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Epidemiology and risk of psychiatric disorders among patients with celiac disease: A population-based national study

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Abstract

Background and Aim: Celiac disease (CD) is a chronic disorder resulting from an immune reaction to gluten in genetically predisposed individuals. Although several studies have linked CD to psychiatric diseases, there are limited data on this topic. Using a large database, we sought to describe the epidemiology of several psychiatric disorders in CD.
Methods: We queried a multicenter database (Explorys Inc), an aggregate of electronic health record data from 26 major integrated healthcare systems from 2016 to 2020 consisting of 360 hospitals in the USA. A cohort of patients with a Systematized Nomenclature Of Medicine – Clinical Terms diagnosis of CD was identified. Multivariate analysis was performed using Statistical Package for Social Sciences version 25.
Results: Of the 37 465 810 patients in the database between 2016 and 2020, there were 112 340 (0.30%) individuals with CD. When compared with patients with no history of CD, patients with CD were more likely to have a history of anxiety (odds ratio [OR]: 1.385; 95% confidence interval [CI]: 1.364–1.407), depression (OR: 1.918; 95% CI: 1.888–1.947), bipolar (OR: 1.321; 95% CI: 1.289–1.354), attention-deficit hyperactivity disorder (OR: 1.753; 95% CI: 1.714–1.792), eating disorder (OR: 15.84; 95% CI: 15.533–16.154), and childhood autistic disorder (OR: 4.858; 95% CI: 3.626–6.508). Patients with CD and psychiatric conditions were more likely to be smokers, with history of alcohol and substance abuse as well as a history of personality disorder.
Conclusions: In this large database, patients with CD are at increased risk of having multiple psychiatric diseases including anxiety, depression, bipolar, attention-deficit hyperactivity disorder, eating disorder, and childhood autism. Individual care and referral to psychiatry when appropriate are warranted while taking care of this group of patients.

Introduction

Celiac disease (CD) is a chronic autoimmune enteropathy with a prevalence of 1% among the western population.[1] The incidence of CD is on the rise, likely due to earlier screening and better diagnostic methods.[2] The disease is multifactorial in etiology and is triggered by an immune reaction to gluten, a protein found in wheat, barley, and rye in genetically susceptible individuals.[3] The clinical presentation is variable with intestinal and extraintestinal symptoms.[4] Classic gastrointestinal symptoms include diarrhea, abdominal pain, weight loss, and bloating.[3] Extraintestinal manifestations are widely variable including metabolic bone disease, skin manifestations, neurologic, and psychiatric diseases among many. To this date, the only accepted treatment for CD is the elimination of gluten from the diet.[3]

Chronic medical diseases are commonly associated with different psychiatric conditions,[5] CD is no exception. Katon *et al.* showed that patients with anxiety or depression had higher numbers of medical symptoms when controlling for disease severity of their medical condiditons.[5] In the literature, CD has been reported to be associated with anxiety, depression, schizophrenia,

bipolar disorder, eating disorders, autism spectrum disorder (ASD), and attention-deficit hyperactivity disorder (ADHD). Psychoaffective comorbidities significantly affect the quality of life of patients with CD. Different mechanisms were proposed to explain this association including a direct gut–brain relationship,[6] autoimmunity,[7] toxic gluten metabolites,[8] cerebral hypoperfusion,[9] dietary restrictions compromising daily social relationships,[10] and vitamin deficiencies[11] to elucidate a few.

The current literature on the association of psychiatric diseases with CD is conflicting. Using a large population-based database, we aim to describe the epidemiology and association between CD and different psychiatric conditions.

Methods

Database. This is a retrospective, observational cohort study utilizing a multi-institutional data analytics and research platform (Explorys) developed by IBM Corporation, Watson Health.[12] Explorys is a cloud-based database that spans 26 healthcare systems, consisting of 360 hospitals in the USA from 1999 to the present date. The participating healthcare systems are granted access to Explorys. Data from more than 50 million unique patients, representing the population from all 50 states, thus provide a broad regional and climatic distribution of source population. All database records are anonymized and fully compliant with US patient confidentiality requirements. Ethical review and informed consent were waived because there are no identifiers associated with any of the patient data. For diagnoses, International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes are mapped into the Systematized Nomenclature Of Medicine – Clinical Terms (SNOMED-CT) hierarchy[13] while prescription drug orders are mapped into RxNorm.[14] Billing inquiries are used for data collection. The data are collected from both inpatient and outpatient settings; the data also include patients with all types of insurance as well as those who are self-pay. Explorys allows for the generation of multiple cohorts based on the presence or absence of SNOMED-CT diagnoses.

