gastrointestinal disorders

MDPI

Editorial

Editorial: Pediatric Functional Gastrointestinal Disorders: Challenges in Diagnosis and Treatment

Angharad Vernon-Roberts [1,*], Mark Safe [2] and Andrew S. Day [1]

[1] Department of Paediatrics, University of Otago Christchurch, Christchurch 8011, New Zealand; andrew.day@otago.ac.nz
[2] Department of Paediatric Gastroenterology, Royal Children's Hospital, Melbourne, VIC 3052, Australia
* Correspondence: angharad.hurley@otago.ac.nz

Functional gastrointestinal disorders (FGIDs) are classified as those with no organic cause and those not attributable to structural or biochemical abnormalities [1]. FGIDs are also defined as 'Disorders of Gut–Brain Interaction' [2]. The etiology of FGID is multifactorial and may include altered brain–gut interactions, genetic predisposition, dysbiosis, dysregulation of the intestinal barrier, and environmental factors [3,4]. FGIDs are characterized by chronic gastrointestinal symptoms and occur in a high proportion of children. FGIDs account for approximately 5% of presentations to primary care physicians [5] and are the cause of many referrals to tertiary care services for further investigation or to exclude serious organic disease [6]. Pediatric FGIDs are now considered to be a global health problem associated with high healthcare utilization and psycho-socioeconomic burden for families [7]. Children with FGIDs have been shown to have lower health-related quality of life (HRQoL) and experience interference with sleep, school, and social activities, thereby representing significant symptom burden as well as other sequelae [1,8–10]. There are many facets of ongoing research into pediatric FGIDs, and the aim of this Special Issue is to gather evidence of the challenges in diagnosing and treating FGIDs in children and to add to the growing body of evidence advancing the topic.

An important aspect of assessing the burden of any condition in a population is to study the epidemiology, either as the incidence of new diagnoses during a time period, or the prevalence of those who are assessed as having the condition. The standardization of these assessments is vital to gain a true representation of the burden of FGIDs throughout the world and to compare epidemiology over time or between regions. The most widely known and implemented of the FGID tools are the Rome IV assessments—symptom based criteria with versions available for neonates/toddlers and children/adolescents [11,12]. With the widespread implementation of the Rome criteria has come the opportunity to compare epidemiological trends. It has been reported that approximately 22% of children in both age cohorts (neonates/toddlers and children/adolescents) experience at least one FGID, with some of the highest rates reported in the Americas [13,14]. There is little published epidemiological data available worldwide. In this Special Issue, Vernon-Roberts et al. addressed this gap in New Zealand by measuring the prevalence of FGID in a cohort of New Zealand children attending a tertiary care hospital while concurrently measuring HRQoL. This research showed that 29% of the children aged four years of age or more, within the population studied, had FGID, with the most common being functional constipation and functional dyspepsia. The presence of FGID was not found to be related to HRQoL overall, but within the domain of 'feeling sad, worried or unhappy', there was an association between having FGID and scoring lower in this domain than those without FGID. Of note was that associations were also seen between having an FGID and being of Māori ethnicity, the indigenous population of New Zealand who have known health disparities compared to other ethnic groups. Having a parent with self-reported FGID was also associated with children having FGID.

check for updates

Citation: Vernon-Roberts, A.; Safe, M.; Day, A.S. Editorial: Pediatric Functional Gastrointestinal Disorders: Challenges in Diagnosis and Treatment. *Gastrointest. Disord.* **2024**, *6*, 308–312. https://doi.org/10.3390/gidisord6010021

Received: 5 March 2024
Accepted: 6 March 2024
Published: 8 March 2024

The management of FGID in children can be challenging, as there is considerable variation in the diagnostic categories, thereby preventing a universal approach. According to the Rome IV criteria for children less than 12 months of age, the most common FGIDs have been shown to be infant regurgitation and functional constipation, and for toddlers aged 13-48 months, the most common is functional constipation, with approximately 22% in both age groups experiencing at least one FGID [14]. Infants experiencing FGID are shown to have a lower weight, shorter breast-feeding duration, and are more likely to be formula-fed or have been introduced to cow's milk before those without FGID [15–17]. Infants with FGID are also more likely to have behavioral or developmental problems, migraines, and future GI disorders [16]. Given that these sequalae are deleterious to infant health and longitudinal outcomes, effective symptom management is vital. In this Special Issue, Rishanghan et al. provide a comprehensive overview of the management of FGID in infancy. For each infant FGID, the paper summarizes the possible organic differential diagnoses, outlines the indicative symptoms, and provides a literature review of treatment and management strategies. The findings highlight the importance of clear education and guidelines for parents/families of infants presenting with FGID and summarizes that the management approach is predominantly based around providing parental reassurance.

