Functional Gastrointestinal Disorders and Associated Health Impairment in Individuals with Celiac Disease

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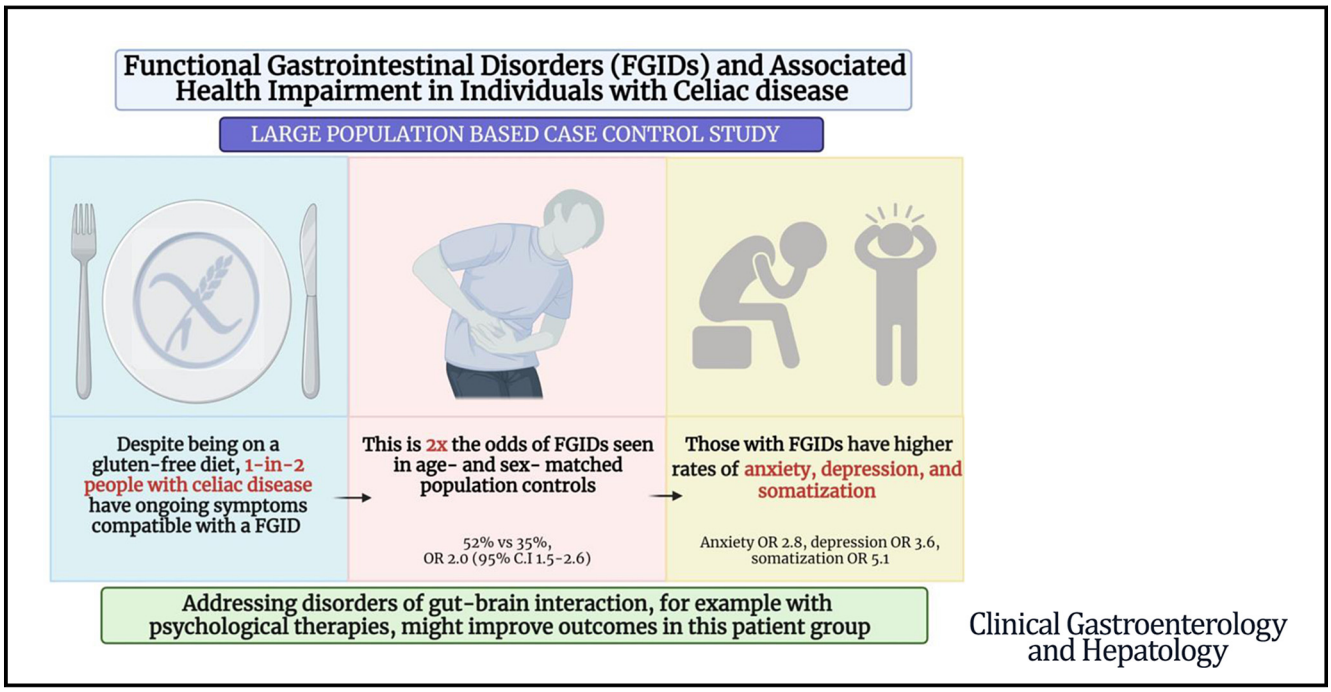

BACKGROUND & AIMS: **Individuals with celiac disease (CD) can experience persisting gastrointestinal symptoms despite adhering to a gluten-free diet (GFD). This may be due to functional gastrointestinal disorders (FGIDs), although there is little data on its prevalence and associated factors.**

METHODS: **An online health questionnaire was completed by adult members of Celiac UK in October 2018. The survey included validated questions on Rome IV FGIDs, nongastrointestinal somatic symptoms, anxiety, depression, quality of life, health care use, GFD duration, and its adherence using the celiac dietary adherence test score (with a value ≤ 13 indicating optimal adherence). The prevalence of FGIDs and associated health impairment in the celiac cohort was compared against an age- and sex-matched population-based control group.**

Abbreviations used in this paper: **CD, Celiac disease; CDAT, Celiac Disease Adherence Tool; CI, confidence interval; FGID, functional gastrointestinal disorder; GAD, General Anxiety Disorder; GFD, gluten-free diet; GI, gastrointestinal; IBS, irritable bowel syndrome; OR, odds ratio; PHQ, Patient Health Questionnaire; SF8-QOL, Short Form 8 Quality of Life; UK, United Kingdom.**

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RESULTS: **Of the 863 individuals with CD (73% female; mean age, 61 years), all were taking a GFD for at least 1 year, with 96% declaring that they have been on the diet for 2 or more years (2–4 years, 20%; ≥5 years, 76%). The adherence to a GFD was deemed optimal in 61% (n = 523), with the remaining 39% (n = 340) nonadherent. Those adhering to a GFD fulfilled criteria for a FGID in approximately one-half of cases, although this was significantly lower than nonadherent subjects (51% vs 75%; odds ratio [OR], 2.0; $P < .001$). However, the prevalence of FGIDs in GFD-adherent subjects was significantly higher than in matched population-based controls (35%; OR, 2.0; $P < .001$). This was accounted for by functional bowel (46% vs 31%; OR, 1.9; $P < .0001$) and anorectal disorders (14.5% vs 9.3%; OR, 1.7; $P = .02$) but not functional esophageal (7.6% vs 6.1%; $P = .36$) or gastroduodenal disorders (8.7% vs 7.4%; $P = .47$). Finally, GFD-adherent subjects with FGIDs were significantly more likely than their counterparts without FGIDs to have abnormal levels of anxiety (5% vs 2%; OR, 2.8; $P = .04$), depression (7% vs 2%; OR, 3.6; $P = .01$), somatization (31% vs 8%; OR, 5.1; $P < .0001$), and reduced quality of life ($P < .0001$).**

CONCLUSION: **One in 2 people with CD, despite having been on a GFD for a number of years and demonstrating optimal adherence, have ongoing symptoms compatible with a Rome IV FGID. This is 2-fold the odds of FGIDs seen in age- and sex-matched controls. The presence of FGIDs is associated with significant health impairment, including psychological comorbidity. Addressing disorders of gut-brain interaction might improve outcomes in this specific group of patients.**

Keywords: Celiac Disease; Functional Gastrointestinal Disorders; Gluten-free Diet; Psychological Distress.

