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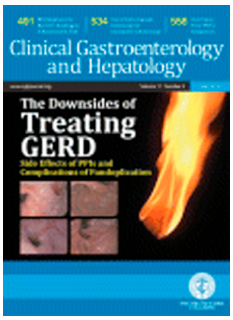

Functional Abdominal Pain Disorders and Constipation in Children on Gluten-Free Diet

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PII: S1542-3565(20)31229-5
DOI: https://doi.org/10.1016/j.cgh.2020.09.001
Reference: YJCGH 57484

To appear in: *Clinical Gastroenterology and Hepatology*
Accepted Date: 1 September 2020

Please cite this article as: Cristofori F, Tripaldi M, Lorusso G, Indrio F, Rutigliano V, Piscitelli D, Castellaneta S, Bentivoglio V, Francavilla R, Functional Abdominal Pain Disorders and Constipation in Children on Gluten-Free Diet, *Clinical Gastroenterology and Hepatology* (2020), doi: https://doi.org/10.1016/j.cgh.2020.09.001.

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Functional Abdominal Pain Disorders and Constipation in Children on Gluten-Free Diet

Running Title: Functional abdominal pain in coeliac disease

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Conflict of Interest: The authors have no conflicts of interest relevant to this article to disclose.

Abbreviations: Abdominal migraine (AM); coeliac disease (CD), endomysial antibodies (EMA), functional abdominal pain disorders (FAPDs), functional abdominal pain non-otherwise specified (FAP-NOS), functional constipation (FC), Functional Gastrointestinal Disorders (FGIDs), functional dyspepsia (FD); gluten-free diet (GFD), irritable bowel syndrome (IBS), transglutaminase-IgA (TTG-IgA).

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Authors' specific contribution: Prof Ruggiero Francavilla and Dr Fernanda Cristofori: conceptualized and designed the study, collected, analysed and interpreted data, drafted the initial manuscript, and reviewed and revised the manuscript. Dr Mariaelena Tripaldi, Giusi Lorusso, Flavia Indrio, Vincenzo Rutigliano, Domenico Piscitelli, Vincenzo Bentivoglio, Stefania Castellaneta: collected data, reviewed and revised the manuscript critically for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Abstract:

Background & Aims: We studied the prevalence of functional abdominal pain disorders (FAPDs) and functional constipation (FC) in a large prospective cohort of children with coeliac disease on strict gluten free diet (GFD).

Methods: We performed a prospective cohort study, from 2016 through 2018, in a tertiary care center in Italy, of 417 patients (37% male; mean age, 13.7 years) with a diagnosis of coeliac disease (ESPGHAN criteria) who had been on a strict GFD for more than 1 year and had negative results from serologic tests after being on the GFD. Parents and children (older than 10 years) were asked to fill in a questionnaire on paediatric gastrointestinal symptoms, according Rome IV criteria. Patients' closest siblings (or cousins) who had negative results from serologic test for coeliac disease were used as controls (n=373; 39% male; mean age, 13.5 years).

Results: We found a higher prevalence of FAPDs among patients with coeliac disease (11.5%) than controls (6.7%) (P<0.05); the relative risk (RR) was 1.8 (95% CI, 1.1–3.0). Irritable bowel syndrome (IBS) and functional constipation (FC) defined by the Rome IV criteria, were more prevalent in patients with coeliac disease (7.2% for IBS and 19.9% for FC) than controls (3.2% for IBS and 10.5% for FC) (P<.05 and P<.001); the RR for IBS was 2.3 (95% CI, 1.1–4.6) and the RR for functional constipation was 2.1 (95% CI, 1.4–3.2). We found no differences in the prevalence of other subtypes of FAPDs. A logistic regression showed that younger age (P<.05) and a higher level of anti-transglutaminase IgA at diagnosis (P<.04) were associated with FAPDs (in particular for IBS) irrespective of GFD duration.

Conclusions: Coeliac disease is associated with an increased risk of IBS and FC. Strategies are needed to manage IBS and FC in patients with coeliac disease.

