Psychiatric Disorders in Patients With a Diagnosis of Celiac Disease During Childhood From 1973 to 2016

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BACKGROUND & AIMS: **Few studies have explored the link between childhood celiac disease and long-term psychiatric comorbidities. We performed a population-based cohort study of associations between childhood celiac disease and psychiatric disorders and investigated whether risk persists into adulthood.**

METHODS: **We performed a nationwide study in Sweden using data from the Epidemiology Strengthened by histoPathology Reports in Sweden cohort. In this cohort, 19,186 children with a diagnosis of biopsy-verified celiac disease from 1973 through 2016 were identified from Sweden's 28 pathology departments. Each patient was matched with as many as 5 reference children (controls, n = 94,249). Data on psychiatric disorders were obtained from the patient register. We used Cox proportional modeling to estimate hazard ratios (HRs).**

RESULTS: **During a median follow-up period of 12.3 years, 3174 children (16.5%) with celiac disease received a new diagnosis of a psychiatric disorder, compared with 13,286 controls (14.1%). Corresponding incidence rates were 12.2 per 1000 person-years (95% CI, 11.8–12.7) vs 10.3 per 1000 person-years (95% CI, 10.2–10.5). Childhood celiac disease was associated with a 19% increase in risk of any psychiatric disorder (95% CI, 1.14–1.23); the increase in risk was observed in all childhood age groups. The highest HRs were seen in the first year after celiac diagnosis (HR, 1.70; 95% CI, 1.41–2.05). The risk increase persisted into adulthood (age, >18 y: HR, 1.11; 95% CI, 1.04–1.17). We found increased risks of mood disorders (HR, 1.20; 95% CI, 1.12–1.28), anxiety disorders (HR, 1.12; 95% CI, 1.06–1.19), eating disorders (HR, 1.34; 95% CI, 1.18–1.51), attention deficit hyperactivity disorder (HR, 1.29; 95% CI, 1.20–1.39), and autism spectrum disorder (HR, 1.47; 95% CI, 1.32–1.64). We found no statistically significant risk increase for psychotic disorders, psychoactive substance misuse, behavioral disorders, personality disorders, suicide attempt, or suicide. Celiac disease also was linked to an increased use of psychiatric drugs (HR, 1.34; 95% CI, 1.24–1.43). A conditional logistic regression found that psychiatric disorders also were more common before a diagnosis of celiac disease (odds ratio, 1.56; 95% CI, 1.39–1.76).**

CONCLUSIONS: **Childhood celiac disease is associated with an increased risk of subsequent psychiatric disorders, which persists into adulthood. Mental health surveillance should be integral in the care of celiac disease.**

Keywords: Depression; ADHD; Psychiatry; Epidemiology; Comorbidity.

Abbreviations used in this paper: ADHD, attention-deficit hyperactivity disorder; HR, hazard ratio; OR, odds ratio.

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In celiac disease, an immune-mediated enteropathy is triggered by intake of dietary gluten in genetically susceptible individuals. The prevalence is approximately 1% to 2% in Western populations[1] and 0.3% to 2.9% in children,[2] with increasing rates in recent years.[3] In Europe, the highest prevalence is seen in Sweden and Finland, and lower rates are seen in Germany.[4]

Several studies have described the wide range of extraintestinal manifestations in celiac disease such as fatigue,[5] neurologic conditions[6] including headache and neuropathy,[7] but also psychiatric disorders.[8] A study from 2017 showed a 1.4-fold increased risk of developing a future psychiatric disorder in children with celiac disease compared with the general population.[9] However, that study did not specifically evaluate the risk of psychiatric disorder in adulthood. Although a few studies have reported an increased prevalence of neuropsychiatric disorders before a celiac disease diagnosis,[10,11] these generally lacked power to provide precise risk estimates.

The aim of this study was to investigate the connection between a childhood diagnosis of celiac disease and later psychiatric morbidity including suicide, and to assess if any such risk increases persist into adulthood.

What You Need to Know

Background

Little is known about the association between childhood celiac disease and long-term psychiatric comorbidities.

Findings

A population-based study in Sweden found that childhood celiac disease is associated with a 19% increase in risk of subsequent psychiatric disorders, which persists into adulthood. Children with celiac disease have an increased risk of mood disorders, anxiety disorders, eating disorders, attention deficit hyperactivity disorder, and autism spectrum disorder.

Implications for patient care

Mental health surveillance should be integral in the care of celiac disease.

Methods

Celiac Disease

The Epidemiology Strengthened by histoPathology Reports in Sweden cohort consists of 6.1 million gastrointestinal biopsy reports from 2.1 million individuals. Biopsy reports were classified according to the Systematized Nomenclature of Medicine Clinical Terms, and originated from 1965 to 2017 from Sweden's 28 pathology departments. Data collection took place between October 12, 2015, and April 10, 2017.

Through a computerized search of the Epidemiology Strengthened by histoPathology Reports in Sweden cohort (Supplementary Table 1 lists the topography codes equivalent to the duodenum and jejunum, and relevant Systematized Nomenclature of Medicine codes) we identified individuals with villus atrophy (Marsh III, in this study equivalent to celiac disease). An earlier patient chart validation found that 108 of 114 (95%) patients with villus atrophy had celiac disease.[12] Because that validation was performed on individuals who underwent a biopsy up until 2008, one of the authors (J.F.L.) re-reviewed the free text of 100 randomly selected biopsy reports with villus atrophy originating from 2009 to 2017. Of these, 98 had sufficient information to be validated, and 97 had celiac disease (positive predictive value, 99.0%; 1 patient had misclassified microscopic colitis; personal communication, March 23, 2020).

Because our outcome measure was any psychiatric disorder, we restricted our study to patients diagnosed during the years spanning from 1973 (the onset of psychiatric diagnosis availability in the National Patient Register) through 2016, the latest availability of follow-up data.

Reference Individuals

For each individual with celiac disease, the government agency Statistics Sweden identified up to 5 reference individuals (n = 94,249) matched for age, sex, county, and calendar year from the Swedish Total Population Register.[13] None of the reference individuals had celiac disease at a matching date, and if they developed celiac disease their follow-up evaluation was censored at the date of diagnosis.

Secondary reference individuals

In a separate analysis we compared 13,015 individuals with celiac disease with their nonceliac siblings (n = 18,024). Sibling analyses takes shared intrafamilial confounding, including genetic and early environmental factors, into account.

