Depression and insomnia among individuals with celiac disease or on a gluten-free diet in the USA: results from a national survey

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Background There is uncertainty regarding the prevalence of psychiatric illnesses in patients with celiac disease (CD) and people who avoid gluten (PWAG) without a diagnosis of CD.
Participants and methods We obtained data from 22 274 participants from the 2009–2014 National Health and Nutrition Examination Survey to compare the prevalence of depression, insomnia, quality-of-life variables, and psychotropic medication use in CD participants and PWAGs to controls. We used multivariable logistic regression to assess for independent associations between CD/PWAG status and the outcomes of these variables.
Results Depression was present in 8.2% of controls compared with 3.9% of participants with CD ($P = 0.18$) and 2.9% of PWAGs ($P = 0.002$). After adjustment for age, sex, race, income, and access to healthcare, PWAGs maintained lower odds of depression compared with controls (odds ratio = 0.25; 95% confidence interval: 0.12–0.51; $P = 0.0001$). The prevalence estimates of sleep difficulty among controls (27.3%) compared to participants with CD or PWAGs were 37.7% ($P = 0.15$) and 34.1% ($P = 0.11$). Those with diagnosed CD had increased odds of sleep difficulty (odds ratio = 2.41; 95% confidence interval 1.04–5.60), but this was no longer significant after multivariable adjustment ($P = 0.17$).
Conclusion Among a nationally representative US sample, participants with CD overall showed no increased odds of depression or sleep difficulty. PWAGs showed lower odds of depression compared with controls. Future research should investigate the relationship between a diagnosis of CD and the development of psychiatric conditions. Eur J Gastroenterol Hepatol 29:1091–1096

Introduction

Celiac disease (CD) is a disorder characterized by small bowel inflammation in response to gluten ingestion [1]. CD can manifest as gastrointestinal distress, malabsorption, and extraintestinal symptoms, including neurological and psychiatric disorders [1–4]. The sole treatment of CD is adherence to a gluten-free diet (GFD), which may eliminate many of the disease's symptoms, but can be socially isolating, expensive to maintain, and cause a significant treatment burden [1,4,5]. Despite its many challenges, there is increased interest in and adoption of the GFD among individuals without CD. People without CD who avoid gluten (PWAG) may do so for its perceived health and energy benefits or to alleviate gastrointestinal symptoms believed to be triggered by gluten [1,6–11]. Strict criteria for the diagnosis of nonceliac gluten sensitivity [7] and pathophysiological mechanisms [1] for this disease are not well defined. Most PWAGs have initiated a GFD on their own without physician input [1,8,9]. One study in the United States (US) found that CD and PWAG were just as common, with each having a prevalence of 0.8% [12].

There is inconsistent evidence on the relationship between gluten and sleep or depression [4]. Although depression [13–27] and poor sleep [28,29] have both been associated with CD, other studies refute these findings [30–35]. Less is known about depression and sleep problems in PWAGs, although both symptoms have been described before GFD initiation [36,37]. In our study, we use a nationally representative US sample to assess the prevalence of depression and insomnia among patients with CD, both diagnosed and undiagnosed, and PWAGs.

Participants and methods

National Health and Nutrition Examination Survey

We carried out a population-based cross-sectional study using data obtained from the 2009–2014 National Health and Nutrition Examination Survey (NHANES), which is a nationally representative survey that collects interview, physical examination, and laboratory data from over 5000 participants per year from the civilian population of the US [38]. The NHANES design has been described in further detail elsewhere [38].

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Celiac disease diagnostic criteria

Participants were classified into three categories: diagnosed CD, undiagnosed CD, and PWAG, using both serologic and interview data, as has been described [12,39]. Diagnosed CD was based on a self-reported diagnosis of CD and adherence to a GFD as asked on the medical conditions questionnaire. Undiagnosed CD was defined as serum immunoglobulin A (IgA) tissue transglutaminase antibodies of at least 4.0 U/ml and a positive IgA endomysial antibody result in the absence of a self-reported history of a CD diagnosis [12,39]. Participants on a GFD without a serological or a self-reported diagnosis of CD were classified as PWAGs. The control group included participants who had negative CD serology. Of the 30 468 participants in NHANES 2009–2014, 22 278 participants were tested for CD serology. Three participants were excluded as they had positive IgA serology with no subsequent IgA endomysial antibodies testing and one other was excluded for not answering questions related to the self-directed CD diagnosis. Participants who fulfilled the criteria for both diagnosed and undiagnosed CD were classified as diagnosed CD.