The clinical manifestations of celiac disease (CD) are similar to that of some functional gastrointestinal disorders (FGIDs, recently termed disorders of gut-brain interaction) – such as irritable bowel syndrome (IBS) – and can lead to the diagnosis of CD being overlooked or delayed due to misclassification.[1,2] In fact, there is a 4-fold increased prevalence of CD in patients presenting with symptoms compatible with IBS compared with controls who do not report these symptoms.[3] Individuals with CD may also report extra-intestinal symptoms, such as anxiety and depression, in addition to experiencing reduced quality of life.[1] Following a diagnosis, patients are commenced on a life-long gluten-free diet (GFD), aiming for symptom resolution, improvement in quality of life, and avoidance of long-term complications.[1]

However, individuals with CD may experience lingering gastrointestinal (GI) symptoms despite adhering to a GFD. A meta-analysis of 7 studies published in 2013 reported that the pooled prevalence of IBS-type symptoms in all adult patients with CD was 38%, with an almost 6-fold higher odds compared with controls.[4] There was an almost 4- and 12-fold higher odds for IBS-type symptoms among patients who did and did not adhere to a GFD, respectively, compared with controls. However, the authors of the meta-analysis noted significant heterogeneity between the 7 studies, mainly because 3 of them were cross-sectional observational case series,[5–7] whereas the other 4 were case-control studies, comprising a total of 626 patients with CD and only 1 control group from the general population.[8–11] Moreover, they used historic Rome I–III criteria to define IBS and did not assess for duration of a GFD or its adherence using a validated scoring tool. There is also little information on the presence of other FGIDs in CD, with data in adults being limited to a case series from a single center where, at baseline and at 1 year following commencement of a GFD, the prevalence of IBS decreased from 52% to 22% and functional dyspepsia decreased from 28% to 7%, whereas functional bloating increased from 9% to 16%.[12] A summary of studies assessing the presence of FGIDs in adults with CD is provided in Supplementary Table 1. Finally, factors associated with the presence of FGIDs in patients with CD adhering to a GFD are poorly understood, with some evidence to suggest that those with IBS have lower quality of life and mood scores than those without IBS.[6,8,10,13] These preliminary findings warrant further evaluation as they mirror those seen in inflammatory bowel disease in remission, where the presence of IBS-type symptoms is associated with higher levels of psychological distress and somatization than those without IBS, suggesting that addressing psychological well-being might improve outcomes in this specific group of patients.[14]

In summary, there is sparse data assessing the prevalence of, and factors associated with, FGIDs in adults with CD adhering to a GFD. We sought to address this issue by undertaking a large population-based case-control study using contemporary diagnostic criteria and validated questionnaires.

Methods

Study Design and Participants

In October 2018, an online general health questionnaire from our research group was sent out by the charity organization, Coeliac UK. The society has almost

80,000 members, of which just over 21,000 are contactable under general data protection regulations. After randomly selecting every fourth person aged 18 years or over, we sent the survey out to 5297 adults (69% female; age ranges: 18–39 years, 10.5%; 40–64 years, 46.7%; 65+ years, 42.8%), with an e-mail reminder at 2 weeks and the survey closing at 1 month. In total, 998 of 5297 (19%) completed the questionnaire. We subsequently excluded individuals without CD (n = 105) and also those with CD but having been on a GFD for less than a year (n = 30), as the latter would be considered too early to assess adequate clinical response to a GFD.[15] This left 863 individuals with CD who were taking a GFD for at least 1 year. These were further subdivided as having optimal (n = 523) and suboptimal (n = 340) adherence to a GFD, based on a validated CD adherence tool described later.

Our controls were selected from a nationally representative sample of 1994 population-based adults in the United Kingdom (UK) who had completed a similar survey in 2015, which at that time was used to determine the prevalence of FGIDs within the general population.[16] From this sample, 54 were excluded due to having an organic GI disease, leaving 1940 subjects. As a final step, we performed computer generated case-control matching (for age and gender) between those with CD adhering to a GFD and those from the general population, leaving 462 subjects in each group. The study flow chart describes this in greater detail (Figure 1).

What You Need to Know

Background

Individuals with celiac disease (CD) can have ongoing gastrointestinal symptoms despite adhering to a gluten-free diet. These symptoms may be caused by functional gastrointestinal disorders (FGIDs). There is limited evidence on the prevalence of, and factors associated with, FGIDs in those with CD.

Findings

One in 2 individuals with CD, despite taking a gluten-free diet for many years and showing optimal adherence, have lingering symptoms compatible with a Rome IV FGID. These individuals also have higher rates of psychological comorbidity, somatization, and reduced quality of life compared with those without FGIDs.

Implications for patient care

Health care providers should be aware of the high prevalence of FGIDs and associated health impairment in those with treated CD. Future studies should aim to address disorders of gut-brain interaction in this cohort, for example with the use of psychological therapies.

Questionnaires

The comprehensive questionnaire collected information on: (1) Basic demographics; (2) Rome IV FGIDs; (3) Patient Health Questionnaire (PHQ)-12 somatization; (4) PHQ-9 depression; (5) General Anxiety Disorder (GAD)-7; (6) Short Form 8 Quality of Life (SF8-QOL); and (7) health care use. In those with CD, we also assessed for the duration of a GFD and its adherence, the latter using the Celiac Disease Adherence Tool (CDAT), where a value $\leq$13 is considered to demonstrate very good or excellent

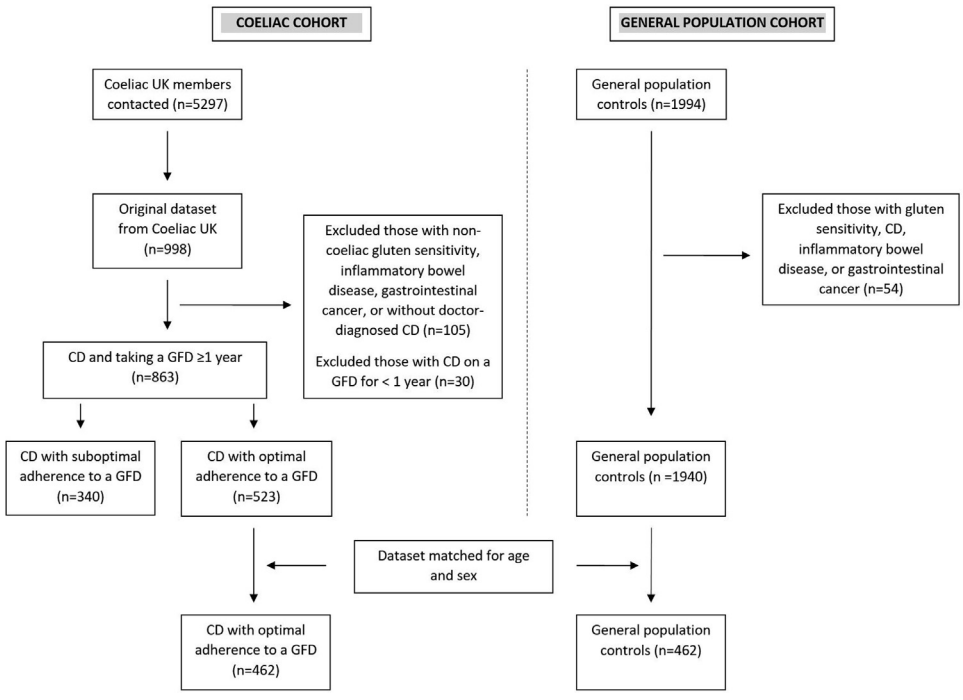

Figure 1. Study flow chart.

adherence, which for the purpose of this study was classed as being optimal or GFD-adherent. In contrast, a CDAT score >13 was deemed as being suboptimal or GFD-nonadherent. Detailed information on the questionnaires is provided in the Supplementary Methods.