Pediatric feeding disorders are another common group of problems facing children, parents, and clinicians. While no direct link has been established between the presence of FGID and feeding disorders, many children with FGID have symptoms induced by eating specific foods and may subsequently practice food avoidance or meal modification [4]. Pediatric feeding disorders have been defined as impaired oral intake that is associated with medical, feeding skill, nutritional, and/or psychosocial dysfunction [18]. Feeding disorders may have multiple etiologies, with influencing factors including medical, nutritional, behavioral, psychological, and environmental causes [19]. Feeding disorders among children are common, with the reported prevalence being 25% in all children, and 80% in children with developmental disabilities [19]. Between 3 and 10% of children will go on to develop chronic feeding issues that may be associated with a number of negative medical and developmental outcomes [20]. In this Special Issue, Dharmaraj et al. provide a guideline for the evaluation and management of pediatric feeding disorders, with overviews of associated medical conditions, diagnostic criteria, and initial evaluation and assessment methods. They provide a multifactorial management approach with the aim to increase oral intake, reduce tube feeding, improve eating behaviors, and reduce parental stress through interdisciplinary intervention.

With the high prevalence of FGID in the pediatric population, effective interventions that may help us to ameliorate symptoms are required. However, intervention studies have been hampered by small sample sizes and limited effect sizes. Pharmacological treatments such as anti-depressants, anti- or synbiotics, anti-spasmodics, and anti-emetics have shown limited benefits [21]. There is also a lack of high quality nutritional intervention trials in children for diets such as the low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet, the fructose- or lactose-restricted diet (FRD/LRD), and the gluten-free diet. For this reason, and due to the risk of nutritional inadequacy or disorder eating behaviors, these have been stated as having no or limited place in daily clinical practice for FGID in children [22,23]. Showing greater promise are non-pharmacological interventions such as hypnotherapy, cognitive behavioral therapy (CBT), probiotics, and fiber supplements [24]. Specifically within the FGID of functional abdominal pain (FAP), pharmacological intervention studies have been hampered by small sample sizes and minimal effects [25]. Some patients, specifically those with irritable bowel syndrome (IBS) and FAP, may experience some benefit from low FODMAP or FRD/LRD [22]. However, CBT has shown more promise in reducing symptoms and improving HRQoL, among other outcomes [26,27]. Group education among adults with IBS has also been shown to be effective at reducing symptoms and increasing HRQoL, but this has not been trialed in children [28]. To address this gap in knowledge, in this Special Issue, Löfgren et al. reported on a feasibility study of group education for children and adolescents

with FAP. Twenty-three parent/child dyads participated in the intervention that consisted of two lecture sessions delivered by a pediatric gastroenterologist, a psychologist, and a dietitian. This group education was shown to be feasible and acceptable to participants and was effective at increasing knowledge and HRQoL, and reducing symptoms and food avoidance behavior.

A diagnosis of FGID requires an appropriate medical evaluation to ensure that symptoms cannot be attributed to another medical condition [12]. With a number of cross-over symptoms between FGID and organic GI conditions, and the co-existence of FGID and some medical conditions such as inflammatory bowel disease [29], alarm symptoms that may be indicative of organic conditions warrant particular attention. While the latest Rome IV criteria advocate for selective or no testing to support a positive diagnosis of an FGID [12], children and adolescents presenting with alarm symptoms of organic conditions may undergo invasive clinical investigations as part of the elimination process. In particular, for children with FAPDs, the most common of which are IBS and functional dyspepsia (FD), investigations such as upper endoscopy may be utilized to exclude *Helicobacter pylori* infection, and to assess for inflammation, although the presence of inflammation or eosinophilia does not rule out FD [30,31]. One alarm symptom that has been historically used to predict diagnostic yield on endoscopy for children with symptoms indicative of FD is nocturnal pain. However, the evidence in support of this being an indication to support performing an upper endoscopy is limited [32,33]. The symptom of nocturnal pain was further investigated by Cindrich et al. in this Special Issue, with the finding that this particular alarm symptom was not associated with esophageal, gastric, or duodenal histologic inflammation. Nocturnal pain was, however, associated with increased social stress, depression, disordered sleep, excessive daytime sleepiness, and night sweats. The study conclusion was that nocturnal pain is not useful to predict upper gastrointestinal inflammation but that this symptom should be used to facilitate the further exploration of psychosocial well-being and sleep disturbances.

