Paediatric functional abdominal pain disorders

Nikhil Thapar[1,2,14]✉, Marc A. Benninga[3], Michael D. Crowell[4], Carlo Di Lorenzo[5], Isabelle Mack[6], Samuel Nurko[7], Miguel Saps[8], Robert J. Shulman[9], Hania Szajewska[10], Miranda A. L. van Tilburg[11,12,13] and Paul Enck[6]✉

Abstract | Paediatric functional abdominal pain disorders, currently referred to as disorders of gut–brain interaction, comprise irritable bowel syndrome, functional dyspepsia, abdominal migraine and functional abdominal pain not otherwise specified, as defined by the Rome IV diagnostic criteria. Functional abdominal pain disorders are common disorders with a prevalence of 3–16% depending on country, age and sex. A greater understanding of aetiopathogenesis and pathophysiology is emerging and includes intestinal components (inflammation, motility and the microbiota), central factors (psychological aspects, sensitization and/or differences in connectivity or activity of certain brain regions) as well as extrinsic factors (infections). In particular, the timing of disruption of the microbiota–gut–brain axis seems to be important. Diagnosis is challenging but is primarily based on clinical symptoms and exclusion of other organic causes, with an emphasis on avoiding unnecessary invasive diagnostic procedures. The available pharmacological interventions are limited in children and, therefore, management has focused on combined approaches, including mind-targeted interventions (hypnotherapy and cognitive behavioural therapy), diet (probiotics) and percutaneous electrical nerve field stimulation. The evidence for their clinical efficacy, although limited, is favourable, with positive impacts on symptoms and overall quality of life. The coming decades hold promise for improved understanding and management of these enigmatic disorders.

Hyperalgesia
An abnormally heightened sensitivity to pain.

Dedication: We dedicate this manuscript to the memory of Paul E. Hyman, MD, who passed away on 7 August 2020. Paul was a true pioneer and master of the field of functional gastrointestinal disorders and dedicated much of his career to caring for children suffering from such conditions. A great family man, friend, colleague, mentor and inspiration to so many.

Functional abdominal pain disorders (FAPDs) are some of the most commonly encountered disorders in childhood, affecting up to 25% of all children and infants worldwide[1]. Given their biopsychosocial aetiology involving complex interactions within the gut–brain axis, FAPDs are currently referred to as 'disorders of gut–brain interaction'[2]. Furthermore, the gut–brain axis is now accurately referred to as the 'microbiota–gut–brain axis', reflecting an explosion in our understanding of the magnitude, complexity, role and interactions of the microbial populations hosted within the lumen of the gastrointestinal tract[3,4].

Akin to adults, paediatric FAPDs are subclassified utilizing the Rome IV criteria into a number of clinically distinct entities, namely irritable bowel syndrome (IBS), functional dyspepsia, abdominal migraine and functional abdominal pain not otherwise specified (FAP-NOS)[4]. FAPDs are frequently characterized by the presence of visceral hyperalgesia as well as increased central perception of visceral stimuli leading to disability, which seems to occur as the final outcome of sensitizing psychosocial factors and medical factors superimposed on a background of genetic predisposition and early-life events (FIG. 1). Early life is likely to include all childhood and adolescent stages where growth as well as the structural and functional development of organs occurs, although the vulnerability of the gut–brain–microbiota axis seems to be highest during the perinatal period and first years of life. FAPDs are grouped according to symptom profile, which differs based on the section of gastrointestinal tract that is primarily involved (for example, functional dyspepsia versus IBS) or depending on similarities with other conditions such as headache migraine (BOX 1).

IBS describes a symptom profile reflecting distal gastrointestinal tract involvement; abdominal pain in IBS can be associated with defaecation or a change in the frequency or form of the stool but does not resolve with resolution of any associated constipation. Paediatric IBS

✉*e-mail: nikhil.thapar@health.qld.gov.au; paul.enck@uni-tuebingen.de*

https://doi.org/10.1038/s41572-020-00222-5

Author addresses

[1]Neurogastroenterology and Motility Unit, Department of Paediatric Gastroenterology, Great Ormond Street Hospital NHS Foundation Trust, London, UK.
[2]UCL Great Ormond Street Institute of Child Health, London, UK.
[3]Emma Children's Hospital, Amsterdam University Medical Center, Amsterdam, Netherlands.
[4]Department of Gastroenterology and Hepatology, Mayo Clinic, Scottsdale, AZ, USA.
[5]Division of Pediatric Gastroenterology, Nationwide Children's Hospital, Columbus, OH, USA.
[6]University Hospital Tübingen, Department of Internal Medicine VI: Psychosomatic Medicine and Psychotherapy, Tübingen, Germany.
[7]Boston Children's Hospital, Harvard medical School, Boston, MA, USA.
[8]Division of Pediatric Gastroenterology, Hepatology and Nutrition, University of Miami, Miller School of Medicine, Miami, FL, USA.
[9]Children's Nutrition Research Center, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA.
[10]Department of Pediatrics, The Medical University of Warsaw, Warsaw, Poland.
[11]College of Pharmacy and Health Sciences, Campbell University, Buies Creek, NC, USA.
[12]Division of Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, NC, USA.
[13]School of Social Work, University of Washington, Seattle, WA, USA.
[14]Present address: Queensland Children's Hospital, Paediatric Gastroenterology, Hepatology and Liver Transplant, Brisbane, Australia.

Postprandial fullness
Unpleasant sensation thought to emanate from the stomach for a considerable period after eating a meal giving the feeling of the persistence of food.

can be further divided into subtypes analogous to adults based on the predominant stool pattern[5] (BOX 2).

Functional dyspepsia describes a symptom profile predominantly from the proximal gastrointestinal tract involving epigastric abdominal pain and/or bothersome postprandial fullness and/or early satiation. Similar to the criteria in adults, subtypes of paediatric functional dyspepsia now recognized include postprandial distress syndrome and epigastric pain syndrome, accepting a frequent overlap between them[6–8].

Abdominal migraine is characterized by the presence of paroxysmal prolonged episodes of intense, acute periumbilical, midline or diffuse abdominal pain. These painful episodes are typically incapacitating and interfere with normal activities and occur in a stereotypical pattern (that is, in a set form or pattern, for example, with regards to the presence or form of aura and the escalation of symptoms, severity and frequency) for the individual patient. The episodes are often but not always associated with other symptoms (such as anorexia, nausea, vomiting, headache, photophobia and pallor), which might precede or coincide with the duration of pain, and such symptomatic episodes may be separated by weeks to months.

FAP-NOS accounts for those instances of episodic pain or continuous abdominal pain that does not occur solely during physiological events and does not meet criteria for the other FAPDs[4].

For paediatric cases, the Rome IV criteria heralded a number of key milestones with respect to defining and characterizing these disorders. First, the term 'functional abdominal pain disorders' superseded the previously used terminology 'abdominal pain-related functional gastrointestinal disorders', allowing better focus for clinicians on the four subclassifications. Second, in the Rome IV classification, the previous criterion phrase "no evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms" has been replaced with "after appropriate medical evaluation, the symptoms cannot be attributed to another medical condition"[9]. This modification has allowed greater autonomy to the clinicians to use their expertise to decide whether selective testing, or, in some cases,

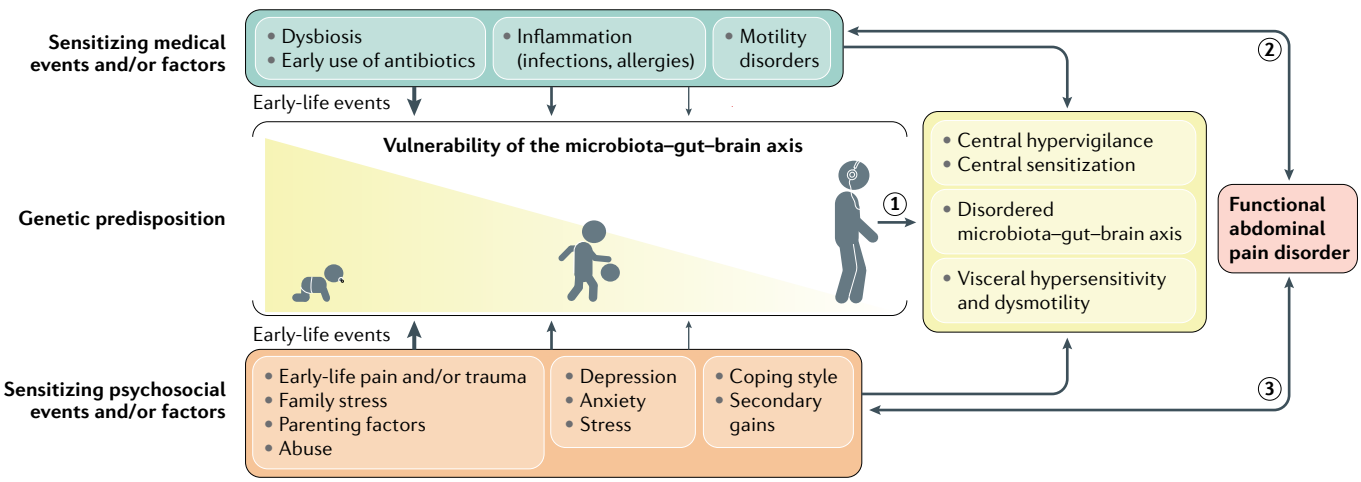

Fig. 1 | **Summary of the aetiopathogenesis and pathophysiology of FAPDs.** This figure illustrates the likely contribution of genetic predisposition as well as of sensitizing psychosocial and medical events to the disruption of the structure and/or function of the microbiota–gut–brain axis and to the development of the core disturbances of functional abdominal pain disorders (FAPDs), namely visceral hypersensitivity (with or without motor disturbances) and central hypervigilance. Although insults can occur at any time in life, early postnatal life represents an especially vulnerable period to disrupt the gut–brain axis, yet the core disturbances may not be evident until later in life (1). The reasons for this delay are not clear and may relate to other, as yet unknown and, presumably, additive or threshold-lowering factors such as changes in the hypothalamic–pituitary–adrenal axis, sex hormones, or changes in the brain structure or function. These changes might explain why children in the second decade of life are most vulnerable to the development of FAPDs. Bidirectional arrow (2) denotes the possibility of FAPDs and their consequences (both medical and psychosocial, for example, deconditioning, stress and anxiety) driving medical events or factors (such as mast cell degranulation and interaction with nerves) through mechanisms such as stress. Bidirectional arrow (3) denotes the possibility of FAPDs and their consequences driving psychosocial events/factors (for example, anxiety, stress, depression, poor coping and familial stress), which may further exacerbate the condition. Details of 'early-life events' associated with the development of FAPDs are explained and discussed in the manuscript.

Box 1 | **Rome IV diagnostic criteria for functional abdominal pain disorders**

Irritable bowel syndrome
The criteria must be fulfilled for at least 2 months and include all of the following.
- Abdominal pain at least 4 days per month associated with defaecation and/or a change in the frequency of stool and/or a change in the appearance of stool
- Abdominal pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not irritable bowel syndrome)
- After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

Functional dyspepsia
The criteria must be fulfilled for at least 2 months before diagnosis and must include one or more of the following bothersome symptoms at least 4 days per month.
- Postprandial fullness
- Early satiation
- Epigastric pain or burning not associated with defaecation
- After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

Abdominal migraine
The criteria must be fulfilled for at least 6 months before diagnosis and include all of the following occurring at least twice.
- Paroxysmal episodes of intense, acute periumbilical, midline or diffuse abdominal pain lasting 1 hour or more (should be the most severe and distressing symptom)
- Episodes are separated by weeks to months; the pain is incapacitating and interferes with normal activities; stereotypical pattern and symptoms in the individual patient
- The pain is associated with two or more of the following: anorexia, nausea, vomiting, headache, photophobia or pallor
- After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

Functional abdominal pain not otherwise specified
The criterial must be fulfilled for at least 2 months before diagnosis and at least four times per month and include all of the following.
- Episodic or continuous abdominal pain that does not occur solely during physiological events (for example, eating and menses)
- Insufficient criteria for irritable bowel syndrome, functional dyspepsia or abdominal migraine
- After appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition

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even no testing, is needed to establish a positive diagnosis of a FAPD. In addition, FAPDs have been recognized to coexist with other medical conditions, such as lactose intolerance, and different FAPDs can frequently coexist in the same patient[10,11].

Overall, these changes in definitions reflect a real shift in the knowledge of these common but impactful, yet poorly understood, disorders towards a clinically appropriate entity concomitantly considering the major scientific advancements in the field. The imperative for change is also underscored by the failure to improve the clinical outcomes in a meaningful way, which is reflected by the fact that quality of life continues to be rated as low as for severe gastrointestinal disease entities such as inflammatory bowel disease[12,13]. Despite FAPDs being now termed 'disorders of gut–brain interaction', the word 'functional' is used in this Primer to align with the terminology used to subclassify these disorders (for example, functional dyspepsia and FAPD-NOS) as well as to reflect that a disordered function (that is, sensory function or motor function of nerves) underlies these conditions. The term is not, nor should be, used to imply a 'non-organic' condition.

