The Virtual Celiac Symptoms Study: reported symptoms over 12 weeks in adults

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Introduction

- Celiac disease (CeD) is an autoimmune condition triggered by gluten consumption and characterized by autoantibodies and inflammation of the small intestine.[1,2]
- CeD is estimated to affect approximately 1% of people worldwide.[3]
- The only management option for CeD is strict adherence to a gluten-free diet (GFD), but this has major limitations and many individuals may still experience symptoms and/or intestinal damage owing to inadvertent gluten ingestion or barriers to sufficient adherence such as food availability, financial constraints or patient perceptions.[4–7]
- Symptoms are an important metric in CeD and have a significant impact on patient lives.[2]
- The Virtual Celiac Symptoms Study (VCSS) is the first prospective observational study to assess daily symptom patterns and impacts of CeD in US adults and adolescents following a GFD.
  – The baseline disease characteristics of the adult population of this study were previously described.[8]

Objectives

- To assess GFD experience and CeD-related symptoms in the adult population of the VCSS over 12 weeks.

Methods

Study design

- An observational prospective study (VCSS; NCT05309330) was conducted in US adults and adolescents with CeD.
- Participants self-reported information via a smartphone app regarding:
  – CeD diagnosis, demographics and clinical characteristics
  – occurrence and severity of daily symptoms over 12 weeks (via the Celiac Disease Symptom Diary 2.1; CDSD 2.1[c]),[9] which included questions regarding the severity of diarrhea, abdominal pain, bloating, nausea and tiredness, and the frequency of vomiting and diarrhea
  – known and suspected inadvertent gluten exposure over 12 weeks.
- Participants were recruited by the Celiac Disease Foundation via digital advertisements (email, social media channels, app push notifications, website advertisements and a study microsite).
- Data collection began on July 25, 2022, and completed on March 4, 2023.

Inclusion criteria

- English-speaking, aged ≥ 18 years (for the adult cohort) and residing in the USA.
- Diagnosis of CeD for ≥ 1 year, confirmed via self-reported biopsy and serology.
- Adherence to a GFD for ≥ 6 months.
- CeD-related symptoms (patient-reported) within the past 3 months.
- Daily access to a smartphone and Internet/Wi-Fi/cellular data.

Exclusion criteria

- Planned or current involvement in any clinical study with an investigational drug, or surgical procedure or gluten challenge during the 3-month observation period.

Data analysis

- The number of days with core CeD symptoms during the 12-week study period was recorded and a weighted mean number of days with each symptom was determined to account for any days with missing data (weighted mean was calculated as the mean proportion of days with reported symptom(s) across participants weighted by the total study period of 84 days).
- Prevalence of core CeD symptoms during the 12-week study period was stratified by self-reported level of GFD adherence at study initiation and by irritable bowel syndrome (IBS) status of participants.
  – An assessment of symptom prevalence in participants with and without IBS was of interest because a significant proportion (> 20%) of participants reported IBS as a comorbidity.
- Participants were included in these analyses if they experienced any symptom at least once during the 12-week study period.
- All measures were analyzed using descriptive statistics with R version 4.0.4. The p values were generated using a χ^2 test for categorical variables (or Fisher's exact test when expected value < 5) and analysis of variance (ANOVA) for continuous variables.

Results

Demographics and clinical characteristics

- Adults (≥ 18 years at enrollment) comprised 338 (70.4%) of the 480 enrolled participants (**Table 1**).
  – The mean (standard deviation; SD) age was 37.9 (12.5) years, 87.9% self-identified as female, 98.5% reported to be of White race and 66.0% had a college or graduate (master's or doctorate) degree.
  – The majority (71.0%) of adult participants self-reported moderate (38.5%) or severe (32.5%) symptoms at baseline.
- At study initiation, severity of symptoms was unrelated to adult participant demographics, clinical characteristics and time since diagnosis of CeD.
- The most common self-reported comorbidities at baseline were anxiety (56.8%) and depression (42.3%) (**Table 1**).
- Although 90.0% of adult participants reported at least one comorbidity, only IBS and anemia were related to severity of symptoms at study initiation.

