

Autoimmune and Allergic Disorders are More Common in People With Celiac Disease or on a Gluten-free Diet in the United States

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Goals: We analyzed demographics, lifestyle patterns, and clinical characteristics of people with celiac disease (CD) and people without CD avoiding gluten (PWAG) to better understand associations with medical conditions and consumer behavior.

Background: Clinical significance of CD and gluten avoidance in the general population is incompletely understood. Recently, a high incidence of CD in adolescents with susceptibility genotypes, similar to other autoimmune or allergic disorders, and regional differences in consumer practices of gluten avoidance were reported.

Methods: Among 22,277 participants in the National Health and Nutrition Examination Survey 2009-2014, we identified persons with CD by testing CD serology or by both a health care provider diagnosis and adherence to a gluten-free diet. Similarly, PWAG were defined as adherent to a gluten-free diet without a CD diagnosis. Consumer behavior and characteristics of both groups, CD and PWAG were compared with those without these conditions, using survey-weighted generalized logistic regression.

Results: Participants with CD considered nutrition very important when grocery shopping and tended to have more constipation and thyroid disease. PWAG tended to spend more money on groceries, purchase organic foods, and check food labels more frequently during grocery shopping. They also reported having more food allergies, asthma, and thyroid disease.

Conclusions: Our study confirms that CD and PWAG share comorbidities of autoimmune nature. PWAG had more autoimmune/allergy-related disorders that may be associated with non-celiac gluten sensitivity a self-justifiable reason to be on the diet.

Key Words: celiac disease, gluten-free diet, non-celiac gluten sensitivity, NHANES

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Celiac disease (CD) is a chronic small intestinal immune-mediated enteropathy caused by intolerance to dietary glutes in genetically susceptible individuals.¹ The estimated cumulative incidence of CD was recently reported to be as high as 3.1% by age 15 years in a community study of adolescents with susceptibility genotypes.² In contrast, another recent study found a declining trend in the incidence of biopsy-diagnosed CD in the adult population of Finland, suggesting that exposure to as yet unidentified triggers has plateaued.³ According to recent studies based on the National Health and Nutrition Examination Survey (NHANES) from 2009 to 2014, the prevalence of CD in the United States is estimated to be around 0.7% or 1.8 million Americans.^{4,5} The number of people without CD avoiding gluten (PWAG) has increased, especially among the young, female individuals, and non-Hispanic white individuals, with an estimated overall prevalence of 1.7% or 4.3 million Americans in 2013-2014. In addition, the gluten-free market is expected to grow at an annual rate of 10.4% from \$4.63 billion spent in 2015 to \$7.59 billion expected expenditures in 2020 with many people on a gluten-free diet (GFD) believing in beneficial effects on weight loss and other chronic illnesses.⁶⁻⁸

NHANES data revealed that PWAG had a smaller waist circumference and reported a higher weight loss over 1 year.⁹ Zylberberg et al¹⁰ reported that PWAG had a lower odds of depression compared with controls. However, the clinical significance and public health impact of CD, along with health effects of the GFD in PWAG, are incompletely understood. Furthermore, non-celiac gluten/wheat sensitivity (NCGS), an entity with gluten/wheat-related symptoms without the typical enteropathy or serology of CD, has recently gained attention.¹¹ Increasing evidence suggesting clinical improvement in people with NCGS who adhere to a GFD has provoked debate about the appropriateness of GFD in the general population.¹¹⁻¹³ However, very few reports are available with regard to comorbidities, associated genetic and environmental risk factors, and sociodemographic characteristics of these people.^{9,10,14-16}

Similar to other autoimmune or allergic disorders, a North-South gradient¹⁷ in the prevalence of CD and significant regional differences in the prevalence of NCGS in the United States were recently reported.¹⁸ Despite lack of intermediate risk factors

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C.E.R. had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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responsible for the association with the latitude of residence, both genetic and environmental factors, including infectious agents such as Reovirus, Rotavirus, or *Borrelia burgdorferi* spirochetes, were assumed to play a role.^{16,19,20} Moreover, it is unknown whether other autoimmune and allergic disorders are associated with CD and the potential effects of the North-South gradient.

Therefore, the goal of our study was to describe the consumer behavior with regard to grocery shopping patterns and demographic, lifestyle, and chronic diseases, especially autoimmune-related and allergic-related comorbidities of CD and PWAG using comprehensive NHANES data, for potential risk stratification or identification of protective factors.