Patient selection. Records of all patients between 1999 and 2020 were first identified. The study cohort (CD cohort) was then identified by searching the database for a SNOMED-CT diagnosis of "celiac disease." The control group was then identified as patients without SNOMED-CT "celiac disease."

Covariates. Age, sex, and race-based data were collected. Medical comorbidities including smoking, alcohol abuse, personality disorder, and different psychiatric conditions including anxiety, depression, bipolar, ADHD, eating disorder, and childhood autism disorders were obtained.

Statistical analysis. Patients with CD were compared with patients without CD. The overall period prevalence was calculated by dividing the total number of individuals with CD by the total number of individuals in Explorys, thus making sure that all patients in the denominator had an equal opportunity of being diagnosed with CD. The prevalence rates of different psychiatric disorders in the study (CD) and control groups (non-CD) were calculated by dividing the total number of individuals with each psychiatric condition over the total number of individuals with CD and without CD, respectively. The odds ratio (OR) for univariable analysis, its standard error, and 95% confidence interval (CI) were calculated according to Altman, 1991, using the MedCalc Statistical Software with a case–control design. To adjust for possible confounding from the covariates listed previously, a multivariate regression model was constructed using binary logistic regression. Statistical analysis for the multivariate model was performed using Statistical Package for Social Sciences (version 25, IBM Corp). The outcome was diagnosis of psychiatric diseases between the celiac group and propensity score-matched controls without CD. For all analyses, a two-sided P value of < 0.05 was considered statistically significant.

Results

Descriptive epidemiology. Baseline characteristics of the study cohort (CD cohort) and control are displayed in Table 1. Of the 37 465 810 patients in the database between 2016 and 2020, there were 112 340 (0.30%) individuals with CD. Patients with CD had more medical comorbidities compared with the general population including smoking, alcohol abuse, and substance abuse. The prevalence of anxiety, depression, bipolar disorder, ADHD, eating disorder, and childhood autism was higher among patients with CD compared with the general population (Table 1).

Table 1 Baseline patients' characteristics

	Celiac	Non-celiac
	N = 112 340	*N* = 37 353 470
Age		
< 18 years old	6290 (5.6)	6 598 300 (17.7)
18–65 years old	78 350 (69.7)	22 231 240 (59.5)
> 65 years old	27 700 (24.7)	8 523 930 (22.8)
Sex		
Male	27 230 (24.2)	16 548 030 (44.3)
Female	85 120 (75.8)	20 805 440 (55.7)
Race		
Caucasian	94 750 (84.3)	22 216 830 (59.5)
African American	4260 (3.8)	4 299 830 (11.5)
Comorbidities		
Smoker	17 140 (15.3)	2 952 800 (7.9)
Alcohol abuse	2910 (2.6)	664 080 (1.8)
Substance abuse	2490 (2.2)	466 510 (1.2)
Hypertension	37 180 (33.1)	9 039 140 (24.2)
Diabetes mellitus	30 080 (26.8)	3 862 860 (10.3)
Hyperlipidemia	42 930 (38.2)	8 122 090 (21.7)
Obesity	13 130 (11.7)	2 272 510 (6.1)
Anxiety disorder	37 320 (33.2)	4 516 530 (12.1)
Depression disorder	45 070 (40.1)	4 761 340 (12.7)
Bipolar disorder	9220 (8.2)	674 660 (1.8)
ADHD	10 500 (9.3)	1 096 220 (2.9)
Eating disorder	15 600 (13.9)	161 250 (0.4)
Childhood autistic disorder	4150 (3.7)	120 910 (0.3)
Personality disorder	1720 (1.5)	200 280 (0.5)
Glucocorticoid exposure	32 450 (28.9)	5 236 950 (14.0)

ADHD, attention-deficit hyperactivity disorder.

Risk and predictors of psychiatric disease in population with celiac disease using univariate analysis model. Patients with CD had increased risk of developing several psychiatric disorders compared with the general population with CD; this includes anxiety (OR: 3.42; 95% CI: 3.37–3.46), depression (OR: 4.37; 95% CI: 4.31–4.42), bipolar (OR: 4.73; 95% CI: 4.63–4.84), ADHD (OR: 4.49; 95% CI: 4.39–4.59), eating disorder (OR: 4.69; 95% CI: 4.26–5.15), and childhood autism (OR: 2.49; 95% CI: 2.20–2.82) (Tables 2 and 3). Among CD, patients who developed psychiatric disorders were more likely to be young (age 18–65), females, and Caucasian and had a history of smoking, alcohol abuse, substance abuse, and personality disorder (Tables 2 and 3).

