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Expert Review of Gastroenterology & Hepatology

ISSN: 1747-4124 (Print) 1747-4132 (Online) Journal homepage: https://www.tandfonline.com/loi/ierh20

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To cite this article: Carrie A. M. Wegh, Margriet H. C. Schoterman, Elaine E. Vaughan, Clara Belzer & Marc A. Benninga (2017) The effect of fiber and prebiotics on children's gastrointestinal disorders and microbiome, Expert Review of Gastroenterology & Hepatology, 11:11, 1031-1045, DOI: 10.1080/17474124.2017.1359539

To link to this article: https://doi.org/10.1080/17474124.2017.1359539

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Accepted author version posted online: 24 Jul 2017.
Published online: 01 Aug 2017.

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EXPERT REVIEW OF GASTROENTEROLOGY & HEPATOLOGY, 2017
VOL. 11, NOS. 7–12, 1031–1045
https://doi.org/10.1080/17474124.2017.1359539

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REVIEW

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The effect of fiber and prebiotics on children's gastrointestinal disorders and microbiome

Carrie A. M. Wegh[a,b], Margriet H. C. Schoterman[c], Elaine E. Vaughan[d], Clara Belzer[a*] and Marc A. Benninga[b*]

[a]Laboratory of Microbiology, Wageningen University and Research, Wageningen, The Netherlands; [b]Department of Pediatric Gastroenterology and Nutrition, Emma's Children's Hospital Academic Medical Center, Amsterdam, The Netherlands; [c]FrieslandCampina, Amersfoort, The Netherlands; [d]Sensus BV (Royal Consun), Roosendaal, The Netherlands

ABSTRACT

Introduction: The bacteria received upon birth are the start of colonization of the approximately 10^{14} bacteria that are present in the mature human gastrointestinal tract, better known as the microbiota. The gut microbiota is implicated in gastrointestinal health, nutrient metabolism and benefits such as prevention of infection. Dietary fiber, including prebiotics, escape digestion in the small intestine and reach the colon intact, where they are partially or completely fermented by the gut microbiota.

Areas covered: The possible interactions between dietary fiber, prebiotics and microbiota are discussed as well as how this relates to functional gastrointestinal disorders. During the first years of life the microbiota have not yet reached a stable state and is sensitive to disturbance by environmental factors. An imbalance in the microbiota early in life is found to be associated with several functional gastrointestinal disorders such as colic, functional abdominal pain, irritable bowel syndrome and constipation.

Expert commentary: A better understanding of how gut microbial changes in early-life can impact gastrointestinal health might lead to new treatments or disease prevention. Nutritional strategies with fiber or prebiotics may support health due to modification of colonic microbiota composition and metabolic activity, for example by growth stimulation of *Bifidobacterium* and *Lactobacillus*.

ARTICLE HISTORY
Received 26 February 2017
Accepted 21 July 2017

KEYWORDS
Gut microbiota; children; dietary fiber; functional gastrointestinal disorders; prebiotics; oligosaccharides

1. The intestinal tract and developing gut microbiota

The thin epithelial layer lining the gastrointestinal (GI) tract is covered with the largest mucosal surface of the body. It has a dual function of absorbing nutrients as well as defending the body against a wide range of compounds that may be damaging, toxic, infectious, or carcinogenic [1,2]. Within the intestinal tract, a complex ecosystem of gut microbiota engages in a symbiotic association with the host [3]. The microbiota can interact with the human body to influence the host's response to the diet, while the host simultaneously can influence the gut microbiota by changes in the diet [4]. There are indications that colonization of the infant gut may already start *in utero* [5]. The microbes received upon birth will stimulate the colonization which will evolve until the age of 3–6 years when the ecosystem becomes relatively stable [6,7]. Ultimately, the microbiota reaches 10^{14} microbes in the mature adult gut, which equals the amount of human eukaryotic cells [8]. The gut microbiota has important roles in GI health among others for protection against pathogens, involvement in nutrient metabolism, vitamin synthesis, and bioavailability of minerals [4]. Furthermore, there is an increasing evidence of its involvement in protection against some disorders, for example, inflammatory bowel disease, diabetes, obesity, and necrotizing enterocolitis [9]. Moreover, it is hypothesized that there is a critical window in the first 1000 days of life during which the influences on the microbiota and the immune system of infants can impact development of disease later in life [6]. Specifically, the composition of the gut microbiota plays an important role in the development of the immune system, although there are also direct microbiota-independent effects described [10]. One prominent mechanism by which microbiota shapes the immune response is via short-chain fatty acids (SCFA), the end products of microbial fermentation. In addition, SCFA are important host modulators and butyrate, for example, serves as an energy source for the host epithelial cells, and low levels of butyrate modify cytokine production profile of T_H-cells and promote intestinal epithelial barrier integrity. The SCFA acetate protects against intestinal inflammation via G-protein-coupled receptor GPR43 [11].

A healthy gut microbiota consists of many different microbes, but before the age of 3 years, the microbiota has a lower diversity compared to adults [12]. Remarkably, the interindividual variability of the microbiome of children is higher compared to that of adults [6]. Upon birth, gut colonization commences with the facultative anaerobes, like *Enterobacteriaceae*, that are believed to lower the oxygen levels still present in the infants gut. In a matter of days these bacteria will create more anaerobic conditions that give rise to strict anaerobes such as *Bifidobacteriaceae* and *Clostridiaceae* [6,13]. The most abundant bacterial families on average during the first 3 years of life are depicted in Figure 1. However, this average microbiota composition can be strongly influenced and modified dramatically by several factors.

First, the mode of delivery is believed to be a major determinant of the gut microbiota colonization of newborns [14]. The gut microbiota of the newborn reflects the type of

CONTACT Carrie A. M. Wegh carrie.wegh@wur.nl Microbiology, Wageningen Universiteit en Researchcentrum, Wageningen 6700 HB, The Netherlands
*These authors contributed equally to this work.

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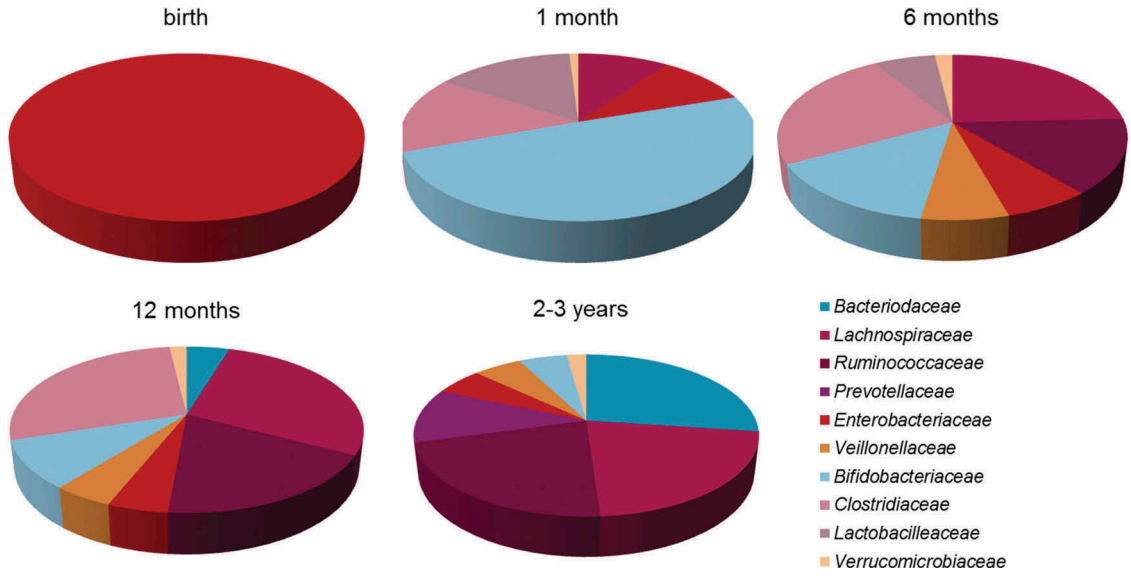


Figure 1. Intestinal microbiota colonization from birth up until the age of 3. Adapted and retrieved from [3–5].

microbiota the infant encountered during birth [6]. Vaginally delivered infants have a gut microbiota that resembles the microbiota of the maternal vagina, whereas infants born via a Caesarean section (C-section) have a gut microbiota that resembles skin microbiota [15–17].

Second, breastfeeding versus formula feeding has an impact on microbiota composition. Breast milk introduces new microbial communities, and contains human milk oligosaccharides (HMOs), which selectively stimulate growth of, among others, *Bifidobacteria* and *Lactobacillus* spp. which are thought to play a role in health [6,16]. For this reason, prebiotics such as galactooligosaccharides, long-chain fructooligosaccharides (lcFOS) and/or inulin are currently being added to infant and follow-on formula [18,19]. The microbiota of formula-fed babies contains more diverse species resembling an adult-like microbiota, and this is influenced by the presence or not of prebiotics in the formula milk [17].

Third, the weaning period, where the child receives a variety of solid foods modifies the gut microbiota. The change of composition in gut microbiota strongly depends on the newly available substrates and the withdrawal of breast- or formula milk [6]. Prior to the introduction of solid foods, the infant gut microbiome harbors genes encoding enzymes that can degrade nondigestible polysaccharides of plant origin. Thereby, the infant microbiome is capable of metabolizing simple plant-derived foods containing polysaccharides and fibers [20,21]. Failure to transfer fiber and prebiotic fermenting microbes from mother to offspring is considered a potential issue for long-term health over the generations [22].