Key Word: coeliac disease, TTG-IgA, comorbidity, FGIDs, abdominal pain

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Introduction

Coeliac disease (CD) is an immune-mediated disorder elicited by gluten in genetically susceptible individuals[1]. Clinical presentation of CD is variable including abdominal pain, chronic diarrhoea, weight loss, bloating and constipation. These symptoms are also present in functional gastrointestinal disorders (FGIDs) especially in case of diarrhoea and abdominal pain that are common in both conditions.

FGIDs are common in children spanning over a wide range of conditions related to the gastrointestinal tract that cannot be attributed to organic abnormalities[2]. FGIDs are diagnosed according to the symptom-based Rome criteria. In 2016, the revised Rome IV criteria were published, and in children and adolescents FGIDs are classified in: a) functional nausea and vomiting disorders, b) functional abdominal pain disorders (FAPDs) and c) functional defecation disorders. FAPDs include functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraine (AM) and functional abdominal pain not otherwise specified (FAP-NOS)[3].

Among FAPDs, IBS[4] is of particular interest in CD since a possible association between CD and IBS is supported by the presence of a 5-fold increase of biopsy-proven CD in patients with IBS as compared to those without[5] and the presence of symptoms compatible with IBS in almost 40% of adult patients with CD[6]. Our group has shown that children presenting with IBS have a 4,2 times higher risk of having CD than children without IBS (95% CI, 2-8.5)[7]. Moreover, the persistence of IBS-like symptoms irrespective to the rigorous adherence to a gluten-free diet (GFD)[6] and the demonstration of visceral hypersensitivity and dysmotility in CD patients further supports this association[8,9]. This study aims to assess the prevalence of FAPDs and functional constipation (FC), prospectively, in a cohort of CD paediatric patients despite a long term GFD.

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Patient and Methods

Study population

This is a prospective observational cohort study conducted between 2016 and 2018 at the Paediatric and Gastroenterology Department of the University Hospital of Bari (Italy).

The study population was composed of consecutive children evaluated during the scheduled follow-up visit at CD outpatient clinic. To be included children had to: a) have age between 4-16 years; b) have a diagnosis of CD according to the European Society for Paediatric Gastroenterology Hepatology, and Nutrition (ESPGHAN) criteria[1], c) be on strict GFD for at least one year and d) have a persistent negative coeliac serology while on GFD.

CD diagnosis

CD diagnosis was based on serum concentrations of IgA, anti-transglutaminase-IgA (TTG-IgA), endomysial antibodies (EMA), and a duodenal biopsy according to ESPGHAN criteria[1]. Quantitative detection of TTG was assessed by an indirect solid-phase enzyme immunoassay (ELISA) test (ORGENTEC Diagnostika; Mainz, Deutschland). EMA was determined by indirect immunofluorescence using monkey's oesophagus sections as substrate (Euroimmun Italia Diagnostica Medica SRL; Padova, Italia). To exclude the presence of selective IgA deficiency, serum IgA levels were assayed by nephelometry. Class II antigens HLA typing was performed by polymerase chain reaction sequence-specific oligonucleotide using DQ-CD Typing Plus; (DiaGene, Palermo, Italy)[10].

According to ESPGHAN guidelines, in children and adolescents with signs or symptoms suggestive of CD, high anti-TTG titers (>10 times), positivity of EMA and HLA DQ2/8, biopsies were omitted[1]. In all other cases, patients underwent upper endoscopy with multiple duodenal biopsies. The same pathologist graded all biopsies specimens according to the Marsh criteria[11]. At diagnosis, and

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on-demand afterwards, an experienced nutritionist instructed families how to guarantee a well-balanced diet with proper gluten avoidance.

Follow-up on GFD

During the follow-up visit, while on GFD, a complete physical examination, investigation including TTG-IgA, full blood count, iron, ferritin, and aminotransferase concentrations were performed. The possible consumption of gluten-containing products was assessed by a combination of CD serology, self-reported adherence questions and an experienced dietician interview. Self-reported adherence questions included two questions: 1) Do you follow a strict GFD? 2) Have you ever experienced accidentally gluten exposure?; while the dietetic interview started from a validated questionnaire[12] but also investigated questions on gluten free food storing, cooking at home and eating habits when eating at restaurants.

