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META-ANALYSIS

Dietary interventions for functional abdominal pain disorders in children: a systematic review and meta-analysis

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ABSTRACT

Background: Functional abdominal pain disorders (FAPDs) are common among children and are associated with decreased quality of life and school attendance. Several dietary interventions have been suggested to improve symptoms of FAPDs. This systematic review assessed the efficacy and safety of dietary interventions for pediatric FAPDs.

Design and methods: Electronic databases were searched (inception–October 2021). Systematic reviews or RCTs were included if children (4–18 years) with FAPDs were treated with dietary interventions and compared to placebo, no diet or any other diet. Data extraction and assessment of quality of evidence based on GRADE system was independently performed by two review authors. Outcomes were treatment success, pain intensity and frequency, and withdrawal due to adverse events.

Results: Twelve articles were included, representing data of 819 pediatric FAPD patients. Trials investigating fibers, FODMAP diet, fructans, fructose-restricted diet, prebiotic (inulin), serum-derived bovine immunoglobulin, and vitamin D supplementation were included. We found very low-certainty evidence that the use of fibers leads to higher treatment success (NNT = 5).

Conclusion: Based on current evidence, the use of fibers can be discussed in daily practice. High-quality intervention trials are highly needed to investigate if other dietary interventions are effective in the treatment of pediatric FAPD.

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KEYWORDS
Abdominal pain; diet; meta-analysis; pediatric

1. Background

Functional gastrointestinal disorders (FGIDs) are common among children and adolescents and are associated with impaired quality of life, functional disability, high rates of school absenteeism, and substantial increases in health-care costs [1–7]. A subset of FGIDs are functional abdominal pain disorders (FAPDs) and include functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraine (AM), and functional abdominal pain – not otherwise specified (FAP-NOS) (Supplementary File 1) [1].

To date, available treatment options are scarce. In general, standard medical treatment consists of education, reassurance and lifestyle interventions. Different dietary advices are recommended such as a lactose-free diet or increasing fiber intake [8]. Furthermore, psychosocial treatment (hypnotherapy and cognitive–behavioral therapy), and different pharmacological compounds have been used successfully as well [9,10]. Management remains mostly symptom-based since the exact pathophysiology of pediatric FAPDs is still not completely known [11].

Different mechanisms have been proposed. These derive from complex interactions of different biopsychosocial factors that influence the brain–gut axis, such as psychosocial distress, low-grade gut inflammation, intestinal dysbiosis, genetic predisposed and visceral hypersensitivity [12–14]. In the last decade increasing attention has been paid to the causative role of food in FADPs. They may interfere with GI motility and sensitivity, barrier function and gut microbiota, causing an irregular modulatory mechanism in the gut, resulting in abdominal pain, diarrhea, or constipation[15]. Recently, the role of diet in adults with IBS has been reviewed [16,17]. It has been perceived that food, such as gluten or products containing high rates of fermentable oligosaccharides, disaccharides, and monosaccharides and polyols (FODMAPs), which are present in stone fruits, beans and lentils, lactose-containing foods, nuts and (artificial) sweeteners, may precede IBS-related symptoms in about 50% of time. The majority of children with FAPDs report that their GI symptoms are food-related. A recent study identified new insights in peripheral

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Supplemental data for this article can be accessed here

mechanisms (i.e. IgE- and mast-cell-dependent) that underlies food-induced abdominal pain, making dietary interventions a potential fundamental treatment option of pediatric FAPDs [18–23]. However, in clinical practice, it is still difficult to distinguish which specific food components trigger FAPD-symptoms, leading to an overflow of diagnostics including screening for allergies, celiac disease or performing a hydrogen breath test, and also leading to a mixture of different recommended dietary interventions, which are largely based on expert opinion [24].

In general, treatment outcomes are suboptimal and children continuing to have symptoms in adulthood [25]. New treatment options, including evidence-based dietary interventions, may therefore be necessary in order to improve pediatric FAPD care. To guide health-care professionals, patients, and their families in treatment decisions, the present systematic review provides an up-to-date overview concerning the efficacy and safety of dietary treatments in children with FAPDs.

2. Methods

2.1. Literature search

PubMed, MEDLINE, EMBASE, PsycINFO, and Cochrane Library (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effect, and Cochrane Central Register of Controlled Trials (CENTRAL)) were searched from inception to October 2021. The ClinicalTrials.gov register, the WHO International Clinical Trials Registry Platform Search Portal, and the Current Controlled Trials meta-Register of Controlled Trials – active registers were searched to identify unpublished or ongoing studies. Reference lists from review articles were searched by hand to identify relevant articles missed by the search strategies. Full search strategies can be acquired upon request. The protocol was registered at The International Prospective Register of Systematic Reviews (PROSPERO 2020 CRD42020159847).

2.2. Study inclusion

After removal of duplicated records, titles and abstracts were independently reviewed by two researchers (R.R. and C.M.A.B.) using Covidence systematic review software®, Veritas Health Innovation, Melbourne, Australia. A third investigator (M.T.) was consulted in the case of inter-researcher disagreements. Inclusion and exclusion criteria are shown in Table 1. The core outcome set (COS) for FAPDs was used to identify outcome measures (Table 1) [26]. There were no language restrictions. All potentially relevant studies were obtained in full text. Authors of ongoing trials were contacted to ascertain that studies were still in progress.

2.3. Quality assessment and data extraction

Data extraction was independently performed by two review authors (R.R. and C.M.A.B.). A pre-designed data extraction form was used (available upon request), containing items on study details (author, publication year, country), participants (subjects, age, gender, disease, and definition), inclusion and exclusion criteria of the study, intervention characteristics (type and length of dietary intervention), control characteristics (no intervention, placebo, or other dietary intervention), total number of patients randomized (number of patients/controls), number of dropouts/withdrawals, outcome measures, instruments, and results (type of outcome measures used, time of assessment, and length of follow-up).

The Cochrane risk of bias tool was independently used by the same authors to assess the risk of bias of all included studies [27]. Bias for individual elements from five domains (selection, performance, attrition, reporting, and other) were judged as high, low, or unclear. The GRADE approach was

Table 1. Eligibility criteria.