Depression, insomnia, and quality-of-life variables

The mental health questionnaire, publically available from participants aged 18 years and older, consisted of a validated depression screen called the Patient Health Questionnaire (PHQ-9) [40]. The PHQ-9 asks nine questions about the frequency of symptoms of depression over the past 2 weeks and one question about the difficulty that these symptoms have caused in activities of daily living. Each question was ranked on a scale of 0–3, with a score of 10 or higher on the first nine questions having an 88% sensitivity and an 88% specificity for major depression [40]. Question 10 of the PHQ-9 was counted as a separate variable called 'difficulty living with depression'. Of the 22 274 participants in our sample, 5615 were excluded from the depression variables as they were younger than 18 years of age. Only 15 021 participants were included in the depression variable (1638 responses were missing on questions 1–9) and only 10 021 were included in the difficulty living with depression variable (6639 participants did not answer question 10).

The sleep disorders questionnaire, administered to participants aged 16 years and older, asked one question about length of sleep at night, another about trouble sleeping, and a third about sleep disorders. The latter two questions were combined into one variable called 'sleep difficulty.' Of the 22 274 participants in our sample, 17 523 participants were included in the analysis of both insomnia variables; 4715 participants were younger than 16 years of age and 35 did not complete the questionnaire.

The physical functioning questionnaire, administered to participants aged older than 20 years, consisted of a series of questions related to quality-of-life factors. Our 'physical, mental, and emotional difficulty' variable was based on the sole question 'Are you limited in any way in any activity because of a physical, mental, or emotional problem?' Two questions on social functioning were combined into one variable called 'difficulty engaging in social activities' and three questions on functioning at home were combined into one variable called 'difficulty functioning in the home.' Participants responded to these questions on a scale of 1–4, with scores of at least two on one of the questions indicating the presence of a difficulty. Of the 22 274 participants in our sample, 6453 participants were excluded as they were younger than 20 years of age. Only 11 872 participants were included in the physical, mental, and emotional difficulty variable (3939 did not answer this question) and only 6961 were included in both the difficulty engaging in social activities and difficulty functioning in the home variables (8860 did not complete the relevant questions).

Psychotropic medication use

The prescription drug use questionnaire, administered to participants from the years 2009 to 2012, asked participants to list all prescribed medications that were taken in the last 30 days. Data on medication use were only available in 6901 participants who were tested for CD serology. We categorized the medications as follows: any psychotropic medication, antidepressants, antipsychotics, anxiolytics, sedatives, and hypnotics, mood stabilizers, and sympathomimetics. (see Supplementary Appendix, Supplemental digital content 1, *http://links.lww.com/EJGH/A206*).

Statistical analysis

We compared the prevalence of depression and insomnia in participants with CD and PWAGs to controls using Rao–Scott χ^2-tests. We then performed multivariable logistic regression, adjusting for age, sex, race/ethnicity, annual household income, number of healthcare visits, and access to health insurance, to assess for associations between CD/PWAG status and the outcomes of depression and insomnia variables. Odds ratios (ORs) and their 95% confidence intervals (CIs) were recorded. We also compared the prevalence of quality-of-life factors among these groups and performed multivariable logistic regression adjusting for age and sex. Finally, we compared each category of psychotropic medication use among participants with CD (diagnosed and undiagnosed), PWAGs, and controls. All estimates were weighted to represent the total US population, unless otherwise indicated. All reported P values are two sided. We used SAS, version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) for all analyses.

Results

Demographic information is shown in Table 1. Among 22 274 participants, there were 213 PWAGs and 106 CD participants, of whom 75% were undiagnosed. Although a plurality of participants with diagnosed CD were 60–69 years of age (weighted 48%), the largest age category of participants with undiagnosed CD and PWAGs was 16–29 years of age (undiagnosed CD weighted 23.4% and PWAGs weighted 22.6%). Women were the majority in all three groups, with the highest percentage in the diagnosed CD group (diagnosed CD: weighted 82.6%; undiagnosed CD: weighted 55.3%; PWAG: weighted 63.4%).

Depression was present in 8.2% of controls compared with 3.9% of participants with CD ($P = 0.18$) and 2.9% of PWAGs ($P = 0.002$) (Table 2). When stratified by sex,

female PWAGs were also less likely to suffer from depression compared with female controls (PWAGs: 1.89% vs. controls 10.53%, $P = 0.0003$). No such difference was found in male PWAGs and male controls (4.23 vs. 5.74%, $P = 0.58$). Depression was reported by 3/52 (2.3%) participants with undiagnosed CD and 3/21 (8.1%) participants with diagnosed CD. Most participants in all three groups reported that their difficulty related to depression was 'not at all difficult' (controls: 72.7% vs. CD: 71.1%, $P = 0.84$; vs. PWAG: 71.8%, $P = 0.43$).

