Epidemiology, Diagnosis and Management of Functional Abdominal Pain in Children

- A look beyond the belly -

Judith Janneke Korterink

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Chapter 1

General introduction and outline of this thesis

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General introduction

Chronic abdominal pain is one of the most common clinical syndromes encountered in day to day clinical pediatric practice. In the vast majority of these children, no explanatory organic cause can be identified. Although common, its definition is confusing, predisposing factors are poorly understood and the pathophysiological mechanisms are not clear. Moreover, there is a lack of large well-performed clinical trials which are needed for evidence based treatment.

In 1909, George Frederic Still, a British pediatrician, wrote “I know of no symptom which can be more obscure in its causation than colicky abdominal pain in childhood”.[1] Today, a century later, both clinicians and researchers are still struggling to understand this enigmatic clinical issue. This lack of understanding often leads to extensive investigations, non-effective therapeutic modalities, poor patient satisfaction, reduced health-related quality of life, staggering health-care costs and an insurmountable amount of suffering in the patients themselves.[2] However, the landscape is changing, especially during the past two decades. Definitions are being refined from the previously labeled and vague ‘chronic or recurrent abdominal pain’ to the more-specific symptom-based Rome III criteria. Pathophysiological mechanisms are being explored and knowledge is expanding. New non-invasive investigational techniques are emerging to elaborate underlying abnormalities. Although the traditional pharmacologic treatment modalities are failing, some novel pharmacologic agents and nonpharmacologic therapeutic components are showing promising results.

Definitions

In 1958, John Apley, a British pediatrician who pioneered research in children with abdominal pain, named the condition as “recurrent abdominal pain syndrome of childhood” and defined it as “at least three episodes of abdominal pain, severe enough to affect their activities over a period longer than 3 months”.[3] Ever since, for nearly four decades, this definition became the standard definition used to diagnose chronic abdominal pain in both research and clinical practice. In 1996, Hyams *et al*. observed that 51% of children with recurrent abdominal pain could be classified as having IBS utilizing criteria designed for adults.[4] In 1999, the Rome II criteria for children were published and were appropriate to be used as diagnostic tools and to advance empirical research.[5] Using these criteria, it was noted that 73–89% of children with recurrent abdominal pain (RAP) could be classified to have a pain-predominant FGID.[6, 7] Since then, the term recurrent abdominal pain (RAP) was replaced by abdominal-pain-predominant FGIDs (AP-FGIDs); namely, functional dyspepsia, IBS, functional abdominal pain (FAP) and abdominal migraine**.** Although the Rome II criteria laid a firm foundation to study pain-predominant FGIDs, they were found to have several limitations. The Rome II criteria demanded persistence of symptoms for over 3 months before the diagnosis.[5] In addition, Saps and Di Lorenzo noted that the diagnostic agreement between pediatric gastroenterologists and gastroenterology fellows when adhering to the Rome II criteria was low.[8] Another study assessing the Rome II criteria reported only limited agreement between physician diagnosis and parent-reported symptoms.[7] These limitations led to the development of the new Rome III criteria, introduced in 2006.[9] The Rome III criteria have been shown to be more inclusive than the Rome II criteria and the majority of children with RAP can be classified as having one or more of FGIDs.[10, 11] Unfortunately, the renewed Rome III criteria failed to improve the diagnostic agreement between pediatric gastroenterologists and gastroenterology fellows compared with the Rome II criteria.[12] Another limitation of the current Rome III criteria is the substantial overlap among FGIDs in children with nausea.[13] The Rome III classification and the definitions for AP-FGIDs are given in Box 1.

A range of studies have noted that the majority of children with RAP have no organic pathology that can account for their symptoms.[6, 14] As epidemiology, pathophysiology and treatment options might be different in these distinct disease entities, it could be helpful for both clinicians and researchers to use up-to-date and accepted criteria to diagnose different types of AP-FGIDs to optimize and tailor individual treatment.

Box 1 | ROME III criteria for AP-FGIDs[9]

Functional dyspepsia[a]

1. Persistent or recurrent pain or discomfort centered in the upper abdomen (above the umbilicus)
2. Not relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not IBS)
3. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms

IBS[a]

1. Abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with 2 or more of the following at least 25% of the time: improved with defecation; onset associated with a change in frequency of stool; onset associated with a change in form (appearance) of stool
2. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms

Abdominal migraine[b]

1. Paroxysmal episodes of intense, acute periumbilical pain that lasts for 1 h or more
2. Intervening periods of usual health lasting weeks to months
3. The pain interferes with normal activities
4. The pain is associated with 2 or more of the following: anorexia; nausea; vomiting; headache; photophobia; pallor
5. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms

Functional abdominal pain[a]

1. Episodic or continuous abdominal pain
2. Insufficient criteria for other FGIDs
3. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms

Functional abdominal pain syndrome (FAPS)[a]

Must include childhood functional abdominal pain at least 25% of the time and 1 or more of the following:

1. Some loss of daily functioning
2. Additional somatic symptoms such as headache, limb pain, or difficulty sleeping.

[a] Criteria fulfilled at least once per week for at least 2 months before diagnosis

[b] Criteria fulfilled 2 or more times in the preceding 12 months

Abbreviation: AP-FGIDs, abdominal-pain-related functional gastrointestinal disorders

Epidemiology

The first epidemiological study on RAP was conducted in the UK by Apley and Naish in 1958. This landmark study found that 10.8% of British school children had RAP.[3] Studies published in the 2000s conducted in Western and Asian countries have reported more or less similar prevalence rates of RAP between 10% and 12 %.[15-19]

Using the Rome III criteria, a school-based study among 1,850 Sri Lankan school children showed that FGIDs related to abdominal pain are highly prevalent. According to this study FAP, IBS, functional dyspepsia and abdominal migraine were found in 9.7%, 4.9%, 0.6% and 1.9%, respectively.[20] Similar

to this finding, a study from Colombia reported a prevalence of pain-predominant FGIDs in 27.9% of children (FAP 2.4%, IBS 5.1%, functional dyspepsia 2.4%, abdominal migraine 1.6%).[21] An observational prospective multicenter study showed that among pediatric patients with IBS, constipation-predominant IBS was the prevalent subtype (45%), with a prevalence in girls at 62% (p<0.005); diarrhea-predominant IBS was reported in 26% of children, with a prevalence in boys at 69% (p<0.005); and alternating-type IBS was described in 29% of children, without a difference between sexes.[22] By contrast, other studies have reported a female preponderance and diarrhea–predominant IBS and mixed-type IBS as the most common forms.[23] The prevalence of functional dyspepsia varies from 0.3-2.5%,[24, 25] and that of abdominal migraine from 1-4.1%.[21, 25, 26]

Risk factors and pathophysiology

The prevailing viewpoint is that the pathogenesis of functional pain syndromes involves the inter-relationship between changes in visceral sensation, so-called visceral hyperalgesia or hypersensitivity, and altered gastrointestinal motility.[27] The symptoms of hypersensitivity are pain and discomfort, whereas the symptoms of altered motility can be diarrhea, constipation, nausea, bloating and distension. Several factors have been linked to this hypersensitivity and altered motility and discussed herein (Figure 1).

Visceral hypersensitivity

Several investigators have studied visceral sensitivity in children with FAP and IBS.[28-31] These studies clearly demonstrate that children with FAP or IBS as a group have a lower sensory threshold for gastric or rectal balloon distension than healthy controls. However, clinical utility value and usefulness of this invasive test is debatable as not all patients have abnormal test results.[30] Imaging studies of adults with IBS have shown that rectal hypersensitivity is associated with greater activation of the rostral anterior cingulate cortex than in healthy individuals.[32, 33] To date, it is unknown whether children with IBS have a similar reduced sensory thresholds (centrally mediated) that lead to visceral hypersensitivity.

Gastrointestinal motility abnormalities

A series of studies have shown an association between abnormalities in physiological function in the stomach and the gastric antrum and AP-FGIDs and RAP. Using a noninvasive ultrasonographical method, delayed liquid gastric emptying and impaired antral motility was found in children with RAP, FAP, IBS or functional dyspepsia.[34-36] The gastric emptying rate had a statistically significant negative correlation with symptom severity in children FAP or functional dyspepsia.[35, 36] Furthermore, among children with IBS, patients who were exposed to stressful events had markedly lower gastric emptying rates than patients who had no history of exposure to stress.[34] Similarly, several other studies have described that children with functional dyspepsia have abnormal gastric emptying to both solids and liquids.[37, 38] In addition, using octanoic acid breath test, Hoffman and Tack demonstrated abnormalities in solid emptying in children with functional dyspepsia.[39]

One important physiological function of the proximal stomach is meal accommodation. Abnormalities in meal accommodation are suggested as a possible pathophysiological mechanism for functional dyspepsia in adults.[40, 41] Two small studies, have demonstrated abnormal gastric accommodation to a solid meal in children with functional dyspepsia.[38, 42]

Muscular activity of the stomach is preceded by gastric electrical activity, therefore, it is possible that children with RAP and FGIDs have abnormal gastric myoelectrical activity.

Several studies have demonstrated abnormal electrical rhythms (such as tachygastria and bradygastria) in children with functional dyspepsia.[43, 44] However, the relationship between abnormal gastric motility and clinical symptoms in children with FGIDs is not completely elucidated, not all children with symptoms have disturbed motility and vice versa.

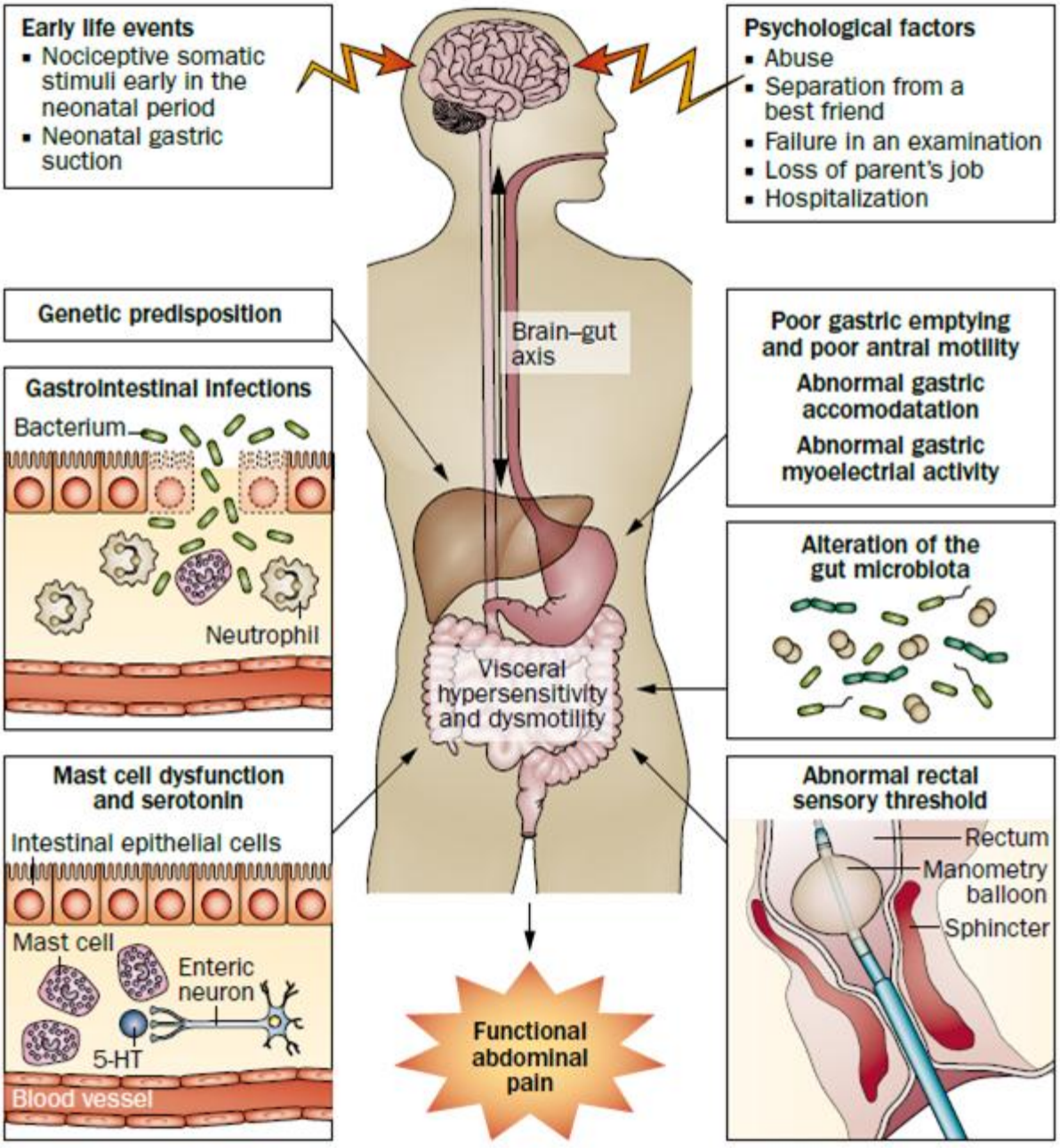

Figure 1 | Pathogenesis of childhood functional abdominal pain

An overview of several risk factors which are associated with changes in visceral hypersensitivity and motility, and contribute to the development of functional abdominal pain

Early life events

Early life events are known to be associated with the development of visceral hyperalgesia and abdominal pain in children, such as hypersensitivity to cow's milk protein, pyloric stenosis, umbilical hernia repair and Henoch-Schonlein purpura.[45-47]

The putative mechanisms include sensitization of spinal neurons, impaired stress response, and/or altered descending limb inhibitory control.[29] In a rat model, Miranda *et al.* found that exposure to

nociceptive somatic stimuli in the early neonatal period resulted in chronic somatic and visceral hyperalgesia.[48] In addition, the same group of researchers found that neonatal gastric suction also led to visceral hyperalgesia through corticotrophin-releasing factor.[49] These observations suggest a possibility of the existence of a critical vulnerable period in early development of the nervous system that can be associated with prolonged structural and/or functional alterations that affect pain perception. Stress is a known trigger for symptoms of FAP and IBS.[50] Therefore, it is conceivable that adverse events in early life might give rise to long-lasting or permanent alterations in central nervous system responses to stress and bowel sensitivity, thereby inducing an increased susceptibility to the development of FGIDs.[49]

Psychological factors

Psychological stress has long been recognized as a risk factor for the development of FGIDs in children. Several patient studies have shown an association between recurrent abdominal pain and exposure to stressful events. [51-55] In children stressful events can be, for example, separation from the best friend at school, failure in an examination, loss of parent's job and hospitalization.[19, 25, 56] In addition, exposure to abuse is also an important risk factor for abdominal pain in children.[57] Studies among adults have shown an association between abuse as a child and development of IBS in later life.[58] Also, in children, an association was found between all three types of child abuse (physical, emotional and sexual) and AP-FGIDs.[15,27] Furthermore, anxiety and depression were reported to be significantly more frequent among children with FGIDs than in healthy children.[59-63]

How these psychological factors lead to the development of FGIDs is still debated. Depression and anxiety can be the result of ineffective mechanisms of coping with stress, as limited coping strategies are demonstrated in children with chronic abdominal pain.[64] This finding might also explain the association with traumatic life events. In addition, stressors have been shown to be associated with enhanced visceral perception.[65] Several functional MRI studies have shown that abuse and related stresses lead to activation of the anterior mid cingulate and posterior cingulate cortices.[66] Furthermore, a simultaneous deactivation of the anterior cingulate cortex supragenual region, an area associated with the downregulation of pain signals, was noted in adults with FGIDs.[67] Animal studies have shown that an exposure to stress predisposes them to develop stress-induced visceral hypersensitivity,[68] altered defecation,[69] intestinal mucosal dysfunction,[70] alterations in the hypothalamo-pituitary-adrenal (HPA) axis[71] and disruption of the intestinal microbiota.[72] Similarly, studies conducted in adults with IBS have revealed stress-induced alterations in gastrointestinal motility, visceral sensitivity, autonomic dysfunction and HPA axis dysfunction.[51] Therefore, it is possible that, through the same mechanisms, abuse and stress lead to the alteration of both the HPA and brain–gut neural axes, predisposing individuals to develop FGIDs.

Inflammation of the intestinal mucosa

Faure and colleges have analyzed the inflammatory cells in colonic and gastric mucosa of children with functional dyspepsia or IBS. Of 12 patients with IBS, 11 had minimal inflammation of the intestinal mucosa, whereas 9 of 17 patients with functional dyspepsia had variable degrees of inflammation; however, the place of inflammation was not specified, which is a clear drawback of this important study.[73] Another study noted that 71% of children evaluated for suspected functional dyspepsia had duodenal eosinophilia (>10 eosinophils per high-power field)[74] The real clinical utility of such findings are still not clear.

Mast cell dysfunction and serotonin

Serotonin (5-hydroxytryptamine, 5-HT) is considered to be an important regulatory chemical compound in the brain–gut axis.[75] Serotonin is released by the enterochromaffin cells of the intestinal mucosa and its action is regulated by the 5-HT selective reuptake transporter (SERT) and organic cation transporter-1 (OCT-1).[76] Studies among adults have shown variable results of 5-HT signaling in colonic mucosa in adults with IBS.[77] One study conducted in children with either IBS or functional dyspepsia was unable to demonstrate increased enterochromaffin cells in gastric mucosa of children with functional dyspepsia and colonic mucosa of children with IBS.[73] However, the serotonin content in the colonic mucosa was increased in the IBS group and normal in the gastric mucosa of individuals with functional dyspepsia. No difference of TpH-2 mRNA expression in the gastrointestinal biopsy samples of both those with IBS and functional dyspepsia. Children with IBS had lower expression of SERT mRNA in the rectal mucosa compared to controls. These findings indicate that children with IBS have an increased availability of 5-HT in their rectal mucosa.[73] Possibly, 5-HT interacts with peripheral nerves in the submucosa and contributes to the development of abdominal pain through heightening visceral sensitivity and stimulating pain pathways in children with FGIDs.

Human microbiome

Alteration of the gut microbiome has long been considered as a potential mechanism for the development of pain-predominant FGIDs. In an elegant study, Saulnier *et al.* noted that children with IBS had greater proportion of phylum Proteobacteria, and genera such as *Dorea* (a member of Firmicutes) and *Haemophilus* (a member of Proteobacteria). In addition, it was noted that species such as *H. parainfluenzae* and *Ruminococcus* were more abundant and Bacteroides were marked less abundant in children with IBS than controls.[78] Another study comparing the fecal microbiota of healthy children and patients with diarrhea-predominant IBS noted that levels of *Veillonella*, *Prevotella*, *Lactobacillus* and *Parasporbacterium* were increased in patients with IBS, whereas a reduction was reported in levels of *Bifidobacterium* and *Verrucomicrobium*.[79] Although further studies are needed to clarify and clearly identify the exact changes in the microbiome of children with FGIDs, these research efforts provide some insight to the possibility of alteration of the microbiome leading to symptom generation. These microbes might alter visceral perception, gut motility, intestinal gas production and gut permeability with their metabolites leading to pain-predominant FGIDs.[80, 81]

Genetic and environmental factors

Genetic and environmental factors have long been considered as risk factors for the development of pain-predominant FGIDs. In a genome-wide association study of adults, a locus on chromosome 7p22.1 has consistently been shown to have a genetic risk of developing IBS, although it still did not reach genome-wide significance in the meta-analysis of combined index and replication findings.[82] The most convincing association of genetic association is the *TNFSF15* polymorphism, which has been observed in three independent cohorts in Sweden, the USA and England.[83, 84] The *TNFSF15* polymorphism has been associated with constipation-predominant IBS, diarrhea-predominant IBS and postinfectious IBS phenotypes. TL1A, the protein encoded by *TNFSF15* modulates inflammatory responses, which supports the role of immune activation in IBS.[83,84]

A twin study, performed by Levy et al,[85] showed a 17% concordance for IBS in monozygotic twin patients with only 8% concordance in dizygotic twins, supporting a genetic contribution to IBS. This study, however, also showed that a parental history of IBS was a stronger predictor of IBS than having a twin with IBS, suggesting that social learning is much more important than genetic factors. Furthermore Buonavolonta *et, al.* noted parents of children with FGIDs have a higher prevalence of similar diseases than parents of children without FGIDs.[86] Another study found that children of parents

with IBS tend to use health care substantially more for gastrointestinal problems than children of parents who do not have IBS.[85]

In addition, parental response to child's pain behaviors seems to be a key factor in the development and recurrence of FAP, and interventions that target changes in parental responses can decrease complaints of pain and other illness behaviors in children.[87] In addition, high somatization scores in mothers and fathers are associated with high somatization scores in children with RAP.[88] Parents' over-reactive behavior during pain episodes probably influences not only the frequency and intensity of the abdominal pain but also the cognition of pain and extraintestinal somatic symptoms, which are an integral part of FAP. These findings suggest the possibility of genetic predisposition and social and environmental susceptibility to develop pain-predominant FGIDs.

Postinfectious causes

Studies in adults have established the possibility of developing IBS after an episode of acute gastroenteritis.[89] The possible mechanisms are genetic predisposition, psychological status during infection, acute inflammation leading to alteration of serotonin metabolism, sensitivity of enteric neurons, ongoing immune cell activation in the gastrointestinal tract and an altered gut microbiome.[90] In one study, children after exposure to an outbreak of *Escherichia coli* gastroenteritis developed IBS. Female gender, longer duration of symptoms, use of antibiotics and weight loss were statistically significant risk factors for developing IBS in this group of children.[91] On the other hand, it was shown that rotavirus gastroenteritis does not seem to be a risk factor for FGIDs in children.[92]

Box 2 | Warning symptoms in childhood AP-FGIDs

Historical findings

- Persistent right upper or right lower quadrant pain
- Persistent vomiting
- Gastrointestinal blood loss
- Chronic severe diarrhea
- Involuntary weight loss
- Unexplained fever
- Family history of inflammatory bowel disease, celiac or familial Mediterranean fever

Examination findings

- Deceleration of linear growth
- Uveitis
- Oral lesions
- Skin rashes
- Icterus
- Anemia
- Hepatomegaly
- Splenomegaly
- Arthritis
- Costovertebralangle tenderness
- Tenderness over the spine
- Perianal abnormalities

Abbreviations: AP-FGIDs, abdominal-pain-related functional gastrointestinal disorders;

Clinical evaluation

A comprehensive history-taking and physical examination of children with AP-FGIDs are essential to rule out most organic causes. Alarm symptoms that might be related to organic causes of AP-FGIDs are summarized in Box 2.[93] Several studies evaluating the medical history of children with chronic abdominal pain have provided some evidence that frequency, severity, location and timing (postprandial, waking during night) of abdominal pain do not help distinguish between organic and functional abdominal pain.[93, 94]

Abdominal pain diaries can be helpful in clarifying details of the abdominal pain and possible triggering factors, such as specific foods or stressors. An assessment of the stool pattern can differentiate between different subtypes of AP-FGIDs. Furthermore, dietary history and the history of previous treatment strategies for AP-FDIGs should be investigated. Owing to the high degree of association of AP-FGIDs with a range of psychological problems, particular attention must be paid to this part of the history. Children suspicious for any psychological disorder should be referred to a mental health professional.

The physical examination should consist of a basic abdominal examination to identify any obvious abnormalities rather than to confirm a diagnosis of an AP-FIGD. A lack of physical findings might be reassuring to both physician and patient.

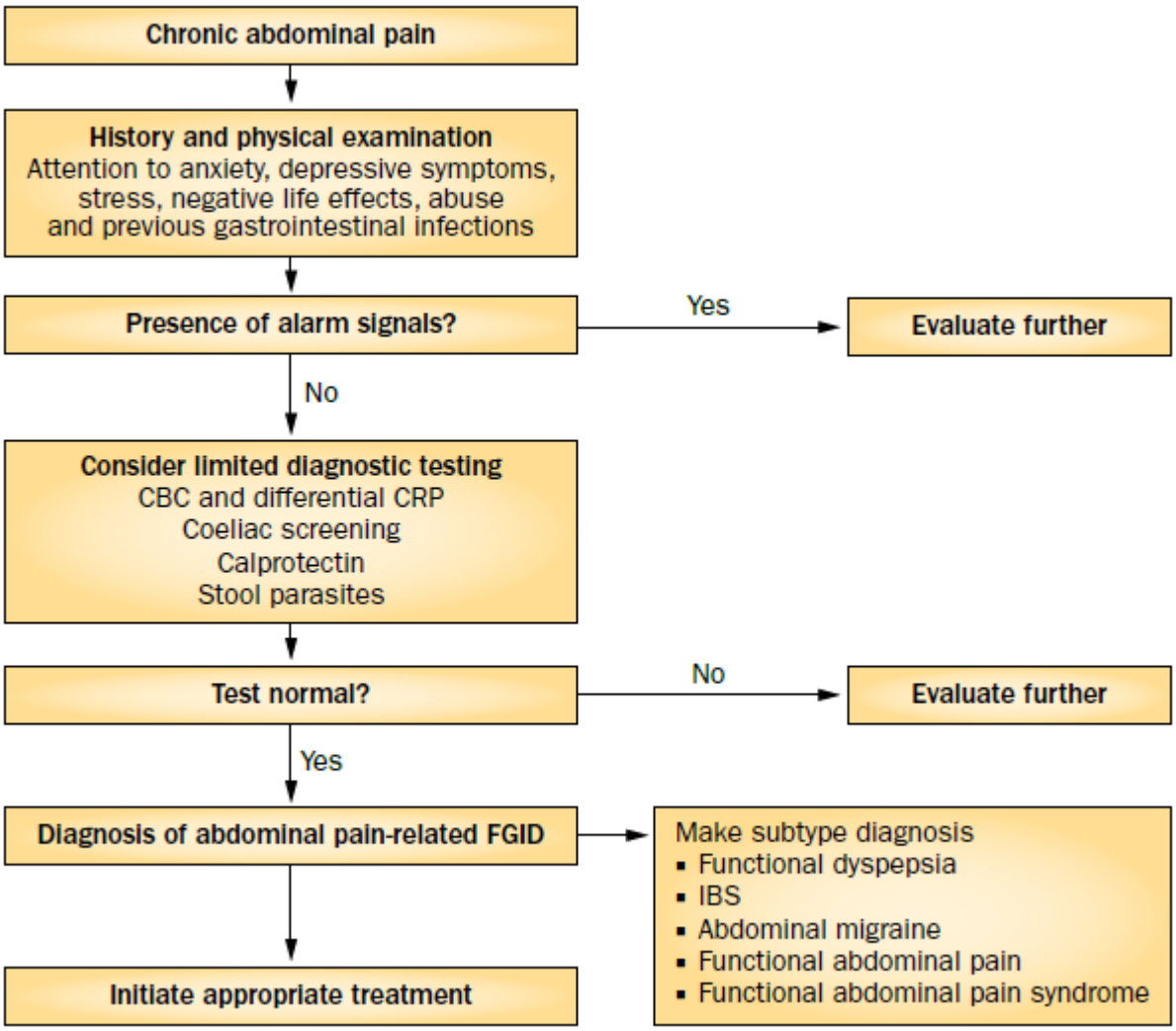

Figure 2 | Diagnostic algorithm for childhood functional abdominal pain

Abbreviations: CBC, complete blood count; CRP, C-reactive protein; FGID, functional gastrointestinal disorder.

Laboratory investigations

Although no evidence to evaluate the predictive value of laboratory tests is available, in general, urinalysis, blood and stool analysis are often ordered by clinicians to distinguish between organic and functional abdominal pain.[95] One should realize that performing multiple tests might provide nonspecific results that are unrelated to the presenting symptom or have no clinical relevance, which might cause confusion and lead to further invasive testing and procedures.[96] A limited and reasonable screening protocol could include a complete blood cell count, levels of C-reactive protein and screening for celiac disease. When a child suffers from diarrhea alongside abdominal pain, one can consider stool analysis for infection with *Giardia lamblia.* Several studies have investigated the prevalence of lactose intolerance in children with abdominal pain, but elimination of lactose often does not result in resolution of abdominal pain.[97, 98] Also, *Helicobacter pylori* infection can be found in children with RAP.[99] This finding does not, however, necessarily indicate a causal relationship between the two, as children with *H. pylori* infection are not more likely to have abdominal pain than children without *H. pylori* infection.[100] In the past few years, elevated concentration of fecal calprotectin has been shown to be a valuable biomarker in diagnosing IBD in children.[101] A study in 126 children with a FGID showed fecal calprotectin concentrations within the normal limit, therefore, this approach seems to be a useful and noninvasive test for distinguishing between functional abdominal pain and IBD in these children.[102] A proposed diagnostic flowchart is shown in Figure 2.

Radiological and endoscopic investigations

A retrospective study in 644 children with RAP showed that abdominal abnormalities were detected by ultrasonographical examination in just 2%.When atypical symptoms were present, such as jaundice, vomiting, back or flank pain, urinary symptoms or abnormal findings on physical examination, abnormalities observed by ultrasonography increased to 11%.[103] Ultrasonography should therefore only be used in children with RAP and atypical clinical features. A prospective study of 290 children with chronic abdominal pain demonstrated a diagnostic value of oesophagogastroduodenoscopy in 38% of the children. At least two alarm symptoms were predictive of diagnostic yield, but without alarm symptoms the diagnostic yield was still 34%, including reflux esophagitis (n = 16), eosinophilic esophagitis or gastroenteritis (n = 6), erosive esophagitis (n = 1), celiac disease (n = 1), and *H. pylori* infection (n = 1).[104] However, medical therapy started after identification of the disorders was effective in only 67% of children during the year after diagnosis, questioning the relationship between the abnormalities found during endoscopy and the clinical symptoms. When presenting with functional dyspepsia, abnormalities have been shown in only 6.3%.[105] The use of esophagogastroduodenoscopy in the presence of alarm symptoms might be considered in the diagnostic work-up of chronic abdominal pain in children.

Management strategies

Treatment of children with an AP-FGID starts with explaining the diagnosis to parents and child. The Rome III criteria encourage physicians to make a positive diagnosis of an AP-FGID, rather than using exhaustive investigations to exclude an underlying organic cause. A multidisciplinary approach to management of childhood AP-FGIDs might be needed in case of social and psychological comorbidities. The primary treatment goal might not always be complete eradication of pain, but resumption of a normal lifestyle with regular school attendance, normal sleep pattern and participation in extracurricular activities. An active listening approach of the physician and encouraging attitude towards treatment helps improve patient's responses to therapeutic attempts.[106] Furthermore, parents

should be informed that a solicitous response by parents might negatively influence the treatment outcomes in children.[107]

Integrative medicine

The National Institutes of Health define complementary and alternative medicine (CAM) as a group of diverse medical and health-care systems, practices and products that are not presently considered to be part of conventional medicine.[108] CAM comprises many different treatment modalities, including acupuncture, yoga, homeopathy, mind–body therapy and musculoskeletal manipulations. Over 40% of children with IBS and FAP use some form of CAM.[109] For those practitioners and patients who want to consider both conventional and CAM medicine in their medical decision-making, an integrative model makes sense. Integrative health combines alternative medicine with evidence-based medicine.[110] It treats the "whole person," focuses on wellness and health rather than on treating disease, and emphasizes the patient-physician relationship. It insist on patients being active participants in their own health care.[111, 112]

In Western civilization yoga is considered as a form of CAM and is becoming more and more popular. Yoga is a mind-body exercise with its origin in Indian philosophy rooting in an over 4000 year-old tradition.[113] The word yoga comes from the Sanskrit word “yuj”, meaning yoke or union, describing the union between mind, body and spirit. Traditional yoga is a complex intervention that comprises advice for ethical lifestyle, spiritual practice, physical activity, breathing exercises, and meditation.[114] Although the ultimate goal of traditional yoga has been described as reaching spiritual enlightenment, yoga has become a popular means to promote physical and mental well-being. In Western civilization, yoga is most often associated with physical postures, breathing techniques and meditation.[115] Two RCTs compared yoga to a waiting list in adolescents and young adults with IBS.[116, 117] Beneficial effects in adolescents were seen in functional disability, gastrointestinal symptoms[117] and physical functioning.[116] A pilot study showed promising results for the improvement of abdominal pain for children with FAP.[118]

In instances of persisting symptoms and serious disruption of a child’s well-being, pharmacologic therapy or nonpharmacologic treatment, including integrative medicine, can be considered. If possible, treatment should be individualized, taking into account risk factors, comorbidities and personal preferences of each patient and their parents. A comprehensive overview of the efficacy and safety of different pharmacologic and nonpharmacologic treatments is given in Chapter 5 and 6 of this thesis.

Prognosis and long-term follow-up

Several longitudinal epidemiological studies exist, linking pediatric FAP to abdominal pain later in life.[119] A comprehensive systematic review evaluating the prognosis of chronic abdominal pain in 1,331 children, demonstrated persisting symptoms in 29.1% of the children after 5 year (median, range 1–29 years) follow-up.[120] In 2014, Horst *et al.* studied 392 children with AP-FGIDs, of whom 41% still met the criteria for AP-FGIDs after 9 years follow-up.[121] Furthermore, there is evidence from prospective studies that adults with IBS began experiencing recurrent FAP as a child.[122] Especially, females are more likely to meet IBS criteria in adulthood.[123] However, another study demonstrated that persistent abdominal pain in childhood did not predict abdominal pain in adulthood.[124] Instead of persisting abdominal pain symptoms in adulthood, Campo *et al.* and Hotopf *et al*. conclude that these children are at increased risk of adult psychiatric disorders, such as anxiety and depressive disorders.[124, 125] This finding was also shown for children with dyspepsia, both children with and

without abnormal histological findings were at increased risk of chronic dyspeptic symptoms, anxiety disorder and reduced quality of life in adolescence and young adulthood.[126]

Several factors influence the prognosis of childhood AP-FGIDs. Children with a history of chronic abdominal pain had a four times higher risk of persistent abdominal pain than children who presented for the first time with chronic abdominal pain.[120] The longer the duration of follow-up, the worse was the prognosis, with persisting symptoms of 25.4% at 1–5 years follow-up to 37.4% at ≥10 years follow-up.[120] In addition, the presence of nongastrointestinal symptoms, such as back pain, headaches, dizziness, weakness and low energy, at the initial pediatric evaluation was associated with an increased likelihood of FGIDs in adolescence and young adulthood.[121, 127] Furthermore, a positive family history of anxiety,[125] RAP or IBS[128] and depressive symptoms[121] are important determinants of persistent abdominal pain in adulthood.

Outline of the thesis

This thesis discusses the epidemiology, diagnosis and management of children with functional abdominal pain and is therefore divided in three parts. The main focus of this thesis is on the nonpharmacologic treatment of functional abdominal pain in children and will evaluate in more detail two forms of complementary therapies: probiotics and yoga therapy.

Part I – Epidemiology

Functional abdominal pain is a common worldwide problem and should be considered a major public health issue in the pediatric population. Knowledge of its epidemiology and risk factors is highly relevant to health care providers. **Chapter 2** is a systematic review and meta-analysis regarding the worldwide-published literature to identify the prevalence of functional abdominal pain in the general pediatric population in order to summarize its geographic, gender and age distribution, and associated factors.

Part II – Diagnosis

The pathophysiology of functional abdominal pain disorders is not completely understood. A biopsychosocial model has been postulated, in which genetic, physiological and psychological factors interplay. The prevailing viewpoint is that part of the symptoms in abdominal pain-related functional gastrointestinal disorders (AP-FGIDs) are associated with dysregulation of the brain-gut axis expressed by visceral hypersensitivity and altered gastrointestinal motility. Alteration of the gut microbiome is thought to interfere with the brain-gut axis, especially since differences in the gut microbiome have been shown in children suffering from IBS compared to healthy children. An abnormal high microbial population level in the small intestine is known as small intestinal bacterial overgrowth (SIBO) and can be diagnosed using a hydrogen breath test. To investigate whether screening for bacterial overgrowth should be incorporated in the diagnostic work-up of pediatric AP-FDIGs, we evaluated the prevalence of SIBO in children with functional abdominal pain. **Chapter 3** reports the results of a glucose hydrogen breath test in a cohort of 161 children with functional abdominal pain and describes its value in the diagnostic management.
Dientamoeba fragilis, a flagellated intestinal protozoan*,* is another pathogen which might disturb the microbiome and is therefore proposed to underlie functional abdominal pain. However, the pathogenicity of this parasite is controversial. Considering *Dientamoeba fragilis* as a pathogen, the parasite should either be excluded or eradicated before the diagnosis of an AP-FGID can be made. Therefore, elucidation of the clinical relevance of dientamoebiasis in children suffering from AP-FGIDs is important. **Chapter 4** presents the results of a case-control study, comparing the extent of a *Dientamoeba fragilis* infection in children with chronic abdominal pain to healthy controls.

Part III – Management

Incomplete understanding of its pathophysiology still hampers the management of pediatric abdominal pain. A considerably number of children does not respond to reassurance, time or simple dietary interventions. Disappointingly, 30% of children continue to experience symptoms even in adulthood. Functional abdominal pain has a great impact on childrens' and adolescents' quality of life, daily activities and school absenteeism. Different therapeutic approaches exist to treat these children but for

many therapies evidence regarding efficacy are lacking. The aim of the third part of the thesis is to designate the appropriate treatment for children with functional abdominal pain. In **chapter 5** we evaluate and rate the available evidence with respect to the effect of different pharmacologic treatments, such as antispasmodic, antidepressant, antireflux, antihistaminic and laxative agents. Besides drug therapy, nonpharmacologic treatments, such as lifestyle, dietary interventions, behavioral interventions, pre- and probiotics and alternative medicine, are widely used. To evaluate the scientific strengths of these treatments we report in **chapter 6** the quantity and quality of all current evidence for the effect of the nonpharmacologic treatments used for pediatric functional abdominal pain.

Two complementary therapies will be further highlighted in the next chapters. **Chapter 7** evaluates more closely the effect of different probiotic strains. Several studies have shown that probiotic therapy can increase the number of beneficial bacteria in the intestine in order to confer a health benefit on the host. In the past decade, the role of probiotics has been studied in children with IBS and FAP. This chapter describes a fourth systematic review in which we systematically review the literature to evaluate the effect of different probiotic strains in the treatment of abdominal pain- and defecation related FGIDs.

Psychological distress is strongly associated with abdominal pain in children. Yoga is an ancient technique used for promoting physical and mental health through postures, the regulation of breathing, and meditation. Yoga therapy has shown its efficacy in stressmanagement and has been recommended as intervention in adults with irritable bowel syndrome. The aim of **chapter 8** was to investigate whether yoga therapy integrated to standard care is more effective than standard medical care in the treatment of children with functional abdominal pain. This chapter presents the result of a RCT, comparing the effectiveness of 10 weeks yoga therapy and standard care on the frequency and intensity of abdominal pain and quality of life (QoL) in children with AP-FGIDs.

This thesis ends with a summary and discussion in **chapter 9**, in which the main findings of the precending chapters are summarized and future directions for research and practice are considerd.

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Chapter 2

Epidemiology of Pediatric Functional Abdominal Pain Disorders; a Meta-analysis

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Submitted

Abstract

Objective

We aimed to review the literature regarding epidemiology of functional abdominal pain disorders in children and to assess its geographic, gender and age distribution including associated risk factors of developing functional abdominal pain.

Methods

The Cochrane Library, MEDLINE, EMBASE, CINAHL and PsychInfo databases were systematically searched up to February 2014. Study selection criteria included: (1) studies of birth cohort, school based or general population samples (2) containing data concerning epidemiology, prevalence or incidence (3) of children aged 4-18 years (4) suffering from functional abdominal pain. Quality of studies was rated by a self-made assessment tool. A random-effect meta-analysis model was used to estimate the prevalence of functional abdominal pain in childhood.

Results

A total of 58 articles, including 196,472 children were included. Worldwide pooled prevalence for functional abdominal pain disorders was 13.5% (95% CI 11.8-15.3), of which irritable bowel syndrome was reported most frequently (8.8%, 95% CI 6.2-11.9). The prevalence across studies ranged widely from 1.6% to 41.2%. Higher pooled prevalence rates were reported in South America (16.8%) and Asia (16.5%) compared to Europe (10.5%). And a higher pooled prevalence was reported when using the Rome III criteria (16.4%, 95% CI 13.5-19.4). Functional abdominal pain disorders are shown to occur significantly more in girls (15.9% vs. 11.5%, pooled OR 1.5) and is associated with the presence of anxiety and depressive disorders, stress and traumatic life events.