This Primer summarizes the current progress in our understanding of paediatric FAPDs in terms of prevalence and aetiopathogenesis, with a specific focus on early-life influences and programming. Furthermore, we discuss the current diagnostic approach and highlight the therapeutic options for the management of these disorders, with a particular focus on IBS and FAP-NOS. Finally, we also discuss the directions for future research that will help understand the pathophysiology and better treat these disorders.

Epidemiology

Although FAPDs are undoubtedly prevalent in children, epidemiological studies have been hampered owing to the lack of appropriate diagnostic criteria. The development of diagnostic criteria and the subclassification of the original vague entity 'recurrent abdominal pain in children' have only become available as of 2005 with the advent of the Rome II criteria[14]. Since then, the two further iterations of the Rome criteria have had substantial changes compounding the problem with elucidating and comparing prevalence data from different studies[4,8,9]. One limiting factor that prevents comparability of the data across the globe is the use of different tools for assessment, which has been overcome only in the past 15 years. Nearly 80% of the studies applying the Rome III criteria used the Questionnaire on Paediatric Gastrointestinal Symptoms–Rome III criteria for assessment, whereas studies applying the Rome I criteria or Rome II criteria used a large variety of instruments.

Additionally, the reliability and validity of methods used to identify the different FAPDs are limited. For example, studies comparing diagnostic reliability have demonstrated marked differences between an independent physician's diagnosis and a child's or a parent's reporting of the diagnostic symptoms[15–17]. The latter reporting is especially critical as parents might have limited knowledge of their children's bowel habits, especially in adolescence[18,19].

These challenges in epidemiological studies are evident in the literature; for example, a large population-based birth cohort (born from 1994 through 1996) in Sweden found that 26% of all children suffered from recurrent abdominal pain on at least one out of three assessment points, namely early childhood (pooling data from questionnaires at 1–2 years of age) and at 12 and 16 years of age[20]. Approximately 20% of children in the 16-year age group reported recurrent abdominal pain but only 12% could be categorized into one of the FAPDs (IBS, functional dyspepsia or functional abdominal pain) according to the Rome III criteria[20]. Furthermore, a cross-sectional retrospective chart review of 106 paediatric patients who completed standardized medical histories as part of their evaluation for chronic abdominal pain showed that significantly more patients were likely to be diagnosed with functional dyspepsia (84.9% versus 52.8%) and IBS (69.8% versus 34%) by the Rome IV criteria than by the Rome III criteria[8]. Conversely, another study found a lower prevalence of any FAPDs

Aura
Temporary symptoms that typically develop prior to and signal a more serious symptom such as abdominal pain or migraine.

(8.2% versus 10.4%) and IBS (2.3% versus 5.1%) but a higher prevalence of functional dyspepsia (3.0% versus 1.0%) diagnosed by the Rome IV criteria than by the Rome III criteria[21]. Similar significant differences in the accurate classification of cases were found between the Rome II and Rome III criteria[22].

The literature regarding epidemiological data on functional dyspepsia and abdominal migraine is relatively sparse. In the Swedish birth cohort study discussed above, of the 12% diagnosed with an abdominal pain-related functional gastrointestinal disorder based on the Rome III criteria, 6% were diagnosed with IBS and 3% each were diagnosed with functional abdominal pain and functional dyspepsia[20]. The presence of abdominal migraine was not assessed in these children and information about functional dyspepsia at earlier time points (that is, at 1–2 years) and at 12 years of age was not available. A cross-sectional observational study in Colombia that employed the Rome IV criteria revealed a prevalence of 3% and 0.5% for functional dyspepsia and abdominal migraine, respectively[21]. A 2015 metanalysis of 58 studies from across the world (excluding Africa and Australia) reported a pooled prevalence of 13.5% (95% CI 11.8–15.3) for all FAPDs and a pooled prevalence of 4.5% for functional dyspepsia and 1.5% for abdominal migraine[23]. Notably, a major variation was reported in the prevalence of FAPDs across studies, ranging from 1.6% to 41.2%. However, the pooled prevalence from each geographical region ranged only between 10.5% (Europe) and 16.8% (South America). Interestingly, in a community-based study in the USA on 949 children using parental reporting based on the Questionnaire on Paediatric Gastrointestinal Symptoms–Rome III criteria, abdominal migraine had the highest prevalence amongst FAPDs, with a reported prevalence of 9.2% compared with 2.8% for IBS and 0.2% for functional dyspepsia[24].

Population studies in children and adolescents (3–16 years of age) worldwide reported a pooled global prevalence of 13.8 for IBS, which varied between 0% and 25.7% based on the ROME I–III criteria (FIG. 2). The study reported a pooled prevalence of 2.3% for FAP-NOS, which ranged between 0.3% and 5.2%. Most of the studies were conducted in North America, South America and Asia, followed by Europe. The pooled prevalence of IBS was found to be highest in Asia (16.2%) and was reported to be 4.8% in the USA and 4.2% in Europe. Asia also had the highest prevalence of FAP-NOS (3.1%), whereas this was reported to be 1.6% in the USA and 1.7% in Europe. Only one study was conducted in Africa, suggesting a prevalence of 5.6%[25], not allowing a firm statement to be made.

Box 2 | **Subclassification of functional abdominal pain disorders**

Irritable bowel syndrome (IBS) subtypes

- Abdominal pain associated with constipation (IBS-C)
- Abdominal pain associated with diarrhoea (IBS-D)
- Abdominal pain associated with constipation and diarrhoea mixed (IBS-M)
- Abdominal pain not otherwise specified (IBS-U)

Functional dyspepsia subtypes

- Postprandial distress syndrome includes bothersome postprandial fullness or early satiation that prevents finishing a regular meal; supportive features include upper abdominal bloating, postprandial nausea or excessive belching
- Epigastric pain syndrome includes all of the following: bothersome pain that is severe enough to interfere with normal activities or burning localized to the epigastrium; the pain is not generalized or localized to other abdominal or chest regions and is not relieved by defaecation or passage of flatus; supportive criteria can include burning pain without a retrosternal component or pain commonly induced or relieved by the ingestion of a meal but can occur while fasting

Other functional abdominal pain disorders

- Abdominal migraine and functional abdominal pain not otherwise specified are not subclassified

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Risk factors

Sex. Studies from across the world have reported a predominance of FAPDs in girls, both in adolescents and in younger children[26]. A metanalysis[23] was performed on epidemiological studies reporting the prevalence or incidence of FAPD according to the different ROME criteria as well as other previously used criteria or defined by the presence of non-organic 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. All but 2 of the 24 studies reported a predominance of FAPD in girls. The pooled prevalence data also revealed a significantly higher proportion of FAPDs among girls than among boys (15.9% versus 11.5%, pooled OR 1.5, 95% CI 1.3–1.7; $P < 0.01$). Notably, this difference was also evident at a pre-pubertal age (10 years) (9.9% girls versus 7.7% boys, OR 1.4, 95% CI 1.16–1.79; $P < 0.001$)[26].

In addition, some studies also reported a higher prevalence of IBS and FAP-NOS in girls, consistent with the findings of the meta-analysis[23], whereas a few other studies reported no difference[5,27,28]. The pooled prevalence of IBS was 17.2% in girls and 15.0% in boys and the pooled prevalence of FAP-NOS was 3% in girls and 2% in boys. Currently, data are lacking on the role of sex in the prevalence of functional dyspepsia and abdominal migraine. Across both conditions, findings have been inconsistent, with a number of studies suggesting no difference in prevalence between sexes[24,29] and a number of studies reporting otherwise[22,30].

Age. The role of age in the aetiology of FAPD is inconclusive, mainly owing to the heterogeneous results of studies reporting the effects of age. For IBS, nine studies reported no differences in prevalence with age, six studies reported an increase in prevalence with age and four studies reported a decrease in prevalence with age. These findings are in line with those of a meta-analysis conducted in 2015, which pooled data from 36 studies worldwide involving children aged <12 years and >12 years, showing no significant difference in the prevalence of FAPDs across different age groups[23]. Additionally, one study reported a peak prevalence of IBS (12%) at 11 years of age and a decreased prevalence in children both younger and older than 11 years of age[31]. The heterogeneity of results from studies investigating age might be due to the diverse age groups included in these studies.

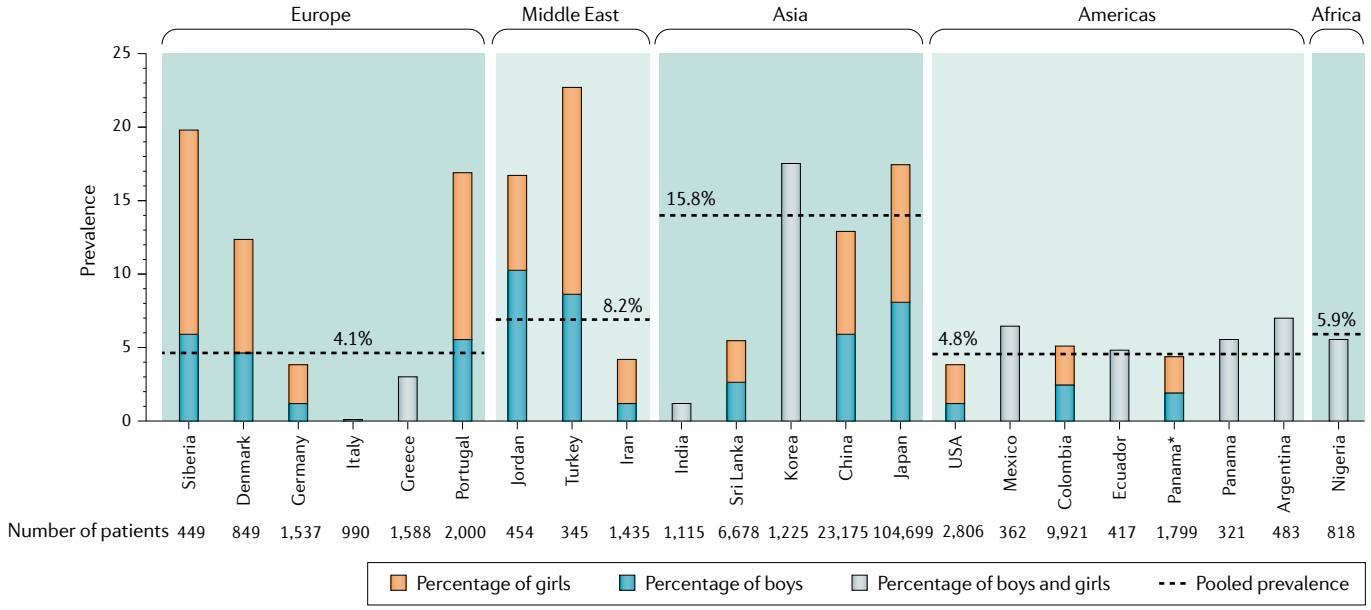


Fig. 2 | **IBS prevalence in children.** Prevalence of irritable bowel syndrome (IBS) in children and adolescents in different jurisdictions of the world, according to single studies as well as meta-analyses[23]. The regions are sorted according to continents, with pooled prevalence for continents represented. The total number of individuals in the cohort are listed. In few areas, prevalence data in girls versus boys were available, whereas in India, Korea and Mexico, only data on the overall prevalence was available (denoted by grey bars). Notably, not all epidemiological studies differentiated IBS and other functional abdominal pain disorders as studies were conducted over a long period of time (between 1958 and 2013), and they used different diagnostic criteria for paediatric functional abdominal pain disorders, introducing substantial variation. Additionally, assessment tools (questionnaires versus interviews) and assessment levels (birth cohorts, population samples and school samples) may contribute to this variability in prevalence. *Panama and other countries: Ecuador, El Salvador, Nicaragua and Mexico.

Psychosocial factors. Although family history, other somatic symptoms (for example, headaches, dizziness and muscle pains), mental health status and socioeconomic variables are often acknowledged as associated factors for all types of FAPD, their effects on prevalence are mostly unreported. Several studies reported that children and adolescents with FAPDs have a poor mental health status, that is, higher levels of anxiety and/or depression and/or emotional problems, higher stress levels or experienced stressful events, and have lower quality of life (see below) than healthy children[32]. Up to 50% of children with FAPD are reported to have clinically relevant anxiety or depression[33]. In addition, girls with FAPDs are more likely to have experienced gastrointestinal infections or surgeries earlier in life. Furthermore, children with FAPDs also exhibit more extraintestinal somatic symptoms, such as headache, fatigue and sleep problems, than healthy children[32]. Social contextual factors such as parental chronic pain have also been linked to increased episodes of pain in children. Indeed, children of mothers with IBS report bothersome gastrointestinal symptoms, miss more days at school and seek health-care professionals more frequently than children in control families[34]. Interestingly, chronic pain in both parents was associated with significantly poorer health in children than having one or neither parent with chronic pain[35]. Extensive literature suggests that using the social learning theory[34,36,37] and the social communication model of pain[38] parents can influence their children's perception of pain by modelling their pain behaviour and reinforcing their children's pain complaints with solicitous responses[39] — children express their pain in the same way as their parents behave with pain.