Finally, other factors that can influence the composition of the microbiota such as the use of pre- and postnatal antibiotics, premature birth, geographic influences, host genetics, diet, stress, and hygiene are reviewed elsewhere [6,23–25].

Adjusting the diet by adding, for example, dietary fibers or prebiotics gives the opportunity to modulate the gut microbiota and exert effects on health.

2. Dietary fiber and prebiotics

The role of dietary fiber was already discussed by Hippocrates in the medical literature in the fourth century BC. His findings focused on the health benefits and laxative effect of whole-grain bread [26]. Over the course of history many references can be found regarding dietary fiber in relation to GI disorders such as functional constipation (FC) and other health effects. More recently, the concept of prebiotics was introduced. Both definitions of dietary fiber and prebiotics partly overlap. The main difference is that prebiotics selectively stimulate certain microbiota species [27,28], while not all fibers show prebiotic properties [29].

Many definitions exist for dietary fiber as it can relate to chemical compounds defined by structure or functional properties [28]. Recent definitions are not only based on their chemical features by the total dietary fiber method, but also on their physiological effects [29]. Therefore, dietary fibers are often defined as nondigestible carbohydrates and lignin that are intrinsic and intact in plants [29] or as non-starch polysaccharides, resistant starches, and oligosaccharides [30,31]. Moreover, from a regulatory perspective, the definition of dietary fiber differs between countries or regions, this difference is mainly based on the degree of polymerization (DP) of the polymer [32,33]. Even though there is no universal definition for dietary fiber, all definitions hold that: 'Dietary fiber is a group of carbohydrate polymers, oligomers, and lignin that escape digestion in the small intestine and reach the colon intact, where they are partially or completely fermented by the gut microbiota' [28]. Additionally, dietary fiber also contributes to fecal bulking directly via their own mass and/or by the mass of the water that they attract and indirectly by stimulating

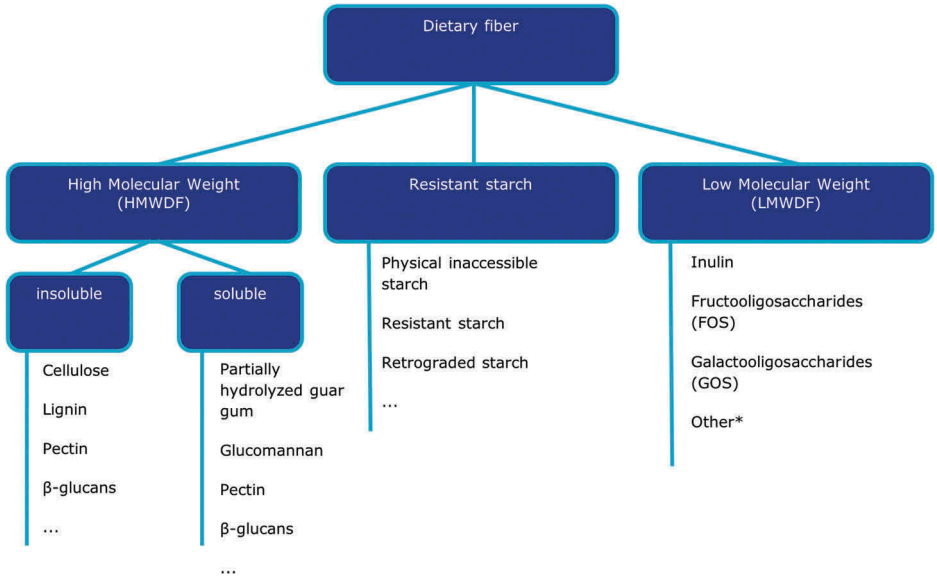


Figure 2. Dietary fiber. Adapted and retrieved from [1, 2]. *This includes manno-, pectic-, soybean-, isomalto-, transgalacto- and xylo-oligosaccharide, and polydextrose [5, 8].

growth of colonic microbiota leading to an increase in microbial biomass [34].

Prebiotics are referred to as: 'Selectively fermented ingredients that result in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health' [35]. This in contrast to probiotics: 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host' [36]. Synbiotics are defined as: 'A product containing both pro- and prebiotics' [27].

An overview of different types of dietary fiber is presented in Figure 2. The low molecular weight dietary fiber subgroup is best known for their prebiotic properties [28]. Most prebiotics are nondigestible oligosaccharides such as manno-, pectic-, soybean-, isomalto-, (trans)galacto-, and xylooligosaccharides [37,38]. The vast majority of prebiotic studies have focused on the prebiotics inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS), and therefore these will be discussed in more detail, descriptions shown in Table 1.

Our diet comprises various plant materials that contain FOS and inulin, such as onion, garlic, wheat, banana, chicory, and some cereals [39,44]. Despite the large variety of plants that contain inulin, the most commonly used source is chicory (*Cichorium intybus*) where inulin is extracted from the fresh roots [34]. In contrast to FOS and inulin, GOS have a dairy origin and are produced by the enzymatic conversion of lactose using beta-galactosidase [40]. Methods of manufacturing inulin, other fructans, and GOS are summarized in Table 1. One of the main differences is the DP which may have a significant impact on the fermentation location; for example, low and high DP fructans tend to be fermented more in the proximal and distal colon, respectively [41,45].

One of the main effects of inulin, FOS, and/or GOS is that, even when consumed in small amounts (0.24–0.8 g/100 ml formula in infants or 1.5–5 g/day in young children), the growth of *Bifidobacterium* and *Lactobacillus* species are stimulated [42,46]. These species are commonly found in breast-fed babies mainly due to fermentation of HMOs, but tend to be at lower levels in formula-fed infants depending on the addition of prebiotics [42]. Studies in infants have shown that supplementing infant formula with prebiotics results in an increase in *Bifidobacterium* and *Lactobacillus* [18,19,47]. Addition of prebiotics to infant formula can also result in physiological benefits such as effects on allergy and incidence of infection [48].

Interestingly, it was found that microbial genes facilitating the breakdown of plant-derived fibers are already present after 100 days of life, despite an exclusive breast-milk diet [21]. This indicates that during this period, the infant microbiome

Table 1. Description of fructans and GOS [40–43].

Type	Composition	Method of manufacturing	Degree of polymerization
Native inulin	β(2–1) Fructans	Extraction from inulin-rich plant material, often chicory root	2–60 Average: 9–12
lc-Inulin (lcFOS)	β(2–1) Fructans	Produced from native inulin from chicory root	10–60 Average: >21
sc-Inulin	β(2–1) Fructans	Produced from native inulin from chicory root	2–10
Oligofructose (FOS)	β(2–1) Fructans	Enzymatic degradation of inulin from chicory root or other plant material	2–10 Average: 4
(sc)FOS	β(2–1) Fructans	Enzymatic synthesis from sucrose	sc: 3–5
GOS	Chains of galactose with a terminal glucose	Produced enzymatically from lactose	sc: 2–8 Average: 3

FOS: fructooligosaccharides; GOS: galactooligosaccharides; lc: long chain; sc: short chain.

becomes metabolically ready to receive simple plant-derived fibers. The gut microbiota uses their carbohydrate-hydrolyzing enzymes to multiply and produce SCFAs, gases (hydrogen, carbon dioxide, hydrogen sulfide, and methane), lactate, and other products [49]. SCFAs are absorbed by the human gut and subsequently metabolized [43]. The difference in gut microbiota of breast- and formula-fed infants results in differential production of SCFAs. In breast-fed infants, lactate is the predominant product and butyrate is usually absent, whereas in formula-fed infants, acetate is the predominant SCFA and small amounts of butyrate are detected [50]. However, a study in infants showed that the addition of 90% GOS and 10% FOS to infant formula can shift the SCFA profile and pH closer to that observed in breast-fed infants, compared to infants fed control formula [51]. After weaning the production of butyrate increases, an important SCFA as it is the preferred energy source for colonic epithelial cells. Moreover, butyrate is considered a key nutrient for determining metabolic activity and growth of epithelial cells of the colon [29]. Hence, lactate, butyrate, acetate, and other SCFAs are important not only as a source of energy for epithelial cells, but also to reduce fecal pH and thereby inhibit growth of pathogens [29].

3. Gut microbiota, dietary fiber, and prebiotics in early life functional gastrointestinal disorders (FGIDs)

An imbalance and/or reduced microbial diversity has been associated with a wide variety of FGIDs in children such as colic, irritable bowel syndrome (IBS), constipation and diarrhea, but also with other diseases such as allergy [9,46]. In addition, many diseases later in life seem to be associated with the gut microbiota early in life, for example, inflammatory bowel disease, celiac disease, obesity, and allergic reactions [9,46]. The impact of dietary fiber and/or prebiotics on different FGIDs in interventions with infants and children will be discussed below. The Cochrane Library and PubMed were searched for relevant studies using the key search terms both as MeSH and key words are listed in Table 2. Studies published in English were included. Trials in children from birth until the age of 18 years were eligible for inclusion. Additional strategies for identifying studies included searching the references lists of the relevant studies found as well as review articles.

Table 2. Key terms, first rows apply to all searches in combination with one of the bottom three rows.