Conclusions

Functional abdominal pain disorders are a common problem worldwide with irritable bowel syndrome as most encountered abdominal pain-related functional gastrointestinal disorder. Female gender, psychological disorders, stress and traumatic life events affect prevalence.

Introduction

Chronic abdominal pain is a common problem in childhood, with prevalence rates ranging from 0.3-19% in school-going children in the United States and Europe.[1] In almost 90% of these children, no explanatory organic cause can be identified.[2] Initially this condition was referred to as 'recurrent abdominal pain' RAP by Apley and Naish in 1957 and defined as "at least three episodes of abdominal pain, severe enough to affect their activities over a period longer than three months".[3] In 1999 the pediatric Rome II criteria introduced the term abdominal pain-related functional gastrointestinal disorders (AP-FGIDs); which include functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraine (AM), functional abdominal pain (FAP) and functional abdominal pain syndrome (FAPS).[4] In order to meet these criteria symptoms had to occur weekly, persisting for over three months before diagnosis. With the introduction of the current Rome III in 2006 this criterion was redefined to persisting symptoms two months prior to diagnosis.[5]
Children with AP-FGIDs report significantly lower quality of life (QoL) scores compared to healthy peers and AP-FGIDs are ranked as second in causing school absence[6,7] In 29.1% of patients with chronic abdominal pain, pain persists even for more than 5 years, despite frequent medical attention.[8] Furthermore, functional abdominal pain disorders in childhood have a huge economic burden, as only the diagnostic workup is approximately 6000 dollar per child in the United States.[9]

The pathogenesis underlying AP-FGIDs remains unclear.[10] Altered gut motility, visceral hypersensitivity, abnormal brain-gut interaction, psychosocial disturbance and immune activation have been suggested as possible explanation for the symptoms.[11,12] Moreover, studies conducted in the United States and Europe reported that psychological symptoms, low socio-economic status, parental gastrointestinal complaints and single parent- and immigrant-households are associated with chronic abdominal pain in children.[1,13,14]
It has been commonly believed that functional abdominal pain disorders are a more evident problem in Western populations compared to developing countries. The purpose of the current study is to perform a systematic review and meta-analysis concerning the epidemiology of functional abdominal pain disorders in children worldwide in order to summarize the existing knowledge about its prevalence, geographic, gender and age distribution. In addition, we aim to review factors associated with functional abdominal pain disorders, such as psychosocial factors, quality of life, school absence, life events and socioeconomic factors.

Methods

Search strategy and study selection

The Cochrane Library, MEDLINE, EMBASE, CINAHL and PsychInfo databases were searched, up to February 2014. Studies on functional abdominal pain disorders were identified using the following terms: chronic or functional or recurrent abdominal pain, functional gastrointestinal disorder, stomach ache, abdominal migraine, irritable bowel syndrome or functional dyspepsia (both as medical subject heading (MeSH) and free text terms). These were combined, using the set operator AND, with epidemiology studies, identified with the terms 'epidemiology, prevalence and incidence' (MeSH and free text terms). A protocol of the current systematic review, including the full search strategy is provided in the supporting information S1.
Abstracts were screened for eligibility. Potentially eligible studies were retrieved and read in full text to assess if they fulfilled all of the following inclusion criteria: (1) children aged 4-18 years; (2) with

functional abdominal pain according to the ROME I, II, III criteria, Apley and Naish criteria or defined by the presence of nonorganic abdominal pain in children with at least three episodes of abdominal pain and/or weekly episodes of abdominal pain and/or a symptom duration of at least 3 months; (3) epidemiology studies of birth cohort, school based or general population samples and (4) results reported on epidemiology, prevalence or incidence. This screening was done by two reviewers (KD and JK) independently. Disagreement between the two reviewers was resolved by consensus when possible, or by consulting a third reviewer (MT) to make the final decision.

Quality assessment

Because there is currently no gold-standard quality assessment tool for epidemiologic studies,[15] we composed a new assessment tool based on a scale for quantitative studies[16] and on a guideline for evaluating prevalence studies.[17] We screened for the following six criteria: (1) is method of subject selection described and appropriate? (2) Are subject characteristics sufficiently described, i.e. do they match the target population regarding to gender and age? (3) Is functional abdominal pain diagnosed appropriately? (4) Are the survey instruments reliable and valid? (5) Are the analytic methods described/justified and appropriate? And (6) were results reported in sufficient detail? Studies were scored to what extent they met each applicable criterion with: no, partial or yes.

Data extraction

The following information related to data collection and results was extracted and entered into an Excel (Microsoft, Redmond, WA) spreadsheet: location, sampling strategy used to identify participants, sample size, age range, definition of functional abdominal pain disorders and the overall prevalence of functional abdominal pain disorders. If available, the gender, age and geographic distribution of the prevalence, socioeconomic factors, quality of life, psychosocial factors, school absence and life events were also reported.

Statistical analyses

Meta-analysis methods were used to assess the prevalence of functional abdominal pain disorders. Either a fixed-effect model or a random-effect model was adopted to pool data according to heterogeneity. When the heterogeneity was significant, the random-effect model was applied, otherwise the fixed-effect model was used. Heterogeneity was calculated by a Cochrane *Q*-statistic, and the degree of heterogeneity was quantified by I^2 test.[18] $p<0.10$ in combination with $I^2>50\%$ indicated significant heterogeneity.[19] Additionally, subgroup analyses were conducted to assess geographical, age and gender distribution of the prevalence. Chi-square test was used to analyze age and gender associations, expressed as pooled odds ratio (OR) with 95% confidence intervals (CI). Level of significance was set at $p<0.05$. Publication bias was assessed by funnel plot and Egger's tests,[20] $p<0.05$ was considered to be statistically significant. All analyses were conducted using StatsDirect Medical Statistic Software (StatsDirect Ltd, Cheshire, England). Remaining results were reported in a descriptive way.

Results

Study selection and characteristics

We found a total of 2196 titles and abstracts. After initial evaluation, 185 were judged potentially eligible. Finally, 127 articles did not meet our inclusion criteria. Reasons for exclusion were: adult study population (n=42), not using appropriate definitions for functional abdominal pain (n=26),

irrelevant outcome measures/subject (n=14), duplication of data (n=18) and reviews, retrospective articles, abstracts or letter to the editors with insufficient information (n=27). 58 articles remained,[3,6,14,21–75] including one systematic review (SR),[34] reviewing three articles[76–78] (Figure 1).

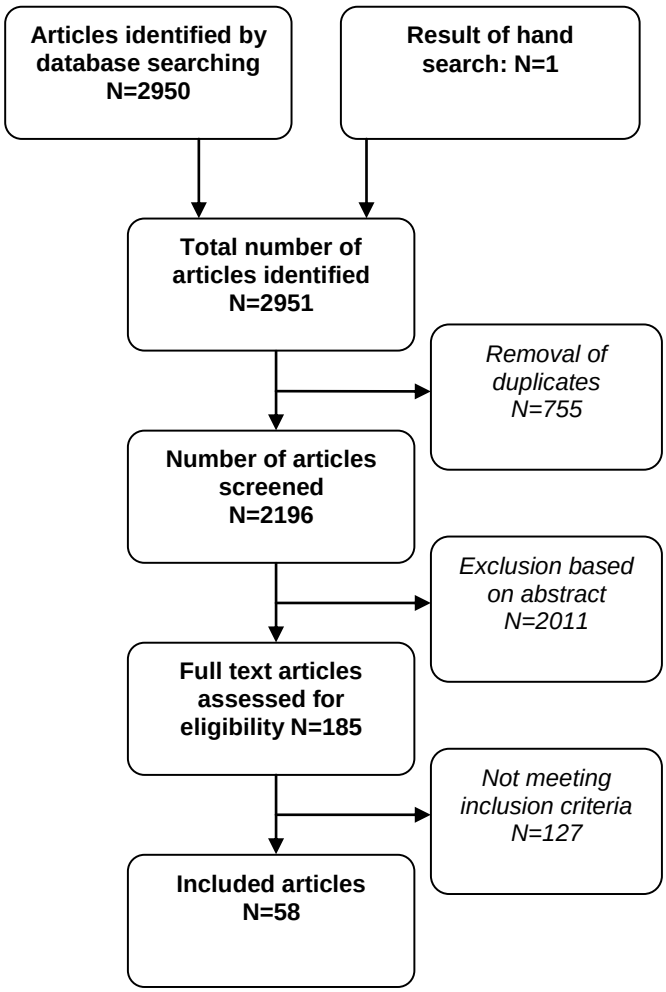

Figure 1 | Flowchart showing results of literature search and study inclusion

A total of 196,472 children with functional abdominal pain disorders were included with sample sizes ranging from 243[68] to more than 65,087.[34] Most children were recruited from school samples or birth cohorts. Several different case definitions of functional abdominal pain disorders were used, including Apley and Naish (n=18), ROME II (n=11), ROME III criteria (n=12) and self-reported functional abdominal pain disorders (n=17). Different methodologies of data collection were used among studies. Questionnaires completed by parents and/or children were mostly used to assess functional abdominal pain data (n=50). Other methods used were face-to-face interview (n=6), clinical examination (n=2) and a combination of questionnaire and interview (n=4). In one single study and in the SR the method of data collection was not clear. Table 1 presents all study characteristics of the included studies.

Due to significant heterogeneity a random effect-model was applied for all meta-analyses.

Table 1 | Characteristics of included studies

Study, year	*Country*	*Population*	*Sample size (N)*	*Age range (years)*	*Method of data collection*	*Case definition*	*Prevalence (%)*
Europe							
Gulewitsch,[22] 2013	Germany	School sample	1537	5-12y	Parental reports of QPGS-III	ROME II	7.7
Romero,[23] 2013	Spain	School sample	2575	8-16y	Child questionnaire	>3x AP in last 3 months	14.4
Luntamo,[25] 2012	Finland	School sample	2215	13-18y	Child questionnaire	Weekly AP in the last 6 months	5.6
Helgeland, [37] 2010	Norway	Birth cohort	456	14y	Questionnaire	Apley and Naish	12.7
Rask,[40] 2009	Denmark	Birth cohort	1327	5-7y	Parental interview	Apley and Naish	7.6
Alfven,[42] 2008	Sweden	General cohort	2597	10-18y	Child and parental interview	AP weekly, for >6 months	19.8
Brun,[46] 2007	Sweden	School sample	1901	9-15y	Questionnaire[a]	last 3 months AP ≥weekly	7.4
Ostberg,[47] 2006	Sweden	Welfare sample	5380	10-18y	Audio questionnaire	last 6 month AP ≥ 1 time a month	19.3
Bakoula,[74] 2006	Greece	Birth cohort	7925	7y	Parental questionnaire	AP ≥weekly	4.1
Dalh,[73] 2005	Denmark	School sample	849	9-13y	Parental questionnaire	ROME II	12.2
Tindberg,[49] 2005	Sweden	School sample	695	9-13y	Child/parent questionnaire	Apley and Naish	12.7
Kokkonen,[69] 2004	Finland	School sample	404	10-11y	Parental questionnaire and clinical examination	Apley and Naish	15.8
Groholt,[75] 2003	Scandinavia Iceland	General cohort	6040	7-17y	Child/parent questionnaire	AP weekly or every 2 weeks	8.3
Petersen,[53] 2003	Sweden	School sample	1121	6-13y	Child/parent questionnaire	AP weekly ≥6 months	19.1
Bode,[51] 2003	Germany	School sample	1143	5-8y	Parental questionnaire[a]	Apley and Naish	2.5
DeGiacomo,[55] 2002	Italy	School sample	808	6-12y	Child/parent questionnaire	ROME II	8.8
Harma,[54] 2002	Finland	School sample	15965	mean 15y	Questionnaire by students	AP weekly,≥6 months	10.0
Perquin,[59] 2000	Netherlands	School sample	4459	4-18y	Child/parent questionnaire	>3 months AP	2.6
O'Donohoe,[61] 1996	UK	School sample	640	4-13y	Parental questionnaire	Apley and Naish	14.2
Abu-Arafeh,[62] 1995	Scotland	School sample	1754	5-15y	Questionnaire and interview	Symon and Russell	3.3
Mortimer,[70] 1993	UK	General cohort	1083	3-11y	Structure interview	Apley and Naish	8.4
Lundby,[72] 1990	Denmark	School sample	648	9-12y	Questionnaire	Apley and Naish	15.4
Faull,[71] 1986	UK	School sample	439	6y	Parental questionnaire/ interview	Apley and Naish	25.1

Table 1 | Characteristics of included studies *(continued)*

Study, year	*Country*	*Population*	*Sample size (N)*	*Age range (years)*	*Method of data collection*	*Case definition*	*Prevalence (%)*
Christensen,[63] 1984	Denmark	School sample	2530	5-16y	Questionnaire	Apley and Naish	11.4
Apley,[3] 1958	UK	School sample	1000	3-15y	Mother/child interview	Apley and Naish	10.8
North America							
Stanford,[45] 2008	Canada	General cohort	2271	12-13y	Child/parent questionnaire	AP weekly in the last 6 months	19.8
Youssef,[6] 2008	USA	Longitudinal Study in Adolesc. Health	20735	13-18y	In-home interview children	2–3 episodes/week the last 12 months	14.0
Malaty,[67] 2007	USA	School sample	925	4-15y	Questionnaire	AP >3 months continuous, interfere daily life	24.0
Uc,[68] 2006	USA	Annual school physicals	243	4-17y	QPGS-RII[a] + clinical evaluation	ROME II	1.6
Hyams,[14] 1996	USA	School sample	507	12-16y	Bowel disease questionnaire[a]	Weekly AP in the last year	15.0
Sharrer,[64] 1991	USA	School sample	250	8-12y	Questionnaire parents	Apley and Naish	10.0
South America							
Saps,[21] 2014	Colombia	School sample	373	8-14y	QPGS-RIII[a]	ROME III	12.1
Silva,[35] 2011	Brazil	Birth cohort	1462	7-11y	Questionnaire	RAP for >3 months, interfering daily life	21.6
Asia							
Sagawa,[24] 2013	Japan	School sample	3976	10-17y	QPGS-RIII[a]	ROME III	12.8
Phavichitr,[26] 2012	Thailand	School sample	1181	12-19y	QPGS-RIII[a]	ROME III	24.0
Song,27 2012	Korea	School sample (girls)	820	12-17y	Child/parent questionnaire	ROME II	12.8
Zheng,[28] 2012	China	School sample	668	mean 14.8y	IBS Inventory[a]	ROME III	4.6
Zhou,[29] 2012	China	School sample	1362	12-18y	Questionnaire	ROME III	14.8
Devanarayana,[30]	Sri Lanka	School sample	1365	13-18y	QPGS-RIII[a]	ROME III	17.8
Park,[79] 2011	Korea	School sample	1877	15-18y	IBS Module[a]	ROME III	19.0
Liu,[34] 2011	China	SR	65087			ROME II	4.6-23.4
Zhou,[36] 2011	China	School sample	3671	12-18y	Questionnaire	ROME III	20.0

Table 1 | Characteristics of included studies *(continued)*

Study, year	*Country*	*Population*	*Sample size (N)*	*Age range (years)*	*Method of data collection*	*Case definition*	*Prevalence (%)*
Devanarayana,[31] 2011	Sri Lanka	School sample	2163	10-16y	QPGS-RIII[a]	ROME III	12.4
Endo,[33] 2011	Japan	School sample	2312	14-15y	ROME II questionnaire, self-reporting IBS questionnaire[a]	ROME II	15.4
Devanarayana,[32] 2011	Sri Lanka	School sample	428	12-16y	QPGS-RIII[a]	ROME III	13.7
Zhou,[38] 2010	China	School sample	2013	10-18y	Questionnaire	ROME III	20.7
Devanarayana,[43] 2008	Sri Lanka	School sample	734	5-15y	Parental questionnaire	Apley and Naish	10.5
Son,[44] 2008	Korea	School sample, (girls)	405	15-18y	unclear	ROME II	25.7
Dong,[48] 2005	China	School sample	5043	6-18y	Questionnaire	ROME II	14.2
Oh,[50] 2004	Singapore	School sample	3590	6-17y	Questionnaire	Apley and Naish	23.4
Boey,[52] 2003	Malaysia	School sample	1971	12y	Questionnaire and interview by pediatrician	Apley and Naish	23.1
Boey,[56] 2001	Malaysia	School sample	1462	9-15y	Interview by pediatrician	Apley and Naish	11.0
Boey,[57] 2001	Malaysia	School sample	1488	5-15y	Questionnaire and interview by pediatrician	Apley and Naish	9.6
Reshetnikov,[58] 2001	Siberia	School sample	449	14-17y	Bowel disease questionnaire[a]	ROME II	20.0
Boey,[60] 1999	Malaysia	School sample	148	11-12y	Parental questionnaire	≥ 3 episodes of AP for ≥ 3 months least	41.2
The Middle East							
Demirceken,[39] 2010	Turkey	Cohort general practitioner	250	5-18y	Questionnaire by child, parent and physician	ROME III	31.2
Sohrabi,[66] 2010	Iran	School sample	1436	14-19y	Questionnaire	ROME II	4.1
Telmesani,[41] 2009	Saudi Arabia	School sample (boys)	316	12-18y	Questionnaire	Apley and Naish	17.4

QPGS-RII/III: Questionnaire on pediatric gastrointestinal symptoms based on Rome II/III
[a]Validated questionnaire

Methodological quality assessment

We assessed the selection of study subjects. In 20 out of 58 studies they were not randomly selected out of a population sample. In 16 studies subjects did not match the target population appropriately, because for example only girls[27] or boys[41] were included, or because age range was limited.[33,37,45,52,69,71,74] In the majority of trials validated instruments were not used (n=41). A detailed overview of the quality scores of all individual studies is listed in the appendix.

Prevalence

In general, pooled prevalence for functional abdominal pain disorders was 13.5% (95% CI 11.8-15.3). The reported prevalence ranged widely, from 1.6% to 41.2%. The funnel plot was symmetric and Egger's linear regression test was not significant, which gives no indication for publication bias.

Pooled prevalence numbers according to the different criteria used to define its presence and validation status of the questionnaire are shown in Table 2. Highest prevalence rates were found when using the ROME III criteria. The pooled prevalence of functional abdominal pain disorder was almost identical between studies that used a validated, compared to a non-validated questionnaire (Table 2). The sub-analyses for Rome II, self-reported criteria and validated questionnaires were subject to publication bias calculated by Egger's test, p=0.04, p=0.04 and p=0.02 respectively. Nineteen out of 58 studies reported prevalence's of subtypes within AP-FGIDs (Table 2). Indication for publication bias was shown for meta-analyses of FD (Egger's test p=0.02).

Table 2 | Pooled prevalence of functional abdominal pain disorders according to criteria used to define its presence, validation status of questionnaire, subtypes of AP-FDIG and geographical location

	Number of studies	Number of subjects	Pooled prevalence (%)	95% CI	Heterogeneity	
					I^2	p value for I^2
All studies	*58*	*196.472*	*13.5*	*11.8-15.3*	*98.6*	*<0.001*
Criteria used to define abdominal pain						
Self-reported criteria	17	77,980	13.2	10.2-16.6	99.4	<0.001
Apley and Naish	18	20,176	12.9	9.9-16.2	97.7	<0.001
Rome II	11	78,989	12.2	9.3-15.5	99.0	<0.001
Rome III	12	19,327	16.4	13.5-19.4	96.6	<0.001
Validation status of questionnaire						
Validated	17	21,809	11.9	9.0-15.2	98.0	<0.001
Not validated	41	174,663	14.1	12.1-16.3	99.3	<0.001
AP-FGID subtypes						
IBS	16	28,399	8.8	6.2-11.9	98.6	<0.001
FD	9	11,516	4.5	1.2-9.9	99.2	<0.001
FAP	7	10,085	3.5	1.8-5.6	95.8	<0.001
AM	9	12.922	1.5	1.0-2.1	83.8	<0.001
FAPS	4	7,322	0.9	0.5-1.5	76.8	0.005
Geographical location						
South America	2	1,835	16.8	8.6-27.0	N/A	N/A
Asia	22	102,213	16.5	14.6-18.5	98.1	<0.001
The Middle-East	3	2,002	15.8	2.8-36.4	98.7	<0.001
North America	6	24,931	13.4	9.4-17.9	97.1	<0.001
Europe	25	65,491	10.5	8.3-12.8	98.8	<0.001

N/A; not applicable, too few studies to assess heterogeneity

Geographic distribution

The majority of studies were conducted in Europe and Asia. A few studies were performed in the Middle East, North- and South America and prevalence data for Africa and Australia are currently lacking. The pooled prevalence of functional abdominal pain disorders subdivided for each continent is provided in Table 2. The prevalence rates did not differ extremely, with lowest prevalence occurring in Europe (10.5%) and the highest in South America (16.8%). Publication bias was only shown for meta-analysis of Europe (Egger's test $p<0.01$). The prevalence per individual country studied is shown in Figure 2.

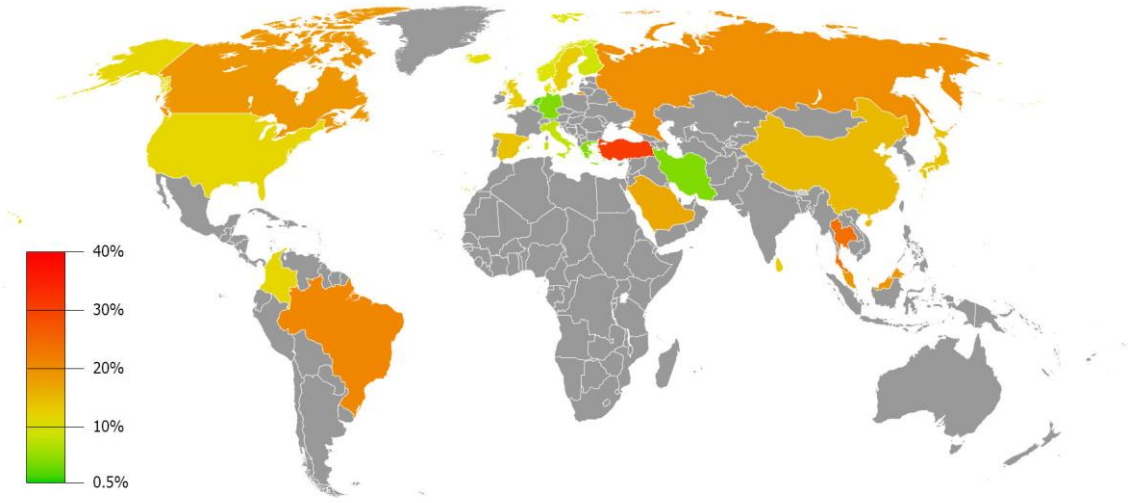

Figure 2 | Geographic distribution of functional abdominal pain in children, presented in pooled-prevalence rates

Gender prevalence

Gender prevalence was reported in 24 studies. All, but two studies,[51,70] reported a female predominance. After pooling data, a significant higher proportion of functional abdominal pain disorders among girls compared to boys was seen (15.9% vs. 11.5%, pooled OR 1.5, 95% CI 1.3-1.7, $p<0.01$). There was no evidence for publication bias by Egger's test.

Age distribution

Relationship between age and functional abdominal pain prevalence has been evaluated in 36 studies. Because different age groups were used, we were unable to pool data for all single ages separately. Therefore, data were pooled for children <12 years and ≥12 years. No significant difference was found for the prevalence of functional abdominal pain disorders in children younger than 12 years as compared to children ≥12 years old (12.4% vs. 13.8%, pooled OR 0.9, 95% CI 0.5-1.4, $p=0.62$). There was no evidence for publication bias ($p=0.26$).

Associated factors

Psychological disorders and Quality of life

Several studies reported an association between psychological factors with functional abdominal pain disorders.[22,25,28,36–38,44–46,48,54] Anxiety and depression were reported significantly more frequent among children with functional abdominal pain disorders compared to healthy children.[33,44,48,65] Furthermore one study showed that abdominal pain was a predictor of depression in 14-16 years old adolescents (girls: OR 2.4, 95% CI 2.0-2.9; boys: OR 2.3, 95% CI 1.7-3.1),[54] and vice versa, one study reported that depressive symptoms predict functional abdominal pain (OR, 2.4; 95% CI 1.1–5.1).[37]

Two studies used the Strengths and Difficulties Questionnaire to screen for psychological problems, which is a 25 item-questionnaire, divided into five scales: hyperactivity–inattention, emotional symptoms, conduct problem, peer problem, and prosocial behavior scales.[22,25] Compared to children without abdominal pain, AP-FGIDs were associated with conduct problems (OR 4.1, 95% CI 2.8–5.9),[25] which especially concerned IBS patients (p<0.05).[22]

Eigthy point five per cent of children with RAP reported school absence, at least one day during the third term of the year, compared to 44.6% of the healthy control group (p<0.01).[43] Furthermore, compared to controls, IBS patients showed significantly lower quality of life (QoL).[33,65] Park *et al*. investigated QoL with the World Health Organization QoL Scale, a 26-item questionnaire, divided into 5 subscales.[65] On each subscale (ranging between 1-5) children with IBS scored significant lower compared to non-IBS children (p<0.01); physical health (3.12 vs.3.42), mental health (2.94 vs. 3.11), social relationships (3.08 vs. 3.19), environment (3.07 vs. 3.18) and overall aspects (3.06 vs. 3.37).

Stress and Negative life events

Numerous studies showed an increase in prevalence of abdominal pain in children with high stress levels.[26,27,33,44,60,64,65] Measured on a 5-point scale (0=never, 5=always), 6.3% girls with mild stress (≤1.7 points) reported IBS, which significantly increased to 20.3% in girls with severe stress (>2.1 points).[27] In addition, mean total stress scores were significantly higher in the IBS group (119.7/200, SD 31.4) compared to healthy controls (95.9/200, SD 34.9, p=0.03), measured on a 40 items Feel Bad Scale.[60] Similarly, patients with functional abdominal pain disorders reported significantly more traumatic- or negative life events.[30,31,50,80]

Twelve point two per cent of children with AP-FGIDs experienced the death of a close family member compared to 7.7% in the control group (p<0.02).[31] Also children with AP-FGIDs reported more frequent punishment by parents (6.7% vs. 3.8%, p=0.04), frequent domestic violence (5.6% vs. 2.9%, p=0.03), parental job loss (5.2% vs. 2.4%, p=0.01) and hospitalization for another illness (16.3% vs. 9.5%, p<0.01).[31] Furthermore, any form of abuse was associated with an increase in the prevalence of functional abdominal pain. AP-FGIDs were significantly higher in those children exposed to sexual abuse (35.3% vs. 17.3%, p=0.01), physical abuse (19.7% vs. 12.6%, p<0.01), and emotional abuse (27.4% vs. 16.9%, p<0.01).[30]

Socioeconomic status

Although a lower family income and low-educated families appeared to result in a higher percentage of children experiencing functional abdominal pain disorders, in most studies this trend was not statistically significant.[22,26,27,31,49,60,67,75] Malaty *et al*. reported the prevalence of RAP in different socioeconomic geographical areas, based on percentage of children receiving free or reduced-price school lunches. Low-income areas did not show a higher prevalence of RAP compared to high-income areas (23% vs. 27%, p=0.38). On the other hand, a contrary finding was described by Groholt *et al*., who measured family income as the family's monthly disposable income and divided this into quartiles. RAP was reported in 6.6% in the highest quartile compared to 12.1% in the lowest quartile (p<0.01).[75] In the same study parental education was assessed. The prevalence of RAP was 7.8% among children living in low educated families (<9 years education) compared to 9.5% in high educated families (>12 years education), which was not significant.[75]

Discussion

This is the first systematic review focusing on the prevalence of functional abdominal pain disorders in Western populations and developing countries. Our systematic analysis of available studies shows a worldwide prevalence of pediatric functional abdominal pain disorders of 13.5%, with approximately comparable rates across the continents. Irritable bowel syndrome (IBS) was the most often reported subtype of the abdominal pain-related functional gastrointestinal disorders (AP-FGIDs). Higher prevalence rates were seen using the ROME III criteria and associations were shown with female gender, anxiety and depressive disorders, stress and traumatic life events.

Our findings are in line with a previous systematic review of Chitkara *et al.*, which reported a high prevalence of childhood recurrent abdominal pain in Western countries.[1] We found a large variation in prevalence across studies, ranging from 1.6% to even 41.2%. This might be due to the variable age groups studied, the different definitions used to classify functional abdominal pain and different type of questionnaires used. However, the pooled prevalence of studies using validated questionnaires did not differ from studies using invalidated tools (Table 2). The lowest prevalence of 1.6% was reported by Uc *et al*., though only African American children were included.[68] Other studies conducted in the USA showed a higher prevalence, ranging from 10-24%. The highest prevalence (41.2%) was reported in a small Malaysian study, including 148 children from a rural area. The authors suggested that this was due to the high prevalence of intestinal parasites in rural Malay school children.[81] In developing countries the prevalence of parasitic infections might be higher owing to potentially limited access to clean water, however, a Sri Lankan study identified parasitic infections as organic cause for RAP in only 7.7 %.[80] Indeed literature shows that an association between AP-FGIDs and amebiasis is questionable.[82,83]
Since the publication of the pediatric Rome criteria for AP-FGIDs in 1999, higher pooled prevalence rates were found regarding studies using these strict AP-FGIDs criteria, up to a prevalence of 16.4%. A Sri Lankan population study even showed that the pediatric Rome III criteria were able to diagnose FGIDs more comprehensively than Rome II.[32]

Prevalence rates range widely between countries. In addition to methodological differences, this may arise from factors such as diverse cultural, dietary, genetic, environmental conditions and different health care systems. The highest prevalence of functional abdominal pain disorders was found in a small sample of 250 Turkish children, reporting a prevalence of FD of 31%, considerably higher than the total pooled prevalence of FD (4.5%, Table 2).[39] An explanation for this high prevalence could be that children were not screened for Helicobacter pylori which might result in an overestimation. In 65% of Turkish children presenting with recurrent abdominal pain and dyspepsia an infection with H.pylori can be found. [39]
According to different continents, the pooled prevalence was more stable, though was slightly lower in European studies and generally higher in studies from South-America and Asia. This finding is in line with the observation that the Rome III criteria were able to diagnose FGIDs more comprehensively than Rome II, since most Asian studies were only recently conducted and as a result used these criteria.[32] Moreover South-America and Asia are upcoming economies, with a change in (fast)food habits, a higher expectation from children, particularly towards their school achievements,[44] and consequently higher levels of stress.

In accordance with earlier data a predominance of functional abdominal pain disorders was found in girls.[1] This dominance in girls was reported in all different continents across the world. It has been suggested that levels of sex hormones might play a role, which is supported by observations that premenopausal patients present with exacerbation of their abdominal pain symptoms at time of menses.[84] Ovarian

hormones can modulate the process of visceral pain perception and the susceptibility to stress.[85] Although younger children have not reached sexual maturity, this can apply to adolescents as well. Furthermore, females have a greater willingness to report somatic experiences, such as pain.[86] High pain profiles, indicating higher levels of pain and lower ability to cope with pain, were more often reported among girls.[87] Predominance of girls has been also described in other functional complaints, like functional constipation[88] and headache.[89,90]

In this systematic review, no association was found between age and prevalence of pediatric AP-FGIDs. Chitkara suggested a bimodal peak, between 4 and 6 year and preadolescence, in which the symptoms of abdominal pain are more prevalent.[1] More recent studies, however, showed a peak prevalence at adolescence.[23,24,27] Unfortunately due to great diversity in selected age groups among studies, we were unable to perform meta-analyses on single or narrow age groups and therefore we could not confirm these previous findings.

Epidemiological studies included in this SR showed that children with functional abdominal pain were significantly more often diagnosed with anxiety or depressive disorders compared to healthy children. Mechanisms and routes by which psychological factors affect functional abdominal pain are not fully known. Abdominal pain can cause psychological problems and conversely,[37,54] once developed abdominal pain and depression/anxiety may worsen each other. Moreover, both pain and symptoms of depression and anxiety can be the result of ineffective mechanisms of coping with stress, since low coping strategies are demonstrated in children with chronic abdominal pain.[91] Association of functional abdominal pain with stress and traumatic life events can be explained by unsuccessful coping styles as well. In addition, stressors have shown to be associated with enhanced visceral perception,[92] which is also described in pediatric IBS and RAP.[93,94] Increased responsiveness of central stress and arousal circuits and subsequently increase activity of the sympathetic nervous system can cause visceral hypersensitivity.[95]

Socioeconomic environment of the child has been reported to be a potential contributory factor to RAP.[47,75] Scandinavian studies have demonstrated that children living in low educated, low-income, worker families have higher levels of recurrent abdominal pain.[47,75] Our SR, however, reported that most studies conducted in Europe, Asia and US did not show any significant effect concerning the association between socioeconomic environment and functional abdominal pain. A recent well-conducted SR among adults, covering worldwide data, supports this latter finding.[96]

Strengths of the current study include a comprehensive and contemporaneous literature search that identified sufficient studies to allow pooling of data from almost 200,000 subjects. Because no language restrictions were applied, this is the first study which accomplishes all worldwide publications about the prevalence of pediatric functional abdominal pain. To date, a validated tool to assess the quality of epidemiological studies is lacking. Therefore a possible limitation of our study is the use of a self-made, not validated tool to assess the quality of the different epidemiological studies. Another limitation comes from the inclusion of studies using self-reported criteria for recurrent abdominal pain, since these criteria were not validated and less strict compared to the Apley and Rome criteria this can have distort the prevalence. However, our subanalyses showed the same prevalence rate in this case compared to the Apley and Rome II criteria. Interpretation of results was hampered by significant heterogeneity of included studies, due to methodological differences. To reduce this effect random effect models were used for meta-analyses. Finally, a limitation arises from the available studies and the reporting data within them. When calculating a pooled prevalence, there was a notable absence or ‘overrepresentation’ of studies conducted in certain geographical regions making it difficult to accurately estimate true global prevalence. For example, prevalence numbers from Turkey were only reflected by one small sampled study.

In summary, functional abdominal pain occurs commonly worldwide. Female gender, psychological disorders, stress and traumatic life events increase the prevalence, while age and socioeconomic state are not associated. This high prevalence worldwide and its substantial impact on patients' well-being justifies investment of resources and educational campaigns directed to prevention and optimal treatment, with special attention to psychological disorders and stress reduction.

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Appendix | Quality assessment: criteria and outcome

Quality assessment criteria

1. Is method of subject selection described and appropriate?
2. Are subject characteristics sufficiently described, i.e. do they match the target population regarding to gender and age?
3. Is functional abdominal pain diagnosed appropriately?
4. Are the survey instruments reliable and valid?
5. Are the analytic methods described/justified and appropriate?
6. Were the results reported in sufficient detail?

Quality assessment outcome

Study, year	***1.***	***2.***	***3.***	***4.***	***5.***	***6.***
Abu-Arafeh,(62) 1995	2	2	2	1	2	1
Alfven,(42) 2008	1	1	2	1	2	1
Apley,(3) 1958	2	2	2	1	2	2
Bakoula,(74) 2006	2	2	2	2	2	1
Bode,(51) 2003	2	2	2	1	2	1
Boey,(52) 2003	2	2	2	1	2	1
Boey,(56) 2001	2	2	2	1	2	1
Boey,(57) 2001	1	2	2	1	2	2
Boey,(60) 1999	2	1	2	1	2	1
Brun,(46) 2007	2	2	2	2	2	1
Christensen,(63) 1984	1	2	2	1	2	2
Dalh,(73) 2005	1	2	2	1	2	2
De Giacomo,(55) 2002	2	2	2	1	2	1
Demirceken,(39) 2010	1	2	2	2	2	1
Devanarayana,(30) 2012	2	2	2	2	2	2
Devanarayana,(31) 2011	2	2	2	2	2	2
Devanarayana,(32) 2011	2	2	2	1	2	2
Devanarayana,(43) 2008	2	2	2	2	2	2
Dong,(48) 2005	2	2	2	1	2	1
Endo,(33) 2011	2	1	2	2	2	2
Faull,(71) 1986	2	1	2	1	1	1
Groholt,(75) 2003	2	2	2	1	2	2
Gulewitsch,(22) 2013	1	1	2	2	2	2
Harma,(54) 2002	2	1	2	1	2	1
Helgeland, (37) 2010	2	1	2	1	2	1
Hyams,(14) 1996	1	1	2	2	2	1
Kokkonen,(69) 2004	2	1	2	1	2	1
Liu,(34) 2011	1	2	2	1	2	2
Lundby,(72) 1990	1	2	2	1	2	2
Luntamo,(25) 2012	2	1	2	1	2	1
Malaty,(67) 2007	1	2	2	1	2	2
Mortimer,(70) 1993	2	2	2	1	2	2
O'Donohoe,(61) 1996	1	2	2	1	2	2
Oh,(50) 2004	2	2	2	1	2	1
Ostberg,(47) 2006	2	2	2	1	2	1
Park,(96) 2011	1	2	2	2	2	2

Perquin,(59) 2000	2	2	2	1	2	1
Petersen,(53) 2003	2	2	2	1	2	2
Phavichitr,(26) 2012	1	2	2	2	2	1
Rask,(40) 2009	2	1	2	1	2	1
Reshetnikov,(58) 2001	2	2	2	2	2	1
Romero,(23) 2013	2	2	2	1	2	1
Sagawa,(24) 2013	2	1	2	2	2	2
Saps,(21) 2014	1	2	2	2	2	1
Sharrer,(64) 1991	2	2	2	1	2	2
Silva,(35) 2011	2	2	2	1	2	1
Sohrabi,(66) 2010	2	2	2	2	2	2
Son,(44) 2008	1	1	2	1	2	2
Song,(27) 2012	1	1	2	1	2	2
Stanford,(45) 2008	2	1	2	1	2	1
Telmesani,(41) 2009	1	1	2	1	2	1
Tindberg,(49) 2005	1	2	2	1	2	1
Uc,(68) 2006	1	2	2	2	2	1
Youssef,(6) 2008	2	2	2	1	1	1
Zheng,(28) 2012	1	2	2	2	2	1
Zhou,(29) 2012	2	2	2	1	2	1
Zhou,(36) 2011	2	2	2	1	2	2
Zhou,(38) 2010	2	2	2	1	2	2

No=0 points; partial=1 point; yes=2 points

Chapter 3

Glucose hydrogen breath test for small intestinal bacterial overgrowth in children with abdominal pain-related functional gastrointestinal disorders

Judith J. Korterink, Marc A. Benninga, Herbert M. van Wering, Judith M. Deckers-Kocken

J Pediatr Gastroenterol Nutr. 2014 nov 17

Abstract

Objectives

A potential link between small intestinal bacterial overgrowth (SIBO) and abdominal pain-related functional gastrointestinal disorders (AP-FGID) has been suggested by symptom similarities and by the reported prevalence of SIBO in children with irritable bowel syndrome and functional abdominal pain. The aim of this study is to evaluate the prevalence of SIBO using the glucose hydrogen breath test (GHBT), in a cohort of Dutch children with AP-FGIDs fulfilling the Rome III criteria, and to identify potential predictors.

Methods

Children aged 6 to 18 years with AP-FGIDs fulfilling the ROME III criteria were included. All children underwent a GHBT. SIBO was diagnosed if the fasting breath hydrogen concentration was ≥ 20 ppm or if an increase of H2 levels of ≥ 12 ppm over the baseline value was measured after ingestion of glucose. Gastrointestinal symptoms were collected using a standardized abdominal pain questionnaire.

Results

161 Dutch children with AP-FGIDs were enrolled. 23 patients (14.3%) were diagnosed with SIBO, as assessed by GHBT. 78% of the children diagnosed with SIBO had fasting hydrogen levels above 20 ppm. Irritable bowel syndrome (IBS) was significantly more found in children with SIBO compared to children without SIBO (p=0.001). An altered defecation pattern (i.e. change in frequency or form of stool) (p=0.013), loss of appetite (p=0.007) and belching (p=0.023) were significantly more found in children with SIBO compared to those without SIBO.

Conclusion

SIBO is present in 14.3% of children presenting with AP-FGIDs. IBS, altered defecation pattern, loss of appetite and belching were predictors for SIBO in children with AP-FGIDs.