Genetic factors. A family history of IBS and other FAPDs has been reported as an epidemiological risk factor[40–42]. For IBS, a substantial overlap in the incidence of abdominal symptoms between mothers and their children has been described[24]. This overlap might be related to certain genes but might more likely be due to a number of social factors, including attentive parental response to child pain behaviours[36]. Although twin studies show that the concordance rate of IBS is significantly higher in monozygotic twins (17.2%) than in dizygotic twins (8.4%), indicating genetic contribution, the low overall concordance strongly implies that social factors and environmental factors are at play[43].

Although several studies in adults have indicated a number of susceptibility genes for the development of FAPDs, the results are inconsistent. No similar studies have been reported in children, although a small pilot study suggested that ~16% of children with IBS have pedigrees suggestive of maternal inheritance, possibly associated with mitochondrial DNA-related dysfunction[44].

Mechanisms/pathophysiology

FAPDs are complex disorders that seem to result from disruption of the functional and/or, more subtly, the structural integrity of one or more elements of the

Social learning theory
A theory of learning that proposes that new behaviours can be acquired by observing and imitating others as well as learning through reinforcement of our behaviours by others.

Social communication model of pain
A model that describes pain as a social transaction between the child experiencing and expressing pain and the caregiver assessing and treating the pain.

microbiota–gut–brain axis. The intricate and multifaceted nature of the interactions that underlie these conditions are brought together into a biopsychosocial model (FIG. 1), which is applicable to all FAPDs. Crucial components of this model are the concepts of visceral hypersensitivity and central hypervigilance, although the relative importance of each of these components is unclear and likely to vary between individuals. The role of genetics versus environmental factors is not conclusive and, although both elements seem to be key, neither factor seems sufficient on its own to contribute to the development of FAPDs[4]. Indeed, the pathogenetic model is far from simple and continues to evolve; this section aims to highlight certain aspects of the pathogenesis of FAPDs from our contemporary understanding.

Visceral hypersensitivity

Visceral hypersensitivity describes a perceptual response (that is, hyperalgesia) to peripheral signals and can be a result of changes in visceral afferent signal processing (reflecting increased visceral afferent input from the gut to the brain) or a consequence of alterations in descending modulation of pain (for example, central sensitization — see below)[45]. Visceral hypersensitivity in children is often manifested by a decreased sensory threshold for pain compared with control children[46]. This gut-specific hypersensitivity might be observed during distension of the bowel (for example, rectal distension in IBS) or in response to exposure to altered chemical composition of the chyme (for example, lipids or acid in functional dyspepsia and bile in IBS), which may, in part, explain responses to treatments such as dietary modification and acid suppression.

Studies involving adults and those using animal models have proposed a number of potential triggers, such as inflammation, infection and stress, for the development of visceral hypersensitivity (FIG. 1). In essence, these triggers can cause changes in mucosal permeability and lead to inflammation, releasing algogenic factors, including serotonin (5-HT), histamine, NGF, proteases and prostaglandins, which are capable of activating receptors on afferent nociceptors (pain-sensing nerves), causing acute pain as well as longer-lasting functional changes (that is, peripheral sensitization) and structural changes (via increased nerve sprouting) key to chronic pain maintenance (FIG. 3). Children seem to be especially susceptible to developing such hypersensitivity early in life.

Central sensitization

Central sensitization refers to the phenomenon of amplification of pain sensitivity via the enhancement of neuronal function and neural signalling within the central nervous system that elicits pain hypersensitivity and is a well-described mechanism in the context of chronic pain development and maintenance[47] (FIG. 3). In addition to pain hypersensitivity, central sensitization results in secondary changes in brain activity, which can be detected by electrophysiological or imaging techniques. Individuals with FAPDs may likely have a higher than normal propensity to developing central sensitization of unclear origin. Furthermore, predisposing insults, such as stress, might occur in certain individuals at a time of vulnerability of the relevant central nervous system pathways (for example, critical periods of neuronal growth or development such as in early life or adolescence), making them susceptible to developing FAPDs. A systematic review performed in 2018 involving 12 case–control studies found evidence for secondary hyperalgesia and altered cortical nociceptive processing in children with functional abdominal pain[48]. In 2015, one study demonstrated heightened temporal summation (that is, a pattern of increased perceived pain intensity in response to repetitive stimulation administered at a constant intensity) in adolescents and young adults (8–17 years of age) with FAPDs since childhood and a history of trauma[49]. Using functional MRI to determine rectal distention-induced brain activation, one study showed that adolescent patients with IBS demonstrated more activation of neural networks (such as the salience network) as well as activation of more neural structures (such as the executive network and the emotional arousal network) involved in pain perception and processing than healthy volunteers[50].

Early-life events

In paediatric FAPDs, the timing of the insult is more critical than the multiple factors that lead to the disruption of the components of the microbiota–gut–brain axis or than the disruption of the axis itself. In the first two decades of life, particularly from the perinatal period through childhood to adolescence, the key processes of development and maturation of all elements of the gut–brain axis that underpin their functionality are crucial. These key processes include the maturation of neuronal subtypes, the organization and integration of interconnected ganglia of the enteric nervous system to form functional circuits, the development of salience networks within the central nervous system, and the establishment of a functionally mature immune system and microbial populations within the gastrointestinal tract. Interference in these developmental processes at a time of vulnerability (for example, damage or disruption of neural fibres or circuits by surgical transection or inflammation) seems to predispose individuals to FAPDs, presumably by resetting the long-term functional integrity of the neural circuits or the gut–brain axis. Understanding this 'programming' process holds tremendous promise for the prevention and management of FAPDs. An apparent delay (>10 years in some cases) between the insult and manifestation of symptomatic FAPDs has been observed in some cases, predominantly in early adolescence, although the reasons for this predominance are not completely understood[42]. This concept of programming of disease has long been established, for example, coronary heart disease in adult life has been associated with malnutrition in early life (reviewed in REF.[51]).

The potency of 'early-life programming' (FIG. 1) is evident in the broad and increasing range of factors (reviewed in REF.[42]) that may precede FAPD development. These factors include surgery (for example, for umbilical herniae[52] and pyloric stenosis[53]), bacterial gastrointestinal infections[54–56], inflammatory or immune-mediated conditions (such as coeliac disease[57], inflammatory bowel disease[11] and Henoch-Schönlein purpura[58]), and

Hypersensitivity
A heightened sensitivity to algogenic factors via lowering of the threshold of pain-sensing neurons.

Hypervigilance
An enhanced state of sensory sensitivity accompanied by an exaggerated intensity of behaviours such as increased alertness.

Secondary hyperalgesia
Centrally mediated condition characterized by increased pain sensitivity outside of the area of injury or inflammation as a result of continuous nociceptor input from the zone of primary hyperalgesia.

Henoch-Schönlein purpura
The most common form of systemic immune-mediated (specifically by IgA) small-vessel vasculitis in children, with a predilection for the skin, gastrointestinal tract, joints and kidneys.

innocuous insults occurring in the first few months of life such as gastric suction at birth[59], allergy to cow milk[60] and early use of antibiotics[61]. Experimental models focusing on elements of the microbiota–gut–brain axis, such as the enteric nervous system, suggest that certain subtypes of FAPD are characterized by sustained biological structural disruption or functional disruption that occurred secondary to early-life stress[62] or physical insults[63]. A similar disruption is observed, for example, in germ-free animals, which fail to establish intestinal microbiota after birth, resulting in the lack of or a malfunctioning enteric nervous system[64]. Abnormalities in enteric nervous system function might also underlie the predisposition of children but not of adults to developing FAPDs after contracting bacterial gastroenteritis in the same epidemic outbreak[56].

Neuroimmune interactions

In some children with FAPDs, evidence shows the presence of a low-grade gut inflammation and a role for neuroimmune interactions in the pathogenesis. One study found increased mast cell numbers in close proximity to nerves in the ileocolonic mucosa of children with IBS compared with healthy children. Moreover, the nerve fibre-associated mast cell counts were reported to correlate with the intensity of abdominal pain and frequency of painful episodes[65]. In children with functional dyspepsia, eosinophils and mast cells in the antral region of the stomach were significantly activated in >50% of patients and were associated with delayed gastric emptying and gastric arrhythmia or dysrhythmia[66]. Similarly, in a retrospective cohort study, functional dyspepsia in children was strongly associated with duodenal eosinophilia in the absence of endoscopic or routine histological findings[67]. In a group of children with functional dyspepsia, one study found higher numbers of nerve-associated mast cells in a subset of children with atopic disease (that is, children with allergy) than in children without atopic disease. This finding also correlated with increased pain intensity and frequency of abdominal pain episodes[65], indicating a lower threshold for nociceptor activation. In children with atopic disease, exposure to cow milk resulted in mast cell degranulation and gastric dysrhythmia[68].

Although immune activation and allergy are implicated in FAPDs, their functions are not proven and are apparent in only a subset of cases. Hence, more evidence is needed to clarify the role of allergy and immune activation in the pathogenesis of FAPDs in children.

Gastrointestinal motility

Gastrointestinal motility abnormalities have been suggested to contribute to the pathophysiology of FAPDs. Specific underlying motor mechanisms have been defined for subtypes of FAPD, including disorders affecting the upper and lower gastrointestinal tracts. Patients with functional upper gastrointestinal symptoms might have delayed gastric emptying and/or reduced gastric accommodation or neither. Patients with functional lower gastrointestinal symptoms might have delayed, accelerated or normal colonic transit, and/or pelvic floor dyssynergia (disturbance of muscular coordination leading to contraction upon attempts to relax pelvic floor muscles). The fact that a single symptom profile can relate to a range of motility disturbances underlies a failure to establish clear causal relationships between upper or lower gastrointestinal motility abnormalities and symptoms. The functioning of the gastrointestinal tract as a single unit might underlie this lack of causality and, therefore, disorders in a specific segment can produce symptoms in a different area; for example, constipation can lead to delayed gastric emptying. Most studies on gastrointestinal motility have been performed in adults with functional dyspepsia and IBS and the contribution of gastrointestinal motility to abdominal migraine and FAP-NOS remains to be established.

Functional dyspepsia. Children with functional dyspepsia have been shown to have abnormalities in gastric function, with disorders in both gastric emptying and gastric accommodation. These disturbances include delayed gastric emptying, impaired initial distribution of a meal within the stomach, impaired accommodation, antral hypomotility, gastric dysrhythmia (tachygastria, bradygastria and mixed dysrhythmia), and altered duodenojejunal motility[69]. Abnormal gastric emptying or electrical gastric rhythm have been found in up to 70% of children with functional dyspepsia[70]. Youth (8–17 years of age) with functional dyspepsia based on the Rome IV criteria were found to lack the normal postprandial gastric myoelectrical response or autonomic nervous system response following a liquid meal[71].

In paediatric patients, nausea might be associated with delayed gastric emptying as measured by scintigraphy[72]. Studies on antral and gastric motility using ultrasonography have described a lower amplitude of antral contractions and antral motility index in children with functional dyspepsia than in healthy children (5.1 versus 8.3) and reported severity scores of abdominal pain to be negatively correlated with the rate of gastric emptying. Abnormalities in gastric myoelectric activity have also been described in children, although their importance in the genesis of symptoms have been difficult to ascertain given the inconsistent correlation between gastric myoelectric abnormalities, gastric emptying and symptoms[73].

Furthermore, using a nutrient drink test, one study showed that children with dyspepsia had a significantly lower maximum ingested volume (maximum volume tolerated before symptoms such as pain, discomfort, nausea and fullness develop, presumed to result from gastric distention) and significantly slower gastric emptying than controls[74]. Similar results were demonstrated with the water-load test[7]. Studies using a gastric barostat (a gold-standard method to measure gastric accommodation) reported that children with FAP-NOS had a lower pain threshold than healthy children, indicative of the presence of visceral hypersensitivity in these children[75].

Although the above-mentioned studies suggest abnormalities in different aspects of gastric function, large studies have failed to find a direct correlation between gastric function abnormalities and symptoms in patients with functional dyspepsia[76,77].

Gastric emptying
Measure of how effectively stomach contents are moved into the intestine, displayed as $t_{1/2}$ (time at which 50% of contents have emptied) or as the percentage of contents remaining within the stomach at pre-defined time intervals (1, 2 and 4 hours).