METHODS

Data Collection

The NHANES is a series of publicly accessible cross-sectional surveys conducted in 2-year cycles by the National Center for Health Statistics of the Centers for Disease Control and Prevention.²¹ This survey is conducted using a complex, stratified, and multistage probability sampling design and consists of standardized household interviews, physical examinations, and testing of biological samples. Currently, NHANES is the only nationally representative survey that has measured CD serology coupled with questions about medical conditions. For our study, we combined the 3 cycles of NHANES (2009-2010, 2011-2012, and 2013-2014) during which CD and PWAG were assessed by interview and serology for participants 6 years and older. The NHANES protocol was approved by the Research Ethics Review Board serving the National Center for Health Statistics,

and written informed consent was obtained from all survey participants. Our current data analyses were deemed exempt by the Institutional Review Board.

Participants

The overall unweighted response rates for the 2009-2010, 2011-2012, and 2013-2014 surveys were 77.3%, 69.5%, and 68.5%, respectively. As described in previous publications,^{4,5,22} CD was defined as having either double-positive serology for immunoglobulin A (IgA) tissue transglutaminase (IgA tTG) and IgA endomysial antibody (IgA EMA) (serologic CD, by LBXTTG and LBXEMA variables) or a reported diagnosis of CD by a health care provider coupled with being on a GFD (reported clinical CD, by MCQ 082: "Ever been told you have celiac disease?" and MCQ 086: "Are you on a gluten-free diet?"). The overall participation rate for CD serologic testing among individuals aged older than 6 who attended a visit at a mobile examination center was 90.2%. Persons with or without available CD serologic testing did not substantially differ by major demographic variables (age, sex, and race/ethnicity). PWAG were defined as those who reported being on a GFD without meeting our CD definition.²³ Of 35,189 sampled persons aged 6 years and older in NHANES 2009-2014, 24,703 (70%) attended a study visit at a mobile examination center. We excluded participants who were missing CD serology (n = 2425) or CD questionnaire responses (n = 1) resulting in an analysis sample of 22,277, including 6454 children and adolescents aged 6 to 19 years and 15,823 adults aged 20 years or older. Among them, there were 106 CD cases and 213 gluten-free followers without CD (Fig. 1).