OR Child[a]
OR Infant[a]
OR Adolescen[a]
OR Pediatric[a]
OR Dietary fiber
OR Inulin
OR Prebiotic[a]
OR Oligosaccharid[a]
OR Fiber
OR Non-digestible oligosaccharide[a]
OR Placebo
OR Control
OR intervention
OR Clinical study
OR Clinical trial
OR RCT
OR Trial[a]
OR Cross-over
AND Constipation OR constipat[a] OR Obstruction OR Obstipation
AND FAP OR IBS OR functional abdominal pain OR IBS OR irritable bowel syndrome
AND Colic OR infant colic OR colic pain

[a]Includes any extension to the listed word.
FAP: functional abdominal pain; IBS: irritable bowel syndrome; RCT: randomized controlled trial.

3.1. Colic

3.1.1. Definition, prevalence, and etiology

Infant colic is a common disturbance and has a worldwide average prevalence of 21% in children younger than 12 months of age [52]. One definition is based on Wessel's description; 'an infant who, otherwise healthy and well-fed, has paroxysms of irritability, fussing or crying lasting for a total of more than three hours a day and occurring on more than three days in any one week' [53]. Other symptoms include drawing up of knees, excessive flatulence, and no relief upon feeding, mainly in the late afternoon and early evening. However, the Wessel criteria have recently undergone revisions in the Rome IV criteria [54] as follows 'For clinical purposes, the diagnostic criteria must include all of the following: 1) An infant who is <5 months of age when the symptoms start and stop; 2) Recurrent and prolonged period of infant crying, fussing or irritability reported by caregivers that occur without obvious cause and cannot be prevented or resolved by caregivers; 3) No evidence of infant failure to thrive, fever, or illness'.

The etiology of excessive crying remains unclear, but in the majority of cases, colic probably represents the upper end of the normal developmental 'crying curve' of healthy infants [54]. Only 5.1% of infants presenting with excessive crying at an emergency department had underlying organic cause, of which urinary tract infection was the most prevalent condition [55]. Others have suggested an important role for environmental factors, such as psychosocial issues, domestic violence, inadequate parent–infant interaction, or parental anxiety [56]. In contrast to this, a relationship between GI causes, such as lactose intolerance, cow's milk allergy, and gastroesophageal reflux disease, and the excessive crying has been suggested [56]. In recent years, it has been further suggested that aberrancies in the infant intestinal microbiota affect gut motor function and gas production, thereby leading to excessive crying.

Available treatments for infant colic range from drug therapies and nutritional interventions to behavioral interventions; however, there is no standard care [57].

3.1.2. Gut microbiota and colic

Several studies were performed to investigate the differences in gut microbiota between healthy infants and infants with colic. In the first study in 2004, Savino et al. [58] detected a significantly lower prevalence of *Lactobacilli* spp. ($p = 0.044$) and a higher abundance of Gram-negative bacteria in infants with colic [58]. Subsequent studies reported that *Proteobacteria* were positively correlated with an increase in crying and fussiness, and especially *Klebsiella*

and *Escherichia* were predominant in the fecal samples of infants with colic [59,60]. Proteobacteria are phyla that contain many opportunistic pathogens, and thus may increase the abundance of inflammatory bacteria. On the other hand, *Bacteroidetes, Actinobacteria,* and *Firmicutes* were reduced in infants with colic compared to controls. Specifically, bifidobacteria were significantly reduced at 1 week after birth in infants with colic (p = 0.049) and lactobacilli were significantly reduced 2 weeks after birth in infants with colic (p = 0.023) [59]. These groups contain many beneficial bacteria typical for a healthy infant microbiota, thus their reduction may also be an indication of decreased gut health. The latter is supported by a study in preterm infants [61]. This study found a higher percentage of a *Firmicute, Clostridium histolyticum*. *Moreover,* a significantly higher proportion of the *Lactobacillus–Lactococcus–Enterococcus* group was found in excessive criers compared to content infants (p = 0.005). Moreover, infants with colic generally show a less diverse microbiota compared to controls [59,60]. This points toward the possibility that children with colic might have less beneficial bacteria because a lower richness in infants (many bifidobacteria and lactobacilli, but a lower overall diversity) is in general found to be beneficial [23,59,60]. It is noteworthy that comparisons were sometimes hampered when only the microbial phylum level was reported in comparison to studies with microbial genus level specifications. Furthermore, several studies were excluded from this review as they used outdated culture- or broth-based techniques to identify microbes, or used a probiotic prior to fecal sampling which might have influenced the microbiota of infants with colic.

3.1.3. Influence of dietary fiber and prebiotics

Only one study was found that investigated the treatment effect of fiber on infant colic (Table 3). This study by Treem et al. [62] evaluated the effect of soy polysaccharide versus a placebo in 27 children, aged 2–8 weeks with colic (defined as crying plus fussing for more than 3 hours a day for at least 3 days of a 6-day baseline period) in a double-blind, randomized, crossover study. No significant differences were found in the average daily time spent by the infants for fussing and crying with ingestion of soy fiber [62] An observational prospective study by Savino et al. [63] in 214 infants with colic, aged up to 3 months (mean: 1.35 ± 0.77 months) evaluated a formula containing 90% GOS, 10% lc-FOS, sn-2 palmitic acid, and partially hydrolyzed proteins. This study showed a reduction in frequency of colic in 79% of children (from 4.1 ± 2.0 per day to 2.0 ± 1.8) at the end of the study [63]. In order to confirm the effect of the formula, a prospective randomized controlled study was conducted with the same formula with added simethicone (6 mg/day) (Table 3). In this study [64], 199 infants, aged up to 4 months (mean: 1.39 ± 0.84 months), completed the study. Infants who received the new formula had a statistically significant (p < 0.0001) but also clinically relevant decrease in colic episodes compared to the control formula. Colic episodes decreased from 5.99 ± 1.84 per day to 2.47 ± 1.94 per day after 1 week in comparison to 5.14 ± 1.88 per day to 3.72 ± 1.98 after 1 week in the control group. Moreover, at day 14, the crying episodes were significantly

Table 3. Summary of intervention studies for infant colic.

Study	Intervention	Power	Age group	Duration	Dosage	Disease	Outcome
Dietary fiber							
Treem et al., 1991 [62]	Soy fiber vs. placebo	27	2–8 weeks	9 days	1.1 g/100 ml	Infant colic	No significant difference in average daily time crying and fussing between fiber and placebo. Significant increase in stool frequency in fiber group.
Prebiotics							
Savino et al., 2003 [63]	90% GOS, 10% lc-FOS, sn-2 palmitic acid, partially hydrolyzed proteins	214	>3 months	14 days	0.8 g/100 ml	Infant colic	Reduction in frequency of colic in 79% of children (from 4.1 ± 2.0 per day to 2.0 ± 1.8) at the end of the study
Savino et al., 2006 [64]	90% GOS, 10% lc-FOS, sn-2 palmitic acid, partially hydrolyzed proteins vs. standard formula + 6 mg/kg simethicone	199	0–4 months	14 days	0.8 g/100 ml	Infant colic	Significant and clinically relevant decrease in colic episodes between prebiotic and control group after 7 and after 14 days.
Partty et al., 2013 [61]	Polydextrose, GOS 1:1, probiotic or placebo	94	1–60 days	60 days	1–30 days: 600 mg/day, 31–60 days: 1200 mg/day	Colic in preterm infants	Significantly less excessive criers in the prebiotic group vs. placebo.

lcFOS: long-chain fructooligosaccharides; GOS: galactooligosaccharides.

different ($p < 0.0001$) between the two groups (1.76 ± 1.60 for new formula compared to 3.32 ± 2.06 in the control formula) [64].

Pärtty et al. [61] investigated the effect of GOS:polydextrose 1:1 versus a probiotic and a placebo in 94 preterm infants (gestational age 32–36 weeks), aged 1–60 days in a randomized, double-blind, placebo-controlled study. A total of 27 out of 94 were classified as excessive criers, while this was significantly less in the prebiotic and probiotic group than in the placebo group (19% vs. 19% vs. 47%, $p = 0.02$).

Further research is needed not only to understand the delicate balance of the gut microbiota in colicky infants, but also large randomized controlled studies to investigate if the effect found by Savino et al. [64] is caused by the prebiotics, the other compounds found in formula milk, such as sn-2 palmitic acid (as this can reduce the amount of calcium soaps in the gut and thereby improve the consistency of stools) or the combination of compounds [65].

3.2. Functional constipation

3.2.1. Definition, prevalence, and etiology

FC in children is a common GI disorder with a worldwide prevalence ranging from 0.7% to 29.6% (defined here as defecation frequency of <3/wk) [66]. Complaints include infrequent bowel movement, painful defecation due to hard and/or large stools, fecal incontinence, and abdominal pain [67]. The etiology of FC is still incompletely understood but is likely to be multifactorial. Some important factors in children include: withholding behavior of stools, psychosocial factors, behavioral disorders, parental child-rearing attitudes, low fiber intake, and the gut microbiota composition [67,68].

3.2.2. Gut microbiota and FC

In the last decades, only a few studies reported on microbiota in children with constipation. These studies gave different results, which might be caused by the differences in study populations. Two studies were conducted in otherwise healthy children with FC [69], while another study was conducted in obese children with FC [70]. Zoppi et al. [69] found a significant increase in clostridia ($p < 0.001$) and bifidobacteria ($p < 0.02$) in children with FC compared to healthy children [69]. An increased abundance of bifidobacteria was confirmed in the study of de Meij et al. in constipated children [71]. In obese children with FC, this effect was not seen [70]. In this study population, a significant decrease of *Prevotella* ($p = 0.010$) and increase in several genera of firmicutes was seen ($p < 0.05$). These differences may be explained by obesity, which has been associated with a particular gut microbiota composition [72]. De Meij et al. [71] also used a supervised statistical learning method in which they were able to discriminate the microbiota of constipated children from healthy controls with 82% accuracy [71].