Inclusion criteria
Study was a systematic review or RCT
Study population consisted of children aged 4–18 years
Functional abdominal pain disorders (FAPDs) were diagnosed, treated, or its course followed. FAPDs included • Irritable bowel syndrome (IBS); • Functional dyspepsia (FD); • Abdominal migraine (AM); and • Functional abdominal pain – not otherwise specified (FAP-NOS).
FAPDs in alignment with Rome criteria, other international criteria, or a precise definition by the author
Dietary interventions were • FODMAP diet (low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet) • (Additional) fiber intake • Lactulose-free diet • Gluten-free diet • Histamine-free diet • Decrease in gas producing foods • Extra fluid intake
Outcomes measures[a] (assessed before and after start of dietary intervention) were • Treatment success as defined by the authors (to be reported) • Pain frequency or change in frequency of pain • Pain intensity or change in pain intensity • Withdrawal due to adverse events • Quality of life or change in quality life measured using any validated defined measurement tool. • Anxiety/depression using any validated defined measurement tool. • Serious adverse events • Adverse events • Stool consistency (*disease-specific (IBS-C/D)*) as defined by authors (Bristol stool or similar) at study end • Frequency of defecation at study end • Adequate relief (as reported by patient or parent) • School attendance or change in school attendance or performance
Exclusion criteria Studies including children with • Hirschsprung's disease; • Previous bowel surgery; and • Complex congenital disorders.
If the range of children's age was wider than 4–18 years, authors were requested for separate data of the children aged 4–18 years. If not available or no response the study was excluded;
Quasi randomized, none randomized, cohort, case–control, animal studies, editorial, commentary, case reports;
Abstract were considered if they met the inclusion criteria, if not enough data to judge was presented, the authors were contacted and if no response was received within 2 weeks, abstracts were excluded.
If inclusion could not be decided based on full text, authors were contacted. If no response was received within 2 weeks, the study was excluded.

[a]Outcome measures were identified according to the 'core outcome set' for FAPDs.

used to assess the overall quality of evidence for each outcome (Supplementary File 2) [28,29]. A third investigator (M.T.) was consulted in the occasion of inter-researcher disagreements.

2.4. Data analysis

Odds ratios (ORs) or relative risks (RRs) along with 95% confidence intervals (CIs) were reported in case of dichotomous outcomes. If outcomes were continuous, mean differences (MDs) with 95% CIs were reported. Chi^2 tests and the I^2 statistics were used to quantify heterogeneity. First, a random effects model was performed, and then a fixed-effects analysis was performed to further test for heterogeneity. If trials used a cross-over study design, if possible only data from the first phase of the study were extracted (i.e. before the crossover occurred). Data from individual trials were combined for meta-analysis if consensus was reached on similarity of interventions, patient groups, and outcomes. Meta-analysis was performed using the Cochrane Collaboration Review Manager (RevMan) software (version 5.3).

3. Results

A total of 6013 potentially relevant articles and abstracts were identified (Figure 1 PRISMA flow diagram). After removal of duplicates (n = 1207) and screening of title and abstract, 96 full-text articles were assessed for eligibility. Sixty-one articles did not meet the inclusion criteria and were excluded. Details of excluded studies are shown in Supplementary File 3. Sixteen systematic reviews were identified [8, 30–43]. Search by hand from through reference lists from these systematic reviews did not reveal other relevant articles. Seven ongoing trials were identified. Authors of ongoing trials were contacted. Finally, 12 articles were included for analysis [44–55].

Data of 819 FAPD patients aged 4–18 years, with the majority suffering from IBS, were included for analysis. Sample sizes varied from 20 to 116 children from Africa, Asia, Europe, and North America. Period of follow-up ranged from no follow-up after end of intervention to 4 weeks. Five trials evaluated treatment with fibers compared to placebo [44,45,48,49,54], two trials investigated a diet low in FODMAPs [50,55]. Remaining studies determined whether fructans worsen symptoms [51], studied fructose-restricted diet [46], evaluated treatment with prebiotic (inulin) [47], compared oral serum-derived bovine immunoglobulin (SBI) versus placebo [52], and vitamin D supplementation [53]. No studies were included studying additional fluid intake or histamine-free diet as dietary intervention.

Data from seven individual trials were combined for meta-analyses: 4 trials on the efficacy of fibers [44,45,48,49] and 2 trials on the safety of fibers [49,54]. Due to heterogeneity and lack of reporting results with absolute numbers, no further meta-analysis was possible. Primary outcomes and meta-analysis are described for trials evaluating fibers and