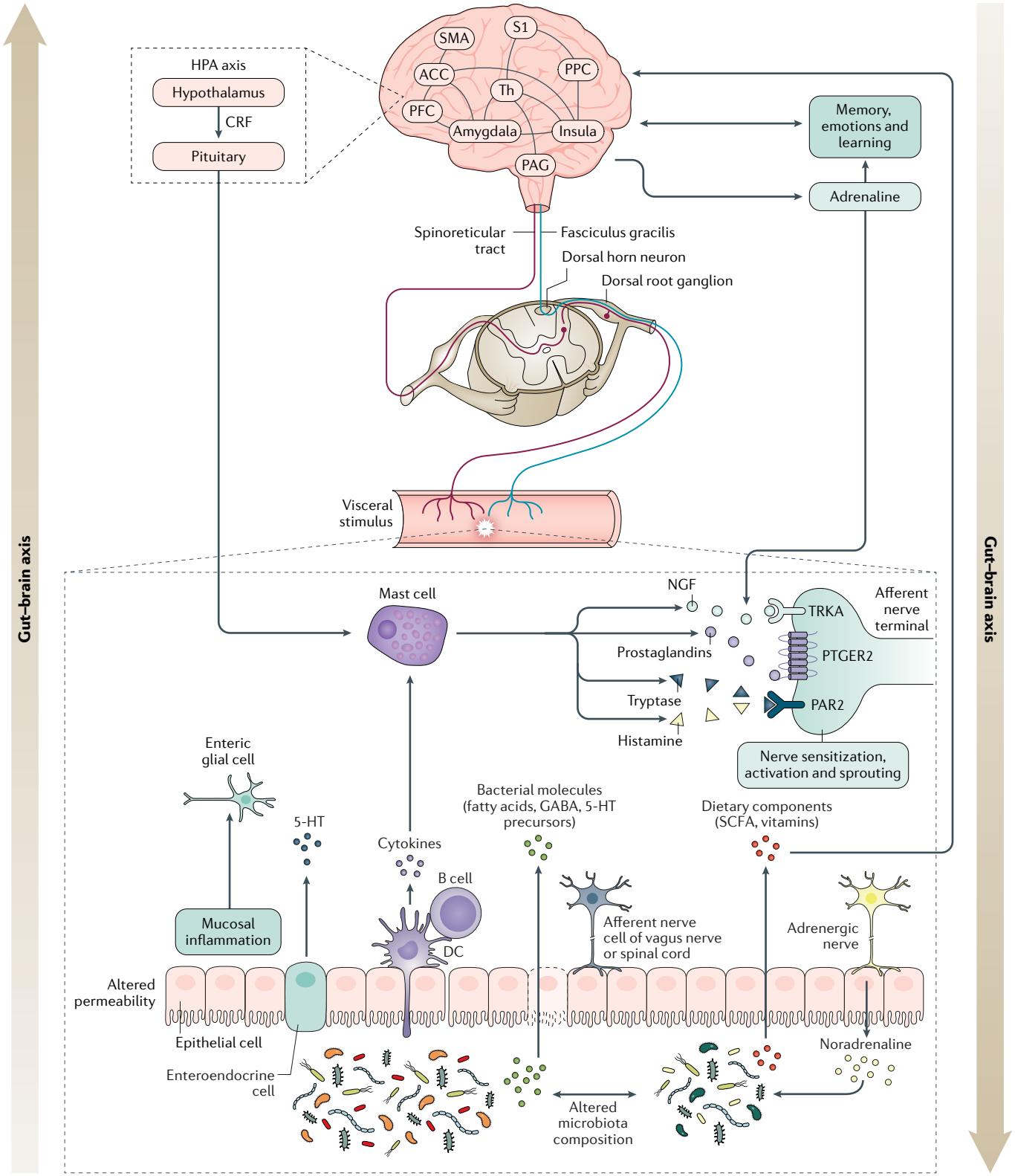
Gastric arrhythmia or dysrhythmia
Abnormal myoelectrical rhythms of the stomach, a normal rhythm is ~3 cycles per minute.

Gastric accommodation
Vagus nerve-mediated reflex associated with a reduction in gastric tone as well as with an increase in gastric volume and gastric compliance, which allows temporary storage of ingested food before controlled release into the intestine.

Tachygastria
Increased (>3 cycles per minute) rate of electrical pacemaker activity in the stomach.

Bradygastria
Decreased (<3 cycles per minute) rate of electrical pacemaker activity in the stomach.

Mixed dysrhythmia
Elements of both bradygastria and tachygastria present within an electrogastrography reading.



Irritable bowel syndrome. Abnormalities in colonic function and rectal perception have been described in children and adults with IBS[78]. Colonic function is generally assessed using colonic transit measurements such as radiopaque markers, wireless motility capsule or scintigraphy. Adults with IBS-constipation (IBS-C) have delayed colonic transit and those with IBS-diarrhoea (IBS-D) have accelerated colonic transit compared with the general population[79]. Unfortunately, most studies investigating colonic function in children have been conducted in a subset of children with severe constipation and therefore do not allow conclusions on colonic transit in IBS-D. In case of abdominal pain, motor alterations (delayed transit) may be associated in some

◀ Fig. 3 | **Aetiopathogenesis of hypersensitivity in FAPDs.** Central to the biopsychosocial model of functional abdominal pain disorders (FAPDs) is the concept of hypersensitivity occurring at any point from the periphery (gastrointestinal tract) to the central nervous system, often referred to as visceral hypersensitivity and central hypervigilance. The figure illustrates the potential aetiopathogenesis that underlies the disruption of the functional and/or, more subtly, structural integrity of one or more elements of the microbiota–gut–brain axis. This axis is a bidirectional communication system enabling gut microorganisms to communicate with the gut (enteric nervous system and immune cells) and the brain as well as the brain with the gut. The mechanisms of interaction are complex and not fully elucidated but include neural (for example, vagus nerve), endocrine, immune and metabolic pathways between the gut and the brain. The gut microbiota might produce neurotransmitters (such as serotonin (5-HT), GABA, noradrenaline, dopamine and acetylcholine), which can cross the mucosal layer of the intestines and influence the enteric nervous system and, indirectly, the brain. Microbial metabolic products (for example, short-chain fatty acids (SCFAs)) may also exert central effects. Signalling from gut to brain is also mediated by immune-mediated production of cytokines, such as IL-1 and IL-6, which can travel via the bloodstream to the brain. In the hypothalamus, these cytokines can activate the hypothalamic–pituitary–adrenal (HPA) axis, bringing about the release of cortisol, a potent activator of the stress system. The HPA axis can also substantially impact the brain–gut–microbiota axis. Brain structures, such as the amygdala, integrate both memory, emotions and learning as well as pain signals (via the periaqueductal grey (PAG)) and stress (prefrontal cortex (PFC) and anterior cingulate cortex (ACC)) and feed them into a matrix of further brain centres such as the insula and the thalamus (Th), which then integrate with signals in the somatosensory cortex (S1, S2 and SMA) from the periphery. DC, dendritic cell; PPC, posterior parietal cortex.

patients with constipation[80]. Three patterns of colonic motility — normal motility, segmental dysmotility or total colonic dysmotility — have been demonstrated in children with constipation[81]. Unfortunately, discriminating symptoms such as pain, constipation and diarrhoea have not always been possible between patients with different colonic motilities. Indeed, pain tends to occur independently of the presence of stool retention and is an important diagnostic marker of IBS. In addition, children with IBS have been shown to have decreased rectal compliance and contractile response to meals[82].

So far, no clear relationship has been demonstrated between motility abnormalities and symptoms in children with all FAPDs[83]. Whether the observed gastrointestinal motor abnormities are important or a cause or effect of the FAPD is yet to be determined. Indeed, treatment focusing only on improving gastric motility abnormalities (such as improving bowel transit or gastric emptying) does not provide complete symptom relief, indicating the importance of the sensory abnormalities that may accompany motor dysfunction. Nevertheless, owing to the invasive nature of the testing procedures, motor dysfunction is not well investigated both in children and in adults.

Microbiota

Growing evidence indicates that gut microbiota diversity and composition contribute to FAPDs, particularly IBS[84,85]. However, longitudinal interventional studies establishing the causality between symptoms and the reported cross-sectional dysbiosis are lacking. A 2019 systematic review[86] assessed gut microbiota composition in healthy individuals and in patients with IBS, both adults and children. Twenty-four studies, most involving adults with various subtypes of IBS (IBS-D, IBS-C and mixed type IBS) and only three studies (reported in two articles) investigating children, met the inclusion criteria. Most studies used faecal sampling owing to its non-invasive nature and for convenience purposes, whereas two studies involving adults assessed mucosal microbiota (via biopsy samples). Overall, the systematic review found a decrease in the abundance of *Bifidobacterium* spp. and *Faecalibacterium* spp., and particularly of *Faecalibacterium prausnitzii*, which is associated with anti-inflammatory effects[87], in patients with IBS compared with healthy adults. Additionally, the abundance of uncultured protective bacteria, such as Clostridiales I, was decreased, whereas that of potentially harmful bacteria, such as *Lactobacillaceae* spp., Enterobacteriaceae spp. and *Bacteroides* spp., were increased in patients with IBS compared with healthy individuals. In addition, the diversity of faecal microbiota was either decreased or remained unchanged in patients with IBS. The authors of the review concluded that their findings were inconsistent and attributed the lack of a standardized approach for microbiota sample identification, collection and processing as a possible reason for this inconsistency. The role of the gut microbiota in symptom induction has been further supported by studies showing that faecal microbiome composition or metabolome composition can predict the patients likely to benefit from the diet[88,89]. Hence, further studies are needed that investigate early-life factors such as mode of delivery (vaginal birth versus caesarean section), diet (breast-feeding versus formula-feeding) and medication use (particularly antibiotics or proton pump inhibitors), all of which are linked to dysbiosis[90]. In addition to bacteria, fungi or viruses might also play a part in FAPD pathophysiology. However, the available data on fungal microbiota dysbiosis or viral microbiota dysbiosis are limited[91–93], and current studies focus mainly on inflammatory bowel disease[94] rather than on IBS. Additionally, no studies investigating the role of microbiota in other FAPDs are available to date.

Nutrition

Diet plays a vital part in children with FAPDs, with up to 93% identifying at least one food and/or food type as worsening gastrointestinal symptoms, without evidence of food allergy[95,96]. Children with FAPDs frequently self-implement additional dietary strategies such as removing ingredients from the foods they eat[95–97]. Nowadays, the internet is the main source of information, although, unfortunately, the quality and reliability of dietary information for both children and adults with IBS is poor[98]. In general, nutritional status and growth do not seem to be affected by these dietary manipulations; however, disordered eating (such as bulimia nervosa) might contribute to an increased incidence of obesity in children with IBS, as reported by one study[99].

Despite the clinical experience of diet being associated with gastrointestinal symptoms, several issues exist in clearly defining causative foods. For example, children with FAPDs identify a wide variety of potential culprit foods[96,100]. However, when asked to rate symptom correlation (rarely, sometimes, often or always), children do not consistently identify the same foods and rate them as 'often' or 'always' causing their gastrointestinal symptoms, possibly explaining the high percentage of children with FAPDs consuming a potential culprit food in a 24-hour dietary recall[95].

Malabsorption of carbohydrates can induce gastrointestinal symptoms. Malabsorption might be related to specific enzyme deficiencies (such as lactose in lactase deficiency; sucrose and starches in sucrase-isomaltase deficiency) or related to limited absorptive capacity for carbohydrates such as fructose, sorbitol or mannitol. In the case of smaller sugars, the osmotic load engendered can lead to small bowel luminal distention and rapid transit[101]. For larger sugars such as fructans, humans do not possess the enzymatic ability for digestion and, therefore, malabsorbed sugars are fermented by the colonic microbiota, leading to the formation of gas and potential colonic distention[101].

Psychological factors

The physiology of the gut–brain axis is complex and includes afferent and efferent components. Signal transmission occurs via different pathways, including neural, hormonal and immunological components. The hypothalamic–pituitary–adrenal axis is hypothesized to be at the centre of gut–brain interactions owing to its important role in regulating psychological stress and mood, although the autonomic nervous system has also been found to play an important role[102]. The hypothalamic–pituitary–adrenal axis promotes gut–brain interactions via a feedback loop through the release of cortisol and corticotropin-releasing factor (both of which are increased in stressful conditions) as well as by stimulating mast cells and by inducing the release of pro-inflammatory cytokines[102,103]. Stress has been shown to increase gut inflammatory markers such as faecal calprotectin and CRP in both adults and paediatric patients with FAPDs[102]. Moreover, studies have reported that gut–brain interactions involve top-down and bottom-up processes and, therefore, gut microbiota can also influence brain function[102–104]. Under stressful conditions, gut microbiota can increase the permeability of the epithelial barrier, enabling antigens and/or pathogens to pass through and engendering an inflammatory reaction. The resultant circulating pro-inflammatory cytokines, such as IFNγ, IL-1 and IL-6, might communicate with the central nervous system to stimulate an immune response in the brain, which may cause or exacerbate psychological symptoms (for example, anxiety and depression)[105]. A randomized controlled trial (RCT) found that probiotics can reduce depressive symptoms in adults with IBS and these improvements were associated with reduced reactivity of the limbic regions in the brain[106]. However, this RCT was a pilot study with a small sample size, making it difficult to draw any clear conclusions about the effectiveness of probiotic intervention. Whether the effect of probiotics is predominantly peripheral (intestinal) or central in nature is unknown and yet to be elucidated.