To assess the prevalence of FAPDs and FC, the parent-report form of the Rome IV Diagnostic Questionnaire for Paediatric FGIDs for children and adolescent was used[13]. Children older than 10 years filled in a self-report form for Children and Adolescents too. This questionnaire is based on the Questionnaire for Paediatric Gastrointestinal Symptoms-Rome III developed by Walker [14,15], and modified according to the new criteria. This questionnaire, valuable in clinical care and research setting[13], comprises 5 sections: pain or discomfort in the upper abdomen above the umbilicus, pain or discomfort in the lower abdomen around and/or below the umbilicus, bowel habits, nausea and vomiting, other gastrointestinal symptoms. A member of the research team (FC) administered the first three sections of the questionnaire and assisted parents and children in completing answers. If a child was suffering from constipation and abdominal pain related to defecation, he was firstly treated for constipation only[16] and, if despite treatment, the abdominal pain persisted, the child was diagnoses as IBS with constipation. In the presence of alarm signs

and/or clinical symptoms, further investigations were performed to exclude other organic diseases, as appropriate[3].

The closest sibling of the patient (same-sex if available), with persistently negative TTG-IgA antibody (at least twice) or a cousin (if no siblings were available) was used as control.

The study adhered to the Declaration of Helsinki and the local Institutional ethical committee has approved the study. All the authors have access to the study data and had reviewed and approved the final manuscript.

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Statistics

Normally distributed grouped data were expressed as the mean (±SD) and compared using the paired and unpaired t-tests. Non-parametric grouped data are expressed as media [95%CI] and compared with the Mann-Whitney rank-sum test (paired) or Wilcoxon´s signed-rank test (unpaired). Proportionate data were compared with Fisher´s exact test or the $\chi 2$ test. Significance was established at $p<0.05$ With the assumption that IBS would be expected in 4,2% of the general Italian paediatric population[17] and in 7,3% of CD[18], we calculated that a sample of 371 children with CD would be required for the study to have 80% power based on a two-sided type 1 error rate of 5%. This sample size has a 95% power based on a two-sided type 1 error rate of 1% to identify a difference in prevalence of FAPD in CD patients versus controls considering a prevalence of FAPD in 9% of controls [17] and 18% of CD[18-20].

Risk models were developed using a decision tree. A model was developed to predict the risk of having FAPDs in children with CD. Precision rate, sensitivity, specificity, positive and negative predictive values of the decision tree were calculated. The relationship of several risk factors to the outcome was further evaluated using logistic regression. The statistical analysis was performed using SPSS 13.0 (Chicago, IL, USA).

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Results

A total of 876 children were evaluated for the study and 90 were excluded; therefore, 790 children (417 CD and 373 controls) were available for the analysis (Figure 1). Out of 417 CD patients, 53% presented with typical symptoms, 40% with an atypical presentation and 7% were diagnosed following family screening. Among controls 55% were siblings and 45% were first-degree cousins of CD patients. Demographic data of the two groups are reported in table 1.

The analysis of the Diagnostic Questionnaire showed that CD children have a significantly higher risk of having FAPDs as compared to controls [11,5 vs 6,7%; $p<0.05$; RR 1,8 (95%CI: 1,1-3)]. We found no differences between CD patients and controls in the prevalence of FD, AM, FAP-NOS (table 1). However, we revealed a significantly higher prevalence of IBS [(7,2% vs. 3,2%; $p<0,05$); RR 2,3 (95%CI: 1,1-4,6)] in CD patients as compared to controls.

We found no difference in the duration of FAPDs between CD patients and controls.

Using logistic regression, we found that younger age and a higher level of TTG-IgA at diagnosis were predictive of developing FAPDs and IBS irrespective of GFD duration (table 2).

FC was the most frequent disorder in both CD and controls (19,9% vs. 10,5%; $p<0,001$) with a relative risk of having functional constipation in children with CD of 2,1 (95% CI: 1,4-3,2). No differences were found for demographic and laboratory data between CD patients with and without FC.

Among the 180 CD children who had abdominal pain at diagnosis, 27 (15%) were still complaining pain at follow-up (defined as "*persistent*"), while 153 (85%) did not (defined as *"regressed"*). Out of the 237 patients without abdominal pain at diagnosis, 21 (9%) developed it while on GFD (defined as "*new onset*"), whereas 216 (91%) did not (defined as *"no-pain"*).