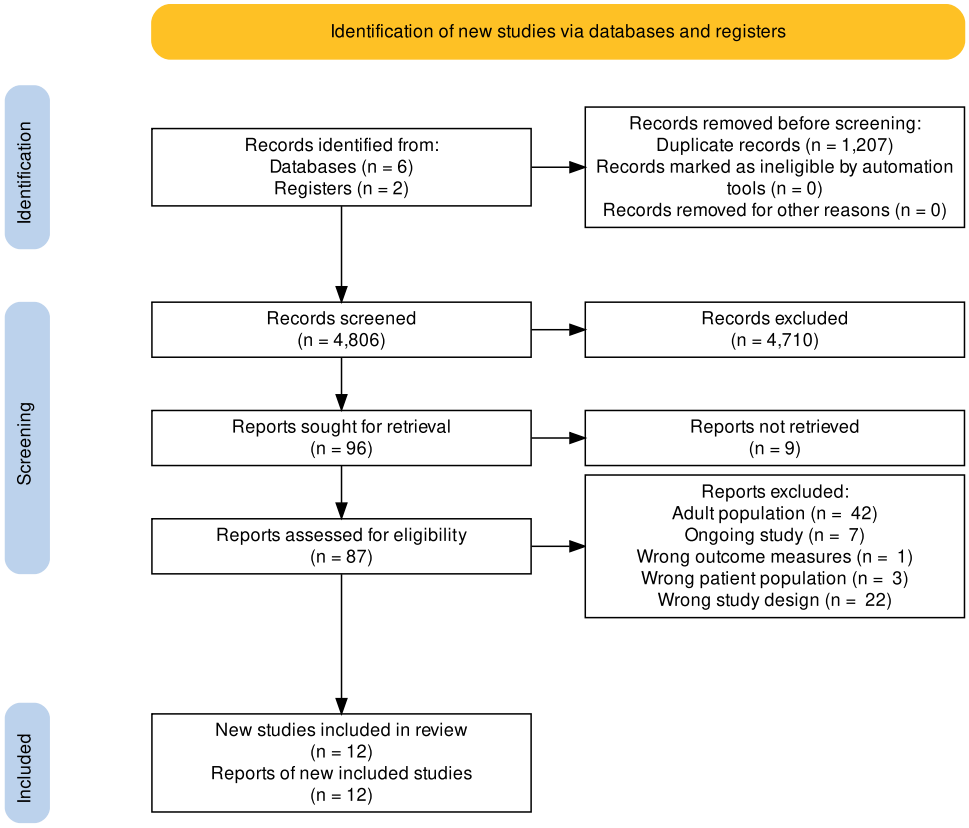


Figure 1. PRISMA 2009 flow diagram.

Table 2. Study characteristics of included studies.

Study	Participants	Intervention	Outcome measures and instruments
Fibers			
Feldman et al. (1985); Canada	Children aged 5–15 years (N = 52) RAP (Apley Criteria)	Fiber cookie vs placebo Dosage: 5 g corn per cookie, 2 cookies a day Treatment period: 6 weeks	Treatment success Improvement: 50% decrease in frequency of attacks Instrument: Stomachache Diary (four specific times each day) Adverse effects Instrument: recorded by parents using a specially developed questionnaire, every 2 weeks
Horvath et al. (2013); Poland	Children 7–17 years (N = 89) AP-FGIDs (ROME III)	Glucomannan vs placeboDosage: 2.52 g/day, 1 sachet of 1.26 g 2 times a day Treatment period: 4 weeks	Treatment success Improvement: self-reported 'no pain' or a decrease of ≥ 2/6 points Instrument: FACES Pain Scale Revised Pain frequency Instrument: Self-reported on 4-point scale (pain 1–3 times per month, pain 1–2 times per week, pain >2 times per week, pain every day) Pain intensity Instrument: FACES Pain Scale Revised, 6-point Likert Scale (0 = no pain and 5 = highest pain). School attendance/performance Instrument: Self-reported absenteeism from school Adverse events reported
Romano et al. (2013); Italy	Children 8–16 years (N = 60) CAP and IBS (ROME III)	Partially Hydrolyze Guar Gum (PHGG) vs placebo Dosage: 5 g/day in 50 ml of fruit-juice, one time a day Treatment period: 4 weeks	Treatment success Improvement: reduction of the abdominal pain intensity Instrument: WBFPRS Pain frequency Instrument: Birmingham IBS symptom score, 6-point Likert scale (0 = none of the time; 5 = all of the time) Pain intensity Instrument: WBFPRS, 6-point Likert Scale (0 = no hurt; 5 = hurts worst) Defecation pattern Improvement: normalization of bowel movements (BSS 3 or 4) Instrument: BSS, 7 categories (1 = hard lump, 7 = entirely liquid) Adverse events reported
Shulman et al. (2016): United States	Children 7–18 years (N = 103) IBS (Rome II criteria)	Psyllium vs placebo Dosage: 6 g (7–11 years), 12 g (12–18 years), single daily dose Treatment period: 6 weeks	Pain frequency Instrument: daily dairy card, number of ratings with pain ≥1 (ratings were made 3 times daily for 2 weeks) Pain intensityInstrument: daily dairy card (ratings were made 3 times daily for 2 weeks) Defecation pattern Instrument: BSS, (1–2 = constipated, 3–5 = normal, 6–7 = diarrheal) Adverse events reported
Jagadeesh et al. (2020) India	Children 4–18 years (N = 81) IBS (Rome IV criteria)	Psyllium vs placebo Dosage: daily dose not specified Treatment period: 4 weeks	Treatment success Improvement: score of <75 Instrument: IBS-SSS Pain frequencyInstrument: IBS-SSS, scored on a scale from 0 to 100. Pain intensityInstrument: IBS-SSS, scored on a scale from 0 to 100. Adverse events reported
FODMAP			
Chumpitazi et al. (2015) United States	Children 7–17 years (N = 33) IBS (Rome III criteria)	Low FODMAP diet vs Typical American Childhood Diet (TACD) Dosage FODMAPs: FODMAP diet: 0,15 g/kg/day (maximum 9 g/day), TACD: 0,7 g/kg/day (maximum 50 g/day) Treatment period: 48 h Wash-out period: 5 days	Treatment success Improvement: ≥50% decrease in frequency of abdominal pain episodes Instrument: daily dairy Pain frequency Instrument: dairy, number of abdominal pain episodes (ratings were made 3 times daily for 24 h) Pain intensity Instrument: dairy, 10-point Likert scale (0 = no pain, 10 = worst pain you can imagine, ratings were made 3 times daily for 24 h) Adverse events reported

(*Continued*)

Table 2. (Continued).