Baseline symptoms

- At study entry, 58.3% of participants reported symptoms in the past week, 31.1% in the past month and 10.7% in the past 3 months (**Table 2**).
- At study initiation, participants reported that symptoms following gluten exposure were "*extremely likely*" (63.0%) and the likelihood was greater in those with severe symptoms than in those with mild symptoms (89.1% versus 10.5%) (**Table 2**).

Frequency of gluten exposure over the 12-week study period

- The mean (SD) number of days with reported gluten exposure was 7.1 (9.3) (**Table 3**).

Key messages

- **Despite adherence to a gluten-free diet, ongoing gastrointestinal (GI) symptoms are common in adult patients with celiac disease (CeD).**

- **This observational study highlights the need for continued monitoring of patients with CeD and that GI symptoms may be appropriate for inclusion as endpoints in clinical trials of potential CeD therapies.**

Table 1. Participant baseline demographics and clinical disease characteristics across categories of self-reported symptom severity

	Overall	Severity of self-reported symptoms at baseline				p value
		Mild	Moderate	Severe	Varies widely	
Number of participants, n (%)	338 (100)	19 (5.6)	130 (38.5)	110 (32.5)	79 (23.4)	–
Age, years, mean (SD)	37.9 (12.5)	40.7 (11.7)	37.4 (12.1)	37.9 (13.6)	38.1 (11.9)	0.75
White race, n (%)	333 (98.5)	18 (94.7)	129 (99.2)	107 (97.3)	79 (100)	0.14
BMI, kg/m², mean (SD)	27.3 (7.4)	26.4 (5.3)	27.5 (6.9)	26.4 (7.7)	28.1 (8.2)	0.42
Sex, n (%)						
Female	297 (87.9)	15 (79.0)	115 (88.5)	97 (88.2)	70 (88.6)	0.65
Male	41 (12.1)	4 (21.1)	15 (11.5)	13 (11.8)	9 (11.4)	–
Education, n (%)						
High school graduate or lower	23 (6.8)	1 (5.3)	10 (7.7)	5 (4.5)	7 (8.9)	0.83
Some college	92 (27.2)	4 (21.1)	31 (23.9)	39 (35.5)	18 (22.8)	0.13
College/graduate degree	223 (66.0)	14 (73.7)	89 (68.5)	66 (60.0)	54 (68.4)	0.47
Time since CeD diagnosis, years, mean (SD)	7.3 (5.3)	5.4 (5.6)	6.8 (4.6)	7.8 (5.9)	7.8 (5.2)	0.13
Comorbidities,[a] n (%)						
At least one comorbidity	304 (89.9)	17 (89.5)	117 (90.0)	101 (91.8)	69 (87.3)	0.76
Anxiety	192 (56.8)	10 (52.6)	70 (53.9)	63 (57.3)	49 (62.0)	0.69
Depression	143 (42.3)	9 (47.4)	46 (35.4)	50 (45.5)	38 (48.1)	0.23
GERD	86 (25.4)	6 (31.6)	28 (21.5)	32 (29.1)	20 (25.3)	0.51
IBS	70 (20.7)	0 (0.0)	19 (14.6)	28 (25.5)	23 (29.1)	0.003
Thyroid disease	70 (20.7)	5 (26.3)	27 (20.8)	26 (23.6)	12 (15.2)	0.46
Anemia	68 (20.1)	3 (15.8)	19 (14.6)	33 (30.0)	13 (16.5)	0.02
Dermatitis herpetiformis	44 (13.0)	3 (15.8)	10 (7.7)	19 (17.3)	12 (15.2)	0.10
Osteoporosis/osteopenia	31 (9.2)	4 (21.1)	9 (6.9)	12 (10.9)	6 (7.6)	0.20
SIBO	18 (5.3)	1 (5.3)	4 (3.1)	7 (6.4)	6 (7.6)	0.41
IBD[b]	8 (2.4)	0 (0.0)	3 (2.3)	2 (1.8)	3 (3.8)	0.84
Type 1 diabetes	6 (1.8)	2 (10.5)	1 (0.8)	2 (1.8)	1 (1.3)	0.07

*Disorders that participants had in addition to CeD. Listed are current medical problems, diagnosed by a doctor or other healthcare professional, for which participants are currently or were receiving treatment within the past 12 months. Participants were allowed to select all that apply. [b]Includes ulcerative colitis and Crohn's disease.
CeD, celiac disease; GERD, gastroesophageal reflux disease; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; SD, standard deviation; SIBO, small intestine bacterial overgrowth.

