Elevated fecal calprotectin is linked to psychosocial complexity in pediatric functional abdominal pain disorders

Erin L. Moorman1*, Michael Farrell2,3, Neha Santucci2,3, Lee Denson2,3, Christine Le4 and Natoshia R. Cunningham5

Abstract

Objective: Children with functional abdominal pain disorders (FAPD) and clinical elevations in three risk areas (anxiety, functional disability, and pain) have been found to be at increased risk for persistent disability. We evaluated if the presence of these three risk factors corresponded with greater gastrointestinal inflammation (measured via fecal calprotectin; FC) compared to those with no risk factors. FC concentration differences between children with three risk factors and those with one and two risk factors were explored.

Results: Fifty-six children with FAPD (M age = 12.23) completed measures of anxiety (Screen for Child Anxiety Related Disorders), disability (Functional Disability Inventory), and pain intensity (Numeric Rating Scale). Participants were stratified into risk groups (range: 0–3). Fisher’s exact tests were conducted to determine if children with three versus fewer risk factors were more likely to have elevated FC (≥ 50 µg/g) versus normal levels. Children with three risk factors (M FC = 86.04) were more likely to have elevated FC compared to children with zero (M FC = 25.78), one (M FC = 38.59), and two risk factors (M FC = 45.06; p’s < 0.05). Those with three risk factors had borderline elevated FC concentrations whereas those with fewer had normal FC concentrations. Findings suggest the importance of a biopsychosocial approach to help elucidate a FAPD phenotype.

Keywords: Fecal calprotectin, Functional disability, Anxiety

Functional abdominal pain disorders (FAPD) are gastrointestinal (GI) conditions characterized by frequent abdominal pain episodes not attributed to an organic cause [1]. FAPD occurs in approximately 11–15% of all children and adolescents worldwide [2], and 25–45% experience persistent (i.e., > 5 years) pain and functional impairment [3]. A biopsychosocial approach may be helpful for understanding and assessing pediatric FAPD [4–6], as the presence of certain psychosocial risk factors (i.e., anxiety) are associated with increased functional impairment in children with FAPD [7–9]. Further, those who present with clinical elevations in three domains (i.e., anxiety, pain, and pain-related disability) are at increased risk for persistent disability [7, 8]. However, it is unknown how biological factors, such as GI inflammation, may relate to this complex clinical presentation of FAPD.

Although FAPD are typically thought to be non-inflammatory [10–12], low-grade GI inflammation may be present, and may relate to greater functional disability [13]. The goal of the current study is to establish the relationship between psychological and biological factors associated with complex FAPD. We predicted that the most clinically complex FAPD group (i.e., those characterized by clinically elevated anxiety, disability, and pain levels)
[7, 8] would have clinically elevated fecal calprotectin (FC) levels, a GI inflammatory biomarker, compared to those in the lowest risk group (i.e., those with no elevations in anxiety, disability, and pain). We also explored differences in FC concentrations based on numbers of risk factors (ranging from 0 to 3).

Main text

Methods

Clinical data were gathered from 56 children between the ages of 9–14 with FAPD from a large Midwestern children’s hospital using de-identified data as a part of an Institutional Review Board approved process. These youth were also involved in prior studies examining (1) clinical characteristics of youth with FAPD [7–9], (2) neuroimaging of pain, or (3) behavioral interventions for FAPD [14, 15]. The participant’s gastroenterologist confirmed that the patient met criteria for FAPD based on ROME IV guidelines and also performed an FC assay. Patients were ineligible if they had a significant medical condition(s) with an identifiable organic cause or a documented developmental delay. Participants did not have an active infection at the time of study enrollment.

Measures

Demographic and background information

Demographic (e.g., age, sex) and background information (e.g., abdominal pain location) was collected from the parent and from the patient’s electronic medical record (EMR).

Fecal calprotectin (FC)

Fecal calprotectin is a biomarker of neutrophilic intestinal inflammation and is commonly assayed to evaluate a patient’s risk for inflammatory bowel disease (IBD) [16]. FC concentrations are obtained via a fecal assay and, due to a high negative predictive value to exclude IBD, have been used to differentiate IBD from functional GI conditions [17]. FC has greater sensitivity (70%) and specificity (93%) in children than adults [18]. To obtain FC concentrations, participants provided a stool sample as part of their clinical care. The Inova Quanta Lite® Calprotectin ELISA assay was used to test FC levels. These values were recorded in the participants’ EMR and obtained via chart review. Manufacturer-recommended clinical cut-offs for interpreting FC concentrations include normal (< 50 µg/g), borderline (50–120 µg/g), and abnormal (> 120 µg/g).