Introduction

Functional gastrointestinal disorders (FGIDs) in children and adults are among the most frequent reasons to visit a healthcare provider[1, 2] and have a high impact on healthcare costs.[3] Abdominal pain-related functional gastrointestinal disorders (AP-FGIDs) is a subgroup of FGIDs and affects approximately 20% of school-going children in the United States and Europe.[1] AP-FGIDs are best discribed by the ROME III criteria[4] and include functional abdominal pain (FAP), irritable bowel syndrome (IBS), functional abdominal pain syndrome (FAPS), functional dyspepsia (FP) and abdominal migraine (AM). The pathophysiological mechanisms underlying these AP-FGIDs are not completely understood.[5] Altered gut motility, visceral hypersensitivity, abnormal brain-gut interaction, differences in the microbiome, psychosocial disturbance and immune activation have been suggested to play a role in these children.[6, 7] Saps et al.[8] found a significant increase in the risk of developing FGIDs in children after a bacterial gastrointestinal infection.

Recent studies have pointed to increased microbial levels in the small intestine as a mechanism for generating symptoms in children with IBS and FAP.[9] An abnormally high microbial population level in the small intestine is known as small intestinal bacterial overgrowth (SIBO). This condition is the result of a retrograde shift of the native bacterial population of the large intestine.[10] The expansion of bacteria into the small intestine usually leads to bloating, diarrhea and abdominal discomfort or pain.[11] Similar symptoms can be found in children with AP-FGIDs. It has been demonstrated that adult patients [12] as well as pediatric patients[9] suffering from IBS or FAP have a higher prevalence of abnormal microbial fermentation compared to healthy controls. These data, further supports the hypothesis that SIBO may play a role in AP-FGIDs.

Conventionally, the diagnosis of SIBO has been based on a jejunal aspirate and culture,[13] but this technique is invasive and due to the limited access of the instrumentation, patients with isolated distal SIBO remain undiagnosed.[11] Although the accuracy is still controversial, noninvasive hydrogen breath tests using lactulose or glucose have been widely used as a diagnostic tool to establish SIBO.[14,15] A greater diagnostic accuracy is demonstrated for glucose hydrogen breath test (GHBT), because the lactulose hydrogen breath test (LHBT) has more false positive results in comparison to the GHBT.[15, 16]
So far, no study has assessed the prevalence of SIBO using a GHBT, in children with AP-FGIDs fulfilling the ROME III criteria. The aim of this study is to demonstrate the prevalence of SIBO in children with AP-FGIDs by using the GHBT and to identify potential predictors of SIBO in children with AP-FGIDs.

Materials and methods

Study Population

We conducted a prospective cohort study among consecutive children with abdominal pain, ages 6 to 18 years, referred to the outpatient clinic of a secondary hospital in Den Bosch and Breda, The Netherlands. A standardized abdominal pain questionnaire was used to establish the medical history. Furthermore demographic data of all subjects were recorded as well as information about medication use and type of feeding (breast or formula) during infancy.
All of the children fulfilling the Rome III criteria for AP-FGIDs subsequently underwent a GHBT. Organic causes of abdominal pain such as inflammatory bowel disease, coeliac disease and infection were excluded by blood and fecal analyses. Subjects with predisposing conditions of SIBO (e.g. hypothyroidism, diabetes mellitus, scleroderma, gut anatomic abnormalities) and subjects who had taken

antibiotics or probiotics within the preceding 4 weeks of the test were excluded. The local Medical Ethics Committee waived the need for informed consent.

Glucose Hydrogen Breath Test (GHBT)

Evaluation of SIBO was done by GHBT. To minimize and give stable values of basal H_2 excretion, subjects were instructed to take a carbohydrate-restricted dinner the day before the test and to be fasting for 12 hours before the test. Before the start of the GHBT, patients brushed their teeth and did a mouthwash with chlorhexidine 20 mL at 0.05%. The test was rescheduled when preparation was not proper. End-expiratory breath samples were collected. At the start of the test, fasting breath hydrogen was measured twice; the mean value was taken as the basal breath hydrogen. After ingesting a solution of 2 g/kg glucose (maximum 50 gram) in 200 mL of water, every 15 minutes for 2 hours end-expiratory breath samples were collected.[16] Breath samples were analyzed immediately for H_2 using a Gastrolyzer (Bedfont Scientific Ltd., United Kingdom). Results were expressed as parts per million (ppm). GHBT was considered as indicative of the presence of SIBO when fasting breath hydrogen concentration was ≥ 20 ppm or H_2 levels increased ≥ 12 ppm over the baseline value.[17-19]

Statistical Analysis

For continuous variables, data are expressed as mean ± standard deviation. Categorical variables are expressed as percentages. Comparison of continuous variables was done by an independent samples *t*-test for normally distributed data or a Mann-Whitney *U* test for non-normally distributed data. For comparison of categorical variables, a Pearson chi-square test or Fisher exact test was used. Using a univariate logistic regression, odds ratios for the relationship between SIBO and different diagnoses of AP-FDIG were calculated. All statistical tests were 2-tailed, and $p<0.05$ was considered statistically significant. The data were analyzed using IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.

Table 1 | Patient characteristics of patients with AP-FGIDs with and without SIBO

	SIBO+ *N*=23	**SIBO- *N*=138**	**Significance (*p*-value)**
Demography			
Mean age, years (SD)	14.1 (2.8)	12.4 (3.0)	0.010[a] (-3.08, -0.43)
Female	20 (87.0%)	98 (71%)	0.110
Mean BMI[2] (SD)	19.6 (3.12)	19.04 (3.86)	0.523 (-2.27, 1.16)
Duration of symptoms			
> 6 months	19 (82.6%)	117 (84.8%)	0.760
Diagnosis			0.009[ab]
Irritable bowel syndrome	16 (69.6%)	48 (34.8%)	0.002[a]
Functional abdominal pain	1 (4.3%)	30 (21.7%)	0.082
Functional dyspepsia	2 (8.7%)	18 (13%)	0.741
Abdominal migraine	0 (0%)	0 (0%)	-
Functional AP syndrome	4 (17.4%)	42 (30.4%)	0.200
Medication			
Laxatives	7 (30.4%)	32/133 (24.1%)	0.543
PPI	1 (4.3%)	3/133 (2.3%)	0.999

[a] Difference in groups was significant p≤0.05

[b] Using a univariate logistic regression

PPI=proton pomp inhibitor; SIBO=small intestinal bacterial overgrowth

Results

Patient population

Between February 2012 and October 2013, 161 Dutch children fulfilling the ROME III criteria for AP-FGIDs were enrolled in this study. SIBO was diagnosed in 23 patients (14.3%). Patient characteristics are presented in Table 1 and 2. Patients in the SIBO+ group were significantly older and more often diagnosed as having IBS. Type of feeding during infancy was recorded from 80 patients; 4 out of 9 patients (44.4%) of the SIBO+ group and 34 out of 71 patients (47.8%) of the SIBO- group received breast-feeding for at least two months.

Clinical characteristics

Fatigue (75%) was the most prevalent symptom found in the SIBO+ group, followed by an altered defecation pattern (71.4%), nausea (68.2 %) and bloating (66.7%). Altered defecation pattern (i.e. change in frequency or form of stool), loss of appetite and belching were significantly more found in patients with SIBO compared to those without SIBO. Surprisingly, no significant difference between the two groups was found with respect to the prevalence of diarrhea and flatulence.

Table 2 | Clinical features of patients abdominal pain-related FGIDs with and without SIBO

	SIBO+ No. of patients		**SIBO- No. of patients**		**Significance (*p*-value)**
Clinical features[a]					
Abdominal pain	23/23[b]	100%	138/138	100%	N/A
Fatigue	15/20	75.0%	69/122	56.6%	0.120
Altered defecation pattern	15/21	71.4%	57/136	41.9%	0.012[c]
Nausea	15/22	68.2%	65/125	52.0%	0.160
Bloating	14/21	66.7%	62/121	51.2%	0.191
Cramps	12/19	63.2%	70/117	59.8%	0.783
Diarrhea / loose stools	13/23	56.5%	48/136	35.3%	0.053
Loss of appetite	11/21	52.4%	32/132	24.2%	0.008[c]
Belching	10/21	47.6%	28/121	23.1%	0.019[c]
Flatulence	9/19	47.4%	58/123	47.2%	0.986
Constipation	10/23	43.5%	47/136	34.6%	0.409
Pyrosis	5/15	33.3%	32/79	40.5%	0.602
Sleeplessness	5/19	26.3%	43/113	38.1%	0.325
Vomiting	4/19	21.1%	11/131	8.4%	0.101
Fecal blood loss	4/21	19.0%	10/138	7.2%	0.093
Weight loss	4/21	19.0%	9/134	6.7%	0.090
Mucus	3/21	14.3%	10/137	7.3%	0.384

[a] Some children reported more than one symptom

[b] number of positive cases/known cases

[c] Difference in groups was significant p≤0.05

SIBO=small intestinal bacterial overgrowth

GHBT results

Results of the GHBT are given in Table 3. A fasting hydrogen level above 20 ppm was found in 18 children of the SIBO+ group, with a mean level of 26.2±5.7 ppm (range 20-40 ppm). Six children were diagnosed with SIBO after a rise of ≥ 12 ppm (mean rise 16.5±7.8 ppm, 12-25 ppm) over baseline during

the GHBT, of whom one also had a fasting level >20 ppm. In all, but one child, peak hydrogen levels were reached within 30 minutes in the SIBO+ group.

Table 3 | Results of GHBT in patients with and without SIBO with and without SIBO, specified into AP-FGID subtypes

	Fasting level (ppm) (range)	**Maximum H_2 (ppm) (range)**	**Increase from baseline (ppm) (range)**
SIBO + (n=138)	*21.5±10.4 (1-40)*	*26.0±10.0 (8-51)*	*4.6±10.2 (-18-25)*
IBS (n=16)	20.3±10.6 (1-36)	24.8±8.6 (13-39)	4.4±10.5 (-18-20)
FAP (n=1)	25	8	-17
FD(n=2)	25.5±2.1 (5-40)	29±5.9 (25-33)	3.5±3.5 (1-6)
FAPS (n=4)	23.3±14.4 (24-27)	34.3±11.9 (23-51)	11±10.2 (1-25)
SIBO – (n=23)	*6.3±4.3 (0-19)*	*7.9±4.9 (1-25)*	*1.8±2.3 (-5-8)*
IBS(n=48)	5.8±4.1 (1-19)	8.0±5.0 (2-25)	2.2±2.5 (-5-7)
FAP (n=30)	5.0±3.9 (0-15)	6.6±5.0 (1-19)	1.6±2.1 (-4-6)
FD (n=18)	6.4±4.5 (1-15)	7.9±4.8 (2-20)	1.4±2.5 (-5-5)
FAPS (n=42)	7.2±4.6 (0-18)	8.9±4.7 (1-20)	1.7±1.9 (-2-8)
Significance (p-value)[a] SIBO+ vs. SIBO-	<0.001	0.03	<0.001

Numbers are means±SD

[a]Using a Mann-Withney U test

Discussion

This study showed that SIBO, using the GHBT, was found in 14.3% of Dutch children with AP-FGIDs. SIBO was more prevalent in children with IBS compared to the other AP-FGIDs. In addition, an altered defecation pattern, loss of appetite and belching were significantly more found in children with SIBO compared to those without SIBO.

Wide variations in prevalence rates of SIBO have been reported in adults and children with IBS ranging from 4% to 91%.[9, 20] These variations may be explained by the use of different diagnostic tests to establish SIBO and different diagnostic criteria for IBS. A study by Rana et al.[21] demonstrated that 34.4% of their IBS patients had a positive lactulose hydrogen breath test (LHBT), whereas only 6.2% of these patients were positive on a GHBT, underlining a lack of discriminatory utility of LBT for SIBO in IBS patients and controls. Furthermore, Yu *et al.* demonstrated that an abnormal LHBT in IBS patients indicated variations in oro-caecal transit time rather than the rise in hydrogen could be explained by SIBO.[22] The prevalence of SIBO in children with AP-FGIDs (14.3%) using GHBT found in this study was lower compared to other studies using the GHBT. Previous studies showed prevalence numbers of SIBO up to 31% in adult IBS patients[23] and 34% among pediatric patients.[24] The difference between our results and the latter pediatric study might be because Boissieu *et al.* enrolled patients with chronic diarrhea, and therefore could have a higher pretest probability of SIBO.[24]

As shown in this study, children with an altered defecation pattern, belching and loss of appetite were significantly more likely to have SIBO, as well as those who were older and diagnosed as having IBS. An altered defecation pattern was not mentioned before as a predictor of SIBO, although several studies have demonstrated SIBO in patients with either IBS-diarrhea or IBS-constipation.[25-27] It has been hypothesized that during the digestion of carbohydrates osmotically active byproducts are produced, which promote osmotic diarrhea.[14] On the contrary, constipation is suggested to be a result of the production of methane, which might lead to a slower small intestinal transit time.[28, 29] To our knowledge, there is no previous published clinical evidence that SIBO is more common in patients complaining of either belching or a loss

of appetite. Abnormal gastrointestinal flora has been demonstrated to produce excessive intestinal gas which may explain the increased number of patients complaining of belching in our study.[20, 30] We have no good explanation why more children experienced loss of appetite.

This study showed that SIBO was more prevalent in patients with IBS. This higher prevalence might be attributed to an altered intestinal microbiota in children with IBS. Using16S metagenomics by PhyloChip DNA hybridization and deep 454 pyrosequencing, children with IBS yielded greater proportions of the phylum Proteobacteria, the class γ-Proteobacteria, and genera such as *Dorea* (member of Firmicutes) and *Haemophilus* (member of γ-*proteobacteria*) compared to healthy controls.(37) Increased levels of the *Veillonella* specie have been putatively associated with IBS symptoms and SIBO.[31]

It is remarkable that most of our patients diagnosed with SIBO, exhibited high basal H_2 levels. To define SIBO based on fasting hydrogen level above 20 ppm is controversial because of the possibility of representing an improper test preparation.[32, 33] The preparation rules, in our study, however were maintained strictly. In accordance with the landmark study by Perman *et al.*, in healthy subjects a carbohydrate-restricted dinner resulted in uniformly low fasting breath hydrogen values, where as in patients with bacterial overgrowth, the fasting breath hydrogen remained elevated.[34] Therefore, this finding, despite an appropriate dietary preparation before the test, can be a useful indication of the presence of SIBO.[24, 35]

The strength of this study is the use of a well-defined AP-FGIDs population using the ROME III criteria and the first time the GHBT is used to define SIBO in a large cohort of children with AP-FGIDs. A limitation derives from the fact we did not measure the methane concentration in the breath samples, underestimating the prevalence of SIBO because methane production may be associated with constipation.[36] Secondly, 8 to 27% of humans do not have detectable H_2 production from their gastrointestinal microbiota, but instead produce methane.[37] On the contrary, Rana *et al.* concluded that methane does not make any significant difference for the investigation of SIBO among IBS patients.[21] In addition, it has been shown that IBS patients produce less methane compared to healthy controls.[21, 38] Furthermore, glucose is completely absorbed in the proximal small intestine; it is conceivable that patients who have distal SIBO might be missed by the GHBT.[32] The clinical relevance of such findings, however is questionable, as the distal ileum is normally colonized with 10^{5-8} cfu/ml.[39, 40] Hence, it is important to know that GHBT can underestimate SIBO, but it is unlikely to overestimate SIBO. Lastly, the confinement to a symptomatic group of patients did not allow us to compare our findings with healthy controls, which is another drawback of the present study. In previous studies the GHBT, however, showed no abnormalities and no elevated fasting levels in 2 small samples of healthy control children.(24, 40) Moreover, a GHBT performed in healthy adults showed significantly less abnormalities (21, 38) and significantly lower baseline levels compared to adult patients with IBS.(38,[41]

In conclusion, based on our findings, SIBO is less common among Dutch children with AP-FDIG than reported in the literature, with a prevalence of 14.3%. So far, there is insufficient evidence to justify the routine exclusion of SIBO in children with AP-FGIDs. GHBT incorporated in the diagnostic work up of AP-FGIDs should, however, be considered in children with IBS, an altered defecation pattern, loss of appetite and belching, which seem predictors for SIBO. Given the imperfect nature of breath tests, more work is needed to better understand the role of the microbiota in the development of gastrointestinal symptoms. Defining the microbiome in children with AP-FGIDs can help to identify which children with AP-FGIDs could benefit from therapeutic manipulation of gut microbiota, using antibiotics or probiotics.

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Chapter 4

Dientamoeba fragilis and chronic abdominal pain in children: a case-control study

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Abstract

Background

The association between *Dientamoeba (D.) fragilis* and the etiology of functional gastrointestinal disorders (FGIDs) in children is unclear.

Aim

The aim of this retrospective case-control study is to clarify the clinical relevance of *D. fragilis* in children with chronic abdominal pain.

Methods

From April 2011 until April 2013 a total of 132 patients with chronic abdominal pain (AP), aged 8-18 years, referred to a non-academic hospital, and 77 control patients, aged 8-18 years without gastrointestinal symptoms referred to a psychiatric hospital, were included in the study. *D. fragilis* was diagnosed by real-time PCR in fecal samples. Symptomatic children without a *D. fragilis* infection fulfilled the ROME III criteria for AP-related FGIDs (AP-FGIDs). Clinical data were retrospectively analyzed by examining patients' hospital records from the Jeroen Bosch Hospital and Herlaarhof in The Netherlands.

Results

D. fragilis was detected in 57 patients with chronic AP (43.2%) and in 39 controls (50.6%) (p=0.255). No significant differences in symptomatology were found between *D. fragilis*-infected children and children fulfilling the criteria for AP-FGIDs. Parasitological eradication was achieved in 61.7% of patients after treatment with metronidazole or clioquinol, while clinical improvement occurred in only 40.4% of patients (p=0.435).

Conclusions

There were no differences in symptoms comparing children with and without D. *fragilis* infection. Furthermore, no relation was found between clinical and microbiological response after treatment for *D. fragilis*. This retrospective study suggests that there is no association between chronic AP and *D. fragilis* infection.

Introduction

With a prevalence of 15%, chronic or recurrent abdominal pain (AP) is a major problem in school-aged children in the US and Europe resulting in school absence and frequent medical consultation.[1-4] In the majority of children, no explanatory organic cause for their abdominal pain can be identified.[5] Children suffer either from pain in the upper abdomen or from abdominal discomfort in the lower abdomen with or without an altered stool pattern. These different characteristics of abdominal pain are described in the Rome III AP-related functional gastrointestinal disorders (AP-FGIDs).[6] The pathogenesis of AP-FGIDs remains unclear, although several mechanisms have been proposed, such as altered gut motility, visceral hypersensitivity, abnormal brain-gut interaction, psychosocial disturbance and immune activation.[7, 8] Another pathophysiological mechanism that has been proposed to underlie functional abdominal pain is an infection with *Dientamoeba (D.) fragilis.*[9-13]

D. fragilis is a flagellated protozoan found worldwide in the human gastrointestinal tract.[11, 14, 15] Neither its epidemiology nor its transmission route is completely known.[14, 16] Prevalence rates vary widely from 0.4% to 52% depending on the population studied and diagnostic method used.[11, 14, 15] *D. fragilis* infection is diagnosed most commonly at ages below 20 years, with a peak in children approximately 7 years of age.[17-23] Probably due to adaptive immunity,[23] children might be more susceptible to dientamoebiasis and, when infected, present with clinical symptoms, that is AP and diarrhea, more often than adults.[17, 19, 24-26]

Since the first description of this parasite in 1918 by Jepps and Dobell,[27] its clinical relevance has been controversial. Most researchers assume *D. fragilis* as a pathogen[9, 11, 16, 17, 19, 21, 22, 25, 28-30] because many studies show that in the setting of *D. fragilis* infection, gastrointestinal symptoms often subside after antimicrobial eradication.[11, 14, 22, 24, 30, 31] On the other hand, some consider it a commensal organism[27] because *D. fragilis* is frequently found in asymptomatic individuals.[26, 31] Also, *D. fragilis* infection could have a self-limiting character because clinical improvement has been observed without treatment.[26, 32]
Considering *D. fragilis* as a pathogen, by definition the parasite should either be excluded or eradicated before the diagnosis of an AP-FGID can be made. Therefore, elucidation of the clinical relevance of dientamoebiasis in children suffering AP-FGIDs is important.
For that reason the first objective of the present study was to investigate the prevalence of D. *fragilis* in a population referred for chronic AP and in a population without AP. The second aim of the study was to compare symptomatology between children with chronic AP and children fulfilling the AP-related Rome III criteria. Lastly, we investigated the association between chronic AP and the extent of *D. fragilis* infection, in terms of symptomatology, parasitical load and treatment.

Materials and methods

Patient population

This study is a retrospective case-control study performed at a non-academic center, the Jeroen Bosch Hospital in The Netherlands. Since April 2011 the triple feces test for detecting *D. fragilis* has been replaced in our hospital by the diagnostically superior PCR.[33, 34] All patients attending the outpatient clinic with chronic AP between April 2011 and April 2013 were eligible for inclusion when they were aged between 8 and 18 years, had symptoms of AP at least once per week for at least 2 months, and had no evidence of an inflammatory, anatomic, metabolic or neoplastic process that could explain the symptoms, that is, physical examination and laboratory tests were normal. Stool PCR on parasites was performed, and patients infected with Giardia lamblia, Entamoeba histolytica or Cryptosporidium species were

excluded. Patients with a Blastocystis species were not excluded, because until now Blastocystis species has not been associated with clinical symptoms[35, 36] and, therefore not considered as a pathogen. Patients referred to the psychiatric hospital Herlaarhof in Vught, The Netherlands, served as controls as they did not present with somatic symptoms. To reduce the risk of missing an underlying gastrointestinal complaint in all children suspected of a psychiatric problem, children were screened comprehensively by an experienced general pediatrician. A standardized history and a thorough physical examination were performed. Furthermore, blood and stools were routinely collected in all admitted patients and were examined in the same laboratory as the children in the study group. Since no abnormalities were detected, these children were considered physically healthy and, therefore suitable as a control group. Patients on antiparasitic treatment were excluded from the study.
Ethics approval was not necessary due to the retrospective nature of the study.

Data collection

Clinical data were extracted from patients' records. The following information was recorded: AP, loose stools, constipation, nausea, vomiting, ructus, flatulence, bloating abdomen, abdominal cramps, blood or mucus in stool, changed stool pattern, fatigue, weight loss, anorexia, fever, sleeplessness and other functional symptoms like headache, back pain or neck pain. Presence of eosinophilia, defined as peripheral blood eosinophilic leukocytes ≥0.4 x 10^9/l was recorded. Cycle threshold (Ct) values of parasitic DNA load before and after treatment were recorded to measure the quantity of *D. fragilis* in the colon. Antiparasitic treatment of choice, dosage and duration of treatment were noted. Clinical response was defined by patient or parental-reported improvement of AP and altered stool pattern. Microbiological response was defined by a negative stool PCR after treatment. Clinical and microbiological responses were evaluated approximately 2 months after treatment was finished.

Microbiological analysis

Laboratory detection of *D. fragilis*, Blastocystis species, Giardia lamblia, Entamoeba histolytica and Cryptosporidium species was performed by real-time PCR as previously described by Stark *et al*.[34]

Data analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) V.19.0.0. For continuous variables, data were summarized as mean ± SD. Categorical variables are expressed as percentages. With regard to the continuous variables, we first judged for fit to the normal distribution by using stem-and-leaf plots and quantile-quantile plots. Comparison of continuous variables was done by an independent samples *t* test for normally distributed data, or a Mann-Whitney U test for non-normally distributed data. As part of the t test analysis, the Levene's F test for equality of variances was used to test the assumption of equality of variances. For comparison of categorical variables, a logistic regression analysis, Pearson χ^2 test or Fisher's exact test were used. All statistical tests were 2-tailed, and $p<0.05$ was considered statistically significant. For significant group differences at baseline, interaction was assessed. The interaction terms were formed by multiplication of the two parameters involved. When an interaction effect showed a *p*-value <0.10, stratified analysis were performed.

Results

Demographic characteristics

A total of 135 patients fulfilled the inclusion criteria of chronic AP. Three children were excluded because of infection with other parasites than *D. fragilis* and Blastocystis species.

Eighty patients without gastrointestinal symptoms, admitted to a psychiatric hospital, were eligible as controls, of which three were excluded because they were on antiparasitic treatment and, therefore, assumed to have gastrointestinal symptoms. As shown in Table 1 significantly more males were included in the control group. Except for coinfection with Blastocystis species, no other pathogenous parasites were isolated from the stools.

Table 1 | Patient characteristics of symptomatic and asymptomatic patients with and without *D. fragilis* (DF) infection

	Symptomatic		**Asymptomatic**		**Significance**
	With DF	**Without DF**	**With DF**	**Without DF**	***p*-value (95%CI)**
Number of patients	57	75	39	38	
Demography					
Mean age (years)	11.19	13.15	10.92	13.39	0.697 (-0.949-0.969)*
Range	8-17	8-17	8-18	7-16	
Male (%)	23 (40.4)	26 (34.7)	26 (66.7)	27 (34.7)	<0.001*
Infection					
Dientamoeba (%)	43.2		50.6		0.296
Blastocystis spp. (%)	40.4		35.9		0.660

* Difference between symptomatic and asymptomatic patients

Prevalence of *D. fragilis* infection

D. fragilis was demonstrated on stool PCR in 57 patients with chronic AP (43%), whereas, it was negative in 75 patients (57%). In the control group, *D. fragilis* was found in 51% of the cases. As shown in Table 1, the prevalence of *D. fragilis* did not significantly differ between children with chronic AP and asymptomatic controls. As the groups showed a different gender distribution at baseline, a logistic regression analysis including an interaction term (gender x setting) was performed. Regression analysis revealed a non-significant p value (p=0.465) for the interaction term.

Clinical characteristics of symptomatic patients

As summarized in Table 2, presence of individual symptoms often related to AP-FGIDs such as bloating, nausea, altered defecation frequency, constipation and flatulence was not significantly affected by presence of *D. fragilis* infection. Other functional complaints (i.e. headache, back pain or neck pain) were significantly more found in children with AP-FGIDs, and eosinophilia in children with chronic AP and a D. *fragilis* infection. Fatigue (59.4%) was found the most prevalent symptom in the D. *fragilis* group, followed by bloating (58.7%) and nausea (50.9%). In total 53.8% of the patients reported school absence more than once a month and 30.3% even once a week. No association was found in duration of symptoms between children with chronic AP and a D. *fragilis* infection and children suffering AP-FGIDs (p=0.406).

Parasitic DNA load

There was no statistically significant difference regarding parasitic DNA load between symptomatic and asymptomatic infected children, Ct values were, respectively, 24.28 and 24.53 (p=0.830).

Microbiological and clinical response

A total of 52 out of 57 patients received antiparasitic treatment of which 39 patients were treated with metronidazol and 8 with clioquinol. For five patients, treatment data were not available. Of the patients treated with either metronidazole or clioquinol, 14 (35.9%) and 5 patients (62.5%) reported improvement of symptoms, respectively (p=0.163). In 23 patients treated with metronidazole (59.0%) and 6 patients treated with clioquinol (75%), there was a microbiological response, that is, PCR for D. *fragilis* was

negative after treatment (p=0.396). There was no association between clinical and microbiological response in patients with chronic AP treated for D. *fragilis* regardless which medication was used (p=0.435).

Table 2 | Clinical features of symptomatic patients with and without *D. fragilis* infection

	Chronic AP and *D. fragilis* infection Number of patients*		**AP-FGIDs Number of patients**		**Significance *p*-value**
Clinical features†					
Abdominal pain	57/57	100%	75/75	100%	N/A
Fatigue	22/37	59.4%	30/49	61.2%	0.205
Bloating	27/46	58.7%	41/70	58.8%	0.989
Nausea	28/55	50.9%	44/74	59.5%	0.333
Altered defecation frequency	29/57	50.9%	38/75	50.7%	0.981
Cramps	29/57	50.1%	40/75	53.3%	0.780
Diarrhea / loose stools	26/57	45.6%	26/75	34.7%	0.202
Sleeplessness	17/39	43.6%	19/47	40.4%	0.245
Ructus	19/49	38.8%	19/73	26.0%	0.136
Flatulence	19/51	37.3%	37/75	49.3%	0.180
Other functional complaints	19/55	34.5%	43/75	57.3%	0.010‡
Constipation	14/57	26.3%	25/75	33.3%	0.274
Anorexia	13/53	24.5%	14/73	19.2%	0.470
Vomiting	11/55	20.0%	6/71	8.5%	0.060
Fever	1/6	16.7%	0	N/A	0.205
Weight loss	5/37	13.5%	6/67	9.0%	0.469
Mucus	6/46	13.0%	6/64	9.4%	0.543
Fecal blood loss	4/47	8.5%	6/64	9.4%	0.875
Microbiological features					
Eosinophilia	11/44	25.0%	5/58	8.6%	0.024[c]
Duration of complaints					
Acute onset	31/57	54.4%	28/75	37.3%	0.051
<6 months	19/57	33.3%	20/75	26.7%	0.406
>6 months	38/57	66.7%	55/75	73.3%	

* Not all symptoms could be collected from the medical records from all patients, therefore there are different denominators

† Some children reported more than one symptom

‡ Difference in groups was significant $p \leq 0.05$

AP=abdominal pain; FGIDs=functional gastrointestinal disorders

Discussion

AP-related FGIDs (AP-FGIDs) can be considered a heterogeneous group of disorders and D. *fragilis* has been proposed as a possible mechanism underlying FGIDs. This retrospective case-control study, however, found no difference in the presence of gastrointestinal symptoms between D. *fragilis*-infected children with chronic AP and children suffering from AP-FGIDs. Moreover, similar prevalence rates for D. *fragilis* were found in children with chronic AP and healthy asymptomatic controls. Last, after treatment only 40.4% of the D. *fragilis*-infected children reached clinical improvement.

In this study, the prevalence of *D. fragilis* was 43.2% in chronic AP patients and 50.6% in asymptomatic controls. Previous studies in symptomatic and asymptomatic children reported prevalence rates between

8 and 19.8%.[18, 20, 22, 37] The low sensitivity of light microscopy, as compared to PCR, might explain the high prevalence rates found in this study compared to earlier studies.[34] Indeed, another study using the PCR technique as well, showed a comparable high prevalence among children and adults with gastrointestinal symptoms, with a peak among younger children,[23] unfortunately, no prevalence rates among asymptomatic controls were investigated in this study.
By contrast with earlier studies, the presence of *D. fragilis* was not significantly associated with any gastrointestinal symptom.[24-26, 30, 31] Moreover, this study demonstrated that based on symptomatology, no distinction could be made from children with AP-FGIDs. Not surprisingly, AP-FGIDs patients had significantly more other functional complaints such as headache, back pain or neck pain. These latter findings are in line with the diagnostic criteria for childhood functional AP syndrome which further includes symptoms as limb pain, difficulty sleeping and some loss of daily functioning.[6]

This study showed that 50% of asymptomatic children were carrier of *D. fragilis.* Some researchers consider *D. fragilis* as a commensal since this parasite is indeed frequently found in asymptomatic individuals.[26, 27] The connection between presence or absence of disease could be due to different genotypes of *D. fragilis*, as has been described in other enteric protozoa, such as Giardia lamblia.[11] Up until now, only one genotype for *D. fragilis* has been described in both symptomatic and asymptomatic patients.[14, 32, 33] Another explanation could be a difference in quantity of parasitic load in the colon. Hypothetically, a higher parasitic DNA load would be expected in patients with more clinical symptoms compared to those without symptoms. Our study, however, did not show a significant difference in the Ct values of parasitic DNA load between children with and without symptoms of AP.

Although a causal relation between *D. fragilis* and gastrointestinal symptoms is not clear, in daily clinical practice *D. fragilis* is frequently treated with antiparasitical medication. Numerous studies show clinical improvement following appropriate treatment.[22, 24, 26, 30, 31] In our study, parasitological eradication was achieved in 61.7% after the first treatment with either metronidazole or clioquinol, but only 40.4% of patients reported clinical improvement. The eradication rate, as well as the observed clinical improvement percentage, are lower than reported in previous studies.[22, 30, 31] This difference might be due to the different populations studied. In accordance with our study Engsbro *et al.* observed a clinical response after metronidazole, defined as adequate relief of symptoms, in 7 of 22 patients (32%), whereas, microbiological response was 68%. In a logistic regression analysis, however, the investigators were unable to show a significant association between clinical and microbiological response.[12]

Another retrospective study found an eradication rate of *D. fragilis* in 50% of affected children with AP. No significant difference in decrease in AP was, however, found between those children treated with metronidazole or tinidazole, and children receiving no treatment.[26] Using a more heterogeneous population (0-90 years), Vandenberg *et al.* described a clinical success rate of 78.9% (12/19) in patients with and 71% (5/7) without treatment, suggesting a possible self-limiting character of the infection.[32]
The strength of our study is the use of a well-defined AP-related FGID-population using the ROME III criteria and an asymptomatic control group. The limitations of this study derive from its retrospective character. The description of the patients' histories and clinical symptoms were sometimes subjective, which could have introduced some selection bias. On the other hand, such histories are quite representative for daily clinical practice. Furthermore, in some children with an underlying psychiatric disorder it might be difficult to obtain a reliable medical history. However, all patients and their parents were interviewed by an experienced general practitioner working in a general hospital as well as a psychiatric hospital, diminishing the risk of missing a gastrointestinal complaint

In conclusion, our study showed that *D. fragilis* is a frequently encountered parasite both in children with chronic AP and in asymptomatic children. Additionally, presence of gastrointestinal symptoms did not differ between chronic AP patients with *D. fragilis* infection and AP-FGID patients without *D. fragilis* infection. Furthermore, no association was found between clinical and microbiological response after treatment. These findings suggest that the association between AP-related FGIDs and *D. fragilis* infection is doubtful. In keeping with this, well-designed large placebo-controlled studies in distinct subsets of AP-FGID-infected patients are warranted to establish clearly whether eradication of the *D. fragilis* infection improves specific AP-related symptoms.

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Chapter 5

Pharmacologic treatment in pediatric functional abdominal pain disorders: a systematic review

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Abstract

Objective

To systematically review literature assessing efficacy and safety of pharmacologic treatments in children with abdominal pain-related functional gastrointestinal disorders (AP-FGIDs).

Study design

MEDLINE and Cochrane Database were searched for systematic reviews and randomized controlled trials investigating efficacy and safety of pharmacologic agents in children aged 4-18 years with AP-FGIDs. Quality of evidence was assessed using Grades of Recommendation, Assessment, Development and Evaluation approach.

Results

We included 6 studies with 275 children (4.5-18 years) evaluating antispasmodic, antidepressant, antireflux, antihistaminic and laxative agents. Overall quality of evidence was very low. Compared to placebo, some evidence was found for peppermint oil in improving symptoms (OR 3.3 (95% CI 0.9-12.0) and for cyproheptadine in reducing pain frequency (RR 2.43, 95% CI 1.17-5.04) and pain intensity (RR 3.03, 95% CI 1.29-7.11). Compared with placebo, amitriptyline showed 15% improvement in overall QoL-score (p=0.007) and famotidine only provides benefit in global symptom improvement (OR 11.0; 95% CI 1.6-75.5; p=0.02). Polyethylene glycol with tegaserod significantly decreased pain intensity compared with polyethylene glycol only (RR 3.60, 95% CI 1.54-8.40). No serious adverse effects were reported. No studies were found concerning antidiarrheal agents, antibiotics, pain medication, anti-emetics or antimigraine agents.

Conclusions

Because of the lack of high-quality, placebo-controlled trials of pharmacologic treatment for pediatric AP-FGIDs, there is no evidence to support routine use of any pharmacologic therapy. Peppermint oil, cyproheptadine and famotidine might be potential interventions, but well-designed randomized controlled trials are needed.

Introduction

When evidence for an organic disorder is not present in children with chronic or recurrent abdominal pain, they are diagnosed with one of the abdominal pain-related functional gastrointestinal disorders (AP-FGIDs) defined by the Rome III criteria (Appendix 1, online).[1] AP-FGIDs affect approximately 20% of children worldwide and include functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraine (AM), functional abdominal pain (FAP) and FAP syndrome (FAPS).[1, 2] IBS is most frequently diagnosed in up to 45% of pediatric AP-FGIDs.[3-6]
AP-FGIDs have a significant impact on families because these children report significantly lower quality of life (QoL),[7] increased risks for depressive symptoms, social isolation, and school absenteeism.[8] Furthermore, AP-FGIDs have a great impact on health care costs. Average costs of diagnostics are approximately 6000 US dollar per child.[9]

To date, pathophysiological mechanisms underlying AP-FGIDs are not completely understood. A biopsychosocial model has been postulated, in which genetic, physiological and psychological factors interplay.[10] Part of the symptoms in AP-FGIDs are thought to be associated with dysregulation of the brain-gut axis expressed by visceral hypersensitivity and altered gastrointestinal (GI) motility.[11] Because of increasing understanding of the brain-gut axis, potential targets for pharmacologic treatment were identified including smooth muscle cells throughout the GI-tract, peripheral receptors, central interneurons and cortical regions involved in conscious perception of pain.[12]

However, incomplete pathophysiological understanding still hampers management. Treatment, therefore, remains symptomatic, and 30% of children continue to experience symptoms into adulthood.[13-15] Data on efficacy and safety of pharmacologic therapies in children are scarce. Consequently, a variety of agents are frequently prescribed by pediatricians mainly based on their own clinical experiences and results of adults studies, which can be harmful because evidence from adults cannot be directly extrapolated to children. Data on pharmacologic therapies, covering literature published to 2006, concluded that evidence of benefit in children with recurrent abdominal pain was weak.[16] Since then, various pharmacologic studies may have been published including new agents. Therefore, our aim is to give an update by systematically reviewing efficacy and safety of different pharmacologic treatments.

Methods

Literature search

Cochrane Library and MEDLINE were searched for systematic reviews (SRs) and randomized controlled trials (RCTs) from inception to October 2013. Medical Subject Headings terms used were functional abdominal pain, irritable bowel syndrome, functional dyspepsia, abdominal migraine, child, adolescent, pharmacologic treatment or therapy. Reference lists of reviews and included studies were searched by hand to identify additional studies. Full search strategy is available from the corresponding author.

Study selection

Two reviewers independently screened all abstracts for eligibility. In case of disagreement, consensus was reached by discussion. Inclusion criteria were: (1) study was a SR or RCT; (2) study population consisted of children aged 4-18 years; (3) diagnosis of FAP(S), IBS, FD or AM according to Rome or Apley's criteria or other criteria well-defined by the authors; (4) interventions were antispasmodics, antidepressants, antidiarrheal agents, antibiotics, pain medication, antireflux agents, anti-emetics, anti-

migraine agents, antihistaminic agents or laxatives; (5) intervention was compared with placebo, no treatment, or any other pharmacologic treatment; and (6) outcome measures were abdominal pain intensity and/or frequency, QoL, functional disability (e.g. school absence) and/or adverse effects. Exclusion criteria were: (1) treatment arm with <10 patients; and (2) non-English language.

Quality assessment, data extraction and analysis

Two reviewers independently rated methodological quality using the Cochrane risk of bias tool. For each outcome, quality of evidence was assessed by using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.[17-19] These reviewers extracted data by using structured data extraction forms, which contained items such as author, year of enrollment, participants, study setting, interventions, and outcomes. Disagreements of both steps were resolved through consensus, or by a third person.

Results

A total of 557 potentially relevant articles and abstracts were identified. After removal of duplicates (n=247) and screening of the abstracts (n=246), 64 full-text articles were assessed for eligibility. Sixty articles did not meet inclusion criteria: adult study population (n=44), irrelevant outcome measures/subject (n=8), and no SR or RCT (n=8). Four articles including six studies remained: two SRs [16, 20] and two RCTs.[21, 22] One review [16] originally included a third study,[23] but this study was excluded because of <10 patients per treatment arm (Figure 1).

Compared with placebo, one trial investigated antispasmodics,[24] two trials studied antidepressants,[25, 26] one trial studied antireflux medication[27] and one antihistaminic agents.[22] One trial evaluated polyethylene glycol 3350 oral solution (PEG3350) compared with PEG3350 combined with tegaserod[21] No studies were included on antidiarrheal agents, antibiotics, pain medication, anti-emetics and antimigraine agents.