There was a trend toward increased prevalence of sleep difficulty among participants with CD (37.3%) and PWAGs (34.1%) versus controls (27.4%), although these results were not statistically significant ($P = 0.15$ and 0.11, respectively). Sleep difficulty was reported in 15/56 (33%) participants with undiagnosed CD and 13/27 (47.6%) participants with diagnosed CD. Most controls (64.5%) reported sleeping less than 8 hours at night and did not significantly differ from patients with CD (55.4%, $P = 0.15$) or PWAGs (64.3%, $P = 0.96$).

On multivariate analysis (Table 3), lower odds of depression were found among participants with undiagnosed CD (OR = 0.26; 95% CI: 0.07–0.96) and PWAGs (OR = 0.34; 95% CI: 0.17–0.69), but not participants with diagnosed CD (OR = 0.99; 95% CI: 0.17–5.88). This relationship remained significant when adjusting for age and sex. However, when adjusted for race/ethnicity, annual household income, number of healthcare visits, and presence of health insurance (Table 3, model 3), the lower odds of depression in undiagnosed CD was no longer statistically significant (OR = 0.30; 95% CI: 0.08–1.19, $P = 0.09$), but remained significant in PWAGs (OR = 0.25; 95% CI: 0.12–0.51; $P = 0.0001$). Increased odds of sleep difficulty were found in diagnosed CD (OR = 2.41; 95% CI: 1.04–5.60), undiagnosed CD (OR = 1.31; 95% CI: 0.55–3.11), and PWAGs (OR = 1.37; 95% CI: 0.93–2.04), although statistical significance was only found in those with diagnosed CD ($P = 0.04$). This finding was no longer significant when adjusting for age and sex (OR = 1.99; 95% CI: 0.91–4.37; $P = 0.08$).

Analyses of quality-of-life factors are shown in Table 4. The presence of physical, mental, and emotional limitations was reported in 2.9% of controls compared with 13.8% of participants with diagnosed CD ($P = 0.004$), 9.6% of those with undiagnosed CD ($P = 0.02$), and 5.1% of PWAGs ($P = 0.18$). Higher odds of physical, mental, and emotional limitations were found in diagnosed CD (OR = 4.22; 95% CI: 1.24–14.38; $P = 0.02$) and undiagnosed CD (OR = 4.02; 95% CI: 1.23–13.12; $P = 0.02$). On both univariate and multivariate analyses, participants

Table 1. Characteristics of patients with celiac disease and people who avoid gluten

Clinical characteristics	Diagnosed CD [*n* (unweighted%; weighted%)]	Undiagnosed CD [*n* (unweighted%; weighted%)]	PWAG [*n* (unweighted%; weighted%)]
n	27 (0.12; 0.18)	79 (0.35; 0.50)	213 (0.96; 1.11)
Age (years)			
≤15	0	23 (29.11; 18.57)	23 (10.80; 8.01)
16–29	2 (7.41; 13.91)	16 (20.25; 23.44)	42 (22.11; 22.59)
30–39	2 (7.41; 11.56)	12 (15.19; 16.00)	27 (14.21; 13.24)
40–49	3 (11.11; 9.11)	12 (15.19; 17.88)	39 (20.53; 17.05)
50–59	3 (11.11; 3.91)	9 (11.39; 18.54)	28 (14.74; 20.06)
60–69	10 (37.04; 47.57)	4 (5.06; 3.47)	31 (16.32; 11.82)
≥70	7 (25.93; 13.94)	3 (3.80; 2.12)	23 (12.11; 7.23)
Sex			
Male	6 (22.22; 17.37)	33 (41.77; 44.75)	95 (44.60; 36.63)
Female	21 (77.78; 82.63)	46 (58.23; 55.25)	118 (55.40; 63.37)

Table 3. Risk of depression and sleep difficulty in celiac disease and people who avoid gluten