Outcomes

Our primary outcome was any psychiatric disorder. Secondary outcomes were psychiatric disorders defined according to International Classification of Diseases codes (suicide attempts, psychotic disorders, mood disorders, anxiety disorders, psychoactive substance misuse, eating disorders, behavioral disorders, attention-deficit hyperactivity disorder [ADHD], autism spectrum disorders, and personality disorders), suicide, and suicide attempt (Supplementary Table 2). Psychiatric

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disorder data were obtained through the National Patient Register. For selected psychiatric disorders, this register has a positive predictive value of 85% to 95%.[14,15]

Although data on suicide attempts were retrieved from the Patient Register, data on suicides were obtained from the Cause of Death Register. ADHD was defined as having a relevant ADHD medication in the Prescribed Drug Register.[16]

Statistics

We began follow-up evaluation on the date of celiac disease diagnosis (or corresponding date in the reference group). Follow-up evaluation ended with a psychiatric diagnosis/suicide, death, emigration, or December 31, 2016, whichever occurred first.

The Cox proportional hazard model was used to estimate hazard ratios (HRs) and 95% CIs for psychiatric disorders. Stratified analyses were performed according to years of follow-up evaluation (<1, 1 to <5, 5 to <10, 10 to <20, and ≥20 y), age at celiac disease diagnosis (<2, 2 to <6, 6 to <11, 11 to <16, and 16 to <18 y) sex, level of parental education (≤9, 10–12, and ≥13 y), and country of birth (Nordic, other). We repeated the analysis, restricting the outcome definition to patients with a prescription for a psychiatric drug in the Prescription Drug Register (Supplementary Table 3 contains a list of included drugs). Because the Prescribed Drug Register started on July 1, 2005, this sensitivity analysis was performed in celiac patients diagnosed from July 1, 2006, or later. In separate analyses we examined the risk of psychiatric disorders in patients with celiac disease vs siblings. In that study, only celiac individuals with a sibling (n = 13,015) were included. Given that persistent villus atrophy after a celiac disease diagnosis is associated with adverse outcomes including lymphoproliferative disease[17] and osteoporotic fracture,[18] we compared those children who had persistent villus atrophy with those whose villi healed in the subset of subjects who underwent a follow-up biopsy.

We also explored the risk of psychiatric disorders in adulthood in patients diagnosed with celiac disease in childhood in an analysis restricted to patients who reached the age of adulthood (age, 18 y) during the follow-up evaluation. As a sensitivity analysis, we also evaluated this risk when including all patients, even those with a psychiatric diagnosis preceding the diagnosis of celiac disease or preceding age 18 years. To rule out that any association between celiac disease and psychiatric disorder was not caused by an underlying intellectual disability (triggering celiac testing and predisposing to a psychiatric disorder), we excluded anyone with a diagnosis of an intellectual disability in a sensitivity analysis.

We used SAS v.9.4 and STATA v.16.0 for all statistical analyses.

Ethics

The current study was approved by the Stockholm Ethics Review Board (2014/1287-31/4) on August 27, 2014. The ethics review board did not require informed consent because this was strictly a register-based study.

Results

We identified 19,583 individuals with celiac disease diagnosed in childhood (age, <18 y) during the years spanning from 1973 to 2016. In the primary analysis, 397 were excluded because of a previous history of a psychiatric disorder. The remaining 19,186 patients were matched with 94,249 comparators without any history of a psychiatric disorder (Figure 1).

Baseline Characteristics of the Main Study Cohort

The mean age at the time of celiac disease diagnosis was 6.6 years (SD, 5.2 y) with almost 30% diagnosed at younger than 2 years of age (Table 1). Follow-up time ranged from 0 to 42 years, with a median follow-up time of 12.2 years in individuals with celiac disease.

Celiac disease diagnosed in childhood was associated with a 19% increased risk of any psychiatric disorder (95% CI, 1.14–1.23) (Table 2), with the most increased risk within the first year after a celiac diagnosis (HR, 1.70; 95% CI, 1.41–2.05). Restricting follow-up evaluation until the age of 18 years, celiac disease was linked to a 26% increased risk of any psychiatric disorder (95% CI, 1.20–1.33) (Supplementary Table 4).

The risks of each psychiatric disorder in celiac disease patients vs controls are listed in Table 3. Children with celiac disease were at an increased risk of developing mood disorders, anxiety disorders, eating disorders, ADHD, and autism spectrum disorder.

Follow-Up Evaluation From Age 18 Years

In analyses of adults (age, ≥18 y) with celiac disease diagnosed in childhood and free of psychiatric disease as of age 18, we matched 11,207 celiac disease patients with 49,252 reference individuals (Supplementary Table 5). The median follow-up time after age 18 was 6.4 years for the celiac disease patients and 6 years for the comparators. The overall risk of any psychiatric disorder was increased in celiac disease patients by 11% (HR, 1.11; 95% CI, 1.04–1.17). Having a family history of psychiatric disorder yielded a 1.25-fold increase (HR, 1.25; 95% CI, 1.08–1.46) (Supplementary Table 6).

Adults with childhood celiac disease had an increased risk later for mood disorders, ADHD, and autism spectrum disorder (Supplementary Table 7). When repeating the analysis, now including all subjects regardless of whether they had been diagnosed with psychiatric