Clinical risk

Participants were stratified into risk groups (range: 0–3) based on their scores on the measures detailed below. These measures were administered as part of their clinical care to determine risk status [7, 15]. Clinical elevations in all three domains listed below were defined as the most clinically complex FAPD group. This approach has been shown to identify patients at greatest risk for pain-related impairment over time [7].

Screen for Child Anxiety Related Disorders—Child Report (SCARED) [19, 20]

A 41-item measure (total score range: 0–82) that assesses anxiety symptoms. It has been validated in pediatric chronic pain samples [21, 22] and is used to screen for anxiety in children with FAPD [8, 15]. A cut-off of ≥ 25 is indicative of clinically significant anxiety [19, 20] and has been shown to correspond to increased pain-related impairment and pain levels in youth with chronic pain including FAPD [7, 8, 14, 15]. Therefore, this cut-off was used to determine presence of risk in the current study.

Functional Disability Inventory—Child Version (FDI) [23]

A validated measure of daily functional impairment due to pain symptoms. The FDI consists of 15 items (total score range: 0–60) and has established cut-offs [24]. Participants with at least moderate disability (FDI ≥ 13) were considered clinically elevated.

Numeric Rating Scale (NRS) Pain Intensity [25]

Participants rated their average pain intensity over the past 2 weeks using a scale ranging from 0 to 10, with higher scores indicating higher pain levels. Participants reporting at least moderate pain (NRS ≥ 4) were considered clinically elevated.

Additional clinical data

Erythrocyte sedimentation rates (ESR), c-reactive protein (CRP), albumin, immunoglobulin A (IgA), and anti-tissue transglutaminase antibodies (tTG-IgA) are laboratory markers commonly obtained via blood test for differential diagnostic purposes in GI clinics [26, 27]. ESR and CRP are sometimes used by providers to help establish a diagnosis of IBD. ESR, the rate at which erythrocytes settle in a blood sample, indicates inflammation in the body and has been shown to correlate with clinical activity in individuals with IBD [28]. CRP is a protein produced by the liver that is released into the bloodstream often after inflammation onset [29]. It has also been associated with clinical activity in pediatric IBD, particularly with Crohn’s disease [29]. The tTG-IgA test is positive in about 98% of patients with celiac disease on a gluten-containing diet and is therefore used to rule out celiac disease [30]. A total serum IgA test is used to detect whether or not a patient has an IgA deficiency, which is associated with celiac disease and can result in a false negative tTG-IgA finding [30]. Esophagogastroduodenoscopies (EGDs) and colonoscopies are sometimes administered for pediatric patients with GI complaints for the diagnosis of a range
of organic GI conditions, like IBD and celiac disease [31]. They allow for the visualization of the digestive tract and can be used to obtain biopsies [31]. Tests were offered at the discretion of each patient’s gastroenterologist to rule out IBD and were individualized based on the patient’s presenting symptoms. In general, patients with FC concentrations > 250 µg/g and epigastric abdominal pain in the absence of weight loss and anemia were also routinely administered an EGD.

**Data analytic approach**

Data were analyzed using SPSS version 27 [32]. The data are available from the corresponding author on reasonable request. Item level data were available for all participants but one that was missing SCARED data; thus, no statistical adjustments for missing data were made. Descriptives were used to examine demographic and clinical characteristics and to categorize youth by presence of clinical elevations in anxiety, disability, and pain (ranging from 0 to 3) [7]. Normality of data was assessed. As expected, FC concentration was negatively skewed so non-parametric analyses were used. FC concentration was dichotomized into normal (<50 µg/g) and elevated (≥ 50 µg/g). Fisher’s exact tests were performed to examine the relation between those with three risk factors versus fewer risk factors in FC elevation. Exploratory Fisher’s exact analyses were conducted to examine differences in FC elevation between other risk groups. Exploratory analyses were also conducted to evaluate the relationships between FC concentration and socio-economic index (SEI) and type of abdominal pain. Given that additional clinical tests were not given to the entire sample, we were unable to evaluate their associations with FC elevation.