Data of 275 children aged 4.5-18 years were included. Sample sizes varied from 25 to 90 children and duration of follow-up from two to thirteen weeks. See *et al.* stated to have one year follow-up without showing data .[27] Five studies were conducted in North America [21, 24-27] and one in Asia.[22] Five studies were performed at the pediatric gastroenterology department of both secondary and tertiary centers,[22, 24-27] one study did not report their setting.[21]

A range of different outcomes were measured. Even if a same outcome was measured, different measurement instruments were used. All trials measured abdominal pain as primary or secondary outcome. Three studies reported on QoL or overall symptom relief.[25-27] Disability was measured in two studies.[25, 26] Adverse effects were reported in all but one study.[27]

Methodological quality

Overall quality of evidence was very low (Table 1). GRADE evidence profiles are shown in Appendix 2 (online). All six included studies were RCTs, but details on concealment of allocation were only reported in two studies.[21, 22] At baseline, treatment groups were similar with respect to demographic and clinical features in five studies.[21, 22, 24, 26, 27] Bahar *et al.* did not present a baseline table.[25] Risk of performance and detection bias was low in five RCTs, since they were double-blind and placebo-controlled.[22, 24-27] Bahar *et al.* did not provide information on how blinding was performed.[25] Khoshoo *et al.* used no blinding for type of medication. Symptoms were recorded by children and reported by phone twice weekly to the same member of the research team. However, this outcome assessor was not blinded.[21] In four studies no patients were lost to follow-up.[21, 22, 25, 27]

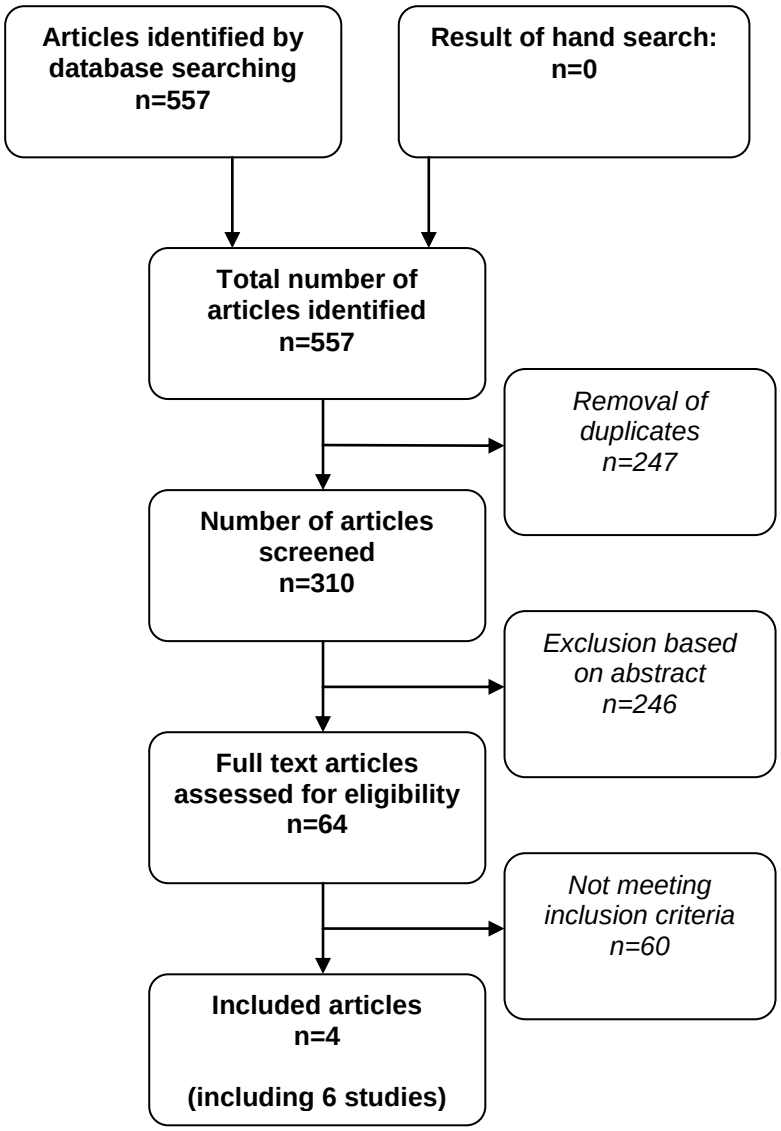

Figure 1 | Flowchart showing results of literature search and study inclusion

Dropout was considerable in the Saps *et al.* trial, with seven children not completing the trial (7.8%).[26] The authors performed intention to treat analyses which reduces risk for attrition bias, but it is not reported whether they imputated missing data.[26] In Kline *et al.*, attrition bias was considered high, since 16% of children (n=8) did not complete the study and dropout rates per group were not reported.[24]
Because of heterogeneity of all studies with respect to study population, design and outcomes, we refrained from statistical pooling and the six included studies are discussed separately. Characteristics and results are shown in Table 1.

Antispasmodics
Kline *et al.* performed a randomized, double-blind controlled trial, including 50 children, aged 8-17 years with IBS according to the Rome or Manning criteria[24] Children were assigned to 2 weeks of treatment with 3 times a day pH-dependent, enteric-coated capsules containing peppermint oil or placebo (arachis oil). Peppermint oil and placebo capsules were provided under the same trademark, but further details about differences like taste were not reported. Main outcomes were severity of pain, changes in symptoms, and side effects. A 1-5 scale based on a model derived from prior studies was used by clinicians to rank both severity of pain (1=excellent, 2=good, 3=fair, 4=bad, and 5=terrible) and change in symptoms (1=much

better, 2=better, 3=no effect, 4=worse, and 5=much worse). Daily symptom diaries were kept by children and/or parents and the 4-point GI Symptom Rating Scale was measured for 15 GI-symptoms (0=absence of symptom, 3=extreme degree of symptom). After 2 weeks, 76% of children receiving peppermint oil reported improvement in severity of symptom scale vs 19% of children receiving placebo (p<0.001). Mean severity of pain symptoms based on diaries was also mentioned to be significantly lower in the peppermint oil group. However, authors did not clarify how the diaries were analyzed. Significantly more children receiving peppermint oil (71%) reported improvement on the change of symptom scale compared with placebo (43%; OR 3.3 [95% CI 0.9-12.0]; p<0.002).[16, 24] They also reported no differences on the Gastrointestinal Symptom Rating Scale, but data were not shown. No side effects were reported.

Antidepressants

Two double-blind randomized placebo-controlled trials including 123 children evaluated amitriptyline.[25, 26] Bahar *et al.* included 33 adolescents aged 12-18 years, and Saps *et al.* included 90 children aged 8-17 years. Duration of treatment in the Bahar *et al.* study was 8 weeks, in Saps *et al.* 4 weeks. Placebo capsules were identical to amitriptyline capsules in the Saps trial, and details about the appearance of the placebo were not reported by Bahar *et al.*

Improvement in overall QoL score was primary outcome measure in the Bahar study. A 34-item IBS-QoL questionnaire, validated in adults, was used, but two questions on sexual activity were omitted. Items were scored on a 1-5 scale (1 = not at all, 5 = extremely). Minimum and maximum scores on this IBS-QoL questionnaire were not reported. In addition, a symptoms checklist, pain-rating scale, and visual analog scale were used for assessing associated IBS symptoms, interference with daily life, and pain frequency and intensity. At baseline, differences in mean QoL scores between the amitriptyline and placebo group were borderline significant (109.4 vs 127.5, p=0.05). Reported mean overall QoL scores at week 6, 10, and 13 were 127.6, 128.0, and 126.2 in the amitriptyline group and 132, 129.4, and 129.8 in the placebo-group, respectively, without reporting p-values. Improvement in overall QoL-scores, children receiving amitriptyline reported significantly greater improvements at all 3 moments (p=0.019, p=0.004, and p=0.013, respectively). However, absolute change in overall QoL-scores was not reported, but only displayed in a figure. Immediately and three weeks after treatment, significantly more children in the amitriptyline group reported at least 15% of improvement in QoL (p=0.007 and p=0.002, respectively). Again, no absolute percentages were reported. Authors did not clarify on the ratio for this cut-off value of 15%. Scores on almost all associated IBS-symptoms, interference with daily life, and pain frequency and intensity did not differ between groups. No adverse effects were reported.

Saps *et al.*[26] used overall assessment of satisfactory relief and satisfaction with treatment as primary outcome. Two questions regarding the subject's overall status (better, same, or worse) and sense of improvement (excellent, good, fair, poor, or failed) were used. Secondary outcomes included effects on disability. Validated, self-reported, and age-appropriate questionnaires were used. At end of treatment, 59% of children in the amitriptyline group compared with 53% in the placebo group reported to feel better (relative risk (RR) 1.12 [95% CI 0.77-1.63; p=0.54]).[20] Significant abdominal pain reduction compared with baseline was reported in both groups (p<0.0001), but there was no significant difference (p=0.18). Absolute numbers, however, were not reported.

No significant differences were shown with regards to disability. Mild adverse events occurred in first two weeks of treatment, but how adverse effects were assessed was not reported. Two children in the amitriptyline group dropped out because of fatigue, rash, and headaches, and one child in the placebo group discontinued the study because of dizziness. The proportion of patients experiencing at least 1 adverse event did not differ between groups (RR 1.91, 95% CI 0.18-20.35; 0.59).[20]

Table 1 | Study characteristics and results from included trials

Study	Participants & Diagnosis	Interventions	Outcome measures & instruments	Results	Overall quality (GRADE)
Kline *et al.* (2001)	Children 8-17 years (n=50) IBS (Rome/Manning criteria)	Peppermint oil vs. placebo Dosage: 0.1 or 0.2 ml 3 times daily Treatment period: 2 weeks	*Severity of pain and change in symptoms* Instruments: pain and symptom scales (5-point scale), symptom diaries, Gastrointestinal Symptom Rating Scale (GSRS) *Adverse effects* Instrument: recorded by investigator and patient	Significantly more children in peppermint oil group reported improvement in symptoms 71% vs 43%; $p<0.002$ (OR=3.3 (95% CI 0.9-12.0). No significant differences in GSRS. No adverse effects reported	Very low
Bahar *et al.* (2008)	Children 12-18 years (n=33) IBS (Rome II criteria)	Amitriptyline vs. placebo Dosage: 10 mg/day (30-50 kg), 20 mg/day (50-80 kg), 30 mg/day (>80 kg) Treatment period: 8 weeks	*Improvement in overall QoL* Instrument: IBS-QoL questionnaire *Frequency and intensity of abdominal pain* Instrument: Visual analog scale (0-10) *Interference with daily life* Instrument: Pain-rating scale (0-6) *Adverse effects* Instrument: not reported	Amitriptyline group significantly greater improvements overall QoL during and after treatment ($p=0.019$, $p=0.004$ and $p=0.013$) No significant differences ($p>0.05$) No significant differences ($p>0.05$) No adverse effects reported	Very low
Saps *et al.* (2009)	Children 8-17 years (n=90) IBS, FAP and FD (Rome II criteria)	Amitriptyline vs. placebo Dosage: 10 mg/day (<35 kg), 20 mg/day (>35 kg) Treatment period: 4 weeks	*Overall satisfactory relief + satisfaction with treatment* Instrument: 2 questions about overall status and sense of improvement *Disability* Instrument: Pediatric Functional Disability Inventory (PFDI) *Adverse effects* Instrument: not reported	No significant difference ($p=0.81$) in percentage of children feeling better: 59% vs. 53% (RR 1.12; 95% CI 0.77-1.63) No significant differences in PFDI ($p=0.31$) Mild adverse effects reported (RR 1.91; 95% CI 0.18-20.35)	Very low

Table 1 | Study characteristics and results from included trials *(continued)*

Study	Participants & Diagnosis	Interventions	Outcome measures & instruments	Results	Overall quality (GRADE)
See *et al.* (2001)	Children 5-18 years (n=25) FD (Apley's criteria)	Famotidine vs. placebo Dosage: 0.5 mg/kg/dose 2 times daily (max. 40 mg/day) Treatment period: 3+3 weeks (cross-over)	*Level of abdominal pain* Instrument: pain diaries scoring pain frequency, intensity and peptic index *Global improvement of symptoms* Instrument: question feeling better, not better, worse	No significant differences in level of abdominal pain, regardless of order of drugs Significantly more children receiving famotidine improved: 66.7% vs. 15.4% (p=0.015) (OR 11.0; 95% CI 1.6-75.5)	Very low
Sadeghian *et al.* (2008)	Children 4.5-16 years (n=29) FAP (Rome II criteria)	Cyproheptadine vs. placebo Dosage: 0.25-0.5 mg/kg/day (max 12 mg/day children 2-6 yr; max. 16 mg/day children 7-14 yr) Treatment period: 2 weeks	*Frequency and intensity of abdominal pain* Instrument: self-reported diary (scale 1-6) *Global improvement of symptoms* Instrument: self-reported diary (scale 1-4) *Adverse events* Instrument: recorded by research nurse	Significantly more children in the cyproheptadine group improved/resolved with respect to abdominal pain frequency (p=0.002) with RR 2.43 (95% CI 1.17-5.04) and pain intensity (p=0.001) with RR 3.03 (95% CI 1.29-7.11) Significantly more children globally improved in cyproheptadine group (86.7% vs. 35.7%; p=0.005). No adverse effects reported	Very low
Khoshoo *et al.* (2006)	Children 13-18 years (n=48) IBS-C (Rome II criteria)	PEG 3350 vs. PEG 3350 + tegaserod Dosage: 17 gr/day PEG 3350, Tegaserod 6 mg 2 times daily Treatment period: 4 weeks	*Adequate reduction of abdominal pain* Instrument: daily pain diaries (scale 0-10); adequate pain reduction: ≥3 points *Adverse effects* Instrument: not reported	Significantly more children receiving PEG 3350 + tegaserod adequate pain reduction (66.7% vs. 18.5%; p<0.05) (RR 3.60: 95% CI 1.54-8.40) No adverse effects reported	Very low

CI=confidence interval; FAP=functional abdominal pain; FD=functional dyspepsia; GSRS= Gastrointestinal Symptom Rating Scale; IBS=irritable bowel syndrome; IBS-C=irritable bowel syndrome constipation predominant; OR=odds ratio; PEG 3350= polyethylene glycol 3350 oral solution; PFDI=Pediatric Functional Disability Inventory; QoL=quality of life; RR=relative risk

Antireflux agents

See *et al.* included 25 children aged 5-18 years with recurrent abdominal pain according to Apley criteria and dyspeptic symptoms, such as epigastric pain, pain before and after eating, chest pain, nausea, vomiting, and loss of appetite.[27] Children were randomly assigned to treatment with twice daily famotidine or placebo during 3 weeks (treatment period 1). In case of persisting symptoms after treatment period 1, crossover occurred directly afterward and continued for another three weeks (treatment period 2). In patients demonstrating improvement after treatment period 1, crossover occurred only if symptoms recurred and persisted for three weeks. Placebo was prepared with sugar suspension matching the famotidine suspension, and both famotidine and placebo were inserted in a white opaque gelatin capsule. Abdominal pain was assessed using abdominal pain score, which combined pain frequency, pain severity (affective facial scale), and a peptic index (amount of experienced peptic symptoms). In addition, global improvement (better, not better, or worse) was assessed. No significant difference in abdominal pain score was shown between both groups. When analyzing global improvement, 66.7%of children improved on famotidine, compared with 15.4% on placebo (OR 11.0; 95% CI 1.6-75.5; *p*=0.015).

Antihistaminic agents

Sadeghian *et al.*[22] studied cyproheptadine in a double-blind placebo-controlled trial including 4.5- to 12-year-old children with FAP according to Rome II criteria (n = 29). Children were randomized to either cyproheptadine or placebo. Placebo was prepared in similar bottles as cyproheptadine syrup. Primary outcome was self-reported change in frequency and intensity of abdominal pain using a 6-point scale (1 = complete resolved, 2 = very much improved, 3 = improved, 4 = no change, 5 = become worse, and 6 = become much worse). In addition, global assessment of improvement was measured using a 4-point scale (1 = no pain, 2 = become better, 3 = no change, 4 = become worse). Questionnaires used were not validated. After 2 weeks of treatment, 86.7% of children in the cyproheptadine group vs 35.7% receiving placebo reported improvement/resolution with respect to pain frequency (RR 2.43 [95% CI 1.17-5.04]; *p*=0.002). Significantly more children in the cyproheptadine group reported improvement/ resolution with respect to pain intensity (86.7% vs 28.6%; RR 3.03 [95% CI 1.29-7.11]; *p*=0.001). Global assessment of improvement reported by children was significantly better in the cyproheptadine group (86.7% vs 35.7%; *p*=0.005). No serious adverse effects were reported.

Laxatives

Khoshoo *et al.*[21] performed a trial in 48 children aged 13-18 years with constipation predominant IBS according to Rome II criteria. Patients were randomly allocated to PEG 3350 or combination therapy consisting of PEG 3350 and tegaserod. All patients received same dosage of laxatives. Daily diaries were kept to assess abdominal pain using standard pain rating scale (0 = no pain, 10 = worst possible pain) and frequency of bowel movements. Adequate pain reduction was defined as reduction of ≥3 points on pain rating scale.

After four weeks of treatment, significantly more children receiving the combination of laxatives reported adequate pain reduction, compared with children receiving PEG 3350 alone (66.7% vs 18.5%; RR 3.60 [95% CI 1.54-8.40]; *p*<0.05). No adverse effects were reported, but again it was unclear how adverse effects were assessed.

Discussion

This systematic review clearly reveals a lack of adequately powered, high-quality, placebo-controlled drug trials in children with AP-FGIDs. Weak evidence was found that treatment with peppermint oil or cyproheptadine or combination of two laxatives is effective in children with IBS and FAP for some outcome measures. Famotidine did not show significant improvement of abdominal pain, however, when analyzing global symptom improvement, famotidine was more effective compared to placebo among children with recurrent abdominal pain and dyspepsia. Amitriptyline seems to improve QoL, but no effect in reduction of abdominal pain was demonstrated compared to placebo.

Kline *et al.*[24] reported beneficial effect of peppermint oil for children with IBS. It is unknown whether taste of placebo was similar to peppermint oil. It is likely that recognizable taste of peppermint influences effect in favor of this drug. Peppermint oil has shown its efficacy and safety in adult IBS patients.[28-30] The menthol component is known to block Ca2+ channels,[31, 32] which may lead to reduction of colonic spasms.[33] It is noteworthy that trials evaluating effects of another widely used antispasmodic, mebeverine, are lacking. Pediatric use of this compound is based on adult trials, where it is considered clinically effective. Two meta-analyses, however, report inconsistent data regarding efficacy of mebeverine.[34, 35] More importantly, evidence on efficacy in adults cannot be directly extrapolated to children.

Tricyclic antidepressants like amitriptyline and selective serotonin reuptake inhibitors are antidepressants, both used in treating AP-FGIDs.[36] Low dose of amitriptyline is believed to work primarily by inducing pain tolerance through peripheral or central antinociceptive properties and anticholinergic effects [25, 37] and has been demonstrated to have beneficial effect in treatment of adults with IBS and FD [37-41] These effects were not confirmed in pediatric AP-FGIDs, when comparing amitriptyline to placebo.[25, 26] However, Bahar *et al.* concluded that amitriptyline significantly improved QoL, after they measured greater improvement of scores in the intervention-group.[25] Because baseline scores were already substantially higher in the placebo group, greater improvement of absolute scores is needed to reach the 15% margin, therefore these results were limited. Furthermore, absolute mean QoL scores after treatment did not differ significantly. It is conceivable that the dose used in children (10-30mg) was too low compared to 75mg used in adults with IBS.[37] Higher placebo success rate in children (53%) compared to adults (40%) with IBS may explain the lack of statistical difference in favor of amitriptyline.[42]

Significant benefit of famotidine was only found when assessing global symptom improvement in children with recurrent abdominal pain and dyspepsia, whereas no significant decrease in abdominal pain was demonstrated.[27] Famotidine inhibits gastric acid secretion [43] and is, therefore, promising in patients with dyspeptic symptoms. Among adult patients with dyspeptic symptoms, H2-receptorantagonist demonstrated statistically significant improvement in dyspeptic symptoms,[44, 45] and famotidine showed significant improvement in belching, heartburn, and feeling of acid regurgitation compared with placebo.[46]

Cyproheptadine is an antihistaminic agent and has been successfully applied for migraine.[47] Mechanism of action is probably due to Ca2+ channel blocking or antiserotonin effect.[47-50] Because of the antiserotonin effect, cyproheptadine was hypothesized to be effective in pediatric AP-FGIDs. Sadeghian reported significant effect of cyproheptadine on frequency and severity of FAP, without

serious side effects.[22] Again, results should be cautiously interpreted, because of very low methodological quality, usage of non-validated questionnaires and limited follow-up of two weeks. Recent retrospective trials showed significant effect for children with abdominal migraine [51] and FD.[52]

Just one study evaluated efficacy of laxatives in children with AP-FGIDs. Khoshoo[21] showed that tegaserod in addition to PEG 3350 significantly reduced abdominal pain in IBS-constipation predominant (IBS-C), compared with PEG 3350 alone. Tegaserod acts upon 5-hydroxytryptamine4 (5-HT4) GI-receptors, which play a key role in motility and moderate visceral sensitivity.[53] Adult studies also show promising results in IBS-C for relief of abdominal pain, bloating, and constipation.[53, 54] Nevertheless, tegaserod has been associated with serious cardiovascular ischemic events and was, therefore, withdrawn from the market on order of the Food and Drug Administration (FDA). [55] In the last decade, new laxatives as prucalopride, lubiprostone, and linaclotide have been shown effective in treating adult IBS-C.[39] However, these compounds have not been evaluated in children with IBS-C.

Results in this review should be interpreted cautiously, given the very low quality of all studies. This was often due to small sample sizes, poorly reported side effects, lack of follow-up, or because of considerable risk of bias. Performing placebo-controlled studies on children is complicated since ethical considerations must balance protection of individual children with the importance of allowing research needed to improve pediatric medicine, but also because parents often refuse to have their child participating in placebo-controlled trials because of "risk" of being assigned to the placebo arm.[56] Interpretation of results was also hampered by heterogeneity of study population, a wide range of different outcomes and differences in instruments used to measure these outcomes. Furthermore, it is important to realize that two studies[24, 25] were funded by pharmaceutical industry. One of the limitations of this SR concerns possible publication bias, that is, statistical significant positive results being more likely to be published. Furthermore, our search was restricted to English language. To minimize risk of not including all relevant studies, we carried out a comprehensive and contemporaneous literature search. GRADE approach aims to prevent heterogeneity of included studies as much as possible. As a consequence, however, possible interesting studies that do not fulfill predefined outcome measures must be excluded. The RCT of Collins *et al.* on rifaximin in children with chronic abdominal pain, for example, was, therefore, excluded.[57] Another limitation includes the possibility of bias in reporting outcomes because children aged 4-18 years are included and (part of) outcomes may be reported by parents. Sadeghian reported outcomes recorded by children and caregivers separately and both reported similar answers with respect to treatment response.[22] Unfortunately, all other studies did not report whether children completed questionnaires themselves or with help of their caregivers. They did use age-appropriate questionnaires, but the possibility of bias due to reporting by children versus caregivers cannot be excluded. All studies used well-defined inclusion criteria. One study used Apley criteria and although these criteria are not validated and possibly arbitrary, they are well-defined and were widely used for decades because validated criteria were lacking prior to the introduction of the Rome criteria. However, the remaining five studies used Rome and Rome II criteria which are validated, thereby increasing the applicability of outcomes of this review.[4]

High success rates for placebo were often reported for pediatric patients with FGIDs,[22, 24, 58-60] up to 53% in Saps' study. It is known an active listening approach and encouraging attitude towards treatment help improve subjects' responses to both therapeutic attempts and placebo.[58, 61] Furthermore, high placebo response might point towards natural course of disease or fluctuations in symptoms.

In the last decade, several non-pharmacologic therapies (e.g. hypnotherapy[62, 63] and cognitive behavioral therapy)[64-67] have shown their efficacy in treating of children with AP-FGIDs, with success rates up to 85%.[68, 69] Moreover, these therapies are not hampered by severe side effects.

Conclusion

Evidence for pharmacologic treatment in children with AP-FGIDs is very low. It is not possible to recommend any specific pharmacologic treatment. Clinicians may choose to prescribe drugs in children in whom symptoms are severe and have not responded to physician reassurance, time or simple dietary interventions. Peppermint oil, cyproheptadine or famotidine may be considered in treating children with either FAP or IBS, but well-designed trials with long-term follow-up are needed to confirm data presented in this review.

This review clearly demonstrated that more research is needed to investigate pharmacologic therapies in these children.[70] We recommend, while designing new studies, to take into account use of homogeneous outcome measures, use of validated instruments to measure abdominal pain, anxiety, depression, adequate relief and QoL, placebo arm, sufficient sample size and long-term follow-up.

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Appendix 1 | Rome III criteria for AP-FGIDs

Functional dyspepsia[a]

1. Persistent or recurrent pain or discomfort centered in the upper abdomen (above the umbilicus)
2. Not relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e, not IBS)
3. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms

IBS[a]

1. Abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with 2 or more of the following at least 25% of the time: improved with defecation; onset associated with a change in frequency of stool; onset associated with a change in form (appearance) of stool
2. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms

Abdominal migraine[b]

1. Paroxysmal episodes of intense, acute periumbilical pain that lasts for 1 h or more
2. Intervening periods of usual health lasting weeks to months
3. The pain interferes with normal activities
4. The pain is associated with 2 or more of the following: anorexia; nausea; vomiting; headache; photophobia; pallor
5. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms

Functional abdominal pain[a]

1. Episodic or continuous abdominal pain
2. Insufficient criteria for other FGIDs
3. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms

Functional abdominal pain syndrome (FAPS)[a]

Must include childhood functional abdominal pain at least 25% of the time and 1 or more of the following:

1. Some loss of daily functioning
2. Additional somatic symptoms such as headache, limb pain, or difficulty sleeping.

[a] Criteria fulfilled at least once per week for at least 2 months before diagnosis

[b] Criteria fulfilled 2 or more times in the preceding 12 months

Abbreviation: AP-FGIDs, abdominal-pain-related functional gastrointestinal disorders

Appendix 2 | GRADE evidence profile

GRADE approach, was categorized as follows:

- *Very low*: Any estimate of effect is uncertain.
- *Low*: Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- *Moderate*: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- *High*: Further research is unlikely to change our confidence in the estimate of effect.

GRADE evidence profile peppermint oil

Question: Should Peppermint oil vs placebo (arachis oil) be used for IBS according to the Rome criteria?

Settings: University hospitals (two), private clinic (one)

Bibliography: Kline *et al.* 2001

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Peppermint oil**	**Placebo (arachis oil)**	**Relative (95% CI)**	**Absolute**		
Improvement in symptoms (follow-up 2 weeks; assessed with: scales recording severity and change of symptoms and a symptom dairy)												
1	randomized trials	very serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	15/21 (71.4%)	9/21 (42.9%)	OR 3.33 (0.93 to 12.01)	999 more per 1000 (from 30 fewer to 1000 more)	VERY LOW	CRITICAL
								0%		-		
Adverse events (follow-up 2 weeks)												
1	randomized trials	very serious[1]	no serious inconsistency[2]	no serious indirectness	no serious imprecision	none	0/21 (0%)	0/21 (0%)	-	-	LOW	CRITICAL
								0%		-		

[1] Concealment of allocation was unclear. Eight patients withdrew and it was not clear from which group.

[2] One study only.

[3] Total number of events is less than 300 and 95% CI around the pooled estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm.

GRADE evidence profile Amitriptyline

Question: Should Amitriptyline vs placebo be used for abdominal pain-related functional gastrointestinal disorders?

Settings: Bahar: private clinic California, Saps: six centers

Bibliography: Bahar *et al.* 2008, Saps *et al.*, 2009

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Amitriptyline**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Feeling better (Saps) (follow-up 4 weeks; assessed with: question)												
1	randomized trials	very serious[1]	no serious inconsistency[2]	serious[3]	serious[4]	none	27/46 (58.7%)	23/44 (52.3%)	RR 1.12 (0.77 to	63 more per 1000	VERY LOW	CRITICAL

									1.63)	(from 120 fewer to 329 more)		
								0%		-		
Quality of life (Bahar) (follow-up 13 weeks; measured with: IBS quality of life questionnaire; Better indicated by lower values)												
1	randomized trials	very serious[5]	no serious inconsistency[2]	no serious indirectness	serious[6]	none	16	17	-	MD 14.5 higher (0 to 0 higher)	VERY LOW	CRITICAL
Abdominal pain reduction (Saps) – insufficient data for GRADE profiling												
Disability (Saps) - insufficient data for GRADE profiling												
Adverse events (Saps: unclear how the adverse events were assessed)												
1	randomized trials	very serious[7]	no serious inconsistency[2]	serious[3]	no serious imprecision	none	3/46 (6.5%)	1/44 (2.3%)	RR 1.91 (0.18 to 20.35)	20 more per 1000 (from 19 fewer to 299 more)	VERY LOW	CRITICAL
								0%		-		
School attendance (Saps) - insufficient data for GRADE profiling												

[1] Concealment of allocation unclear. Seven patients were lost to follow-up.

[2] One study only.

[3] Only tertiary care patients.

[4] Total number of events is less than 300 and 95% CI around the pooled estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm.

[5] Concealment of allocation was unclear. The baseline table was not presented.

[6] The sample size is very low (n=33).

[7] Concealment of allocation unclear and it was unclear how adverse events were assessed.

GRADE evidence profile Famotidine

Question: Should Famotidine vs placebo be used for Apley criteria for recurrent abdominal pain?

Settings: Medical Center New York

Bibliography: See *et al.* 2001

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Famotidine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Global improvement in symptoms (follow-up 14 days; assessed with: question: do you feel better, not better, worse)												
1	randomized trials	very serious[1]	no serious inconsistency[2]	serious[3]	serious[4]	none	8/12 (66.7%)	2/13 (15.4%)	OR 11.00 (1.6 to 75.5)	1000 more per 1000 (from 92 more to 1000 more)	VERY LOW	CRITICAL
								0%		-		

[1] No detail of the generation of the randomization sequence is provided. Results are taken from the first period of the trial, before the crossover.

[2] One study only.

[3] The outcome is a global assessment of pain only.

[4] Total number of events is less than 300 and 95% CI around the pooled estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm.

GRADE evidence profile Cyproheptadine

Question: Should Cyproheptadine vs placebo be used for functional abdominal pain?

Settings: University hospital Theran, Iran

Bibliography: Sadeghian *et al.* 2008

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cyproheptadine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Frequency abdominal pain (follow-up 2 weeks; assessed with: self-reported by parents and children, six-point scale)												
1	randomized trials	serious[1]	no serious inconsistency[2]	serious	serious[3,]	none	13/15 (86.7%)	5/14 (35.7%)	RR 2.43 (1.17 to 5.04)	511 more per 1000 (from 61 more to 1000 more)	VERY LOW	CRITICAL
								0%		-		
Intensity abdominal pain (follow-up 2 weeks)												
1	randomized trials	serious[1]	no serious inconsistency[2]	serious	Serious[3,]	none	13/15 (86.7%)	4/14 (28.6%)	RR 3.03 (1.29 to 7.11)	580 more per 1000 (from 83 more to 1000 more)	VERY LOW	CRITICAL
								0%		-		
Adverse events (follow-up 2 weeks)												
1	randomized trials	serious[1]	no serious inconsistency[2]	serious	no serious imprecision	none	2/15 (13.3%)	0/14 (0%)	RR 4.69 (0.24 to 89.88)	-	LOW	
								0%		-		

[1] Short follow-up (two weeks only).

[2] One study only.

[3] Total numbers of events is less than 300 and 95% CI around the pooled estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm.

GRADE evidence profile laxative with tegaserod

Question: Should Laxative with tegaserod vs Laxative be used for adolescents with constipation dominated IBS?

Settings: Medical Center New Orleans

Bibliography: Khoshoo *et al.* 2006

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Laxative with tegaserod**	**Laxative**	**Relative (95% CI)**	**Absolute**		
Adequate pain reducation (follow-up 4 weeks; assessed with: scale 0-10)												
1	randomized trials	serious[1]	no serious inconsistency[2]	serious[3]	serious[4]	none	14/21 (66.7%)	5/27 (18.5%)	RR 3.60 (1.54 to 8.40)	481 more per 1000 (from 100	VERY LOW	CRITICAL

										more to 1000 more)		
								0%		-		
Adverse events (follow-up 4 weeks)												
1	randomized trials	serious[1]	no serious inconsistency[2]	serious[3]	no serious imprecision	none	0/21 (0%)	0/27 (0%)	-	-	LOW	CRITICAL

[1] There was no blinding for type of medication.

[2] One study only.

[3] The study was not placebo-controlled.

[4] Very low sample size (n=48).

Chapter 6

Nonpharmacologic treatment of functional abdominal pain disorders: A systematic review

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Abstract

Objective

Various nonpharmacologic treatments are available for pediatric abdominal pain-related functional gastrointestinal disorders (AP-FGIDs). Data on efficacy and safety are scant. The goal of this study was to summarize the evidence regarding nonpharmacologic interventions for pediatric AP-FGIDs: lifestyle interventions, dietary interventions, behavioral-interventions, prebiotics and probiotics, and alternative medicine.

Methods

Searches were conducted of the Medline and Cochrane Library Databases. Systematic reviews and randomized controlled trials (RCTs) concerning nonpharmacologic therapies in children (3-18 years) with AP-FGIDs were included, and data were extracted on participants, interventions, and outcomes. The quality of evidence was assessed by using the GRADE approach.

Results

Twenty-four RCTs were found that included 1390 children. Significant improvement of abdominal pain was reported after hypnotherapy compared with standard care/wait-list approaches and after cognitive behavioral therapy compared with a variety of control treatments/wait-list approaches. Written self-disclosure improved pain frequency at the 6-month follow-up only. Compared with placebo, *Lactobacillus rhamnosus* GG (LGG) and VSL#3 were associated with significantly more treatment responders (LGG: relative risk 1.31 [95% confidence interval 1.08 to 1.59]; VSL#3: $p<0.05$). Guar gum significantly improved irritable bowel syndrome symptom frequency; however, no effect was found for other fiber supplements (relative risk 1.17 [95% confidence interval 0.75 to 1.81]) or a lactose-free diet. Functional disability was not significantly decreased after yoga compared with a wait-list approach. No studies were found concerning lifestyle interventions; gluten-, histamine- and carbonic acid-free diets; fluid intake; or prebiotics. No serious adverse effects were reported. The quality of evidence was found to be very low to moderate.

Conclusions

Although high-quality studies are lacking, some evidence shows efficacy of hypnotherapy, cognitive behavioral therapy and probiotics (LGG and VSL#3) in pediatric AP-FGIDs. Data on fiber supplements are inconclusive.

Introduction

Abdominal pain-related functional gastrointestinal disorders (AP-FGIDs), diagnosed according to the Rome III criteria, are defined as chronic or recurrent abdominal pain, not explained by underlying organic disorders.[1] AP-FGIDs affect ~20% of children worldwide and include functional dyspepsia, irritable bowel syndrome (IBS), abdominal migraine, functional abdominal pain (FAP) and functional abdominal pain syndrome.[1,2] AP-FGIDs have great impact on children and adolescents' quality of life, daily activities, and school absenteeism and can have long-term psychological implications.[3] Moreover, patients are at risk for continued symptoms in adulthood, and costs are substantial.[4–6]

Standard medical care consists of reassurance, education and, dietary advice.[7] Despite ongoing efforts to identify causal and contributing factors in AP-FGIDs, successful management is complicated by an incomplete pathophysiological understanding. The biopsychosocial model, based on a complex interplay of genetic, physiological, and psychological factors, is conceptualizing the etiology of FGIDs.[7] It is hypothesized that pediatric AP-FGIDs are strongly associated with stress and psychological disorders such as anxiety and depression,[8] wherein the coping potentials of children with AP-FGIDs are low compared to those of healthy children.[9] Therefore, interventions such as cognitive behavioral therapy (CBT), hypnotherapy (HT), and yoga are aiming to teach alternative responses to stress.[10] Systematic reviews have concluded that CBT and HT offer beneficial effects for children with AP-FGIDs.[11,12]
The role of food in FGIDs has been revisited recently in the adult literature.[13,14] Food may trigger symptoms in FGID patients who already have physiologic alterations, subsequently making them susceptive for hypersensitivity.[13] However, recognition which specific food components trigger symptoms is difficult and can lead to profusion of investigations and dietary therapies, largely based on expert opinion.[14] Two previous systematic reviews reported that fiber supplements are ineffective in treating AP-FGIDs, whereas conclusions were contradictory regarding probiotics.[15,16]

Treatment of children who have AP-FGIDs can be challenging, especially because high-quality evidence for pharmacologic interventions is lacking.[17] Although several systematic reviews summarizing different nonpharmacologic interventions exist,[11,15,18] the present systematic review provides an up-to-date overview regarding the efficacy and safety of all nonpharmacologic treatments for pediatric AP-FGIDs. Such a comprehensive and recent overview is warranted.

Methods

Literature search

The Cochrane Library and Medline databases were searched for systematic reviews and randomized controlled trials (RCTs) from inception to October 2013. Search terms used items related to pediatric AP-FGIDs and various nonpharmacologic treatments. To identify additional studies, reference lists of reviews and included studies were searched by hand. The full search strategy and keywords are available from the authors.

Study inclusion

Two authors (L.M.A.J.V. and M.M.T.) independently assessed eligibility of all abstracts. In case of disagreement, consensus was reached through discussion. Inclusion criteria were: (1) study was a systematic review or RCT; (2) study population comprised children aged 3 to 18 years; (3) diagnosis

of recurrent abdominal pain (RAP), FAP, IBS, functional dyspepsia, abdominal migraine, or functional abdominal pain syndrome as defined by authors; (4) interventions were lifestyle advice such as physical exercise, dietary interventions (fiber supplements; lactose-, gluten-, histamine-, and carbonic acid-free diets; and fluid intake), behavioral interventions such as HT, CBT, prebiotics and probiotics and alternative medicine (acupuncture, homeopathy, mind-body therapy, musculoskeletal manipulations such as osteopathic and chiropractic manipulations and spiritual therapies such as yoga); (5) the intervention was compared with placebo, no treatment, any other nonpharmacologic treatment or pharmacologic agent; and (6) outcomes were abdominal pain intensity and/or frequency, quality of life, functional disability (eg, school absence), and adverse effects. Exclusion criteria were: (1) treatment arm with <10 patients; and (2) language other than English. Potentially relevant studies and studies in which title and abstract provided insufficient information were retrieved as full-text articles.

Quality assessment and data extraction

Two authors (L.M.A.J.V. and M.M.T.) independently rated the methodologic quality of the included studies using the Cochrane risk of bias tool. For each outcome, quality of evidence was assessed using the GRADE approach and was categorized as very low, low, moderate, or high.[19–21]

The same authors extracted data from included studies using structured data extraction forms containing items on participants, study setting, interventions, and outcomes. Disagreements were resolved through consensus or by a third reviewer (M.A.B.).

Data analysis

Dichotomous outcomes were analyzed as odds ratios (ORs) or relative risks (RRs) along with 95% confidence intervals (CIs). For continuous outcomes, mean differences (MDs) with 95% CIs were reported. Heterogeneity was quantified by using $\chi 2$ tests and the I^2 statistic, which can be interpreted as the percentage of the total variation between studies that is attributable to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, whereas larger values show increasing heterogeneity. If heterogeneity was not revealed, results of the fixed effect model are presented. If there was substantial heterogeneity (>50%), the random effect model was used.