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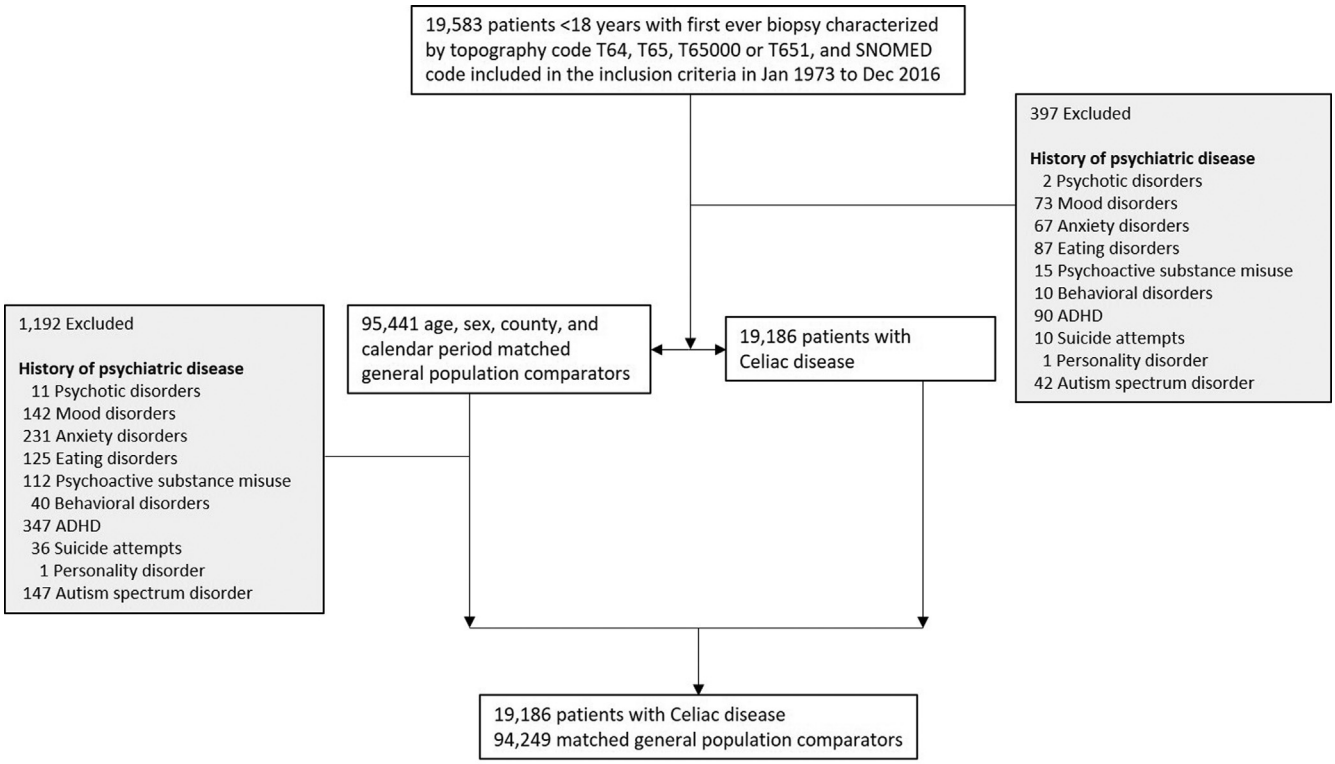

Figure 1. Flow chart of identified patients and their matched comparators. ADHD, attention deficit hyperactivity disorder; SNOMED, Systematized Nomenclature of Medicine.

disease before a celiac disease diagnosis or before reaching the age of 18 years, the association of childhood celiac disease and psychiatric disorders in adulthood was strengthened (HR, 1.17; 95% CI, 1.11–1.22). When excluding individuals with a diagnosis of intellectual disability before study entry (celiac patients, 19,101; controls, 93,612), the positive association with psychiatric disorders remained (HR, 1.18; 95% CI, 1.14–1.23).

Sibling Comparisons

We repeated the earlier-described analyses using celiac-free siblings as comparators (n = 18,024), restricting our cohort to 13,015 children with celiac disease and at least 1 sibling (Supplementary Table 8 shows participant characteristics). After conditioned on matching set (within family) and further adjustment for age and sex, celiac disease patients were at a 12% increased risk of a psychiatric disorder compared with siblings (95% CI, 1.05–1.20). Sibling analyses yielded very similar data to those of our main analyses with general population reference individuals (Supplementary Table 9). Sibling comparisons found a positive association between celiac disease and mood disorders, anxiety disorders, eating disorders, and autism spectrum disorder (Supplementary Table 10).

Mucosal Healing and Psychiatric Disorder

During follow-up evaluation, 2604 children with celiac disease had a follow-up biopsy (mucosal healing: n = 2071, 79.5%; persistent villus atrophy: n = 533, 20.5%) (Supplementary Table 11). We found no association between mucosal healing and a subsequent psychiatric disorder (HR, 1.21; 95% CI, 0.95–1.53) (Supplementary Table 12).

Sensitivity Analyses

In sensitivity analyses, we defined a psychiatric disorder as having a prescription for a psychiatric drug (Supplementary Table 3). Because of the construction of the Swedish Prescribed Drug Register, this analysis was restricted to children diagnosed between July 2006 and December 2016 (Supplementary Table 13). Using this definition, the incidence rate for any psychiatric disorder was 26.9 (95% CI, 25.3–28.6) per 1000 person-years in celiac disease and 20.5 (95% CI, 19.8–21.2) in the reference group (Supplementary Table 14). The HR for any psychiatric disorder was 1.34 (95% CI, 1.24–1.43) (Supplementary Table 14).

The increased risk was significant in all categories of psychiatric drugs: antidepressants (HR, 1.35; 95% CI, 1.25–1.46), anxiolytics, hypnotics and sedatives (HR, 1.32; 95% CI, 1.23–1.42), and antipsychotics (HR, 1.34; 95% CI, 1.23–1.46) (Supplementary Table 15).

History of Psychiatric Disorder Preceding Celiac Disease

In children with celiac disease a prior history of a psychiatric disorder (preceding the diagnosis of celiac

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Table 1. Baseline Characteristics of Study Cohort

Characteristic	Celiac disease (n = 19,186)	Matched comparators (n = 94,249)
Girls, n (%)	12,076 (62.9)	59,358 (63.0)
Boys, n (%)	7110 (37.1)	34,891 (37.0)
Age at celiac disease diagnosis, *y*		
Mean (SD)	6.6 (5.2)	6.5 (5.2)
Median (IQR)	5.3 (1.7–10.9)	5.2 (1.7–10.7)
Range, minimum–maximum	0.0–18.0	0.0–18.0
Categories, n (%)		
<2 y	5694 (29.7)	27,579 (29.3)
2 to <6 y	4545 (23.7)	23,460 (24.9)
6 to <11 y	4244 (22.1)	20,944 (22.2)
11 to <16 y	3508 (18.3)	17,025 (18.1)
16 to <18 y	1195 (6.2)	5241 (5.6)
Country of birth, n (%)		
Nordic country	18,837 (98.2)	90,009 (95.5)
Other	348 (1.8)	4236 (4.5)
Missing	1 (0.0)	4 (0.0)
Highest attained level of education by parents, n (%)		
≤9 y	659 (3.4)	4333 (4.6)
10–12 y	8371 (43.6)	40,792 (43.3)
>12 y	10,136 (52.8)	48,844 (51.8)
Missing	20 (0.1)	280 (0.3)
Starting year of follow-up evaluation		
1973–1989	1909 (9.9%)	9504 (10.1%)
1990–1999	5458 (28.4%)	27,113 (28.8%)
2000–2009	7643 (39.8%)	37,524 (39.8%)
2010–2016	4176 (21.8%)	20,108 (21.3%)
Psychiatric diagnoses in family before index date, n (%)		
Parents	2260 (11.8)	11,449 (12.1)
Siblings	331 (1.7)	1725 (1.8)
Any of parents or siblings	2505 (13.1)	12,627 (13.4)
Follow-up period, *y*		
Mean (SD)	13.5 (8.4)	13.6 (8.4)
Median (IQR)	12.2 (6.6–20.2)	12.3 (6.7–20.3)
Range, minimum–maximum	0.0–42.0	0.0–44.0

IQR, interquartile range.