Table 2. Symptom occurrence at study initiation among adult participants with CeD across categories of baseline disease severity

|	Overall	Severity of self-reported symptoms at baseline				p value
		Mild	Moderate	Severe	Varies widely	
Number of participants, n (%)	338 (100)	19 (5.6)	130 (38.5)	110 (32.5)	79 (23.4)	–
Most recent CeD symptoms experienced at study initiation, n (%)						
In the past week	197 (58.3)	8 (42.1)	82 (63.1)	62 (56.4)	45 (57.0)	0.32
In the past month	105 (31.1)	11 (57.9)	34 (26.2)	34 (30.9)	26 (32.9)	0.05
In the past 3 months	36 (10.7)	0 (0.0)	14 (10.8)	14 (12.7)	8 (10.1)	0.48
Likelihood of symptoms after gluten exposure, self-reported at study initiation, n (%)						
Extremely likely	213 (63.0)	2 (10.5)	58 (44.6)	98 (89.1)	55 (69.6)	< 0.0001
Likely	71 (21.0)	4 (21.1)	46 (35.4)	6 (5.5)	15 (19.0)	< 0.0001
Somewhat likely	39 (11.5)	8 (42.1)	22 (16.9)	4 (3.6)	5 (6.3)	< 0.0001
Unlikely	8 (2.4)	5 (26.3)	1 (0.8)	0 (0.0)	2 (2.5)	< 0.0001
Extremely unlikely	7 (2.1)	0 (0.0)	3 (2.3)	2 (1.8)	2 (2.5)	1.00
Level of GFD adherence,[a] self-reported at study initiation, n (%)						
I eat a GFD and rarely eat gluten on purpose	26 (7.7)	1 (5.3)	10 (7.7)	7 (6.4)	8 (10.1)	0.83
I eat a GFD and rarely eat gluten accidentally	241 (71.3)	16 (84.2)	93 (71.5)	76 (69.1)	56 (70.9)	0.61
I eat a GFD and never eat gluten accidentally or on purpose	71 (21.0)	2 (10.5)	27 (20.8)	27 (24.6)	15 (19.0)	0.56

*None of the participants reported "*eating gluten-free diet sometimes*" or "*eating gluten-containing foods regularly*".
CeD, celiac disease; GFD, gluten-free diet; SD, standard deviation.

Table 3. Frequency of reported symptoms and gluten exposure among adult participants with CeD across categories of baseline disease severity during the 12-week study period

|	Overall	Severity of self-reported symptoms at baseline				p value
		Mild	Moderate	Severe	Varies widely	
Number of participants, n (%)	338 (100)	19 (5.6)	130 (38.5)	110 (32.5)	79 (23.4)	–
Frequency of symptoms/gluten exposure (days) number of days during 12-week study period						
Symptoms reported	60.3 (20.0)	61.5 (17.8)	58.7 (20.7)	60.0 (21.4)	63.1 (17.3)	0.49
Gluten exposure (known or suspected)	7.1 (9.3)	8.5 (14.2)	7.1 (8.2)	7.4 (10.9)	6.2 (6.0)	0.78

CeD, celiac disease; SD, standard deviation.

