgO group. Abdominal pain was significantly less prevalent in the Lcr35 group compared to the MgO group; mean number of episodes of abdominal pain during the 4 weeks of treatment: Lcr35: 1.9 ± 1.6 vs MgO: 4.8 ± 3.7 (P = .04).

**Bifidobacterium lactis**
Tabbers *et al.* studied the use of fermented milk, containing *Bifidobacterium lactis* DN-173 010 compared with a non-fermented milk control product in 148 children. The defecation frequency increased notably in both groups, but there was no significant difference between both groups. Other outcome measures such as fecal incontinence, painful defecation and abdominal pain also did not show any significant differences.

**Bifidobacterium longum**
In a crossover trial comparing yogurt containing *Bifidobacterium longum* with yoghurt alone in 59 children, the authors reported that overall a significant difference was found for defecation frequency, painful defecation and abdominal pain between both groups. However, aside from the P-values, the numeric data to support these statements were not provided.

**Multispecies Probiotics**
Sadeghzadeh *et al.* studied the effect of a combination of seven probiotics with placebo alongside the use of lactulose in 48 children. The authors report that stool frequency, fecal incontinence and abdominal pain significantly improved. However, due to incomplete reporting of the results, it is difficult to interpret these results.
TABLE 3. Study characteristics of RCTs on probiotics. Significant results are bold.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>n (age)</th>
<th>Diagnosis</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Duration</th>
<th>Outcome</th>
<th>Effect</th>
<th>Adverse events</th>
</tr>
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<tbody>
<tr>
<td>Banaszkiewicz, 2005</td>
<td>84 (2-16 yrs)</td>
<td>&lt;3 bowel movements per week for at least 12 weeks.</td>
<td><em>Lactobacillus rhamnosus</em> GG&lt;sup&gt;a&lt;/sup&gt; + lactulose&lt;sup&gt;b&lt;/sup&gt; + toilet training</td>
<td>placebo + lactulose&lt;sup&gt;b&lt;/sup&gt; + toilet training</td>
<td>26 weeks (12 weeks treatment)</td>
<td>1. defecation frequency/week (mean±SD)</td>
<td>I:6.1±1.8 vs C:6.8±3.1 10.8±1.8 vs C:0.3±0.9 1.3±1.5 vs C:1.6±1.8 172% vs C:68%</td>
<td>-no serious adverse effects</td>
</tr>
<tr>
<td>Coccorullo, 2010</td>
<td>44 (&gt;6mo)</td>
<td>Rome III criteria</td>
<td><em>Lactobacillus reuteri</em>&lt;sup&gt;c&lt;/sup&gt;</td>
<td>placebo</td>
<td>8 weeks</td>
<td>1. defecation frequency results presented in a graph, actual numbers not reported</td>
<td>-no (serious) adverse effects</td>
<td></td>
</tr>
<tr>
<td>Bu, 2007</td>
<td>41 (33)&lt;sup&gt;1&lt;/sup&gt; (&lt;10 yrs)</td>
<td>&lt;3 bowel movements per week for &gt;2 months and ≥1 of the following symptoms: anal fissures with bleeding, fecal soiling, or passage of large and hard stool.</td>
<td><em>Lactobacillus casei</em> rhamnosus&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Magnesium oxide (MgO)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>4 weeks</td>
<td>1. defecation frequency/day (mean±SD)</td>
<td>I:0.6±0.2 vs C:0.6±0.1 I:2.1±3.8 vs C:2.7±5.1 I:9.1±6 vs C:4.8±3.7</td>
<td>Lactulose use (1 mL /kg per day) was allowed when no stool passage for 3 days was noted. Glycerin enema was used only when no defecation was noted for &gt;5 days or abdominal pain was suffered due to stool impaction. Lactulose use (1 mL /kg per day) was allowed when no stool passage for 3 days was noted. Glycerin enema was used only when no defecation was noted for &gt;5 days or abdominal pain was suffered due to stool impaction. -no (serious) adverse effects</td>
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### TABLE 3. (continued)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>n (age)</th>
<th>Diagnosis</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Duration</th>
<th>Outcome</th>
<th>Effect</th>
<th>Adverse events</th>
</tr>
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<tbody>
<tr>
<td>Tabbers, 2011</td>
<td>148</td>
<td>Rome III criteria, but all should fulfill the criterion of having a defecation frequency of &lt;3 times.</td>
<td>Bifidobacterium lactis DN-173 010&lt;sup&gt;a&lt;/sup&gt; + toilet training</td>
<td>control product&lt;sup&gt;b&lt;/sup&gt; + toilet training</td>
<td>5 weeks (3 weeks treatment)</td>
<td>1. defecation frequency/week (mean)</td>
<td>I: 4.5 vs C: 3.9</td>
<td>-2 adverse events (unrelated)</td>
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<td></td>
<td>(3-16 yrs)</td>
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<td>2. defecation frequency improvement (mean±SD)</td>
<td>I: 2.9±3.2 vs C: 2.6±2.6</td>
<td>-no serious adverse effects</td>
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<td>3. % fecal incontinence</td>
<td>I: 37% vs C: 49%</td>
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<td>4. % painful defecation</td>
<td>I: 49% vs C: 41%</td>
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<td>5. abdominal pain</td>
<td>I: 58% vs C: 54%</td>
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<td>6. % treatment success (≥3 bowel movements per week and &lt;1 fecal incontinence episode in 2 weeks over the last 2 weeks of product consumption)</td>
<td>I: 38% vs C: 24%</td>
<td></td>
</tr>
<tr>
<td>Guerra, 2011</td>
<td>59</td>
<td>Rome III criteria</td>
<td>Bifidobacterium longum&lt;sup&gt;c&lt;/sup&gt;</td>
<td>control product</td>
<td>10 weeks (crossover after 5 weeks)</td>
<td>1. defecation frequency</td>
<td>results are presented in a graph, actual numbers not reported</td>
<td>-no data on adverse effects</td>
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<td></td>
<td>(5-15 yrs)</td>
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<td>2. painful defecation</td>
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<td>3. abdominal pain</td>
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<tr>
<td>Sadeghzadeh, 2014</td>
<td>48</td>
<td>Rome III criteria</td>
<td>Protexir&lt;sup&gt;d&lt;/sup&gt; + lactulose&lt;sup&gt;k&lt;/sup&gt;</td>
<td>placebo + lactulose&lt;sup&gt;k&lt;/sup&gt;</td>
<td>4 weeks</td>
<td>1. defecation frequency (mean±SD)</td>
<td>I: 2.1±0.7 vs C: 1.5±1.0</td>
<td>-no (serious) adverse effects</td>
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<td></td>
<td>(4-12 yrs)</td>
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<td></td>
<td>2. % fecal incontinence</td>
<td>I: 31% vs C: 78%</td>
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<td>3. % abdominal pain</td>
<td>I: 44% vs C: 66%</td>
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</table>