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disease) was more common compared with controls (odds ratio [OR], 1.56; 95% CI, 1.39–1.76) (Table 4). This association was statistically significant for mood disorders (OR, 2.05; 95% CI, 1.54–2.72), anxiety disorders (OR, 1.51; 95% CI, 1.20–1.91), and eating disorders (OR, 3.10; 95% CI, 2.39–4.02).

Discussion

In this nationwide and population-based cohort study, we followed up more than 19,000 individuals with childhood celiac disease diagnosed during the years spanning from 1973 to 2016. During follow-up evaluation, we found a 19% increased risk of any psychiatric disorder. The overall risk increase is consistent with earlier findings correlating psychiatric comorbidity with celiac disease in children, as well as in adults.[19,20]

The overall risk for psychiatric disorder was highest in the first year after diagnosis. This may be owing in part to surveillance bias, but it also is possible that the systemic inflammatory response is mediating this relationship. In addition to these purported mechanisms, the psychosocial stress associated with adapting to a gluten-free diet may account for the early increase in the risk of psychiatric disorders. Unlike most chronic medical conditions that are managed via pharmaceutical

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Table 2. Risk of Any Psychiatric Disorder Overall and by Subgroup in Patients With Celiac Disease and Matched General Population Comparators

	N (%)		Events, n (%)		Incidence rate (95% CI) per 1000 PY		
Group	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	HR[a] (95% CI)
Overall	19,186 (100)	94,249 (100)	3174 (16.5)	13,286 (14.1)	12.2 (11.8–12.7)	10.3 (10.2–10.5)	1.19 (1.14–1.23)
Follow-up period							
0 to <1 y	19,186 (100)	94,249 (100)	148 (0.8)	417 (0.4)	7.8 (6.5–9.1)	4.5 (4.0–4.9)	1.70 (1.41–2.05)
1 to <5 y	18,762 (97.8)	92,140 (97.8)	629 (3.4)	2260 (2.5)	9.0 (8.3–9.7)	6.6 (6.3–6.9)	1.38 (1.26–1.51)
5 to <10 y	15,909 (82.9)	78,384 (83.2)	791 (5.0)	3188 (4.1)	11.6 (10.8–12.4)	9.5 (9.1–9.8)	1.24 (1.15–1.34)
10 to <15 y	11,474 (59.8)	56,869 (60.3)	690 (6.0)	3135 (5.5)	14.7 (13.6–15.8)	13.5 (13.0–14.0)	1.11 (1.02–1.21)
15 to <20 y	7379 (38.5)	36,593 (38.8)	541 (7.3)	2584 (7.1)	17.9 (16.4–19.4)	17.2 (16.5–17.9)	1.02 (0.93–1.12)
≥20 y	4885 (25.5)	24,236 (25.7)	375 (7.7)	1702 (7.0)	14.6 (13.1–16.1)	13.3 (12.6–13.9)	1.10 (0.98–1.23)
Sex							
Girls	12,076 (62.9)	59,358 (63.0)	2027 (16.8)	8772 (14.8)	12.5 (11.9–13.0)	11.0 (10.7–11.2)	1.14 (1.08–1.20)
Boys	7110 (37.1)	34,891 (37.0)	1147 (16.1)	4514 (12.9)	11.8 (11.2–12.5)	9.3 (9.1–9.6)	1.28 (1.20–1.37)
Age, *y*							
<2	5694 (29.7)	27,579 (29.3)	1001 (17.6)	4408 (16.0)	8.9 (8.3–9.4)	8.2 (7.9–8.4)	1.06 (0.98–1.13)
2 to <6	4545 (23.7)	23,460 (24.9)	578 (12.7)	2691 (11.5)	10.0 (9.2–10.8)	8.9 (8.6–9.3)	1.11 (1.01–1.22)
6 to <11	4244 (22.1)	20,944 (22.2)	707 (16.7)	2753 (13.1)	16.1 (14.9–17.3)	12.5 (12.0–13.0)	1.32 (1.21–1.44)
11 to <16	3508 (18.3)	17,025 (18.1)	668 (19.0)	2655 (15.6)	19.9 (18.4–21.4)	15.7 (15.1–16.3)	1.28 (1.17–1.39)
16 to <18	1195 (6.2)	5241 (5.6)	220 (18.4)	779 (14.9)	18.9 (16.4–21.5)	14.5 (13.5–15.5)	1.31 (1.12–1.53)
Year							
1973–1989	1909 (9.9)	9504 (10.1)	405 (21.2)	1760 (18.5)	7.8 (7.0–8.6)	6.8 (6.5–7.1)	1.15 (1.03–1.28)
1990–1999	5458 (28.4)	27,113 (28.8)	1140 (20.9)	5052 (18.6)	10.4 (9.8–11.1)	9.4 (9.1–9.6)	1.12 (1.05–1.19)
2000–2009	7643 (39.8)	37,524 (39.8)	1303 (17.0)	5352 (14.3)	15.9 (15.0–16.8)	13.3 (12.9–13.6)	1.22 (1.14–1.29)
2010–2016	4176 (21.8)	20,108 (21.3)	326 (7.8)	1122 (5.6)	19.4 (17.3–21.6)	13.7 (12.9–14.5)	1.43 (1.26–1.62)
Year, first 5 years of follow-up evaluation							
1973–1989	1909 (9.9)	9504 (10.1)	13 (0.7)	16 (0.2)	1.4 (0.6–2.1)	0.3 (0.2–0.5)	3.84 (1.81–8.15)
1990–1999	5458 (28.4)	27,113 (28.8)	55 (1.0)	160 (0.6)	2.0 (1.5–2.6)	1.2 (1.0–1.4)	1.69 (1.24–2.30)
2000–2009	7643 (39.8)	37,524 (39.8)	408 (5.3)	1525 (4.1)	11.0 (9.9–12.1)	8.4 (8.0–8.8)	1.32 (1.19–1.48)
2010–2011	1707 (8.9)	8300 (8.8)	143 (8.4)	509 (6.1)	17.5 (14.7–20.4)	12.7 (11.6–13.9)	1.39 (1.15–1.68)
Country of birth							
Nordic	18,837 (98.2)	90,009 (95.5)	3121 (16.6)	12,774 (14.2)	12.2 (11.7–12.6)	10.3 (10.1–10.5)	1.18 (1.14–1.23)
Other	348 (1.8)	4236 (4.5)	53 (15.2)	512 (12.1)	17.2 (12.5–21.8)	12.6 (11.5–13.7)	0.99 (0.45–2.19)
Level of education, *y*							
≤9	659 (3.4)	4333 (4.6)	148 (22.5)	779 (18.0)	13.2 (11.0–15.3)	12.2 (11.3–13.0)	0.82 (0.48–1.39)
10–12	8371 (43.6)	40,792 (43.3)	1604 (19.2)	6676 (16.4)	13.1 (12.4–13.7)	11.4 (11.1–11.6)	1.17 (1.09–1.25)
>12	10,136 (52.8)	48,844 (51.8)	1419 (14.0)	5817 (11.9)	11.3 (10.7–11.9)	9.2 (9.0–9.5)	1.20 (1.13–1.29)
Psychiatric diagnoses in family							
Parents or sibling	2505 (13.1)	12,627 (13.4)	582 (23.2)	2505 (19.8)	24.8 (22.8–26.8)	20.6 (19.8–21.5)	1.28 (1.08–1.52)