Several studies have shown increased psychological distress and behavioural problems in children with FAPDs compared with healthy children[32,107]. In contrast to adults, current evidence does not support the assumption that psychological symptoms such as depression and anxiety precede gut symptoms, such as abdominal pain, in children[108]. Psychological factors might be both a cause and a consequence of FAPDs, although psychological factors alone are not proven to be sufficient to cause FAPDs. Their aetiological role is hypothesized to be through interaction with other pathophysiological factors.

In addition, psychological factors are shown to have an impact on treatment outcomes once symptoms are already manifested. For example, in children with FAPDs, anxiety, depression, somatization (expressing multiple symptoms) and catastrophizing are associated with increased severity of symptoms, increased disability and disease persistence over several years[32]. These observational findings are supported by evidence from clinical trials showing that psychological interventions, such as cognitive behavioural therapy (CBT) and hypnotic therapy, are beneficial in reducing symptoms and disability as well as in increasing the quality of life[109].

Despite the above-mentioned findings, the current literature reports that anxiety and depression might not be the most important factors in FAPD. Indeed, several studies found that specific pain-related cognitions and coping behaviours are directly related to pain and disability. For example, one study[110] found that the effect of anxiety and depression on abdominal pain was mediated by somatization and pain catastrophizing. Studies on the active ingredients of CBT also found that treatment effects on disability and pain can be predicted by changes in pain-related cognitions such as catastrophizing, disease threat and avoidance behaviours[111,112]. This finding indicates the need to examine pain-specific psychological factors rather than anxiety and depression alone.

Diagnosis, screening and prevention

Patient history

In most cases, children with FAPDs present with fairly stereotypical symptoms (BOX 1). Experienced medical providers frequently need little testing, if any, to make a prompt and a correct diagnosis. A detailed patient history and thorough physical examination are typically the necessary measures needed to establish FAPD diagnoses and to provide effective reassurance of the benign nature of the disease. The key elements in patient history include elucidating the characteristics of the pain, including location, quality, severity, duration, factors (especially food) that trigger or alleviate it, and its occurrence during sleep and excluding potential red flags such as involuntary weight loss or loose stools with blood. Clarifying whether symptom development was associated with a stressful event, for example, after an infection or traumatic episode such as the beginning of the school year, is particularly important. A detailed insight into the psychosocial history of both the child and the family is essential to uncover traits such as anxiety or catastrophizing, which are very prevalent in children with FAPDs and their parents. Typical hints that are indicative of a child with FAPD include the following: pain that is periumbilical and never goes away (that is, present for 24 hours every day); pain that does not consistently wake the child up at night but worsens under stress (for example, morning of school days); and co-occurrence of multiple somatic symptoms such as headaches, dizziness, arthralgias, myalgias and joint pain. Children with FAPDs may be as functionally disabled as children with organic diseases such as inflammatory bowel disease[12].

Somatization
The manifestation of psychological distress in the form of physical symptoms, for which medical help is often sought.

Catastrophizing
A cognitive distortion that results in the person assuming that things are worse than they are or will have a far worse outcome than is realistic and often characterized by a lack of confidence and control.

Disease threat
An increased perception of the duration, frequency and seriousness of the symptoms.

Avoidance behaviours
Any act or series of actions that enables an individual to anticipate or avoid unpleasant or painful situations, stimuli or events.

Arthralgias
Any discomfort or pain in the joints, although joint pain is not related to an inflammatory condition such as arthritis.

Myalgias
Muscle aches and pain, which can involve ligaments, tendons and fascia, that is, the soft tissues that connect muscles, bones and organs.

During the abdominal examination, evaluating whether distraction leads to a resolution of pain is important, a sign implying the presence of a FAPD. Performing the Carnett test (that is, evaluation of abdominal tenderness) is often helpful to differentiate abdominal wall pain syndrome from intra-abdominal pain originating from the viscera[113].

Diagnosis

The Rome criteria are often used to achieve a positive diagnosis[4] (FIG. 4). A child fulfilling a series of clinical criteria is eligible to receive a diagnosis of FAPD and can usually avoid any additional testing. The bottom of the Rome criteria for FAPDs includes the wording "after appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition"; thus, the onus is on the physician to decide what an 'appropriate evaluation' might be. Evaluation certainly may include only history and a physical examination but the conception that this holds true in every case remains a platitude rather than a fact. Indeed, some blood and stool testing in children with a presumed FAPD is almost regularly done by the paediatric gastroenterologist (and consistently expected by parents); once referral is made to a subspecialist, the cost of care increases fivefold (excluding the cost of endoscopy)[114].

Laboratory testing. Laboratory testing, when performed, needs to be targeted and limited to avoid overinterpretation of minor findings with no clinical significance. Serological testing for coeliac disease and measurement of faecal calprotectin seem to be the only

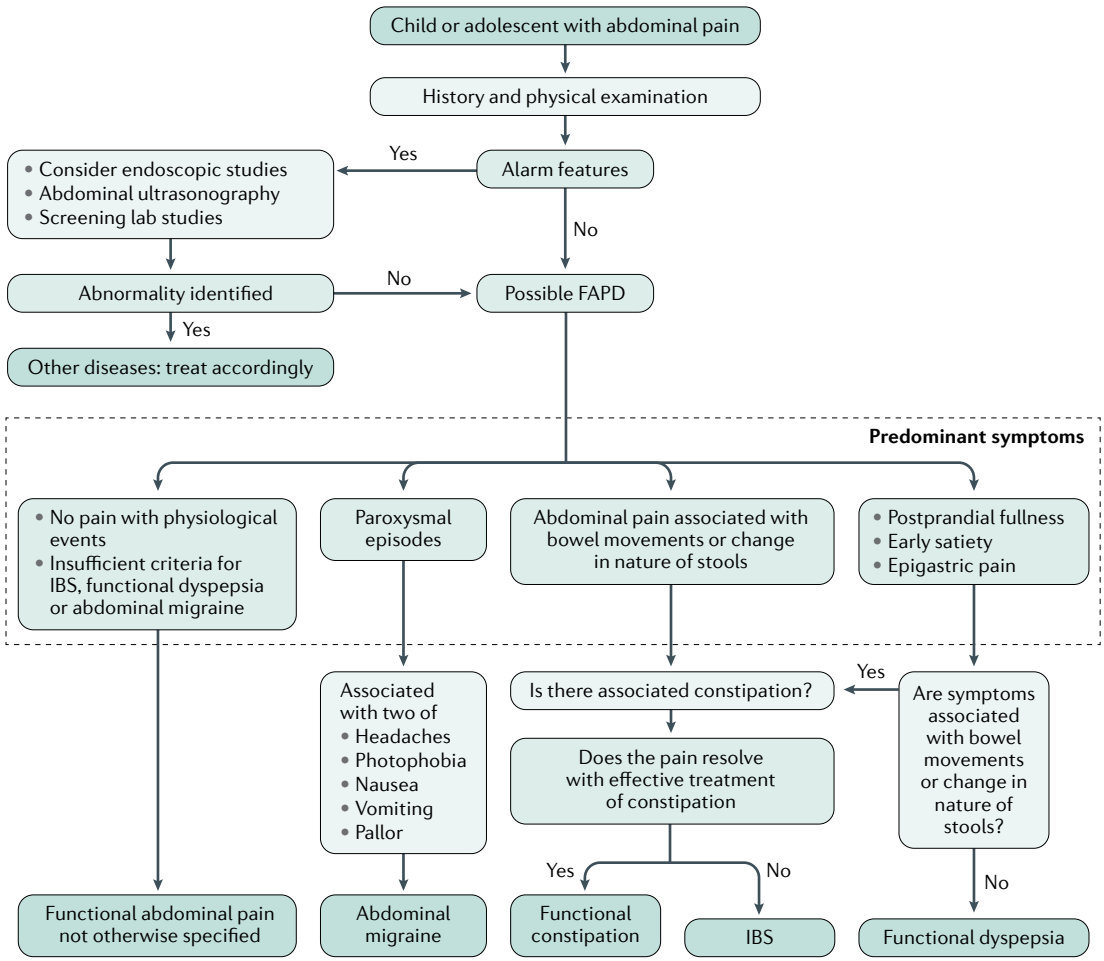


Fig. 4 | **Rome IV diagnostic workflow of FAPDs.** This figure illustrates the suggested algorithm for the diagnosis of a functional abdominal pain disorder (FAPD). Children presenting with symptoms of chronic or recurrent abdominal pain without an obvious organic pathology should undergo a careful clinical assessment (history and examination) to exclude alarm features. The patient history should include a detailed history from early life, family history and assessment of potential psychosocial factors. If an organic disorder is suspected, clinicians need to select appropriate investigations, which may include laboratory tests (for example, full blood count, serology testing for coeliac disease and faecal calprotectin), imaging (abdominal ultrasonography) and possibly endoscopy with mucosal assessment. In the absence of an obvious organic pathology, the clinician should consider the possibility and assess whether the symptom profile (using the Rome IV criteria) supports the diagnosis of one of the FAPDs (functional dyspepsia, irritable bowel syndrome (IBS), abdominal migraine and functional abdominal pain not otherwise specified). Notably, different types of FAPD may overlap in a single patient and with other functional gastrointestinal disorders such as 'functional constipation', which should be excluded before a diagnosis of IBS is made. Adapted with permission from REF.[195], Copyright 2016 Rome Foundation, Inc. All Rights Reserved.

FODMAP
Fermentable, Oligosaccharides, Disaccharides, Monosaccharides and Polyols, which are short-chain carbohydrates that are believed to be either slowly absorbed or not digested in the small intestine.

cost-effective laboratory test in children with typical symptoms of FAPDs without alarm signs. An Italian study reported a 4% prevalence of coeliac disease in children fulfilling clinical diagnostic criteria for IBS[115]. However, one multinational, cross-sectional study failed to show a significant difference in the relative risk for FAPDs between patients with coeliac disease on a gluten-free diet and sibling controls without coeliac disease. Nevertheless, both groups showed a fourfold increase in the risk of FAPD compared with unrelated non-coeliac controls[116]. Thus, testing for coeliac disease by measuring serum tissue transglutaminase antibody and total IgA seems reasonable and should be considered, especially in children with an IBS-D phenotype. Evaluation of faecal calprotectin levels is being increasingly utilized for the non-invasive screening of intestinal mucosal inflammation and seems to be superior to standard serological testing such as complete blood count or CRP. Thus, in children with calprotectin levels <50 μg/g, endoscopy and histology add very little diagnostic value[117]. The role of *Helicobacter pylori* in children is controversial, although data suggest that *Helicobacter pylori* infections are not associated with FAPDs and its eradication does not correlate with improvement of abdominal pain[118].

Endoscopy and imaging. The clinical value of gastrointestinal endoscopy in children with symptoms indicative of FAPD is limited. Minor macroscopic (for example, lymphonodular hyperplasia) and histopathological (increased mucosal mast cells and eosinophils) changes are frequently encountered on endoscopy and/or histology but lack clear clinical value. For example, emerging literature demonstrates the presence of inflammation with a predominance of mast cells and eosinophils in a proportion of children with functional dyspepsia.

Despite the common argument that a negative laboratory test leads to parental reassurance about the absence of an organic disease, evidence actually shows increased anxiety that something serious is missed[119]. Another study has shown that the prognosis is similar between children with FAPD who underwent a negative endoscopy and those who were not endoscopically tested[120].

Abdominal radiographs are often used to reveal 'occult constipation', which might be a source of abdominal pain, even in children who seem to have normal bowel habits. However, credible scientific evidence is lacking to prove that treatment with laxatives alleviates abdominal pain in a child who does not fulfil the Rome criteria for functional constipation. Indeed, when the aetiology of the pain is attributed to constipation, the evidence from the emergency department shows that these children are likely to experience a surgical outcome (for appendectomy)[121].

Early diagnosis of FAPD in children increases the chances of a prompt resolution of symptoms[122]. Thus, the merits of any investigations that could potentially delay or distract from the diagnosis of a FAPD as well as the initiation of appropriate management should be carefully considered. Certainly, endoscopy should not be performed routinely for the diagnosis of FAPDs but only in cases where histological findings might support management options or in cases where differential diagnoses amenable to endoscopic (or histological) confirmation cannot be otherwise excluded.

Box 3 | **Treatment options for functional dyspepsia**

The treatment of functional dyspepsia is multifaceted. Patient education is essential and all patients must be provided psychosocial support. Initially, dietary changes may be indicated, which may include smaller meals and avoidance of fatty foods and carbonated beverages. If the initial approach does not work[240], then other modalities are tailored to the subtype of functional dyspepsia as outlined in the box below.

- For those with postprandial distress syndrome, which is believed to be associated with problems in gastric emptying and accommodation, cyproheptadine is recommended as one of the first-line drugs[241,242]. The latest use of a peppermint oil-based preparation has also been shown to be beneficial[243–245]. The next step in treatment is the use of prokinetics, including 5-HT_4 agonists, and when those fail, 5-HT_1 receptor agonists such as buspirone, which relax the proximal stomach, are recommended[246]. Antiemetics such as ondansetron, diphenhydramine, prochlorperazine and/or promethazine can be helpful to reduce nausea but can be sedating[247]. When all these treatments fail, neuromodulators in combination with cognitive behavioural therapy can be considered[246,248].
- For those with epigastric distress syndrome, the use of antacids is usually the first-line therapy[245,249]. Similar to postprandial syndrome, the subsequent therapies are focused on altering stomach sensitivity and accommodation, with the use of cyproheptadine or herbal medications. If those fail, neuromodulation and psychological techniques are indicated.