Results

A total of 568 potentially relevant articles and abstracts were identified (Fig. 1). After removal of duplicates (*n*=316) and abstracts screening (*n*=210), 42 full-text articles were assessed for eligibility. Twenty-nine articles were excluded because of the following: adult study population (*n*=6), irrelevant outcome measures, such as improvement in rectal sensitivity or gastrointestinal symptoms without abdominal pain (*n*=2), no systematic review or RCT (*n*=15), or inclusion of only trials which were already included by another systematic review (*n*=6). Thirteen articles remained for analysis: 7 systematic reviews[11,12,15,16,18,22,23] (including 18 RCTs) and 6 RCTs.[24–29] Two included trials concerned follow-up studies,[26,30] which will be discussed by their original studies.[31,32]

Two systematic reviews[11,12] included studies with <10 patients per treatment arm and these studies were therefore excluded[33-35]

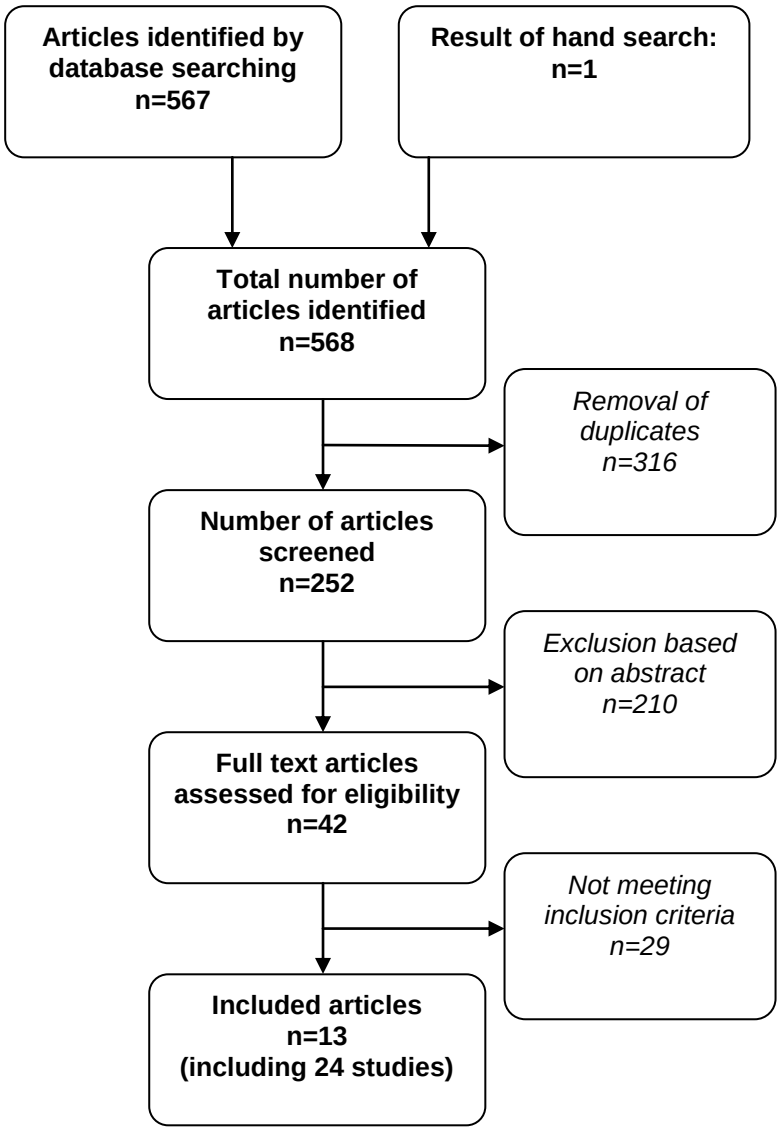

Figure 1 | Flowchart showing results of the literature search and study inclusion

Data of 1390 children aged 3 to 18 years were included for analysis. Sample sizes ranged from 21 to 200, and follow-up varied from 2 weeks to 5 years. Four trials investigated fiber supplements compared with placebo,[24,36–38] and 2 trials studied a lactose-free diet.[39,40] Four trials investigated probiotics,[27,41–43] and 3 trials compared HT versus standard care or a wait-list.[25,32,44] Seven studies compared CBT with standard care, physiotherapy, fiber supplements, biofeedback, and/or parental support.[28,31,45–49] One trial compared yoga with a wait-list[50] and 1 trial evaluated written self-disclose (WSD) in addition to standard care.[29] No studies were included on lifestyle advice or prebiotics. A range of different outcomes were measured, and even if the same outcome was measured, different measurement instruments were used. All trials measured abdominal pain as the primary or secondary outcome.

Nine studies reported disability or school absenteeism.[25,31,32,38,42,44,47,49,50] Four studies assessed quality of life,[25,28,29,44] and 8 studies assessed adverse effects.[24,25,37,38,41–44] Data of 3 studies were used to perform a meta-analysis of the efficacy of fiber supplements,[36–38] and 3 studies were used to perform a meta-analysis on probiotics.[41–43]

Table 1 presents the characteristics of the included studies.

Table 1 | Study characteristics of included studies

Study	Participants	Interventions	Outcome measures & instruments	Quality
Fiber supplements and guar gum				
Christensen[36] (1986) Denmark	Children aged 3-14 y (*N*=40) RAP (at least 10 episodes of abdominal pain during the last 6 wk, organic causes of pain were excluded)	Fibers (ispaghula husk) vs placebo Dosage: Visiblin 5 mL twice daily; crushed crisp bread with 66% fiber Treatment period: 6 wk	*Abdominal pain frequency score* Improvement: <10 episodes of pain during the study period Instrument: pain diary	Low
Feldman[37] (1985) Canada	Children aged 5-15 y (*N*=52) RAP (organic causes of pain were excluded on the ground of history, examination, and simple laboratory tests)	Fiber cookies vs placebo Dosage: 5 g of corn fiber per cookie; 1 cookie twice daily Treatment period: 6 wk	*Abdominal pain frequency score* Improvement: 50% decrease in frequency of attack Instrument: pain diary	Low
Horvath[38] (2013) Poland	Children aged 7-17 y (*N*=90) IBS, FAP and functional dyspepsia (Rome III criteria)	GNN vs placebo Dosage: 2.52 g/d Treatment period: 4 wk Follow-up: -	*Severity of pain* Improvement: no pain or a decrease ≥2/6 points on the FPS-R Instrument: FPS-R *School absenteeism* *Changes in daily activity* Instrument: self-reported at baseline and final visit	Low
Romano[24] (2013) Italy	Children aged 8-16 y (*N*=60) IBS-C and IBS-D (Rome III criteria)	PHGG vs placebo Dosage: 5g/d Treatment period: 4 wk Follow-up: 4 wk	*IBS symptoms* Treatment success: improvement IBS symptoms Instrument: Birmingham IBS Symptom Questionnaire score *Intensity of abdominal pain* Instrument: Wong-Baker FACES Pain Rating Scale	Moderate
Fructose and lactose				
Dearlove[39] (1983) United Kingdom	Children aged > 3 y (*N*=21) RAP (>1/ 4 d in the last 3 mo)	Lactose vs placebo Dosage: 2 g/kg Treatment period: 2 wk Follow-up: 3 mo	*Abdominal pain* Instrument: reported at final visit (better, worse, same)	N/A

Table 1 | Study characteristics of included studies *(continued)*

Study	Participants	Interventions	Outcome measures & instruments	Quality
Lebenthal[40] (1981) United States	Children aged 6-14 y (*N*=38) RAP (intermittent episodes of unexplained abdominal pain, in a 4-mo period)	Lactose vs lactose-free formula Dosage: 2dd 200mL Treatment period: 6 wk Follow-up: 12 mo	*Abdominal pain (severity and frequency)* Instrument: pain diary	N/A
Hypnotherapy				
Gulewitsch[25] (2013) Germany	Children aged 6-12 y (*N*=38) FAP and IBS (Rome II criteria)	HT program consist of 4 sessions, 2 children's sessions and 2 parent's sessions in a weekly sequence. Control: wait-list Treatment duration: 4 wk Follow-up: 3 mo	*Abdominal pain index* Clinical remission: > 80% decrease of days of pain, duration, and intensity of abdominal pain Instrument: abdominal pain dairy *Quality of life* Instrument: German KINDL questionnaire *Disability* Instrument: Pediatric Pain Disability Index *School absenteeism* Instrument: abdominal pain dairy	Low
Van Tilburg[44] (2009) United States	Children aged 6-15 y (*N*=34) FAP (abdominal pain at least once a week in the past 3 mo)	Standard care + guided imagery; 3 biweekly sessions, including 1 booster session + 3 daily sessions. Listen to tape with self-exercises ≥ 5 d/wk Control: standard care Treatment period: 2 mo Follow-up: 6 mo	*Improvement of abdominal pain* Treatment response: >50% reduction of abdominal pain score Instrument: Abdominal Pain Index *Quality of life* Instrument: Peds QL *Disability* Instrument: Functional Disability Inventory *School absenteeism* Instrument: abdominal pain dairy	Low

Table 1 | Study characteristics of included studies *(continued)*

Study	Participants	Interventions	Outcome measures & instruments	Quality
Vlieger[30,32] (2007/2012) the Netherlands	Children aged 8-18 y (*N*=53) FAP and IBS (Rome II criteria)	6 HT sessions Control: Standard medical care + supportive therapy Treatment period: 3 mo Follow-up: 1 y and 5 y	*Abdominal pain score* Clinical remission: > 80% decrease of intensity and frequency of abdominal pain Instrument: abdominal pain dairy *School absenteeism* Instrument: abdominal pain dairy	Low
Cognitive behavioral therapy				
Duarte[45] (2006) Brazil	Children aged 5-14 y (*N*=32) RAP (Apley's criteria)	4 monthly sessions of CBT-family Control: standard care Treatment period: 4 mo Follow-up: -	*Abdominal pain intensity* Instrument: red and white VAS *Abdominal pain frequency* Instrument: daily numbers of pain in pain dairy	Low
Sanders[46] (1994) Australia	Children aged 7-14 y (*N*=44) RAP (Apley's criteria)	6-session CBT-family Control: standard care Treatment period: 8 wk Follow-up: 6 and 12 mo	*Abdominal pain intensity* Instrument: VAS	Very low
Robins[47] (2005) United States	Children aged 6-16 y (*N*=69) RAP (Apley's criteria)	5-session CBT-family + standard care Control: standard care Treatment period: 10 mo Follow-up: 3 and 6 mo	*Abdominal pain* Instrument: Abdominal Pain Index. *Disability* Instrument: Functional Disability Inventory *School absenteeism* Instrument: Record of school attendance	Low
Levy[26,31] (2010/2013) United States	Children aged 7-17 y (*N*=200) RAP (≥3 episodes of abdominal pain during a 3-mo period)	3-session social learning + CBT-family Control: education + support intervention Treatment period: 3 wk Follow-up: 12 mo	*Abdominal pain intensity* Instrument: FPS-R *Disability* Instrument: Functional Disability Inventory	Very low
Alfvén and Lindstrom[48] (2007) Sweden	Children aged 6-18 y (*N*=48) RAP (Apley's criteria)	Psychological + psychotherapy Control: physiotherapy Treatment period: at least 2 sessions, according to the expressed needs Follow-up: 12 mo	*Abdominal pain intensity* Instrument: VAS *Pain score at one year follow-up:* Instrument: VAS + duration (min) + frequency (per week)	Very low

Table 1 | Study characteristics of included studies *(continued)*

Study	Participants	Interventions	Outcome measures & instruments	Quality
Humphreys and Gevirtz[49] (1998) United States	Children aged 4-18 y (*N*=64) RAP	4 groups: 1. Fiber + biofeedback + CBT + parental support 2. Fiber + biofeedback + CBT 3. Fiber + biofeedback 4. Fiber Treatment period: 8-session CBT Dosage: 10+ g/d fiber cookies or bars Follow-up: -	*Abdominal pain intensity* Instrument: VAS *School absenteeism* Instrument: Record of school attendance	Moderate
Groß and Warschburger[28] (2013) Germany	Children aged 6-12 y (*N*=29) CAP (Rome III criteria)	6-session CBT (group sessions) + listen to CD with self-exercises Control: wait-list Treatment period: 2 mo Follow-up: 3 mo	*Abdominal pain intensity* Instrument: VAS *Abdominal pain frequency (times per day)/duration (hours per day)* Instrument: pain diary *Quality of life* Instrument: PedsQL	Low
Written self-disclosure				
Wallander[29] (2011) USA	Children aged 11-17 y (*N*=63) RAP (Apley's criteria)	WSD + standard care: 3 writing sessions of 20 min Control: standard care Treatment period: 5 d Follow-up: 6 m	*Abdominal pain frequency* Instrument: abdominal pain frequency rating *Quality of life* Instrument: PedsQL	Low
Probiotics				
Bausserman and Michail[41] (2005) USA	Children aged 6-17 y (*N*=64) IBS (Rome II criteria)	LGG vs placebo Dosage:10^{10} CFU, twice daily Treatment period: 6 wk Follow-up: -	*Abdominal pain severity* Responders: decreased pain score of ≥1 point Instrument: severity of symptom scale	Moderate

Table 1 | Study characteristics of included studies *(continued)*

Study	Participants	Interventions	Outcome measures & instruments	Quality
Francavilla[43] (2010) Italy	Children aged 5-14 y (*N*=141) IBS and FAP (Rome II criteria)	LGG vs placebo Dosage: $3x10^9$ CFU, twice daily Treatment period: 8 wk Follow-up: 8 wk	*Abdominal pain (frequency/severity)* Treatment success: a decrease of at least 50% in the number of episodes and intensity of pain Instrument: VAS	Moderate
Gawrońska[42] (2007) Poland	Children aged 6-16 y (*N*= 104) FAP, functional dyspepsia, and IBS (Rome II criteria)	LGG vs placebo Dosage: $3x10^9$ CFU, twice daily Treatment period: 4 wk Follow-up: -	*Abdominal pain intensity* Improvement: no pain or a change in the FPS-R by at least 2 faces Instrument: FPS-R *School absenteeism* Instrument: Record of school attendance	Moderate
Guandalini[27] (2010) Italy and India	Children aged 4-18 y (*N*=59) IBS (Rome II criteria)	VSL#3 vs placebo Dosage: 4-11y: 1 sachet, 12-18y: 2 sachets Treatment period: 6 wk Follow-up: -	*Abdominal pain score (frequency and intensity)* Responders: decreased pain score of ≥1 point Instrument: self-administered questionnaire	Very low
Alternative medicine				
Kuttner[50] (2006) Canada	Children aged 11-18 y (*N*=25) IBS (Rome I criteria)	Yoga intervention for 1 hour followed by daily home practice guided by a video Control: wait-list Treatment period: 4 wk Follow-up: -	*Abdominal pain intensity* Instrument: numeric rating scale *Disability* Instrument: Functional Disability Inventory	Very low

CAP=chronic abdominal pain; CFU=colony-formic units; FPS-R=faces pain scale-revised; GNN=glucomannan; IBS-C=irritable bowel syndrome constipation predominant; IBS-D=irritable bowel syndrome diarrhea predominant; N/A=not available; PedsQL=Pediatric Quality of Life Inventory; VAS=visual analog scale

Methodological Quality

The overall quality of evidence was very low to moderate. Appendix 1 shows the GRADE evidence profiles. Concealment of allocation was unclear in 6 studies.[36,44–46,48,49] Due to the nature of HT, CBT, WSD, and yoga, blinding was not possible for the caregiver or patient.[25,28,29,31,32,44–50] Dropout was considerable in 4 studies,[36,40,41,47] or vaguely described in 3 others.[31,46,50] Two studies excluded patients, due to poor compliance.[40,41] The method of randomization was unclear in 3 studies.[27,31,50] Alfvén and Lindstrom[48] provided no information on outcome blinding or treatment duration. Six trials did not present results with absolute numbers and could therefore not be included in the meta-analysis.[27,39,40,44,47,48] Analyses for follow-up were uncontrolled for baseline differences by Levy *et al.*[31] Because participants were recruited through physician referral and flyers, these patients were therefore seriously motivated, which can cause bias.

Dietary interventions

No studies were included evaluating gluten-, histamine- and carbonic acid-free diets or fluid intake.

Fiber supplements

Two systematic reviews[15,16] including 3 RCTs[36–38] and 1 RCT[24] evaluated the efficacy of fiber supplements compared with placebo for RAP. A systematic review by Huertas-Ceballos *et al.*[15] included 2 RCTs, involving 92 children aged 3 to 15 years.[36,37] Children received fiber supplements for 6 weeks. No information was available regarding daily fiber intake before and/or during intervention weeks. Information about abdominal pain was collected through the use of diaries, but the authors did not clarify how these diaries were analyzed. The systematic review by Horvath *et al.*,[16] included a third trial with 90 children (aged 7 to 17 years) receiving 4 weeks of glucomannan or identical placebo.[38] Pain severity was assessed by using the Faces Pain Scale Revised(6 faces ranging from relaxed to intense pain).[51] School absenteeism and changes in daily activities were self-reported. The primary outcome in all studies was degree of improvement based on abdominal pain frequency or intensity. After pooling, there was no significant difference between the fiber group in experiencing “no pain” and/or “satisfactory improvement” (52.4%) and the placebo group (43.5%) (RR: 1.17 [95% CI 0.75 to 1.81]). Concerning secondary outcomes, no significant differences for school absenteeism (10% vs 14%; p=0.56) or daily activities (27% vs 19%; p=0.37) after glucomannan treatment compared with placebo were found.[38]

Romano *et al.*[24] enrolled 60 patients (aged 8 to 16 years) comparing 4 weeks of partially hydrolyzed guar gum (PHGG), a water-soluble, dietary fiber, with placebo. Symptoms were assessed by using the Birmingham IBS Symptom Questionnaire, which contains questions on frequency of IBS symptoms (0=none, 5=all the time),[52] and the Wong-Baker FACES Pain Rating Score, which was used to evaluate abdominal pain severity (0=no hurt, 5=hurts worst).[53] The primary outcome was the reduction in frequency and intensity of IBS symptoms. Improvement in the frequency of IBS symptoms was significantly more likely in the PHGG group compared with the control group (43% vs 5 %; p=0.025) after 8 weeks. Effects on pain intensity were not significant.

Three studies assessed adverse effects.[24,37,38] Unknown small numbers of children in both groups reported gas or diarrhea in the trial by Feldman *et al.*[37] Horvath *et al.*[38] and Romano *et al.*[24] reported no adverse effects.

Lactose-free diet

Huertas-Ceballos *et al.*[15] included 2 trials evaluating a lactose-free diet in RAP.[39,40] Lebenthal *et al.*[40] enrolled 95 participants. After an intestinal biopsy was conducted, those patients with abnormal lactase activity (12-20 U) were excluded: 69 children received 6 weeks of a lactose-containing or

lactose-free infant formula. Abdominal pain was documented in diaries by parents. Remarkably, 31 children were excluded due to a lack of compliance; 38 children remained. A lactose tolerance test was performed, the results of which were used to divide children into 2 groups: lactose malabsorbers (*n*= 21) and lactose absorbers (*n*=17). Increased symptoms were described in 48% of the lactose malabsorbers and 24% of lactose absorbers after lactose intake; however, *p*-values were not reported. Forty of the 69 children continued with a 12-month lactose-free diet. Improvement of abdominal pain after 12 months was similar in both groups (40% vs 38%). Detailed data were not reported, however, and meta-analysis and GRADE evidence profiling were therefore not possible.

Dearlove *et al.*[39] included 21 children with RAP in a double-blind, single cross-over study. After 2 weeks of collecting baseline data, all children underwent a 2-week lactose-free diet, followed by another 2 weeks of lactose tonic (2 g/kg) or similarly flavored placebo. Primary and secondary outcomes were not specified. After 3 months, parents were asked whether their child's symptoms (including abdominal pain) were better, worse, or the same. There was no difference in the number of children claiming relief from lactose-free or lactose-containing formula.

Hypnotherapy

One systematic review[11] (including 2 RCTs[32,44]) and 1 RCT[25] evaluated the effects of HT for FAP and IBS. Two studies examined HT by therapists [25,32] and 1 examined HT with self-exercises on CD.[44] All studies used diaries to assess pain intensity and frequency. Gulewitsch *et al.*[25] recalculated pain scores into an abdominal pain index. The abdominal pain index, disability and school absenteeism were the primary outcomes. Clinical remission was defined as > 80% decrease on the abdominal pain index: 55% (11 of 20) of children showed clinical remission after HT, compared to 5.6% (1 of 18) of wait-list control subjects (RR 9.90 [95% CI 1.14 to 69.28]).

Vlieger *et al.*[30,32] included 53 children in their research. Clinical remission, defined as a >80% reduction of abdominal pain scores, was the primary outcome. After 3 months of HT, 59% showed clinical remission compared to 12% receiving standard care ($p<0.001$). Differences persisted after 1 (85% vs 25%; $p<0.001$) and 5 years (68% vs 20%; $p=0.005$).[30,32]

Van Tilburg *et al.*[44] compared 19 children receiving 2 months of standard care plus HT through self-exercises on CD with 15 children receiving standard care. Primary or secondary outcomes were not specified. Efficacy was based on an abdominal pain index,[54] with higher scores indicating more abdominal pain (range 0-40). After treatment, children receiving HT reached an improvement of 9.7 points vs 3.1 points in control subjects ($p=0.02$). Significantly more children responded to HT compared to controls (63% vs 27%, $p=0.03$). At 6 months follow-up, beneficial effects persisted in 62.5% of the HT-group.

Two trials assessed quality of life, but results were conflicting.[25,44] To evaluate this secondary outcome, Gulewitsch *et al.*[25] used the validated German KINDL questionnaire. No significant effects were reported by children ($p=0.120$) or parents ($p=0.678$) compared with control subjects. Van Tilburg *et al.*[44] demonstrated a significant quality of life improvement compared to standard care ($p=0.049$), measured by using the validated Pediatric Quality of Life Inventory. Two studies reported significant improvement of disability.[25,44] Gulewitsch *et al.* used Pediatric Pain Disability Index to assess impairment in 12 daily activities. HT had a significant beneficial effect on the self-reported disability compared to control subjects (MD -9.14 [95% CI -14.41 to -3.87]).[25] Van Tilburg *et al.* used the Functional Disability Inventory.[44] Children receiving HT exhibited a significant reduction of disability compared to control subjects ($p=0.01$).

Two studies did not describe differences in school absenteeism between either treatment group.[32,44] In 1 trial, school absenteeism was seldom reported, and therefore no calculation was performed.[25] One

child dropped out because of transient headaches after listening to the CD.[44] Gulewitsch *et al.*[25] reported no side effects.

Cognitive behavioral therapy

Two systematic reviews[12,22] (including 6 RCTs)[31,45–49] and 1 RCT[28] were included in the assessment of the various CBT-methods. Four trials evaluated the efficacy of family-focused cognitive behavioral therapy (CBT-family).[31,45–47] A visual analog scale (VAS)[45,46] and Faces Pain Scale-Revised[31] were used to assess pain intensity. Robins *et al.*[47] used the Abdominal Pain Index for assessments.[47] Only Levy *et al.*[31] specified primary outcomes, which were abdominal pain intensity and disability scores. A significantly higher proportion of children in the trial by Sanders *et al.*[46] were pain free after CBT-family compared with standard care (MD -3.61 [95% CI -5.76 to -1.46]); these changes persisted at 6 months (p=0.02), but disappeared at the 12-month follow-up. Duarte *et al.*[45] reported significantly decreased abdominal pain frequency at 3 months follow-up (p=0.001), but no effect was seen for pain intensity. In the study by Robins *et al.*,[47] CBT-family added to standard care resulted in a significantly lower Abdominal Pain Index compared with standard care alone (p<0.05), with continuing effects at 6 and 12 months follow-up. Levy *et al.*[31] compared CBT-family with education and support intervention in 200 children. A significant reduction in pain intensity as indicated by parents was reported after 3 sessions of CBT-family (p<0.01). This reduction persisted for 12 months but was not significant when reported by children.[26] There was no beneficial effect of CBT-family for disability,[31,47] but a significant improvement in school absenteeism was reported after CBT-family plus standard care (p=0.047).[47]

Two studies evaluated the effects of individual CBT.[48,49] Alfvén and Lindstrom[48] randomized children to undergo CBT plus physiotherapy (N=25) or physiotherapy alone (N=23). Pain intensity score (1-3), frequency score (1-3), and duration score (1-3) were summed into individual pain scores ranging from 3 to 9. Pain score reduction at the 1-year follow-up was not significantly different between groups (46% vs 44%; p-value not reported). Humphreys and Gevirtz[49] divided 64 patients (aged 4-18 years) into 4 groups to compare CBT, fiber supplements, biofeedback, and parental support in different combinations. Children kept diaries and reported pain intensity using a VAS; the primary outcome was the number of self-reported pain free days. Results of the first 3 groups (CBT, biofeedback, and parental support) were combined and compared with a group receiving fiber supplements. After treatment, 33 (72%) of 46 children in the intervention groups were pain free compared to 1 (7.1%) of 14 children taking fiber supplements only (OR 33.0 [95% CI 3.9 to 278.5]).[22] Humphreys and Gevirtz[49] investigated school absenteeism and reported significant effects favoring CBT.

Groß and Warschburger[28] compared CBT group sessions (N=15) versus wait-list control subjects (N=14).[28] Pain intensity was assessed using a VAS. Although primary outcomes on pain intensity (p=0.001), frequency (p=0.003) and duration (p=0.002) significantly improved after CBT, only pain duration was still significant at 3 months follow-up (p=0.014). Quality of life was measured as a secondary outcome, using the Pediatric Quality of Life Inventory. A significant improvement favoring CBT was reported on physical functioning (p<0.001), psychological functioning (p=0.003), social functioning (p=0.044), and school functioning (p=0.012). However, results disappeared after 3 months of follow-up.

Written self-disclosure (WSD)

Wallander *et al.*[29] evaluated WSD in addition to standard care in 63 children (aged 11-18 years) with RAP. In three 20-minute sessions, patients were asked to write about their “deepest thoughts and feelings about the most distressing experience in their life”. Primary and secondary outcomes were not specified. Seven patients were lost to follow-up and excluded from analyses. Abdominal pain frequency was rated using a 6-point scale. Although there were no differences at 3 months, pain

frequency was significantly less after WSD and standard care at 6-month follow-up compared with standard care alone (F [1.51] = 6.50, p=0.014, Cohen's d=0.61). Physical and psychosocial quality of life was measured by using the Pediatric Quality of Life Inventory, and no significant differences were reported.

Pre- or probiotics

One systematic review[18] (including 3 RCTs[41–43]) evaluated the effects of *Lactobacillis rhamnosus* GG (LGG) compared with placebo. Data were pooled by Horvath *et al.* for treatment responders and treatment success, which were secondary outcomes. Baussermann and Michail[41] classified children as responders if abdominal pain severity decreased ≥1 points on a 4-point Likert scale. Francavilla *et al.*[43] used a VAS and defined treatment success as a decrease of >50% of pain episodes and intensity. Gawrońska *et al.*[42] defined treatment success as no pain or change in Faces Pain Scale-Revised by ≥2 faces. LGG supplementation was associated with significantly more treatment responders (67%) compared with placebo (51%) (N= 290; RR 1.31 [95% CI 1.08 to 1.59]; number needed to treat 7 [95% CI 4 to 22]).[18] Subgroup analysis showed results being mainly applicable for IBS (N = 167; RR 1.70 [95% CI 1.27 to 2.27]; number needed to treat 4 [95% CI 3 to 8]). Guandalini *et al.*[27] conducted a crossover trial, comparing 6 weeks of VSL#3 versus placebo in 59 children with IBS. VSL#3 is a probiotic mixture comprising 8 different strains of *Bifidobacterium, Lactobacillus, and Streptococcus.* After a 2-week washout period, each patient switched to the other group for another 6 weeks of treatment. Abdominal pain was measured as secondary outcome: frequency and intensity were rated on a 5-point Likert scale. After treatment, a significant reduction in the abdominal pain score of 1.0±0.2 was reported in the VSL#3 group versus 0.5±0.2 in control subjects (p<0.05). One study evaluated school absenteeism, but no significant difference was found.[42] No adverse effects of LGG were reported, although it was unclear in 2 studies how adverse effects were assessed.[41,42]

No studies were included on prebiotics.

Alternative medicine

One study of the systematic review by Birdee[23] *et al.* was included regarding alternative therapy. Kuttner *et al.*[50] compared 14 children receiving yoga to 11 wait-list control subjects. After 4 weeks, questionnaires were completed, and control subjects received 4 weeks of yoga and completed additional questionnaires. Pain intensity was measured on a numeric scale of 1 to 10. Results before the crossover phase were not reported because of baseline differences. Functional disability decreased after yoga, but increased in control subjects (MD -9.60 [95% CI -19.66 to 0.46]). Primary or secondary outcomes were not specified.

No studies were included evaluating acupuncture, homeopathy, mind-body therapy, musculoskeletal manipulations such as osteopathic and chiropractic manipulations.

Discussion

This systematic review includes 24 studies with very low to moderate methodologic quality. Some evidence was found indicating beneficial effects of PHGG, HT, CBT and probiotics (LGG and VSL#3). No beneficial effects were reported for fiber supplementation other than PHGG and a lactose-restricted diet. No studies were included on life-style advice, other dietary advice, or prebiotics. No serious adverse effects were reported.

Dietary interventions are frequently used in AP-FGIDs, because many patients and some physicians consider symptoms to be meal related.[55] Fiber supplementation is believed to be helpful because it

softens stools and enhances colonic transit.[56] However, studies in children and adolescents evaluating ispaghula husk and glucomannan found no favorable effects.[36,38] Improvement in abdominal pain frequency was reported after administration of corn fiber,[37] but questions were raised whether statistical analyses were adequate. Re-analyses by Huertas-Ceballos *et al.*,[15] failed to replicate the findings. Adult studies produced conflicting results and a meta-analysis reported only beneficial effects for ispaghala husk.[56] The main component of PHGG is galactomannan, which softens stool, improves fecal output and increases bulk capacities.[57] PHGG treatment in IBS children found a reduced frequency in IBS symptoms, but pain intensity was not decreased.[24] Results of an open PHGG trial in adult patients with IBS produced significant improvements in gastrointestinal symptoms, quality of life, and psychological distress, but the effects tended to fade out after the 12-week treatment period.[57]

Malabsorption and intolerance to carbohydrates such as fructose and lactose are believed to cause symptoms such as bloating, diarrhea and abdominal pain.[55] However, neither lactose nor fructose intolerance was established as a cause of pain in 220 children with RAP in a recent study,[58] and lactose restriction did not improve symptoms in pediatric trials.[39,40] Recently, diets of low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) have been extensively studied in adults. FODMAPs are poorly absorbed short-chain carbohydrates, which may cause gas production, bloating, and abdominal pain.[59] A low FODMAP diet seems beneficial in adult IBS trials, but due to heterogeneity in study design and outcomes and because of unknown long-term safety and efficacy, definitive conclusions cannot be drawn.[60] Recently, a randomized, double-blind, crossover trial in 33 IBS children reported improvement in abdominal pain after receiving a 48-hour low FODMAP diet.[61] Although these results seem promising, more longterm studies are needed to further assess the efficacy and safety of a low FODMAP diet in children and adolescents.

In HT, suggestions toward control and normalization of gut functioning, ego-strengthening, and stress reduction are conveyed to patients after inducing a hypnotic state.[62] Results of studies in children and adolescents found significantly lower abdominal pain levels and symptom scores after HT, either through individual or group sessions with therapists or with self-exercises on a CD.[25,32,44] Effects persist up to 5 years after treatment.[30] Results are in accordance with adult IBS trials showing that HT is superior to a variety of control treatments, with long-lasting effects.[63–66] Working mechanisms of HT are still poorly understood, but outcomes of adult studies hypothesize that HT affects both physiological processes, such as colonic motility and pain processing brain regions, and psychological factors such as stress and dysfunctional cognitions.[67–69]

CBT aims to change attitudes, cognitions and behavior that may play a role in generating or maintaining symptoms and is effective in improving pain and other IBS symptoms in adults.[70] Trials in children and adolescents also indicate beneficial effects of CBT, especially CBT-family, in improving pain and disability and effects appear to be long-lasting.[26,28,31,45–47] Results of the trial by Levy *et al.* trial are of particular interest since it includes 200 children and adolescents.[31] A RCT on individual CBT published shortly after the literature search of the present systematic review, showed improvement in 60% of children with FAP after CBT, but results did not differ compared to standard care (including 6 supportive sessions with the pediatric gastroenterologist).[71] However, children receiving CBT reported significantly less symptoms of anxiety or depression compared to children receiving standard care.

WSD targets psychosocial stress and may work through changing expression and increasing insight about emotions. It is reportedly effective in a wide variety of adult organic and functional disorders.[72] WSD in addition to standard care significantly reduced pain frequency after 6 months in pediatric RAP

but not after 3 months. Although further research is needed, WSD may be a useful adjunct to other treatment regimens because it can be easily integrated, requires little training, and has low costs.[29]

Probiotics are beneficial species of bacteria that may improve AP-FGID symptoms by preventing overgrowth of potentially pathogenic bacteria, maintaining integrity of gut mucosa and/or altering intestinal inflammatory responses.[73] RCTs in children and adolescents evaluating LGG and VSL#3 in FAP, IBS and functional dyspepsia indicate beneficial effects over placebo, but probiotics seem mostly effective in IBS.[27,41–43] Probiotics also seem effective in adults with AP-FGIDs, but future research must clarify which probiotic strains are most effective.[74]

Although >40% of children with IBS and FAP use complementary and alternative medicine,[75] data are lacking on the efficacy and safety of almost all forms of this treatment in these children and adolescents. Yoga may address psychosocial factors and decrease stress.[76] Kuttner *et al.*[50] reported significantly lower levels of functional disability and gastrointestinal symptoms after yoga, but it is noteworthy that *p* values <0.1 were considered reflective of statistical trends worthy of interpretation. However, a pilot study in children and adolescents aged 8 to 18 years with IBS and FAP also showed significant short-term improvement in abdominal pain frequency and intensity.[76] It thus seems worthwhile to further explore efficacy of yoga. Because treatment protocols in CBT, HT, and yoga all incorporate relaxation exercises, one might hypothesize that relaxation training alone can also be beneficial in AP-FGIDs. This therapeutic approach may be interesting to address in future research because it has been shown to be effective in children and adolescents with recurrent headaches as well.[77]

The methodologic quality of the included studies varied from very low to moderate, and the results should therefore be interpreted cautiously. The low quality was mainly due to small sample sizes, lack of adequate follow-up, substantial dropout rates, or considerable risk of bias. However, it should be taken into account that blinding of patients and caregivers is not possible in psychological therapies such as HT or CBT. By using validated diagnostic criteria for AP-FGIDs, applicability of results is increased, which strengthens the results. Due to considerable heterogeneity of studies, meta-analysis could only be conducted for fiber supplementation and probiotics. Other possible limitations of this systematic review include the possibility of publication bias and language restriction to English. However, by conducting a comprehensive and contemporaneous literature search, we attempted to minimize the risk of missing relevant studies. Use of a wide variety of definitions for clinical improvement also hampers the interpretation of results. Clinical relevance of a 1-point reduction on a 4-point Likert scale may be questioned,[41] while an 80% reduction in abdominal pain frequency and intensity scores seems overly conservative.[30,32] Unfortunately, a standard definition of improvement for therapeutic studies on AP-FGIDs is lacking. Consensus on a standard definition is necessary because it increases homogeneity of future trials and allows better comparison of results. In addition, performing analyses on number needed to treat and RR is often restricted because most RCTs fail to report on numbers or percentages of patients experiencing significant improvement.

A limited number of RCTs (*n*=8) reported on adverse effects, thereby hindering interpretation of results on safety. However, in those studies, no serious adverse effects were shown, apart from a small number of children reporting gas or diarrhea.[37] In interpreting FGID trials, the placebo effect may play an important role. Placebo responses in trials of adults with IBS vary from 16.0% to 71.4%,[78] and high placebo rates up to 53% were reported in RCTs on children and adolescents.[41,43,79] High placebo responses may also display natural course of FGIDs with fluctuating symptoms.[80] Improving the

patient-practitioner relationship and active listening approaches are essential in mediating placebo responses, which may be especially important in nonpharmacologic therapies in which contact with therapists is mostly frequent.[81,82]

Conclusion

To date, high-quality studies on nonpharmacologic treatments in pediatric AP-FGIDs are lacking, and the need for these studies is evident. However, available evidence indicates beneficial effects of HT, CBT and probiotics (LGG and VSL#3) in some children. Data on fiber supplementation for children and adolescents with AP-FGIDs is inconclusive, but PHGG may be an option. No serious adverse effects were reported.

Since symptoms may resolve without active treatment in a significant proportion of children, the first step in management may consist of physician reassurance and education. However, approximately one-third of children continue to experience symptoms.[83] Clinicians may consider HT, CBT or probiotics (LGG and VSL#3), especially in children with persisting symptoms. Additional high-quality studies are required in children with mild symptoms as well as severe symptoms to further assess the effectiveness of nonpharmacologic therapies and to identify factors predicting response, with the goal of optimizing and tailoring individual treatment. Because abdominal pain is the key symptom in AP-FGIDs and to decrease heterogeneity, we emphasized the importance of including abdominal pain severity, frequency, and/or intensity as a primary outcome measure in trials evaluating (non)pharmacologic treatments for AP-FGIDs. In addition, adverse effects need to be reported systematically to better assess safety.

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APPENDIX 1 | GRADE profiles

GRADE approach, was categorized as follows:

- *Very low*: Any estimate of effect is uncertain.
- *Low*: Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- *Moderate*: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- *High*: Further research is unlikely to change our confidence in the estimate of effect.

Dietary advices (n=4)

Question: Should fiber supplements vs placebo be used for recurrent abdominal pain?

Settings: private practices (Feldman), hospital (Christensen)

Bibliography: Christensen *et al.* 1986, Feldman *et al.* 1985, Horvath *et al.* 2013

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Fiber supplements**	**Placebo**	**Relative (95% CI)**	**Absolute**		
no pain and/or satisfactory improvement												
3	randomized trials	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	43/82 (52.4%)	37/85 (43.5%)	RR 1.17 (0.75 to 1.81)	76 more per 1000 (from 111 fewer to 361 more)	LOW	CRITICAL
								0%		-		

[1] Christensen: >20% was lost to follow-up.

[2] Moderate: I=40%

[3] Total number of events is less than 300 and 95% CI around the pooled estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm.

Question: Should guar gom vs placebo be used for chronic abdominal pain and irritable bowel syndrome?

Settings: Gastroenterology unit University

Bibliography: Romano *et al.* 2013

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Guar gom**	**Placebo**	**Relative (95% CI)**	**Absolute**		
intensity abdominal pain (follow-up 8 weeks; measured with: Wong-Baker face pain Rating score; Better indicated by lower values)												
1	randomized trials	no serious risk of bias	no serious inconsistency[1]	no serious indirectness	serious[2]	none	30	30	-	MD 0.42 lower (0.51 to 0.33 lower)	MODERATE	CRITICAL

[1] One study only.

[2] Low sample size (<400).

Hypnotherapy (n=3)

Question: Should hypnotherapy vs standard care / wait-list be used for functional abdominal pain or irritable bowel syndrome?

Settings: diverse

Bibliography: Vlieger *et al.* 2007, van Tilburg *et al.* 2009, Gulewitsch *et al.* 2013

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hypnotherapy	Standard care / wait-list	Relative (95% CI)	Absolute		
Abdominal pain index[1] (follow-up 2 weeks; assessed with: diary (days with pain, duration and intensity))												
1	randomized trials	serious[2]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	11/20 (55%)	1/18 (5.6%)	RR 9.90 (1.41 to 69.28)	494 more per 1000 (from 23 more to 1000 more)	LOW	CRITICAL
								0%		-		
Abdominal pain score[5] (follow-up 2 months; measured with: Likert scale (0-40); Better indicated by lower values)												
1	randomized trials	serious[6]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	19	15	-	MD 6.6 higher[7]	LOW	CRITICAL
Abdominal pain score[8] (follow-up 12 months; assessed with: diary card (>80% of patients with complete remission of pain))												
1	randomized trials	serious[9]	no serious inconsistency	no serious indirectness	serious[4]	none	22/26 (84.6%)	6/24 (25%)	RR 3.38 (1.66 to 6.9)	595 more per 1000 (from 165 more to 1000 more)	LOW	CRITICAL
								0%		-		
Quality of life[7,10] (measured with: question; Better indicated by lower values)												
1	randomized trials	serious[6]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	19	15	-	MD 18.9 higher	LOW	CRITICAL
School absence[8] (follow-up 5 years; assessed with: question)												
1	randomized trials	serious[9]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	7/22 (31.8%)	3/27 (11.1%)	RR 0.35 (0.10 to 1.19)	72 fewer per 1000 (from 100 fewer to 21 more)	LOW	CRITICAL
Disability score[1] (follow-up 2 weeks; measured with: questionnaire; Better indicated by higher values)												
1	randomized trials	serious[2]	no serious inconsistency[4]	no serious indirectness	serious[4]	none	20	18	-	MD 9.14 lower (14.41 to 3.87 lower)	LOW	CRITICAL

[1] Gulewitsch (2013)

[2] A wait-list design does not control for attention or expectation of a future symptom improvement.

[3] One study only.

[4] Low sample size.