HR, hazard ratio; PY, person-year.
[a]Conditioned on matching set (age, sex, county, and calendar period) and adjusted further for highest education level attained by parents.

approaches, a diagnosis of celiac disease mandates a major lifestyle change for the patient, with a new requirement to attend to ingredient lists, restaurant menus, and social circumstances, given the intermingling of diet with socializing, and the ubiquity of gluten. This treatment has been rated by patients to be highly burdensome,[21] and may lead to maladaptive eating patterns[22] and hypervigilance, with attendant diminished quality of life.[23] The stress associated with this burden may contribute to the increased incidence of psychiatric disorders in both the short and long term. However, this risk is unlikely to be owing to the gluten-free diet alone because we also observed an increased risk of psychiatric disorders preceding the diagnosis of celiac disease, possibly related to the systemic inflammatory response described earlier.

Specific Psychiatric Disorders

The specific psychiatric disorders found to be increased in this study of childhood-diagnosed celiac

Table 3. Risk of Psychiatric Disorders in Patients With Celiac Disease and Matched General Population Comparators

Group	Events, n (%)		Time at risk, *y*		Incidence rate (95% CI) per 1000 PY		HR[a] (95% CI)
	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	
Psychotic disorders	69 (0.4)	349 (0.4)	278,665	1,359,892	0.2 (0.2–0.3)	0.3 (0.2–0.3)	0.96 (0.74–1.25)
Mood disorders	1 190 (6.2)	4 832 (5.1)	272,972	1,337,367	4.4 (4.1–4.6)	3.6 (3.5–3.7)	1.20 (1.12–1.28)
Anxiety disorders	1 573 (8.2)	6 829 (7.2)	270,938	1,327,339	5.8 (5.5–6.1)	5.1 (5.0–5.3)	1.12 (1.06–1.19)
Eating disorders	331 (1.7)	1 187 (1.3)	277,015	1,354,829	1.2 (1.1–1.3)	0.9 (0.8–0.9)	1.34 (1.18–1.51)
Psychoactive substance misuse	720 (3.8)	3 257 (3.5)	274,655	1,342,496	2.6 (2.4–2.8)	2.4 (2.3–2.5)	1.07 (0.99–1.16)
Behavioral disorders	72 (0.4)	366 (0.4)	278,683	1,359,752	0.3 (0.2–0.3)	0.3 (0.2–0.3)	0.98 (0.76–1.27)
ADHD	904 (4.7)	3 453 (3.7)	274,772	1,345,438	3.3 (3.1–3.5)	2.6 (2.5–2.7)	1.29 (1.20–1.39)
Suicide attempt	304 (1.6)	1 442 (1.5)	276,846	1,352,432	1.1 (1.0–1.2)	1.1 (1.0–1.1)	1.02 (0.90–1.16)
Suicide	14 (0.1)	90 (0.1)	279,134	1,361,982	0.1 (0.0–0.1)	0.1 (0.1–0.1)	0.78 (0.44–1.37)
Personality disorders	167 (0.9)	719 (0.8)	278,176	1,358,106	0.6 (0.5–0.7)	0.5 (0.5–0.6)	1.13 (0.95–1.34)
Autism spectrum disorder	417 (2.2)	1 396 (1.5)	276,809	1,354,405	1.5 (1.4–1.7)	1.0 (1.0–1.1)	1.47 (1.32–1.64)
Any psychiatric disorder	3 174 (16.5)	13 286 (14.1)	259,633	1,284,011	12.2 (11.8–12.7)	10.3 (10.2–10.5)	1.19 (1.14–1.23)

NOTE. n celiac disease/n comparators = 19,186/94,249.
ADHD, attention deficit hyperactivity disorder; HR, hazard ratio; PY, person-year.
[a]Conditioned on matching set (age, sex, county, and calendar period) and further adjusted for highest attained education in parents

disease include mood and anxiety disorders, eating disorders, ADHD, and autism-spectrum disorders. The association between celiac disease and depression and anxiety has been studied extensively, largely in the adult population.[24] Eating disorders[25] likewise have been linked to celiac disease, although autism has not,[11] despite the popular use of a gluten-free diet among children with this condition.[26]

Table 4. Risk of Psychiatric Disorders in Patients With Celiac Disease and Matched General Population Comparators Before Start of Follow-Up Evaluation

Group	Events, n (%)		Odds ratio[a] (95% CI)
	Celiac disease	Comparators	
Any psychiatric disorder	397 (2.0%)	1301 (1.3%)	1.56 (1.39–1.76)
Psychotic disorders	2 (0.0%)	12 (0.0%)	0.76 (0.15–3.93)
Mood disorders	73 (0.4%)	171 (0.2%)	2.05 (1.54–2.72)
Anxiety disorders	95 (0.5%)	314 (0.3%)	1.51 (1.20–1.91)
Eating disorders	95 (0.5%)	154 (0.2%)	3.10 (2.39–4.02)
Psychoactive substance misuse	16 (0.1%)	143 (0.1%)	0.52 (0.31–0.87)
Behavioral disorders	13 (0.1%)	65 (0.1%)	1.01 (0.55–1.85)
ADHD	112 (0.6%)	478 (0.5%)	1.19 (0.96–1.48)
Suicide attempt	17 (0.1%)	75 (0.1%)	1.10 (0.64–1.88)
Personality disorders	1 (0.0%)	2 (0.0%)	2.16 (0.12–37.96)
Autism spectrum disorder	69 (0.4%)	269 (0.3%)	1.26 (0.96–1.65)

NOTE. n celiac disease/n comparators = 19,583/97,362.
ADHD, attention-deficit hyperactivity disorder.
[a]Conditioned on matching set (age, sex, county, and calendar period) and adjusted further for highest education attained by parents.