**Results**

**Demographic and clinical characteristics**

Demographic and clinical data for the sample are presented in Table 1. The majority of the sample was Caucasian (n = 50, 89.3%) and female (n = 37, 66.1%) and the mean age was 12.23 ± 2.71 years. There were no significant differences between the risk groups with regards to age [H(3) = 4.346, p = 0.226], gender [X^2(3) = 2.738, p = 0.434], SEI [H(3) = 3.751, p = 0.290], or abdominal pain location [p = 0.902, Fisher’s exact test, Cramer’s V = 0.255]. The mean FC concentration for the total sample was 51.20 ± 71.44 µg/g, which is considered in the borderline range. Overall, 75% of participants had normal FC concentrations (n = 42) and 25% had elevated FC concentrations (n = 14). FC concentration did not differ by age (r_s = 0.068, p = 0.620), gender [H(1) = 1.187, p = 0.276], SEI (r_s = −0.265, p = 0.109), or type of abdominal pain [H(4) = 7.668, p = 0.104].

**Risk status**

Participants were classified into four groups by number of risk factors based on clinical elevations: zero (16.1%), one (26.8%), two (30.4%), and three (26.8%; Fig. 1). Children with three risk factors were significantly more likely to have elevated FC concentrations than those with zero risk factors (p = 0.048, one-tailed Fisher’s exact test, Cramer’s V = 0.422). Similarly, children with three risk factors were more likely to have elevated FC concentrations compared to children with one (p = 0.025, one-tailed Fisher’s exact test, Cramer’s V = 0.424) and two risk factors (p = 0.040, one-tailed Fisher’s exact test, Cramer’s V = 0.375). There were no significant differences in FC elevations between those with zero, one, and two risk factors (all p’s > 0.05).

Those with three risk factors (i.e., the most clinically complex manifestation of FAPD) had greater average levels of FC than those with two or fewer risk factors. There were no significant differences in FC elevations between those with zero, one, or two risk factors (all p’s > 0.05).

**Exploratory analysis**

Given the scope of the study, all participants who underwent an EGD as part of their clinical care had unremarkable endoscopy findings. Existing clinical test and EGD data for participants were gathered via chart review. Overall, 11 participants had EGD with routine biopsies. Twelve had colonoscopies with ileal intubation and routine biopsies, which were all within normal limits. Exploratory analyses revealed no significant differences in the other clinical test values by risk status groups (p’s > 0.05).

**Discussion**

The present study evaluates a biomarker of gastrointestinal inflammation in pediatric FAPD and demonstrates significantly associated elevated FC amongst those with a clinically complex FAPD profile (elevations in anxiety, disability, and pain) compared to those with two or fewer elevations. Few studies have examined FC in pediatric FAPD [13]. While a recent study detected an association between low-grade inflammation and increased pain interference in pediatric FAPD, [13] no study has examined how FC relates to high risk FAPD. This is an important area of investigation because it is already known that the high risk FAPD group (those categorized by elevations in anxiety, disability, and pain) is more likely to exhibit persistent disability [7].

Use of clinical data available through the EMR yielded meaningful information in this exploratory study. Future research efforts should seek to replicate our findings in larger, prospective trials. Although FC is the most commonly researched indicator of inflammatory response,
levels of other GI inflammation biomarkers (e.g., fecal lactoferrin, S100A12, polymorphonuclear elastase, M2-PK [33]) should be evaluated. Additionally, it will be important to examine if GI inflammation differs by FAPD subtype and abdominal pain location in larger scale studies.

The study findings are potentially important for forming a stronger biopsychosocial conceptualization of pediatric FAPD. By defining a phenotype of complex pediatric FAPD characterized by clinically elevated levels of anxiety, disability, and pain, [7] in addition to increased FC levels, we may be better able to better identify youth with persistent FAPD and ultimately develop more targeted and effective treatments.

**Limitations**

- The sample was relatively small with an unequal gender distribution in this exploratory investigation.
- Due to the use of real world clinical data, some children received more investigations than others prior to receiving a diagnosis of FAPD from their gastroenterologist.
- Collecting clinical data limited our ability to monitor/control for other factors (e.g., administration of