Study	Participants	Intervention	Outcome measures and instruments
Boradyn et al. (2020) Poland	Children 5–12 years (N = 29) FAP (Rome III)/FAP – NOS (Rome IV)	Low FODMAP diet vs Diet based on the NICE guidelines Dosage in accordance with the Human Nutrition Recommendations for Polish Population for the specific age groups (4–6 , 7–9 , 10–12 years), gender, weight, and activity level. Treatment period: 4 weeks	Pain frequency Instrument: dairy, number of events Pain intensity Instrument: WBFPRS, score 0–5 Defecation pattern Instrument: BSS, (1–2 = constipated, 3–5 = normal, 6–7 = diarrheal) Adverse events reported
Fructose-restricted diet			
Wirth et al. (2014); Germany	Children 3–18 years (N = 116) RAP as defined by the authors	Fructose-restricted diet vs regular diet Dosage: NA Treatment period: 2 weeks	Pain frequency Improvement: reduction in pain episodes Instrument: questionnaire, frequency of pain per week Pain intensity Instrument: questionnaire, 10-point Likert scale (0 = no pain, 10 = very strong pain)
Fructan			
Chumpitazi et al. (2018); United States	Children 7–18 years (N = 31) IBS (Rome III criteria)	Fructan (Inulin-FOS*) vs placebo Dosage fructan: 0.5 g/kg/day (maximum 19 g/day) Treatment period: 72 h Wash-out period: ≥ 10 days	Pain frequency Instrument: dairy, number of abdominal pain episodes (ratings were made 3 times daily for 24 h) Pain intensity Instrument: dairy, 10-point Likert scale (0 = no pain, 10 = worst pain you can imagine, ratings were made 3 times daily for 24 h) Defecation pattern Instrument: stool diary (modified Bristol stool form) Adverse events reported
Prebiotic			
Basturk et al. (2016); Turkey	Children 4–16 years (N = 76) IBS (Rome III criteria)	Synbiotic vs Probiotic vs. Prebiotic Dosage: synbiotic: 5×10^9 CFU B. lactis B94 and inulin 900 mg, probiotic: 5×10^9 CFU B. lactis, prebiotic: inulin 900 mg Treatment period: 4 weeks	Treatment success Improvement: improvement in all the presenting symptoms after 4 weeks (postprandial swelling, belching-abdominal distension, mucoid defecation, difficulty in defecation, feeling of incomplete defecation, urgent defecation) Instrument: questionnaire Defecation pattern Instrument: question "difficulty in defecation" (yes/no). Adverse events reported
Serum-derived bovine immunoglobulin			
Arrouk et al. (2018); United States	Children 8–18 years (N = 15) IBS-D (Rome III criteria)	Oral serum-derived bovine immunoglobulin (SBI) vs placebo Dosage: 5 g (minimum of 50% IgG along with other serum proteins) Treatment period: 3 weeks	Pain intensity Instrument: dairy, 5-point Likert scale (0 = no pain, 4 = severe pain you) Quality of life Instrument: Peds-QoL Defecation pattern Instrument: BSS, (1–2 = constipated, 3–5 = normal, 6–7 = diarrheal) Adverse events reported
Vitamin D			
El Amrousy (2018); Egypt	Children 14–18 years (N = 112) IBS (Rome III criteria) with vitamin D serum level <20 ng/ml	Oral vitamin D3 vs placebo Dosage: 1000 IU, two drops daily Treatment period: 6 months	Treatment success Improvement: A decrease of ≥50 in the total score Instrument: IBS-SSS, total score on 5 items (severity and frequency of abdominal pain, bloating, satisfaction with bowel habits and quality of life), each item was scored on a scale from 0 to 100 Quality of life Instrument: IBS-QoL Adverse events reported

[a]Inulin-FOS includes a mixture of short and long inulin-type fructans.

AP-FGIDs, abdominal pain predominant functional gastrointestinal disorders; BSS, Bristol Stool Scale; CAP, chronic abdominal pain; IBS, irritable bowel syndrome; IBS-SSS, IBS severity scoring scale; NICE, National Institute for health and Care Exellence; PedsQoL, Pediatric Quality of Life Inventory for Gastrointestinal Symptoms. RAP, recurrent abdominal pain; WBFPRS, Wong–Baker FACES Pain Rating Scale.

low-FODMAP diet. Results of remaining studies are reported in Supplementary File 4. Table 2 shows the characteristics of all included studies. Secondary outcomes are shown in Table 3.

3.1. Methodologic quality

Overall, two studies were rated as having high risk of bias. In the study of Wirth et al., there was lack of blinding of

Table 3. Secondary outcomes.

Study	Quality of life	Anxiety/ depression	Adequate relief	School attendance/ performance	Defecation pattern
Fibers					
Feldman; *Corn*	-	-	-	-	-
Horvath; *Glucomannan*	-	-	-	School absence: at 4 weeks 10% (Glucomannan) vs 14% (placebo) (P = .56)	-
Romano; *Guar Gum*	-	-	-	-	Normalization of bowel movements at 4 weeks: 40% (Guar Gum) vs 13.3% (placebo) (P = .025)
Shulman; *Psyllium*	-	-	-	-	Change from baseline psyllium vs placebo: lower percentage of diarrheal stools (P = .078) and higher percentage of constipated stools (P = .048)
Jagadeesh; *Psyllium*	-	-	-	-	-
Low-FODMAP					
Chumpitazi (2015); *Low FODMAP diet*	-	-	-	-	-
Boradyn; *Low FODMAP diet*	-	-	-	-	Normalization of bowel movements at 4 weeks: 61% (FODMAP) vs 93% (placebo) (P = .106)
Fructose-restricted diet					
Wirth; *Fructose-restricted diet*	-	-	-	-	-
Fructan					
Chumpitazi (2018); *Low FODMAP diet with fructan*	-	-	-	-	Mean stool type did not differ between interventions[a]
Prebiotic					
Basturk; *Inulin*	-	-	-	-	Difficulty in defecation at 4 weeks in 48% probiotic vs. 22% prebiotic (P = .155)
Serum-derived bovine immunoglobulin					
Arrouk; *Serum-derived bovine immunoglobulin (SBI)*	Significant improvement in overall PedsQOL score after treatment in SBI group (P = .01, placebo: P = .14).	-	-	-	There was no significant reduction in stool frequency per week. Improved stool form in SBI group: baseline BSS 5.3 ± 0.8[b] vs. after treatment BSS 4.2 ± 1.2 (P = .05), placebo: 5.1 ± 0.6 vs. 4.2 ± 2 (P = .28).
Vitamin					
El Amrousy; *Vitamin D*	Significant improvement in overall IBS-QOL score after treatment in Vit.D group (P < .001, placebo: P = 47).	-	-	-	-

[a]No separate results were reported for the first phase of the trial (i.e. before the cross-over occurred).
[b]Mean ± SD.

participants (performance bias) and lack of blinding of outcome assessors (detection bias), because patients were not blinded for the allocated intervention (fructose-restricted-diet vs. normal eating practice) [46]. In the study of Chumpitazi et al., it was not clear if the type of food or drink provided during interventions was similar (performance bias). Second, since it was a cross-over study and washout period was only 5 days, the carry over effect could not be excluded [55]. Furthermore, 6 of the 12 studies (50%) were rated as having unclear risk of bias in at least one domain as a result of inadequate reporting [44–46,50–52]. Five studies had low risk of bias across all domains (Figures 2 and 3) [47–49,53,54]. Supplementary File 5 presents detailed information about the risk of bias for the included studies.