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Strengths and Limitations

Through data retrieval from Sweden's all 28 pathology departments, we were able to identify 19,101 children with celiac disease, with follow-up evaluation through 2016. This compares with 10,903 children followed up through 2010 in a previous population-based study in Sweden.[9] This expanded sample size and follow-up period allowed us to evaluate additional outcomes including long-term, adult-onset, psychiatric disease; this study examined the development of psychiatric disorder, particularly in adults with celiac disease diagnosed in childhood. The large sample size and long-term follow-up period (a total of 259,633 person-years in people with childhood-diagnosed celiac disease) allowed us to detect even minor risk increases for specific psychiatric disorders. We also were able to perform sensitivity analyses including a comparison with siblings and evaluation of mucosal healing. Our access to follow-up biopsy data allowed us to examine potential mechanisms behind the association with psychiatric disorder; however, we found no link between mucosal healing (at least in the short term) and psychiatric disorders.

This study also had some limitations. The International Classification of Diseases codes and thus the criteria used for psychiatric diagnoses (Supplementary Table 1) have changed throughout the years, and this might influence the rates of psychiatric diagnosis. Because this was an observational study, we cannot rule out that residual confounding contributed to the association between celiac disease and psychiatric disorders.

The lack of association between mucosal healing and psychiatric risk in our study contrasts with a study of 53 patients that found that deterioration of quality of life after a diagnosis is associated with lower adherence to a gluten-free diet.[27] This may be because mucosal healing is an imperfect marker of adherence, particularly given the possibility of gradual healing (ie, persistent villus atrophy that eventually resolves with further time while maintaining the gluten-free diet).

Clinical Implications

This study showed that although small in absolute magnitude, there is an increased risk of a psychiatric disorder in individuals diagnosed with celiac disease in childhood with an increased risk in the long term, emphasizing the importance of not just somatic surveillance but also mental health surveillance for timely support and intervention.

Conclusions

In conclusion, this nationwide population-based study including more than 19,000 children with celiac disease found an increased risk of psychiatric disorder. This risk was highest in the first year after celiac disease diagnosis but persisted over a long time and into adulthood. Mental health surveillance should be integral in the care of celiac disease.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.08.018.

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Acknowledgments Q15
CRediT Authorship Contributions: xxx Q16
This project (2014/1287-31/4) was approved by the Research Ethics Committee in Stockholm, Sweden, on August 27, 2014.

Other researchers can apply for our data through the different Swedish pathology departments, and through the Swedish National Board of Health and Welfare.

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Conflicts of interest Q4
This author discloses the following: Jonas Ludvigsson coordinates a study on behalf of the Swedish IBD quality register (SWIBREG). The remaining authors disclose no conflicts.

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Supplementary Table 1. Definitions of Celiac Disease and Normal Mucosa Using SNOMED Codes

Disease/condition	Topographic code	SNOMED codes
Celiac disease	All T64, only T65, T65000, and T651	D6218, D62180, D62188, D6218X, D6218Y; M58, M5800, M58000, M58001, M58005, M58006, M58007
Normal mucosa	All T64, only T65, T65000, and T651	M00100, M00110

SNOMED, Systematized Nomenclature of Medicine.

Supplementary Table 2. ICD Codes Used for Outcomes

Comorbidity	ICD-8 (1969–1986)	ICD-9 (1987-1996)	ICD-10 (1997–present) Q17
Psychotic disorders	295, 297–299	295, 297, 298	F20–F29
Mood disorders	296, 300.4	296, 300E, 311	F30–F39
Anxiety disorders	300 except 300.4, 307	300 except 300.E, 308–309	F40–F45, F48
Eating disorders		307B, 307F	F50
Psychoactive substance misuse	291, 303, 304	291, 303, 304, 305A, 305X	F10–F19
Behavioral disorders			F91
ADHD		314	F90
Suicide attempt and completed suicide	E950–E959	E950–E959	X60–X84
Personality disorders	301	301	F60–F62, F69
Autism spectrum disorder		299A	F84

ADHD, attention-deficit hyperactivity disorder; ICD-8, International Classification of Diseases, 8th revision; ICD-9, International Classification of Diseases, 9th revision; ICD-10, International Classification of Diseases, 10th revision.

Supplementary Table 3. ATC Codes Used for Outcomes

Drug	ATC code
Antidepressants	N06A
Anxiolytics, hypnotics, and sedatives	N05B, N05C
Antipsychotics	N05A

ATC, ____. Q18

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Supplementary Table 4. Risk of Any Psychiatric Disorder Overall and by Subgroup in Patients With Celiac Disease and Matched General Population Comparators, With Follow-Up Evaluation Ending at Age 18 Years