Statistical Analysis

Statistical analysis was carried out using SPSS version 26.0 software (SPSS Inc, Chicago, IL), with significance set at a *P*-value of $< .05$. There was no missing data because the online questionnaire required participants to complete each applicable question before being allowed to move onto the next step. Categorical variables were summarized by descriptive statistics, including total numbers and percentages, with comparisons between groups performed using the χ^2 test. Continuous variables were summarized by mean and standard deviation, with differences between 2 independent groups assessed using the unpaired Student *t* test. Odds ratios (ORs) with 95% confidence intervals (CIs) were also calculated. Correlations were assessed using the Pearson test.

Results

Characteristics of the CD Cohort

Of the 863 individuals with CD, the mean age was 61 years, with 8.7% (n = 75) aged between 18 and 39 years, 47.6% (n = 411) aged between 40 and 64 years, and the remaining 43.7% (n = 377) being 65 years and older. The majority of the cohort were female (73%) and of white race (98%). The duration of a GFD for all individuals was at least 1 year, with 96% declaring that they had been on a GFD for 2 or more years (2–4 years, 20%; ≥5 years, 76%).

The prevalence of fulfilling symptom-based criteria for any Rome IV FGID was 60%, mainly accounted for by functional bowel disorders (55%), anorectal disorders (18%), gastroduodenal disorders (13%), and esophageal disorders (12%). There was only 1 case each of functional biliary and centrally mediated disorders of GI pain, and they will not be discussed further. The presence of individual FGIDs within each GI organ domain is detailed in Table 1.

The use of GI medication was reported by 33%, most commonly antacids (26%). GI surgery was reported in up to 16% of cases. A substantial proportion of individuals with CD also reported more than moderate levels of anxiety (9%; n = 80) and depression (13%; n = 114) and medium-high severity of somatization (32%; n = 273).

Comparison Between GFD-adherent Versus GFD-nonadherent Subjects With CD

The adherence to a GFD in the 863 subjects with CD was deemed optimal in 61% (n = 523), as demonstrated by a CDAT score of ≤13, with the remaining 39% (n = 340) classified as GFD-nonadherent. Those adhering to a GFD fulfilled criteria for a FGID in approximately one-half of cases, although this was significantly less than in GFD-nonadherent subjects (51% vs 75%; OR, 2.0; 95% CI, 1.5–2.6) (Table 1). The prevalence of FGIDs remained stable in both groups irrespective of the duration of a GFD (Supplementary Table 2).

GFD-nonadherent subjects were significantly more likely than GFD-adherent subjects to have symptoms compatible with functional esophageal disorders (18% vs 8%; OR, 2.5; 95% CI, 1.6–3.8), functional gastroduodenal disorders (20% vs 8%; OR, 2.7; 95% CI, 1.8–4.1), functional bowel disorders (70% vs 45%; OR, 2.9; 95% CI, 2.2–3.9), and functional anorectal disorders (24% vs 15%; OR, 1.8; 95% CI, 1.2–2.5). The prevalence of individual FGIDs within the specific GI organ domains is detailed in Table 1.

GFD-nonadherent subjects experienced abdominal pain "at least one day per week" more frequently than those who were GFD-adherent (31% vs 11%; OR, 3.7; 95% CI, 2.5–3.3). They also were more likely to be taking GI-related medication (39% vs 29%; OR, 1.5; 95% CI, 1.1–2.0) and have undergone cholecystectomy (OR, 1.7; 95% CI, 1.1–2.9), with a trend towards higher rates of hysterectomy (OR, 1.5; 95% CI, 0.99–2.2), but not appendectomy (OR, 0.8; 95% CI, 0.6–1.2).

GFD-nonadherent subjects were also significantly more likely than their GFD-adherent counterparts to have more than moderate levels of anxiety (18% vs 4%; OR, 5.8; 95% CI, 3.4–9.9) and depression (27% vs 4%; OR, 7.9; 95% CI, 4.9–12.9), and medium-to-high severity of somatization (51% vs 19%; OR, 4.3; 95% CI, 3.2–5.8). Quality of life scores were significantly lower in all domains for GFD-non-adherent subjects ($P < .0001$).

Prevalence of FGIDs in GFD-adherent CD Subjects Versus Age- and Sex-matched Population Controls

Despite GFD-adherent subjects having a lower prevalence of FGIDs than GFD-nonadherent individuals, they were still significantly more likely to have FGIDs compared with age- and sex- matched population controls (52% vs 35%; OR, 2.0; 95% CI, 1.5–2.6) (Table 2). This was seen across different age categories (Figure 2). The difference was accounted for by functional bowel (46% vs 31%; OR, 1.9; 95% CI, 1.5–2.5) and anorectal disorders (14.5% vs 9.3%; OR, 1.7; 95% CI, 1.1–2.5) but not functional esophageal (7.6% vs 6.1%; $P = .36$) or gastroduodenal disorders (8.7% vs 7.4%; $P = .47$). Within the bowel domain, GFD-adherent CD subjects had a higher rates of IBS (7.6% vs 4.5%; OR, 1.7; 95% CI, 1.0–3.0) and unspecified functional bowel disorders (15% vs 9%; OR, 1.8; 95% CI, 1.2–2.8), with a trend towards higher prevalence of functional bloating/distention (5.8% vs 3.5%; $P = .09$), than

Table 1. Characteristics of Individuals With CD Stratified According to Adherence to a GFD