Variables	OR (95% CI) for depression	*P* value	OR (95% CI) for sleep difficulty	*P* value
Model 1[a]				
Controls	1.00	–	1.00	–
Diagnosed CD	0.99 (0.17–5.88)	0.99	2.41 (1.04–5.60)	0.04
Undiagnosed CD	0.26 (0.07–0.96)	0.04	1.31 (0.55–3.11)	0.55
PWAG	0.34 (0.17–0.69)	0.003	1.37 (0.93–2.04)	0.11
Model 2[b]				
Controls	1.00	–	1.00	–
Diagnosed CD	0.90 (0.15–5.46)	0.91	1.99 (0.91–4.37)	0.08
Undiagnosed CD	0.25 (0.06–0.98)	0.046	1.40 (0.61–3.22)	0.43
PWAG	0.30 (0.15–0.62)	0.001	1.31 (0.89–1.93)	0.17
Model 3[c]				
Controls	1.00	–	1.00	–
Diagnosed CD	1.00 (0.13–7.65)	0.99	1.82 (0.77–4.30)	0.17
Undiagnosed CD	0.30 (0.08–1.19)	0.09	1.51 (0.60–3.80)	0.39
PWAG	0.25 (0.12–0.51)	0.0001	1.17 (0.77–1.78)	0.46

CD, celiac disease; CI, confidence interval; OR, odds ratio; PWAG, people who avoid gluten.
[a]Unadjusted.
[b]Adjusted for age and sex.
[c]Adjusted for age, sex, race/ethnicity, annual household income, number of healthcare visits, and presence of health insurance.

Table 2. Depression and insomnia in patients with celiac disease, people who avoid gluten, and controls

Clinical characteristics	Controls [*n* (%)]	CD [*n* (%)]	*P* value[a]	PWAG [*n* (%)]	*P* value[b]
Major depression (*n* = 15 021)					
<10 – no	13 388 (91.85)	70 (96.11)	0.18	164 (97.1)	0.002
≥10 – yes	1381 (8.15)	6 (3.89)		12 (2.90)	
Difficulty related to depression (*n* = 10 021)					
Not at all difficult	7078 (72.68)	38 (71.05)	0.84	81 (71.81)	0.43
Somewhat difficult	2234 (22.57)	14 (26.35)		34 (26.07)	
Very difficult	368 (3.28)	3 (1.96)		4 (1.49)	
Extremely difficult	164 (1.47)	1 (0.64)		2 (0.64)	
Insomnia (*n* = 17 425)					
No sleep difficulty	12 924 (72.63)	55 (62.35)	0.15	123 (65.88)	0.11
Yes sleep difficulty	4327 (27.37)	28 (37.65)		67 (34.12)	
≥8 h a night	6202 (35.50)	35 (44.64)	0.15	68 (35.70)	0.96
<8 h a night	11 049 (64.50)	48 (55.36)		122 (64.30)	

CD, celiac disease; PWAG, people who avoid gluten.
[a]CD vs. controls.
[b]PWAG vs. controls.

Table 4. Quality-of-life factors in celiac disease, people who avoid gluten, and controls

Variables	*n* (%)	*P* value[a]	Adjusted OR[b]	95% CI	*P* value
Physical, mental, and emotional limitations					
Controls (*n* = 11 686)	283 (2.86)	–	1.00	–	–
Diagnosed CD (*n* = 15)	2 (13.84)	0.004	4.22	1.24–14.38	0.02
Undiagnosed CD (*n* = 42)	3 (9.58)	0.02	4.02	1.23–13.12	0.02
PWAG (*n* = 129)	5 (5.06)	0.18	1.86	0.78–4.44	0.16
Difficulty engaging in social activities					
Controls (*n* = 6842)	1703 (22.46)	–	1.00	–	–
Diagnosed CD (*n* = 20)	5 (11.04)	0.13	0.40	0.13–1.23	0.11
Undiagnosed CD (*n* = 18)	4 (34.08	0.42	1.47	0.34–6.43	0.61
PWAG (*n* = 81)	24 (32.40)	0.96	0.92	0.43–1.95	0.82
Difficulty functioning in the home					
Controls (*n* = 6842)	1870 (25.65)	–	1.00	–	–
Diagnosed CD (*n* = 20)	6 (14.86)	0.26	0.47	0.14–1.57	0.22
Undiagnosed CD (*n* = 18)	4 (32.30)	0.66	1.14	0.27–4.83	0.86
PWAG (*n* = 81)	35 (22.79)	0.36	1.26	0.62–2.58	0.52

CD, celiac disease; CI, confidence interval; OR, odds ratio; PWAG, people who avoid gluten.
[a]All *P* values compared with controls.
[b]Adjusted for age and sex.