In practice, the population of children with constipation is very heterogeneous; therefore, it may be useful to link altered gut microbiota signatures to specific subgroups of children. Moreover, in order to draw conclusions, well-conducted large studies are needed in otherwise healthy children with FC, but also in specific subgroups such as children with constipation and obesity.

The conventional approach for FC treatment includes dietary advise, a toilet training program, and laxatives [73].

3.2.3. Influence of dietary fiber and prebiotics

An overview of four RCTs that studied the effect of dietary fiber on constipation in children is presented in Table 4. Loening-Baucke et al. [74] evaluated the effect of glucomannan (a fiber gel polysaccharide from the tubers of the Japanese Konjac plant) and placebo in 31 children, 4.5–11.7 years of age (mean: 7 ± 2 years) with chronic FC in a double-blind, randomized, crossover study. Significantly more children were successfully treated while on fiber (45% with ≥3 bowel movements/wk and /or ≤1 soiling episodes/3 weeks with no abdominal pain in the last 3 weeks of each 4-week treatment period) as compared with placebo treatment 13%; $p < 0.02$). It is noteworthy to mention that 71% of the children had a low initial dietary fiber intake [74].

Second, Castillejo et al. [75] compared the effect of cocoa husk supplement (4 g cocoa husk and 1 g of betafructosans) to a placebo in 48 children, aged between 3 and 10 years (mean: 6.3 ± 2.2 years) with chronic FC in a parallel, randomized, double-blind, controlled trial. This study used a combination of dietary intervention or placebo with toilet training and showed a significant reduction in the percentage of patients with hard stools in the cocoa husk group compared to the placebo group (41.7% vs. 75%; $p = 0.017$). However, no significant differences were found in defecation frequency or pain during defecation, as reported by parents. Both the treatment and placebo group had a mean basal dietary fiber intake near the recommended daily allowance (age + 10 g/day, 12.3 ± 4.1 g/day and 13.4 ± 5.6 g/day, respectively) [75].

The third study by Üstündağ et al. [76] evaluated the effect of fiber (partially hydrolyzed guar gum) and lactulose in 61 children, 4–16 years of age with chronic FC in a prospective, randomized, controlled study. Both groups showed a significant ($p < 0.05$) improvement in defecation frequency (increase from 4 ± 0.7 to 5 ± 1.7 in PHGG group and from 4 ± 0.7 to 6 ± 1.1 in the lactulose group), stool consistency, and abdominal pain. However, children in the lactulose group had significantly more bowel movements after treatment compared to the PHGG group ($p < 0.05$) [76].

The last study by Chmielewska et al. [77] investigated the effect of glucomannan compared to a placebo (maltodextrin in the same dosage) in 72 children, aged 3–16 years (mean: 6.1 ± 3.3 years for the glucomannan group and 5.9 ± 2.5 in the placebo group) with chronic FC in a double-blind, placebo-controlled, randomized study. No significant differences were found between the glucomannan and placebo group in terms of treatment success (defined as three or more bowel movements with no episodes of soiling during the last week of product consumption). Stool consistency score was significantly ($p < 0.0001$) higher at week 1 in the glucomannan group compared to placebo (2.9 ± 1.2 vs. 1.7 ± 1.5, respectively), but lower at week 3 ($p = 0.008$) and similar at weeks 2 and 4. Stool frequency was higher in the glucomannan group only in week 3 ($p = 0.007$). Abdominal pain episodes were more frequent in the glucomannan group compared to

Table 4. Summary of intervention studies in children with functional constipation.

Study	Intervention	Power	Age group	Duration	Dosage	Disease	Outcome
Dietary fiber							
Loening-Baucke et al., 2004 [74]	Glucomannan vs. placebo	31	4–12 years	8 weeks (2 × 4 weeks crossover)	100 mg/kg body weight per day (max 5 g/day)	Chronic functional constipation	No significant change in defecation or fecal incontinence frequency. Significant difference in the percentage of children with <3 bowel movements per week; 19% glucomannan vs. 52% placebo and abdominal pain; 10% glucomannan vs. 42% placebo
Castillejo et al., 2006 [75]	Cocoa husk and betafructosans vs. placebo	48	3–10 years	4 weeks	3–6 years: 2 × 5.2 g per day 7–10 years: 2 × 10.4 g per day	Chronic functional constipation	No significant differences in defecation frequency or pain during defecation, reported by parents.
Üstündağ et al., 2010 [76]	PHGG vs. lactulose	61	4–16 years	4 weeks	4–6 years: 3 g per day 6–12 years: 4 g per day 12–16 years: 5 g per day	Chronic functional constipation	Significant improvement in defecation frequency, stool consistency, and abdominal pain was found in both groups. Significant more bowel movements in the lactulose group.
Chmielewska et al., 2011 [77]	Glucomannan vs. placebo	72	3–16 years	4 weeks	2 × 1.26 g per day	Chronic functional constipation	No significant differences in treatment success between both groups. Higher stool frequency in the glucomannan group, but only at week 3 significant.
Prebiotics							
Bongers et al., 2007 [65]	Sn-2 palmitic acid and oligosaccharide mix formula (90% GOS, 10% lcFOS) vs. control formula	35 (24 full crossover)	3–20 weeks	6 weeks	0.8 g/100 ml	Chronic functional constipation	Period 1: Nonsignificant improvement of stool consistency in OS-formula group. Period 2: significant improvement in stool consistency in OS-formula group compared to control formula.

(*Continued*)

Table 4. (Continued).

Study	Intervention	Power	Age group	Duration	Dosage	Disease	Outcome
Kokke et al., 2008 [78]	Fiber mixture (GOS, inulin, soy fiber, resistant starch) vs. lactulose	97	1–12 years	13 weeks	10 g per day	Chronic functional constipation	No significant difference in defecation or fecal incontinence frequency, abdominal pain, flatulence, and the need for step-up medication. Consistency of stools was significant softer in lactulose group.
Weber et al., 2014 [79]	Fiber mixture (FOS, inulin, gum arabic, resistant starch, soy fiber, cellulose) vs. placebo	54	4–12 years	4 weeks	<18 kg bw: 3.8 g per day, >18 kg bw: 7.6 g per day	Chronic functional constipation	No significant difference in colonic transit time and therapeutic failure. Significant change in daily bowel movements and passage of non-hardened stools was significant in the fiber group compared to placebo.
Beleli et al., 2015 [80]	GOS vs. placebo	20	4–16 years	75 days	1.7 g/day	Chronic functional constipation	Significant increase of bowel movement, relief of defecation straining, and decrease in stool consistency in GOS vs. placebo
Closa-Monasterolo et al., 2016 [81]	Inulin-type fructans (70:30 scFOS:inulin) vs. placebo	17	2–5 years	8 weeks	2 × 2 g per day	Chronic functional constipation	Significant improved stool consistency in inulin group

bw: body weight; FOS: fructooligosaccharides; GOS: galactooligosaccharides; lcFOS: long-chain fructooligosaccharides; OS: oligosaccharide; PHGG: partially hydrolyzed guar gum; scFOS: short-chain fructooligosaccharides.

placebo in week 1 ($p = 0.04$) and week 4 ($p > 0.0001$) but were similar in weeks 2 and 3 [77].

In conclusion, studies that investigated the effect of dietary fiber in children with chronic FC are highly heterogeneous, not only in study design, population, duration, follow-up, dosages of treatment, and types of fibers used, but also in primary outcomes.

Prebiotics may be beneficial for children with FC due to multiple factors; for example, by their fermentation in the colon they increase microbial numbers and biomass, and they influence the gut microbiome [82]. Five RCTs investigated the effect of prebiotics on FC in children, as summarized in Table 4.

The first study by Bongers et al. [65] investigated the effect of a formula containing 90% GOS, 10% lcFOS, sn-2 palmitic acid, and partially hydrolyzed whey proteins compared to placebo in 35 children, aged 3–20 weeks with chronic FC in a double-blind, randomized crossover trial. Improvement in stool consistency was found more often in the prebiotic group; however, it did not reach statistical significance (90% in the prebiotic group, 50% in the placebo group, $p = 0.14$). Only 25 infants completed the full crossover study; in this analysis, stool consistency was significantly different between both formulae (17% had soft stools in the prebiotic group, and hard stools in the placebo group, whereas no infants had soft stools in the placebo group and hard stools in the prebiotic group, $p = 0.046$).

The second study by Kokke et al. [78] evaluated the effect of a prebiotic and fiber mixture (GOS, inulin, soy fiber, resistant starch) versus lactulose in 97 children, aged 1–13 years, median (range) 5.5 (1–12) and 5.0 (1–12) years in the prebiotic and lactulose group, respectively, with chronic FC in a prospective, double-blind, controlled study. No difference was found between groups after the treatment period in defecation frequency, fecal incontinence frequency, abdominal pain, flatulence, and the need for step-up medication. However, stool consistency was softer in the lactulose group ($p = 0.01$) [78].