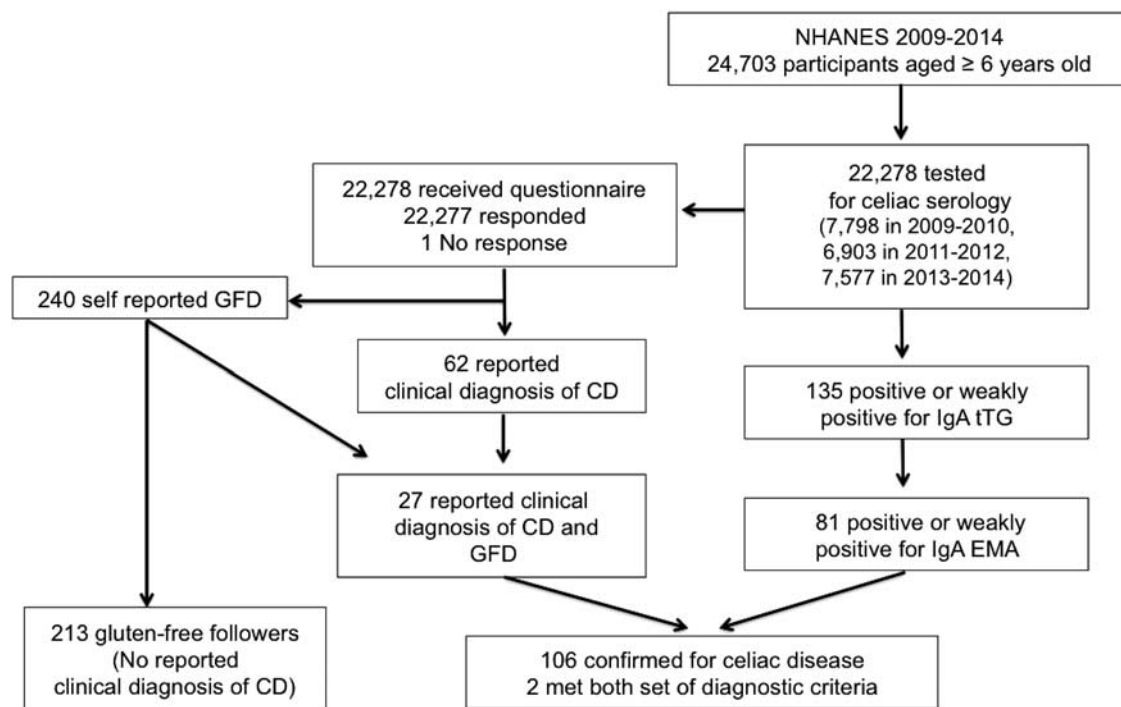


FIGURE 1. From an eligible population of 24,703 participants in NHANES 2009-2014, 22,278 had serologic samples tested for CD, with 81 found positive by sequential serologic testing. Of 240 participants who reported (by direct interview) being on a GFD, 27 (2 of whom also met serologic criteria) reported having been given a clinical diagnosis of CD. CD indicates celiac disease; EMA, endomysial antibody; GFD, gluten-free diet; IgA, immunoglobulin A; NHANES, National Health and Nutrition Examination Survey; tTG, tissue transglutaminase. Consort diagram (Original diagram by the authors, created using data from Rubio-Tapia et al¹³).

CD Serologic Tests

Serum specimens were shipped to the Celiac Disease Research Laboratory at Mayo Clinic, Rochester, MN, for sequential serological testing. Serum was tested for IgA tTG as a screening test (sensitivity, ~98%) with an enzyme-linked immunosorbent assay that uses human recombinant tTG (Inova Diagnostics, San Diego, CA), and results were categorized as positive (>10 U/mL), weakly positive (4 to 10 U/mL), or negative (<4.0 U/mL).^{22,24} Persons with a positive or weakly positive IgA tTG were tested for IgA EMA as a confirmatory test (specificity, 99% to 100%) by indirect immunofluorescence using the reticulin component of the endomysium of the smooth muscle in monkey esophagus tissue (Inova Diagnostics), and results were considered positive if fluorescence was observed at a dilution of 1: ≥5. Sequential serology has been shown in previous studies to be effective at detecting undiagnosed CD cases in the general population.^{25,26}

Covariates

We investigated the characteristics of participants with CD and PWAG, including the following: age [divided into age groups (years): 6 to 19, 20 to 39, 40 to 64, and ≥65], sex, race/ethnicity (non-Hispanic whites, non-Hispanic blacks, Hispanics, and others), birthplace (United States or foreign), poverty index,²⁷ a ratio of family income to poverty threshold, (≤1.3, >1.3 to 1.85, >1.85 according to the poverty guidelines used by federal programs in determining eligibility), latitude of residence (degree N) (<35, 35 to <40, and ≥40), education level (below high school, high school, and above high school), marital status (never married, married/with a partner, separated/widowed/divorced), smoking status (current, former, and never), and heavy alcohol use (>3 drinks/d in men or >2 drinks/d in women). Consumer behavior included monthly grocery cost (\$), purchased organic foods in past 30 days (yes or no), importance of price when grocery shopping (“very important”: yes or no), importance of nutrition (“very important”: yes or no), importance of taste (“very important”: yes or no), and check food labels for participants’ food allergies (yes or no), and other family members’ food allergies (yes or no). Medical conditions (yes or no) were based on self-reported and included gastrointestinal symptoms in the past 30 days, constipation, diabetes, hypertension, dyslipidemia, liver disease, thyroid disease, asthma, anemia, psoriasis, chronic bronchitis, any arthritis, osteoarthritis, rheumatoid arthritis, osteoporosis, and food allergies.²⁸ Further information about NHANES data collection can be found elsewhere.²⁹ Geocoding data on latitude are restricted and were used through the National Center for Health Statistics Research Data Center.³⁰

Statistical Analyses

Data were analyzed using SAS software version 9.4, SUDAAN software version 11.0.1, and R software version 3.2.2, using the “survey” package.³¹ We used published weights³² for all analyses to account for oversampling and nonparticipation in the household interview and physical examination. All variance calculations took into consideration the design effects of the survey using Taylor series linearization.³³ Multivariate analyses excluded persons with missing values for any factor included in the model. In order to compare characteristics of participants with CD and PWAG to persons without these conditions (controls), we used survey-weighted generalized logistic regression (SUDAAN PROCs MULTILOG and RLOGIST) to control for the effects

of demographic variables available to all age groups: age, sex, race/ethnicity, birthplace, latitude of residence, and poverty index. The comparison was summarized with odds ratio estimates and 95% confidence intervals (CI). We used survey-weighted linear regression analysis (SUDAAN PROC REGRESS) to estimate mean monthly grocery cost adjusted for demographic factors listed above. *P*-values were 2-sided, and a *P*-value of <0.05 was considered to indicate statistical significance.