	Overall CD cohort (n = 863)	GFD-adherent (n = 523)	GFD-non-adherent (n = 340)	*P*-value
Demographics				
Mean age, *years* (SD)	61 (13.2)	61 (13.0)	59 (13.4)	.002
Female	630 (73)	345 (68)	276 (81)	< .0001
White race	848 (98)	514 (98)	334 (98)	.96
Duration of a GFD				
1 year	32 (4)	18 (3)	14 (4)	
2–4 years	174 (20)	93 (18)	81 (24)	
≥5 years	657 (76)	412 (79)	245 (72)	.07
Prevalence of Rome IV FGIDs				
Any FGID	521 (60)	265 (51)	256 (75)	< .0001
A. Esophageal disorders				
Functional chest pain	29 (3.4)	14 (2.7)	15 (4.4)	.17
Functional heartburn	30 (3.5)	8 (1.5)	22 (6.5)	< .0001
Globus	10 (1.2)	4 (0.8)	6 (1.8)	.18
Functional dysphagia	54 (6.3)	20 (3.8)	34 (10)	< .0001
Any esophageal disorder	103 (12)	42 (8)	61 (18)	< .0001
B. Gastroduodenal disorders				
Functional dyspepsia	76 (9)	27 (5)	49 (14)	< .0001
Belching disorder	22 (2.5)	8 (1.5)	14 (4.1)	.02
Rumination syndrome	36 (4.2)	14 (2.7)	22 (6.5)	.006
Nausea and vomiting disorders	11 (1.3)	4 (0.8)	7 (2.1)	.1
Any gastroduodenal disorder	112 (13)	44 (8)	68 (20)	< .0001
C. Bowel disorders				
IBS	105 (12)	39 (8)	66 (19)	< .0001
Functional constipation	111 (13)	56 (11)	55 (16)	.02
Opioid-induced constipation	8 (0.9)	3 (0.6)	5 (1.5)	.18
Functional diarrhea	55 (6)	32 (6)	23 (7)	.70
Functional bloating/distention	65 (8)	28 (5)	37 (11)	.003
Unspecified functional bowel disorder	131 (15)	77 (15)	54 (16)	.64
Any bowel disorder	473 (55)	234 (45)	239 (70)	< .0001
D. Central nervous system disorders of GI pain				
Centrally mediated abdominal pain syndrome	1 (0.1)	0 (0)	1 (0.3)	.22
E. Biliary disorders				
Functional biliary pain	1 (0.1)	0 (0)	1 (0.3)	.22
F. Anorectal disorders				
Fecal incontinence	49 (6)	30 (6)	19 (6)	.93
Levator ani syndrome	26 (3)	10 (1.9)	16 (4.7)	.02
Proctalgia fugax	98 (11)	47 (9)	51 (15)	.007
Any anorectal disorder	158 (18)	78 (15)	80 (24)	.001
Frequency of abdominal pain				
≤ 2 to 3 days per month	701 (81)	466 (89)	235 (69)	< .0001
1 day per week	37 (4)	16 (3)	21 (6)	< .0001
2 to 3 days, or most days, per week	108 (13)	35 (7)	73 (21)	< .0001
Every day to multiple times a day	17 (2)	6 (1)	11 (3)	< .0001
GI medication use				
Laxatives	74 (9)	40 (8)	34(10)	.23
Antidiarrheals	27 (3)	11 (2)	16 (5)	.03
Antiemetics	12 (1)	4 (1)	8 (2)	.05
Antacids	222 (26)	117 (22)	105 (31)	.005
Antispasmodics	47 (5)	20 (4)	27 (8)	.01
Any of the above GI medication	285 (33)	154 (29)	131 (39)	.006
Surgical history				
Cholecystectomy	65 (8)	31 (6)	34 (10)	.03
Appendectomy	138 (16)	89 (17)	49 (14)	.30
Hysterectomy	111 (13)	58 (11)	53 (16)	.05

Table 1. Continued

	Overall CD cohort (n = 863)	GFD-adherent (n = 523)	GFD-non-adherent (n = 340)	*P*-value
Extra-intestinal symptoms				
Anxiety				
Mean GAD-7 anxiety score	3.6 (4.3)	2.4 (3.1)	5.4 (5.0)	< .0001
≥ Moderate anxiety levels, GAD-7 ≥10	80 (9)	19 (4)	61 (18)	< .0001
Depression				
Mean PHQ-9 depression score	4.6 (4.7)	3.0 (3.3)	7.1 (5.5)	< .0001
≥ Moderate depression levels, PHQ-9 ≥10	114 (13)	23 (4)	91 (27)	< .0001
Somatization				
Mean number of somatic sites, max = 12	4.8 (2.5)	4.0 (2.3)	5.9 (2.3)	< .0001
Mean PHQ-12 total score	6.0 (3.7)	4.8 (3.0)	7.8 (3.9)	< .0001
Medium to high somatization severity, PHQ-12 ≥8	273 (32)	101 (19)	172 (51)	< .0001
Quality of life				
Mean physical functioning	48.6 (7.7)	50.1 (6.6)	46.4 (8.8)	< .0001
Mean role physical	49.1 (7.7)	50.7 (6.4)	46.6 (8.9)	< .0001
Mean bodily pain	50.0 (8.2)	51.8 (7.4)	47.1 (8.6)	< .0001
Mean general health	47.2 (7.5)	49.3 (6.6)	44.0 (7.5)	< .0001
Mean vitality	49.9 (7.7)	52.4 (6.5)	46.1 (7.9)	< .0001
Mean social functioning	49.5 (7.7)	51.6 (6.1)	46.4 (8.8)	< .0001
Mean role emotional	49.2 (6.1)	50.6 (4.7)	47.1 (7.3)	< .0001
Mental health	49.5 (8.8)	51.7 (6.9)	46.1 (10.2)	< .0001

Note: Categorical data are presented as number (%), and continuous variables are presented as mean (standard deviation). *P*-values are between GFD-adherent versus GFD-nonadherent subjects.
CD, Celiac disease; FGID, functional gastrointestinal disorder; GAD, General Anxiety Disorder; GFD, gluten-free diet; GI, gastrointestinal; IBS, irritable bowel syndrome; PHQ, Patient Health Questionnaire.

matched population controls. Within the anorectal domain, GFD-adherent CD individuals were significantly more likely than matched population controls to have proctalgia fugax (10% vs 5.4%; OR, 1.9; 95% CI, 1.2–3.2).

Of those with CD who had FGIDs, 62% had 1 region affected, whereas 38% had multiple regions. A similar pattern was seen in population controls with FGIDs, with 64% afflicted with 1 region and 36% with multiple regions.