Risk of psychiatric disease in population with celiac disease using multivariate analysis model. After adjusting for factors including age, sex, and race, patients with CD had increased risk of developing several psychiatric disorders compared with the general population with CD; this includes anxiety (OR: 1.385; 95% CI: 1.364–1.407), depression (OR: 1.918; 95% CI: 1.888–1.947), bipolar (OR: 1.321; 95% CI: 1.289–1.354), ADHD (OR: 1.753; 95% CI: 1.714–1.792), eating disorder (OR: 15.84; 95% CI: 15.533–16.154), and childhood autistic disorder (OR: 4.858; 95% CI: 3.626–6.508) (Fig. 1).

Discussion

In this large population-based study of 37 million patients, 112 340 patients had CD (0.30%). Our sample showed that compared with the general population, patients with CD were more likely to have anxiety, depression, bipolar disorder, eating disorders, ADHD, and childhood autism. Patients with CD and psychiatric conditions were generally young, females, and Caucasian. Patients with CD with psychiatric conditions were more likely to be smokers and have a history of alcohol and substance abuse as well as personality disorders.

A wide range of psychiatric conditions has been described to be associated with CD in the literature. Although depression was reported to be common comorbidity among patients with CD in some studies,[15,16] others reported no difference compared with the general population.[17,18] It is thought that depressive symptoms usually start as a consequence of ongoing symptoms such as diarrhea or pain. Interestingly, more severe gastrointestinal symptoms were shown to correlate well with the severity of depressive symptoms.[19] Treatment with a gluten-free diet (GFD) led to an improvement of depressive symptoms in some studies.[20,21] However, other studies showed persistence of the depressive symptoms,[22,23] possibly due to dietary restrictions that impair patients' social relationships and reduce their quality of life.[24] Furthermore, non-compliance with a GFD might be a consequence or a cause of persistent depression.[25]

Based on the current literature, anxiety was reported to be more common in patients with CD when compared with the general population,[17,24] and symptoms improved with a GFD.[23] Furthermore, social phobia[26] and panic disorder[16] also have been reported to be associated with CD. However, a recent meta-analysis declined the association between CD and anxiety.[15]

Several studies evaluated the potential association of bipolar disorder with CD, although results are conflicting with some showing an increased risk of bipolar disorder in patients with CD[16] while others did not.[27] In 2011, Dickerson *et al*. found higher levels of CD-related antibodies in patients with bipolar disorder compared with the control group.[28] However, a recent meta-analysis of four case-controlled studies concluded no difference in the risk of bipolar disorder between CD compared with the general population.[29]

Early reports brought attention that there might be a possible association of ADHD in patients with CD. Niederhofer and Pittschieler evaluated 132 patients with CD and followed for 6 months on GFD. The study demonstrated that ADHD symptoms were more severe in patients with CD compared with the general population, and a 6-month GFD improved ADHD symptoms in the majority of patients.[30] Even though other studies confirmed the same result,[31,32] there are some reports that did not conclude a significant association between ADHD and CD.[33–35]

The current literature regarding the association of autism spectrum disorder (ASD) and CD is discrepant, with some studies suggested an association with CD,[36] while other recent studies denied it.[37] In a retrospective study conducted in Italy, 382 children diagnosed with ASD using DSM-IV criteria performed a serological CD screening. The overall CD prevalence was significantly higher among children with ASD compared with the general pediatric population; Calderoni *et al*. highlighted the importance of regular

Table 2 Risk association of anxiety, depression, and bipolar disorders in population with celiac disease using univariate analysis

	Anxiety	Depression	Bipolar
Celiac disease	3.42 (CI: 3.37–3.46)	4.37 (CI: 4.31–4.42)	4.73 (CI: 4.63–4.84)
Age 18–65	1.05 (CI: 1.02–1.09)*	1.34 (CI: 1.30–1.38)	0.99 (CI: 0.94–1.04)**
Female	1.28 (CI: 1.24–1.32)	2.05 (CI: 1.99–2.12)	0.79 (CI: 0.75–0.83)
Caucasian	1.60 (CI: 1.53–1.67)	1.20 (CI: 1.12–1.28)	0.77 (CI: 0.70–0.86)
Alcohol abuse	3.70 (CI: 3.43–4.00)	3.58 (CI: 3.29–3.88)	5.50 (CI: 5.07–5.96)
Smoker	2.93 (CI: 2.83–3.03)	3.44 (CI: 3.32–3.56)	6.31 (CI: 6.04–6.61)
Substance abuse	3.73 (CI: 3.55–3.91)	5.34 (CI: 5.06–5.64)	7.18 (CI: 6.82–7.57)
Personality disorder	8.78 (CI: 7.73–9.97)	9.08 (CI: 7.82–10.54)	9.30 (CI: 8.39–10.31)
Corticosteroid	2.30 (CI: 2.23–2.37)	1.49 (CI: 1.45–1.54)	1.30 (CI: 1.24–1.36)

*$P = 0.0006$.
**$P = 0.6427$.
CI, confidence interval.