[5] Van Tilburg (2009)

[6] Concealment of allocation unclear. Intervention unblinded.

[7] In the article not sufficient data are given to present (complete) results.

[8] Vlieger (2007)

[9] Intervention unblinded.

Cognitive behavioral therapy (n=7)

Question: Should cognitive-behavioral family therapy vs standard pediatric care be used for recurrent abdominal pain?

Settings: diverse

Bibliography: Sander *et al.* 1994, Robins *et al.* 2005, Duarte *et al.* 2006

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive-behavioral family therapy	Standard paediatric care	Relative (95% CI)	Absolute		
Pain intensity (follow-up 6 months; Better indicated by lower values)												
1	randomized trials	very serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	22	22	-	MD 3.61 lower (5.76 to 1.46 lower)	VERY LOW	CRITICAL
Median frequency of episodes of pain (Better indicated by lower values)												
1	randomized trials	serious[4]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	15	17	-	median 6 higher (0 to 0 higher)[5]	LOW	CRITICAL
Abdominal pain index (Better indicated by lower values)												
1	randomized trials	serious[6]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	40	29	-	MD 3.3 higher (0 to 0 higher)[5]	LOW	CRITICAL

[1] Concealment of allocation was unclear. Outcome was assessed by parents and children who could not be blinded. In total 38/44 participants completed the study but we were unable to ascertain the numbers by group to which they were allocated.

[2] One study only.

[3] Low sample size.

[4] Concealment of allocation was unclear.

[5] In the article not sufficient data are given to present (complete) results.

[6] There is significant differential loss to follow-up in this study with outcome data are available for 40/46 patients in the intervention group and 29/40 in the control group.

Question: Should cognitive-behavioral interventions and dietary fiber vs dietary fiber alone be used for recurrent abdominal pain?

Settings: community Southern California, USA

Bibliography: Humphreys *et al.* 1998

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive-behavioral interventions and dietary fiber	Dietary fiber alone	Relative (95% CI)	Absolute		
Pain free (follow-up 8 weeks; assessed with: child's pain diary)												
1	randomized trials	serious[1]	no serious inconsistency[2]	no serious indirectness	no serious imprecision	none	33/46 (71.7%)	1/14 (7.1%)	OR 33.0 (3.9 to 278.5)	646 more per 1000 (from 159	MODERATE	CRITICAL

										more to 884 more)		
								0%		-		
School absences (follow-up 8 weeks; assessed with: Record of school attendence)												
1	randomized trials	serious[1]	no serious inconsistency[2]	no serious indirectness	no serious imprecision	none	-	-	-	-	MODERATE	CRITICAL
								0%		-		

[1] Concealment of allocation was unclear.

[2] One study only.

Question: Should psychological treatment and physiotherapy vs physiotherapy only be used for recurrent abdominal pain?

Settings: primarily, secondarily and tertiary referred children from suburban areas of Stockholm

Bibliography: Alfvén *et al.* 2007

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Psychological treatment and physiotherapy**	**Physiotherapy only**	**Relative (95% CI)**	**Absolute**		
Pain intensity (follow-up 1 years; measured with: VAS scale; Better indicated by lower values)												
1	randomized trials	very serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	25	23	-	MD 0.2 higher (0 to 0 higher)[4]	VERY LOW	CRITICAL

[1] Concealment of allocation and blinding of outcomes was unclear. Duration of treatment has not been described.

[2] One study only.

[3] Low sample size (n=48).

[4] In the article not sufficient data are given to present (complete) results.

Question: Should cognitive behavioral therapy vs education be used for functional abdominal pain?

Settings: Seattle, Washington and Morristown

Bibliography: Levy *et al.* 2010

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cognitive behavioral therapy**	**Education**	**Relative (95% CI)**	**Absolute**		
Pain reported by parents (follow-up 12 months; measured with: faces pain scale; Better indicated by lower values)												
1	randomized trials	very serious[1]	no serious inconsistency[2]	serious[3]	no serious imprecision	none	75	63	-	MD 0.77 lower (1.66 lower to 0.13 higher)	VERY LOW	CRITICAL
Functional disability reported by parents (follow-up 12 months; measured with: functional disability inventory; Better indicated by lower values)												
1	randomized trials	very serious[1]	no serious inconsistency[2]	serious[3]	no serious imprecision	none	75	63	-	MD 0.16 lower (0.48 lower to 0.15	VERY LOW	CRITICAL

										higher)		
Pain reported by child (follow-up 12 months; measured with: faces pain scale; Better indicated by lower values)												
1	randomized trials	very serious[1]	no serious inconsistency[2]	serious[3]	no serious imprecision	none	75	63	-	MD 0.55 lower (1.31 lower to 0.2 higher)	VERY LOW	CRITICAL

[1] Attrition is described, significant differences between completers and non-completers are not reported. Randomization unclear. Baseline differences.

[2] One study only.

[3] Participants were a volunteer group who had been referred by providers or responded to notices regarding the study. Consequently, they may not be representative of the larger population of families and children with FAP.

Question: Should cognitive behavioral group therapy vs wait-list be used for functional abdominal pain?

Settings: not reported

Bibliography: Groß *et al.* 2013

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cognitive behavioural group therapy**	**Wait-list**	**Relative (95% CI)**	**Absolute**		
Pain intensity (follow-up 3 months; measured with: VAS scale; Better indicated by lower values)												
1	randomized trials	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	15	14	-	MD 1.47 lower (1.45 lower to 0.01 higher)	LOW	CRITICAL
Pain frequency (follow-up 3 months; times per day measured with pain diary; Better indicated by lower values)												
1	randomized trials	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	15	14	-	MD 0.38 lower (0.38 lower to 0.03 lower)	LOW	CRITICAL
Pain duration (follow-up 3 months; hours per day measured with pain diary; Better indicated by lower values)												
1	randomized trials	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	15	14	-	MD 0.59 lower (0.71 lower to 0.19 lower)	LOW	CRITICAL
Quality of life (follow-up 3 months; measured with PedsQL; Better indicated by higher values)												

1	randomized trials	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	15	14	-	*Physical functioning:* MD 35.96 higher (31.66 higher to 11.16 lower) *Psychological functioning:* MD 18.36 higher (25.33 higher to 2.85 higher) *Social functioning:* MD 11.4 higher (11.33 higher to 1.07 lower) *School functioning:* MD 17.62 higher (18 higher to 1.79 lower)	LOW	CRITICAL

[1] No blinding

[2] One study only.

[3] Low sample size

Written self-disclosure (n=1)

Question: Should written self-disclose + standard care vs standard care be used for functional abdominal pain?

Settings: GI clinic USA

Bibliography: Wallander *et al.* 2011

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**WSD+ standard care**	**Standard care**	**Relative (95% CI)**	**Absolute**		
Pain frequency (follow-up 6 months; measured with Abdominal Pain Frequency Rating; Better indicated by lower values)												
1	randomized trials	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	32	24	-	MD 0.97 lower (0.58 lower to 0.29 higher)	LOW	CRITICAL
Quality of life (follow-up 6 months; measured with PedsQL; Better indicated by higher values)												
1	randomized trials	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	32	24	-	*Physical functioning:* MD 2.51 higher (1.96 higher to 0.51 lower) *Psychological functioning:* MD 1.91 higher (2.35 higher to 1.56	LOW	CRITICAL

										higher)		

[1] No blinding
[2] One study only
[3] Low sample size

Probiotics (n=4)

Question: Should lactobacillus rhamnosus vs placebo be used for abdominal pain-related functional gastrointestinal disorders?

Settings: countries: Poland, Italy, US

Bibliography: Horvath *et al.* 2011

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lactobacillus rhamnosus**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Pain intensity												
3	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	97/144 (67.4%)	75/146 (51.4%)	RR 1.31 (1.08 to 1.59)	159 more per 1000 (from 41 more to 303 more)	MODERATE	CRITICAL
								0%		-		

[1] In Bausserman the lost-to-follow up was >20%.

Question: Should VSL#3 vs placebo be used for IBS (ROME II)?

Settings: 5 pediatric tertiary care centers in Italy and India

Bibliography: Guandalini *et al.* 2010

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**VSL#3**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Abdominal pain (follow-up 6 weeks)												
1	randomized trials	serious[1]	no serious inconsistency[2]	serious[3]	serious[4]	none	-	-	-	-	VERY LOW	CRITICAL[5]

[1] No details about randomization mentioned.
[2] One study only.
[3] Only children with IBS have been included.
[4] Low sample size.
[5] In the article not sufficient data are given to present (complete) results.

Alternative medicine (n=1)

Question: Should yoga vs wait-list be used for IBS?

Settings: gastroenterology clinic at the local children's hospital and community (posters)

Bibliography: Birdee *et al.* 2009

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Yoga	Wait-list	Relative (95% CI)	Absolute		
Functional disability (follow-up 5 weeks; Better indicated by lower values)												
1	randomized trials	serious[1]	no serious inconsistency[2]	serious[3]	serious[4]	none	14	11	-	MD 9.60 lower (19.66 lower to 0.46 higher)	VERY LOW	CRITICAL

[1] No details about randomization. No description of the reasons for lost to follow-up.

[2] One study only.

[3] Children aged 11-18 years with IBS.

Chapter 7

Probiotics for childhood functional gastrointestinal disorders: a systematic review and meta-analysis

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Abstract

Objective

A systematic review and meta-analysis was performed to investigate the quantity and quality of the current evidence regarding the effect of different probiotics strains in the treatment of functional gastrointestinal disorders (FGIDs) in children and adolescents.

Conclusion

Probiotics are more effective than placebo in the treatment of patients with abdominal pain-related FGIDs, especially with respect to patients with irritable bowel syndrome. To date, however, probiotics have not proved effective for children with functional constipation.

Introduction

Functional gastrointestinal disorders (FGIDs), as currently diagnosed according to the Rome III criteria, are defined as a variable combination of chronic or recurrent gastrointestinal symptoms that cannot be explained in terms of structural or biochemical abnormalities.[1] For children and adolescents, FGID are classified into three categories: abdominal pain- and defecation-related FGIDs, vomiting and aerophagia. Abdominal pain-related FGIDs are present in 0.3-19% of school children in the US and Europe and is one of the most frequent reasons to visit a paediatrician.[2] Functional constipation has a prevalence of 3% in the Western world.[3] Although the prognosis of FGIDs is benign, its overall impact can seriously disminish indivuals' well-being and quality of life.[4]

The pathogenesis underlying abdominal pain-related FGIDs remains unclear. Altered gut motility, visceral hypersensitivity, abnormal brain-gut interaction, psychosocial disturbance and immune activation have all been suggested as explanations for the symptoms.[5, 6] Furthermore it has been established that enteric microbiota can directly influence gut homeostasis by affecting the bowel motility and modulation of intestinal pain, immune responses and nutrient processing.[7-9] Recently an association has been suggested between the microbiome and development and manifestation of symptoms of irritable bowel syndrome (IBS).[10] Indeed, children with IBS yielded greater proportions of the phylum *Proteobacteria* than healthy children.[10] This observation underlines the potential importance of microbial manipulation strategies in the prevention and management of recurrent abdominal pain.

The pathophysiology of childhood constipation is multifactorial and not well understood. In more than 90% of all age groups no obvious cause can be identified.[11] Genetic predisposition, low socioeconomic status, inadequate daily fiber intake, insufficient fluid intake and immobility have been proposed as factors leading to constipation.[3] The exact character of the relationship between functional constipation and disturbances in the microflora of the bowel has not been determined. Nevertheless, it is known that commensal bacteria influence motility, and that the *Bacterium bifidum*, in particular, tends to promote short chain fatty acid production which reduces transit time. In contrast, an absence of this probiotic bacterial species tends to prolong transit time in both human and animal models.[12]

In the past decade, the role of probiotics, defined as live microorganisms which, when administered in adequate amounts, confer a health benefit on the host, has been studied in children with IBS[13, 14] and constipation.[15, 16,17]. Different probiotic strains have shown efficacy in the treatment of childhood infectious diarrhoea and antibiotic associated diarrhoea,[18] but results with respect to the treatment of IBS and constipation have been conflicting.[13, 15, 19, 20]
Therefore, we systematically reviewed the literature to evaluate the effect of different probiotic strains in the treatment of abdominal pain- and defecation related FGIDs.

Methods

Literature search

We systematically searched the Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library issue 8, 2012), MEDLINE (1966-2012), EMBASE (1980-2012) and CINAHL (1982-2012) up to June 2013. Studies on FGIDs were identified with the search terms vomit, aerophagy,

abdominal migraine, constipation, faecal incontinence, abdominal pain, gastrointestinal diseases, functional gastrointestinal disorder, irritable bowel syndrome, recurrent abdominal pain or functional abdominal pain (both as medical subject heading (MeSH) and free text terms). These were combined, using the set operator AND, with studies identified with the terms: probiotic, Lactobacillus or Bifidobacterium (MeSH and free text terms). The search was restricted to children and adolescents. No other limits were applied to any of the searches. Additional strategies for identifying studies included searching the reference lists of review articles and included studies. When necessary, we contacted the authors for additional information.

Selection

We included randomised controlled trials (RCT) comparing the effects of any probiotic therapy with placebo in children and adolescents with functional gastrointestinal disorders. Studies were included when a definition of FIGD was given according to the ROME II, ROME III criteria or as defined by the authors. The study population consisted of children and adolescents aged 0 to 18 years. Trials that permitted other concomitant therapies were eligible, as long as these therapies were administered to both the intervention and control arms. There was no restriction for dose or duration of the treatment. Primary outcome was treatment success, defined as the absence of, or a reduction of, abdominal pain (decrease of intensity or frequency of pain) or an improvement of stool pattern (defecation at least three times per week and no faecal incontinence or episodes of faecal incontinence less than one time in two weeks). Secondary outcome measures were: abdominal pain (frequency/intensity), stool pattern (defecation frequency/stool consistency), bloating/flatu-lence and adverse events.

Data extraction and validity assessment

Two reviewers (JK and LO) independently determined the eligibility of studies based on the titles and abstracts. Differences of opinion were reconciled by consensus and, if necessary, together with the third reviewer (JD). Data were extracted by two reviewers (JK and LO), who used structured data extraction forms including: setting, participants (age, number), location, dose and duration of treatment, comparisons, criteria used to define abdominal pain- and defecation related FGIDs, outcome measures and duration of follow-up. Included studies were assessed regarding methodological quality of the study using the following methodological criteria according the Cochrane Collaboration guidelines: method of randomisation, clear concealment of allocation, blinding of patients and care providers, blinding of outcomes, comparability of baseline characteristics, loss to follow-up and use of intention to treat analysis. In all cases an answer of '1' indicates a low risk of bias and an answer of '0' indicates a high risk of bias.[21]

Data analysis

A qualitative descriptive analysis examining specific design features results of each study was performed. If the necessary data were presented in the article or obtainable from authors, results from different studies were pooled using a random effects model [22]. Meta-analysis was undertaken using the Cochrane Collaboration's Review Manager Software (RevMan version 5.1. Copenhagen: The Nordic Cochrane Centre, Denmark, 2011). Meta-analyses were performed for abdominal pain-related FGIDs and defecation-related FGIDs separately. Abdominal pain-related FGIDs were separated into functional abdominal pain (FAP), IBS, functional dyspepsia (FD) and abdominal migraine. Binary outcomes were analyzed as risk ratios (RR) along with 95% confidence intervals. In the forest plots, RR values > 1 represented a favour for probiotic and < 1 a favour for placebo. The size of the squares was correlated with the weight of the respective study. Tests of heterogeneity assessed whether the variation in treatment effect between trials was greater than that expected by sampling variation alone.

Therefore the I^2 test was used; with a threshold of 50%, and the X^2 test, with a *p*-value <0.10, to define statistically significant heterogeneity.[23]

Results

Results of the search

A total of 438 articles were found and 22 articles were retrieved for evaluation after the screening of the title and abstract. After examining the full text of the 22 articles, 13 studies were excluded for not meeting the inclusion criteria or because they were not available as full texts.

Reviewers were not blinded to any aspect of the studies (eg. journal type, author's names etc.). The remaining nine studies were eligible for inclusion,[13-16, 19, 20, 24-26] data from one trial were not eligible for meta-analysis because no absolute numbers for mean and SD were given (only the *p*-value).[20]

These papers represented five studies among patients with abdominal pain-related FIGD, including children with IBS, FAP and FD. Four studies were included regarding patients with constipation. No studies were found regarding abdominal migraine, vomiting or aerophagia. Trials were conducted in primary and tertiary care centres, whereas one single trial was conducted in a public school. Figure 1 outlines the number of included studies. The characteristics of all included studies are summarized in Table 1.

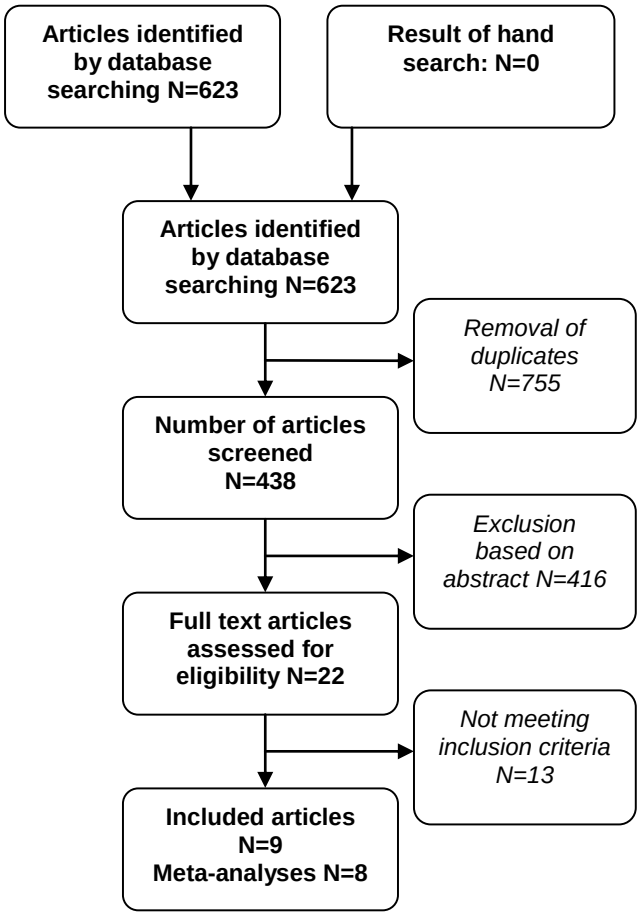

Figure 1 | Flow chart of included studies

Table 1 | Study characteristics

First author	No (age range)	Diagnostic criteria	Probiotics	Follow up	Primary outcome	Secondary outcomes	Adverse effects
Abdominal pain-related FGIDs							
Bausserman 2005, USA	50 (6-17)	ROME II for IBS	LGG 2dd 10^{10} cfu, for 6 weeks	None	Change in abdominal pain severity	Number of responders vs. non responders in each group, changes in GSRS	None
Gawronska 2007, Poland	104 (6-16)	ROME II for IBS, FAP, FD	LGG 2dd $3x10^{9}$ cfu, for 4 weeks	None	Treatment success defined as no pain at the end of intervention	Improvement of abdominal pain (frequency/severity) defined as a change in FPS by at least two faces score, use of medication, school absenteeism	None
Francavilla 2010, Italy	136 (5-14)	ROME II for IBS, FAP	LGG 2dd $3x10^{9}$ cfu, for 8 weeks	8 weeks	Change in abdominal pain (frequency/severity)	Treatment success, perception of children's pain according to their parents, modification of intestinal permeability	None
Romano 2010, Italy	56 (6-16)	ROME III for FAP	*Lactobacillus reuteri DSM 17 938* 2dd 10^{8} cfu, for 4 weeks	4 weeks	Change in abdominal pain intensity	Abdominal pain (frequency)	None
Guandalini 2010, Italy, India	59 (4-18)	ROME II for IBS	VSL#3, for 6 weeks	None	Change in global assessment of relief (SGARC)	Abdominal pain, stool pattern, bloating/gassiness, Quality of life	None
Defecation-related FGIDs							
Banaskiewicz 2005, Poland	84 (2-16)	Constipation Defined as: stools <3x/wk, > 12 wks	LGG + Lactulose 2dd 10^{9} cfu, for 12 weeks	12 weeks	Treatment success defined as ≥ 3 spontaneous BM per week with no episodes of fecal soiling	Number of spontaneous bowel movements, episodes of fecal soiling, stool consistency, straining frequency	Vomiting and abdominal pain, comparable to placebo

Table 1 | Study characteristics *(continued)*

First author	No (age range)	Diagnostic criteria	Probiotics	Follow-up	Primary outcome	Secondary outcomes	Adverse effects
Bu 2007, Taiwan	45 (<10)	Constipation Defined as: stools <3x/wk, >2mths, and anal fissures or soiling or hard/large stools	*Lactobacillus casei DN 114 001* 2dd $8x10^8$ cfu, for 4 weeks	None	Treatment success defined as ≥ 3 spontaneous BM per week with no episodes of fecal soiling	Frequency of defecation, consistency of stools, episodes of soiling, abdominal pain, use of Lactulose of enema	None
Tabbers 2011, Holland, Poland	148 (3-16)	ROME III for constipation	*Bifidobacterium lactis DN 173 010* 2dd $4.25x10^9$ cfu, for 3 weeks	None	Change in stool frequency	Treatment success, rate of responders, frequency of defecation, stools consistency, frequency of fecal incontinence episodes, digestive symptoms (abdominal pain, flatulence), use of Bisacodyl	Gastro-enteritis and vomiting, comparable to placebo
Guerra 2011, Brazil	59 (5-15)	ROME III for constipation	*Bifidobacterium longum* 1dd 10^9 cfu, for 5 weeks	None	Change in defecation frequency	Stool consistency, abdominal pain, defecation pains	None

Cfu: colony forming units; IBS: irritable bowel syndrome; FAP: functional abdominal pain; FD: functional dyspepsia, LGG: *Lactobacillus rhamnosus* GG, GSRS: gastrointestinal symptom rating scale, FPS: faces pain scale, BM: bowel movements; dd: de die/per day.

The ROME criteria for paediatric FGIDs were used in seven studies, whereas two studies used an author-defined definition of constipation. Age range in the different studies varied between two and 18 years. The different trials varied in type and dose of probiotic(s) used. Number of probiotic strains varied from one to a mixture of strains. One study used probiotics as an additional therapy to Lactulose.[16] Besides probiotics and placebo, another study also compared the effect of magnesium oxide (MgO) for constipation. We excluded this arm of the study, as this comparison did not meet our inclusion criteria.[24] Table 2 shows the results of the methodological quality assessment. According to the Cochrane Collaboration guidelines all trials were of good methodological quality, three trials scored six out of a possible seven and the other trials scored a seven.

Table 2 | Assessment of methodological quality of randomized trials.

	Banas-kiewicz 2005	**Bausser-man 2005**	**Bu 2007**	**Gawronski 2007**	**Franca-villa 2010**	**Guanda-lini 2010**	**Romano 2010**	**Tabbers 2011**	**Guerra 2011**
Randomization	1	1	1	1	1	1	1	1	1
Concealment of allocation	1	1	1	1	1	1	1	1	1
Double-blinding	1	1	1	1	1	1	1	1	1
Blinding of outcome	1	0	0	1	1	0	1	1	1
Baseline characteristics	1	1	1	1	1	1	1	1	1
Lost to follow-up	1	1	1	1	1	1	1	1	1
Intention to treat	1	1	1	1	1	1	1	1	1

1 clear reporting of the methodological quality; 0 not clear from the paper

Effects of intervention

Abdominal pain-related FGIDs

Data of five studies were pooled using a random effects model (Figure 2). Treatment success was defined as no abdominal pain or a reduction in pain (decrease of intensity or frequency of pain) [13, 14, 19, 25, 26]. Dichotomous data showed that treatment success of LGG, *L reuteri DSM 17 938* and VSL#3 was significantly higher compared to placebo. Pooled risk ratio (RR) was 1.50 (95% confidential interval (CI): 1.22, 1.84). Testing for heterogeneity showed no significance (p=0.24) and small inconsistency (I^2 = 28%). When analyses were made for the subgroups of abdominal pain-related FGIDs (IBS, FAP and FD) this significant effect of probiotics was only seen among IBS patients. The pooled data from four studies concerning LGG and VSL3# for IBS showed a risk ratio of 1.62 (95% CI: 1.27, 2.06), with small heterogeneity I^2 = 20%, p=0.29.[13, 14, 25, 26] Pooled risk ratio from two studies for FAP was 1.10 (95% CI: 0.80, 1.53) and heterogeneity I^2 was 0%, p=0.88.[14, 26] No subanalysis could be carried out for FD because of limited data.

High heterogeneity was found between studies (I^2= 85%, p=0.001) (Figure 3). Pooled data from the same studies showed that the use of probiotics was associated with a significant decrease in the intensity of abdominal pain compared to placebo (296 participants, SMD -0.72 (95% CI -1.13, -0.32), heterogeneity was not significant (I^2= 35%, p=0.21) (Figure 4). Two studies[13, 25] described the effect of LGG and VSL#3 among children with IBS with respect to stool pattern. The questionnaires used gathered information about defecation frequency and consistency. Bausserman[13] did not find a significant improvement in stool pattern comparing LGG to placebo (50 participants, p=0.61). Guandalini [25] also failed to show a significant effect of VSL#3 on improving stool pattern in children with IBS (59 participants, p=0.06).

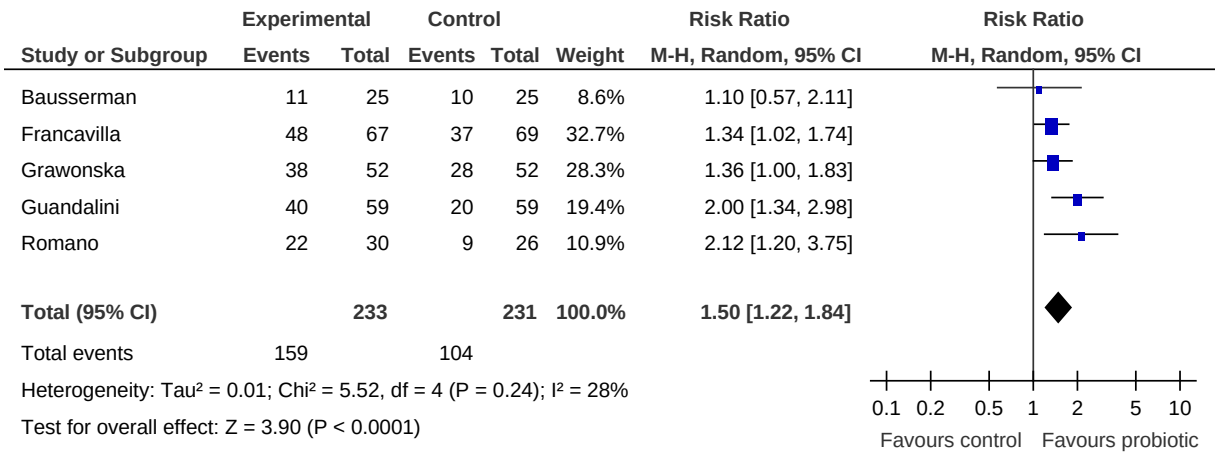

Figure 2 | Forest plot of comparison: Probiotic versus control, outcome: Treatment success

Only one single study[25] reported on bloating. The frequency of bloating was measured on a 0-4 scale, from absent (0 points) to >four times per week (4 points), Guandalini showed improvement of bloating from 2.4 to 1.05 times per week after the use of LGG. In the placebo-arm the score decreased only from 2.1 to 1.6 times a week. A significant difference in changes in bloating (p<0.05) was found between children receiving LGG and those receiving placebo.

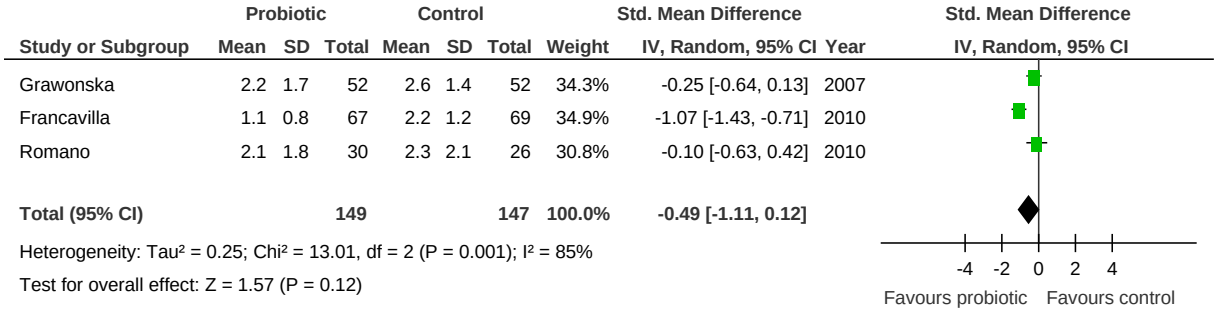

Figure 3 | Forest plot of comparison: Probiotic versus control, outcome: Abdominal pain frequency

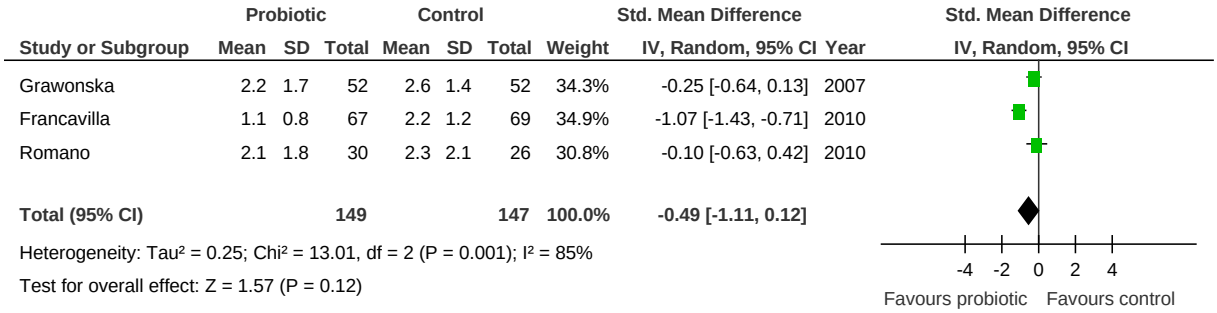

Figure 4 | Forest plot of comparison: Probiotic versus control, outcome: Abdominal pain intensity

Defecation-related FGIDs

Three studies reported the treatment success of probiotics for constipation, defined as defecation at least three times a week and no faecal incontinence or less than one episode of faecal incontinence in 2 weeks.[15, 16, 24] Dichotomous data showed no significant effect of probiotics compared to placebo with respect to treatment success. Pooled risk ratio was 1.16 (95% CI 0.83, 1.62) (Figure 5). Testing for heterogeneity showed no significant result (p=0.10) but inconsistency was moderate (57%). Evaluating

the different strains individually, only a significant effect of L *casei* was found, however the number of patients included in this study was small.

Four studies[15, 16, 20, 24] involving a total of 282 participants reported an increase in defection frequency among children with constipation. Data from Guerra's study were not available for pooling, because no absolute numbers were given. Pooled continuous data showed no significant effect in favour of the different probiotics used, LGG, *L casei DN 114 001* and *B lactis DN 173 010*, for increasing defecation frequency (270 participants, SMD 0.44 (95% CI -0.35, 1.24). Testing for heterogeneity showed a highly significant result (p=0.004) and high inconsistency (I^2 = 87%). Moreover, no significant effect was found for each strain individually.

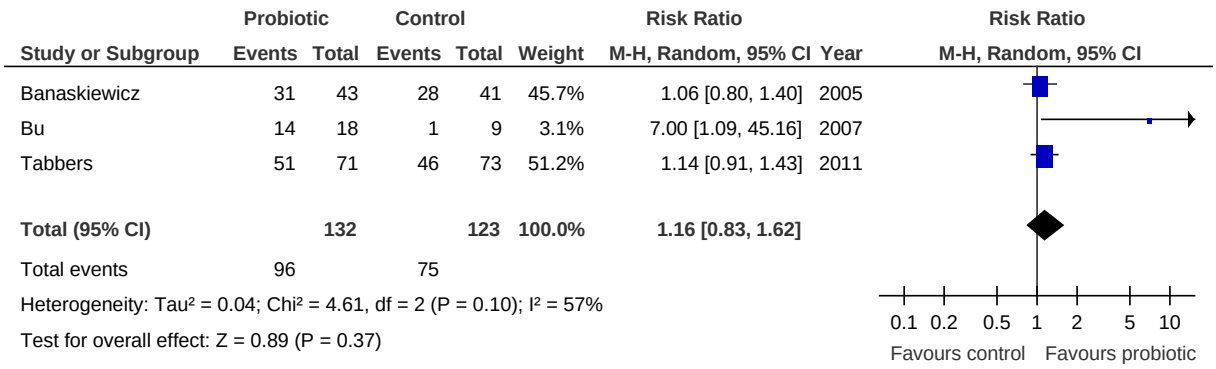

Figure 5 | Forest plot of comparison: Probiotic versus control, outcome: Treatment success

Three studies aimed to report stool consistency among children with constipation, yet incomparable data prevented pooling of the results. Two studies[20, 24] reported a significant improvement of stool consistency in children with constipation compared to placebo. In Bu's study[24] 22.4% of the children in the *L casei DN 114 001* group (n=18) still experienced hard stools after the intervention, compared to 75.5% in the placebo group (n=9) (p=0.02). Guerra[20] compared *B longum* with placebo (n=59) and noted an improvement in both groups, but this improvement was higher in the probiotic group during the first part of the intervention when a significant difference was observed between the two groups (p=0.03). Results were graphically presented without reporting absolute numbers. This significant difference was not observed after crossing over in the second part of the trial. Tabbers *et al.*[15] used the 7-point Bristol stool scale for scoring stool consistency. A score of 1 describes stools that are hard lumps, a score of 4 describes normal stools (smooth and soft), and a score of 7 describes watery stools. They found no statistically significant difference in stool consistency between *B lactis DN 173 010* (n=79, 3.3) and placebo (n=80, 3.5) after the intervention (p=0.07).

One study[15] evaluated the effect of *B lactis DN 173 010* on flatulence. Tabbers measured flatulence on a 2-point scale (1, yes; 2, no) among children with constipation. Flatulence was reported less frequently in the *B lactis DN 173 010* group compared with the placebo group (23.6% versus 34.7%, p=0.02).

Adverse events

The different probiotic strains described in this systematic review were well tolerated. Tabbers reported one case of gastroenteritis and three cases of vomiting, and Banaszkiewicz reported three cases of abdominal pain and one case of vomiting.[15, 16] These adverse events were comparable with the placebo groups. Other trials did not report any adverse events.

Discussion

Summary of main results

The aim of this systematic review was to investigate the quantity and quality of the current evidence regarding the effects of different probiotics in the treatment of functional gastrointestinal disorders (FGIDs) in children and adolescents. Our meta-analysis showed that the use of LGG, *Lactobacillus reuteri DSM 17 938* and VSL#3 significantly increases treatment success in children with abdominal pain-related FGIDs, particularly among children with IBS. In addition, LGG and *L reuteri DSM 17 938* significantly decrease the intensity of abdominal pain. There is also some evidence that LGG diminishes bloating, but this observation was just based on one single study. There was a trend towards a decrease in frequency of abdominal pain, but studies were too heterogeneous to draw firm conclusions. In addition, no evidence was found that LGG or VSL#3 improve stool pattern in children with abdominal pain-related FGIDs.

With respect to defecation-related FGIDs there is no evidence showing that probiotics are more effective than placebo regarding treatment outcome or increasing defecation frequency in constipated children. Moreover, provided data were inconsistent with respect to the improvement of stool consistency. Two studies evaluating the effect of *L casei DN 114 001* or *B longum* showed an improvement in stool consistency, but the design[20, 24] of these studies was of low quality. No serious adverse events associated with any of the probiotics were reported in the different trials.

Strengths and limitations

This study has several strengths. We carried out a comprehensive and contemporaneous literature search that identified sufficient studies, which allowed pooling of data of only placebo-controlled randomised trials. In general the quality of the studies was good. We should note, however, that one included study had a cross-over design.[20] Whereas in another study the control group was very small.[24] The evaluation of study eligibility and data extraction were carried out by two investigators independently in order to decrease the likelihood of reviewer error and bias. Furthermore, in three trials we obtained additional information from the authors as their presentation of data was inadequate for pooling.[15, 19, 20]

The main limitation of this review is the variety of species, strains and dosages of the probiotics used in all studies. Health-promoting activities of probiotics are strain-specific and therefore it is preferable not to carry out a meta-analysis. In adult IBS studies, however, it has been suggested that different species of probiotics are synergistic in promoting a therapeutic effect.[27] The data from this systematic review are not sufficient to make any subanalysis for a specific strain and draw any conclusion regarding the optimum probiotic strategy to use.

Another limitation of this study concerns the uncertainty regarding the size of the therapeutic effect in the different studies due to possible publication bias, i.e. publication or non-publication of data depending on the results, with negative findings being less likely to be published irrespective of the methodological quality. Three abstracts were excluded because data were not available for meta-analysis.

Agreements and disagreements with other studies or reviews

Abdominal pain-related FGIDs

The rationale for using probiotics derives from recent evidence which suggests that the microbiome may be involved in the pathogenesis of FGIDs.[10] Epidemiological studies in both children and adults have identified gastrointestinal infection as a predictor for the development of IBS.[28] Furthermore,

significant differences have been found in the composition of intestinal bacteria between patients with IBS and healthy individuals.[28] The ultimate goal of treatment is the use of a specific probiotic strain in order to change altered microbial flora and abnormalities in fermentation, gas production and absorption, which drive the symptoms of IBS.[29]

In accordance with an earlier meta-analysis, we presented evidence that LGG moderately increases treatment success in children with abdominal pain-related FGIDs, particularly among children with IBS.[30] Although VSL#3 was superior to placebo with respect to the decrease in the intensity of pain and a significant reduction in bloating among children with IBS, frequency of abdominal pain episodes did not decrease in these children. These findings are in line with previous data in adults with IBS and bloating using the same probiotic mixture.[31] In contrast with Romano *et al.*, Niv *et al.*[32] reported no benefit of *L reuteri DSM 17 938* over placebo with respect to reduction in abdominal pain among adult IBS subjects.

Based on the data presented here, it is however not possible to recommend a specific strain or combination of probiotic strains in the routine treatment of children with abdominal pain-related FGIDs.

Defecation-related FGIDs

Our systematic review clearly shows that insufficient evidence exists for the use of probiotics for paediatric functional constipation. Although administration of *B. lactis DN-173 010* indicates improved colonic transit time in adults with IBS and constipation and although dysbiosis with increased number of clostridia and bifidobacteria was reported in constipated children,[12, 33-35] this systematic review did not find any evidence for increasing defecation frequency using different probiotic strains. It has been suggested that this is probably due to a difference in pathophysiology between adults and children. Constipation in children is frequently caused by the voluntary withholding of faeces due to fear of painful defecation. In contrast to children, adult patients with constipation commonly show a slow transit or 'colonic inertia'[36] without withholding of faeces. For this reason it is more likely that *Bifidobacteria* can have a benefit in such circumstances.

Implications for research

A lack of data did not allow us to conclude whether any particular probiotic is more effective than another in children with abdominal pain-related and defecation-related FGIDs. Future studies need to determine which species, specific strains, combination of strains and dose of probiotics are most efficacious in abdominal pain-related FIGDs and functional constipation. Moreover long-term, follow-up studies using different probiotic strains are needed since there is a lack of data providing evidence that the use of probiotics is effective and safe for a prolonged period of time.

In conclusion, our systematic review has demonstrated that probiotics are more effective than placebo in the treatment of patients with abdominal pain-related FGIDs, especially for IBS patients. Sufficient scientific evidence is found for LGG, but data are too scarce to draw any conclusion about *Lactobacillis reuteri DSM 17 938* and VSL#3. In contrast, no evidence supports the use of any probiotic strain in the treatment of functional childhood constipation.

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Chapter 8

Yoga Therapy for Children with Abdominal pain-related Functional Gastrointestinal Disorders. A randomized controlled trial

Judith J. Korterink, Lize E. Ockeloen, Mirrian Hilbink, Marc A. Benninga, Judith M. Deckers-Kocken

Submitted

Abstract

Objectives

To compare the effect of 10 weeks yoga therapy (YT) and standard medical care (SMC) on abdominal pain and quality of life (QoL) in children with abdominal pain-related functional gastrointestinal disorders (AP-FGIDs).

