HHS Public Access

Author manuscript

Eur J Gastroenterol Hepatol. Author manuscript; available in PMC 2018 September 01.

Published in final edited form as:

Eur J Gastroenterol Hepatol. 2017 September ; 29(9): 1091–1096. doi:10.1097/MEG.0000000000000932.

Depression and Insomnia among Individuals with Celiac Disease or on a Gluten-Free Diet in the United States: Results from a National Survey

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Abstract

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.

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 to 3.9% of participants with CD (p=0.18) and 2.9% of PWAGs (p=0.002). After adjustment for age, gender, race, income, and access to health care, PWAGs maintained lower odds of depression compared to controls (OR 0.25; 95% CI 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 (OR 2.41; 95% CI 1.04–5.60), but this was no longer significant after multivariable adjustment (p=0.17).

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Conflicts of Interest: All authors declare that they have no conflicts of interest, financial or otherwise, to declare.

Details of ethics approval: This analysis was deemed exempt by Columbia University's Institutional Review Board because the data used was completely de-identified.

Guarantor of the Article: Dr. Lebwohl

Authors Contributions:
Study concept and design: HMZ, RD, JAM, PHRG, BL
Acquisition of data: HMZ, RD, BL, JAM
Analysis and interpretation of data: HMZ, RD, JAM, PHRG, BL
Drafting of the manuscript: HMZ, BL
Critical revision of the manuscript for important intellectual content: HMZ, RD, JAM, PHRG, BL
Statistical analysis: HMZ, RD, BL
Study supervision: BL

Conclusion—Among a nationally representative United States sample, participants with CD overall showed no increased odds of depression or sleep difficulty. PWAGs showed lower odds of depression compared to controls. Future research should investigate the relationship between a diagnosis of celiac disease and the development of psychiatric conditions.

Keywords

celiac disease; gluten disorder; depression; insomnia

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 thought to be triggered by gluten.[1,6–11] Strict criteria for the diagnosis of non-celiac 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 about the relationship between gluten and sleep or depression.[4] While 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, though 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.

Methods

NHANES

We conducted 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 5,000 participants per year from the civilian population of the US.[38] The NHANES design is described in further detail elsewhere.[38]

CD 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 ≥ 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 self-reported diagnosis of CD were classified as PWAGs. The control group consisted of 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 EMA testing and one was excluded as they did not answer questions related to the self-directed CD diagnosis. Participants who met 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 two weeks and one question about the difficulty 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 9 questions having an 88% sensitivity and 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, 5,615 were excluded from the depression variables as they were younger than 18. Only 15,021 participants were included in the depression variable (1,638 responses were missing on questions 1–9) and only 10,021 were included in the difficulty living with depression variable (6,639 participants did not answer question 10).

The sleep disorders questionnaire, given 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; 4,715 participants were younger than 16 and 35 did complete the questionnaire.

The physical functioning questionnaire, given to participants aged greater 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 about social functioning were combined into one variable called “difficulty engaging in social activities” and three questions about 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 2 on one of the questions indicating the presence of a difficulty. Of the 22,274 participants in our sample, 6,453 participants were excluded as they were younger than 20. Only 11,872 participants were included in the physical, mental, and emotional difficulty variable (3,939 did not answer this question) and only 6,961 were included in both the difficulty engaging in social activities and difficulty functioning in the home variables (8,860 did not complete the relevant questions).

Psychotropic Medication Use

The prescription drug use questionnaire, given to participants from years 2009–2012, asked participants to list all prescribed medications that were taken in the last 30 days. Data on medication use was only available in 6,901 participants who were tested for CD serology. We categorized the medications as follows: any psychotropic medication, antidepressants, anti-psychotics, anxiolytics, sedatives, and hypnotics, mood stabilizers, and sympathomimetics.