Comparison Between GFD-adherent CD Subjects With and Without FGIDs

Finally, we compared demographic characteristics, levels of psychological distress, somatization, and health care use in the 523 GFD-adherent subjects with CD with associated FGIDs (51%; n = 265) and without associated FGIDs (49%; n = 258) (Table 3). The duration of a GFD was similar between the groups, but those with associated FGIDs were more likely to be female (72% vs 64%; $P = .05$), albeit of a similar mean age. Following adjustments for gender, GFD-adherent subjects with FGIDs were significantly more likely (than their counterparts without FGIDs) to be taking GI-related medication (37% vs 21%; OR, 2.2; 95% CI, 1.5–3.2), and have more than moderate levels of anxiety (5% vs 2%; OR, 2.8; 95% CI, 1.0–8.0) and depression (7% vs 2%; OR, 3.6; 95% CI, 1.3–10.1), medium-to-high levels of somatization (31% vs 8%; OR, 5.2; 95% CI, 3.1–8.9), and lower quality of life scores in all domains ($P < .0001$). The substratified levels of psychological distress and somatization between GFD-adherent subjects with and without FGIDs are shown in Figure 3. Finally, the presence of multiple FGIDs correlated with increasing anxiety (r = 0.28), depression (r = 0.46), and somatization scores (r = 0.45; all $P < .001$).

Discussion

The main findings from this case control study are that 1 in 2 people with CD, despite having been on a GFD for a number of years and demonstrating optimal adherence, have ongoing chronic GI symptoms that are compatible with a Rome IV FGID. Although the presence of FGIDs in GFD-adherent individuals is appreciably lower than those who do not adhere to a GFD, it is still 2-fold the odds seen in age- and sex-matched population controls. Moreover, the presence of FGIDs in people with CD is associated with higher levels of psychological distress, somatization, and reduced quality of life, compared with those without associated FGIDs.

Our findings are in keeping with a systematic review that highlighted IBS-type symptoms to be common in subjects with CD.[4] However, substantial limitations were raised by the systematic review, including significant heterogeneity between the studies analyzed, the use of historic Rome I–III criteria, lack of an appropriately matched control group, and the absence of a validated tool to assess the duration or adherence to a GFD.[4] Moreover, there was sparse data on the prevalence of other FGIDs in CD.[12] Finally, factors associated with the

Table 2. Prevalence of FGIDs in GFD-adherent Subjects With CD Versus Age- and Sex-matched Population Controls

	General population controls (n = 462), n (%)	GFD-adherent subjects with CD (n = 462), n (%)	*P* value	Odds ratio (95% CI)
Demographics				
Female	303 (66)	303 (66)	1.0	–
Mean age, years (SD)	60 (12.6)	60 (12.6)	1.0	–
Age range, *years*				
18–39	41 (9)	41 (9)		
40–64	231 (50)	231 (50)	1.0	–
65+	190 (41)	190 (41)		
Prevalence of FGIDs				
Any FGID	163 (35)	239 (52)	< .0001	2.0 (1.5–2.6)
A. Esophageal disorders				
Functional chest pain	9 (1.9)	10 (2.2)	.82	1.1 (0.5–2.8)
Functional heartburn	6 (1.3)	7 (1.5)	.78	1.2 (0.4–3.5)
Globus	2 (0.4)	4 (0.9)	.69	2.0 (0.4–11.0)
Functional dysphagia	14 (3)	17 (3.7)	.58	1.2 (0.6–2.5)
Any esophageal disorder	28 (6.1)	35 (7.6)	.36	1.3 (0.8–2.1)
B. Gastroduodenal disorders				
Functional dyspepsia	22 (4.8)	23 (5)	.88	1.1 (0.6–1.9)
Belching disorder	6 (1.3)	7 (1.5)	.78	1.2 (0.4–3.5)
Rumination syndrome	14 (3)	14 (3)	1.0	1.0 (0.4–2.1)
Nausea and vomiting disorders	3 (0.6)	4 (0.9)	.70	1.3 (0.3–6.0)
Any gastroduodenal disorder	34 (7.4)	40 (8.7)	.47	1.2 (0.7–1.9)
C. Bowel disorders				
IBS	21 (4.5)	35 (7.6)	.05	1.7 (1.0–3.0)
Functional constipation	35 (7.6)	49 (10.6)	.11	1.4 (0.9–2.3)
Opioid-induced constipation	11 (2.4)	3 (0.6)	.03	0.3 (0.1–0.97)
Functional diarrhea	22 (4.8)	31 (6.7)	.20	1.4 (0.8–2.5)
Functional bloating/distention	16 (3.5)	27 (5.8)	.09	1.7 (0.9–3.3)
Unspecified functional bowel disorder	41 (9)	70 (15)	.003	1.8 (1.2–2.8)
Any bowel disorder	142 (31)	214 (46)	< .0001	1.9 (1.5–2.5)
D. Anorectal disorders				
Fecal incontinence	14 (3)	21 (4.5)	.23	1.5 (0.8–3.0)
Levator ani syndrome	9 (1.9)	9 (1.9)	1.0	1.0 (0.4–2.5)
Proctalgia fugax	25 (5.4)	46 (10)	.01	1.9 (1.2–3.2)
Any anorectal disorder	43 (9.3)	67 (14.5)	.02	1.7 (1.1–2.5)

CD, Celiac disease; CI, confidence interval; FGID, functional gastrointestinal disorder; GFD, gluten-free diet; IBS, irritable bowel syndrome; SD, standard deviation.

presence of FGIDs in individuals with CD adherent to a GFD have not previously been studied in depth. In contrast, the key strength of our study is that it is a large, population-based, age- and sex-matched case-control study using contemporary and validated questionnaires to evaluate the prevalence of – and factors associated with – the spectrum of all Rome IV FGIDs in people with CD based on adherence to a GFD.

Our study does have limitations. First, selection bias is an issue when conducting surveys, irrespective of where they are performed (eg, population-based, primary or secondary care, societal groups) or the methodology used to collect the data (eg, postal, telephone, or online). Conceivably, symptomatic subjects may be more likely to respond than those asymptomatic. However, we attempted to reduce potential bias by promoting our survey as "general health" and not "gastroenterology-related." In addition, quality assurance measures were built in within the online questionnaire system to ensure there was no missing data and that we could also exclude inconsistent responders, the latter by attention check and repeat questions. Secondly, we had a response rate of 19% from the online Coeliac UK society cohort, which may not be reflective of nonresponders or non-societal members. Nevertheless, it is still the largest study of this nature to date, and we did sample individuals throughout the UK, as opposed to within the confines of a single center. The age and gender profile of respondents was almost identical to the randomly selected cohort of 5297 adults in whom the survey was initially sent out to, and also in line with UK and global data characterizing CD.[17,18] However, our cohort was predominantly of white race, and the findings may not be generalized to other ethnicities, although CD and FGIDs are common conditions independently seen worldwide.[18,19] Thirdly, we did not have access to medical records to confirm the