Management

Regardless of the therapeutic approach, the importance of the patient–clinician relationship, effective communication and patient education at the outset cannot be emphasized enough, and these aspects remain at the heart of successful FAPD management. Ample time must be taken to explain the diagnosis to the carers of each individual patient as well as to discuss the biopsychosocial model (as it relates to each individual patient), subsequently designing a management plan, ensuring realistic expectations of prognosis and outcomes. We discuss the management with a particular focus on IBS and have highlighted the treatment options for functional dyspepsia (BOX 3).

The management of FAPDs is limited by several factors. First, owing to the biopsychosocial nature of the disorder, every child has a unique set of pathophysiological factors and responds differently to therapies (FIG. 5). In addition, the evidence base in children with FAPD is small and many treatment suggestions are therefore based on studies in adults. Nevertheless, as described below, children often do not respond similarly to adults. Even if a child would have access to all existing treatments, not all children respond adequately to current therapies. Finally, several efficacious treatments are behavioural (dietary and psychological) and are not readily available owing to a lack of allied health-care professionals as well as a lack of insurance coverage.

With the growing recognition of the role of gut microbiota, a number of interventions targeting gut microbiota, including probiotics, a low FODMAP diet, prebiotics and antibiotics, are increasingly being used for the management of FAPDs and several new therapies are on the horizon[123].

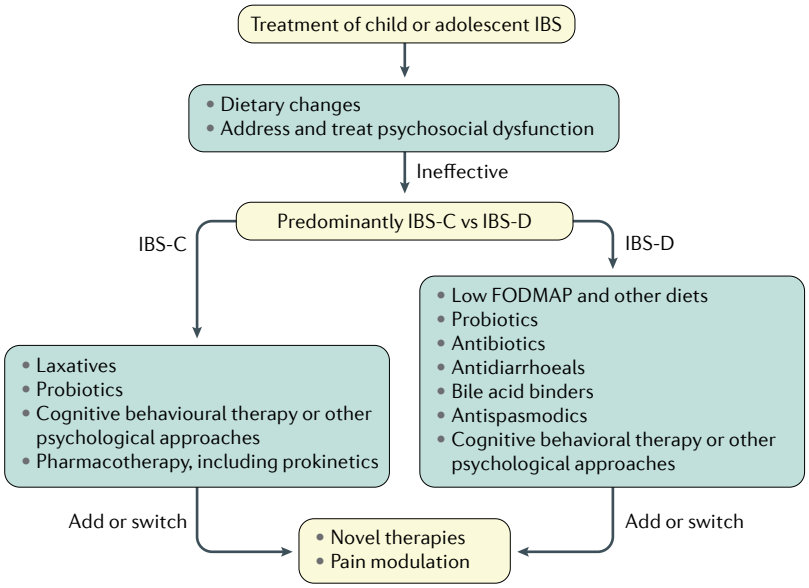


Fig. 5 | **Therapeutic algorithm for IBS in children.** Once a diagnosis of irritable bowel syndrome (IBS) is established, early engagement with psychosocial management is advised to develop a relationship for ongoing support and institution of the most effective therapeutic modality. Dietary interventions to optimize nutrition or help limit symptoms (for example, limited time trial of dietary exclusion if high possibility of food allergy is suspected or initiating low FODMAP diets) is recommended. Oversight of appropriate nutritional intake, preferably utilizing clinical dietitians or nutritionists, could also be undertaken. If these initial and non-invasive strategies are ineffective, the predominant type of IBS present, namely with constipation (IBS-C) or diarrhoea (IBS-D), must be determined. This information should then be used to design management strategies, although psychosocial management (such as behavioural interventions and hypnosis) should be utilized and maintained. Probiotics may also have some benefit in both the subtypes. The use of laxatives and/or prokinetics in IBS-C and of antibiotics, antidiarrhoeals or antispasmodics in IBS-D could be tested with appropriate review. For a select few patients, newer modalities such as neuromodulation may be beneficial. Adapted with permission from REF.[195], Copyright 2016 Rome Foundation, Inc. All Rights Reserved.

Dietary modifications

Although dietary factors are implicated in the pathogenesis of FAPDs, the benefits of dietary modifications remain controversial. One new study reviewing data from a large metropolitan health-care system in the USA showed that 43% of patients with FAPDs received dietary recommendations in tertiary care or primary care settings[124]. However, the guidance provided was highly variable and only 20% of patients who were recommended dietary modifications received a consultation from a dietitian. Almost all published studies investigating the role of diet in the management of FAPDs involve IBS, with surprisingly little information on functional dyspepsia, abdominal migraine or FAP-NOS. For the management of functional dyspepsia, clinicians often promote small and frequent meals and low-fat foods, with little objective evidence showing benefit. Two systematic reviews on the use of diet to manage functional dyspepsia in adults acknowledged a lack of high-quality evidence to support dietary therapy in functional dyspepsia[125,126].

Low FODMAP diet. Studies suggest that some patients with IBS are more sensitive to carbohydrate malabsorption than healthy individuals and, therefore, a low FODMAP diet is usually also recommended for children with IBS. The rationale for the low FODMAP diet is a presumed reduction in microbial gas production and luminal distension, with a resultant decrease in pain[127]. Indeed, a few RCTs involving both children and adults have supported the use of low FODMAP diets or a specific reduction of fructans in the diet for a reduction of gastrointestinal symptoms[88,128–130]. However, current studies suggest that adult patients with IBS are more sensitive to FODMAP-induced luminal distension (rather than experiencing greater distension per se) than healthy individuals[131], supporting the concept of visceral hypersensitivity. Furthermore, evidence also shows that FODMAP ingestion is associated with the generation of low-grade gut inflammation and barrier dysfunction[132,133].

However, a low FODMAP diet is complex and requires assistance from a dietitian[134]. A number of issues remain unresolved, including identifying which subset of patients will respond, the fact that the microbiome analysis of the stool is not practical as it requires standardized stool sampling and storage at home, and the predictive value of the lactulose breath test being controversial[88,129,135]. In addition, the impact of removing potentially 'healthy' foods and the duration of the diet (response has been described within 2–7 days but longer durations of treatment are often recommended) are yet to be elucidated[88,128]. Furthermore, how and when eliminated foods should be reintroduced has to be determined as continuing a low FODMAP diet carries potential risks, which include a reduction in fibre, calcium and antioxidant intake and a decrease in some potentially beneficial gut bacteria (for example, *Bifidobacteria* spp. and *Faecalibacterium prausnitzii*)[136].

Lactase deficiency seems to be less prevalent in children with FAPDs than in adult patients with IBS[137,138]. Different polymorphisms in genes regulating sucrase-isomaltase activity seem to be more frequent in those with IBS-like symptoms than in the general population[139]. Molecular studies indicate a multitude of synthetic and trafficking defects that could affect the amount of functional enzyme produced, accounting for the wide variation in enzyme activity and thereby resulting in the diverse clinical phenotype[140]. Adults carrying polymorphisms associated with decreased sucrase-isomaltase activity might be less likely to respond to a low FODMAP diet[141].

Gluten-free diet. Few studies have highlighted the potential role of non-IgE-mediated food allergy in causing IBS symptoms. Wheat, yeast, milk, soy and egg white were found to increase duodenal permeability and to cause lymphocytic and eosinophilic mucosal inflammation and clinical symptoms, predominantly abdominal pain in adults with IBS[142,143]. Of 108 patients with IBS, 61% reacted to wheat. These food types are among the most common food allergens in the USA[144]. Future research is warranted to show whether such non-coeliac gluten hypersensitivity is of clinical importance in functional gastrointestinal disorders not only in adults but also in children.

Lactulose breath test
A test used to measure an increase in hydrogen and/or methane excreted in the breath, presumed to arise from the metabolism of ingested lactulose by intestinal bacteria. This test is used as a measure of small intestinal bacterial overgrowth or small bowel transit and to predict a patient's response to a low FODMAP diet.

Prebiotics. Prebiotics can modify the gut microbial population and, presumably, the response to incompletely absorbed dietary components. Increasing the abundance of lactose-fermenting bacteria has been shown to improve symptoms of lactose-intolerance in adults with a history of self-reported milk intolerance[145]. A prebiotic (β-galactooligosaccharide) was shown to be more effective in improving IBS symptoms than a low FODMAP diet in adults; the improvement of IBS symptoms (pain, distension and flatulence) outlasted the duration of prebiotic administration, whereas the response to the low FODMAP diet ended upon return to a normal diet[146].

Enzyme and fibre supplementation. Enzyme supplementation has long been used to treat lactase deficiency and sucrase-isomaltase deficiency in children; however, in the latter deficiency, supplementation might not correct starch maldigestion[147,148]. Trials in adults have suggested that a similar strategy might be useful to treat malabsorption associated with certain FODMAP carbohydrates by improving their digestion and, in turn, reducing their availability to either exert an osmotic effect or to be fermented by bacteria, which are thought to distend the bowel and elicit IBS symptoms[149,150]. The use of enzyme supplementation may also allow some relaxation of the very restrictive low FODMAP diet and thereby improve compliance.

Insufficient dietary fibre intake in childhood has been associated with the development of FAPDs[151,152]. Meta-analyses of studies involving adults have shown benefits of soluble fibre in treating IBS[153,154]. Following advice from studies in adults[155], a randomized, double-blind controlled study in children reported a decrease in the frequency of abdominal pain in children with IBS treated with the soluble fibre psyllium compared with placebo (maltodextrin)[156].

Probiotics

Multiple studies have examined the efficacy of probiotics (using a vast array of organisms) in the treatment of FAPDs, although the majority have been performed in adults with IBS. These investigations suggest that particular combinations of probiotics or specific species might be effective but their role remains unclear owing to study limitations such as sample size, blinding, differences in the probiotics used and the different dosing[157]. Although meta-analyses of paediatric trials have been performed, only few studies exist and with similar caveats to the adult meta-analyses[158,159]. Among five RCTs investigating children with FAP-NOS, the probiotic *Lactobacillus reuteri* DSM 1793 improved abdominal pain in three studies[160–162], reduced functional disability but not abdominal pain in one study[163], and was not superior to placebo in another[164], although the methods of pain evaluation were different across studies. In children with IBS, two studies found that *Lactobacillus rhamnosus* GG was effective in reducing abdominal pain symptoms[165,166] and one study reported no improvement in abdominal pain but an improvement in perceived abdominal distention; measures of pain differed yet again among the different studies. In one multicentre, crossover RCT performed in children with IBS, VSL#3 (a mixture of eight probiotic strains) was found to be safe and more effective than placebo in ameliorating symptoms and in improving quality of life[167].

Psychological interventions

Psychological interventions, such as CBT and hypnotherapy, have thus far proved to be the most successful interventions in managing FAPDs, arguing for their universal inclusion in the management strategies.

Cognitive behavioural therapy. CBT is the most studied psychological therapy for the treatment of IBS and it aims to alter the cognitions, emotions and behaviours, all of which might play a role in exacerbating or maintaining IBS symptoms. Studies in adults and children have shown that CBT is effective in improving pain and the ability to participate in social life as well as in alleviating symptoms of anxiety or depression compared with educational and other control interventions[168–170]. Twelve RCTs, involving 990 children (7–18 years of age) with IBS, showed the acute and long-lasting beneficial effects of CBT on quality of life, school performance and social participation. CBT can be provided as a face-to-face therapy[171–173] or targeted to children via the internet[174] or to parents via the telephone[175]. However, the evidence is limited owing to the low quality of the trials. Owing to the limited access to comprehensive CBT programmes in most countries, internet-delivered CBT has the potential to increase the availability of treatment and reduce health-care costs[176,177]. Despite the small sample sizes and methodological weaknesses of these trials, the consistency and the magnitude of the reported effects of CBT prove its usefulness in improving pain and disability in children with IBS. Preliminary data suggest that internet-delivered CBT might also be useful for adolescents with functional dyspepsia[112]. Additionally, CBT focused only on parents is shown to be effective in reducing disability[175]. Although CBT has been used to treat migraine, evidence of its use in abdominal migraine or FAP-NOS is lacking. CBT in children with FAPDs is largely focused on learning to cope with the symptoms and reducing disability and, therefore, these therapies should ideally be part of an integrative care approach (for descriptions of such approaches see REF.[109] and REF.[178]).