Statistical Analysis

We compared the prevalence of depression and insomnia in participants with CD and PWAGs to controls, using Rao-Scott chi square tests. We then performed multivariable logistic regression, adjusting for age, gender, 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 gender. 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 2-sided. We used SAS version 9.4 (Cary, NC) 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. While 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%). Females 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 to 3.9% of participants with CD (p=0.18) and 2.9% of PWAGs (p=0.002) (Table 2). When stratified by gender, female PWAGs were also less likely to suffer from depression compared to 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%) subjects with undiagnosed CD and 3/21 (8.1%) subjects 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 for increased prevalence of sleep difficulty among participants with CD (37.3%) and PWAGS (34.1%) vs. controls (27.4%) although these results were not statistically significant (p=0.15 & 0.11, respectively). Sleep difficulty was reported in 15/56 (33%) subjects with undiagnosed CD and 13/27 (47.6%) subjects 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 gender. 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), though statistical significance was only found in those with diagnosed CD (p=0.04). This finding was no longer significant when adjusting for age and gender (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 to 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 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 to 29.6% of CD participants, and 23.2% of PWAGs, though 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 difference.

Discussion

Though 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 compliance1[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 to controls. This null finding cannot be explained by medical treatment of depression in CD participants, since they were not more likely to use antidepressants. We found that both diagnosed and undiagnosed CD participants had similar odds of depression compared to controls on multivariate analysis (Table 3). These results suggest that depression, regardless 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 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 6 individuals meeting 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 exhibited lower odds of depression (when only adjusted for age and gender), 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 prior to diagnosis (OR 2.5; 95% CI: 1.1–5.7). [46] That study's assessment of depression 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 regarding major depression, both groups reported higher rates of physical, mental, and emotional limitations. This suggests that while patients with CD may not meet 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 to controls regarding 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 to 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 to controls. Depression [36], fatigue [36] and mood changes [36] have been reported as presenting symptoms in people with non-celiac gluten sensitivity, though the prevalence of these symptoms has not been well studied. Additionally, the effect that gluten plays in the development of depression in this group is unclear. While 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 that of CD patients. [48] It is possible that in our study GFD adherence contributed to the PWAG's lower odds of depression, though 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. While 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 US CD population. 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, though this did not meet significance when adjusted. While it is possible that we lost significance by over-adjusting for too many variables, we decided to present multiple models to allow for many interpretations based on 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 people were mistaken in their diagnosis of CD. However, all but two patients with diagnosed CD had a negative tTG test which, while 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 reasons for avoiding gluten when celiac disease was present, and so could not factor these elements into our analyses.

In conclusion, our study found no increased risk of depression and insomnia in participants with CD compared to a group of non-affected controls. PWAGs showed no difference in insomnia compared to controls, but did show a decreased risk of depression. To our knowledge this study is among the first to measure depression and insomnia in non-celiac gluten avoiders. Our findings raise the possibility that GFD adherence may not affect the development of depression in patients with CD, but might lower the risk of depression in patients without CD who adhere to a gluten free diet 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 non-celiac gluten sensitivity before and after treatment, and explore the role of gluten in depression.

Acknowledgments

Source of Funding: There was no source of funding.