	N (%)		Events, N (%)		Incidence rate (95% CI) per 1000 PY		
Group	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	HR[a] (95% CI)
Overall	19,186 (100)	94,249 (100)	1747 (9.1)	6861 (7.3)	9.9 (9.4–10.4)	7.9 (7.7–8.1)	1.26 (1.20–1.33)
Follow-up period, *y*							
0 to <1	19,186 (100)	94,249 (100)	141 (0.7)	402 (0.4)	7.5 (6.3–8.8)	4.4 (3.9–4.8)	1.70 (1.40–2.06)
1 to <5	18,180 (94.8)	89,819 (95.3)	492 (2.7)	1764 (2.0)	7.7 (7.0–8.4)	5.6 (5.3–5.8)	1.40 (1.26–1.55)
5 to <10	13,656 (71.2)	67,406 (71.5)	525 (3.8)	1994 (3.0)	9.7 (8.9–10.5)	7.5 (7.1–7.8)	1.31 (1.19–1.45)
10 to <15	8467 (44.1)	41,719 (44.3)	456 (5.4)	2038 (4.9)	14.1 (12.8–15.3)	12.7 (12.2–13.3)	1.10 (0.99–1.22)
15 to <20	4671 (24.3)	23,007 (24.4)	133 (2.8)	663 (2.9)	18.1 (15.0–21.2)	18.1 (16.8–19.5)	0.98 (0.80–1.19)
Sex							
Girls	12,076 (62.9)	59,358 (63.0)	1094 (9.1)	4463 (7.5)	9.8 (9.2–10.4)	8.1 (7.9–8.4)	1.22 (1.14–1.30)
Boys	7110 (37.1)	34,891 (37.0)	653 (9.2)	2398 (6.9)	10.0 (9.2–10.8)	7.4 (7.1–7.7)	1.35 (1.23–1.47)
Age, *y*							
<2	5694 (29.7)	27,579 (29.3)	526 (9.2)	2210 (8.0)	6.2 (5.7–6.7)	5.5 (5.2–5.7)	1.10 (0.99–1.21)
2 to <6	4545 (23.7)	23,460 (24.9)	387 (8.5)	1726 (7.4)	8.4 (7.5–9.2)	7.2 (6.9–7.5)	1.16 (1.03–1.30)
6 to <11	4244 (22.1)	20,944 (22.2)	463 (10.9)	1677 (8.0)	15.2 (13.9–16.6)	11.1 (10.6–11.6)	1.40 (1.25–1.55)
11 to <16	3508 (18.3)	17,025 (18.1)	324 (9.2)	1157 (6.8)	22.6 (20.1–25.0)	16.3 (15.4–17.3)	1.41 (1.24–1.60)
16 to <18	1195 (6.2)	5 241 (5.6)	47 (3.9)	91 (1.7)	41.6 (29.7–53.4)	16.7 (13.3–20.2)	2.32 (1.57–3.44)
Year							
1973–1989	1909 (9.9)	9504 (10.1)	93 (4.9)	362 (3.8)	3.4 (2.7–4.1)	2.7 (2.4–2.9)	1.29 (1.02–1.63)
1990–1999	5458 (28.4)	27,113 (28.8)	506 (9.3)	2130 (7.9)	7.0 (6.4–7.6)	5.9 (5.7–6.2)	1.17 (1.06–1.29)
2000–2009	7643 (39.8)	37,524 (39.8)	872 (11.4)	3461 (9.2)	14.1 (13.2–15.1)	11.4 (11.0–11.7)	1.26 (1.17–1.36)
2010–2016	4176 (21.8)	20,108 (21.3)	276 (6.6)	908 (4.5)	18.4 (16.2–20.6)	12.3 (11.5–13.1)	1.49 (1.30–1.71)
Year, first 5 years of follow-up evaluation							
1973–1989	1909 (9.9)	9504 (10.1)	8 (0.4)	15 (0.2)	0.9 (0.3–1.5)	0.3 (0.2–0.5)	2.89 (1.19–7.02)
1990–1999	5458 (28.4)	27,113 (28.8)	40 (0.7)	127 (0.5)	1.5 (1.1–2.0)	1.0 (0.8–1.2)	1.51 (1.06–2.17)
2000–2009	7643 (39.8)	37,524 (39.8)	327 (4.3)	1206 (3.2)	9.7 (8.7–10.8)	7.3 (6.8–7.7)	1.37 (1.21–1.55)
2010–2011	1707 (8.9)	8300 (8.8)	115 (6.7)	424 (5.1)	15.6 (12.8–18.5)	11.7 (10.6–12.8)	1.36 (1.10–1.68)
Country of birth							
Nordic	18,837 (98.2)	90,009 (95.5)	1718 (9.1)	6643 (7.4)	9.8 (9.4–10.3)	7.8 (7.6–8.0)	1.25 (1.19–1.32)
Other	348 (1.8)	4236 (4.5)	29 (8.3)	218 (5.1)	15.6 (9.9–21.2)	8.9 (7.8–10.1)	1.41 (0.46–4.37)
Level of education, *y*							
≤9	659 (3.4)	4333 (4.6)	66 (10.0)	343 (7.9)	10.7 (8.1–13.2)	9.2 (8.3–10.2)	1.23 (0.50–3.01)
10–12	8371 (43.6)	40,792 (43.3)	872 (10.4)	3411 (8.4)	10.6 (9.9–11.3)	8.7 (8.4–9.0)	1.24 (1.13–1.36)
>12	10,136 (52.8)	48,844 (51.8)	808 (8.0)	3097 (6.3)	9.2 (8.5–9.8)	7.0 (6.7–7.2)	1.25 (1.15–1.37)
Psychiatric diagnoses in family							
Parents or sibling	2505 (13.1)	12,627 (13.4)	348 (13.9)	1487 (11.8)	20.7 (18.5–22.9)	17.3 (16.4–18.2)	1.36 (1.10–1.67)

HR, hazard ratio; PY, person-years.
[a]Conditioned on matching set (age, sex, county, and calendar period) and adjusted further for the highest education attained by parents.

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Supplementary Table 5. Analysis Limited to Those With Available Follow-Up Evaluation Starting at Age 18 Years: Baseline Characteristics of Study Cohort

Characteristic	Celiac disease (n = 11,207)	Matched comparators (n = 49,252)
Girls, n (%)	6958 (62.1)	30,266 (61.5)
Boys, n (%)	4249 (37.9)	18,986 (38.5)
Age, *y*		
Mean (SD)	18.0 (0.0)	18.0 (0.0)
Median (IQR)	18.0 (18.0–18.0)	18.0 (18.0–18.0)
Range, minimum–maximum	18.0–18.0	18.0–18.0
Country of birth, n (%)		
Nordic country	11,025 (98.4)	47,181 (95.8)
Other	182 (1.6)	2070 (4.2)
Missing	(0.0)	1 (0.0)
Highest education level attained by parents, n (%)		
≤9 y	476 (4.2)	2524 (5.1)
10–12 y	5365 (47.9)	23,098 (46.9)
>12 y	5360 (47.8)	23,581 (47.9)
Missing	6 (0.1)	49 (0.1)
Start year of follow-up evaluation		
1973–1989	83 (0.7)	385 (0.8)
1990–1999	782 (7.0)	3744 (7.6)
2000–2009	4985 (44.5)	22,484 (45.7)
2010–2016	5357 (47.8)	22,639 (46.0)
Psychiatric diagnoses in family before index date, n (%)		
Parents	2063 (18.4)	9237 (18.8)
Siblings	962 (8.6)	4066 (8.3)
Any of parents or siblings	2712 (24.2)	11,997 (24.4)
Follow-up, *y*		
Mean (SD)	7.4 (5.4)	7.7 (5.5)
Median (IQR)	6.4 (3.5–10.2)	6.6 (3.6–10.5)
Range, minimum–maximum	0.0–35.4	0.0–35.7

IQR, interquartile range.