Decision tree analysis

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A decisional tree was built to predict factors associated with the persistence of FAPDs while on G-FD (Figure 2) and the highest risk was assigned to patients with a history of GFD shorter than ten years and age at diagnosis less than 4,7 years. In patients with a history of GFD longer than ten years the greatest risk of persistence of FAPDs was the presence of constipation. This decisional tree correctly classifies 16/27 children [p<0,004; sensitivity: 59,6% (95%CI 38.8-77.6%); specificity: 74.5% (95%CI 66.8-81.2%); positive predictive value: 29,3% (95%CI 21,3-38,2%); negative predictive value: 91,2% (95%CI 86,6-94,2%)].

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Discussion

The present prospective study, conducted in a large cohort of children with CD, shows that the prevalence of FAPDs is significantly higher in CD compared to controls despite a strict adherence to a GFD. In detail, CD patients presented a higher prevalence of FC and IBS as compared to controls. Our data show that abdominal pain disappears after GFD in more than 80% of the cases, 9% of patients start to complain symptoms while on GFD. We found that a late diagnosis and a follow-up shorter than ten years are associated with the persistence of the abdominal pain; therefore, it is possible to hypothesize that FAPDs in CD might be transitory.

Saps et al. have conducted a study on 289 children (United States and Italy). The cohort included children with CD on GFD for more than 6 months, siblings and unrelated controls. FAPDs were present in 8.2% of CD participant, 8.2% of sibling, and 2.1% of unrelated subjects. The relative risk of abdominal pain associated with FGIDs was not significantly different among patients with CD on GFD and sibling control. Although there was a 4-fold increase between these two groups compared to unrelated controls, there was still no statistical difference between them[19]. A similar result was reported in 46 paediatric patients with CD on GFD versus siblings as control[20]. Turco et al, in a cohort of Italian CD children adherent to a GFD, reached a different conclusion. They found a higher risk of FGIDs in CD patients as compared to controls; FC was the most frequent disorder[18]. The available studies on children are reported in table 3. In adults, the association between CD and IBS-like symptoms is well known; symptoms compatible with IBS are present in almost 40% of patients with CD. A meta-analysis from 7 studies indicates that there is a 5-fold increase in IBS-type symptoms in CD compared to healthy controls[6]. However, adults with CD have a longer duration of symptoms before diagnosis, leading to a long-standing mucosal inflammation[21] and this might explain the difference in prevalence between children and adults.

There are still unanswered questions regarding the pathophysiology underlying both IBS and CD

and although these conditions may not be mutually exclusive, it is fascinating to speculate a shared pathophysiology. A straightforward explanation behind the persistence of gastrointestinal symptoms would be a continuous intentional or inadvertent gluten intake; however, other possible causes might be the presence of another unrecognized gastrointestinal disease, altered bowel motility due to low-fibre content in GFD, microbiota modifications or rarely, refractory CD. Previous studies on various gastrointestinal inflammatory conditions have consistently found that children with gastrointestinal inflammation were at risk of developing FAPDs[22-26]. There is evidence suggesting that IBS symptoms might be caused by continuous low-grade mucosal inflammation[27,28] which may persist in CD despite a strict GFD[29, 30] and/or that small-intestinal bacterial overgrowth, often accompanied by mucosal inflammation, may account for symptoms in both conditions[31-34]. The positive correlation founded between a high titre of TTG and FAPDs might be explained by the severity of enteropathy in patients with high TTG titre. It is possible to speculate that the worse the damage the higher the chance of persistence of intestinal inflammation, leading to the emergence/maintenance of visceral hyperalgesia and chronic pain.