Table 5. Psychotropic medication use in celiac disease, people who avoid gluten, and controls, National Health and Nutrition Examination Survey 2009–2012

Psychotropic medications	Total sample	Controls [*n* (%)]	CD [*n* (%)]	*P* value[a]	PWAG [*n* (%)]	*P* value[b]
None	5213 (72.35)	5127 (72.33)	30 (70.43)	–	56 (76.81)	–
Any	1688 (27.65)	1661 (27.67)	13 (29.57)	0.82	14 (23.19)	0.60
Antidepressant	1091 (19.35)	1073 (19.38)	11 (24.67)	0.47	7 (11.66)	0.30
Antipsychotic	189 (2.14)	186 (2.17)	0	NC	3 (1.57)	0.61
Anxiolytics, sedatives, and hypnotics	572 (8.98)	566 (9.08)	3 (4.46)	0.28	3 (3.02)	0.04
Mood stabilizer	88 (1.49)	86 (1.44)	0	NC	2 (7.65)	0.02
Sympathomimetic	248 (3.47)	245 (3.49)	1 (3.92)	0.90	2 (0.87)	0.04

CD, celiac disease; PWAG, people who avoid gluten.
[a]CD vs. controls.
[b]PWAGs vs. controls.

with diagnosed CD, undiagnosed CD, and PWAGs did not show any association with difficulty engaging in social activities and difficulty functioning in the home.

Psychotropic medication use is reported in Table 5. Of the total sample, 27.7% used any psychotropic medication, with antidepressants the most commonly used medication type (19.4%). Psychotropic medication was used by 27.7% of controls compared with 29.6% of CD participants and 23.2% of PWAGs, although no statistical significance was found. Antidepressants remained the most commonly used medication in each group, at 19.4% in controls, 24.7% in CD participants, and 11.7% in PWAGs, and showed no statistically significant differences.

Discussion

Although depression has been associated with CD, there has been an overall lack of consistency in the literature. Before CD diagnosis, depression has been linked to gastrointestinal symptoms [4] or malabsorption of metabolites [41–43]. After diagnosis, studies have found that CD patients who adhere to a GFD do not suffer from depression [30,33–35] and depression is mitigated with stricter diet compliance and longer diet duration [27,36]. However, other studies report depression even in treated CD [13–17], with one suggesting that depression worsens with stricter GFD compliance [16]. Still, other studies found a lack of correlation between depression and diet compliance [4,17] or disease duration in CD patients [17].

In our study of a nationally representative US sample, major depression was not more prevalent in participants with CD compared with controls. This null finding cannot be explained by medical treatment of depression in CD participants as they were not more likely to use antidepressants. We found that both diagnosed and undiagnosed CD participants had similar odds of depression compared with controls on multivariate analysis (Table 3). These results suggest that depression, irrespective of gluten avoidance, may not be an inherent pathophysiological characteristic of CD. Instead, any association between depression and CD might be related to other factors such as the presence of gastrointestinal symptoms, feelings of treatment burden [5], adjustment to the chronic nature of disease, or presence of medical comorbidities. In fact, one study found that a decreased quality of life in patients with CD could be predicted by a long duration of symptoms before diagnosis and the presence of psychiatric, neurologic, or gastrointestinal comorbidities [44]. Other studies have found that the prevalence of depression in CD patients was similar to that in patients with other chronic diseases [14,25,31,33] and higher in patients with CD who have comorbid autoimmune disorders [18,31]. Nevertheless, as our CD sample size is small ($n = 106$), with only six individuals fulfilling the criteria for major depression, it is possible that our reported prevalence of depression in CD may be underestimated.

To our knowledge, this is the first study to measure depression in individuals with CD who were not aware of their CD status when undergoing depression screening.

As these individuals had lower odds of depression (when only adjusted for age and sex), this raises doubts about the benefit of mass screening for CD in patients with mental health difficulties, especially when CD has been associated with significant treatment burden [5] and decreased sexual satisfaction [45]. Somewhat contrary to our finding, a UK study found that subsequent CD diagnosis was associated with the presence of depression and/or anxiety before diagnosis (OR = 2.5; 95% CI: 1.1–5.7) [46]. The assessment of depression in that study, which was based on chart review from general practitioners and not based on a questionnaire, may have led to an overestimation of depression and anxiety in their CD population. Still, more research is needed to assess the relationship between undiagnosed CD and depression.

Despite finding no difference between diagnosed and undiagnosed CD in major depression, both groups reported higher rates of physical, mental, and emotional limitations. This suggests that although patients with CD may not fulfill the criteria for a diagnosis of depression, they may still have a significant treatment burden, as has been described [5], or difficulties coping with symptoms. Given that both groups did not report any differences compared with controls in terms of difficulty in social activities or functioning in the home, the reason for their physical, mental, and emotional limitations remains unclear. Further investigation into other factors that may contribute toward these symptoms is warranted.