While work continues in the realm of identifying and managing pediatric FGID, a focus has also been drawn on identifying causes and risk factors to try and identify those more likely to develop FGID in order to develop preventative strategies [7]. One area of particular interest is the gut microbiota, with disruption of the microbial equilibrium (known as dysbiosis) known to play a role in the development of FGID [34]. The gut microbiota in children with FGID has been reported to differ from healthy controls [35] and modulation of the microbiota using pre- and pro-biotics may lead to improved HRQoL for those with FGID [3]. While dysbiosis in children may be caused by a number of factors, such as gastrointestinal infections, organic disease, and treatment with antibiotics [36,37], dysbiosis may also occur in neonates due to factors such as maternal diet during pregnancy, delivery mode, prematurity, breast feeding, and antibiotic exposure [36]. Although the uterine/placental microbiome does not seem to be associated with the neonatal microbiome [36], in this Special Issue, Smith et al. have provided a thorough review of the inheritance of the maternal microbiome and the opportunities for early identification and intervention to prevent future childhood FGIDs. In this paper, the importance of the initial 'handshaking' between the maternal and neonatal microbiome is explained as being vital to the proper development of the brain–gut axis and causes of disruption in this process have been outlined. While the optimal microbiome components for neonates at birth are yet to be elucidated, this paper proposes that, once identified, a 'birth probiotic' could be developed and could provide neonates with the essential microbes that may be preventative of later FGID.

The work presented in this Special Issue has contributed to the ever-growing body of literature on pediatric FGID from many facets. The ongoing collection of epidemiological data will allow the global burden of FGID to be assessed and updated, thus allowing for increased awareness to facilitate research on both effective management and preventative strategies. Outlining management strategies for FGID among infants and for those with feeding disorders may help to ameliorate symptoms and reduce the associated negative

child and parental health and psychosocial outcomes. Further research to identifying effective interventions and reduce invasive investigations should be prioritized to reduce healthcare utilization. Preventative strategies such as identifying the essential neonatal microbes for future health will be essential in reducing the global burden of pediatric FGID. A large proportion of children with FGID are known to have symptoms that persist into adulthood, in particular FAP [7,38–40], and early-life risk factor identification and prevention must be prioritized.