The third study by Weber et al. [79] investigated the effect of a prebiotic and fiber mixture (FOS, inulin, gum arabic, resistant starch, soy fiber, cellulose) versus a placebo in 54 children, aged 4–12 years (means 8.5 ± 1.8 and 7.7 ± 2.4 years for the prebiotic and placebo group, respectively), with chronic FC in a randomized, placebo-controlled, double-blind clinical trial. No significant difference was found in therapeutic failure between the prebiotic group (34.6%) and the placebo group (35.7%, $p = 0.933$). A significant difference was found in the mean increase of stool frequency (0.53 in the prebiotic group compared to 0.23 in the placebo group, $p = 0.014$). Moreover, the passage of non-hardened stool was higher in the fiber group; 60.0% in the prebiotic group and 16.7% in the placebo group ($p = 0.003$) [79].

The fourth study by Beleli et al. [80] investigated the effect of GOS versus a placebo in 20 children, aged 4–16 years (mean 8.8 ± 4.1), with chronic FC in a double-blind, placebo-controlled crossover study. There were significant changes for several parameters, namely an increase in bowel movement frequency ($p < 0.0001$), decrease in stool consistency ($p = 0.0014$), and relief of defecation straining ($p < 0.0001$) [80].

Lastly, Closa-Monesterolo et al. [81] investigated the effect of inulin-type fructans (70% oligofructose, 30% lcFOS) versus a placebo in 17 children, 2–5 years of age (means 3.72 ± 1.07 and 4.03 ± 0.79 years in the prebiotic and placebo groups, respectively), with chronic FC in a double-blind, randomized, placebo-controlled parallel group trial. Stools were significantly softer in the prebiotic group compared to placebo (1.63 ± 0.64 vs. 2.57 ± 0.58, respectively, $p = 0.003$). Moreover, stool consistency became softer in the prebiotics group (from 2.2 to 2.6 on the modified Bristol Stool Scale, $p = 0.040$) over time while there was no change in the placebo group.

In conclusion, prebiotics in children with chronic FC are highly heterogeneous, not only in study design, population, duration, follow-up, dosages of treatment, and types of prebiotics used, but also in primary outcomes. However, there seems to be a trend toward softer stools in studies that used prebiotics in children with FC. As for infant colic, studies on the role of the gut microbiota in children with FC in comparison to healthy children is clearly needed as well as large, high-quality RCTs with fibers and/or prebiotics.

3.3. Functional abdominal pain (FAP) and IBS

3.3.1. Definition, prevalence, and etiology

FAP and IBS are common FGIDs in children with an estimated worldwide prevalence of 13.5% for 4- to 18-year-old children [83]. These disorders are associated with a reduced quality of life [84], excess use of health care services [85–87], school absenteeism, and comorbid anxiety and depression [88–90]. About 30% of health-care visits from children aged 4–16 years are due to abdominal pain [91]. FAP and IBS are two FGIDs that, after appropriate medical evaluation, cannot be attributed to another medical condition [92]. FAP and IBS are diagnosed according to the Rome IV criteria [54]. Complaints of IBS include abdominal discomfort or pain, and altered bowel habits. Four types of IBS can be distinguished based on bowel dysfunction; diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), alternating stool forms (IBS-A), and unsubtyped (IBS-U) [93]. Despite its high prevalence, the cause of IBS is not fully understood and it is unlikely that one single factor will be the cause for all subtypes of IBS. Gut hypersensitivity and altered gut motility are implicated in both FAP and IBS [94]. Multiple risk factors have been linked, including hypersensitivity to food products, psychological factors such as child abuse, stress, depression and anxiety, genetic factors, and alterations of the gut microbiota [91,95].

Pharmacological options for the treatment of FAP and IBS include antispasmodics, antidepressants, antireflux agents, antihistaminic agents, and laxatives. Nonpharmacological options include: cognitive behavioral therapy, hypnotherapy, dietary interventions, and pre-, pro-, or synbiotics [95].

3.3.2. Gut microbiota, FAP, and IBS

In terms of microbiological differences in children with IBS compared to healthy children, one study found a significantly greater percentage of *γ-Proteobacteria* ($p > 0.05$) (a group containing many opportunistic pathogens). Furthermore, *Haemophilus, Dorea,* and *Veillonella* were more abundant with reduced potential butyrate-producing *Eubacterium* and

Anaerovarax [91]. However, in the second study in children with IBS-D, the proportions of *Veillonella, Prevotella, Lactobacillus*, and *Parasporobacterium* were increased together with reducing members, also described as beneficial, *Bifidobacterium* and *Verrucomicrobium* [96]. Moreover, the species *Haemophilus parainfluenzae* was identified as a prominent component in children with IBS. In addition, specific IBS subtypes could be successfully classified according to their gut microbiota with accuracies exceeding 95% [91]. This indicates that there are not only microbial differences between healthy children and children with IBS, but also differences according to the IBS subtypes.

3.3.3. Influence of dietary fiber and prebiotics

Five RCTs were identified that studied the effect of dietary fiber in children with functional abdominal pain or irritable bowel syndrome (Table 5).

The first study by Feldman et al. [97] dates back to 1985. This study investigated the effect of corn fiber versus a placebo in 52 children, aged 5–15 years (mean; 9.37 years), with simple, idiopathic, recurrent abdominal pain in a randomized, double-blind, placebo-controlled study. A statistically significant and clinically relevant decrease in pain attacks (at least 50% less) was found in 13 children in the fiber group, compared to 7 in the placebo group ($p = 0.04$) [97].

A year later Christensen [98] investigated the effect of ispaghula husk (seed coats of the plant *Plantago ovata Forssk*) versus a placebo in 31 children, aged 3–14 years, with recurrent abdominal pain in a double-blind, randomized, controlled trial. No significant differences were found in the number of abdominal pain episodes between both groups [98].

More recently Romano et al. [99] studied the effect of partially hydrolyzed guar gum versus a placebo in 60 children, aged 8–16 years (means of 12.3 ± 2.0 and 13.1 ± 1.5 years in the fiber and placebo group, respectively), with chronic abdominal pain and IBS in a randomized, double-blind, placebo-controlled study. A significant higher level of efficacy was found for the fiber group compared to the control group (43% vs. 5%, $p = 0.025$), reduced clinical symptoms of the Birmingham IBS score (media 0 ± 1 vs. 4 ± 1, $p = 0.025$), and also normalized bowel habit (40% vs. 13.3%, $p = 0.025$).

The most recent study by Horvath et al [100] investigated the effect of glucomannan versus a placebo in 84 children, aged 7–17 years (means of 11.6 ± 3.0 and 11.3 ± 2.5 in the fiber and placebo group, respectively), with abdominal pain-related FGIDs in a double-blind, placebo-controlled, randomized trial. No differences were found for the parameters 'no pain' and 'treatment success' (defined as no pain or a decrease ≥ 2/6 points on the FACES Pain Scale Revised) between groups. Moreover, no significant differences were found in the secondary outcomes either (i.e. abdominal cramps, abdominal bloating, nausea or vomiting, and stool consistency) [100].

Shulman et al. [101] performed a randomized, double-blind study in 103 children (mean: 13 ± 3 years) with IBS seen at primary or tertiary care settings. Children were assigned to groups given psyllium ($n = 37$) or placebo (maltodextrin, $n = 47$). Children in the psyllium group had a greater reduction in the mean number of pain episodes than children in the placebo group (mean reduction of 8.2 ± 1.2 and 4.1 ± 1.3 after receiving psyllium or placebo, respectively; $p = 0.03$); the level of pain intensity did not differ between the groups. At the end of the study period, the percentage of stools that were normal (Bristol scale scores, 3–5), breath hydrogen or methane production, intestinal permeability, and microbiota composition, were similar between groups. However, a limitation of the study mentioned above is that of the three primary outcomes (i.e. change in the severity of abdominal pain, frequency of abdominal pain, and the proportion of stools that were normal), only change in abdominal pain frequency showed a significant benefit ($p = 0.03$) for children treated with psyllium [105]. In contrast, there was no significant difference in the total abdominal pain frequency after treatment between groups, whereas the third primary outcome even showed a trend toward a negative effect of psyllium compared with placebo.

In conclusion, three studies with fibers showed a clinically and statistically significant improvement in symptoms [97] and pain attacks [99] in children with FAP or IBS. On the contrary, another two studies did not find any significant differences or changes in the number of abdominal pain episodes [98,100]. These contradictory findings might be due to the overall low methodological quality of the two studies [97,99]; in addition, all the studies used different types of fibers, different dosages, and different primary outcomes. Moreover, the name and definitions of 'FAP' and 'IBS' disorders have changed over time which makes it hard to compare studies. No RCTs were identified that had investigated the effect of prebiotics on FAP and IBS in children so far and thereby recommendations cannot be provided. This emphasizes the need for well-conducted RCTs investigating the effect of prebiotics in children with FAP or IBS. Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) are short-chain carbohydrates which are implicated in IBS. Mechanisms may involve poor absorption of some FODMAPS (notably fructose) in the small intestine thereby distending the small intestine with water due to osmotic load, and/or they reach the colon (e.g. inulin) where they are fermented by the microbiota producing gas and flatulence. Such effects are implicated in symptoms experienced by IBS patients [106]. It seems contradictory that fermentable oligosaccharides, some of which are prebiotics, might improve IBS symptoms, and yet exclusion on a low FODMAP diet might also relief symptoms for some patients with IBS. This can be due to the multifactorial etiology of IBS and heterogeneity of symptoms. The efficacy of a low FODMAP diet has been reported in children in two studies (Table 5).