Table 3 Risk association of attention-deficit hyperactivity disorder, eating disorder, and autism disorders in population with celiac disease using univariate analysis

	ADHD	Eating disorder	Childhood autism	*P* value
Celiac disease	4.49 (CI: 4.39–4.59)	4.69 (CI: 4.26–5.15)	2.49 (CI: 2.20–2.82)	—
Age 18–65	1.20 (CI: 1.14–1.26)	1.57 (CI: 1.23–2.00)*	16.76 (CI: 6.91–40.63)	*$P = 0.0003$
Female	0.65 (CI: 0.62–0.68)	4.09 (CI: 2.82–5.92)	0.14 (CI: 0.11–0.19)	—
Caucasian	1.16 (CI: 1.08–1.24)	1.33 (CI: 0.96–1.85)*	0.98 (CI: 0.67–1.43)**	*$P = 0.0820$ **$P = 0.9117$
Alcohol abuse	3.68 (CI: 3.38–4.01)	4.33 (CI: 3.22–5.83)	0.67 (CI: 0.28–1.63)	—
Smoker	4.50 (CI: 4.30–4.71)	1.52 (CI: 1.21–1.90)*	0.21 (CI: 0.11–0.40)	*$P = 0.0003$
Substance abuse	4.76 (CI: 4.50–5.02)	3.43 (CI: 2.74–4.30)	1.01 (CI: 0.64–1.60)*	*$P = 0.9530$
Personality disorder	3.91 (CI: 3.49–4.38)	8.51 (CI: 6.31–11.48)	12.55 (CI: 8.91–17.66)	—
Corticosteroid	1.28 (CI: 1.22–1.35)	2.10 (CI: 1.73–2.55)	0.61 (CI: 0.44–0.86)*	*$P = 0.0043$

ADHD, attention-deficit hyperactivity disorder; CI, confidence interval.

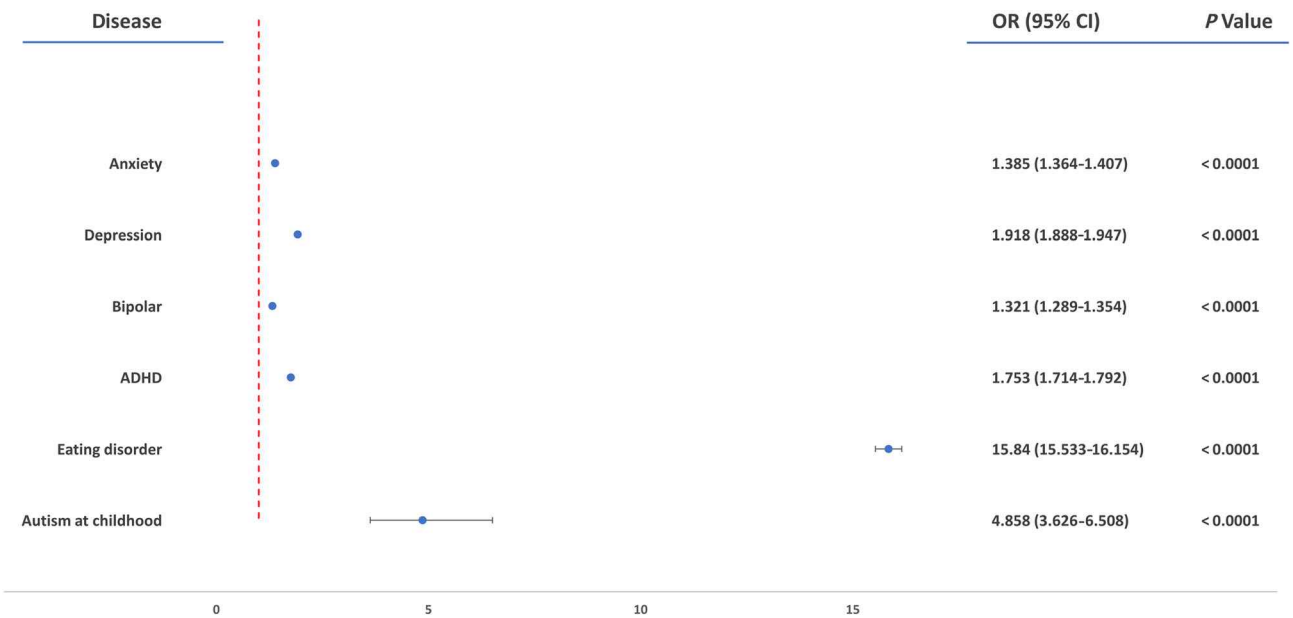

Figure 1 Risk of psychiatric diseases among patients with celiac disease. ADHD, attention-deficit hyperactivity disorder; CI, confidence interval; OR, odds ratio. [Color figure can be viewed at wileyonlinelibrary.com]