### Table 1  Sample Characteristics

| Variable (total possible range) | % (n) | Mean* (SD) | Clinical reference range |
|---------------------------------|-------|------------|-------------------------|
| **Demographics**                |       |            |                         |
| Age in years (9–14)             | –     | 12.23 (2.71)| –                       |
| Sex                             |       | –          |                         |
| Male                            | 33.9 (19) | – | – |
| Female                          | 66.1 (37) | – | – |
| **Race/ethnicity**              |       | –          |                         |
| Caucasian                       | 89.3 (50) | – | – |
| African American                | 3.6 (2) | – | – |
| Asian American                  | 3.6 (2) | – | – |
| American Indian/Alaskan Native  | 1.8 (1) | – | – |
| Hispanic/Latinx                 | 1.8 (1) | – | – |
| **Abdominal pain location**     |       | –          |                         |
| Generalized                     | 51.3 (28) | – | – |
| Periumbilical                   | 33.3 (19) | – | – |
| Epigastric                      | 10.3 (6) | – | – |
| Right lower quadrant            | 2.6 (1) | – | – |
| Left lower quadrant             | 2.6 (1) | – | – |
| **FC**                          | 100.0 (56) | 20.0 (71.44) | ≥ 50 µg/g |
| **Psychosocial risk factors (0–3)** |       |            |                         |
| SCARED                          | 98.2 (55) | 32.25 (18.73) | ≥ 25 |
| FDI (0–60)                      | 100.0 (56) | 16.66 (9.58) | ≥ 13 |
| NRS Pain (0–10)                 | 100.0 (56) | 4.24 (1.84) | ≥ 4 |
| **Additional diagnostic work-up** |       |            |                         |
| ESR^                           | 62.5 (35) | 7.50 (8.12) | > 15.0 mm/h           |
| CRP^                           | 62.5 (35) | 0.29 (0.69) | > 1.0 mg/dL          |
| Albumin                        | 57.1 (32) | 4.11 (0.43) | < 3.5 or > 5.5 gm/dL |
| IgA                            | 64.3 (36) | 121.29 (56.37) | < 68.0 or > 378.0 mg/dL |
| tTG-IgA                        | 64.3 (36) | 3.89 (1.43) | > 19 CU              |
| EGD                            | 19.6 (11) | – | – |
| Colonoscopy                     | 21.4 (12) | – | – |

Additional diagnostic work-up was offered at the discretion of the GI provider.

SCARED Screen for Child Anxiety and Related Disorders; FDI Functional Disability Inventory; NRS Pain Numeric Rating Scale; FC fecal calprotectin; ESR erythrocyte sedimentation rate; CRP C-reactive protein; IgA immunoglobulin A; tTG-IgA anti-tissue transglutaminase antibodies.

* Non-normally distributed; therefore median value is presented. Clinical ranges of the diagnostic tests are standards used in clinical care in the gastroenterology division at Cincinnati Children’s Hospital Medical Center.
other clinical tests, patient consumption of corticosteroids or mesalamine anti-inflammatory medications before the time of assay) [33] that might affect FC levels.

- Caucasian children may be more likely to receive specialized care for FAPD, contributing to overrepresentation in research conducted in these settings [15, 34, 35] and in our study specifically.

### Abbreviations
FAPD: Functional abdominal pain disorders; GI: Gastrointestinal; FC: Fecal calprotectin; EMR: Electronic medical record; IBD: Inflammatory bowel disease; SCARED: Screen for Child Anxiety Related Disorders; FDI: Functional Disability Inventory; NRS: Numeric Rating Scale; ESR: Erythrocyte sedimentation rates; RP: C-reactive protein; IgA: Immunoglobulin A; tTG-IgA: Anti-tissue transglutaminase antibodies; EGD: Esophagogastroduodenoscopy; SEI: Socioeconomic index.

### Acknowledgements
Not applicable.

### Authors’ contributions
ELM: contributed to the conceptualization of the current study, data acquisition, statistical analyses, interpretation of the data, and writing and editing.

---

![Figure 1](image)  
**Fig. 1** FC concentrations by risk factor classification. *Borderline FC concentration 50.1–120.00 μg/g. Children with three risk factors were more likely to have elevated FC concentrations compared to children with one (p = 0.025, one-tailed Fisher’s exact test, Cramer’s V = 0.424) and two risk factors (p = 0.040, one-tailed Fisher’s exact test, Cramer’s V = 0.375). The differences in FC concentrations between those with zero, one, and two risk factors were not significant (all p’s > 0.05)
the manuscript. MF: contributed to the data acquisition, interpretation of the data, and editing of the manuscript. NS: contributed to the data acquisition, interpretation of the data, and editing of the manuscript. LD: contributed to the conceptualization of the current study, data acquisition, interpretation of the data, and editing of the manuscript. CL: contributed to the data acquisition and editing of the manuscript. NRC: contributed to the conceptualization of the current study, data acquisition, statistical analyses, interpretation of the data, and writing and editing the manuscript. All authors read and approved the final manuscript.