Chumpitazi et al. [102] investigated if a diet low in FODMAPs decreased IBS symptoms in a pilot study with 8 children, aged 7–16 years. Significant decreases were found compared to baseline in pain frequency (from 11.5 ± 6.3 to 6.3 ± 6.8, $p < 0.05$), pain severity (from 1.8 ± 1.1 to 0.8 ± 0.7, $p < 0.05$), and pain-related interference with activities (from 9.9 ± 7.9 to 6.3 ± 7.2, $p < 0.05$). Moreover, four children were identified as responders (50%, responders, defined as; >50% decrease in abdominal pain and pain frequency while on the FODMAP diet) [102].

Table 5. Summary of studies in children with FAP or IBS.

Study	Intervention	Power	Age group	Duration	Dosage	Disease	Outcome
Dietary fiber							
Feldman et al., 1985 [97]	Corn fiber vs. placebo	52	5–15 years	6 weeks	2 × 5 g corn starch per day	RAP	Clinically and statistically significant decrease in pain attacks in corn fiber group; 50% in corn fiber group vs. 27% in placebo group
Christensen, 1986 [98]	Ispaghula husk vs. placebo	31	3–14 years	6 weeks	2 × 5 ml solution per day, amount of fiber not given	RAP	No difference in the number of episodes of abdominal pain
Romano et al., 2013 [99]	PHGG vs. placebo	60	8–16 years	4 weeks	5 g PHGG per day	IBS-C, IBS-D, or CAP	Clinical symptom improvement and improvement in bowel habits in PHGG group
Horvath et al., 2013 [100]	Glucomannan vs. placebo	84	7–17 years	4 weeks	2 × 1.26 g glucomannan per day	FGIDs	No significant differences
Shulman et al., 2016 [101]	Psyllium fiber vs. placebo	103	7–18 years	6 weeks	7–11 years of age: 6 g/day 12–18 years of age: 12 g/day	IBS	Significant reduction in the mean number of pain episodes in the psyllium group. No differences between groups in pain intensity, percentage of normal stools, breath hydrogen and methane production, intestinal permeability, and microbiome composition
FODMAP							
Chumpitazi et al., 2014 [102]	Low FODMAP compared to baseline period	8	7–16 years	2 weeks	n/a	IBS	Significant decrease in the number of pain episodes, mean and max pain severity, and pain-limiting activities
Chumpitazi et al., 2015 [103]	Low FODMAP vs. typical American childhood diet	33	7–17 years	2 weeks	n/a	IBS	Significant decrease in abdominal pain frequency in low FODMAP group

CAP: chronic abdominal pain; FGIDs: functional gastrointestinal disorders; FODMAP: fermentable oligosaccharides disaccharides monosaccharides and polyols; IBS: irritable bowel syndrome; IBS-C: irritable bowel syndrome constipation-predominant; IBS-D: irritable bowel syndrome diarrhea-predominant; PHGG: partially hydrolyzed guar gum; RAP: recurrent abdominal pain.

Subsequently, Chumpitazi et al. [103] conducted a second study to evaluate the efficacy of a diet low in FODMAPs versus a typical American childhood diet in 33 children, aged 7–17 years, with IBS in a double-blind, crossover trial. Compared to the baseline, children had fewer episodes of abdominal pain during the low FODMAP diet ($p < 0.01$), but more episodes during the typical American childhood diet ($p < 0.01$) [103].

These two pediatric IBS studies on a low FODMAP diet show a decrease in abdominal pain; however, both studies have low power and only investigated short-term effects. Therefore, more interventions that are sufficiently powered are needed to investigate long-term safety, efficacy, and effects in children with FAP or IBS [104].

4. Conclusion

In this review, differences in the composition of the microbiota between healthy children and children with FGIDs are described. There are indications for the presence of a specific microbial signature in the gut microbiota of infants with colic. The limited data for children with IBS also suggest that the gut microbiota composition is different compared to healthy controls. In contrast, the data for the microbiota composition of constipated children in comparison with healthy controls is contradictory. Currently, the differences in analysis methods, reporting of the level of taxonomy rank and high interindividual variability, prevent strong conclusions from being drawn, and thus clearly more data are required. Furthermore, the function of the microbial groups and impact on health is often not completely clear, which makes it hard to formulate hypotheses on potential mechanisms. Studies on the crosstalk between the microbiome and the host are ongoing and technical advances in analyzing genomes, transcriptomes, and proteomes will help to clarify the roles of the gut microbiome in health and disease.

In addition, this review stresses the need for well-designed large randomized controlled trials evaluating the effect of different dietary fibers and prebiotics in infant colic, constipation, FAP, and IBS. The studies as described in this review are heterogeneous in design, population, duration, follow-up, dosages of treatment, and types of fibers or prebiotics used as well as primary outcomes, which makes it difficult to draw general conclusions on the influence of fibers and prebiotics in FGIDs in children.

5. Expert commentary

FGIDs are a prevalent and serious issue in the pediatric population which have a significant impact on quality of life of patients and patient families, besides health costs [84,87,107,108]. Modification of the gut microbiota via diet and foodstuffs provides a powerful route to influence health. Increasing evidence suggests associations between the microbiome and health outcomes. Differences have been identified between healthy children and children with diseases of the intestinal tract. Moreover, there is evidence that the gut microbiota can affect health in the long run. However, it remains a challenge to determine whether there is a causal link between the gut microbiota and the disease state for many diseases. Causality has been shown in animal models for some diseases, for example, obesity [109], but it is essential to underpin causality in humans as well. This will require large prospective cohort studies in order to investigate the development of the gut microbiome in healthy compared to a disease state. A better understanding of the gut microbiota in healthy children and children with a disease is essential in order to improve our understanding of the role of the gut microbiota in disease development. Furthermore, more studies in children are needed to study the effect of dietary fiber and prebiotics for the full range of GI diseases and other diseases.

6. Five-year view

Although the number of studies that address the complexity and dynamics of the gut microbiome is increasing, the knowledge so far does not bridge the gap between pathogenesis in the host, individual microbes, and alterations in the gut microbial metabolism and function. Understanding of the host–microbe interactions is vital to be able to assign specific bacterial entities or microbial communities that can use specific fibers or prebiotics, of which the resulting microbiota composition and fermentation products of microbiota metabolism may promote health. In the future, the use of supervised machine learning and data-processing algorithms, that can predict the response of an individual to a given food based on their microbiome, might be used to predict the response of individuals to dietary interventions, and thereby positively influence health outcomes. Ideally, microbiota analysis might be used to specifically design individual recommendations in terms of personalized food, specific prebiotics, and/or fibers in order to promote health outcomes.

In addition to the research on the gut microbiota, studies are needed to investigate the development of FGIDs in children. Importantly, large studies that assess the microbiota in both healthy children with and without FGIDs are needed. Furthermore, interventions are required that determine if certain prebiotics and/or fibers show clinically relevant effects. The more we understand the complexity of the gut microbiome, the more we will be able to recommend specific prebiotics and/or other food ingredients in order to promote health outcomes.

Key issues

- FGIDs, including colic, functional abdominal pain, irritable bowel syndrome and functional constipation are common problems in children worldwide. The involvement of the gut microbiome is clear, but proof for causality and how to adapt the gut microbiota for the better is still scarce in children.
- Microbiological differences exist between healthy children and children with several FGIDs, however giving a proper conclusion is hard due to differences in analysis methods, reporting of the level of taxonomy rank and high inter-individual variability.

- There is a lack of large randomized placebo controlled trials evaluating the effect of different fibers and prebiotics in children with FGIDs

Funding

This paper was not funded.