RESULTS

Relationships With Demographic and Lifestyle Characteristics

The prevalence of CD and PWAG in the sampled US population was 0.7% (95% CI, 0.5%-0.95%; *n* = 106), and 1.1% (95% CI, 0.8%-1.4%; *n* = 213), respectively.¹⁷ Demographic and lifestyle characteristics of CD and PWAG are summarized with the number of participants and weighted prevalence by selected demographic variables (Table 1). In multivariate-adjusted analyses, CD was more prevalent among non-Hispanic whites, people with a higher education level, and those living at higher latitudes.¹⁷ PWAG were more frequently women, persons with higher household income, and those residing at higher latitudes.

Relationships With Consumer Behavior

Grocery shopping patterns, including monthly grocery cost, factors considered important in grocery shopping, and consumer behavior such as checking food labels and purchasing organic foods, are summarized in Table 2. Participants with CD considered nutrition to be a very important factor when grocery shopping compared with controls [odds ratio, 7.62 (95% CI, 2.38-24.38)]. Similarly, PWAG were more likely to have a higher monthly grocery cost (\$496 vs. \$440 for controls, *P*-value 0.06, data not shown in table), check food labels for their food allergies, and purchase more organic foods.

Relationships With Chronic Medical Conditions

Compared with controls, participants with CD tended to have more constipation and thyroid disease (Table 3). A borderline statistically significant association with chronic bronchitis (*P*-value, 0.06) was also observed. PWAG had higher odds of having food allergies, thyroid disease, history of asthma, current asthma, and osteoarthritis. We did not find statistically significant associations with other chronic conditions, including gastrointestinal symptom in the past month, diabetes, hypertension, dyslipidemia, liver disease, anemia, psoriasis, rheumatoid arthritis, and osteoporosis.

Clinical Laboratory and Dual-energy x-ray Absorptiometry (DEXA) Values

Lastly, we conducted multivariate linear regression analyses to compare the clinical laboratory and DEXA findings by participants with CD and PWAG (Table 4). Participants with CD had a lower adjusted mean serum-free T4, body mass index, and bone mineral density in both spine and femur. Among PWAG, there was no statistically significant difference in clinical laboratory values or DEXA findings compared with controls although PWAG had a higher mean thyroid peroxidase antibody, the most common autoantibody in Hashimoto thyroiditis (48.8 vs. 21.0 IU/mL; *P*-value, 0.33).³⁴

TABLE 1. Demographic and Lifestyle Characteristics of Persons With Celiac Disease and PWAG Among NHANES Participants 6+ Years, United States, 2009-2014 (N = 22,277)