Hypnotherapy. In this approach, a patient is induced into a hypnotic state, guided by a therapist, to respond to suggestions to alter one's subjective experience, perception, emotion, thought or behaviour. In adults, hypnotherapy has been demonstrated to lead to changes in colonic motility, improve visceral hypersensitivity, and to reduce psychological factors such as somatization and psychological stress that persist long term[179–181]. However, in children with IBS, no reduction in hypersensitivity (tested experimentally) was found after hypnotherapy, although pain scores and somatization scores were lower than for children in standard medical care[182]. Five RCTs of children with IBS or FAP-NOS ($n = 412$; 6–18 years of age), hypnotherapy, given either as individual therapy or as self-exercise at home using a CD, showed substantial long-lasting beneficial effects on quality of life, number of doctor visits and missed days

of school (number needed to treat = 3)[171,183]. At the 1-year and 5-year follow-up, 85% and 68%, respectively, of patients receiving hypnotherapy were symptom free whereas only 25% and 20% of patients, respectively, were in remission in the control group[184]. Shortcomings of hypnotherapy include limited access, its rare coverage by commercial insurances and the lack of adequate well-trained hypnotherapists. As home-based hypnotherapy was non-inferior to therapist-based hypnotherapy, hypnotherapy using a CD might provide an attractive alternative treatment option for these children[184].

Yoga therapy. Yoga practice has been shown to improve stress-induced underactivity of the parasympathetic nervous system. Three RCTs, including 127 children (7–18 years of age) with IBS, found positive effects of yoga therapy in decreasing abdominal pain compared with wait-list control or standard medical care[171]. However, a Dutch study showed that, at the 1-year follow-up, yoga intervention was not more effective than standard care that did not include CBT[185]. Owing to major flaws in study methods, a recommendation regarding yoga as a routine intervention for children with FAPDs cannot yet be made.

Neurostimulation

Several studies have shown the efficacy of electrical stimulation of the spinal cord and brain in modulating pain pathways[186,187]. This currently experimental technology was able to decrease the firing of >50% of neurons in the spinal cord and central amygdala, thereby alleviating visceral pain. One study showed that percutaneous electrical nerve field stimulation (PENFS) modulated the response characteristics of neurons of the amygdala and the spinal cord and significantly reduced the development of visceral hypersensitivity in rats[187]. Subsequently, the same group showed, in a randomized, sham-controlled trial of 115 adolescents (11–18 years of age) with FAPDs, that PENFS with an active device improved well-being and resulted in a significant reduction in pain and disability compared with the sham-stimulated group[188]. Moreover, the beneficial effects of PENFS were sustained during the 2-month follow-up. Despite some ear discomfort, no serious adverse events were reported. Thus, PENFS seems to be a safe and effective approach and should be considered as a non-pharmacological alternative in children with FAPDs.

Complementary and alternative medicine

Complementary and alternative medicine includes different approaches and methodologies, ranging from acupuncture and ayurvedic medicine to chiropractic therapy, osteopathy, homeopathy, spiritual healing, massage and body–mind techniques like meditation. Approximately 40% of Australian and Dutch children diagnosed with FAPDs use one of these alternative therapies, with herbal remedies being the most common (46%)[189,190]. Many of these complementary therapies are considered 'natural' by the general public and are therefore deemed safer and gentler than the armamentarium of modern medicine. Fear of the adverse effects associated with allopathic medication and the low perceived benefit of conventional treatment in children with FAPDs are potential reasons for parents to seek complementary and alternative therapies[190]. However, to date, RCTs evaluating the effect of herbal therapy, acupuncture, homeopathy, mind–body therapy or musculoskeletal manipulations, such as osteopathic and chiropractic manipulations, in children with FAPDs are not available[170].

Owing to the high spontaneous remission of FAPDs (30–70%), a step-wise approach to management is judicious; education, identification and modification of stress factors and dietary interventions, if necessary, might be the first steps. When symptoms persist or reoccur, the next step could be initiating one of the psychological treatments, such as CBT and hypnotherapy, or PENFS.

Pharmacological therapy

Evidence supporting the efficacy of pharmacological treatments in children with FAPDs is lacking. In addition, the quality of the evidence is generally poor in existing studies, with only a few RCTs assessing the safety and efficacy of the most commonly used drugs (TABLE 1). The quality of these trials are criticized because of their small sample size, limited follow-up, inadequate concealment of allocation, lack of power and the use of non-validated questionnaires[191]. The heterogeneity of study design, study outcomes, inclusion criteria and duration of treatments does not allow the pooling of data to perform a meta-analysis[191]. The treatment effects are also difficult to separate from the placebo response, which is generally known to be high in functional disorders[192], higher in children than in adults[193] and often driven by proxies — parent reports of outcomes in RCTs show placebo effects as if they were the patients[194].

The absence of conclusive data to support treatments based on scientific evidence and the lack of approved medications for the treatment of FAPDs in children challenge the physicians in daily practice. To fill this void, the Rome foundation has published the GI Genius Interactive Clinical Decision Toolkit[195], which is a new, on-demand, online interactive software that combines the diagnostic and treatment decision algorithms to assist physicians in the management of patients with FAPDs. This toolkit was created through consensus of the Rome foundation board of directors and the Rome IV committee[195]. According to this online tool, the use of antispasmodics is recommended as the first-line treatment.

Antispasmodics. Only three RCTs have been conducted on the use of antispasmodics in children. A small, albeit positive, peppermint oil study (randomized double-blind, placebo-controlled trial) in children with IBS may be included in the list of RCTs evaluating antispasmodics[196]. Peppermint oil is assumed to act directly on intestinal smooth muscles or indirectly via receptor blockade on nerves of the intestinal smooth muscles to reduce intestinal contractions, which are deemed to manifest as spasms or cramps in patients with FAPDs. After 2 weeks, 75% of children receiving peppermint oil reported reduced pain intensity compared with the placebo group, although

Table 1 | **Drug treatment trials in children with FAP**

Intervention	Inclusion criteria	Results	Ref.
Antispasmodics			
Trimebutine[a]	Children and adolescents (4–18 years of age), Rome III criteria for IBS	Clinical recovery (in pain or discomfort): 94.9% of children in the treatment group, 20.5% in the control group ($P<0.0001$)	198
Mebeverine[b]	Children with FAP (6–18 years of age)	Response rate (reduction in pain) on ITT analysis: 40.6% with mebeverine, 30.3% with placebo	199
Drotaverine[b]	Children (4–12 years of age), recurrent abdominal pain (Apley criteria)	Decrease in abdominal pain frequency ($P=0.01$); decrease in school absenteeism ($P=0.05$)	200
Poorly absorbed antibiotics			
Rifaximin[b]	Children (3–15 years of age), Rome II criteria for IBS	Benefit in improving abdominal pain, bloating and flatulence ($P<0.005$)	201
Rifaximin[b]	Children with recurrent abdominal pain (8–18 years of age), Rome II criteria	20% of children treated with rifaximin (vs placebo) achieved a normalized repeat LBT; no significant difference in symptom improvement between groups	202
Tricyclic antidepressant			
Amitriptyline[b]	Adolescents with newly diagnosed IBS (12–18 years of age)	Improvement in quality of life at weeks 6, 10 and 13 ($P=0.19$, 0.004 and 0.13, respectively); improvement in periumbilical pain at week 10 ($P=0.018$)	203
Amitriptyline[c]	Children with FAP, functional dyspepsia and IBS (8–17 years of age), Rome II criteria	ITT analysis: in amitriptyline group, 59% of children reported improvements in pain and anxiety; in placebo group, 53% of children reported improvements in pain ($P=0.81$)	204
SSRI antidepressant			
Citalopram[d]	Children and adolescents (7–18 years of age) with recurrent abdominal pain	21 patients; 84% were classified as responders (abdominal pain, anxiety, depression, other somatic symptoms and functional impairment), Clinical Global Impression Scale-Improvement score ≤2	205
Citalopram[b]	Children with FAP (6–18 years of age), Rome III criteria	40.6% of children responded (pain) to treatment, 30.3% responded to placebo at 4 weeks ($P=0.17$); 52.5% of children responded (pain) to treatment, 41% responded to placebo at 8 weeks ($P=0.15$)	206

Adapted from REF.[191]. FAP, functional abdominal pain; IBS, irritable bowel syndrome; ITT, intention to treat; LBT, lactulose breath test; SSRI, selective serotonin reuptake inhibitor. [a]Randomized clinical trial (blinding not specified). [b]Double-blind randomized placebo-control trial. [c]Clinical trial with no placebo control. [d]Open label trial.

none of the antispasmodics routinely used in clinical practice in the USA was studied. Trimebutine is an opioid agonist that induces the release of motilin (which controls the pattern of smooth muscle cell contraction) and modulates the release of vasoactive intestinal peptide, glucagon and gastrin[197]. An RCT found trimebutine to be effective in relieving pain in children with IBS[197,198] (TABLE 1). Additionally, a double-blind placebo-controlled trial in children with FAP-NOS showed significant benefit with the use of mebevirine (an anticholinergic agent that relaxes the intestinal smooth muscles and decreases peristalses) on pain compared with placebo[199]. A 4-week double-blind RCT investigating drotaverine (a non-cholinergic inhibitor) for the treatment of recurrent abdominal pain (Rome criteria were not applied) reported a significant decrease in abdominal pain frequency and absenteeism from school in children receiving drotaverine compared with placebo[200].

Antibiotics. Rifaximin, a non-absorbable antibiotic, has been approved by the FDA for the treatment of IBS in adults[94,197]. An open trial showed that rifaximin significantly improved abdominal pain, bloating and flatulence in a group of 50 children with IBS with an abnormal lactulose breath hydrogen test compared with placebo[201]. Conversely, an RCT in children comparing rifaximin with placebo showed no benefit[202] (TABLE 1). The lack of benefit was attributed to the low percentage of children treated with rifaximin who had normalization of the lactulose breath hydrogen test; therefore, more studies are required. Currently, routine use of rifaximin is not recommended for FAPDs and its use should be balanced against the potential adverse effects, including its potential interference with the establishment of a normal microbiome in young children.

Antidepressants. The Rome IV GI Genius Interactive Clinical Decision Toolkit recommends the use of antidepressants for patients who failed to improve with first-line treatment[195]. An RCT involving adolescents with IBS found benefit in overall quality of life in patients receiving amitriptyline for 13 weeks compared with placebo. However, the study found no improvement in abdominal pain in all quadrants and at all times, although periumbilical pain was reduced at week 10 out of 13 weeks treatment[203]. Furthermore, a large multicentre placebo-controlled RCT found no significant difference in global end points (such as quality of life and pain intensity)

between amitriptyline and placebo after 4 weeks of treament[204]. However, anxiety scores were significantly improved in the amitriptyline group compared with placebo[204]. An open label study conducted in 25 children and adolescents with recurrent abdominal pain (Rome criteria not employed) evaluating the efficacy and safety of citalopram (a selective serotonin reuptake inhibitor) showed a beneficial effect[205], although a subsequent RCT in children with FAP-NOS failed to show significant benefit[206]. Currently, studies assessing the efficacy of antidepressants in other FAPDs are missing. Despite the lack of conclusive scientific evidence, antidepressants are commonly used in clinical practice to manage abdominal pain in children and adolescents. In 2004, the FDA issued a black-box warning following evidence suggesting that anti-depressants might be associated with increased suicidal thoughts and behaviours[207]. Although no data are available that show similar risks with the reduced dosing used for chronic pain treatment, this concern should be addressed with families when children are prescribed antidepressants. In addition, acquiring an electrocardiogram to screen for idiopathic long QT syndrome prior to antidepressant use owing to their potential to prolong the QT interval is commonly practised.

Analgesics and laxatives. Two small studies addressing the efficacy of gabapentin and pregabalin in adults with IBS[208,209] have demonstrated improvement in abdominal pain, urgency and bloating; however, no studies have been conducted in children with IBS so far.

Prucalopride (a 5-HT_4 receptor agonist), lubiprostone (a prostaglandin E_1 derivative) and linaclotide (a guanylate cyclase C agonist) have shown efficacy in the treatment of IBS-C in adults, although no trials have investigated these drugs in children with IBS[85]. However, RCTs in children with functional constipation did not show a significant benefit for prucalopride and lubiprostone compared with placebo[210,211]. As both drugs tend to accelerate transit, their use in IBS-D and in other FAPDs is not indicated.

The paucity of clinical trials, the lack of approved medications and the suboptimal outcomes of current treatments[212] has prompted the Rome Foundation to publish recommendations for clinical trials for IBS in children[213]. These recommendations were reviewed and discussed by a group of paediatric and adult gastroenterologists, psychologists, stakeholders, advocacy groups and members of the pharmaceutical industry at the GREAT 5 meeting in 2018 (REF.[214]). The proceedings of this meeting are due to be published soon.

Quality of life

The severity and frequency of gastrointestinal symptoms have different impacts on the functional status of different patient groups. Patient-reported measures of health-related quality of life (HRQOL) should provide insight into the differential impact of FAPDs on the functional status of children and adolescents, including physical, emotional, behavioural, social and cognitive aspects[215].

Patient-reported outcomes that assess the impact of symptoms and HRQOL have become accepted measures of clinical status and treatment outcomes in adults. However, self-reported HRQOL measures in the paediatric setting have encountered challenges in instrument development and clinical application, in part owing to concerns about children's ability to reliably self-report health-related information.