screening for CD among children diagnosed with ASD.[36] However, other studies concluded no statistically demonstrable association between CD and risk of developing ASD.[37,38] In a recent meta-analysis including nine studies with only one study showing a positive association, the pooled prevalence of ASD among CD was 8.7% with an overall modest increased risk of ASD among patients with CD.[29] Furthermore, the impact of a GFD in autistic patients remains unclear and limited by patient numbers. In an early trial by Sponheim on seven patients only, there was no connection between patients' behaviors and gluten exposure.[39] However, another randomized control trial on 10 autistic children showed a better development on a gluten and casein-free diet.[40]

Few studies have investigated the association between eating disorders and CD. In two cross-sectional studies, the prevalence of eating disorders was significantly higher in patients with CD when compared with controls, with a higher prevalence among women.[41,42] In a Swedish study, women with CD were more likely to develop anorexia nervosa.[43] There are scant data regarding the effect of a GFD on eating disorders in patients with CD, one study evaluating patients with anorexia nervosa and only a single case with CD that was started on a GFD with no change in the eating habits.[44]

The relation of psychiatric diseases with CD is complex and still not fully understood. Several mechanisms were speculated to explain this association including "gut–brain" relationship as well as psychosocial consequences of disease diagnosis and food restriction.[6,45] Furthermore, proposed mechanisms include autoimmunity,[7] toxic gluten metabolites,[8] cerebral hypoperfusion,[9] dietary restrictions compromising daily social relationships,[10] and vitamin deficiencies.[11]

Some proposed a protective effect of GFD while others claim that it may increase the risk of psychiatric disorders due to detrimental consequences of GFR on life's quality.[46] Poor dietary adherence has been shown to be associated with poor quality of

life in patients with CD.[47-49] However, poor adherence with the GFD in patients with CD could be a reflection, or a cause, of underlying psychiatric conditions. Psychological counseling has been shown to improve general well-being and diet compliance in patients with CD with some authors suggesting the early implementation of these interventions to improve compliance to the GFD and decrease complications.[25]

The gut–brain relationship was proposed in particular to anxiety and schizophrenia; theories describe a potential role for inflammation and autoimmunity. It is thought that the breakdown of gluten into immunogenic peptides may potentially interfere with the brain's functions.[6,50–52] Furthermore, alterations in gut microbiota have been identified in patients with CD, which believed to be a partial cause of inflammatory response to gluten.[53] Gut microbiota has been linked to influence mood and behavior, as it has been implicated in psychiatric disorders including anxiety and depression.[54]

To our best knowledge, this is the first study to address substance use disorder in adults with CD. In pediatrics, however, a population-wide Swedish study showed no significant increase in substance misuse among patients with CD compared with patients without CD. Our data revealed that patients with CD were more likely to have a history of substance abuse.[55]

This study has few limitations, mostly related to the nature of the database. The patient data are prone to misclassification leading to a misrepresentation of certain diagnoses. Unfortunately, validation of SNOMED-CT diagnostic code is not possible as patient information in the database is de-identified. Another limitation of using large databases is the lack of access to laboratory, endoscopic, and pathology reports to confirm the diagnosis of CD. There was also no access to the patients' clinical data to confirm the adherence to diagnostic criteria of psychiatric conditions. Despite these limitations, the strengths of this study lie in that it is one of the largest population-based studies to ever address psychiatric diseases in patients with CD to our best knowledge. ICD coding has been validated with high predictive diagnostic certainty in large databases.[56–58] In addition, SNOMED-CT allows for more concepts to be coded per clinical document compared with ICD, making it more accurate in terms of documenting diagnoses and pertinent patient information. It is worth highlighting that the use of Explorys platform has been validated in multiple fields including gastroenterology, cardiology, hematology, oncology, neurology, gynecology, and surgery among others.[59–67] In conclusion, CD is associated with different psychiatric conditions that could lead to poor quality of life and impairment of dietary compliance affecting overall morbidity. The clinician must be aware of these conditions that warrant further attention and referral to mental health services.

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