Methods

Sixty-nine patients, aged 8-18 years, with an AP-FGID, were randomized to either standard medical care complemented with YT or SMC alone. Hatha yoga is a mixture of yoga poses, meditation and relaxation exercises and was given once a week. SMC consists of education, reassurance, dietary advice and fibers/mebeverine if necessary. Pain intensity (PIS; 0-5) and frequency (PFS; 0-4) were scored in a pain diary and QoL was measured with the KIDSCREEN-27. Follow-up was twelve months. Treatment response was defined as a ≥50% reduction of weekly pain scores.

Results

At 1 year follow-up, treatment response was accomplished in 58% of the YT group and 29% of the control group (p=0.01), no significant differences for other timepoints were found. YT, and not SMC, resulted in a significant reduction of PIS (p<0.01) and PFS (p<0.01) after 12 months, however, during the study YT was not significantly superior compared to SMC. Subanalyses for different timpoints demonstrated only a significant greater reduction of PIS at 12 months in favor of YT. No effects were found for QoL. During the study, YT was significantly more effective in the reduction of children who reported monthly school absence (p=0.03).

Conclusion

At one year follow-up, YT in addition to standard care was superior compared to SMC according to treatment success, PIS and reduction of school absence. However, YT was not significantly more effective in the improvement of PFS or QoL, compared to SMC.

Introduction

Recurrent abdominal pain is present in 0.3-19% of school-going children in the US and Europe and is one of the most frequent reasons to visit a pediatrician.[1] This type of abdominal pain is frequently categorized as functional, i.e. no organic cause is found to explain the symptoms. Abdominal pain is often associated with other somatic complaints such as headache and backpain. These symptoms can markedly interfere with quality of life and rank second in the causes of absence from school.[2] The benefits of standard treatment (reassurance, dietary alteration) and of pharmacologic therapy are limited and adult as well as pediatric patients are often referred for additional psychological or behavioral therapy,[3,4] these may include psycho-education, relaxation-based programmes and cognitive behavioral therapy (CBT). In 29.1% of patients with chronic or recurrent abdominal pain, pain persists for more than 5 years, despite frequent medical attention and interventions.[5]

Several studies have shown that psychological distress is strongly associated with abdominal pain in children, not just as a consequence of the pain, but probably also as a predictor of symptoms.[6] This explains why relaxation-based therapy results in improved quality of life and fewer complaints. Relaxation-based therapy, such as hypnotherapy (HT), and CBT have shown to be more effective than standard medical therapy in children with functional abdominal pain (FAP) or irritable bowel syndrome (IBS).[7,8]

Another type of relaxation-based therapy is yoga therapy.[9,10] Yoga is a mind-body exercise with its origin in Indian philosophy rooting in an over 4000 year-old tradition.[11] It has been widely used to reduce stress and anxiety.[12] Moreover, yoga is simple, can be easily applied at home, and has considerably lower costs than HT and CBT. In Western civilization, yoga is most often associated with physical postures, breathing techniques and meditation to promote physical and mental well-being.[13] Limited research has shown that yoga decreases stress in children, including psychological and physical symptoms.[14,15] Furthermore, stress reduction as a result of compassion based meditation, has been correlated to structural changes in stress responding areas of the brain.[16,17] A pilot study showed promising results for the efficacy of yoga for children with functional abdominal pain.[18] However, there is a clear need to further investigate and confirm the effects of yoga on children with chronic abdominal pain. The aim of this study is therefore to compare the effect of yoga exercises complementary to standard care and standard care alone on pain frequency, pain intensity and quality of life in children with functional abdominal pain.

Methods

Study Population

This prospective randomized controlled trial was performed at a non-tertiary center, the Jeroen Bosch Hospital in The Netherlands. Between February 2011 and July 2013 all patients visiting the outpatient clinic, between 8 and 18 years, with abdominal pain fulfilling the Rome III criteria for abdominal pain-related functional gastrointestinal disorders (AP-FGIDs) were eligible for inclusion.[19] Children who already participated in yoga therapy, hypnotherapy, psychotherapy or any form of other relaxation therapy for functional abdominal pain in the past were excluded as well as children with mental retardation. The study protocol was approved by the Medical Ethical Committee of the Hospital and was carried out in accordance with the Declaration of Helsinki. All children and/or their legal guardians gave written informed consent to participate in the study.

Yoga Sessions

Hatha yoga sessions of 1.5 h each were provided by certified children's yoga teachers (NvE/HD). Patients received one treatment session each week for 10 weeks. Children aged 8-12 years and 13-18 years were divided into two groups; with an approach conform their age. The study groups consisted of 5-10 children each. The sessions were based on classic Hatha yoga principles in combination with specialized yoga exercises for children.[20,21] The sessions were a mixture of classical yoga poses, meditation techniques and relaxation exercises in which the children learned to relax with yoga breathing techniques. Patients were taught to relax the abdomen and to focus their thoughts on a single positive topic or good experience instead of random wandering of thoughts or thinking about negative experiences, what is described in compassion based meditation.[22] In doing this the yoga-teacher used standard practices using several animations: e.g. dog, cat, snake and sun. The overall goals of the yoga lessons were to achieve balance, flexibility, concentration and relaxation, and to improve the positive self-awareness in breathing. Every participant received a work book with the yoga exercises and was encouraged to practice on a daily basis at home.

Design

Eligible patients were randomly assigned to either yoga therapy and standard medical care (SMC) or SMC alone. Random numbers were generated by a computer program with an allocation ratio of 1:1 and with well-balanced blocks. A stratification scheme was used to assure a balance between the groups with respect to age (age group 8-12 years and age group 13-18 years). Prior to enrolment in the study all children had received standard medical care, i.e. education about their diagnosis, reassurance, dietary advice, extra fibers, and mebeverine if considered necessary. During the trial clinicians were easily available for consultation by telephone or e-mail.

Outcomes were assessed at baseline, directly after finishing the treatment, six and twelve months after baseline. Participants were asked to keep a 4-week abdominal pain diary (APD), in which they recorded the intensity and frequency of abdominal pain daily. Pain intensity was scored using the validated six-face Faces Pain Scale-Revised.[23] ranging from 0 (=no pain) to 5 (very much pain). Pain frequency was scored as 0 = no daily pain, 1 = 0-20 min of daily pain, 2 = 20-40 min of daily pain, 3 = 40-90 min of daily pain and 4 = more than 90 min of daily pain. The daily scores were added up, and mean week scores were used to obtain a pain intensity score (PIS) and a pain frequency score (PFS) for these different time points. Diaries were completed each week, for four weeks. In case of a missing week, data of the available weeks were used for the mean weekly pain scores.

At the same time points the Kidscreen-27 Quality of Life questionnaire was administered to the patients and their parents, with permission of the authors.[24] The Kidscreen questionnaire is a validated 27-item quality of life screening instrument for children of 8 years and above and their parents that encompasses physical wellbeing (5 items), psychological well-being (7 items), autonomy and parents (7 items), social support and peers (4 items) and school functioning (4 items). A 5-point response scale was used. Higher scores indicate a better quality of life. Also additional functional complains, i.e. headache, back pain, neck pain and tiredness, were scored on a 2-point scale, 0 is 'no' and 1 is 'yes' and school absenteeism was scored on a 5-point scale, as 0=never, 1= once a year, 2= more than once a year, 3= every month and 4=every week.

Patients completed the questionnaires online at home, using a data managing system (Research Manager, Nova Business Software, the Netherlands). Results could only be saved when questionnaires were completed in total; therefore we had no missing data of the Kidscreen-27. Rasch-scores and *t*-values were calculated according to the Kidscreen 27 manual, a higher values indicating

a higher health related QoL. *T*-values for children and their parents were compared between the intervention and the control group.

Primary outcome measure was the treatment response, defined as a decrease of the combined abdominal pain scores (PIS and PFS) of ≥50%, during one year follow-up. Secondary outcome measures were the improvement of the pain intensity score, pain frequency score, results of the Kidscreen-27 questionnaire and school absenteeism.

Statistical Analysis

The sample size was based on the treatment response in both groups. The trial was designed to detect a minimal intervention-induced difference between the control and the intervention group of 35% at one year follow-up: a treatment response of at least 50% was anticipated in more than 35% of the patients in the standard care / control group and in at least 70% of the patients in the intervention group. Under the assumption of a within subject correlation of 0.7 and using the formulas provided by Twisk,[25] a total of 52 children would be needed (α=0.05, β=0.80). To allow for a dropout rate of at least 20% because of withdrawal, a total number of 69 subjects were randomly assigned. Descriptive statistics were used to characterize the study sample and to document information for all variables measured within the present study. Between-group differences of treatment response, pain intensity, pain frequency, Quality of Life and school absence were analyzed with generalized estimating equations (GEEs). GEE takes into account that the observations within each subject are correlated. This longitudinal data analysis technique is suitable to investigate the course over time of the outcome variables and to compare this overall effect between study arms. In all models, the outcome variable (i.e., pain intensity measured after intervention, at 6 months follow-up, and at 12 months follow-up) was analyzed as a dependent variable using study group as key independent variable adjusted for the baseline measurement. Adjustment for baseline leads to equal starting points for both groups, and therefore, the intervention effect is presented by the coefficient on the study group. The group-time interaction provides information about whether the observed effect is stronger at the beginning or at the end of the study.[26] Furthermore, possible effect modification was analyzed for the following variables: gender and age. Subgroup analyses were performed in cases where significant effect modification ($p<0.10$ for the interaction term) was detected. An exchangeable correlation structure was assumed in all GEE analyses. All analyses were on an intention-to-treat basis and variability in the number of subjects in the analysis is due to incomplete data sets. The criterion $p<0.05$ was applied to indicate statistical significance. All analyses were conducted using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

Results

Between April 2012 and August 2013 a total of 105 children with an AP-FGID were eligible for inclusion. Of these 69 agreed to participate in the study, of whom 35 patients were allocated to YT complemented to SMC and 34 patients to SMC alone. Figure 1 shows the number of participants involved in the trial from the assessment for eligibility through follow-up.

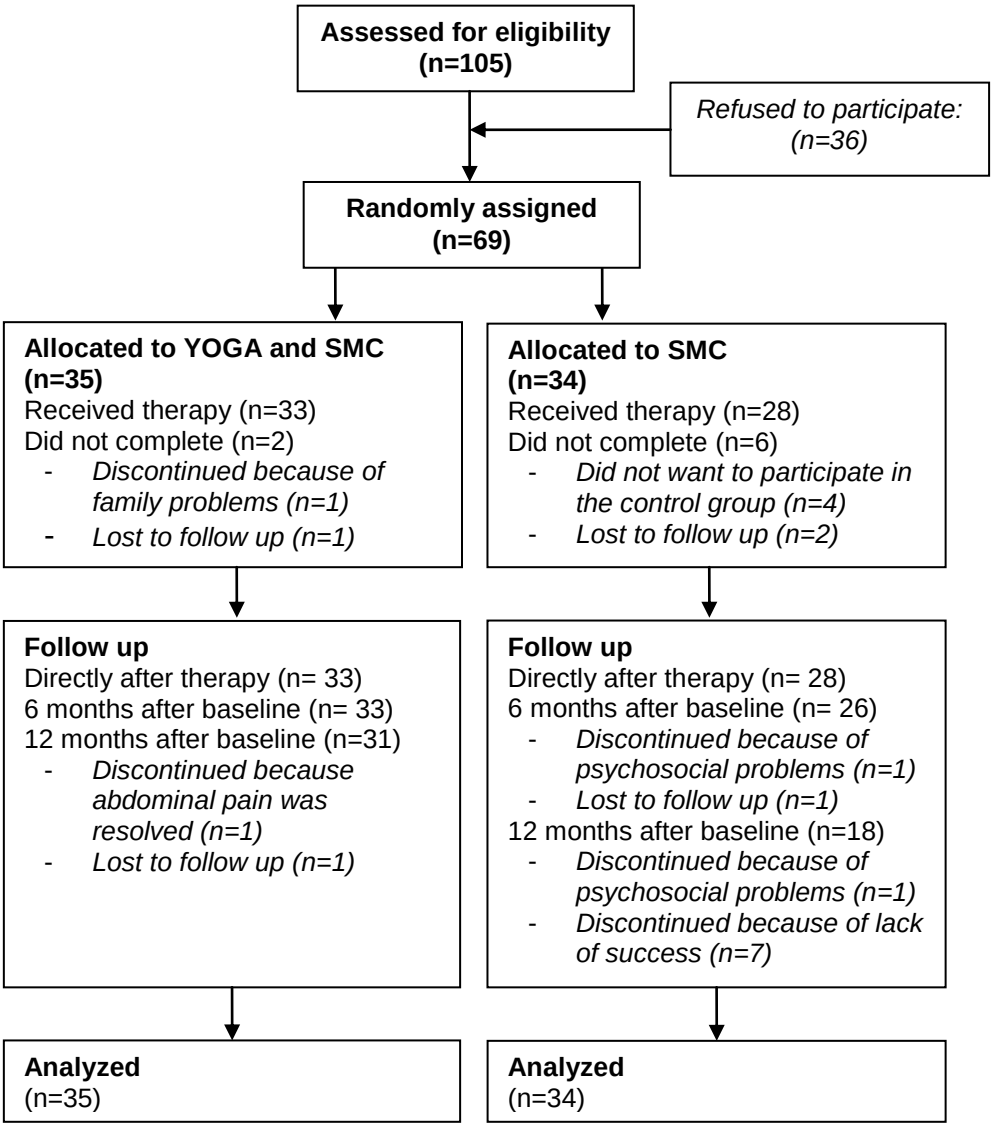

Figure 1 | Flow diagram of trial progress

Thirty-three children of the yoga group and 28 children from the SMC group finished the treatment period. Four children from the YT group and 16 children from the SMC group withdrew from the study before starting the intervention or discontinued treatment during follow-up. Data of all 69 included children were used for analysis. As depicted in Table 1, the baseline characteristics of the participants in the 2 groups were similar, only constipation was more common in family members of the yoga group.

Treatment response and abdominal pain scores

Treatment response, decrease of the combined abdominal pain scores (PIS and PFS) of ≥50%, increased after YT and SMC during time of follow-up; 21.2%, 32.2% and 58.1%, and 20%, 26.9% and 28.9%, respectively, at post intervention, 6 months and 12 months follow-up. Only at twelve months after baseline YT was significantly more effective than SMC (p=0.012).

Figure 2 displays the progression of child-reported abdominal pain scores throughout the study. Mean scores for each time point and the results of the GEE investigating differences between the 2 treatments, are displayed in Table 2.

Table 1 | Baseline characteristics

	YOGA N=35	**SMC N=34**
Demography		
Age (y)[a]	12.2 (2.9)	12.1 (2.7)
Girls (%)	29 (83)	25 (73.5)
Rome III diagnosis (%)		
IBS	12 (34.3)	14 (41.2)
FAP(S)	18 (51.4)	17 (50.0)
FD	5 (14.3)	3 (8.8)
Duration of symptoms (%)		
<1 y	8 (22.8)	9 (26.5)
1-2 y	7 (20)	5 (14.7)
2-5 y	12 (34.3)	10 (29.4)
>5 y	8 (22.9)	10 (29.4)
Other functional symptoms (%)		
Headache	20 (57.1)	20 (58.8)
Back pain	7 (20.6)	11 (32.4)
Neck pain	7 (20.6)	8 (23.5)
Tiredness	14 (46.7)	15 (55.6)
Family member with functional symptoms (%)		
Functional abdominal pain/IBS	21 (60)	16 (47.1)
Constipation	18 (51.4)	11 (32.4)
Headache	13 (38.2)	16 (47.1)
Back pain	16 (51.6)	8 (25)
School absenteeism (%)		
<Monthly	15 (45.5)	12 (35.3)
Monthly	18 (54.5)	15 (64.7)

IBS, irritable bowel syndrome; FAP(S), functional abdominal pain (syndrome); FD, functional dyspepsia;
[a]Data are mean (SD).

The PIS decreased from 17 to 8 at the final end point 12 months after baseline in the yoga group (p<0.01) and from 16 to 12 in the SMC group (p=0.83). The PFS decreased from 16 to 8 (p<0.01) in the YT group and from 16 to 14 in the SMC group (p=0.40). Overall effect measured with GEE showed no significant differences between the study groups for PIS or PFS alone.

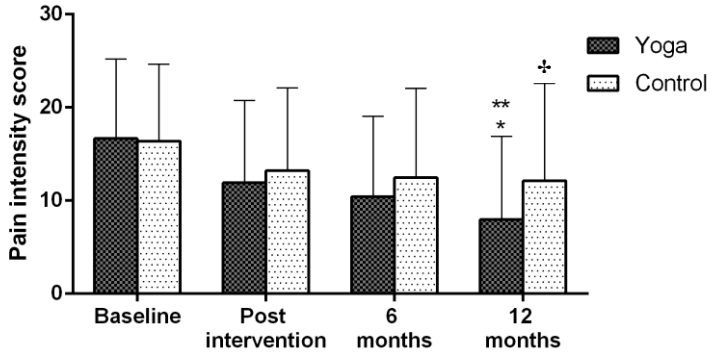

Figure 2a | Mean and SD of pain intensity scores throughout the study. *p<0.01 compared with baseline. **p=0.039 between groups at 12 months (subanalysis). †p=0.83 compared with baseline

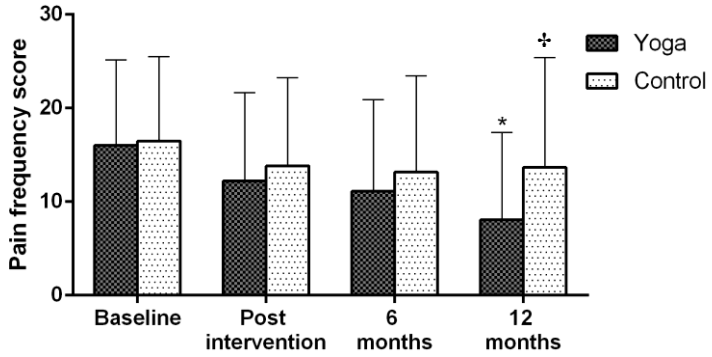

Figure 2b | Mean and SD of pain frequency scores throughout the study. *p<0.01 compared with baseline. †p=0.40 compared with baseline

No significant (p<0.10) interaction between time, gender and age on the one hand and PIS and PFS on the other hand was found in any of the analyses. However, subanalysis showed a significant lower PIS in favor of YT compared to SMC, at 12 months follow-up (p=0.039), this significant difference was not found directly after therapy or at six months follow-up. Children aged 13-18 years were more likely to report a decrease in PIS after yoga therapy compared to SMC, but this did not reach significance (p=0.059).

Table 2 | Mean scores of outcome measures at all time points, overall effect tested with GEE

	Before treatment		**Directly after treatment**		**6 months after baseline**		**12 months after baseline**			
	YT	SMC	YT	SMC	YT	SMC	YT	SMC	**β**	***P* value**
Abdominal pain scores										
Pain intensity score	16.65	16.39	11.91	13.18	10.42	12.47	7.99	12.14	-2,676	0.088
Pain frequency score	16.04	16.49	12.23	13.83	11.15	13.15	8.06	13.66	-1,899	0.198
Quality of life scores										
Kidscreen child										
Physically well being	44.2	44.5	46.2	45.8	46.7	46.4	47.3	46.8	1,016	0.426
Psychological well being	44.1	45.6	47.9	47.2	48.3	47.3	49.5	46.8	2,569	0.055
Autonomy and parent relation	53.7	52.4	54.8	55.3	55.9	56.0	53.7	53.3	-0,726	0.623
Peers and social support	53.8	52.0	52.9	51.4	54.7	51.1	54.5	52.6	1,235	0.462
School environment	50.0	49.6	54.0	52.1	54.3	53.1	53.1	53.8	0,844	0.584
Kidscreen parents										
Physically well being	41.3	42.3	42.1	44.4	45.5	43.5	47.5	46.3	0,605	0.718
Psychological well being	40.6	41.6	44.7	43.7	47.4	47.0	49.5	45.3	1,854	0.252
Autonomy and parent relation	54.2	53.7	54.0	55.8	54.8	57.8	53.7	56.3	-2,590	0.124
Peers and social support	54.0	53.0	55.1	53.2	55.0	54.5	55.7	54.2	0,647	0.675
School environment	50.1	51.8	52.7	52.9	54.7	52.5	54.3	52.6	1,851	0.170

Groups did not differ on any of the outcome measures before treatment.
For the QoL scales, higher scores reflect better well-being. European normdata: mean 50.0.
β=coefficient; GEE=generalized estimating equations; SMC=standard medical care; YT= yoga therapy

Quality of life

Compared to baseline, QoL-scores increased at each timepoint for 4 out of 5 QoL-subscales, except for 'autonomy and parents relation'. Yoga was not more effective than SMC for any of the subscales (Table 2). A trend was shown for better psychological well-being reported by children receiving YT (p=0.055).

School absenteism

GEE analysis showed an overall significant effect in favor of YT (p=0.029). Subanalysis for different timepoints showed, however, that this significant difference was only present at 12 months follow-up. Directly after YT and SMC, schoolabsence decreased from 55% to 12.5% and from 65% to 36%, respectively (p=0.062). Improvement continued at 1 year follow-up, 7% of children in the YT group and 33% in the SMC group reported school absence (p=0.027) (Figure 3).

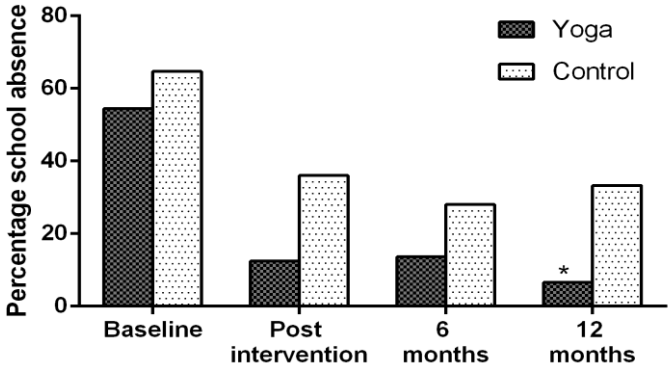

Figure 3 | Percentage school absence at least once a month at different time points. * p<0.05 between groups

Adverse events

No serious adverse events were reported.

Discussion

This randomized controlled trial in children with AP-FGIDs shows that yoga therapy in addition to standard care is significantly more effective in reaching treatment response at one year follow-up and in decreasing school absence than standard care alone. A total of 58% of the children in the yoga group reached an improvement of abdominal pain of at least 50%, whereas this was only 29% after standard medical care. Moreover, yoga therapy resulted in a significant reduction of abdominal pain intensity and frequency, which was not reported after standard medical care. However, only at 12 months follow-up YT was superior to SMC regarding pain intensity scores. No significant effects were found in improving quality of life. No adverse events were reported in the yoga group.

In accordance with earlier studies yoga showed to be a safe, cheap and feasible intervention for children and adolescents with IBS.[9,27] Two randomized controlled trials were conducted evaluating the effects on yoga therapy in children and adolescents with IBS compared to waitlist controls.[9,27] In line with our results no significant effects on abdominal pain were reported directly after yoga therapy. In our study, however, significant effects were found for yoga therapy on pain scores at 12 months follow-up. Other data reporting the long term efficacy of yoga are currently not available. It is difficult to explain why effects were noted only at 12 months follow-up. Improvement of abdominal pain scores were found after therapy in both groups, but only children in the yoga group continued to experience

further improvement in symptoms at long term follow-up. Similar post-treatment effects were reported after HT and CBT in children with IBS and FAP.[28,29] This effect could be caused by the suggestion that benefits of the treatment would persist and become even more effective over time or by the ongoing use of home exercises by the participants. Sustained yoga practice and discipline seems to be the most important factor to reach long term effectiveness.

The mechanism by which yoga can reduce pain is not well understood. Increased knowledge of the pathophysiology of AP-FGIDs has led to a biopsychosocial model, in which both physiological, psychological and emotional factors are integrated in a complex way to modulate the symptoms in any given individual.[30] Yoga therapy is likely to exert its effect on the psychosocial factor of this model. Stress and anxiety are known triggers for symptoms of FAP and IBS.[31] Studies have shown that the practice of yoga reduces perceived stress and negative feelings and that it improves psychological symptoms by lowering the levels of anxiety and anger, in both adults and children.[32–34] Studies focusing on meditation, often a component of yoga practice, have proved that stress-reduction is supported by altering brain activation. After a mindfulness-based stress reduction program changes in gray matter concentration were demonstrated in brain regions involved in emotional regulation and arousal, measured by MRI.[35] This is an interesting finding, since increased gray matter density in IBS patients was observed in brain regions involved in the stress and arousal circuit.[36–38] Furthermore, meditation can produce increases in relative left-sided anterior activation that are associated with reductions in anxiety and negative affect and increases in positive affect.[39] Future studies are needed to clarify if yoga therapy also results in changes in brain structures and activity in children with AP-FDIGs.

The current study demonstrated that YT was superior to SMC in the reduction of school absence. This is an important finding, as abdominal pain ranks second in the causes of absence from school.[2] Furthermore, children with low school attendance or drop out are at increased risk for displaying social-emotional problems, risky behavior and having limited economic opportunities.[40] Improvement of functional disability after yoga therapy was previously reported in adolescents[9] and young adults with IBS.[27] Yoga may appear as an important intervention to increase general functioning and social participation.

The observed therapeutic effect of an intervention will be influenced by the comparator.[41] In the current study yoga therapy was compared to an active control group. Children in the control group received standard medical care, including education, medical treatment if neccesary and the same number of appointments with the physician as the intervention group. Both groups received treatment by the same physician at the outpatient clinic for children with chronic abdominal pain, therefore results of this study were not distorted by expertise bias. However, the lack of a significant effect in the control group is a remarkable observation, since this is often reported in other intervention trials in children with functional abdominal pain.[28,29] In contrast to our study, these studies incorporated a more active nature of the control conditions, such as extra appointments with the physician, in their control group. It is well known the patient-practitioner relationship and active listening approach may account for a considerable part of treatment effectiveness.[42–44] This underlines the importance of attention and a supportive relationship between patient and physician in treating children with functional abdominal pain.

Limitations of our study are common to many nonpharmacologic trials for chronic pain, and include inability to blind participants to their treatment assignment, and differential attrition between the

groups. By not blinding the participants, response expectancy may spuriously amplify the difference in treatment effect between the intervention and the control, because people assigned to usual care may expect to *not* get better without yoga therapy. In total, 4 times as many participants from the control group did not finish the complete study period compared with the yoga group. This attrition was partly due to disappointment of allocation to the standard care group, after randomization already 4 children withdrew from the study. GEE analysis, however, can handle missing data in longitudinal studies under the assumption that such data are missing completely at random.[45] Based on earlier observed data, we verified that the subject attrition in this study was not associated with one of the covariates or the dependent variable. Therefore, results at 12 months follow-up can considered as a reliable representation.

Other relaxation-based therapies, such as HT and CBT, have shown to be effective therapies with long lasting effects for children with recurrent and functional abdominal pain. Success rates up to 85% were reported after HT.[28] A disadvantage of CBT, however, is that parents can be reluctant in accepting the existence of psychosocial influences on their child's symptoms and often refuse to engage with psychological services.[46] Also HT suffers from definite misgivings and belief in myths surrounding hypnosis. This might be different with yoga therapy, as this is becoming very popular and more common in Western countries. Furthermore, yoga therapy is simple, can be easily applied at home, and has considerably lower costs than HT and CBT.

Future research should compare yoga to these other relaxation-based therapies to determine which of these treatments has the most potent and sustained effect and whether there is an individual likelihood which increases the responsiveness to a particular therapy. More research is needed whether different intensity and duration of yoga treatment might increase effectiveness directly after therapy. Also the efficacy for different AP-FGID subgroups should be explored. To further distinguish the effects of yoga from the natural course of AP-FGIDs, effects of follow-up should be compared to a waiting list. However, persisting symptoms of abdominal pain were reported in 30-40% of children with functional abdominal pain, up to 15 years follow-up.[5,47] Furthermore, most of the children included in this study have complaints of abdominal pain for more than 2-5 years. A spontaneous remission within 12 months is therefore less likely.

In conclusion, yoga is an effective intervention for functional abdominal pain in childhood. It is cost-effective and easy to implement. For the first time, we demonstrated that ten weeks yoga intervention resulted in a significant reduction of school absence and improved abdominal pain at 12 months follow-up.

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Chapter 9

Summery and General discussion
Nederlandse samenvatting en discussie

Summery

Chronic abdominal pain represents a common problem in children. In almost 90% of children presenting with chronic abdominal pain, no organic cause is found and a diagnosis of functional abdominal pain is made.[1] Initially this condition was referred to as 'recurrent abdominal pain' by Apley and Naish and it is currently defined as abdominal pain-related functional gastrointestinal disorders (AP-FGIDs); divided into functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraine (AM), functional abdominal pain (FAP) and functional abdominal pain syndrome (FAPS) according to the Rome III criteria.[2] Children with AP-FGIDs report impaired health-related quality of life in relation to physical complaints and AP-FGIDs are ranked as second in causing school absence.[3,4] The underlying pathophysiology of AP-FGIDs is considered to be multifactorial, but needs further elucidation. This lack of understanding often leads to extensive investigations, non-effective therapeutic modalities and staggering healthcare costs. The focus of this thesis is to identify risk factors for developing pediatric AP-FGIDs and to evaluate diagnostic and therapeutic strategies. This thesis ends with the evaluation of a new complementary treatment option.

Part I – Epidemiology

Chapter 2 contains a systematic review and meta-analysis of the published literature regarding the prevalence of functional abdominal pain disorders in children. Data of 58 studies were pooled, showing a worldwide prevalence of pediatric functional abdominal pain disorders of 13.5%. Functional abdominal pain is not only a problem in Western societies, prevalence rates were comparable across different continents (10.5-16.8%). However, data regarding Australia and African countries are lacking. IBS was reported as most encountered AP-FDIG (8.8%). Different diagnostic criteria were used to define functional abdominal pain in the included studies. The highest prevalence rate of 16.4% was found when studies using the Rome III criteria were pooled. Female gender and psychosocial factors affected the prevalence. The presence of anxiety and depressive disorders, stress and traumatic life events increased the prevalence of functional abdominal pain. Emphasis on these psychosocial factors can benefit treatment and therefore deserves attention in the clinical evaluation of children with AP-FGIDs.

Part II – Diagnosis

The pathophysiologicaly underlying functional abdominal pain disorders is considered to be multifactorial and remains not completely understood. The prevailing viewpoint is that the pathogenesis involves the interrelationship between changes in visceral sensation, the so-called visceral hypersensitivity, and altered gastrointestinal motility.[5] Several factors have been linked to this interaction, such as an alteration of the gut microbiome. The expansion of bacteria into the small intestine usually leads to bloating, diarrhea and abdominal discomfort or pain.[6] A condition with an abnormal high microbial population level in the small intestine is known as small intestinal bacterial overgrowth (SIBO). In **chapter 3** a study is described in which we aimed to assess the prevalence of SIBO in children with AP-FGIDs fulfilling the ROME III criteria and to identify potential predictors of SIBO in children with AP-FGIDs. Because a greater diagnostic accuracy has been demonstrated for glucose hydrogen breath test (GHBT) compared to the lactulose hydrogen breath test (LHBT),[7] we diagnosed SIBO using the GHBT. This cohort study showed that small intestinal bacterial overgrowth (SIBO), using the GHBT, was found in 14.3% of Dutch children with AP-FGIDs. SIBO was more

prevalent in children with IBS compared to other AP-FGIDs. In addition, an altered defecation pattern, loss of appetite and belching were significantly more found in children with SIBO compared to those without SIBO. So far, there is insufficient evidence to justify the routine exclusion of SIBO in the diagnostic work up of children with AP-FGIDs. However, GHBT should be considered in children with IBS, an altered defecation pattern, loss of appetite and belching, which seem predictors for SIBO.

To make a diagnosis of AP-FGIDs it is important to rule out an organic cause. Dientamoebiasis has been proposed to underlie functional abdominal pain, because it is associated with clinical symptoms, such as abdominal pain and diarrhea. Since the pathogenicity of *Dientamoeba* (*D.*) *fragilis* is controversial, it is unknown if children with chronic abdominal pain should be screened and treated for this parasite. Therefore, we aimed to reveal the clinical relevance of dientamoebiasis in children suffering from AP-FGIDs. In **chapter 4** the results of a retrospective case-control study are presented, comparing 132 children with chronic abdominal pain to 77 healthy controls. Fifty percent of our asymptomatic children were infected by *D. fragilis*, compared to 43% of children presenting with chronic abdominal pain. The connection between the presence or absence of symptoms could not be explained by a difference in quantity of parasitic load in the colon. Our study did not show a significant difference in the cycle threshold (Ct) values of parasitic DNA load between cases and controls. Furthermore, focusing on children fulfilling the criteria for AP-FGIDs, the presence of *D. fragilis* was not significantly associated with any gastrointestinal symptom. No significant association between clinical and microbiological response was found. Parasitological eradication was achieved in 61.7% of patients after treatment with metronidazole or clioquinol, while clinical improvement occurred in only 40.4% of patients. These findings do not support an association between AP-FGIDs and *D. fragilis* infection. Therefore, screening for *D. fragilis* should not be performed on a routine basis.

Part III – Management

In **chapter 5** a systematic review is presented in which the effectiveness and safety in children with AP-FGIDs of different pharmacologic treatments, including antispasmodics, antidepressants, antidiarrheal agents, antibiotics, pain medication, antireflux agents, anti-emetics, anti-migraine agents, antihistaminic agents and laxatives, is evaluated. Only six randomized controlled trials of very low quality were included in this systematic review. Some evidence was found that treatment with peppermint oil, cyproheptadine or a combination of polyethylene glycol with tegaserod is effective in children with IBS and FAP. Tegaserod, however, has been associated with serious cardiovascular ischemic events and was therefore withdrawn from the market on order of the Food and Drug Administration.[8] Famotidine did not show significant improvement of abdominal pain, but when analyzing global symptom improvement, famotidine was more effective compared to placebo among children with recurrent abdominal pain and dyspepsia. Amitriptyline showed to improve quality of life, but no effect in reduction of abdominal pain was demonstrated compared to placebo. No serious adverse effects were reported for any of the drugs mentioned above. No studies were found concerning the effect of antidiarrheal agents, antibiotics, pain medication, anti-emetics and antimigraine agents in children with AP-FGIDs. This review clearly reveals a lack of adequately powered, high-quality, placebo-controlled drug trials in children with AP-FGIDs. Based on the literature it is currently not possible to recommend any specific pharmacologic treatment for these children. In case of severe and persisting symptoms, physicians may consider drug therapy. In **chapter 6** a systematic review is described concerning the nonpharmacologic treatments in children with functional abdominal pain, including lifestyle advices such as physical exercise, dietary interventions (fiber supplements, lactose-free, gluten-free, histamine-free and carbon acid-free diet and fluid intake),

behavioral interventions such as hypnotherapy and cognitive behavioral therapy, pre- and probiotics and alternative medicine (acupuncture, homeopathy, mind-body therapy, musculoskeletal manipulations such as osteopathic and chiropractic manipulations and spiritual therapies such as meditation and yoga). Available evidence indicates beneficial effects of hypnotherapy, cognitive behavioral therapy and probiotics, however, the quality of these studies was very low to moderate. Data on fiber supplementation for children and adolescents with AP-FGIDs is inconclusive, but partially hydrolyzed guar gum, a water-soluble, dietary fiber, may be an option. No beneficial effects were reported for other fiber supplementation, such as glucomannan or ispaghula husk, lactose-restricted diet or alternative medicine. No (serious) adverse effects were reported for these interventions. Studies on life-style advices, other dietary advices and prebiotics were not included.

As shown in the previous chapter, there is evidence for the efficacy of probiotics in treating children with AP-FDIG. A comprehensive overview of the efficacy of different probiotics is given in **chapter 7.** The rationale for using probiotics comes from recent evidence suggesting that the microbiome is involved in the pathogenesis of AP-FGIDs.[9] Ultimate goal of treatment is using a specific probiotic strain to change an altered microbial flora and abnormalities in fermentation, gas production, and absorption that drive the symptoms of IBS. Compared to placebo, our meta-analyses showed that the use of LGG, *Lactobacillus reuteri DSM 17 938* and VSL#3 significantly increases treatment success in children with AP-FGIDs, particularly among children with IBS. Health-promoting activities of probiotics are strain-specific. Unfortunately, a paucity of data did not allow us to make any sub-analysis for a specific strain and conclude whether any particular probiotic is more effective than another. Therefore, we were not able to draw a conclusion regarding the optimum probiotic strategy to use in the routine treatment of children with AP-FGIDs.

In chapter 2 the association between psychological distress and functional abdominal pain in children is reinforced. This implies that mind and body influence each other bidirectionally. A holistic approach, exploring the interconnection between mind and body, can be of additional value in the treatment of children with functional abdominal pain. Yoga is an ancient technique used for promoting physical and mental health through postures, the regulation of breathing, and meditation.[10] In Western civilization it is considered as a form of complementary and alternative medicine (CAM) and is becoming more and more popular. Yoga therapy has shown its efficacy in stressmanagement and has been recommended as intervention in adults with irritable bowel syndrome.[11] In **chapter 8** we report the findings of a randomized controlled trial conducted in 69 pediatric patients, age 8-18 years, with AP-FGIDs. We compared the effect of 10 weeks yoga therapy (YT) complementary to standard medical care with standard medical care alone (SMC). SMC included education, reassurance, dietary advice and fibers/mebeverine if considered necessary. Hatha yoga comprised a mixture of classical yoga poses, breathing- and meditation technics and relaxation exercises. Yoga therapy appears to be a promising intervention for functional abdominal pain in childhood. YT was significantly more effective in the reduction of children who reported monthly school absence compared to SMC. After one year, school absence decreased from 55% to 7% after YT and from 65% to 33% after SMC. And at one year follow-up, a 50% reduction of weekly abdominal pain scores was accomplished in 58% of the YT group and 29% of the SMC group (p=0.01). Furthermore, a significant greater reduction of pain intensity was demonstrated at 12 months in favor of YT. However, YT was not significantly more effective compared to SMC in the improvement of abdominal pain frequency or quality of life.

Discussion and future perspectives

AP-FGIDs in childhood are a common problem worldwide, as shown in this thesis. Enhancements of the terminology and composing the Rome criteria have encouraged healthcare takers to make a positive diagnosis and have advanced empirical research in childhood AP-FGIDs. Increased knowledge of the pathophysiology has led to a biopsychosocial model, in which genetic, physiological and psychological factors interplay.

The hypothesis that SIBO accounts for the symptoms of AP-FDIGs has helped to focus on the role of bacteria in the intestine and in particular their potential to modulate sensation and motility. Given the imperfect nature of hydrogen breath tests and the absence of a 'gold standard' diagnostic test for SIBO,[12] interpretation of data is challenging. More work is needed to better understand the role of the microbiota in the development of gastrointestinal symptoms. Modern genomic and metabolomic techniques offer much promise in defining true normality. When a normal microbiome is recognized, alterations in the flora in disease states can be identified. Defining the microbiome in children with AP-FGIDs can help to identify which children with AP-FGIDs could benefit from therapeutic manipulation of gut microbiota, using antibiotics or probiotics. Disaggregation of the microbiome to AP-FGID subtypes is of special interest, since this thesis shows that SIBO was more prevalent in children with IBS compared to other AP-FGIDs and beneficial effects of probiotics are particularly seen among children with IBS. Because good data are lacking and the microbiome in children with AP-FGIDs has not been well characterized, we cannot recommend any probiotic therapy. Future studies need to establish which species, specific strain, combination of strains and dose of probiotics are most efficacious in AP-FIGDs. Moreover long-term follow-up studies using different probiotic strains are needed, since there is a lack of data providing evidence that the use of probiotics is effective and safe for a prolonged period of time.

Antimicrobial treatment may have serious or even long-lasting effects on the microbiome on top of its potential to promote microbial resistance. Prescription of antibiotics should, therefore, be done carefully. We questioned the routine screening and antibiotic treatment approach of a *D. fragilis* infection by infirming the association between AP-FGIDs and dientamoebiasis. Though, our results were limited by the retrospective design of the study. A recent placebo-controlled trial, however, confirmed our results and showed no clinical benefit of metronidazole in 96 children with *D. fragilis* and long-term gastrointestinal complaints.[13] This does not preclude the possibility that *D. fragilis* in another setting may be a cause of illness. Future studies evaluating the presence of *D. fragilis* in relation to bacterial composition in health and disease and studies on the temporal relationship between *D. fragilis* status and gastrointestinal symptom development are of great relevance.