Funding
This study was conducted using secondary data collected from studies funded by the Sharon S. Keller Chronic Pain Research Grant of the American Pain Society, the Place Outcomes Research Award from Cincinnati Children's Hospital Medical Center, and a training Grant (K23 AT009458) from the National Center for Complementary and Integrative Health of the National Institutes of Health, all awarded to the senior author (NRC).

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Cincinnati Children’s Hospital Medical Center Institutional Review Board (IRB00000231). The IRB approved the written consent and assent documents and procedures. Given that all participants were minors (under 18 years old), assent was obtained from each child and consent was obtained from their respective parent/legal guardian.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Department of Clinical and Health Psychology, University of Florida, PO. Box 100165, Gainesville, FL 32610-0165, USA. 2 Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA. 3 College of Medicine, University of Cincinnati, Cincinnati, OH, USA. 4 Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA. 5 Department of Family Medicine, Michigan State University, Grand Rapids, MI, USA.

Received: 16 June 2021 Accepted: 3 September 2021 Published online: 15 September 2021

References

1. Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features, and Rome IV. Gastroenterology. 2016;150:1262-1279.e2.
2. Korterink JJ, Diederen K, Benninga MA, Tabbers MM. Epidemiology of pediatric functional abdominal pain disorders: a meta-analysis. PLoS ONE. 2015;10:e0126982.
3. Walker LS, Guite JW, Duke M, Barnard JA, Greene JW. Recurrent abdominal pain: a potential precursor of irritable bowel syndrome in adolescents and young adults. J Pediatr. 1998;132:1010-5.
4. Cunningham CL, Banerjee GA. Pediatric gastrointestinal disorders: biopsychosocial assessment and treatment. Berlin: Springer Science and Business Media; 2007.
5. Lioi CS, Howard RF. Pediatric chronic pain: biopsychosocial assessment and formulation. Pediatrics. 2016. https://doi.org/10.1542/peds.2016-0331.
6. Reed-Knight B, Maddux MH, Deacy AD, Lamparyk K, Stone AL, Mackner L. Brain–gut interactions and maintenance factors in pediatric gastrointestinal disorders: recommendations for clinical care. Clin Pract Pediatr Psychol. 2017;5:93–105.
7. Cunningham NR, Jagpal A, Peugh J, Farrell MK, Cohen MB, Mezoff AG, et al. Risk categorization predicts disability in pain-associated functional gastrointestinal disorders after 6 months. J Pediatr Gastroenterol Nutr. 2017;64:685–90.
8. Cunningham NR, Cohen MB, Farrell MK, Mezoff AG, Lynch-Jordan A, Kashikar-Zuck S. Concordant parent-child reports of anxiety predict impairment in youth with functional abdominal pain. J Pediatr Gastroenterol Nutr. 2015;60:312–7.
9. Cunningham NR, Jagpal A, Tran ST, Kashikar-Zuck S, Goldscheider KR, Coghill RC, et al. Anxiety adversely impacts response to cognitive behavioral therapy in children with chronic pain. J Pediatr. 2016;171:227–33.
10. Tibble JA, Sighthonsson G, Foster R, Forgacs I, Bjarnason I. Use of surrogate markers of inflammation and Rome criteria to distinguish organic from nonorganic intestinal disease. Gastroenterology. 2002;123:450–60.
11. Waugh N, Cummins E, Royle P, Kandala N-B, Shyangdan D, Arasaradnam R, et al. Faecal calprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel diseases: systematic review and economic evaluation. Health Technol Assess. 2013;17:1–211.
12. Olafsdottir E, Aksnes L, Fluge G, Berstad A. Faecal calprotectin levels in infants with infantile colic, healthy infants, children with inflammatory bowel disease, children with recurrent abdominal pain and healthy children. Acta Paediatr. 2002;91:45–50.
13. Shulman RJ, Eakin MN, Czyzewski DI, Jarrett M, Ou C-N. Increased gastrointestinal permeability and gut inflammation in children with functional abdominal pain and irritable bowel syndrome. J Pediatr. 2008;153:646–50.
14. Cunningham NR, Nelson S, Jagpal A, Moorman E, Farrell M, Penttiuk S, et al. Development of the aim to decrease anxiety and pain treatment for pediatric functional abdominal pain disorders. J Pediatr Gastroenterol Nutr. 2018;66:16–20.