Figure 1. Number of days with core CeD symptoms during the 12-week study period among adult participants (N = 338) who experienced each symptom
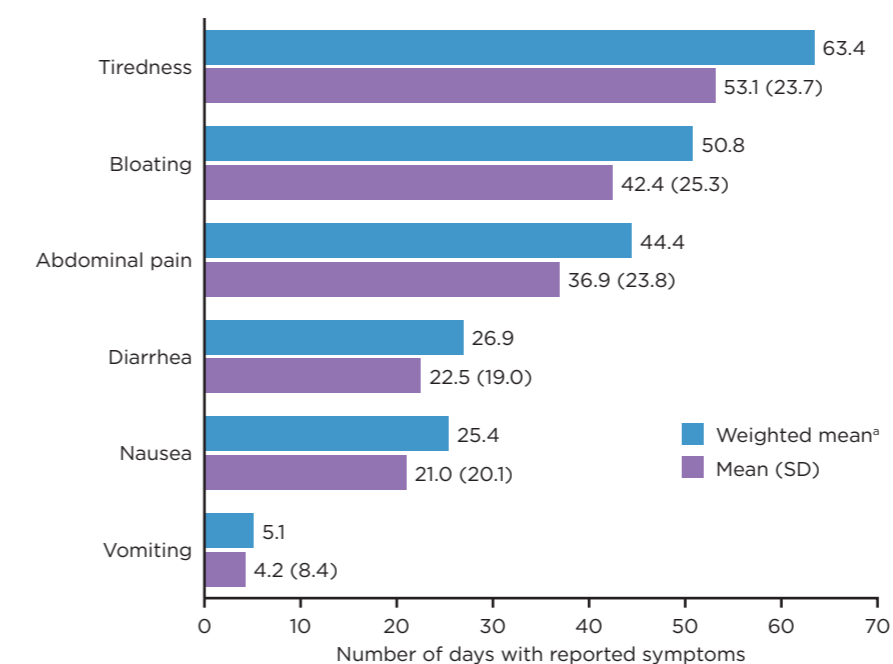
Symptoms were assessed using CDSD 2.1 and included diarrhea, abdominal pain, bloating, nausea, tiredness and vomiting. All participants (N = 338) with available data on ≥ 1 day were included in this analysis.
[a]The weighted mean was calculated as the mean proportion of days with reported symptom(s) across participants weighted by the total study period days (84 days).
CDSD, Celiac Disease Symptom Diary; CeD, celiac disease; SD, standard deviation.