Based on the systematic reviews described in this thesis, we conclude that there is a lack of well-designed trials in the pharmacologic and nonpharmacologic treatment of children with AP-FGIDs. This lack of large well performed clinical efficacy trials undermines evidence based treatment. Future high-quality studies are required in children with mild symptoms as well as severe symptoms to further assess effectiveness of pharmacologic and nonpharmacologic therapies and identify factors predicting response to optimize and tailor individual treatment. Well-designed larger studies are needed with greater methodological rigor. It is of great importance that researchers use the same methods according to standardized protocols as suggested by international experts in the field of both adult and pediatric functional gastrointestinal disorders. In this way, the quality of care will be improved by an

earlier and better recognition of AP-FGIDs and by improved diagnostic and therapeutic strategies. To achieve this goal, homogeneous patient populations and outcome measures should be used, including the standard definition for AP-FGIDs as described in the Rome III criteria. Validated instruments should be used to measure these outcome measures, such as abdominal pain, anxiety, depression, adequate relief and quality of life. Studies involving chronic conditions should also consider long-term outcomes.

It is noteworthy that due to a strong placebo response several studies failed to demonstrate a significant benefit of an intervention, although an absolute improvement was seen. Success rates for placebo up to 53% were reported for pediatric patients with FGIDs.[14] The placebo effect might be due to a high level of expectancy of the children and the parents and the frequent contacts between the doctors and the patients. Furthermore, it is known that an active listening approach and encouraging attitude towards treatment help to improve subjects' responses to both therapeutic attempts and placebo.[15,16] On the other hand, high placebo response might point towards natural course of disease or fluctuations in symptoms.[17] A physician should keep in mind that all these components can result in a considerably chance of improvement, no matter which medication is prescribed.

The biopsychosocial model, the assumption that mind and body represents a unitary entity, and the lack of high quality evidence for pharmacologic interventions, support toward an integrative approach in the treatment of children with functional abdominal pain. Integrative health treats the "whole person," and focuses on wellness and health rather than on treating disease, and emphasizes the patient-physician relationship. It takes into account individual situations and insists on patients being active participants in their own health care. Yoga therapy means to promote physical and mental well-being. Our study is the first to demonstrate that yoga therapy is effective in the treatment of children with long lasting complaints of AP-FGIDs with 59% of the children reporting a 50% reduction of abdominal pain at one year follow-up and a serious reduction of school absence. This is an important finding, since abdominal pain rank second in the causes of absence from school.[4]
There are some caveats regarding our results: in total, 4 times as many participants from the control group did not finish the complete study period compared with the yoga group, which caused attrition bias. Furthermore, due to the nature of yoga, blinding was not possible for caregiver and patient.

As we described in the previous chapters, also cognitive behavioral therapy (CBT) and hypnotherapy (HT) have shown to be effective therapies with long lasting effects for children with recurrent and functional abdominal pain.[18,19] A disadvantage of CBT, however, is that parents can be reluctant in accepting the existence of psychosocial influences on their child's symptoms and often refuse to engage with psychological services.[20] Also HT suffers from definite misgivings and belief in myths surrounding hypnosis. This might be different with yoga therapy, as this is becoming very popular and more common in Western countries. Furthermore, yoga therapy is simple, can be easily applied at home, and has considerably lower costs than HT and CBT.

The mechanism by which yoga can reduce pain is not well understood. Increased knowledge of the pathophysiology of AP-FGIDs has led to a biopsychosocial model, in which both physiological, psychological and emotional factors are integrated in a complex way to modulate the symptoms in any given individual.[21] Yoga therapy is likely to exert its effect on the psychosocial factor of this model. Stress and anxiety are known triggers for symptoms of FAP and IBS.[22] Studies have shown that the practice of yoga reduces perceived stress and negative feelings and that it improves psychological symptoms by lowering the levels of anxiety and anger, in both adults and children.[23–25] Studies

focusing on meditation, often a component of yoga practice, have proved that stress-reduction is supported by altering brain activation. After a mindfulness-based stress reduction program of eight weeks changes in gray matter concentration were demonstrated in brain regions involved in emotional regulation and arousal, measured by MRI.[26] This is an interesting finding, since increased gray matter density in IBS patients was observed in brain regions involved in the stress and arousal circuit.[27–29] Furthermore, meditation can produce increases in relative left-sided anterior activation that are associated with reductions in anxiety and negative affect and increases in positive affect.[30] Future studies are needed to clarify if yoga therapy also results in changes in brain structures and activity in children with AP-FDIGs.

Further research should investigate whether different intensity and duration of yoga treatment might increase effectiveness directly after therapy. Also the efficacy for different AP-FGID subgroups should be explored, in order to tailor individual treatment. Since treatment protocols in CBT, HT and yoga all incorporate relaxation exercises, one might hypothesize that relaxation training alone can also be beneficial in AP-FGIDs. This may be an interesting therapeutic approach to address in future research, since it has been shown to be effective in children and adolescents with recurrent headaches as well.[31] Furthermore, comparison of yoga to these interventions should be studied, to determine which of these treatments has the most potent and sustained effect and whether there is an individual likelihood which increases the responsiveness to a particular therapy.

In today's practice, an integrative approach can be of additional value in the treatment of children with an AP-FGID, exploring the interconnection between mind and body, with a focus on wellness and health rather than on treating disease. Because health exceeds the absence of disease, the primary goal of the therapy may not always be complete eradication of pain, but resumption of a normal lifestyle with regular school attendance, normal sleep pattern and participation in extracurricular activities. The first step in the management of children with an AP-FGID may consist of physician reassurance, education and dietary advices, since symptoms may resolve without active treatment in a significant proportion of children. For those who continue to experience symptoms and in case of serious disruption of a child's well-being, clinicians may consider relaxation based- psychological therapies or probiotics. Treatment should be individualized, focusing on the entire person, taken into account vulnerabilities, co-morbidities and personal preferences of each child and their parents.

This thesis elucidates current and new knowledge regarding epidemiology, pathophysiology, diagnostic workup and treatment of functional abdominal pain to improve the understanding and to maximize the quality of care for children suffering from this condition.

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Nederlandse samenvatting

Chronische buikpijn is een veel voorkomend probleem. Bij meer dan 90% van de kinderen die zich presenteert met chronische buikpijn wordt geen organische oorzaak gevonden en wordt de diagnose functionele buikpijn gesteld.[1] Aanvankelijk werd deze aandoening door Apley en Naish aangeduid met de term *'recurrent abdominal pain'*. In 2006 werd dit opnieuw gedefinieerd volgens de huidige Rome III criteria.[2] Op basis van symptomen is een verdeling gemaakt in vijf buikpijnsyndromen; 1) functionele dyspepsie (FD), 2) prikkelbare darmsyndroom (PDS), 3) abdominale migraine (AM), 4) functionele buikpijn (FB) en 5) het functionele buikpijnsyndroom (FBS). In het vervolg van dit proefschrift wordt de term 'functionele buikpijn' gebruikt om te verwijzen naar de vijf buikpijnsyndromen zoals beschreven volgens de Rome III criteria. De gevolgen van functionele buikpijn kunnen groot zijn. Kinderen met functionele buikpijn hebben een verminderde kwaliteit van leven als gevolg van langdurige lichamelijke klachten. Daarnaast is buikpijn de tweede oorzaak van schoolverzuim.[3,4] Het onderliggend pathofysiologisch mechanisme van functionele buikpijn is multifactorieel, maar moet nog verder opgehelderd worden. Deze beperkte kennis leidt tot uitgebreide diagnostiek, niet effectieve behandelingen en forse kosten binnen de gezondheidszorg.
Dit proefschrift focust zich daarom op het identificeren van risicofactoren die belangrijk zijn in de ontwikkeling van functionele buikpijn en het evalueren van verschillende diagnostische en therapeutische strategieën. Het eindigt met het evalueren van een nieuwe complementaire behandelmogelijkheid.

Deel I – Epidemiologie

Hoofdstuk 2 bevat een systematische review en meta-analyse van gepubliceerde literatuur over de prevalentie van functionele buikpijn in de algemene pediatrische populatie. Gegevens van 58 studies werden samengevoegd en laten een wereldwijde prevalentie van functionele buikpijn op de kinderleeftijd zien van 13.5%. PDS is de meest voorkomende vorm van functionele buikpijn en komt voor bij 8.8% van alle kinderen. Functionele buikpijn is niet alleen een probleem van westerse landen. De prevalentie tussen de verschillende continenten komt redelijk overeen en varieert van 10.5-16.8%. Echter, gegevens over Australië en Afrika ontbreken. In de studies werden verschillende diagnostische criteria gebruikt om functionele buikpijn vast te stellen. De hoogste prevalentie werd gemeten wanneer studies hiervoor de Rome III criteria gebruikten (16.4%). Functionele buikpijn komt significant vaker voor bij meisjes dan bij jongens. Ook psychosociale factoren hebben invloed op de prevalentie. De aanwezigheid van angst en depressieve klachten, stress en traumatische gebeurtenissen verhogen de prevalentie van functionele buikpijn. In de behandeling en begeleiding van kinderen met functionele buikpijn dient er dan ook aandacht te zijn voor de aanwezigheid van eventuele psychosociale factoren.

Deel II – Diagnostiek

De pathofysiologische mechanismen die ten grondslag liggen aan functionele buikpijn, zijn nog niet volledig bekend. Functionele buikpijn wordt beschouwd als een multifactoriële aandoening, waarbij een complex samenspel van genetische, fysiologische en psychosociale factoren een rol speelt bij het ontstaan en persisteren van de klachten.[5] Volgens de huidige opvattingen staat een overgevoeligheid van de darmen, een zogenaamde hypersensitiviteit, samen met een veranderde darmmotiliteit centraal in de pathogenese. Verschillende factoren kunnen dit complexe samenspel beïnvloeden,

bijvoorbeeld een verandering van de darmflora. Een toename van bacteriën in de dunne darm leidt tot klachten van een opgeblazen gevoel, diarree en buikpijn.[6] Een aandoening waarbij er sprake is van een abnormale hoeveelheid bacteriën in de dunne darm is bekend als bacteriële overgroei. Het doel van de studie die in **hoofdstuk 3** wordt beschreven is het vaststellen van de prevalentie van bacteriële overgroei bij kinderen waarbij functionele buikpijn is gediagnosticeerd volgens de Rome III criteria. Tevens worden potentiële factoren geïdentificeerd die de aanwezigheid van bacteriële overgroei bij kinderen met functionele buikpijn kunnen voorspellen. Om bacteriële overgroei aan te tonen hebben we gebruik gemaakt van de glucose waterstof ademtest (GHBT). De GHBT heeft namelijk een grotere diagnostische betrouwbaarheid dan de lactulose waterstof ademtest.[7] Onze cohort studie toonde een prevalentie van bacteriële overgroei van 14.3% bij Nederlandse kinderen met functionele buikpijn. Bacteriële overgroei werd vaker gevonden bij kinderen met IBS dan bij kinderen met een van de andere functionele buikpijnsyndromen. Een veranderd defecatiepatroon, verlies van eetlust en klachten van opboeren werden significant vaker aangetoond bij kinderen met bacteriële overgroei, vergeleken met kinderen zonder bacteriële overgroei. Tot op heden is er onvoldoende bewijs om routinematig diagnostiek te verrichten naar bacteriële overgroei bij kinderen met functionele buikpijn. De GHBT dient wel overwogen te worden bij kinderen met IBS en wanneer klachten van een veranderd defecatiepatroon, verlies van eetlust en opboeren op de voorgrond staan, omdat dit de aanwezigheid van bacteriële overgroei lijkt te voorspellen.

Om de diagnose functionele buikpijn te stellen is het belangrijk dat een organische oorzaak wordt uitgesloten. Er wordt verondersteld dat Dientamoebiasis een rol speelt bij functionele buikpijn, omdat een *Dietamoeba (D.) fragilis* infectie zich eveneens presenteert met symptomen zoals buikpijn en diarree. De pathogeniciteit van *D. fragilis* is echter controversieel, waardoor het onbekend is of deze parasiet als organische oorzaak moet worden uitgesloten voordat de diagnose functionele buikpijn kan worden gesteld. Ons doel is daarom om de klinische relevantie van een *D. fragilis* infectie bij kinderen met functionele buikpijn te verhelderen. In **hoofdstuk 4** worden de resultaten van een retrospectief onderzoek gepresenteerd waarin 132 kinderen met chronische buikpijn werden vergeleken met 77 gezonde kinderen. Vijftig procent van deze gezonde controle groep bleek geïnfecteerd te zijn met *D. fragilis*, vergeleken met 43% van de onderzoekgroep. De aanwezigheid of afwezigheid van klachten kan niet worden verklaard door een verschil in kwantiteit van de parasiet in het colon. Dit kan worden vastgesteld met de cycle threshold (Ct) values van de parasitaire DNA load. Deze studie laat zien dat er geen significant verschil is in Ct value tussen de kinderen met chronische buikpijn en de gezonde kinderen. Vervolgens hebben we ons in deze studie gefocust op de kinderen die voldeden aan de Rome III criteria voor functionele buikpijn. De aanwezigheid van *D. fragilis* was niet geassocieerd met bepaalde gastro-intestinale klachten. Oftewel, in de groep kinderen met chronische buikpijn was er geen verschil in klachtenpatroon tussen kinderen met en zonder *D. fragilis* infectie. Ook werd er geen associatie gevonden tussen een klinisch en microbiologisch effect op de behandeling. Bij 61.7% van de kinderen was de parasiet geeradiceerd na behandeling met metronidazol of clioquinol, echter een klinische verbetering werd bij slechts 40.4% van de patiënten waargenomen. Deze bevindingen laten zien dat er geen associatie is tussen functionele buikpijn en een *D. fragilis* infectie. Screening op deze parasiet hoeft dus ook niet op routinematige basis te gebeuren bij kinderen met functionele buikpijn.

Deel III – Behandeling

In **hoofdstuk 5** evalueren we de effectiviteit en veiligheid van verschillende farmacologische behandelingen, zoals antispasmolytica, antidepressiva, antidiarree medicatie, antibiotica, pijn-medicatie, antireflux medicatie, anti-emetica, anti-migraine medicatie, antihistaminica en

laxeermiddelen. Slechts zes studies konden worden geïncludeerd in ons systematische review. De kwaliteit van de studies was erg laag. Enig bewijs werd gevonden voor de effectiviteit van pepermuntolie, cyproheptadine of een combinatie van polyethylene glycol en tegaserod bij kinderen met IBS en FAP. Echter, tegaserod is geassocieerd met ernstige cardiale bijwerkingen waardoor het van de markt is teruggetrokken in opdracht van de Food and Drug Administration.[8] Famotidine liet geen significante vermindering van buikpijn zien, maar wanneer er naar een globale verbetering van symptomen werd gekeken was famotidine effectiever dan placebo bij kinderen met chronische buikpijn en dyspeptische klachten. Het gebruik van amitriptyline zorgde voor een verbetering van de kwaliteit van leven, maar toonde geen significante vermindering van buikpijnklachten in vergelijking met placebo. Van de overige medicatie, zoals hierboven genoemd, werden geen ernstige bijwerkingen gerapporteerd. Er werden geen studies geïncludeerd die het effect van antidiarree medicatie, antibiotica, pijnmedicatie, anti-emetica of anti-migraine medicatie onderzochten. Dit onderzoek laat duidelijk zien dat er een gebrek is aan kwalitatief goede, placebo gecontroleerde studies naar het effect van medicatie bij kinderen met functionele buikpijn. Momenteel is het niet mogelijk om een specifiek middel aan te bevelen. Bij kinderen met ernstige en aanhoudende klachten kunnen clinici ervoor kiezen om medicatie voor te schrijven.

In **hoofdstuk 6** zijn de resultaten van een systematische review beschreven met betrekking tot de non-farmacologische behandeling van kinderen met functionele buikpijn, zoals leefstijladviezen (beweging), dieet interventies (vezels, lactosevrij-, glutenvrij-, histaminevrij en koolzuurvrij dieet, vochtinname), gedragsinterventies (hypnotherapie (HT), cognitieve gedragstherapie (CGT)), pre- en probiotica, en alternatieve geneeskunde (acupunctuur, homeopathie, mind-body therapie, musculoskeletal manipulaties zoals osteopathie en chiropraxie en tot slot yoga). Beschikbare studies laten goede effecten zien na behandeling met HT, CGT en probiotica, echter de kwaliteit van de betreffende studies is zeer laag tot gemiddeld. Het effect van vezel supplementen in de behandeling van kinderen en adolescenten met functionele buikpijn is niet overtuigend. PGHH, een water oplosbare voedingsvezel, kan echter overwogen worden. Geen significant effect werd gevonden voor andere vezelpreparaten, zoals glucomannan of ispaghula husk, na een lactosevrij dieet of na alternatieve behandeling. Er werden geen ernstige bijwerkingen gerapporteerd voor een van deze interventies. Studies naar het effect van leefstijl adviezen, andere dieetadviezen of prebiotica konden niet worden geïncludeerd.

In het vorige hoofdstuk is het gunstige effect van probiotica aangetoond in de behandeling van kinderen met functionele buikpijn. In **hoofdstuk 7** wordt een uitgebreid overzicht van de effectiviteit van verschillende soorten probiotica gegeven. Het idee om probiotica te gebruiken in de behandeling van kinderen met functionele buikpijn is ontstaan sinds het microbioom gelinkt is aan de pathologie van functionele buikpijn.[9] Het doel van de behandeling is om middels een specifiek probioticum het veranderde darmflora op een gunstige manier te beïnvloeden, waardoor afwijkingen in vertering, gas productie en absorptie afnemen en daardoor ook de klachten van functionele buikpijn. Onze meta-analyse laat zien dat in vergelijking met placebo, het gebruik van LGG, *Lactobacillus reuteri DSM 17 938* en VSL#3 leidt tot een significante toename van behandelsucces bij kinderen met functionele buikpijn, voornamelijk bij kinderen met PDS. Gezondheid bevorderende activiteiten van probiotica zijn verschillend per stam. Helaas waren we door de beperkte gegevens niet in staat om subanalyses uit te voeren naar de effectiviteit van de diverse stammen. Hierdoor zijn we ook niet in staat om een conclusie te trekken over de meest optimale strategie met probiotica in de dagelijkse behandeling van kinderen met functionele buikpijn.

In hoofdstuk 2 is de associatie tussen psychologische stressfactoren en functionele buikpijn bij kinderen wederom aangetoond. Dit is een aanwijzing dat het lichaam en de geest met elkaar in contact staan. Een holistische benadering, waarbij er zowel aandacht is voor de geest als het lichaam, kan daarom van aanvullende waarde zijn in de behandeling van kinderen met functionele buikpijn. Yoga is een eeuwenoude techniek die gebuikt wordt om de fysieke en mentale gezondheid te bevorderen aan de hand van houdingen, ademhalingsoefeningen en meditatie.[10] In Westerse landen wordt yoga gezien als een vorm van complementaire en alternatieve geneeskunde. Ook wint het de laatste jaren aan populariteit. Behandeling met yoga leidt tot een effectieve afname van stress en wordt aanbevolen in de behandeling van volwassen met PBS.[11] In **hoofdstuk 8** rapporteren we de bevindingen van een gerandomiseerde en gecontroleerde studie naar het effect van yoga therapie bij 69 kinderen van 8 tot 18 jaar oud. Het effect van 10 weken yoga als aanvulling op de standaardbehandeling werd vergeleken met alleen de standaardbehandeling. Standaardbehandeling bestaat uit uitleg, geruststelling, voedingsadviezen en zo nodig vezels. Hatha yoga is een combinatie van klassikale houdingen, ademhaling- en meditatietechnieken en ontspanningsoefeningen. Yoga was significant effectiever in de afname van het percentage kinderen dat maandelijks verzuimt van school in vergelijking met de controlegroep. Na 12 maanden follow-up is dit percentage in de yogagroep gedaald van 55% naar 7%, en in de controlegroep van 65% naar 33%. Daarnaast bereikte 58% van de kinderen een afname van minstens 50% van de buikpijnklachten na yoga therapie, vergeleken met 29% van de kinderen na standaard behandeling (p=0.01). Verder werd er een significant grotere reductie van buikpijn intensiteit gezien 12 maanden na start van de behandeling, in het voordeel van yoga therapie. Yoga therapie is echter niet effectiever gebleken dan standaard therapie in het verbeteren van de kwaliteit van leven en het verbeteren van de buikpijn frequentie.

Discussie en toekomstperspectieven

Functionele buikpijn is een probleem dat wereldwijd voorkomt, zoals aangetoond in dit proefschrift. Door verbetering van de terminologie en het ontwikkelen van de Rome criteria worden clinici gestimuleerd om een positieve diagnose te stellen. Daarnaast leidt dit tot verbetering van wetenschappelijk onderzoek. Toegenomen kennis over de pathologie heeft geleid tot de ontwikkeling van een biopsychosociaal model, waarin genetische, fysiologische en psychologische factoren een rol spelen.

De hypothese dat bacteriële overgroei een rol speelt bij het ontstaan van klachten van functionele buikpijn heeft de aandacht gevestigd op de rol van bacteriën in de dunne darm, en in het bijzonder op hun mogelijkheid om de sensitiviteit en motiliteit van de darm te moduleren. Het interpreteren van data over bacteriële overgroei is echter uitdagend. Dit komt door de beperkingen die de waterstof blaastest met zich mee brengt en vanwege de afwezigheid van een ‘gouden standaard’.[12] Meer onderzoek is nodig om de rol van de darmflora in de ontwikkeling van gastro-intestinale klachten beter te begrijpen. Modern moleculaire technieken bieden veelbelovende mogelijkheden bij het definiëren van een microbioom. Wanneer een normaal microbioom kan worden herkend, kunnen bij ziekte de veranderingen ten opzichte van het normale microbioom geïdentificeerd worden. En wanneer het microbioom van kinderen met functionele buikpijn gedefinieerd wordt, kan dit helpen om te identificeren welke kinderen met functionele buikpijn baat kunnen hebben bij therapeutische manipulatie van de darmflora door antibiotica of probiotica. Differentiatie tussen de verschillende functionele buikpijnsyndromen is daarbij van belang. Dit proefschrift heeft namelijk aangetoond dat bacteriële overgroei vaker wordt gezien bij kinderen met PDS, vergeleken met andere

buikpijnsyndromen. Omdat betrouwbare gegevens ontbreken en het microbioom bij kinderen met functionele buikpijn nog niet goed in kaart is gebracht, kunnen we geen optimale behandeling met probiotica aanbevelen. Toekomstige studies zijn nodig om vast te stellen welke soorten, stammen en welke doses van probiotica het meest effectief zijn in de behandeling van kinderen met functionele buikpijn. Verder zijn lange termijn studies van de verschillende stammen nodig om het effect en de veiligheid van probiotica op de lange termijn aan te tonen.

Antibacteriële behandeling kan een serieus langdurig effect op het microbioom uitoefenen, bovenop het feit dat het resistentie van bacteriën in de hand kan werken. Het voorschrijven van antibiotica moet daarom erg zorgvuldig gebeuren. Door het ondermijnen van de associatie tussen functionele buikpijn en dientamoebiasis, hebben wij het routinematige screenen en behandelen van D. *fragilis* ter discussie gesteld. Onze resultaten zijn echter beperkt vanwege het retrospectieve karakter van de studie. Niettemin, heeft een dubbelblinde, gerandomiseerde, placebogecontroleerde studie onlangs onze resultaten bevestigd. Onder 96 kinderen met langdurige gastro-intestinale klachten en een D. *fragilis* infectie werd aangetoond dat behandeling met metronidazol niet geassocieerd is met een betere klinische uitkomst.[13] Dit sluit echter niet uit dat *D. fragilis* in andere omstandigheden wel een oorzaak van klachten kan zijn. Verder onderzoek is nodig waarin de aanwezigheid van *D. fragilis* in relatie tot de darmflora bij ziekte en gezondheid wordt geëvalueerd. Tevens is het relevant om te onderzoeken of er een tijdelijke relatie bestaat tussen *D. fragilis* en het ontwikkelen van gastro-intestinale symptomen.

Gebaseerd op de systematische reviews welke beschreven zijn in dit proefschrift, concluderen we dat er een tekort is aan gecontroleerde studies van goede kwaliteit betreffende de farmacologische en niet-farmacologische behandeling van kinderen met functionele buikpijn. De afwezigheid hiervan belemmert *evidence based medicine*. Toekomstige studies van goede kwaliteit zijn nodig bij kinderen met zowel milde als ernstige symptomen om de effectiviteit van farmacologische en niet-farmacologische behandelingen verder te onderzoeken. Hierbij is het interessant om te kijken naar factoren die een goede reactie op een behandeling kunnen voorspellen, zodat therapie geoptimaliseerd en aangepast kan worden aan het individu. Bij de opzet van nieuwe studies is het van belang dat alle onderzoekers dezelfde studie-opzet gebruiken, zoals beschreven in de protocollen ontwikkeld door internationale experts op het gebied van functionele gastro-intestinale ziekten. Door eerdere en betere herkenning van functionele buikpijn en door verbeterde diagnostische en therapeutische strategieën zal de kwaliteit van zorg verbeterd kunnen worden. Om dit doel te bereiken moet men homogene patiëntenpopulaties en uitkomstmaten gebruiken waarbij ook functionele buikpijn vastgesteld dient te worden volgens de Rome III criteria. Gevalideerde vragenlijsten zijn nodig om de uitkomstmaten te meten, zoals buikpijn, angst, depressie, *adequate relief* en kwaliteit van leven. Daarnaast dienen studies die betrekking hebben op chronische klachten ook de lange termijn uitkomsten te onderzoeken.

Het is opmerkelijk dat door een hoge placeborespons meerdere studies geen significant effect van de interventie aantonen, terwijl er wel een absolute verbetering wordt gezien. Succes percentages voor placebo lopen op tot 53% bij kinderen met functionele gastro-intestinale aandoeningen.[14] Het placebo-effect wordt mogelijk veroorzaakt door de hoge verwachtingen die ouders en kinderen hebben en door de frequente contacten tussen de dokter en de patiënt. Daarnaast is het bekend dat een actieve luisterende houding en een aanmoedigende benadering ten opzichte van de behandeling het effect van een therapie verbeteren, van zowel een nieuwe interventie als van placebo.[15,16] Aan de andere kant kan een placeborespons ook het natuurlijke beloop van een ziekte weergeven of fluctuaties van

symptomen.[17] Een arts dient erop bedacht te zijn dat al deze componenten kunnen bijdragen aan een serieuze verbetering van de klachten, ongeacht welk medicijn is voorgeschreven.

Het biopsychosociale model, de veronderstelling dat lichaam en geest een eenheid zijn, en het gebrek aan bewijs voor farmacologische therapieën, moedigen een integrale behandeling aan bij kinderen met functionele buikpijn. Integrale gezondheidszorg behandelt de 'hele mens' en is gefocust op welzijn en gezondheid, in plaats van op de behandeling van ziekten. Daarbij speelt de relatie tussen arts en patiënt een belangrijke rol. Binnen de visie van de Integrale gezondheidszorg wordt de eigen verantwoordelijkheid van de patiënt voor zijn of haar gezondheid en behandeling erkend. De patiënt wordt dan ook actief bij de behandeling betrokken. Yoga therapie heeft als doel het fysieke en mentale welzijn van een mens te bevorderen. Onze studie is de eerste die aantoont dat yoga therapie effectief is in de behandeling van kinderen met langdurige klachten van functionele buikpijn; 58% van de kinderen rapporteren een ≥50% afname van buikpijn na 1 jaar follow-up en een forse afname van schoolverzuim. Dit laatste is een belangrijke bevinding, aangezien buikpijn de op een na meest voorkomende oorzaak is van schoolverzuim.[4] Onze studie heeft echter wel een aantal beperkingen; in totaal zijn er vier keer zoveel kinderen uitgevallen uit de controle groep in vergelijking met de yoga groep, hierdoor is er sprake van attrition bias. Verder was het, vanwege de aard van yoga, niet mogelijk om de groepen te blinderen voor de interventie.

Zoals in hoofdstuk 6 van dit proefschrift is beschreven zijn ook CGT en HT effectieve behandelingen voor kinderen met functionele buikpijn, met tevens effect op de lange termijn.[18,19] Een nadeel van CGT is echter dat ouders niet altijd willen accepteren dat psychosociale invloeden een rol spelen bij de symptomen van hun kind en daardoor elke psychologische hulp afslaan.[20] Ook HT heeft te lijden onder het bestaan van twijfels en geloof in mythes rondom hypnose. Dit geldt niet voor yoga, dat laat de toename in populariteit in Westerse landen wel zien. Daarnaast is yoga therapie simpel, kan gemakkelijk thuis uitgevoerd worden en is goedkoper dan de eerder genoemde interventies.

Het mechanisme waardoor yoga pijn kan verminderen is niet geheel duidelijk. Een complexe wisselwerking tussen fysiologische, psychologische en genetische factoren speelt een rol in het ontstaan van buikpijnklachten.[21] Yoga therapie oefent vermoedelijk effect uit op de psychosociale factor van het biopsychosociale model. Stress en angst zijn bekende *triggers* van functionele buikpijn en prikkelbare darmsyndroom.[22] Studies onder zowel kinderen als volwassenen, hebben laten zien dat stress en negatieve psychologische symptomen zoals angst en boosheid afnemen na yoga therapie.[23–25] Studies naar het effect van meditatie, veelal een component van yoga, hebben bewezen dat stressreductie samengaat met een verandering in de hersenactiviteit. Na een mindfullness stress reductie programma van acht weken werden veranderingen in de grijze stof concentraties aangetoond in hersengebieden die betrokken zijn bij de emotie regulatie en arousal, gemeten met MRI.[26] Dit is een interessant gegeven, omdat een toename in de grijze stof concentratie is aangetoond in hersengebieden die betrokken zijn bij stress en arousal bij volwassenen met PDS, in vergelijking met een gezonde controle groep.[27–29] Tevens kan door meditatie de activiteit in de linker prefrontale cortex toenemen, wat is geassocieerd met afname van angst en negatieve affectiviteit en een toename van positieve affectiviteit.[30] Toekomstige studies moeten uitwijzen of yoga therapie ook resulteert in veranderingen in hersenstructuren en hersenactiviteit bij kinderen met functionele buikpijn.

Daarnaast moeten toekomstige studies uitwijzen of veranderingen in intensiteit en duur van yoga therapie de effectiviteit direct na de behandeling kan vergroten. Hierbij dient de effectiviteit bij de verschillende buikpijnsyndromen in kaart gebracht te worden, om zo nog gerichter individuele

behandeling te kunnen inzetten. Aangezien de behandelprotocollen van CGT, HT en yoga allemaal ondermeer bestaan uit ontspanningsoefeningen, kan gedacht worden dat ontspanningsoefeningen alléén ook een gunstig effect kunnen hebben op functionele buikpijn. Dit is een interessante therapeutische benadering die in toekomstige studies onderzocht kan worden. Zeker omdat het ook effectief is gebleken in de behandeling van kinderen en adolescenten met chronische hoofdpijnklachten.[31] Verder zou yoga vergeleken kunnen worden met andere op ontspanning gebaseerde therapieën, om te onderzoeken welke van deze behandeling het grootste en langdurigste effect heeft en of er individuele factoren zijn die de respons op een bepaalde therapie vergroten.

In de huidige praktijk kan een integrale benadering van aanvullende waarde zijn bij de behandeling van kinderen met functionele buikpijn. Hierbij is er aandacht voor lichaam en geest en ligt de focus op welzijn en gezondheid, in plaats van op het behandelen van een ziekte. Gezondheid is meer dan alleen de afwezigheid van ziekte. Daarom is het primaire doel van de therapie niet altijd het volledig uitbannen van de pijn, maar gaat het veel meer om het hervatten van een normale levensstijl, met een normale schoolgang, slaappatroon en deelname aan extra curriculaire activiteiten. De eerste stap in de behandeling van kinderen met functionele buikpijn bestaat uit uitleg en geruststelling door de arts, aangevuld met dieetadviezen. Bij een aanzienlijk deel van de kinderen zijn hierna de klachten verdwenen, zonder dat er actieve behandeling is ingezet. Wanneer de klachten aanhouden en wanneer het welzijn van het kind op een ernstige manier wordt aangetast, kunnen artsen ontspanning-gerelateerde psychologische behandeling of probiotica overwegen. De behandeling dient geïndividualiseerd te worden, waarbij er aandacht is voor de gehele persoon, met zijn/haar zwakheden, comorbiditeit en persoonlijke voorkeur.

Dit proefschrift geeft een overzicht van al bestaande en nieuwe kennis rondom de epidemiologie, pathofysiologie, diagnostiek en behandeling van functionele buikpijn. Met als doel functionele buikpijn beter te begrijpen en de kwaliteit van zorg voor deze kinderen te verbeteren.

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Submitted

Dientamoeba fragilis and chronic abdominal pain in children: a case-control study.
JJ. Korterink, M. de Jong, MA. Benninga, M. Hilbink, J.Widdershoven, JM. Deckers-Kocken.
Arch Dis Child. 2014 Dec;99(12):1109-13

Glucose hydrogen breath test for small intestinal bacterial overgrowth in children with abdominal pain-related functional gastrointestinal disorders.
JJ. Korterink, MA. Benninga, H. Van Wering, JM. Deckers-Kocken.
J Pediatr Gastroenterol Nutr. 2014 nov 17

Pharmacologic treatment in pediatric functional abdominal pain disorders; a systematic review.
JJ. Korterink, JM. Rutten, L. Venmans, MA. Benninga, MM. Tabbers.
J Pediatr. 2015 Feb;166(2):424-431

Nonpharmacologic treatment of functional abdominal pain disorders; a systematic review.
JJ. Korterink, JM. Rutten, L. Venmans, MA. Benninga, MM. Tabbers.
Pediatrics 2015 Mar;135(3):522-535

Probiotics for childhood functional gastrointestinal disorders; a systematic review and meta-analysis.
JJ. Korterink, L. Ockeloen, MM. Tabbers, MA. Benninga, M.Hilbink, JM. Deckers-Kocken. Acta Paediatr. 2014: 103(4), pp 365-372

Comparison of the effect of yoga and standard care on functional abdominal pain: pain reduction and improvement of quality of life? A randomized controlled trial.
JJ. Korterink, L. Ockeloen, M. Hilbink, MA. Benninga, JM. Deckers-Kocken.
Submitted

Other

Pseudothrombocytopenia in a neonate due to mother?
JJ.Korterink, B. Boersma, M. Schoorl, L. Porcelijn, P.Bartels.
Eur J pediatr. 2013: vol172(7), p987-989

Portfolio

Name PhD student: Judith Korterink
PhD period: January 2012 – January 2015
PhD supervisor: Prof. M.A. Benninga
PhD co-supervisor: Dr. J.M. Deckers-Kocken

	Year	ECTS
General courses		
- Good clinical practice	2012	0.9
- Practical biostatistics	2014	1.1
Seminars, workshops and master classes		
- Presentation course; Dutch Pediatric Federation	2014	0.5
- Amsterdam Pediatric symposium, Amsterdam	2013-2014	1
- European Society of Pediatric Gastroenterology, Hepatology and Nutrition: Young investigators Forum	2014	1.5
- Masterclass, Amsterdam Pediatric symposium	2015	0.5
Oral Presentations		
- Probiotics for functional abdominal pain in childhood; a systematic review and meta-analysis: European Society of Pediatric Gastroenterology, Hepatology and Nutrition, London	2013	0.5
Research meeting Jeroen Bosch Hospital, 's Hertogenbosch	2013	0.5
- *Dientamoeba fragilis* and abdominal pain-related functional gastrointestinal disorders in children: Annual autumn Conference Dutch Society for Gastroenterology, Veldhoven	2014	0.5
Dutch Pediatric Federation	2014	0.5
- Efficacy of a probiotic mixture in the treatment of children with chronic abdominal pain and small intestinal bacterial overgrowth; a randomized controlled trial: Dutch Pediatric Federation	2014	0.5
- Comparison of the effect of yoga and standard care on functional abdominal pain: pain reduction and improvement of quality of life? A randomized controlled trial: Annual spring Conference Dutch Society for Gastroenterology, Veldhoven	2015	0.5
Poster prestentation		
- *Dientamoeba fragilis* and abdominal pain-related functional gastrointestinal disorders in children: European Society of Pediatric Gastroenterology, Hepatology and Nutrition, Jerusalem	2014	0.5
- Efficacy of a probiotic mixture in the treatment of children with chronic abdominal pain and small intestinal bacterial overgrowth; a randomized controlled trial: European Society of Pediatric Gastroenterology, Hepatology and Nutrition, Jerusalem	2014	0.5

-	Comparison of the effect of yoga and standard care on functional abdominal pain: pain reduction and improvement of quality of life? A randomized controlled trial: European Society of Pediatric Gastroenterology, Hepatology and Nutrition, Amsterdam	2015	0.5
	Digestive Disease Week, Washington	2015	0.5
-	Epidemiology of paediatric functional abdominal pain worldwide; a meta-analysis: European Society of Pediatric Gastroenterology, Hepatology and Nutrition, Amsterdam	2015	0.5
	Digestive Disease Week, Washington	2015	0.5

(Inter)national conferences

-	Annual Pediatric Gastroenterology Symposium Amsterdam	2013-2014	0.5
-	Annual Conference Dutch Pediatric Federation, Veldhoven	2012, 2014	0.5
-	European Society of Pediatric Gastroenterology, Hepatology and Nutrition, London/Jerusalem/Amsterdam	2013-2015	3
-	Annual spring and autumn Conference Dutch Society for Gastroenterology, Veldhoven	2014-2015	0.5
-	Digestive Disease Week, Washington	2015	1

Lecturing

-	Teaching session on childhood functional abdominal pain for paediatricians and paediatric residents, Utrecht	2014	0.5
-	Teaching sessions on childhood defecation disorders for Dutch federation of Physiotherapists, Doorn	2015	0.5

Supervising

	Supervising research internship student (6 months). Project: *Dientamoeba fragilis* and abdominal pain-related functional gastrointestinal disorders in children. Department of Pediatrics, Jeroen Bosch Hospital, ‘s Hertogenbosch	2013	2

Awards and Prizes

-	Young investigator award, European Society of Pediatric Gastroenterology, Hepatology and Nutrition	2013-2014
-	Masterclass, Amsterdam Pediatric symposium	2015
-	Poster of distinction Digestive Disease Week	2015

Curriculum Vitae

Judith Korterink werd geboren op 7 oktober 1981 te Heino. In 1999 haalde zij haar HAVO-diploma aan het Greijdanus College te Zwolle. Vervolgens ging zij naar het Carmel College in Raalte om daar haar VWO-diploma te halen. Met dat diploma op zak startte zij in datzelfde jaar haar studie geneeskunde aan de Vrije Universiteit te Amsterdam.
Tijdens haar co-schappen groeide haar voorliefde voor de kindergeneeskunde. Reislustig als ze is, vertrok ze in 2008 naar Kathmandu in Nepal om daar een co-schap kindergeneeskunde te lopen. Na het afronden van haar studie geneeskunde in 2009 begon zij haar carrière als arts-assistent kindergeneeskunde in het Zaans Medisch Centrum en vervolgens in het Medisch Centrum Alkmaar.
In 2012 kreeg Judith de mogelijkheid om als arts-onderzoeker in het Jeroen Bosch ziekenhuis te gaan werken. Hier heeft zij, onder leiding van dr. Judith Deckers-Kocken, een buikpijnpoli opgericht en onderzoek verricht naar verschillende behandelmogelijkheden bij kinderen met functionele buikpijn. Dit onderzoek kon worden uitgebreid tot een promotietraject bij prof. dr. Marc Benninga in het Academisch Medisch Centrum. Het resultaat daarvan is het proefschrift dat nu voor u ligt.
Tijdens haar promotieonderzoek heeft zij meegewerkt aan het opstellen van de Nederlandse richtlijn voor kinderen met functionele buikpijn.
In april 2015 is Judith gestart met haar opleiding tot kinderarts in het Leids Universitair Medisch Centrum onder leiding van dr. W. Kollen.