<sup>a</sup> Lactobacillus rhamnosus strain GG (ATCC 53103), 10<sup>9</sup> colony-forming units, twice daily.
<sup>b</sup> 70% lactulose, 1mL/kg/day.
<sup>c</sup> Lactobacillus reuteri (DSM 17938), 10<sup>9</sup> colony-forming units in 5 drops of a commercially available oil suspension, once per day.
<sup>d</sup> Lactobacillus casei rhamnosus: 8 x 10<sup>8</sup> colony-forming units/day, twice daily.
<sup>e</sup> Magnesium oxide: 50mg/kg/day, twice daily.
<sup>f</sup> Probiotic product: 125-g pot (containing <5 g of lactose) manufactured with lactic cultures including Bifidobacterium lactis DN-173 010 (strain number I-2494, at least 4.25 x 10<sup>9</sup> colony-forming units per pot), yogurt starter cultures Lactobacillus delbruecki ssp. Bulgaricus CNCM strain numbers I-1632 and I-1519, and Streptococcus thermophilus CNCM strain number I-1630, at least 1.2 x 10<sup>9</sup> colony-forming units per pot and Lactococcus cremoris (CNCM strain number I-1631). Patients took 2 pots a day.
<sup>g</sup> Control product: a milk-based, nonfermented dairy product (125-g pot) without probiotics and with a low content of lactose (<2.5 g per pot). Patients took 2 pots a day.
<sup>h</sup> Probiotics: 1mL of goat yogurt supplemented with Bifidobacterium longum 10<sup>9</sup> colony-forming units/mL.
<sup>i</sup> Control product: 1mL of goat yogurt only.
<sup>j</sup> Each sachet contained Lactobacillus casei PXN 37, Lactobacillus rhamnosus PXN 54, Streptococcus thermophilus PXN 66, Bifidobacterium breve PXN 25, Lactobacillus acidophilus PXN 35, Bifidobacterium infantis PXN 27, and Lactobacillus bulgaricus PXN 39, total viable count: 1 x 10<sup>9</sup> colony-forming units.
<sup>k</sup> 1mL/kg/day.