Characteristics	Celiac Disease (n = 106)			PWAG (n = 213)			People Without Gluten-related Disorders (n = 21,958)	
	N	Weighted Prevalence (%)	Multivariate Adjusted	N	Weighted Prevalence (%)	Multivariate Adjusted	N	Weighted Prevalence (%)
			OR (95% CI)*			OR (95% CI)*		
Age group (y)								
6-19	29	18.9	0.96 (0.56-1.63)	29	10.1	0.48 (0.29-0.82)	6396	18.8
20-39	26	29.8	REF	63	33.8	REF	5326	29.5
40-64	33	38.2	0.84 (0.46-1.56)	89	44.5	0.97 (0.58-1.61)	6695	37.1
≥ 65	18	13.1	0.70 (0.36-1.36)	32	11.7	0.68 (0.34-1.34)	3541	14.6
Sex								
Male	39	37.5	REF	95	36.6	REF	10,890	49.1
Female	67	62.5	1.67 (0.98-2.83)	118	63.4	1.76 (1.28-2.43)	11,068	50.9
Race								
Non-Hispanic white	72	87.9	REF	84	69.0	REF	8494	64.9
Non-Hispanic black	6	2.0	0.18 (0.07-0.46)	53	11.6	1.33 (0.87-2.05)	4766	11.4
Hispanic	19	7.1	0.54 (0.20-1.41)	43	11.4	1.23 (0.78-1.93)	6038	16.0
Other	9	3.0	0.38 (0.13-1.15)	33	8.0	1.55 (0.81-2.99)	2660	7.7
US born								
Yes	90	90.8	REF	167	88.3	REF	16,749	83.9
No	16	9.2	0.93 (0.34-2.58)	46	11.7	0.61 (0.35-1.08)	5196	16.1
Poverty index†								
< 1.3	33	21.3	0.96 (0.54-1.68)	56	14.6	0.49 (0.29-0.81)	7778	26.0
1.3-1.85	9	8.2	0.81 (0.31-2.11)	20	9.1	0.72 (0.31-1.67)	2594	10.9
> 1.85	58	70.5	REF	122	76.3	REF	9800	63.1
Latitude (degrees N)								
< 35	16	5.9	REF	60	19.5	REF	7400	26.9
35- < 40	26	26.3	3.15 (1.44-6.91)	55	18.8	0.75 (0.44-1.29)	6546	31.3
≥ 40	64	67.8	5.22 (2.56-10.65)	98	61.7	1.93 (1.16-3.20)	8010	41.7
Education (20+years)								
< High school	8	5.7	0.35 (0.15-0.80)	28	11.2	0.82 (0.39-1.73)	3838	16.9
High school	13	12.0	0.45 (0.22-0.91)	30	13.7	0.62 (0.34-1.16)	3454	21.7
> High school	56	82.3	REF	125	75.1	REF	8253	61.4
Marital status (20+years)								
Never married	15	22.8	REF	41	26.1	REF	2946	18.4
Married/with partner	47	60.9	0.63 (0.25-1.58)	110	61.0	0.62 (0.31-1.23)	9149	63.0
Separated/widowed/divorced	15	16.3	0.63 (0.23-1.72)	33	12.9	0.46 (0.20-1.09)	3459	18.6
Smoking (20+years)								
Never smoker	51	71.6	REF	114	58.6	REF	8638	55.7
Former smoker	15	16.6	0.52 (0.25-1.05)	47	26.5	1.12 (0.78-1.63)	3681	24.3
Current smoker	11	11.9	0.47 (0.22-1.04)	23	14.9	0.83 (0.40-1.73)	3240	20.0
Heavy alcohol use (20+years)*								
Yes	5	4.0	REF	10	6.8	REF	1050	8.9
No	67	96.0	0.38 (0.11-1.24)	164	93.2	0.72 (0.25-2.10)	12,979	91.1

*Compared with people without gluten-related disorders and adjusted for age, sex, race/ethnicity, US born, latitude of residence, and poverty index.

†Family income to poverty threshold ratio.²⁷

‡> 3 drinks/day for men or > 2 drinks/day for women.

CI indicates confidence interval; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; REF, Reference.

DISCUSSION

Our study provides a description of demographic and lifestyle factors, consumer behavior, and chronic conditions of people with CD and PWAG, using nationally representative data and uniquely accounting for North-South gradient. Our findings confirm that people with CD and PWAG are a heterogeneous group, implying that multiple etiologies, from genetics to sociodemographic and environmental factors, are involved.

Persons with CD considered nutrition to be a very important factor when grocery shopping. This finding was somewhat expected given that a GFD is the main management of CD. They also tended to buy more organic foods, consider taste an important factor, and have self-reported food allergies although these associations did not reach statistical significance. Moreover, they had more constipation and thyroid disease. Thyroid disease diagnoses

TABLE 2. Grocery Shopping Patterns of People With Celiac Disease and PWAG Among NHANES Participants 6+ Years, United States, 2009-2014 (N = 22,277)