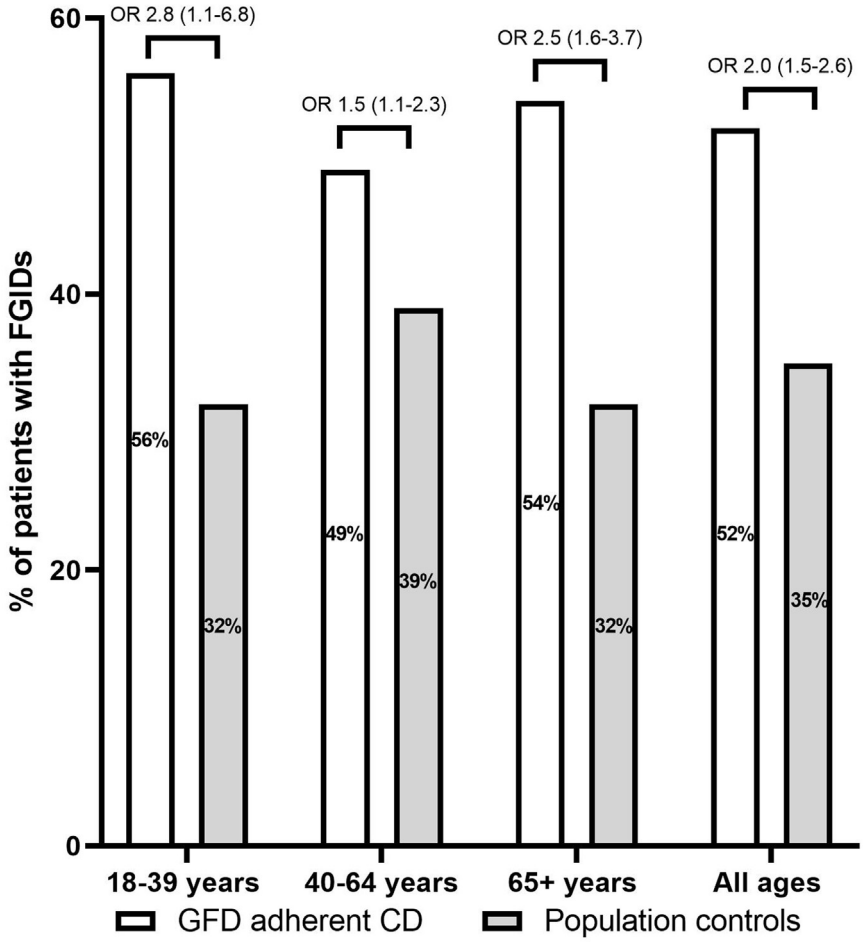

Figure 2. Prevalence of FGIDs across different age groups in GFD-adherent subjects with CD versus age- and sex-matched population controls. OR, Odds ratio.

declared doctor diagnosis of CD, nor could we perform celiac serology or duodenal biopsies to assess whether those demonstrating optimal adherence to a GFD (based on a CDAT score $\leq$13) were in disease remission. However, as approximately 80% had been taking a GFD for at least 5 years, and the CDAT is superior to celiac serology in assessing GFD adherence,[20] we feel it is likely that the vast majority of individuals would be in histologic remission. This argument is supported by data reporting histologic remission rates to range from 34% to 65% at 2 years after diagnosis, and 66% to 85% at 5 years.[15] Moreover, refractory CD is rare, reported to affect between 0.3% and 4% of patients with CD.[15] Fourthly, other organic GI conditions associated with CD may be the cause of ongoing symptoms in those who are GFD-adherent, most notably microscopic colitis, which is seen in roughly 4% of cases; although this could potentially account for diarrhea, it would not explain the high prevalence of other commonly reported symptoms such as functional dyspepsia, bloating, constipation, or anorectal disorders.[21]

The study raises a number of important considerations that will pave the way for future clinical trials in CD and advance patient care. We show that almost 40% of individuals are not adequately adhering to a GFD and that they have a much higher prevalence of FGID-type symptoms, health care use, mood disturbances, and reduced quality of life than those who are GFD-adherent. Although this study was not geared towards identifying reasons for poor adherence (eg, social and financial circumstances and access to dietitians), it does emphasize the need for regular long-term clinical follow-up so that ongoing education/resources can be provided to better optimize dietary adherence and improve well-being.

Yet, we also show that despite the remaining 60% having optimal adherence to a GFD, one-half of these individuals still have ongoing symptoms compatible with a FGID and that this is associated with increased health care use, psychological comorbidity, somatization, and reduced quality of life. The reasons for the presence of FGIDs in subjects with CD who are GFD-adherent is unclear, but, given that it is 2-fold greater than that seen in age- and sex- matched controls, the mucosal insult triggered by CD may have led to a disorder of gut-brain interaction, similar to that seen with postinfectious IBS/dyspepsia or inflammatory bowel disease.[14,22] Indeed, post-infectious IBS/dyspepsia affects approximately 10% of individuals following a bout of gastroenteritis, whereas a third of individuals with inflammatory bowel disease in remission have symptoms

Table 3. Characteristics of GFD-adherent Subjects With CD (n = 523), Stratified According to Those With and Without FGIDS

	GFD-adherent subjects with CD without FGID (n = 258)	GFD-adherent subjects with CD with FGID (n = 265)	*P*-value
Demographics			
Mean age, *years*	62 (12.7)	61 (13.3)	.62
Female	164 (64)	190 (72)	.05
White race	253 (98)	261 (99)	.71
Duration of a GFD			
1 year	8 (3)	10 (4)	
2–4 years	51 (20)	42 (16)	
≥5 years	199 (77)	213 (80)	.48
Extra-intestinal symptoms			
Anxiety			
Mean GAD-7 anxiety score	1.7 (2.7)	3.0 (3.3)	< .0001
≥ Moderate anxiety levels, GAD-7 ≥10	5 (2)	14 (5)	.04
Depression			
Mean PHQ-9 depression score	2.1 (2.5)	3.9 (3.7)	< .0001
≥ Moderate depression levels, PHQ-9 ≥10	5 (2)	18 (7)	.01
Somatization			
Mean number of somatic sites, max=12	3.2 (2.1)	4.8 (2.2)	< .0001
Mean PHQ-12 total score	3.6 (2.6)	6.0 (3.0)	< .0001
Medium-high somatization severity, PHQ-12 ≥8	20 (8)	81 (31)	< .0001
Quality of life			
Mean physical functioning	51.5 (5.1)	48.7 (7.5)	< .0001
Mean role physical	52.2 (4.4)	49.2 (7.6)	< .0001
Mean bodily pain	54.0 (6.6)	49.8 (7.6)	< .0001
Mean general health	51.5 (6.0)	47.3 (6.5)	< .0001
Mean vitality	54.0 (5.6)	51.0 (7.1)	< .0001
Mean social functioning	53.3 (4.2)	50.0 (7.1)	< .0001
Mean role emotional	51.5 (3.1)	49.7 (5.7)	< .0001
Mental health	53.2 (5.2)	50.2 (7.6)	< .0001
GI medication use			
Laxatives	5 (2)	35 (13)	< .0001
Antidiarrheals	4 (1.6)	7 (3)	.39
Antiemetics	0 (0)	4 (1.5)	.12
Antacids	44 (17)	73 (28)	.004
Antispasmodics	8 (3.1)	12 (4.5)	.39
Any of the above GI medication	55 (21)	99 (37)	< .0001
Surgical history			
Cholecystectomy	11 (4)	20 (7.5)	.11
Appendectomy	49 (19)	40 (15)	.24
Hysterectomy	22 (8.5)	36 (14)	.07