Abbreviations: FC, functional constipation; ns, not significant; vs, versus.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>n (age)</th>
<th>Diagnosis</th>
<th>Interventions</th>
<th>Duration</th>
<th>Outcome</th>
<th>Effect</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khodadad, 2010</td>
<td>97 (4-12 yrs)</td>
<td>Rome III criteria</td>
<td>Group A: liquid paraffin(^a) + placebo; Group B: synbiotic(^b) + placebo; Group C: liquid paraffin(^a) + synbiotic(^b); All groups received toilet training advice.</td>
<td>4 weeks</td>
<td>1. defecation frequency/week (mean±SD) 2. fecal incontinence/week (mean±SD) 3. % painful defecation 4. abdominal pain 5. successful treatment (≥3 bowel movements per week and ≤2 fecal incontinence episodes in the last month with no abdominal pain)</td>
<td>A:6.8±2.6 vs B:5.2±1.9 vs C:7.5±4.4 A:0.2±1.3 vs B:0.1±0.3 vs C:0.0±0.0 A:7% vs B:10% vs C:11% A:14% vs B:7% vs C:14% A:83% vs B:71% vs C:76%</td>
<td>-seepage of oil was reported in the majority of children in groups A and C; no adverse effects in group B. -no serious adverse effects.</td>
</tr>
</tbody>
</table>

\(^a\) 1.5 ml/kg/day oral

\(^b\) Synbiotic consisted of probiotic strains containing L. casei, L. rhamnosus, S. thermophilus, B. breve, L. acidophilus, B. infantis and fructooligosaccharide as prebiotic (1x10^9 colony-forming units/sachet). 1 sachet per day.
TABLE 5. Risk of bias assessment according to the Cochrane Collaboration’s tool for assessing risk of bias: + (red) = low risk of bias; - (green) = high risk of bias; ? (yellow) = unclear risk of bias.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>sequence generation</th>
<th>allocation concealment</th>
<th>blinding of participants/personnel</th>
<th>blinding of outcome assessment</th>
<th>incomplete outcome data</th>
<th>selective outcome reporting</th>
<th>other sources of bias</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loening-Baucke, 2004</td>
<td>++</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>unclear blinding of outcome assessor, unclear diagnosis FC, 33% loss to follow-up, use of laxatives</td>
</tr>
<tr>
<td>Castillejo, 2006</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Kokke, 2008</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>-</td>
<td>28% loss to follow-up, use of laxatives</td>
</tr>
<tr>
<td>Üstündağ, 2010</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>not blinded, treatment success defined but not reported, difference in fluid intake between both groups</td>
</tr>
<tr>
<td>Chmielewska, 2011</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>study in asymptomatic patients in weaning phase of treatment</td>
</tr>
<tr>
<td>Weber, 2014</td>
<td>++</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>use of laxatives</td>
</tr>
<tr>
<td>Banaszkiewicz, 2005</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Coccorullo, 2010</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>treatment success defined but not reported, results presented in a graph (actual numbers not reported)</td>
</tr>
<tr>
<td>Bu, 2007</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>treatment success defined but not reported (only in abstract)</td>
</tr>
<tr>
<td>Tabbers, 2011</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Guerra, 2011</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>results are presented graphically (actual numbers not reported), unclear how diagnosis of FC was made in this population of schoolchildren and exclusion of children with fecal incontinence.</td>
</tr>
<tr>
<td>Sadeghzadeh, 2014</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>outcome measures reported different than described in methods, unequal assessment of outcome measures for different children, use of laxatives</td>
</tr>
<tr>
<td>Khodadad, 2010</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>comparison of 3 groups but no post hoc analyses, use of laxatives</td>
</tr>
</tbody>
</table>
Synbiotics