Author Contributions: Conceptualization, A.V.-R., M.S. and A.S.D.; methodology, A.V.-R., M.S. and A.S.D.; resources, A.V.-R., M.S. and A.S.D.; writing—original draft preparation, A.V.-R.; writing—review and editing, M.S. and A.S.D.; project administration, A.V.-R., M.S. and A.S.D. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Lewis, M.L.; Palsson, O.S.; Whitehead, W.E.; van Tilburg, M.A.L. Prevalence of Functional Gastrointestinal Disorders in Children and Adolescents. *J. Pediatr.* **2016**, *177*, 39–43.e3. [CrossRef]
2. Drossman, D.A.; Hasler, W.L. Rome IV—Functional GI Disorders: Disorders of Gut-Brain Interaction. *Gastroenterology* **2016**, *150*, 1257–1261. [CrossRef]
3. Giorgio, V.; Margiotta, G.; Stella, G.; Di Cicco, F.; Leoni, C.; Proli, F.; Zampino, G.; Gasbarrini, A.; Onesimo, R. Intestinal Permeability in Children with Functional Gastrointestinal Disorders: The Effects of Diet. *Nutrients* **2022**, *14*, 1578. [CrossRef] [PubMed]
4. Carlson, M.J.; Moore, C.E.; Tsai, C.M.; Shulman, R.J.; Chumpitazi, B.P. Child and Parent Perceived Food-Induced Gastrointestinal Symptoms and Quality of Life in Children with Functional Gastrointestinal Disorders. *J. Acad. Nutr. Diet.* **2014**, *114*, 403–413. [CrossRef]
5. Gieteling, M.J.; Lisman-van Leeuwen, Y.; van der Wouden, J.C.; Schellevis, F.G.; Berger, M.Y. Childhood Nonspecific Abdominal Pain in Family Practice: Incidence, Associated Factors, and Management. *Ann. Fam. Med.* **2011**, *9*, 337–343. [CrossRef] [PubMed]
6. Martins, G.P.; Sandy, N.S.; Alvarenga, L.R.; Lomazi, E.A.; Bellomo-Brandão, M.A. Functional abdominal pain is the main etiology among children referred to tertiary care level for chronic abdominal pain. *Arq. Gastroenterol.* **2022**, *59*, 97–101. [CrossRef]
7. Lu, P.L.; Saps, M. Functional Gastrointestinal Disorders: All Roads Lead to Prevention. *Clin. Gastroenterol. Hepatol.* **2018**, *16*, 814–816. [CrossRef]
8. Jansen, J.; Shulman, R.; Ward, T.M.; Levy, R.; Self, M.M. Sleep disturbances in children with functional gastrointestinal disorders: Demographic and clinical characteristics. *J. Clin. Sleep Med.* **2021**, *17*, 1193–1200. [CrossRef]
9. Saps, A.M.; Velasco-Benitez, J.J.C.; Blom, A.P.; Benninga, X.M.; Nichols-Vinueza, X.D. Prospective Study of Gastrointestinal Symptoms in School Children of South America. *J. Pediatr. Gastroenterol. Nutr.* **2018**, *66*, 391–394. [CrossRef]
10. Varni, J.W.; Bendo, C.B.; Denham, J.; Shulman, R.J.; Self, M.M.; Neigut, D.A.; Nurko, S.; Patel, A.S.; Franciosi, J.P.; Saps, M.; et al. PedsQL™ Gastrointestinal Symptoms Scales and Gastrointestinal Worry Scales in pediatric patients with functional and organic gastrointestinal diseases in comparison to healthy controls. *Qual. Life Res.* **2015**, *24*, 363–378. [CrossRef] [PubMed]
11. Benninga, M.A.; Faure, C.; Hyman, P.E.; St James Roberts, I.; Schechter, N.L.; Nurko, S. Childhood Functional Gastrointestinal Disorders: Neonate/Toddler. *Gastroenterology* **2016**, *150*, 1443–1455.e2. [CrossRef]
12. Hyams, J.S.; Di Lorenzo, C.; Saps, M.; Shulman, R.J.; Staiano, A.; van Tilburg, M. Functional Disorders: Children and Adolescents. *Gastroenterology* **2016**, *150*, 1456–1468. [CrossRef]
13. Velasco-Benitez, C.A.; Collazos-Saa, L.I.; Garcia-Perdomo, H.A. A systematic review and meta-analysis in schoolchildren and adolescents with functional gastrointestinal disorders according to Rome IV criteria. *Arq. Gastroenterol.* **2022**, *59*, 304–313. [CrossRef] [PubMed]
14. Vernon-Roberts, A.; Alexander, I.; Day, A.S. Systematic Review of Pediatric Functional Gastrointestinal Disorders (Rome IV Criteria). *J. Clin. Med.* **2021**, *10*, 5087. [CrossRef] [PubMed]
15. Bellaiche, M.; Oozeer, R.; Gerardi-Temporel, G.; Faure, C.; Vandenplas, Y. Multiple functional gastrointestinal disorders are frequent in formula-fed infants and decrease their quality of life. *Acta Paediatr.* **2018**, *107*, 1276–1282. [CrossRef] [PubMed]
16. Vandenplas, Y.; Abkari, A.; Bellaiche, M.; Benninga, M.; Chouraqui, J.P.; Çokura, F.; Harb, T.; Hegar, B.; Lifschitz, C.; Ludwig, T.; et al. Prevalence and Health Outcomes of Functional Gastrointestinal Symptoms in Infants from Birth to 12 Months of Age. *J. Pediatr. Gastroenterol. Nutr.* **2015**, *61*, 531–537. [CrossRef] [PubMed]
17. Campeotto, F.; Marie-Odile, B.; Hospital, V. Functional Gastrointestinal Disorders in Outpatients Aged up to 12 Months: A French Non-Interventional Study. *Int. J. Environ. Res. Public Health* **2020**, *17*, 4031. [CrossRef] [PubMed]
18. Goday, P.S.; Huh, S.Y.; Silverman, A.; Lukens, C.T.; Dodrill, P.; Cohen, S.S.; Delaney, A.L.; Feuling, M.B.; Noel, R.J.; Gisel, E.; et al. Pediatric Feeding Disorder: Consensus Definition and Conceptual Framework. *J. Pediatr. Gastroenterol. Nutr.* **2019**, *68*, 124–129. [CrossRef] [PubMed]
19. Manikam, R.; Perman, J.A. Pediatric Feeding Disorders. *J. Clin. Gastroenterol.* **2000**, *30*, 34–46. [CrossRef] [PubMed]