Declaration of interest

M.A. Benninga has acted as a consultant for Shire, Sucampo, Astrazeneca, Norgine, Coloplast, Danone, FrieslandCampina, Sensus and Novalac. M.H. C. Schoterman is an employee of FrieslandCampina, a producer of GOS. E. E. Vaughan is an employee of Sensus, producer of inulin. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Hollander D. Intestinal permeability, leaky gut, and intestinal disorders. Curr Gastroenterol Rep. 1999;1:410–416.
2. Fasano A. Leaky gut and autoimmune diseases. Clin Rev Allergy Immunol. 2012;42:71–78.
3. Scholtens PA, Oozeer R, Martin R, et al. The early settlers: intestinal microbiology in early life. Annu Rev Food Sci Technol. 2012;3:425–447.
4. Sonnenburg JL, Bäckhed F. Diet-microbiota interactions as moderators of human metabolism. Nature. 2016;535:56–64.
   •• **Extensive review on the influence of gut microbiota on obesity and metabolic diseases.**
5. Collado MC, Rautava S, Aakko J, et al. Human gut colonisation may be initiated in utero by distinct microbial communities in the placenta and amniotic fluid. Sci Rep. 2016;6:23129.
6. Arrieta M-C, Stiemsma LT, Amenyogbe N, et al. The intestinal microbiome in early life: health and disease. Front Immunol. 2014;5:427.
   •• **Extensive review on gut mirobiome development, influences, and related diseases.**
7. Rodríguez JM, Murphy K, Stanton C, et al. The composition of the gut microbiota throughout life, with an emphasis on early life. Microb Ecol Health Dis. 2015;26. DOI:10.3402/mehd.v26.26050
8. Sender R, Fuchs S, Milo R. Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. Cell. 2016;164:337–340.
9. Weber TK, Polanco I. Gastrointestinal microbiota and some children diseases: a review. Gastroenterol Res Pract. 2012;Article ID: 676585, 12 pages.
10. Akbari P, Fink-Gremmels J, Willems RH, et al. Characterizing microbiota-independent effects of oligosaccharides on intestinal epithelial cells: insight into the role of structure and size. Eur J Nutr. 2016;55:1–12.
11. Kau AL, Ahern PP, Griffin NW, et al. Human nutrition, the gut microbiome and the immune system. Nature. 2011;474:327–336.
    • **Perspective on how the gut microbiome can influence the immune system.**
12. Yatsunenko T, Rey FE, Manary MJ, et al. Human gut microbiome viewed across age and geography. Nature. 2012;486:222–227.
13. Flint HJ, Scott KP, Louis P, et al. The role of the gut microbiota in nutrition and health. Nat Rev Gastroenterol Hepatol. 2012;9:577–589.
14. Chu DM, Ma J, Prince AL, et al. Maturation of the infant microbiome community structure and function across multiple body sites and in relation to mode of delivery. Nat Med. 2017;23:314–326. Epub 2017/01/24.
15. Dominguez-Bello MG, De Jesus-Laboy KM, Shen N, et al. Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. Nat Med. 2016;22:250–253.
16. Mueller NT, Bakacs E, Combellick J, et al. The infant microbiome development: mom matters. Trends Mol Med. 2015;21:109–117.
17. Bäckhed F, Roswall J, Peng Y, et al. Dynamics and stabilization of the human gut microbiome during the first year of life. Cell Host Microbe. 2015;17:852.
18. Giovannini M, Verduci E, Gregori D, et al. Prebiotic effect of an infant formula supplemented with galacto-oligosaccharides: randomized multicenter trial. J Am Coll Nutr. 2014;33:385–393.
19. Sierra C, Bernal M-J, Blasco J, et al. Prebiotic effect during the first year of life in healthy infants fed formula containing GOS as the only prebiotic: a multicentre, randomised, double-blind and placebo-controlled trial. Eur J Nutr. 2015;54:89–99.
20. Vaishampayan PA, Kuehl JV, Froula JL, et al. Comparative metagenomics and population dynamics of the gut microbiota in mother and infant. Genome Biol Evol. 2010;2:53–66.
21. Koenig JE, Spor A, Scalfone N, et al. Succession of microbial consortia in the developing infant gut microbiome. Proc Natl Acad Sci. 2011;108:4578–4585.
22. Sonnenburg ED, Smits SA, Tikhonov M, et al. Diet-induced extinctions in the gut microbiota compound over generations. Nature. 2016;529:212–215.
23. Lozupone CA, Stombaugh JI, Gordon JI, et al. Diversity, stability and resilience of the human gut microbiota. Nature. 2012;489:220–230.
24. Maslowski KM, Mackay CR. Diet, gut microbiota and immune responses. Nat Immunol. 2011;12:5–9.
25. Gritz EC, Bhandari V. The human neonatal gut microbiome: a brief review. Front Pediatrics. 2015;3:17.
26. Slavin J. Whole grains and human health. Nutr Res Rev. 2004;17:99–110.
27. Schrezenmeir J, de Vrese M. Probiotics, prebiotics, and synbiotics—approaching a definition. Am J Clin Nutr. 2001;73:361s–4s.
28. Fuller S, Beck E, Salman H, et al. New horizons for the study of dietary fiber and health: a review. Plant Foods Hum Nutr. 2016;71:1–12.
    • **Review on differences in dietary fiber and their health effects.**
29. Slavin J. Fiber and prebiotics: mechanisms and health benefits. Nutrients. 2013;5:1417–1435.
30. Anderson JW, Baird P, Davis RH, et al. Health benefits of dietary fiber. Nutr Rev. 2009;67:188–205.
31. Englyst HN, Kingman SM. Dietary fiber and resistant starch. In: Dietary fiber. Kritchevsky D, Bonfield C, Anderson JW, editors. Springer; 1990. p. 49–65.
32. Parliament E, Council t. Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004. Off J Eur Union. 2011;50:18–63.
33. Jones JM. CODEX-aligned dietary fiber definitions help to bridge the 'fiber gap'. Nutr J. 2014;13:34.
34. Flamm G, Glinsmann W, Kritchevsky D, et al. Inulin and oligofructose as dietary fiber: a review of the evidence. Crit Rev Food Sci Nutr. 2001;41:353–362.
35. Gibson GR, Scott KP, Rastall RA, et al. Dietary prebiotics: current status and new definition. Food Sci Technol Bull Funct Foods. 2010;7:1–19.
36. Hill C, Guarner F, Reid G, et al. Expert consensus document: the International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Macmillan Publishers Limited, part of Springer Nature. Nat Rev Gasteroenterol Hepatol. 2014;11:506–514.

37. Macfarlane S, Blackett KE, Macfarlane GT. Synthesis and utilization of exopolysaccharides and prebioitcs. In: Bifidobacteria: genomics and molecular aspects. Norfolk (UK): Caister Academic Press; 2010. p. 175–194.
38. Macfarlane G, Steed H, Macfarlane S. Bacterial metabolism and health-related effects of galacto-oligosaccharides and other prebiotics. J Appl Microbiol. 2008;104:305–344.
39. Gupta AK, Kaur N. Fructan storing plants: a potential source of high fructose syrups. J Sci Ind Res. 1997;56:447–452.
40. Coulier L, Timmermans J, Bas R, et al. In-depth characterization of prebiotic galacto-oligosaccharides by a combination of analytical techniques. J Agric Food Chem. 2009;57:8488–8495.
41. Singh RS, Singh RP, Kennedy JF. Recent insights in enzymatic synthesis of fructooligosaccharides from inulin. Int J Biol Macromol. 2016;85:565–572.
42. Macfarlane S, Macfarlane G, Cummings J. Review article: prebiotics in the gastrointestinal tract. Aliment Pharmacol Ther. 2006;24:701–714.
43. Firmansyah A, Chongviriyaphan N, Dillon DH, et al. Fructans in the first 1000 days of life and beyond, and for pregnancy. Asia Pac J Clin Nutr. 2016;25:652–675. Epub 2016/10/06.
44. Kumar VP, Prashanth KH, Venkatesh Y. Structural analyses and immunomodulatory properties of fructo-oligosaccharides from onion (*Allium cepa*). Carbohydr Polym. 2015;117:115–122.
45. Meyer D, Stasse-Wolthuis M. The bifidogenic effect of inulin and oligofructose and its consequences for gut health. Eur J Clin Nutr. 2009;63:1277–1289.
46. Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. Nat Rev Immunol. 2009;9:313–323.
47. Moro G, Minoli I, Mosca M, et al. Dosage-related bifidogenic effects of galacto-and fructooligosaccharides in formula-fed term infants. J Pediatr Gastroenterol Nutr. 2002;34:291–295.
48. Arslanoglu S, Moro GE, Schmitt J, et al. Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. J Nutr. 2008;138:1091–1095.
49. Topping DL, Clifton PM. Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides. Physiol Rev. 2001;81:1031–1064.
50. Roy CC, Kien CL, Bouthillier L, et al. Short-chain fatty acids: ready for prime time? Nutr Clin Pract. 2006;21:351–366.
51. Knol J, Scholtens P, Kafka C, et al. Colon microflora in infants fed formula with galacto- and fructo-oligosaccharides: more like breast-fed infants. J Pediatr Gastroenterol Nutr. 2005;40:36–42.
52. Vandenplas Y, Abkari A, Bellaiche M, et al. Prevalence and health outcomes of functional gastrointestinal symptoms in infants from birth to 12 months of age. J Pediatr Gastroenterol Nutr. 2015;61:531–537.
53. Wessel MA, Cobb JC, Jackson EB, et al. Paroxysmal fussing in infancy, sometimes called "colic". Pediatrics. 1954;14:421–435.
54. Benninga MA, Nurko S, Faure C, et al. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology. 2016;150:1443–1455. e2.
55. Freedman SB, Al-Harthy N, Thull-Freedman J. The crying infant: diagnostic testing and frequency of serious underlying disease. Pediatrics. 2009;123:841–848.
56. Shamir R, St James-Roberts I, Di Lorenzo C, et al. Infant crying, colic, and gastrointestinal discomfort in early childhood: a review of the evidence and most plausible mechanisms. J Pediatr Gastroenterol Nutr. 2013;57:S1.
57. Hall B, Chesters J, Robinson A. Infantile colic: a systematic review of medical and conventional therapies. J Paediatr Child Health. 2012;48:128–137.
58. Savino F, Cresi F, Pautasso S, et al. Intestinal microflora in breastfed colicky and non-colicky infants. Acta Paediatr. 2004;93:825–829.
59. de Weerth C, Fuentes S, Puylaert P, et al. Intestinal microbiota of infants with colic: development and specific signatures. Pediatrics. 2013;131:e550–e558.
60. Rhoads JM, Fatheree NY, Norori J, et al. Altered fecal microflora and increased fecal calprotectin in infants with colic. J Pediatr. 2009;155:823–828.e1.
61. Pärtty A, Luoto R, Kalliomäki M, et al. Effects of early prebiotic and probiotic supplementation on development of gut microbiota and fussing and crying in preterm infants: a randomized, double-blind, placebo-controlled trial. J Pediatr. 2013;163:1272–1277. e2.
62. Treem WR, Hyams JS, Blankschen E, et al. Evaluation of the effect of a fiber-enriched formula on infant colic. J Pediatr. 1991;119:695–701.
63. Savino F, Cresi F, Maccario S, et al. "Minor" feeding problems during the first months of life: effect of a partially hydrolysed milk formula containing fructo- and galacto-oligosaccharides. Acta Paediatr. 2003;92:86–90.
64. Savino F, Palumeri E, Castagno E, et al. Reduction of crying episodes owing to infantile colic: a randomized controlled study on the efficacy of a new infant formula. Eur J Clin Nutr. 2006;60:1304–1310.
65. Bongers ME, de Lorijn F, Reitsma JB, et al. The clinical effect of a new infant formula in term infants with constipation: a double-blind, randomized cross-over trial. Nutr J. 2007;6:8.
66. van den Berg MM, Benninga MA, Di Lorenzo C. Epidemiology of childhood constipation: a systematic review. Am J Gastroenterol. 2006;101:2401–2409.
67. Koppen IJN, Lammers LA, Benninga MA, et al. Management of functional constipation in children: therapy in practice. Pediatr Drugs. 2015;17:349–360.
68. Vandeputte D, Falony G, Vieira-Silva S, et al. Stool consistency is strongly associated with gut microbiota richness and composition, enterotypes and bacterial growth rates. Gut. 2015. gutjnl-2015-309618.2015;65:57–62.
69. Zoppi G, Cinquetti M, Luciano A, et al. The intestinal ecosystem in chronic functional constipation. Acta Paediatr. 1998;87:836–841.
70. Zhu L, Liu W, Alkhouri R, et al. Structural changes in the gut microbiome of constipated patients. Physiol Genomics. 2014;46:679–686.
71. de Meij TG, de Groot EF, Eck A, et al. Characterization of microbiota in children with chronic functional constipation. PLoS ONE. 2016;11:e0164731.
    - **High-quality study that investigates the differences microbiota between healthy and constipated children.**
72. Ley RE, Turnbaugh PJ, Klein S, et al. Microbial ecology: human gut microbes associated with obesity. Nature. 2006;444:1022–1023. Epub 2006/12/22.
73. Tabbers M, DiLorenzo C, Berger M, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr. 2014;58:258–274.
74. Loening-Baucke V, Miele E, Staiano A. Fiber (glucomannan) is beneficial in the treatment of childhood constipation. Pediatrics. 2004;113:e259–e264.
75. Castillejo G, Bulló M, Anguera A, et al. A controlled, randomized, double-blind trial to evaluate the effect of a supplement of cocoa husk that is rich in dietary fiber on colonic transit in constipated pediatric patients. Pediatrics. 2006;118:e641–e648.
76. Ustundag G, Kuloglu Z, Kirbas N, et al. Can partially hydrolyzed guar gum be an alternative to lactulose in treatment of childhood constipation. Turk J Gastroenterol. 2010;21:360–364.
77. Chmielewska A, Horvath A, Dziechciarz P, et al. Glucomannan is not effective for the treatment of functional constipation in children: a double-blind, placebo-controlled, randomized trial. Clin Nutr. 2011;30:462–468.
78. Kokke FT, Scholtens PA, Alles MS, et al. A dietary fiber mixture versus lactulose in the treatment of childhood constipation: a double-blind randomized controlled trial. J Pediatr Gastroenterol Nutr. 2008;47:592–597.
79. Weber TK, Toporovski MS, Tahan S, et al. Dietary fiber mixture in pediatric patients with controlled chronic constipation. J Pediatr Gastroenterol Nutr. 2014;58:297–302.