Characteristics	Celiac Disease			PWAG			People Without Gluten-related Disorders
	N	Weighted Prevalence (%)	Multivariate Adjusted OR (95% CI)*	N	Weighted Prevalence (%)	Multivariate Adjusted OR (95% CI)*	
Bought organic foods [†]							
No	14	34.3	REF	21	29.3	REF	58.6
Yes	13	65.7	2.81 (0.79-10.00)	21	70.7	4.04 (1.43-11.41)	41.4
Important during grocery shopping:							
Price [‡]							
No	19	82.3	REF	17	56.9	REF	60.7
Yes	8	17.7	0.53 (0.24-1.17)	25	43.1	1.31 (0.36-4.75)	39.3
Nutrition [‡]							
No	6	15.2	REF	7	20.9	REF	40.2
Yes	21	84.8	7.62 (2.38-24.38)	35	79.1	2.53 (0.88-7.29)	59.8
Taste [‡]							
No	5	9.8	REF	10	33.5	REF	23.3
Yes	22	90.2	2.76 (0.51-15.04)	32	66.5	0.60 (0.24-1.48)	76.7
Check labels for my food allergies ^{†‡}							
No	—	—	—	35	52.6	REF	93.5
Yes	—	—	—	14	47.4	13.45 (5.38-33.57)	6.5
Check labels for family members' food allergies ^{†‡}							
No	—	—	—	44	92.6	REF	93.0
Yes	—	—	—	5	7.4	1.12 (0.23-5.41)	7.0

*Compared with people without gluten-related disorders and adjusted for age, sex, race/ethnicity, US born, latitude of residence, and poverty index.

[†]Measured in NHANES 2009-2010 only.

[‡]Analyses were not conducted for celiac disease due to <5 participants in a cell.

CI indicates confidence interval; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio.

were based on self-report; however, among adult participants with data on prescription medications (N = 14,097), 64% of those with a thyroid disease diagnosis were using thyroid hormones or antithyroid agents compared with 0.4% of persons without a thyroid disease diagnosis, providing support for the correct classification of participants with regard to thyroid disease. We were unable to investigate associations with detailed malabsorption symptoms including diarrhea or weight loss in NHANES.

PWAG spent more on their monthly groceries, purchased organic foods, and checked food labels, suggesting that these people are cautious and interested in their diet. This could be in part explained by the demographic characteristics of PWAG who tended to be young women with higher household income (Table 1). A recent study using Google Trend data also suggests that being on a GFD could be associated with socio-demographic characteristics, rather than the result of health-related factors.⁸ Notably, PWAG were more likely to have food allergies, thyroid disease, and asthma.

The significant association with autoimmune/allergic disorders among PWAG was especially interesting in that these people could conceivably have NCGS or another type of gluten sensitivity. Currently, the prevalence of NCGS is unknown due to the controversial definition of NCGS and the lack of validated biomarkers, but is assumed to be more common than CD. Sapone et al³⁵ suggested that the pathogenesis of NCGS involves mainly the intestinal innate immune system rather than an adaptive immune response, the key pathogenesis in CD. This is supported by the lack of enteropathy with villous blunting in NCGS, a typical characteristic of CD because of an HLA-driven adaptive immune response. Because of the increased awareness and popularity of the GFD, many people with gastrointestinal

symptoms self-diagnose their symptoms as gluten sensitivity and begin a GFD. However, the scientific evidence as to the health effects of a GFD for those without CD or wheat allergy is insufficient. Herfarth et al³⁶ reported 19.1% of patients with inflammatory bowel disease (IBD) have tried a GFD and 65.6% of them experienced improvement of their gastrointestinal symptoms. The GFD has also been suggested to reduce gastrointestinal symptoms in patients with dermatitis herpetiformis, irritable bowel syndrome, rheumatoid arthritis, type1 diabetes, HIV-associated enteropathy, systemic lupus erythematosus, thyroiditis, psoriasis, and neurological disorders such as gluten ataxia and multiple sclerosis.^{37,38} Furthermore, avoiding gluten was reported to reduce the incidence of autoimmune disease symptoms.³⁹ However, it is still controversial whether avoiding the gluten component was the major factor responsible for alleviating symptoms since there are other components in gluten-containing products. People may experience improvement of symptoms by eliminating highly processed foods and refined carbohydrates, such as white bread and pizza, from their diet while increasing consumption of fruits and vegetables.⁴⁰ In one systemic review, 16% of suspected NCGS patients (38/231) had gluten-related symptoms and 40% of them showed a nocebo effect (similar or increased symptoms in response to placebo), raising doubt about whether gluten is the culprit food in most patients with presumed NCGS.⁴¹

Although genetic predisposition, mainly HLA DQ2 and DQ8, plays a major role in the pathogenesis of CD, only a small fraction of those with a susceptible allele develop CD, suggesting environmental factors also play a role among PWAG.^{42,43} Adjusting for North-South gradient had little effect on the relationships of CD with