The overall certainty of evidence based on the GRADE system was very low to low, with reasons for downgrading of certainty presented in Supplementary File 2.

3.1.1. Fiber

Five randomized placebo-controlled trials met the pre-specified inclusion criteria (n = 385, age 4–18 years). Horvath et al. [45] compared glucomannan, a water-soluble high-molecular-weight dietary fiber (HMWDF), with placebo. Romano et al. [49] also investigated another soluble HMWDF and compared Partially Hydrolyze Guar Gum (PHGG) versus placebo. Jagadeesh et al. [48] and Shulman et al. [54] compared psyllium, a plant-based soluble fiber (high water-holding capacity) versus placebo. Feldman et al. [44] randomized patients to receive either a fiber cookie (containing 5 g corn per cookie) or a placebo cookie twice a day. The predominant components of corn fiber are water-soluble cellulose and hemicellulose, which increases fecal bulk and decreases gastro-intestinal transit time [56,57].

3.1.1.1. Primary outcomes

3.1.1.1.1. Treatment success. Four studies reported treatment success as primary outcome. The study of Feldman [44] reported an improvement in 13/26 (50%) in the fiber cookie group vs 7/26 (27%) in the placebo group (P = 0.004). Horvath et al. 45 concluded that 23/41 (56%) (glucomannan group) versus 20/43 (47%) (placebo group) reported treatment success (RR 1.21, 95% CI 0.79–1.83). Jagadeesh et al. [48] showed

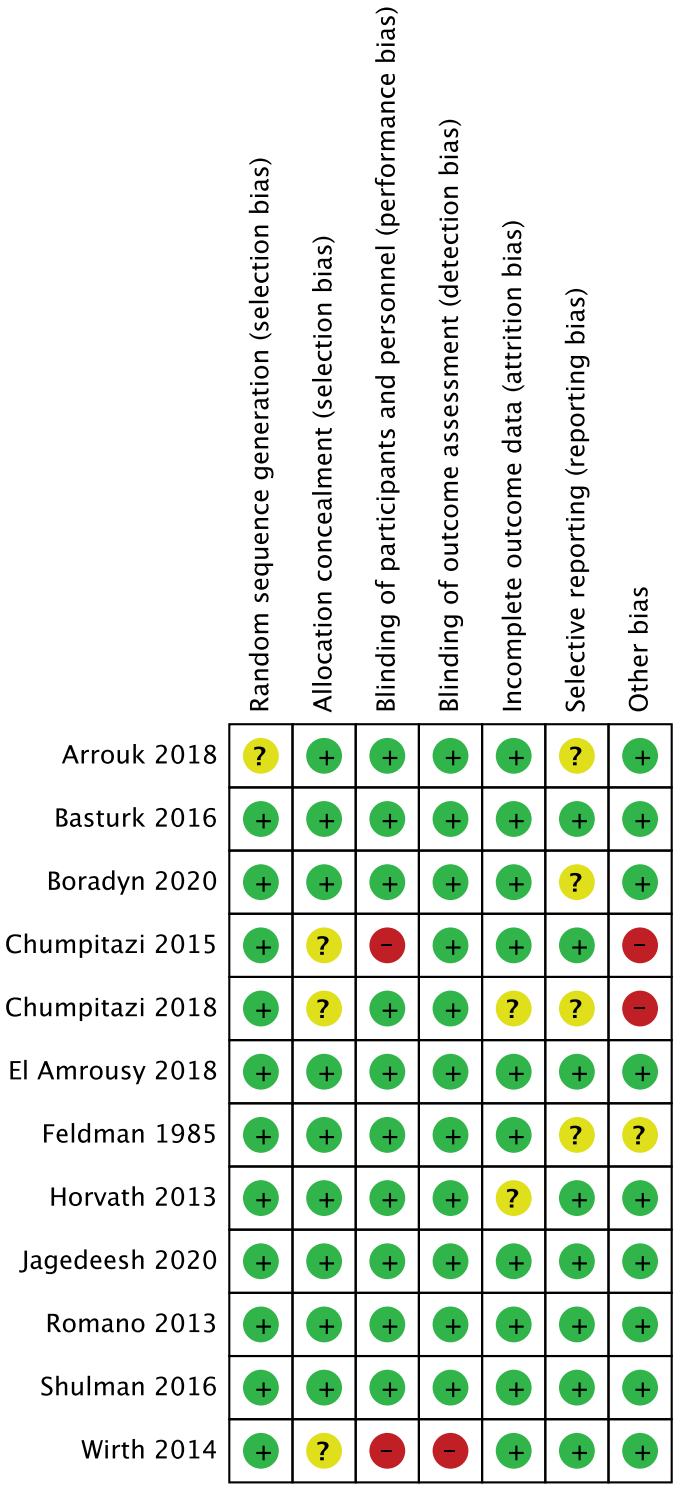


Figure 2. Risk of bias graph.

that treatment success was reported in 18/41 (44%) in the psyllium group compared with 3/31 (10%) in the placebo group ($P < 0.001$). Romano et al. [49] reported treatment success in 13/30 (43%) in the PHGG group and 2/30 (7%) in the placebo group ($P = 0.025$). Shulman et al. [54] did not predefine treatment success.