Figure 2. CeD core symptoms during the 12-week study period stratified by level of adherence to GFD and IBS diagnosis reported at baseline
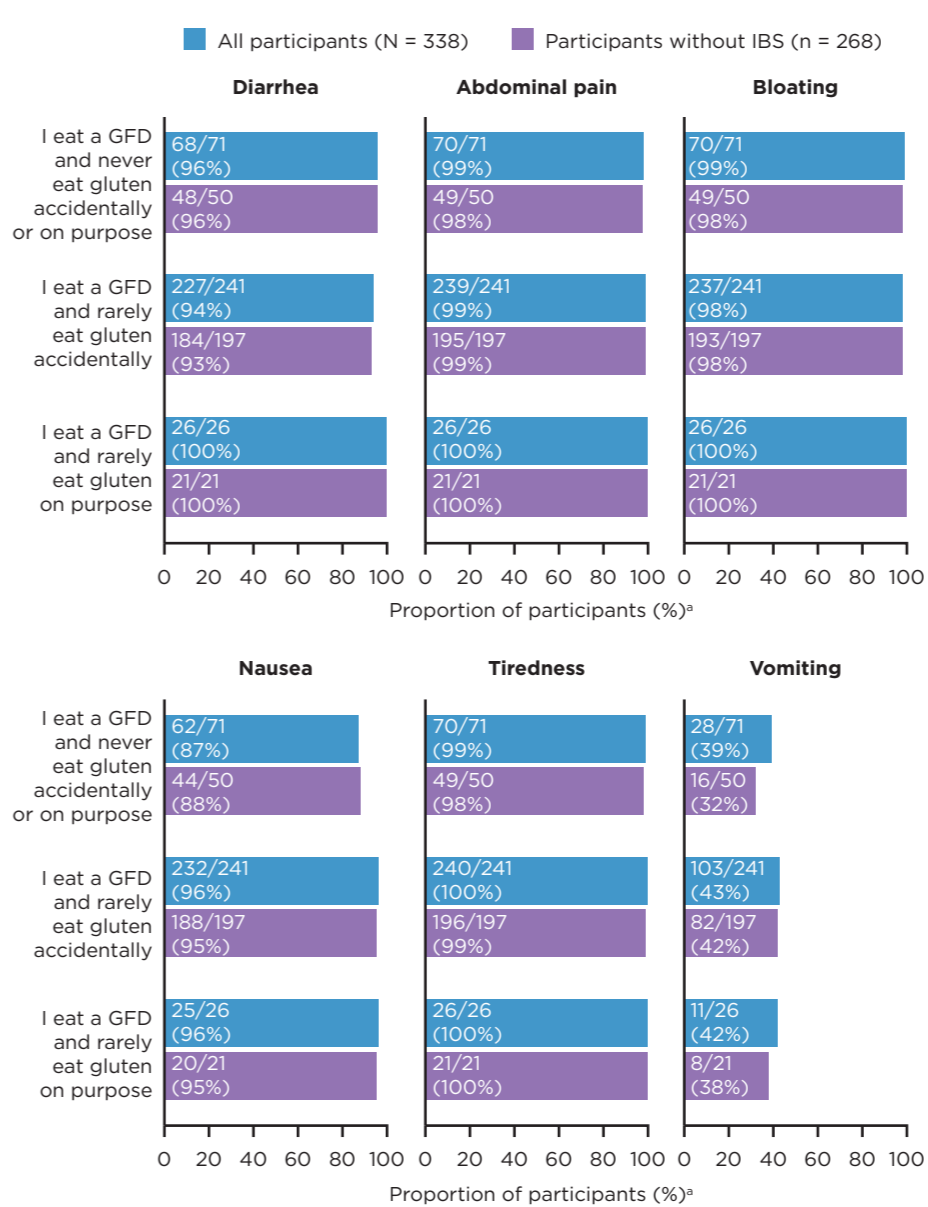
[a]None of the participants reported "*eating gluten-free diet sometimes*" or "*eating gluten-containing foods regularly*".
Small discrepancies in percentages are due to rounding errors. Data inside bars represent n/N (%).
CeD, celiac disease; GFD, gluten-free diet; IBS, irritable bowel syndrome.

Frequency and prevalence of symptoms over the 12-week study period

- The mean (SD) number of days of reported symptoms was 60.3 (20.0) (**Table 3**).
- Tiredness, bloating and abdominal pain were the most frequently experienced symptoms during the 12 weeks of the study (**Figure 1**).
- All adult participants reported at least one core CeD symptom.
  – Each GI symptom, with the exception of nausea (in participants who reported adhering to a GFD and "*never eating gluten accidentally or on purpose*") and vomiting, occurred at least once in over 90.0% of adult participants (**Figure 2**).
  – Participants experienced symptoms regardless of their level of GFD adherence (self-reported at baseline) or diagnosis of IBS (**Figure 2**).

Limitations

- There is currently no classification of symptom severity for CeD, thus participant self-assessment was used for this study.
- The self-reporting of daily symptoms and dietary intake are subject to inherent biases.[10] Furthermore, daily reporting could increase awareness of GFD adherence, which may lead to changes in participants' dietary choices during the course of the study.
- There may be misclassification of CeD status by participants.
- Generalizability of these results might be limited because the participants of this study were US adults who were mostly White, highly educated and recruited from a patient advocacy group.

Conclusions

- Adult participants reported frequent CeD symptoms during the 12-week study period, regardless of level of adherence to a GFD (self-reported at baseline) or IBS diagnosis.
- This study further highlights the unmet need for additional treatments for patients with CeD beyond management with a GFD.
- GI symptoms such as diarrhea, nausea, bloating and abdominal pain may be relevant co-endpoints for assessment of treatment effects in clinical trials of potential CeD therapies.
- Further CeD populations should be assessed to explore regional variations in these outcomes.

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