TABLE 3. Association of Chronic Medical Conditions With Celiac Disease and PWAG Among NHANES Participants 6+ Years, United States, 2009-2014 (N = 22,277)

Characteristics	Celiac Disease			PWAG			People Without Gluten-related Disorders Weighted Prevalence (%)
	N	Weighted Prevalence (%)	Multivariate Adjusted OR (95% CI)	N	Weighted Prevalence (%)	Multivariate Adjusted OR (95% CI)*	
Gastrointestinal symptoms in past month							
No	93	97.3	REF	182	91.7	REF	93.2
Yes	6	2.7	0.39 (0.13-1.19)	18	8.3	1.20 (0.60-2.42)	6.8
Constipation (Bristol type 1-2) ^{†‡}							
No	21	79.6	REF	—	—	—	93.5
Yes	5	20.4	5.51 (1.28-23.66)	—	—	—	6.5
Diabetes							
No	97	91.7	REF	175	90.8	REF	92.5
Yes	9	8.3	1.39 (0.46-4.17)	38	9.2	1.17 (0.63-2.19)	7.5
Hypertension							
No	65	80.3	REF	122	72.0	REF	69.6
Yes	18	19.7	0.60 (0.26-1.39)	68	28.0	0.87 (0.53-1.43)	30.4
Dyslipidemia							
No	44	63.8	REF	121	68.0	REF	64.8
Yes	28	36.2	0.97 (0.56-1.70)	62	32.0	0.96 (0.65-1.43)	35.2
Liver disease [‡]							
No	—	—	—	176	96.1	REF	97.0
Yes	—	—	—	8	3.9	1.48 (0.53-4.13)	3.0
Thyroid disease							
No	63	79.5	REF	154	75.8	REF	89.6
Yes	14	20.5	2.19 (1.12-4.31)	30	24.2	2.50 (1.30-4.83)	10.4
Asthma history							
No	86	77.8	REF	161	74.0	REF	84.6
Yes	20	22.2	1.56 (0.83-2.92)	52	26.0	1.88 (1.22-2.90)	15.4
Current asthma							
No	94	86.6	REF	182	85.5	REF	91.2
Yes	12	13.4	1.60 (0.73-3.47)	29	14.5	1.80 (1.01-3.21)	8.8
Anemia							
No	101	95.8	REF	198	95.5	REF	96.9
Yes	5	4.2	1.14 (0.42-3.08)	15	4.5	1.23 (0.61-2.48)	3.1
Psoriasis							
No	76	93.7	REF	181	95.3	REF	97.1
Yes	6	6.3	2.08 (0.68-6.36)	9	4.7	1.46 (0.52-4.13)	2.9
Chronic bronchitis							
No	69	87.2	REF	173	91.9	REF	94.7
Yes	8	12.8	2.58 (0.98-6.85)	11	8.1	1.67 (0.76-3.66)	5.3
Total arthritis							
No	51	68.4	REF	128	70.3	REF	75.5
Yes	26	31.6	1.64 (0.91-2.96)	56	29.7	1.52 (0.94-2.46)	24.5
Osteoarthritis							
No	57	83.8	REF	148	80.6	REF	87.8
Yes	14	16.2	1.40 (0.60-3.27)	24	19.4	1.96 (1.26-3.04)	12.2
Rheumatoid arthritis [‡]							
No	—	—	—	159	95.5	REF	95.9
Yes	—	—	—	13	4.5	1.26 (0.58-2.73)	4.1
Osteoporosis [§]							
No	39	87.9	REF	81	93.8	REF	93.8
Yes	6	12.1	2.23 (0.55-8.97)	9	6.2	0.84 (0.33-2.13)	6.2
Food allergies [†]							
No	29	78.8	REF	33	66.6	REF	91.5
Yes	6	21.2	3.60 (0.76-17.03)	15	33.4	5.55 (2.93-10.52)	8.5

*Compared with people without gluten-related disorders and adjusted for age, sex, race/ethnicity, US born, latitude of residence, and poverty index.

[†]Measured in NHANES 2009-2010 only.[‡]Analyses were not conducted due to <5 participants in a cell.[§]Measured in NHANES 2009-2010 and 2013-2014 only.