20. Sharp, W.G.; Jaquess, D.L.; Morton, J.F.; Herzinger, C.V. Pediatric Feeding Disorders: A Quantitative Synthesis of Treatment Outcomes. *Clin. Child Fam. Psychol. Rev.* **2010**, *13*, 348–365. [CrossRef]
21. Crawford, J.; Tran, P.; Shaw, J.S.; Shaw, R.J. Current Pharmacological Treatments for Childhood-Onset Somatic Symptom and Related Disorders (SSRD) and Functional Gastrointestinal Disorders (FGID). *Curr. Treat. Options Psychiatry* **2020**, *7*, 120–143. [CrossRef]
22. Katsagoni, C.N.; Vasiliki-Maria, K.; Papadopoulou, A. Efficacy of Different Dietary Patterns in the Treatment of Functional Gastrointestinal Disorders in Children and Adolescents: A Systematic Review of Intervention Studies. *Nutrients* **2023**, *15*, 2708. [CrossRef]
23. Thomassen, R.A.; Luque, V.; Assa, A.; Borrelli, O.; Broekaert, I.; Dolinsek, J.; Martin-De-Carpi, J.; Mas, E.; Miele, E.; Norsa, L.; et al. An ESPGHAN Position Paper on the Use of Low-FODMAP Diet in Pediatric Gastroenterology. *J. Pediatr. Gastroenterol. Nutr.* **2022**, *75*, 356–368. [CrossRef]
24. Rutten, J.M.T.M.; Korterink, J.J.; Venmans, L.M.A.J.; Benninga, M.A.; Tabbers, M.M. Nonpharmacologic Treatment of Functional Abdominal Pain Disorders: A Systematic Review. *Pediatrics* **2015**, *135*, 522–535. [CrossRef] [PubMed]
25. Martin, A.E.; Newlove-Delgado, T.V.; Abbott, R.A.; Bethel, A.; Thompson-Coon, J.; Whear, R.; Logan, S. Pharmacological interventions for recurrent abdominal pain in childhood. *Cochrane Database Syst. Rev.* **2017**, CD010973. [CrossRef] [PubMed]
26. Bonnert, M.; Olén, O.; Lalouni, M.; Benninga, M.A.; Bottai, M.; Engelbrektsson, J.; Hedman, E.; Lenhard, F.; Melin, B.; Simrén, M.; et al. Internet-Delivered Cognitive Behavior Therapy for Adolescents with Irritable Bowel Syndrome: A Randomized Controlled Trial. *Am. J. Gastroenterol.* **2017**, *112*, 152–162. [CrossRef]
27. Lalouni, M.; Ljótsson, B.; Bonnert, M.; Ssegonja, R.; Benninga, M.; Bjureberg, J.; Högström, J.; Sahlin, H.; Simrén, M.; Feldman, I.; et al. Clinical and Cost Effectiveness of Online Cognitive Behavioral Therapy in Children with Functional Abdominal Pain Disorders. *Clin. Gastroenterol. Hepatol.* **2019**, *17*, 2236–2244.e11. [CrossRef]
28. Labus, J.; Gupta, A.; Gill, H.K.; Posserud, I.; Mayer, M.; Raeen, H.; Bolus, R.; Simren, M.; Naliboff, B.D.; Mayer, E.A. Randomised clinical trial: Symptoms of the irritable bowel syndrome are improved by a psycho-education group intervention. *Aliment. Pharmacol. Ther.* **2013**, *37*, 304–315. [CrossRef]
29. Diederen, K.; Hoekman, D.R.; Hummel, T.Z.; de Meij, T.G.; Koot, B.G.; Tabbers, M.M.; Vlieger, A.M.; Kindermann, A.; Benninga, M.A. The prevalence of irritable bowel syndrome-type symptoms in paediatric inflammatory bowel disease, and the relationship with biochemical markers of disease activity. *Aliment. Pharmacol. Ther.* **2016**, *44*, 181–188. [CrossRef]