In contrast to our null findings in CD patients, PWAGs (who likely self-prescribed the GFD) [8,9] were consistently less likely to be depressed compared with controls. Depression [36], fatigue [36], and mood changes [36] have been reported as presenting symptoms in individuals with nonceliac gluten sensitivity, although the prevalence of these symptoms has not been well studied. In addition, the role that gluten plays in the development of depression in this group is unclear. Although one study found that depressive symptoms can be induced in PWAGs after exposure to gluten [47], another study found that somatization was low in PWAGs, and their depression and anxiety ratings were similar to those of CD patients [48]. It is possible that in our study, GFD adherence contributed to the PWAG's lower odds of depression, although this is unlikely, given that the diagnosed CD group also followed the diet and did not show lower odds of depression. Another possibility is that GFD adherence does alleviate depression, but any protective effect in the diagnosed CD group may be counteracted by the burden of having a diagnosed chronic disease.

We found no association between CD and insomnia. Although this differs from the increased fatigue [26], shorter sleep duration [29], and increased odds of poor sleep [28] reported in other studies of CD, our study is the first to investigate sleep problems among a population with CD in the US. The role of a GFD is poorly defined, with one study reporting improved fatigue after GFD initiation [26] and another refuting this finding [28]. Our study did report a slightly increased risk of sleep difficulty in diagnosed CD, although this was not significant when adjusted. Although it is possible that we lost significance by overadjusting for too many variables, we decided to present multiple models to allow for many interpretations on the basis of various possible causal structures and to provide an interpretation of the size of the indirect effect if there is any mediation occurring.

Major strengths of this study include the diagnosis of CD using a highly sensitive and specific serologic testing strategy and the distribution of medical questionnaires in a large US population with an unbiased sampling method. There are also several limitations. As diagnosed CD was classified by participant self-report, it is possible that individuals were mistaken in their diagnosis of CD. However, all except two patients with diagnosed CD had a negative tissue transglutaminase test, which, although not entirely sensitive for recent gluten exposure, would be expected to be positive in a larger proportion of patients if many were not compliant. Our prevalence estimates should be interpreted with caution in cases when the number of individuals in a given cell is less than 20. We also did not know participants' duration of and adherence to a GFD and the reasons for avoiding gluten when CD was present, and thus could not factor these elements into our analyses.

Conclusion

Our study found no increased risk of depression and insomnia in participants with CD compared with a group of nonaffected controls. PWAGs showed no difference in insomnia compared with controls, but did show a decreased risk of depression. To our knowledge, this study is among the first to measure depression and insomnia in nonceliac gluten avoiders. Our findings raise the possibility that GFD adherence may not affect the development of depression in patients with CD, but might decrease the risk of depression in patients without CD who adhere to a GFD for other reasons (PWAGs). Furthermore, our study suggests that depression is not a prominent feature of undiagnosed (and untreated) CD. Future studies should prospectively measure the presence of psychiatric conditions in patients with CD and nonceliac gluten sensitivity before and after treatment, and explore the role of gluten in depression.

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Conflicts of interest

There are no conflicts of interest.

References

1 Lebwohl B, Ludvigsson JF, Green PHR. Celiac disease and non-celiac gluten sensitivity. *BMJ* 2015; 351:h4347.
2 Bushara KO. Neurologic presentation of celiac disease. *Gastroenterology* 2005; 128 (Suppl 1): S92–S97.