CI indicates confidence interval; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio.

autoimmune/allergic conditions also known to have similar geographic distribution of disease prevalence.⁴⁴ Previous studies also suggest potential associations between viral

infections such as adenovirus, rotavirus, hepatitis C virus, and CD pathogenesis.^{20,42,45} Moreover, the prevalence of CD and NCGS varies significantly within the United States

TABLE 4. Clinical Laboratory and DEXA Measures Among NHANES Participants 6+ Years With Celiac Disease and PWAG, United States, 2009-2014 (N=22,277)

Characteristics	Celiac Disease			PWAG			People Without Gluten-related Disorders	
	Adjusted Mean*	SE	P	Adjusted Mean*	SE	P	Adjusted Mean*	SE
Thyroid stimulating hormone (μIU/L) [†]	1.6	0.2	0.063	1.6	0.2	0.063	2.0	0.1
Free thyroxine (ng/dL) [†]	0.76	0.03	0.022	0.91	0.10	0.37	0.82	0.01
Thyroglobulin antibody (IU/mL) [†]	4.1	2.0	0.23	3.3	3.7	0.36	7.1	1.4
Thyroid peroxidase antibody (IU/mL) [†]	21.8	17.7	0.96	48.8	28.2	0.33	21.0	1.8
Eosinophil count (1000 cells/μL)	225	34	0.52	193	10	0.33	203	2
Eosinophils (%)	3.2	0.5	0.50	2.8	0.1	0.66	2.9	0.02
C-reactive protein (mg/dL) [‡]	0.20	0.05	0.016	0.26	0.06	0.22	0.33	0.01
Spine bone mineral density (g/cm ²) [§]	0.95	0.02	0.018	0.96	0.03	0.12	1.01	<0.01
Femur bone mineral density (g/cm ²) [§]	0.88	0.02	<0.001	0.94	0.02	0.40	0.96	<0.01

*Adjusted for age, sex, and race; reference group was people without gluten-related disorders.

[†]Measured in NHANES 2009-2012 only.

[‡]Measured in NHANES 2009-2010 only.

[§]Measured in persons 8+ years in NHANES 2009-2010 and 40+ years in NHANES 2013-2014.

DEXA indicates dual-energy x-ray absorptiometry; NHANES, National Health and Nutrition Examination Survey; PWAG, people without celiac disease avoiding gluten.

and worldwide. The ratio of CD over NCGS was the highest in the Northeast and the lowest in the South.¹⁸ Therefore, further epidemiologic investigations that account for these environmental factors are needed to fully understand gluten-related disorders.

A strength of our study was the use of the only nationally representative data to describe the characteristics of people with CD and PWAG using comprehensive demographic, geographic, socioeconomic, and chronic disease information. However, there were also several limitations of our study. First, in NHANES, CD was defined based on a self-reported health care provider diagnosis and adherence to a GFD or on positive sequential serology. Sequential serology can produce false negatives in some persons with mild CD. However, small intestinal biopsy would be difficult to perform on the general US population and sequential serology has been validated for use in epidemiologic studies.²⁵ An additional limitation of the use of serology is that it may not detect CD in persons with IgA deficiency; however, the prevalence of selective IgA deficiency is low, so few cases of undiagnosed CD should have been missed. Our CD definition was also limited in that use of a GFD was based on self-report and participants were not asked their reason for adopting the diet, the duration or degree of adherence, or whether they had experienced improvement in any gastrointestinal symptoms. Therefore, it is unknown how many PWAG chose a GFD due to autoimmune/allergy-related gastrointestinal symptoms, non-celiac gluten sensitivity, or purely as a fad. Another limitation of our study is that information on chronic diseases was also self-reported with potential recall bias. The small number of CD participants and PWAG despite 6 years of NHANES testing was an additional limitation. Furthermore, due to the cross-sectional study design, a causal relationship between the GFD use and health conditions could not be determined. Lastly, the findings should be interpreted with the caution that the larger the number of associations examined, the

great the possibility that statistically significant associations could occur by chance.

In conclusion, autoimmune and allergic disorders were more common among people with CD and PWAG in the NHANES 2009 through 2014. Both CD and PWAG were associated with thyroid disease. Notably, PWAG also tended to have more food allergies and asthma. These findings may provide insight into characteristics of NCGS that may explain adoption of GFD among people without CD. Further prospective studies and clinical trials to investigate the effects of a GFD on PWAG and personalized genomic/environmental studies to explain risk factors associated with gluten-related disorders are warranted.

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