15. Cunningham NR, Moorman E, Brown CM, Mallon D, Chundi PK, Marra CA, et al. Integrating psychological screening into medical care for youth with abdominal pain. Pediatrics. 2018. https://doi.org/10.1542/peds.2017-2876.
16. Konikoff MR, Denson LA. Role of fecal calprotectin as a biomarker of intestinal inflammation in inflammatory bowel disease. Inflamm Bowel Dis. 2006;12:524–34.
17. Mumolo MG, Bertani L, Ceccarelli L, Laino G, Di Fluri G, Albano E, et al. From bench to bedside: fecal calprotectin in inflammatory bowel disease clinical setting. World J Gastroenterol. 2018;24:3681–94.
18. Carrocco A, Iacono G, Cottone M, Di Prima L, Cartabellotta F, Cavatiero F, et al. Diagnostic accuracy of fecal calprotectin assay in distinguishing organic causes of chronic diarrhea from irritable bowel syndrome: a prospective study in adults and children. Clin Chem. 2003;49:861–7.
19. Birmaher B, Brent DA, Chiappetta L, Bridge J, Monga S, Baugher M. Psychometric properties of the screen for child anxiety related emotional disorders (SCARED): a replication study. J Am Acad Child Adolesc Psychiatry. 1999;38:1230–6.
20. Birmaher B, Khetarpal S, Brent D, Cully M, Balach L, Kaufman J, et al. The screen for child anxiety related emotional disorders (SCARED): scale construction and psychometric characteristics. J Am Acad Child Adolesc Psychiatry. 1997;36:45–53.
21. Jastrowski Mano KE, Evans JR, Tran ST, Anderson Khan K, Weisman SJ, Hainsworth KR. The psychometric properties of the screen for child anxiety related emotional disorders in pediatric chronic pain. J Pediatr Psychol. 2012;37:999–1011.
22. Cunningham NR, Jagpal A, Nelson S, Mano KEI, Tran ST, Lynch-Jordan AM, et al. Clinical reference points for the screen for child anxiety related disorders in two investigations of youth with chronic pain. Clin J Pain. 2019;35:238–46.
23. Claar RL, Walker LS. Functional assessment of pediatric pain patients: psychometric properties of the functional disability inventory. Pain. 2006;121:77–84.
24. Kashikar-Zuck S, Flowers SR, Claar RL, Guite JW, Logan DE, Lynch-Jordan AM, et al. Clinical utility and validity of the functional disability inventory (FDI) among a multicenter sample of youth with chronic pain. Pain. 2011;152:1600–7.
25. Castafiores E, Jensen MP, von Baeyer CL, Miro JD. Psychometric properties of the numerical rating scale to assess self-reported pain intensity in children and adolescents: a systematic review. Clin J Pain. 2017;33:376–83.
26. Vermeire S, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? Gut. 2006;55:426–31.
27. Bai JC, Fried M, Corazza GR, Schuppan D, Farthing M, Catassi C, et al. World Gastroenterology Organisation global guidelines on celiac disease. J Clin Gastroenterol. 2013;47:121–6.
28. Sachar DB, Smith H, Chan S, Cohen LB, Lichtiger S, Messer J. Erythrocytic sedimentation rate as a measure of clinical activity in inflammatory bowel disease. J Clin Gastroenterol. 1986;8:647–50.
29. Tsampalieros A, Griffiths AM, Barrowman N, Mack DR. Use of C-reactive protein in children with newly diagnosed inflammatory bowel disease. J Pediatr. 2011;159:340–2.
30. Al-Toma A, Volta U, Auricchio R, Castillejo G, Sanders DS, Cellier C, et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. United Eur Gastroenterol J. 2019;7:583–613.
31. Tringali A, Thomson M, Dumonceau J-M, Tavares M, Tabbers MM, Furlano R, et al. Pediatric gastrointestinal endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) and European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guideline executive summary. Endoscopy. 2017;49:83–91.
32. Corporation I. SPSS for Windows, version 27.0. Armonk: IBM Corp; 2020.
33. Walsham NE, Sherwood RA. Fecal calprotectin in inflammatory bowel disease. Clin Exp Gastroenterol. 2016;9:21–9.
34. Stone AL, Han GT, Bruehl S, Garber J, Smith CA, Anderson J, et al. Subgroups of pediatric patients with functional abdominal pain: replication, parental characteristics, and health service use. Clin J Pain. 2020. https://doi.org/10.1097/AJP.0000000000000882.
35. Schurman JV, Danda CE, Friesen CA, Hyman PE, Simon SD, Cocjin JT. Variations in psychological profile among children with recurrent abdominal pain. J Clin Psychol Med Settings. 2008;15:241–51.

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