3 Leffler DA, Green PH, Fasano A. Extraintestinal manifestations of coeliac disease. *Nat Rev Gastroenterol Hepatol* 2015; 12:561–571.
4 Zingone F, Swift GL, Card TR, Sanders DS, Ludvigsson JF, Bai JC. Psychological morbidity of celiac disease: a review of the literature. *United European Gastroenterol J* 2015; 3:136–145.
5 Shah S, Akbari M, Vanga R, Kelly CP, Hansen J, Teethira T, *et al*. Patient perception of treatment burden is high in celiac disease compared with other common conditions. *Am J Gastroenterol* 2014; 109:1304–1311.
6 Catassi C, Bai JC, Bonaz B, Bouma G, Calabro A, Caroccio A, *et al*. Non-celiac gluten sensitivity: the new frontier of gluten related disorders. *Nutrients* 2013; 5:3839–3853.
7 Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH, *et al*. The Oslo definitions for coeliac disease and related terms. *Gut* 2013; 62:43–52.
8 Tavakkoli A, Lewis SK, Tennyson CA, Lebwohl B, Green PH. Characteristics of patients who avoid wheat and/or gluten in the absence of celiac disease. *Dig Dis Sci* 2013; 59:1255–1261.
9 Aziz I, Lewis NR, Hadjivassiliou M, Winfield SN, Rugg N, Kelsall A, *et al*. A UK study assessing the population prevalence of self-reported gluten sensitivity and referral characteristics to secondary care. *Eur J Gastroenterol Hepatol* 2014; 26:33–39.
10 Golley S, Corsini N, Topping D, Morell M, Mohr P. Motivations for avoiding wheat consumption in Australia: results from a population survey. *Public Health Nutr* 2015; 18:490–499.
11 Gaesser GA, Angadi SS. Gluten-free diet: imprudent dietary advice for the general population? *J Acad Nutr Diet* 2012; 112:1330–1333.
12 Choung RS, Ditah IC, Nadeau1 AM, Rubio-Tapia A, Marietta EV, Brantner TL, *et al*. Trends and racial/ethnic disparities in gluten-sensitive problems in the United States: findings from the national health and nutrition examination surveys from 1988 to 2012. *Am J Gastroenterol* 2015; 110:455–461.
13 Addolorato G, Capristo E, Ghittoni G, Valeri C, Mascianà R, Ancona C, *et al*. Anxiety but not depression decreases in coeliac patients after one-year gluten-free diet: a longitudinal study. *Scan J Gastroenterol* 2001; 36:502–506.
14 Fera T, Cascio B, Angelini G, Martini S, Guidetti CS. Affective disorders and quality of life in adult coeliac disease patients on a gluten-free diet. *Eur J Gastroenterol Hepatol* 2003; 15:1287–1292.
15 Hallert C, Astrom J, Walan A. Reversal of psychopathology in adult celiac disease with the aid of pyroxidine (vitamin B6). *Scand J Gastroenterol* 1983; 18:229–304.
16 Ciacci C, Iovino P, Amoruso D, Siniscalchi M, Tortora R, di Gilio A, *et al*. Grown-up celiac children: effects of few years on a gluten-free diet in childhood. *Aliment Pharmacol Ther* 2005; 21:421–429.
17 Ciacci C, Iavarone A, Mazzacca G, de Rosa A. Depressive symptoms in adult coeliac disease. *Scand J Gastroenterol* 1998; 33:247–250.
18 Carta MG, Hardoy MC, Boi MF, Mariotti S, Carpiniello B, Usai P. Association between panic disorder, major depressive disorder and celiac disease: a possible role of thyroid autoimmunity. *J Psychosom Res* 2002; 53:789–793.
19 Ludvigsson JF, Reutfors J, Osby U, Ekbom A, Montgomery SM. Coeliac disease and risk of mood disorders – a general population-based cohort study. *J Affect Disord* 2007; 99:117–126.
20 Addolorato G, Stefanini GF, Capristo E, Caputo F, Gasbarrini A, Gasbarrini G. Anxiety and depression in adult untreated celiac subjects and in patients affected by inflammatory bowel disease: a personality 'trait' or a reactive illness. *Hepatogastroenterology* 1996; 43:1513–1517.
21 Hallert C, Åström J. Psychic disturbances in adult coeliac disease. II. Psychological findings. *Scand J Gastroenterol* 1982; 17:21–24.
22 Hallert C, Derefeldt T. Psychic disturbances in adult coeliac disease. I. Clinical observations1982; 17:17–19.
23 Addolorato G, Mirijello A, D'Angelo C, Leggio L, Ferrulli A, Abenavoli L, *et al*. State and trait anxiety and depression in patients affected by gastrointestinal diseases: psychometric evaluation of 1641 patients referred to an internal medicine outpatient setting. *Int J Clin Pract* 2008; 62:1063–1069.
24 Addolorato G, Mirijello A, D'Angelo C, Leggio L, Ferrulli A, Vonghia L, *et al*. Social phobia in coeliac disease. *Scand J Gastroenterol* 2008; 43:410–415.