According to the most recent data, gut microbiota of CD patients is characterized by increased Bacteroides spp., E. Coli, Proteobacteria, and Staphylococcus and decreased Bifidobacterium spp and Lactobacillus[35] and several studies have reported similar changes in microbiota of IBS patients[36,37]. Alterations of microbiota may have a pathogenic implication, leading to persistent gastrointestinal symptoms despite GFD. Wacklin et al. recently reported that symptomatic CD patients despite GFD have a reduced microbial richness, higher abundance of Proteobacteria and lower abundance of Bacteroidetes and Firmicutes as compared to asymptomatic CD patients. The authors speculate that intestinal dysbiosis might be responsible for the persistence of symptoms, even while adhering to a strict GFD[38]. Indeed, GFD although is able to improve the nutritional status of CD patients without causing nutritional problems[39], is only partially effective in restoring

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microbiota and can itself influence its composition due to polysaccharide (fructans) intake reduction which have prebiotic action on bifidobacteria[40]. Indeed, we and others have found a reduction in diversity and a change in abundance of various bacterial species (increase in *Bacteroidetes* and a reduction in *Actinobacteria*)[41,42].

The reduced amount of fiber of GFD may be considered as one of the reasons why CD patients often suffer from FC[18].

The present study has several strengths: a large sample size, well-defined CD and FGIDs diagnoses and well distributed population among typical, atypical CD presentations and screen-detected patients. Moreover, although some studies have be correctly planned to identify a difference in prevalence of FAPDs in CD patients versus controls, our study is the only powered to demonstrate an association between CD and IBS considering that a minimum of 370 patients would be needed.

A limit of our study is the absence of a follow-up endoscopy. The presence of an experienced dietician coupled with a persistently negative serological test make us confident of the strict adherence to the GFD and becomes unlikely that inadvertent/occasional gluten intake would explain the on-going gastrointestinal symptoms. However, this approach limits our possibility to assess whether the lack of compliance might be responsible of symptoms onset. Finally, we were not able to assess whether the amount of processed gluten free foods, fructose or fat content might be involved in the genesis/persistence of IBS symptoms.

The demonstration of a higher prevalence of IBS and FC in CD children should prompt an early detection of these conditions in order to anticipate its diagnoses and to program possible therapeutic interventions and educational programming. This approach will help to decrease the negative impact on daily functioning; improper healthcare utilization and personal search of therapeutic alternatives[42] and improve quality of life[27, 44-46]. The lack of consistent data on the

prevalence of FGIDs in children with CD following a GFD, leads to clinical and treatment dilemma. Based on data reported so far, we suggest that paediatric CD patients with FAPDs should avoid unnecessary testing or insisting on dietary adherence that often frustrates patients and families leading to a stressful relationship between children, families and medical providers. We recommend that the first approach should be that reassuring on the functional nature of the condition optimizing children/familiar symptoms coping skills.

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	Coeliac Patients	Controls	*p-values*
Gender (males %)	37	39	p=NS
Age years mean (min-max)	13,7 (4,4-16)	13,5 (4,3-16)	p=NS
Functional Constipation (%)	19,9	10,5	<0.001
FAPDs (%)	11,5	6,7	<0,05
Irritable Bowel Syndrome (%)	7,2	3,2	<0,05
• **IBS with diarrohea**	23,3	25	p=NS
• **IBS with constipation**	43,3	41,6	p=NS
• **IBS mixed**	33.3	33.3	p=NS
Functional Dyspepsia (%)	1,4	1,6	p=NS
Abdominal Migraine (%)	0,6	0	p=NS
FAP-NOS‡ (%)	2,3	1,9	p=NS

372 **Table 1:** Prevalence of Functional Abdominal Pain Disorders and Functional Constipation in Coeliac
373 patients and controls.

374 †FAPDs: Functional Abdominal Pain Disorders; ‡FAP-NOS: Functional Abdominal Pain non-
375 otherwise specified.