Four studies could be included in meta-analysis [44,45,48,49]. Analysis found very low-certainty, downgraded due to inconsistency and imprecision due to low numbers, evidence that there may be a difference when water-soluble fibers (including corn, glucomannan, PHGG, and psyllium) are compared with placebo in favor of fibers (RR 2.40, 95% CI 1.10–5.25; NNT = 3, 4 studies, 268 participants; I2 = 72%; random-effects model, Figure 4A). When considering the heterogeneity, a visual outlier is the study of Horvath et al. When removing this study, heterogeneity drops to 44% (RR 5.24, 95% CI 2.31–11.91; NNT = 3, 3 studies, 184 participants; $I^2 = 44\%$; random-effects model).

3.1.1.1.2. Pain frequency and intensity. Jagadeesh et al. [48] reported a significant reduction in pain intensity (Median (IQR): 25 (0–25) vs. 50 (25–50), $P < 0.001$), as well as pain frequency (10 (0–27.5) vs. 50 (30–50), $P < 0.001$) scores in the psyllium group compared with the placebo group. Shulman et al. [54] reported that there was a significant reduction in pain episodes in the fiber group compared with the placebo group ($P = 0.03$), whereas no differences were seen in pain intensity between the two groups. Horvath et al. [45] reported pain frequency and pain intensity, with no statistically significant differences between the two groups (RR = 2.1,95%CI: 0.87–5.07). Romano et al. [49] reported that there were no differences in pain frequency in the PHGG group compared to the placebo group (23.0 ± 6.15 vs. 28.7 ± 7.54, $P > 0.05$). Romano et al. [49] also assessed pain intensity, where mean severity of pain scores did not significantly differ between the PHGG group and the placebo group (1.63 ± 0.16 vs. 2.05 ± 0.19, $P > 0.05$).

Two studies could be included in meta-analysis [49,54]. Analysis found no evidence that there may be a difference when water-soluble fibers (including PHGG and psyllium) are compared with placebo (SMD – 0.63, 95% CI −1.61 to 0.35; 2 studies, 135 participants; $I^2 = 87\%$; random-effects model, Figure 4B).

3.1.1.1.3. Withdrawal due to adverse events. Feldman et al. [44] reported that the number of children who experienced gas or diarrhea as side effects was small in both groups and insignificant. All other studies reported that there were no adverse events.

3.1.2. FODMAP

Two RCTs ($n = 79$, age 5–17 years) were included [50,55]. Boradyn et al. [50] investigated FODMAP diet versus diet based on NICE-guidelines (National Institute for health and Care Exellence, Poland). Chumpitazi et al. [55] performed a double-blind, cross-over trial, in which patients received either a FODMAP diet (containing 0.15 g/kg/day of FODMAPs, maximum 9 g/day) or a typical American childhood diet (TACD, contained 0.7 g/kg/day, maximum 50 g/day). No separate results reported for the first and second phase of the study (i.e. before and after cross-over) were described. Patients followed a washout period of 5 days.

3.1.2.1. Primary outcomes

3.1.2.1.1. Treatment success. Only the study by Chumpitazi et al. [55] predefined the primary outcome 'treatment success.' The study reported 8 out of 16 (50%) responders in the FODMAP group and 10/17 (59%) in the TACD group

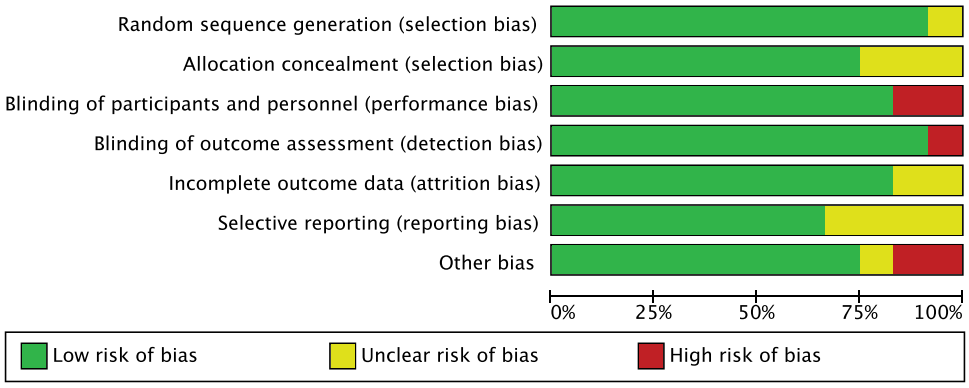
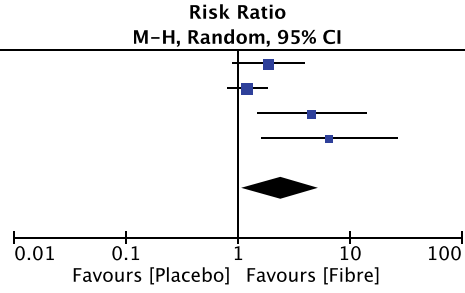


Figure 3. Risk of bias summary.

a

Study or Subgroup	Fibre Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Feldman 1985	13	26	7	26	28.1%	1.86 [0.89, 3.90]
Horvath 2013	23	41	20	43	33.8%	1.21 [0.79, 1.83]
Jagedeesh 2020	18	41	3	31	21.1%	4.54 [1.47, 14.04]
Romano 2013	13	30	2	30	17.1%	6.50 [1.60, 26.36]
Total (95% CI)		**138**		**130**	**100.0%**	**2.40 [1.10, 5.25]**
Total events	67		32			

Heterogeneity: Tau² = 0.43; Chi² = 10.62, df = 3 (P = 0.01); I² = 72%
Test for overall effect: Z = 2.19 (P = 0.03)



b

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Romano 2013	1.86	0.14	30	2.04	0.17	30	98.8%	−0.18 [−0.26, −0.10]
Shulman 2016	3.24	1.58	33	3.46	1.55	42	1.2%	−0.22 [−0.93, 0.49]
Total (95% CI)			**63**			**72**	**100.0%**	**−0.18 [−0.26, −0.10]**

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 4.52 (P < 0.00001)

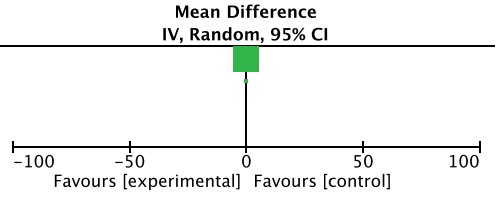


Figure 4. (a) and (b) Meta-analysis.