Appendix

Classification of psychotropic medications into sub-categories

The following medications were listed in each category: Antidepressant: amitriptyline, amitriptyline - chlordiazepoxide, amitriptyline -perphenazine, antidepressants - unspecified, bupropion, citalopram, clomipramine, desipramine, desvenlafaxine, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine, sertraline, trazodone, venlafaxine, vilazodone; Anxiolytics, sedatives, and hypnotics: anxiolytics, sedatives, and hypnotics - unspecified, alprazolam, buspirone, bromazepam, butabarbital, butalbital, clonazepam, clorazepate, diazepam, estazolam, eszopiclone, flurazepam, lorazepam, melatonin, pentobarbital, phenobarbital, primidone, ramelteon, temazepam, triazolam, zaleplon, zolpidem; Anti-psychotic: aripiprazole, asenapine, chlorpromazine, clozapine, fluphenazine, haloperidol, iloperidone, lurasidone, olanzapine, paliperidone, perphenazine, pimozide, prochlorperazine, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, ziprasidone; Mood stabilizer: carbamazepine, lithium, topiramate, valproic acid; Sympathomimetic: amphetamine, armodafinil, atomoxetine, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, methylphenidate, modafinil.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	x1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	x2	Explain the scientific background and rationale for the investigation being reported
Objectives	x3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	x4	Present key elements of study design early in the paper
Setting	x5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	x6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	x7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/measurement	x8 *	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	x9	Describe any efforts to address potential sources of bias
Study size	x10	Explain how the study size was arrived at
Quantitative variables	x11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why

	Item No	Recommendation
Statistical methods	x12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	x13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	x14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	x15*	Report numbers of outcome events or summary measures
Main results	x16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	x17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	x18	Summarise key results with reference to study objectives
Limitations	x19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	x20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	x21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	N/A22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Abbreviations in this article

CD celiac disease

GFD gluten free diet

NHANES	National Health and Nutrition Examination Survey
PWAG	people without celiac disease who avoid gluten
US	United States

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Table 1

Characteristics of Patients with Celiac Disease and PWAGS

Clinical Characteristics	Diagnosed CD n (unweighted %; weighted %)	Undiagnosed CD n (unweighted %; weighted %)	PWAG n (unweighted %; weighted %)
Number	27 (0.12; 0.18)	79 (0.35; 0.50)	213 (0.96; 1.11)
Age (in 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			
Males	6 (22.22; 17.37)	33 (41.77; 44.75)	95 (44.60; 36.63)
Females	21 (77.78; 82.63)	46 (58.23; 55.25)	118 (55.40; 63.37)

Table 2

Depression and Insomnia in Patients with Celiac Disease, PWAGs, and Controls

Clinical Characteristics	Controls n (%)	CD n (%)	p value*	PWAG n (%)	p value•
Major Depression (n = 15, 021)					
< 10 – no	13,388 (91.85)	70 (96.11)	0.18	164 (97.1)	0.002
≥ 10 – yes	1,381 (8.15)	6 (3.89)		12 (2.90)	
Difficulty Related to Depression (n = 10,021)					
Not at all difficult	7,078 (72.68)	38 (71.05)	0.84	81 (71.81)	0.43
Somewhat difficult	2,234 (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	4,327 (27.37)	28 (37.65)		67 (34.12)	
≥ 8 hours a night	6,202 (35.50)	35 (44.64)	0.15	68 (35.70	0.96
< 8 hours a night	11,049 (64.50)	48 (55.36)		122 (64.30)	

*CD vs Controls

•PWAG vs Controls

Table 3

Risk of Depression and Sleep Difficulty in Celiac Disease and PWAGs

Variable	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

[a] Unadjusted

[b] Adjusted for age and gender

[c] Adjusted for age, gender, race/ethnicity, annual household income, number of healthcare visits, and presence of health insurance

Table 4

Quality of life factors in Celiac Disease, PWAGs, and Controls

Variable	n (%)	p Value*	Adjusted OR**	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 = 6,842)	1,703 (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 = 6,842)	1,870 (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

*All p-values compared to controls

**Adjusted for age and gender

Table 5

Psychotropic Medication Use in Celiac Disease, PWAGs, and Controls, NHANES 2009–2012

Psychotropic Medications	Total sample	Controls n (%)	CD n (%)	p value*	PWAG n (%)	p value•
None	5,213 (72.35)	5,127 (72.33)	30 (70.43)		56 (76.81)	
Any	1,688 (27.65)	1,661 (27.67)	13 (29.57)	0.82	14 (23.19)	0.60
Antidepressant	1,091 (19.35)	1,073 (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 vs Controls

•PWAGs vs Controls