A number of validated non-disease-specific (generic) HRQOL measures have been developed to measure the impact of paediatric diseases and treatment outcomes[216] (BOX 4). Generic HRQOL measures provide patient metrics that can be compared with standard values established in healthy controls. In an effort to establish validated and calibrated HRQOL item banks in chronic diseases, the National Institutes of Health has launched the Patient Reported Outcomes Measurement Information System (PROMIS)[217]. The PROMIS Paediatric Cooperative Group developed paediatric self-report item banks for children (8–17 years of age) across five generic health domains (physical functioning, pain, fatigue, emotional health and social health)[218]. The PROMIS gastrointestinal symptom items have been developed and validated in adults but are yet to be validated in paediatric patients[219].

HRQOL of paediatric patients with FAPDs can be assessed using generic and/or disease-specific questionnaires. The Paediatric Quality of Life Inventory 4.0 contains both generic core scales and disease-specific modules[220]. The generic core has been validated and is used to compare healthy children and children with various disorders[221–223]. The multidimensional PedsQL Gastrointestinal Symptoms Scale provides a common metric across both functional and organic gastrointestinal diseases and includes parallel child self-report and parent proxy-report formats (for children 5–18 years of age) and proxy reports from parents (for children 2–4 years of age). The scale assesses stomach pain and stomach discomfort during food and drink intake, trouble swallowing, heartburn and reflux, nausea and vomiting, gas and bloating, constipation, blood in stool and diarrhoea. The Gastrointestinal Symptoms Scale has been well validated in functional and organic gastrointestinal diseases and standardized to healthy controls[224–226].

Quantifying individual gastrointestinal symptoms are important to develop patient-centred and symptom-targeted interventions, which can ameliorate the overall HRQOL. For example, one multicentre study of 259 paediatric patients with functional constipation, functional abdominal pain or IBS found that individual gastrointestinal symptoms best predicted impaired overall HRQOL[217].

Using the PedsQL 4.0 Generic Core Scale, a key study compared HRQOL in paediatric patients with FAPD and in children with organic gastrointestinal disease with a sample of healthy controls matched for sex, age and ethnicity[227]. The sample included 689 families of patients with functional and organic gastrointestinal disorders and 1,114 healthy control families. Patients with FAPDs and organic gastrointestinal disease had decreased HRQOL compared with healthy controls. Paradoxically, children with FAPDs demonstrated lower generic HRQOL scores in all dimensions compared with children with organic disease. This finding might

Box 4 | **HRQOL questionnaires for children**

- PedsQL – This is a modular approach measuring HRQOL in healthy and diseased children and adolescents in four domains (physical, emotional, social and school functioning) and three summary scores (total score as well as physical and psychosocial health scores)[220]
- KIDSCREEN – This is a HRQOL questionnaire for children and adolescents (8–18 years of age) that evaluates children's and adolescents' subjective health and well-being[250]
- KINDL – This is a questionnaire-based generic instrument for assessing HRQOL in children and adolescents 3 years of age and older[251]
- GCQ (Generic Children's QOL) – This instrument is used to measure the quality of life in children 6–14 years of age; the GCQ is not symptom-oriented or problem-specific but focuses on areas of interest for all children such as families, peers and school[252]
- HUI (Health Utilities Index) – This tool classifies the health domains into sensation, mobility, pain, cognition, ambulation and emotion. HUI values are a common component of the quality-adjusted life years calculations used in population health and economics[253]
- ITQOL (Infant Toddler QOL Questionnaire) – This questionnaire adopts the WHO definition of health and was developed for use in infants and toddlers from 2 months to 5 years of age[254]
- TAPQOL (TNO-AZL Questionnaire for Preschool Children's Health-Related Quality of Life) – This instrument was developed to meet the need for a reliable and valid instrument for measuring parental perceptions of HRQOL in preschool children[255]
- TACQOL (TNO-AZL Questionnaire for Children's Health-Related Quality of Life) – This questionnaire allows a description of HRQOL of children (6–15 years of age) with chronic diseases via self-reporting or proxy-reporting by parents[256]
- PROMIS (Patient-Reported Outcomes Measurement Information System) – This tool is a set of patient-centred measures that evaluates and monitors physical, mental and social health in healthy individuals and in adults and children with functional disorders[257]

HRQOL, health-related quality of life.

be explained by patient perception of control over the disease process and response shifts on the metric[228]. An important part of quality of life and an aim of FAPD treatment is disability[213]. Disability in children with FAPD includes school absences, not participating in sports or other peer activities, and avoiding chores. The Functional Disability Inventory is the most widely used scale in research and clinical care to measure disability in FAPD[229,230]. The Functional Disability Inventory assesses activity limitations in daily life that have been shown to be responsive to treatment[170].

Assessment of patient-reported symptoms and HRQOL can provide clinical options for families and children to increase their perceived control over symptoms and encourage appropriate behavioural changes in an effort to improve the quality of life of children[228].

Outlook

FAPDs are common in childhood and present the archetypal functional pain disorder with their biopsychosocial paradigm. FAPDs are likely universal and potentially increasing in prevalence and/or complexity. Therefore, well-designed epidemiological studies from across all geographical regions as well as cultural and ethnic communities across the world are needed to truly understand the nature and the size of the problem.

Mechanisms

Of specific importance is our current understanding of the potential factors that contribute to the aetiopathogenesis of FAPDs in children. Basic and translational science research addressing immune dysfunction and nerve dysfunction using tissue samples from paediatric patients with FAPDs are required. As noted above, early-life programming[42], that is, events, generally insults or traumas (psychosocial or medical), occurring at critical stages of development of the various elements of the complex gut–brain axis, has been shown to predispose susceptible individuals to develop FAPDs. Whether this bears any relevance in the development of FAPDs in adults is unclear, although there is reason to believe this might be the case. Early-life history is probably not often sought or might be overlooked in these patients. Whether childhood FAPDs develop into the same or different functional gastrointestinal disorders in adult life is uncertain. Although current evidence suggests that children with FAPDs are more likely to develop psychological or psychiatric morbidities, long-term cohort studies are warranted to address these questions[231–233].

Factors that aberrantly alter gut microbiota may alter the structural or functional integrity of the enteric nervous system and, in turn, their intricate and carefully balanced interactions with the central nervous system. The consequence may be a reprogramming of the gastrointestinal tract towards a hypersensitive state and of the brain towards a hypervigilant state. Of course, other genetic factors, social factors and physiological changes, such as those occurring at puberty or adolescence, might also contribute to symptom development. Currently, the influences of 'modern age', such as digital or social media, omnipresent electronic gadgets and social changes, imparted by these factors are yet to be elucidated. These modern tools are increasingly associated with anxiety and stress[234] and might therefore potentially have a substantial impact on FAPDs. A deeper understanding of all these influences and their timing in relation to triggering the eventual development of FAPDs may facilitate much-needed, enhanced preventive or therapeutic strategies.

Diagnosis

The diagnosis of FAPDs remains a challenge. By the time children are investigated, the early-life insults may have already occurred and changes in pain sensitivity and/or processing might have been established despite the absence of obvious pathology. To date, consensus on the type of investigations, if any, or of the age at which children should be investigated are not available. Clinical evaluation remains the essential mainstay and presently, outside of research, there is little place for routine investigations, especially those that are more invasive.

Management

The long-term outcomes of therapies for paediatric FAPD, such as hypnotherapy, are still being established, with up to ~40% of children continuing to have symptoms despite treatment[235,236]. Certainly, negative prognostic factors, such as chronicity of the FAPD, presence of nausea and/or extraintestinal symptoms, positive family history of FAPDs, and a failure to engage with appropriate therapies or therapists, play a part[231,232,237–239]. Further clarification of the negative prognostic factors that allow the targeting of patients most at need for

intervention as well as better definition and development of optimal and accessible management are required. To facilitate such a stratification, establishing and validating the most appropriate primary outcome measures and specific tools for the assessment of symptoms and response to therapy in the paediatric population remain a prerequisite.

The use pharmacological therapy for the management of FAPDs remains disappointing. Future studies should focus on understanding the factors underlying the magnitude of placebo effects and how these can be minimized in drug trials or harnessed during therapy. Current data, albeit preliminary, suggests that manipulating the gut microbiome at critical time points has potential therapeutic value but this needs further exploration, especially given that no definitive role for probiotics has been indentified[157]. Despite clear evidence of the advantage and efficacy of psychological therapies and social interventions for the management of FAPDs, the authors of the studies acknowledge considerable variability and the availability of these interventions outside large referral centres. The efficacy of psychological therapies needs to be specifically explored in well-designed studies and addressed in the community and across diverse geographical settings. Interestingly, despite their potential contribution to pathogenesis, newer 'digital' technologies might actually be beneficially utilized to address challenges in health care and facilitate the delivery of therapy 'at home'. Future studies should address this avenue, especially given increased limitations on the availability of face-to-face therapies, highlighted by the global coronavirus pandemic. Unfortunately, a number of poor-quality applications claim to be CBT but have not been validated, highlighting the importance of ensuring content expertise as well as an evidence basis for online or digital therapies. Nonetheless, the urgent need for supporting, effective psychosocial interventions for the management of FAPDs should be considered by governmental agencies and health-care organizations as well as by policymakers working in conjunction with physicians.

Although subdividing FAPDs into distinct disorders is essential, further research into the identification of biological signatures (biomarkers) to compliment or supersede symptom-based phenotyping or even to further define the conditions is critical to progressing the field. Perhaps one of the greatest challenges continues to be the use and abuse of the umbrella term 'functional'. This term was meant to indicate that the gut, albeit healthy, functions differently. However, this term is often misinterpreted as 'fictional' by so many primary care physicians, paediatricians and gastroenterologists alike and seems to reinforce a rather mystical view of the entity of FAPDs. This mix-up is especially challenging given that many FAPDs result from or coexist with distinct organic pathologies such as coeliac disease and inflammatory bowel disease. From our experience, patients and their families often describe a history of battling insinuations of malingering or fabrication. In acknowledgement of distinct, albeit subtle, pathologies underlying what can be devastating disorders as described in this Primer, the Rome committee has recommended functional gastrointestinal disorders, of which FAPDs are a subset of, to be renamed as 'disorders of gut–brain interaction'. Whether this renaming will remove the associated stigma remains to be ascertained. The stigma associated with these disorders is not due to a confusion of the term; other terminologies prior to 'functional' were also stigmatizing, including unexplained or psychosomatic disorders. If physicians continue focusing on biological causes as the only valid reason for symptoms, disorders of gut–brain interactions will soon be perceived as invalid and 'just in one's head'. Focusing solely on biological causes is a disservice not only to this patient population but to all diseases and disorders.

Overall, FAPDs in children have seen considerable progress in the last decade, with the hope that this will herald tangible steps towards harmonizing approaches to classify, diagnose and manage these challenging, often perplexing, conditions.

Published online: 05 November 2020

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Acknowledgements

R.J.S. acknowledges the funding R01 NR013497 and R01 NR016786 from the National Institutes of Health, the USDA/ARS under Cooperative Agreement No. 58-3092-0-001, and P30 DK56338, which funds the Texas Medical Center Digestive Disease Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This work is a publication of the USDA/ARS Children's Nutrition Research Center, Department of Paediatrics, Baylor College of Medicine and Texas Children's Hospital. The contents do not necessarily reflect the views or policies of the USDA nor does the mention of trade names, commercial products or organizations imply endorsement by the US Government.

Author contributions

Introduction (P.E. and N.T.); Epidemiology (P.E., I.M. and N.T.); Mechanisms/pathophysiology (S.N., H.S., M.A.L.v.T. and N.T.); Diagnosis, screening and prevention (C.D.L. and M.A.L.v.T.); Management (M.A.B., M.S. and R.J.S.); Quality of life (M.D.C.); Outlook (N.T.); Overview of Primer (P.E. and N.T.).

Competing interests

N.T. has received grants, membership on advisory boards, speaker fees or travel support from Danone, Nutricia and Takeda. M.A.B. has received grants, membership on advisory boards, speaker fees or travel support from Abbott, Allergan, Coloplast, Danone, Friesland Campina, HIPP, Johnson & Johnson, Norgine, Shire, Sucampo and United Pharmaceuticals. C.D.L. has received grants, membership on advisory boards, speaker fees or travel support from Allergan, Mahana, Mallinckrodt, QOL, Sucampo and Takeda. M.S. has received grants, membership on advisory boards, speaker fees or travel support from Abbott, Allergan, Forest, QOL and Sucampo. H.S. has received grants, membership on advisory boards, speaker fees or travel support from Arla, Biocodex, Biogaia, Ch.Hansen, Danone, Merck, Nestlé and Nutricia. M.A.L.v.T. has received consultancy fees from Mahana. P.E. has received grants, membership on advisory boards, speaker fees or travel support from Alimentary Health, Aptinyx, Arena, Biocodex, CEMET, Danone, Genetic Analysis, Indigo, Merz, MDC, Sanofi, SymbioPharm and 4DPharma. All other authors declare no competing interests.

Peer review information

Nature Reviews Disease Primers thanks Christopher Eccleston, Anne Lynch-Jordan, Emeran Mayer and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.