25 Smith D, Gerdes L. Meta-analysis on anxiety and depression in adult celiac disease. *Acta Psychiatr Scand* 2012; 125:183–193.
26 Siniscalchi M, Iovino P, Tortora R, Forestiero S, Somma A, Capuano L, *et al*. Fatigue in adult coeliac disease. *Aliment Pharmacol Ther* 2005; 22:489–494.
27 Borghini R, di Tola M, Salvi E, Isonne C, Puzzono M, Marino M, *et al*. Impact of gluten-free diet on quality of life in celiac patients. *Acta Gastroenterol Belg*, 79:447–453.
28 Mårild K, Morgenthaler TI, Somers VK, Kotagal S, Murray JA, Ludvigsson JF. Increased use of hypnotics in individuals with celiac disease: a nationwide case–control study. *BMC Gastroenterol* 2015; 15:10.
29 Zingone F, Siniscalchi M, Capone P, Tortora R, Andreozzi P, Capone E, *et al*. The quality of sleep in patients with coeliac disease. *Aliment Pharmacol Ther* 2010; 32:1031–1036.
30 Ciacci C, D'Agate C, de Rosa A, Franzese C, Errichiello S, Gasperi V, *et al*. Self-rated quality of life in celiac disease. *Dig Dis Sci* 2003; 48:2216–2220.
31 Garud S, Leffler D, Dennis M, Edwards-George J, Saryan D, Sheth S, *et al*. Interaction between psychiatric and autoimmune disorders in coeliac disease patients in the Northeastern United States. *Aliment Pharmacol Ther* 2009; 29:898–905.
32 Accomando S, Fragapane ML, Montaperto D, Trizzino A, Amato GM, Calderone F, *et al*. Coeliac disease and depression: two related entities? *Dig Liver Dis* 2005; 37:298–299.
33 Hauser W, Janke KH, Klump B, Gregor M, Hinz A. Anxiety and depression in adult patients with celiac disease on a gluten-free diet. *World J Gastroenterol* 2010; 16:2780–2787.
34 Roos S, Karner A, Hallert C. Psychological well-being of adult coeliac patients treated for 10 years. *Dig Liver Dis* 2006; 38:177–180.
35 Van Hees NJ, van der Does W, Giltay EJ. Coeliac disease, diet adherence and depressive symptoms. *J Psychosom Res* 2013; 74:155–160.
36 Volta U, Bardella MT, Calabro A, Troncone R, Corazza GR. An Italian prospective multicenter survey on patients suspected of having non-celiac gluten sensitivity. *BMC Med* 2014; 12:85.
37 Biesiekierski JR, Newnham ED, Shepherd SJ, Muir JG, Gibson PR. Characterization of adults with a self-diagnosis of nonceliac gluten sensitivity. *Nutr Clin Pract* 2014; 29:504–509.
38 National Health and Nutrition Examination Survey (NHANES). *About the National Health and Nutrition Examination Survey*. Atlanta, GA: Centers for Disease Control and Prevention; 2015.
39 Rubio-Tapia A, Ludvigsson JF, Brantneri TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. *Am J Gastroenterol* 2012; 107:1538–1544.
40 Kroenke K, Spitzer RL. The PHQ-9: a new depression diagnostic and severity measure. *Psychiarric Annals* 2002; 32:1–7.
41 Hallert C, Astrom J, Sedvall G. Psychic disturbances in adult coeliac disease. III. Reduced central monoamine metabolism and signs of depression. *Scand J Gastroenterol* 1982; 17:25–28.
42 Hernanz A, Polanco I. Plasma precursor amino acids of central nervous system monoamines in children with coeliac disease. *Gut* 1992; 32:1478–1481.
43 Hallert C, Grant C, Grehn S, Grännö C, Hultén S, Midhagen G, *et al*. Evidence of poor vitamin status in coeliac patients on a gluten-free diet for 10 years. *Aliment Pharmacol Ther* 2002; 16:1333–1339.
44 Paarlahati P, Kurppa K, Ukkola A, Collin P, Huhtala H, Mäki M, *et al*. Predictors of persistent symptoms and reduced quality of life in treated coeliac disease patients: a large cross-sectional study. *BMC Gastroenterol* 2013; 13:75.
45 Roy A, Minaya M, Monegro M, Fleming, Fleming J, Wong RK, *et al*. Partner burden: a common entity in celiac disease. *Dig Dis Sci* 2016; 61:3451–3459.
46 Cannings-John R, Owen D, Williams D, Crimmins R. A case–control study of presentations in general practice before diagnosis of coeliac disease. *Br J Gen Pract* 2007; 57:636–642.
47 Peters SL, Biesiekierski JR, Yelland GW, Yelland GW, Muir JG, Gibson PR. Randomized clinical trial: gluten may cause depression in subjects with non-coeliac gluten sensitivity – an exploratory clinical study. *Aliment Pharmacol Ther* 2014; 39:1104–1112.
48 Brotteveit M, Vandvik PO, Wojniusz S, Løvik A, Lundin KE, Boye B. Absence of somatization in non-coeliac gluten sensitivity. *Scand J Gastroenterol* 2012; 47:770–777.