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	FAPDs† (n: 48)	IBS^ (n: 30)	No FAPDs† (n: 369)	p values
Family history of CD‡ %	15,2	13,2	14,6	p=NS
Gender Male %	29,2	36,3	37,4	p=NS
Delivery Mode % CS¶	50	47	45,8	p=NS
Breastfeeding Duration mean (95%CI) Months	4,7 (3,1-6,3)	4,6 (3-6,4)	6,1 (5,6-6,7)	p=NS
Age at Diagnosis mean (95%CI) years	5,4 (5-6,8)	4,7 (3,7-5,8)*	7,5 (5,7-7,6)	p<0,05
TTG IgA§ at Diagnosis mean (95%CI) AU/ml	122 (85-160)	119 (96-175)°	96,1 (82-106)	p<0,03
Time to achieve negative CD serology mean (95%CI) years	1,2 (0,9-1,5)	1,1 (0,9-1,8)	1,1 (1-1,3)	p=NS
Follow-up duration mean (95%CI) years	6,4 (5,7-7,8)	7,1 (5,3-8,4)	6,8 (6,5-8,2)	p=NS
Histology %				
• Marsh-1	0	0	0	p=NS
• Marsh-2	4,2	6,6	3	p=NS
• Marsh-3	95,8	93,4	97	p=NS

*IBS vs. No FAPDs; p<0,04
°IBS vs. No FAPDs; p<0,03

Table 2: Demographic and clinical characteristics of patients with and without Functional Abdominal Pain Disorders and Irritable Bowel Syndrome.

CD‡: Coeliac Disease; CS¶: caesarean section; FAPDs†: Functional Abdominal Pain Disorders; IgA§: Immunoglobulin A; Irritable Bowel Syndrome (IBS), TTG° Anti Transglutaminase.

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Reference	Country	Age CD† patients mean (range)	Used Criteria	Population n°	AP-FGIDs‡ (%)	IBS § (%)	FD ¶ (%)	FAP° (%)	AM^ (%)	FC # (%)
Turco R. et al (APT 2011)	Italy	6,6 (4-17)	Rome III	82 CD patients	28	7,3	2	4,8	0	18
				56 controls	8,9	3,5	0	3,5	0	1,8
Saps M. et al (J Pediatrics 2013)	US	11,3 (3-22)	Rome III	49 CD patients	18,3	6,1	4,8	4,8	4.8	-
				48 siblings	8,3	2,1	0	6,3	0	-
Saps M et al (J Pediatrics 2017)	US & Italy	10,8 (4-18)	Rome III	96 CD patients	8	6,2	0	1	0	-
				96 siblings	8	4,1	1	2	0	-
				97 unrelated controls	2	1	0	1	0	-

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Table 3: Previous Studies performed in Children.

CD†: Coeliac Disease; AP-FGIDs‡: Abdominal Pain Related Functional Gastrointestinal Disorders; IBS§: Irritable Bowel Syndrome; FD¶: Functional Dyspepsia, FAP°: Functional Abdominal Pain; AM^: Abdominal Migraine; FC#: Functional Constipation; -: Not reported

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Figure 1. Flow diagram of participants.

Figure 2. Decision Tree: the highest risk for the persistence of FAPDs was assigned to patients with history of GFD shorter than ten years and age at diagnosis less than 4,7 years; while for patients at GFD since more than 10 years the greatest risk for the persistence of FAPDs is the presence of constipation.

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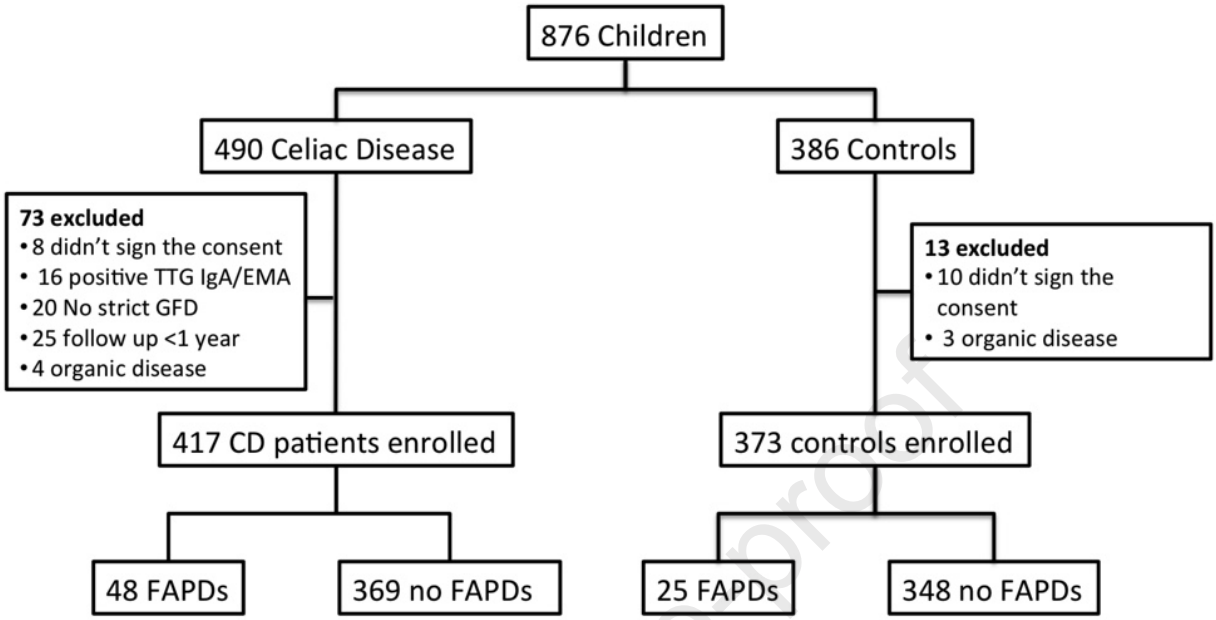