Synbiotics contain both pre- and probiotics, usually the prebiotic compound selectively favors the probiotic compound. We identified one RCT using synbiotics; a combination of probiotic strains of *L. casei*, *L. rhamnosus*, *S. thermophilus*, *B. breve*, *L. acidophilus*, *B. infantis*, and fructooligosaccharide as prebiotic. This study investigated the following three interventions in 97 children: liquid paraffin oil + placebo, synbiotics + placebo and liquid paraffin oil + synbiotics. There was a significant difference in defecation frequency between the three groups after treatment; no separate analyses between the groups were performed, but children who received liquid paraffin oil + synbiotics experienced the largest increase in defecation frequency.

DISCUSSION

Studies were highly heterogeneous with respect to study design, study population, interventions used, dosages of treatment, study duration and follow-up. It is therefore difficult to draw firm conclusions. Although some studies found significant differences for pre- or probiotics with respect to defecation frequency, fecal incontinence or abdominal pain, these studies should be interpreted with caution due to the high risk of bias across studies. In addition, studies with the lowest risk of bias reported mostly non-significant results.

Defecation frequency was the only outcome measure that was used in all studies. Of these studies, 3/6 on prebiotics and 4/6 on probiotics reported a significant increase in defecation frequency compared to controls. However, it is important to take into account that this outcome measure was used differently between studies; some studies reported the mean or median defecation frequency at the end of the study (per day or per week) while others reported defecation frequency as the percentage of children having more than three bowel movements per week. As recently published, there is a need for defining uniform outcome measures and using the same definitions in order to compare results between studies. Furthermore, it is also important to realize that small, statistically significant differences may not always be clinically relevant; this is especially true for the assessment of defecation frequency.

The human microbiome is a fascinating and thrilling area of research that is likely to change our view on health and disease in the near future. However, for now, the precise role of the human microbiota in children with FC is not clear. In order to improve our understanding of the role of the gut microbiota in pediatric FC, a better understanding of the gut microbiota in healthy children is needed. A recently published study has identified a core gut
microbiota in healthy Dutch children between 2–18 years, specifically excluding children with FC. Analysis of fecal samples revealed that microbial compositional stability was 70% on average over a period of 18 months, indicating that a fairly stable core gut microbiota is likely to exist within the gut of healthy children. Also, microbiota stability correlated with higher microbial diversity. The core gut microbiota of these children was dominated by species from the phyla Bacteroidetes and Firmicutes.

Aside from the study by Zhu et al. in obese children, there are no studies that have used culture-independent techniques to assess the microbiota of children with FC. This study found differences between constipated and non-constipated obese children with regard to microbiota composition and diversity. A significantly decreased abundance of Prevotella and an increased representation of several genera of Firmicutes were observed in constipated patients compared with controls. Interestingly, the genera that have been used in most probiotic trials so far (Bifidobacterium and Lactobacillus, from the phyla Actinobacteria and Firmicutes respectively) were not decreased in constipated patients. This may possibly explain the negative outcomes of the probiotic trials as discussed in this systematic review. Furthermore, Zhu et al. demonstrated a lower gut microbiota diversity in children with FC. Microbiota diversity has been shown to be decreased in a number of gastrointestinal and non-gastrointestinal diseases and it has been hypothesized that regaining microbial diversity may potentially be beneficial. In support of this hypothesis, a recent pilot study of fecal microbiota transplantation in adults with FC has shown promising results. Future studies are needed to further investigate the role of the gut microbiota in children with FC and to further evaluate the role of microbial diversity in the pathogenesis. Also, a better understanding of the role of specific pre- and probiotics in the process of defecation is warranted. This will result in a more tailored approach in using pre- and probiotics in the treatment of FC.

In conclusion, there is insufficient evidence to recommend pre-, pro- or synbiotics in the treatment of children with FC. A better understanding of the gut microbiota in healthy and constipated children is needed. Furthermore, large, high-quality randomized controlled trials are warranted.
REFERENCES