Note: Categorical data are presented as number (%), and continuous variables are presented as mean (standard deviation).
CD, Celiac disease; FGID, functional gastrointestinal disorder; GAD, General Anxiety Disorder; GFD, gluten-free diet; GI, gastrointestinal; IBS, irritable bowel syndrome; PHQ, Patient Health Questionnaire.

compatible with IBS, with associated factors being female gender and psychological comorbidity.[14,22] This phenotypic profile resembles the GFD-adherent CD subjects described herein, and although an association between FGIDs and psychological comorbidity was noted in our cohort, the direction of causality cannot be established due to its cross-sectional design. Previous studies in FGIDs have shown that in one-third of individuals a mood disorder precedes gut symptoms, but in two-thirds gut symptoms precede the mood disorder – similar longitudinal studies are needed in CD.[23]

Our study encourages future clinical trials in CD to identify and address FGIDs (recently termed disorders of gut-brain interaction) in those who are GFD-adherent yet have lingering symptoms. A recent single-center randomized controlled trial from Italy comprising 50 patients with CD found that a short-term, low-FODMAP diet in addition to a GFD helped reduce GI symptoms and improve mental well-being compared with a GFD alone.[24] This approach needs corroboration, although there may be inevitable concerns of superimposing one restrictive diet on top of another. The use of a probiotic mixture in patients with CD and persisting IBS-type symptoms has been investigated in a recent randomized, double-blind, placebo-controlled multicenter trial showing promising results, but again requires further replication.[25] Another thoughtful option, which is currently being used to address IBS-type symptoms in

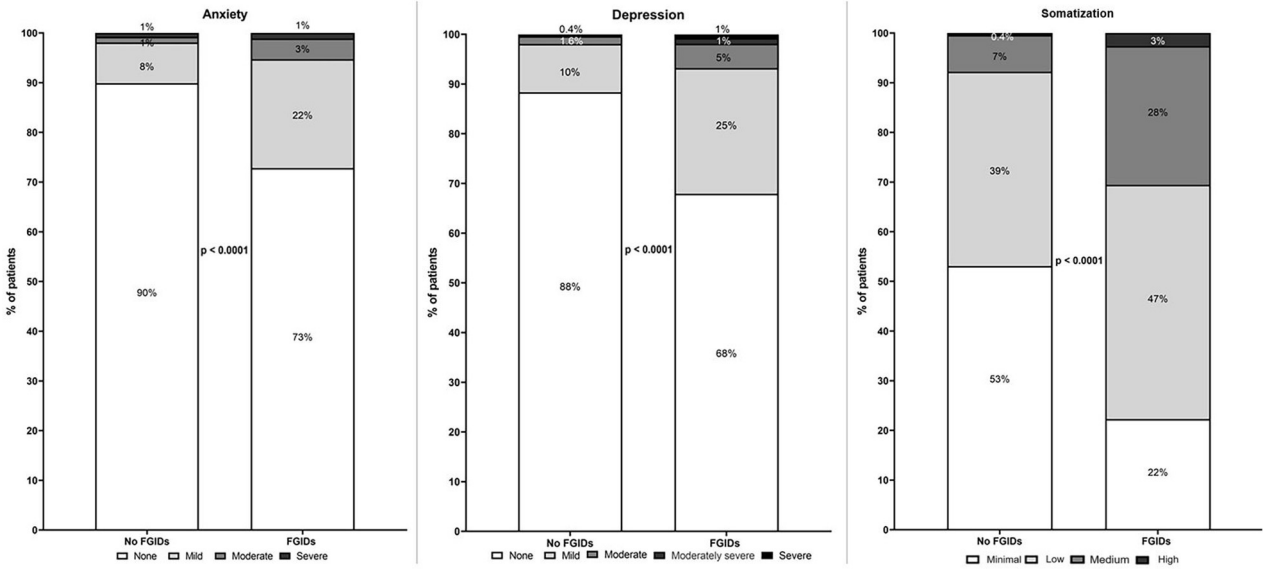

Figure 3. Levels of psychological distress and somatization in GFD-adherent subjects with CD, with and without associated FGIDs.

inflammatory bowel disease but has yet to be extrapolated to CD, is to consider psychological treatments, such as neuromodulators (eg, low dose tricylic antidepressants), hypnotherapy, or cognitive behavioral therapy, given that they are of benefit in FGIDs and also improve mood.[2,14,26]

Conclusions

In conclusion, 1 in 2 individuals with CD, despite having been on a GFD for a number of years and demonstrating optimal adherence, have ongoing symptoms compatible with a Rome IV FGID. The presence of FGIDs is associated with psychological comorbidity, somatization, and reduced quality of life. Addressing the coexistence of disorders of gut-brain interaction in CD patients could improve outcomes in this specific group of patients.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Clinical Gastroenterology and Hepatology at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2021.07.026.

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Conflicts of interest
These authors disclose the following: Magnus Simren has received unrestricted research grants from Danone Nutricia Research and Glycom and served as a consultant/advisory board member or speaker for Biocodex, Danone Nutricia Research, Ironwood, Genetic Analysis AS, Glycom, Tillotts, Menarini, Takeda, Kyowa Kirin, Arena, Adnovate, Alimentary Health, AlfaSigma, Falk Foundation, and Shire. Hans Törnblom has served as a consultant/advisory board member for Almirall and Shire. Olafur S. Palsson has received salary support from a research grants from Takeda Pharmaceuticals, Salix Pharmaceuticals, and the Rome Foundation, from a consulting agreement with Glycom A/S and Ironwood Pharmaceuticals, from an educational grant provided by Takeda Pharmaceuticals, and has received a speaker honorarium in educational programs supported by Ironwood Pharmaceuticals, Takeda Pharmaceuticals, and the Rome Foundation. William E. Whitehead received research grants from Takeda, Ironwood, Salix, and the Rome Foundation; served as a consultant to Biomerica USA, Ono Pharmaceuticals, and Ferring; and received unrestricted educational grants from Takeda and Ferring. Ami D. Sperber has served as a consultant and speaker for Takeda-Israel and has received a research grant from them and as a consultant for Abbvie-Israel. David S. Sanders received an educational grant from Schaer (a gluten-free food manufacturer). The remaining authors disclose no conflicts.