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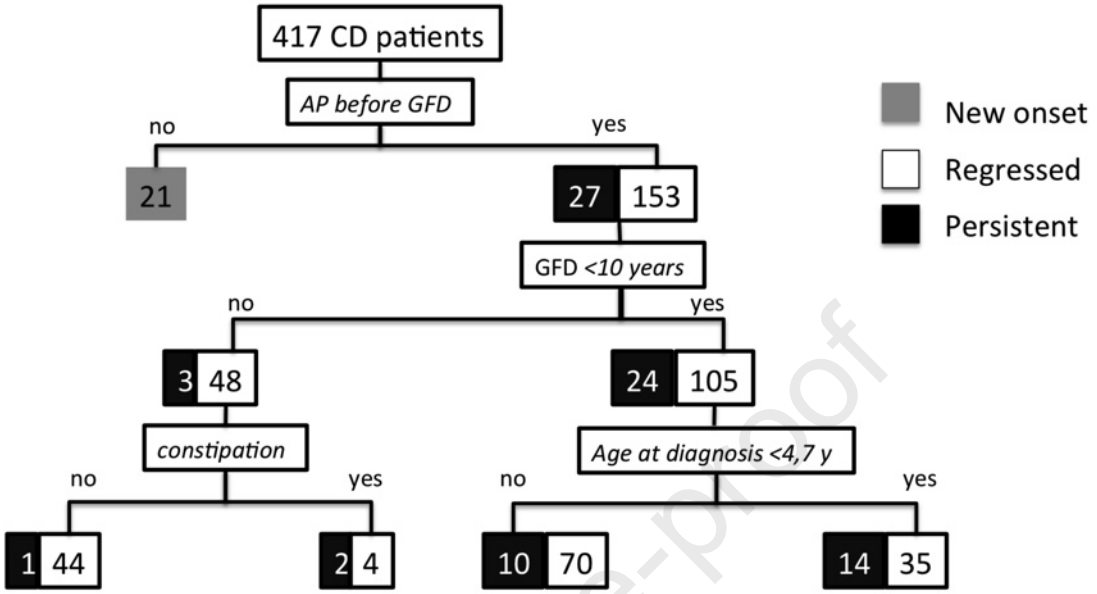

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What you need to know

Background: This study investigated the prevalence of functional abdominal pain disorders (FAPDs) and functional constipation (FC) in a large prospective cohort of children with coeliac disease on strict gluten free diet for more than 1 year.

Findings: This study found a higher prevalence of FAPDs among patients with coeliac disease (11.5%) than controls (6.7%). Irritable bowel syndrome (IBS) and functional constipation (FC) defined by the Rome IV criteria, were more prevalent in patients with coeliac disease (7.2% for IBS and 19.9% for FC) than controls (3.2% for IBS and 10.5% for FC).

Implications for patient care: Coeliac disease is associated with an increased risk of IBS and FC. Strategies are needed to manage IBS and FC in patients with coeliac disease

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