30. Shava, U.; Srivastava, A.; Mathias, A.; Kumar, N.; Yachha, S.K.; Gambhir, S.; Poddar, U. Functional dyspepsia in children: A study of pathophysiological factors. *J. Gastroenterol. Hepatol.* **2021**, *36*, 680–686. [CrossRef] [PubMed]
31. Wauters, L.; Nightingale, S.; Talley, N.J.; Sulaiman, B.; Walker, M.M. Functional dyspepsia is associated with duodenal eosinophilia in an Australian paediatric cohort. *Aliment. Pharmacol. Ther.* **2017**, *45*, 1358–1364. [CrossRef]
32. Thakkar, K.; Chen, L.; Tessier, M.E.; Gilger, M.A. Outcomes of Children After Esophagogastroduodenoscopy for Chronic Abdominal Pain. *Clin. Gastroenterol. Hepatol.* **2014**, *12*, 963–969. [CrossRef]
33. de Assis Carvalho, M.; Nascimento Hercos, G.N.H.; Corrêa Silva, R.G.; Machado, N.C. Children Dyspepsia Symptoms Questionnaire Discriminates Dyspeptic versus Non-Dyspeptic and Organic versus Functional Dyspepsia in Children and Adolescents with Chronic Abdominal Pain. *Eur. J. Med. Health Sci.* **2022**, *4*, 70–76. [CrossRef]
34. Wei, L.; Singh, R.; Ro, S.; Ghoshal, U.C. Gut microbiota dysbiosis in functional gastrointestinal disorders: Underpinning the symptoms and pathophysiology. *JGH Open* **2021**, *5*, 976–987. [CrossRef] [PubMed]
35. Hofman, D.; Kudla, U.; Miqdady, M.; Thi Viet Ha, N.; Morán-Ramos, S.; Vandenplas, Y. Faecal Microbiota in Infants and Young Children with Functional Gastrointestinal Disorders: A Systematic Review. *Nutrients* **2022**, *14*, 974. [CrossRef] [PubMed]
36. Guo, J.; Han, X.; Huang, W.; You, Y.; Zhan, J. Gut dysbiosis during early life: Causes, health outcomes, and amelioration via dietary intervention. *Crit. Rev. Food Sci. Nutr.* **2022**, *62*, 7199–7221.
37. McDonnell, L.; Gilkes, A.; Ashworth, M.; Rowland, V.; Harries, T.H.; Armstrong, D.; White, P. Association between antibiotics and gut microbiome dysbiosis in children: Systematic review and meta-analysis. *Gut Microbes* **2021**, *13*, 1870402. [CrossRef]
38. Horst, S.; Shelby, G.; Anderson, J.; Acra, S.; Polk, D.B.; Saville, B.R.; Garber, J.; Walker, L.S. Predicting Persistence of Functional Abdominal Pain from Childhood into Young Adulthood. *Clin. Gastroenterol. Hepatol.* **2014**, *12*, 2026–2032. [CrossRef] [PubMed]
39. Jarrett, M.; Heitkemper, M.; Czyzewski, D.I.; Shulman, R. Recurrent Abdominal Pain in Children: Forerunner to Adult Irritable Bowel Syndrome? *J. Spec. Pediatr. Nurs.* **2003**, *8*, 81–89. [CrossRef] [PubMed]
40. Walker, L.S.; Sherman, A.L.; Bruehl, S.; Garber, J.; Smith, C.A. Functional abdominal pain patient subtypes in childhood predict functional gastrointestinal disorders with chronic pain and psychiatric comorbidities in adolescence and adulthood. *Pain* **2012**, *153*, 1798–1806. [CrossRef] [PubMed]