($P > 0.05$). Boradyn et al. [50] did not predefine treatment success.

3.1.2.1.2. Pain frequency and intensity. Pain frequency and pain intensity were reported in both studies [50,55]. Chumpitazi et al. [55] reported significant less abdominal pain during the low FODMAP diet versus TACD (1.1 ± 0.2 (SEM) episodes/day vs 1.7 ± 0.4, $P < 0.05$). As compared to baseline, median pain severity decreased significantly in both the FODMAP and TACD group, with no significant differences between the two diets. Boradyn et al. [50] reported no statistically significant differences between the two diets.

3.1.2.1.3. Withdrawal due to adverse events. Both studies reported that there were no adverse events [50,55].

4. Discussion

We systematically reviewed 12 articles to determine the efficacy and safety of dietary interventions in children with FAPDs and demonstrated the lack of high-quality intervention trials. Based on the current evidence we found some beneficial effects for the use of water-soluble fibers (including corn, guar gum, glucomannan, and psyllium) with a slight preference for the use of psyllium, which can therefore be discussed in daily practice. Whilst certainty is very low, impacted by the limited sample size in particular, the magnitude of treatment effect was substantial, with an NNT of 3. Given the low cost, easy availability and observed safety, in spite of these limitations, such therapies appear to have a role in treatment packages. When abdominal pain intensity (assessed with a dairy or validated questionnaire as described in Table 2) was used as primary endpoint, fructose-restricted diet, SBI, and vitamin D supplementation might be potential effective treatments in some children. However, well-designed intervention studies are needed before these conclusions can be firmly drawn, since quality of current evidence based on GRADE system was low to very low. There was no evidence that any other dietary intervention has a significant role in the treatment of pediatric FAPDs. All included interventions (i.e. fibers, FODMAP diet, fructans, fructose-restricted diet, prebiotic (inulin), SBI, and vitamin D supplementation) appear to be safe treatment options, whereas no serious adverse effects

were reported. No studies were included on treatment with extra fluid intake or histamine-free diet [58].

A recently published Cochrane review assessed the efficacy and safety of probiotics and synbiotics for the management of FAPD in children [59]. Therefore, probiotics and synbiotics were outside the scope of this review and not included. In 2017, a Cochrane review on dietary interventions for recurrent abdominal pain in childhood was published [8]. These findings however are not in line with our results. When excluding probiotic intervention studies, the current review included 12 studies compared to only 6 studies in the previous SR, and this review is therefore an improvement on existing literature on this topic. In contrast to the outcome of our study, they found that children treated with fibers were not more likely to experience treatment success. An explanation for this could be that the number of studies included in the previous meta-analysis was limited to two intervention trials and only included a small patient group (136 children).

In the management of pediatric FAPDs, the low FODMAP diet has been of great interest over the last decade. FODMAPs are small molecules containing different carbohydrates and can be found in several daily food products (i.e. common fruits and vegetables, honey, milk, and sweeteners) [60]. It is hypothesized that FODMAPs' mechanism of action is linked to the intestinal osmolarity and is nutritious for the intestinal microbiota [60]. Fermentation of these FODMAPs increases hydrogen, methane, and carbon dioxide production and subsequently leads to increased luminal distension, provoking abdominal pain, bloating, flatulence, and alterations in bowel habits [61]. Reducing the intake of FODMAPs will reduce intestinal osmolarity and gas production and therefore potentially reduces FAPD symptoms. In addition, microbiota composition and functioning will alter, however, the impact of microbiota changes and functional consequences are not completely understood [62]. The low FODMAP diet includes three phases: (1) elimination; (2) reintroduction; and (3) personalization phase [63]. Clinical guidelines for adult IBS patients recommend that the duration of the elimination phase solely should be 2–6 weeks, whereas the duration of the included FODMAP diets in this review were only 48 h and 4 weeks [50,55,63]. Therefore, the results of these included studies should be interpreted with caution. Adult studies on the efficacy of the FODMAP diet showed promising results [64]. Meta-analysis containing 12 studies concluded that a low FODMAP diet in adult patients with IBS reduces GI symptoms and improves quality of life. For this reason, the FODMAP diet can be considered as a symptomatic treatment, especially in children with excessive gas formation. However, evidence to support the use of low FODMAP diet in daily practice in children is still lacking [50,55]. When prescribing the FODMAP diet in clinical practice, it is preferable to involve a dietician to better explain the diet and improve adherence. Adherence to the FODMAP diet is crucial to the overall success of the diet. Adult studies estimated rates of adherence to the FODMAP diet between 75% and 80% [65]. Rates were lower in studies with a duration of diets more than 6 weeks and in studies not providing the participants of foods [66]. Furthermore, when a dietician is not involved, rates will decrease even more [61]. It may be hypothesized that due to the duration of the diet and food restrictions, adherence to the strict FODMAP diet in pediatric population can be challenging. Noteworthy, in both FODMAP studies included in this review, adherence to the strict diet was not assessed and data regarding this issue in pediatric population are lacking [50,55].

As described above, the use of probiotics and synbiotics was not included in this review. However, there is a growing body of evidence for the use of probiotics and synbiotics in the management of pediatric FAPDs. A recently published Cochrane review [59][] on the effectiveness of probiotics and synbiotics concluded that the use of probiotics (i.e. *Lactobacillus rhamnosus* GG and *Lactobacillus reuteri*) provide better symptom relief and can reduce the frequency of pain episodes. Therefore, *Lactobacillus rhamnosus* GG and *Lactobacillus reuteri* may be considered in clinical management in children with FAPDs. Evidence on the effectiveness of synbiotics is sparse and inconclusive and revealed little to no beneficial effects. Also in adult patients with FAPDs, new dietary interventions have been explored. Some preliminary data suggested that low histamine diets [67] and green kiwifruit [68] improve symptoms of abdominal pain. However, evidence on the beneficial effect of these dietary interventions in the pediatric population with FAPDs is lacking. Currently, a double-blind placebo controlled RCT on oral butyrate is ongoing in children with IBS (NCT04566679).