80. Beleli CA, Antonio MA, dos Santos R, et al. Effect of 4'galactooligosaccharide on constipation symptoms. Jornal de Pediatria (Versão em Português). 2015;91:567–573.
81. Closa-Monasterolo R, Ferré N, Castillejo-DeVillasante G, et al. The use of inulin-type fructans improves stool consistency in constipated children. A randomised clinical trial: pilot study. Int J Food Sci Nutrition. 2016;68:1–11.
82. Koppen IJ, Benninga MA, Tabbers MM. Is there a role for pre-, pro-and synbiotics in the treatment of functional constipation in children? A systematic review. J Pediatr Gastroenterol Nutr. 2016;63:S27–S35.
83. Korterink JJ, Diederen K, Benninga MA, et al. Epidemiology of pediatric functional abdominal pain disorders: a meta-analysis. PLoS ONE. 2015;10:e0126982.
84. Varni JW, Lane MM, Burwinkle TM, et al. Health-related quality of life in pediatric patients with irritable bowel syndrome: comparative analysis. J Dev Behav Pediatrics. 2006;27:451–458.
85. Konijnenberg A, Uiterwaal C, Kimpen J, et al. Children with unexplained chronic pain: substantial impairment in everyday life. Arch Dis Child. 2005;90:680–686.
86. Lindley K, Glaser D, Milla P. Consumerism in healthcare can be detrimental to child health: lessons from children with functional abdominal pain. Arch Dis Child. 2005;90:335–337.
87. Hoekman DR, Rutten JM, Vlieger AM, et al. Annual costs of care for pediatric irritable bowel syndrome, functional abdominal pain, and functional abdominal pain syndrome. J Pediatr. 2015;167:1103–1108. e2.
88. Claar RL, Walker LS. Functional assessment of pediatric pain patients: psychometric properties of the functional disability inventory. Pain. 2006;121:77–84.
89. Mulvaney S, Lambert EW, Garber J, et al. Trajectories of symptoms and impairment for pediatric patients with functional abdominal pain: a 5-year longitudinal study. J Am Acad Adolesc Psychiatry. 2006;45:737–744.
90. Campo JV. Annual research review: functional somatic symptoms and associated anxiety and depression–developmental psychopathology in pediatric practice. J Psychol Psychiatry. 2012;53:575–592.
91. Saulnier DM, Riehle K, Mistretta TA, et al. Gastrointestinal microbiome signatures of pediatric patients with irritable bowel syndrome. Gastroenterology. 2011;141:1782–1791.
92. Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology. 2016;150:1456–1468.e2.
93. Drossman DA, Dumitrascu DL. Rome III: new standard for functional gastrointestinal disorders. J Gastrointest Liver Dis. 2006;15:237.
94. Tillisch K, Wang Z, Kilpatrick L, et al. Studying the brain–gut axis with pharmacological imaging. Ann NY Acad Sci. 2008;1144:256–264.
95. Korterink J, Devanarayana NM, Rajindrajith S, et al. Childhood functional abdominal pain: mechanisms and management. Nat Rev Gastroenterol Hepatol. 2015;12:159–171.
96. Rigsbee L, Agans R, Shankar V, et al. Quantitative profiling of gut microbiota of children with diarrhea-predominant irritable bowel syndrome. Am J Gastroenterol. 2012;107:1740–1751.
97. Feldman W, McGrath P, Hodgson C, et al. The use of dietary fiber in the management of simple, childhood, idiopathic, recurrent, abdominal pain: results in a prospective, double-blind, randomized, controlled trial. Am J Dis Child. 1985;139:1216–1218.
98. Christensen MF. Recurrent abdominal pain and dietary fiber. Am J Dis Child. 1986;140:738–739.
99. Romano C, Comito D, Famiani A, et al. Partially hydrolyzed guar gum in pediatric functional abdominal pain. World J Gastroentero. 2013;19:235–240.
100. Horvath A, Dziechciarz P, Szajewska H. Glucomannan for abdominal pain-related functional gastrointestinal disorders in children: a randomized trial. World J Gastroentero. 2013;19:3062–3068.
101. Shulman RJ, Hollister EB, Cain K, et al. Psyllium fiber reduces abdominal pain in children with irritable bowel syndrome in a randomized, double-blind trial. Clin Gastroenterol Hepatol. 2016;15:712–719.
102. Chumpitazi BP, Hollister EB, Oezguen N, et al. Gut microbiota influences low fermentable substrate diet efficacy in children with irritable bowel syndrome. Gut Microbes. 2014;5:165–175.
103. Chumpitazi B, Cope J, Hollister E, et al. Randomised clinical trial: gut microbiome biomarkers are associated with clinical response to a low FODMAP diet in children with the irritable bowel syndrome. Aliment Pharmacol Ther. 2015;42:418–427.
104. Staudacher HM, Irving PM, Lomer MC, et al. Mechanisms and efficacy of dietary FODMAP restriction in IBS. Nat Rev Gastroenterol Hepatol. 2014;11:256–266.
105. Hoekman DR, Zeevenhooven J, Benninga MA. Should we treat our pediatric irritable bowel syndrome patients with psyllium? Clin Gastroenterol Hepatol. 2016;14:1667.
106. Roest R, Dobbs B, Chapman B, et al. The low FODMAP diet improves gastrointestinal symptoms in patients with irritable bowel syndrome: a prospective study. Int J Clin Pract. 2013;67:895–903.
107. Wald A, Sigurdsson L. Quality of life in children and adults with constipation. Best Pract Res Clin Gastroenterol. 2011;25:19–27.
108. Liem O, Harman J, Benninga M, et al. Health utilization and cost impact of childhood constipation in the United States. J Pediatr. 2009;154:258–262.
109. Backhed F, Ding H, Wang T, et al. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci USA. 2004;101:15718–15723. Epub 2004/10/27.