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Supplementary Methods

Questionnaire

The comprehensive questionnaire collected information on the following:

a) Demographics: Age, sex, and race.

b) Rome IV diagnostic questionnaire:[11] This validated questionnaire is benchmarked as the screening tool for individuals with functional gastrointestinal disorders (FGIDs) and their inclusion into clinical trials and for performing epidemiological surveys. For the purpose of this study, we report individuals meeting criteria for FGIDs and then categorize them into 1 of the 6 anatomical gastrointestinal (GI) regions that they belong to (ie, esophageal, gastroduodenal, gallbladder, bowel, anorectal, and centrally mediated disorders of GI pain). Subjects were also asked to report the frequency of abdominal pain over the last 3 months, with answers ranging from "never" to "every day to multiple times per day."

c) Patient Health Questionnaire (PHQ)-9[12] and General Anxiety Disorder (GAD)-7[13] questionnaire: These are 9- and 7-item questionnaires, respectively, which are widely used and validated to assess severity of symptoms of depression and generalized anxiety. The PHQ-9 categorizes symptoms of depression as none (score 0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27). The GAD-7 categorizes symptoms of anxiety as none (score 0–4), mild (5–9), moderate (10–14), and severe (15–21). A value of $\geq$10 on either the PHQ-9 or GAD-7 is considered to be clinically abnormal.

d) Patient Health Questionnaire (PHQ)-12 non-GI somatic symptoms scale:[14,15] The PHQ-12 is a modified version of the widely used PHQ-15 somatization screening questionnaire that excludes the 3 GI symptoms (nausea, abdominal pain, altered bowel habit), as these are likely to be directly related to FGIDs. As a result, the PHQ-12 only records bothersome non-GI symptoms over the past month. The twelve symptoms assessed are back pain, limb pain, headaches, chest pain, dizziness, fainting spells, palpitations, breathlessness, menstrual cramps, dyspareunia, insomnia, and lethargy. Subjects were asked to rate how much they had been troubled by these 12 symptoms over the last 4 weeks as 0 ("not bothered at all"), 1 ("bothered a little"), or 2 ("bothered a lot"). The PHQ-12 responses can be used to calculate (1) the number of sites reporting somatic symptoms (ranging from 0–12), (2) the overall somatization severity score (ranging from 0–24), and (3) the somatization severity category (mild, PHQ $\leq$3; low, PHQ 4–7; medium, PHQ 8–12; high, PHQ $\geq$13). Higher scores represent greater somatization.

e) Short Form (SF)-8 score:[16] This validated questionnaire is commonly used in large-scale epidemiological studies to assess general health-related quality of life over the past month. The 8 items enquire about physical functioning, physical role, bodily pain, general health perceptions, vitality, social functioning, emotional role, and mental health. The scores are normalized to the general population that has a mean score of 50. A high score represents better quality of life, whereas low scores represent poorer quality of life.

f) Health care use: We asked whether the following GI-related medications were being taken on at least a weekly basis: laxatives, anti-diarrheals, anti-emetics, antacids, and antispasmodics. Subjects were asked about history of abdominal surgeries, that being cholecystectomy, appendectomy, and hysterectomy.

g) Duration and adherence to a gluten-free diet (GFD): These questions were only asked of members of Coeliac UK. Participants with celiac disease were asked how long they had been taking a GFD and, having excluded those taking a GFD for less than 1 year, the duration was subdivided as 1 year, 2 to 4 years, or $\geq$5 years.

The validated Celiac Disease Adherence Tool (CDAT) is a clinically relevant, easily administered, 7-item instrument that allows for standardized evaluation of GFD adherence and is superior to tissue transglutaminase serology.[17] The combined score on the CDAT ranges from 7 to 35, with a value $\leq$13 considered to demonstrate very good or excellent adherence, which, for the purpose of this study, was classed as being optimal or GFD-adherent. In contrast, a CDAT score $>$13 was deemed as being suboptimal or GFD-nonadherent.

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Supplementary Table 1. Studies of FGIDs in Adults With CD ± Controls

Author and year	Country	Study design	Total number of subjects (cases with CD, controls)	Criteria used to define FGIDs	Subjects with CD adhering to a GFD	Prevalence of FGIDs in subjects with CD on GFD	Prevalence of FGIDs in controls
O'Leary, 2002[1]	Ireland	Case control	312 (150, 162)	Rome I	69%	IBS 19%	IBS 5%
Murray, 2004[2]	United States	Cross sectional case survey	215	Rome II	100%	IBS 48%	N/A
Hauser, 2006[3]	Germany	Cross sectional case survey	446	Rome I	66%	IBS 26%	N/A
Hauser, 2007[4]	Germany	Cross sectional case survey	412	Rome I	80%	IBS 23%	N/A
Usai, 2007[5]	Italy	Case control[a,b]	1130 (129, 1001)	Rome II	62%	IBS 55%	IBS 10%
Dorn, 2010[6]	United States	Cross sectional case survey	101	Rome III	83%	IBS 58%	N/A
Barratt, 2011[7]	United Kingdom	Case control[a]	573 (225, 348)	Rome II	71%	IBS 22%	IBS 6%
Lorusso, 2011[8]	Italy	Case control	606 (122, 484)	Rome III	100%	IBS 43%	IBS 16%
Silvester, 2017[9]	Canada	Case series	85	Rome III	93% at 1 year	At baseline: IBS 57%, FD 27%, FB 9% At 1 year on GFD: IBS 22%, FD 8%, FB 16%	N/A
Potter, 2018[10]	Australia	Cross sectional case survey	3542	Rome III	Not recorded	IBS 25%, FD 39%	N/A

CD, Celiac disease; FBD, functional bloating; FC, functional constipation; FD, functional dyspepsia; FGID, functional gastrointestinal disorder; GFD, gluten-free diet; IBS, irritable bowel syndrome.
[a]Age- and sex-matched.
[b]Controls taken from the general population.

Supplementary Table 2. Prevalence of FGIDs According to Duration of a GFD

	1 year of GFD	2–4 years of GFD	≥ 5 years of GFD	*P*-value
Overall CD cohort (n = 863)	21/32 (66%)	105/174 (60%)	396/657 (60%)	.82
GFD-adherent (n = 523)	10/18 (56%)	42/93 (45%)	213/412 (52%)	.48
GFD-nonadherent (n = 340)	11/14 (79%)	63/81 (78%)	182/245 (74%)	.79

CD, Celiac disease; FGID, functional gastrointestinal disorder; GFD, gluten-free diet.