The last decade, there is great interest in the role of gluten sensitivity as a potential trigger of gastrointestinal symptoms in adults with IBS. In a double-blind randomized placebo-controlled trial, adult IBS patients with self-reported gluten intolerance (in whom celiac disease was excluded) received either gluten or placebo. Results showed that adequate symptom control differed significantly between two groups (gluten-exposed: 32% vs placebo: 60%) [69]. These results suggest that IBS patients may react to gluten, despite the lack of a celiac disease diagnosis. This clinical condition is known as non-celiac gluten sensitivity (NCGS) and may also be present in children, contributing to their IBS symptoms [70]. Nevertheless, the association between NCGS and FAPDs in the pediatric population is not yet revealed. Future studies are needed before gluten avoidance can be recommended for children with FAPDs. Currently, a trial to evaluate the prevalence of gluten sensitivity in pediatric IBS patients is ongoing (NCT02431585).

The systematic methodology applied in this review is in line with the high-quality standards of the Cochrane Collaboration, which is a major strength of this review. First, in consultation with an Information Specialist from the Cochrane group, the search strategy was developed. Second, two independent reviewers performed the screening process. In case of indistinctness of the study design or need for additional data, authors of included studies were contacted. Furthermore, the Cochrane Risk of Bias tool and GRADE were used to assess the strength of evidence, increasing the transparency of this review and therefore

support readers in interpreting the results. Finally, the number of eligible studies has increased significantly since this topic was last systematically evaluated.

Although there is no direct relationship with our review process, the limitations of this study are mostly associated to low- to very-low-quality evidence that is available nowadays. First, evidence was downgraded due to significant imprecision from extremely sparse data. Because of small sample sizes, no subgroup analyses were possible, in particular for patient characteristics such as gender or by specific pain disorder. However, this is a considerable issue in pediatric literature and future intervention studies should take this into account. Second, two studies used a crossover design without reporting separate results for the first and second phase of the study (i.e. before the cross-over occurred). The combination of selective reporting and the use of such design raises concerns regarding the external validity of the results. Third, there was evidence of heterogeneity in our meta-analyses, including differences in type and length of dietary intervention and the choice of outcome measures. To address this issue, the ROME foundation developed recommendations for designing clinical trials in pediatric FAPDs [71]. This committee recommends considering a treatment period of at least 4 weeks (preferably 6 weeks or more), whereas they highlight that treatment periods shorter than 4 weeks are disrecommended due to the variable course of the disease. Also, the pediatric FAPD COS was recently created [26]. This COS generated a standardized minimum set of outcome measures. If future clinical trials will use these outcome measures, and associated measurement instruments, heterogeneity will decrease and consequently the comparability of study results will increase. This may improve overall quality of available information, GRADE certainty of evidence and finally clinical decision-making [72]. Final, significant changes in the ROME definition have taken place with time. Only one study used the latest ROME IV, the bulk of studies used the ROME III or any other criteria. This should be considered when interpreting the findings.

In clinical practice, management of pediatric FAPDs can be challenging. The first step in treatment consists of reassurance and education[11]. Subsequently, non-pharmacological and pharmacological and interventions could be considered. Non-pharmacological interventions, such as cognitive behavior therapy, hypnotherapy, and dietary interventions, as described in this review, have showed their effectiveness and safety in the pediatric FAPD population [32,73,74]. The following pharmacological agents have been examined in pediatric FAPDs patients: antispasmodics, antidepressants, antibiotics, antihistaminic, anti-emetic, H2-receptor-antagonist, 5-HT4-receptor-agonist, melatonin and buspirone. Based on the current evidence it is not possible to recommend any specific agent, but antispasmodics and antidepressants may be discussed due to their favorable treatment outcomes and lack of important side effects [9]. However, the optimal therapeutic algorithm is undetermined since the pathogenesis of FAPDs in children is not yet fully understood. Therefore, a tailor-made approach for each patient, based on the concomitant symptoms such as nausea, acid, diarrhea, or constipation is proposed to date, where both non-pharmacological and pharmacological interventions should be discussed to encourage shared decision-making during consultations.

5. Conclusion

In summary, based on the findings of this systematic review and low to very low quality of the included studies, it is not possible to recommend any specific dietary intervention for the treatment of pediatric FAPDs. However, evidence demonstrates that the use of fibers can be discussed in daily practice due to their favorable treatment outcomes and reported lack of side effects. These new findings should be considered by international guideline committees. High-quality RCTs on dietary interventions are needed to provide adequate clinical management, since a substantial proportion of children still experience abdominal complaints in adulthood. In future, we recommend to adhere to the guidelines established by the ROME committee and to use homogenous outcome measures and instruments, as recommend by the pediatric FAPD COS.

Abbreviations

AM	Abdominal migraine
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence intervals
COS	Core Outcome Set
FAPDs	Functional abdominal pain disorders
FAP-NOS	Functional abdominal pain – not otherwise specified
FD	Functional dyspepsia
GI	Gastrointestinal
IBS	Irritable bowel syndrome
MD	Mean differences
ORs	Odds ratios
RCTs	Randomized controlled trials
RevMan	Review Manager
RRs	Relative risks
VAS	Visual analog scale

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Data availability

The datasets generated and analyzed during the current study are available upon request.

Trial registration

PROSPERO, registered 28/04/2020, CRD42020159847

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Declaration of interests

Since August 2016, M Gordon has received travel fees to attend international scientific and training meetings from Pharma companies. These grants included no honoraria, inducement, advisory role or any other relationship and were restricted to the travel and meeting-related costs of attending such meetings. These include DDW May 2017, World Congress of Gastroenterology October 2017, DDW May 2018, Advances in IBD December 2018, DDW May 2019. None of these companies have had any involvement in any works completed by M Gordon and he has never had any payments for any other activities for them. M Benninga is a consultant for Shire, Norgine, Coloplast, Danone, Takeda, Allergan, Shire, FrieslandCampina, United Pharamceuticals, HiPP. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or conflict with the subject matter or materials discussed in this manuscript apart from those disclosed.

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