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Supplementary Table 6. Analysis Limited to Those With Available Follow-Up Evaluation Starting at Age 18 Years: Risk of Any Psychiatric Disorder Overall and by Subgroup in Patients With Celiac Disease and Matched General Population Comparators

Group	N (%)		Events, N (%)		Incidence rate (95% CI) per 1000 PY		HR[a] (95% CI)
	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	
Overall	11,207 (%)	49 252 (%)	1427 (12.7)	5833 (11.8)	17.2 (16.3–18.1)	15.4 (15.0–15.8)	1.11 (1.04–1.17)
Follow-up period, *y*							
0 to <1	11,207 (%)	49,252 (%)	245 (2.2)	983 (2.0)	22.7 (19.8–25.5)	20.6 (19.3–21.9)	1.07 (0.93–1.23)
1 to <5	10,405 (92.8)	45,959 (93.3)	680 (6.5)	2662 (5.8)	19.4 (18.0–20.9)	17.0 (16.4–17.7)	1.14 (1.04–1.24)
5 to <10	7024 (62.7)	31,802 (64.6)	349 (5.0)	1497 (4.7)	14.8 (13.2–16.3)	13.8 (13.1–14.5)	1.09 (0.96–1.23)
10 to <15	2870 (25.6)	13,460 (27.3)	96 (3.3)	477 (3.5)	10.7 (8.5–12.8)	11.1 (10.1–12.1)	0.96 (0.76–1.21)
15 to <20	1003 (8.9)	4895 (9.9)	37 (3.7)	155 (3.2)	11.9 (8.1–15.8)	9.9 (8.3–11.5)	1.15 (0.79–1.68)
≥20	355 (3.2)	1815 (3.7)	20 (5.6)	59 (3.3)	13.5 (7.6–19.4)	7.8 (5.8–9.8)	1.77 (1.01–3.09)
Sex							
Girls	6958 (62.1)	30,266 (61.5)	933 (13.4)	3901 (12.9)	18.2 (17.0–19.3)	17.0 (16.4–17.5)	1.06 (0.99–1.15)
Boys	4249 (37.9)	18,986 (38.5)	494 (11.6)	1932 (10.2)	15.6 (14.2–17.0)	13.0 (12.4–13.6)	1.20 (1.08–1.32)
Year							
1973–1989	83 (0.7)	385 (0.8)	19 (22.9)	42 (10.9)	9.1 (5.0–13.2)	4.0 (2.8–5.3)	2.18 (1.21–3.91)
1990–1999	782 (7.0)	3744 (7.6)	160 (20.5)	569 (15.2)	11.6 (9.8–13.4)	8.3 (7.6–9.0)	1.39 (1.16–1.66)
2000–2009	4985 (44.5)	22,484 (45.7)	782 (15.7)	3415 (15.2)	16.6 (15.4–17.7)	15.9 (15.4–16.5)	1.05 (0.97–1.14)
2010–2016	5357 (47.8)	22,639 (46.0)	466 (8.7)	1807 (8.0)	23.4 (21.3–25.5)	21.2 (20.2–22.1)	1.10 (0.99–1.22)
Year, first 5 years of follow-up evaluation							
1973–1989	83 (0.7)	385 (0.8)	4 (4.8)	2 (0.5)	10.0 (0.2–19.7)	1.0 (0.0–2.5)	10.03 (1.21–83.26)
1990–1999	782 (7.0)	3744 (7.6)	42 (5.4)	94 (2.5)	11.1 (7.7–14.4)	5.1 (4.1–6.2)	2.07 (1.43–3.00)
2000–2009	4985 (44.5)	22,484 (45.7)	447 (9.0)	1868 (8.3)	19.0 (17.3–20.8)	17.6 (16.8–18.4)	1.08 (0.97–1.20)
2010–2011	2078 (18.5)	8954 (18.2)	214 (10.3)	843 (9.4)	22.1 (19.1–25.0)	20.1 (18.7–21.4)	1.11 (0.96–1.29)
Country of birth							
Nordic	11,025 (98.4)	47,181 (95.8)	1403 (12.7)	5575 (11.8)	17.2 (16.3–18.0)	15.3 (14.9–15.7)	1.11 (1.04–1.18)
Other	182 (1.6)	2070 (4.2)	24 (13.2)	258 (12.5)	19.6 (11.8–27.4)	17.4 (15.3–19.5)	1.08 (0.30–3.82)
Level of education, *y*							
≤9	476 (4.2)	2524 (5.1)	82 (17.2)	405 (16.0)	16.2 (12.7–19.7)	16.2 (14.6–17.8)	0.64 (0.32–1.26)
10–12	5365 (47.9)	23,098 (46.9)	732 (13.6)	2978 (12.9)	18.0 (16.7–19.3)	16.4 (15.8–17.0)	1.08 (0.98–1.19)
>12	5360 (47.8)	23,581 (47.9)	611 (11.4)	2447 (10.4)	16.4 (15.1–17.7)	14.2 (13.7–14.8)	1.14 (1.02–1.26)
Psychiatric diagnoses in family							
Parents or sibling	2712 (24.2)	11,997 (24.4)	507 (18.7)	1947 (16.2)	32.3 (29.5–35.1)	26.5 (25.3–27.6)	1.25 (1.08–1.46)

HR, hazard ratio; PY, person-years.

[a]Conditioned on matching set (age, sex, county, and calendar period) and adjusted further for the highest education attained by parents.

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Supplementary Table 7. Analysis Limited to Those With Available Follow-Up Evaluation Starting at Age 18 Years: Risk of Psychiatric Disorders in Patients With Celiac Disease and Matched General Population Comparators

	Events, N (%)		Time at risk, *y*		Incidence rate (95% CI) per 1000 PY		
Group	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	HR[a] (95% CI)
Psychotic disorders	44 (0.4)	192 (0.4)	90,425	407,384	0.5 (0.3–0.6)	0.5 (0.4–0.5)	1.06 (0.76–1.48)
Mood disorders	618 (5.5)	2334 (4.7)	87,660	397,260	7.0 (6.5–7.6)	5.9 (5.6–6.1)	1.19 (1.08–1.30)
Anxiety disorders	809 (7.2)	3401 (6.9)	86,843	392,060	9.3 (8.7–10.0)	8.7 (8.4–9.0)	1.06 (0.98–1.14)
Eating disorders	112 (1.0)	418 (0.8)	90,017	406,167	1.2 (1.0–1.5)	1.0 (0.9–1.1)	1.19 (0.96–1.47)
Psychoactive substance misuse	409 (3.6)	1660 (3.4)	88,470	399,948	4.6 (4.2–5.1)	4.2 (4.0–4.4)	1.10 (0.98–1.22)
Behavioral disorders	1 (0.0)	18 (0.0)	90,703	408,403	0.0 (0.0–0.0)	0.0 (0.0–0.1)	0.34 (0.04–2.62)
ADHD	234 (2.1)	773 (1.6)	89,837	405,659	2.6 (2.3–2.9)	1.9 (1.8–2.0)	1.39 (1.19–1.61)
Suicide attempt	135 (1.2)	542 (1.1)	89,787	405,216	1.5 (1.2–1.8)	1.3 (1.2–1.5)	1.15 (0.95–1.39)
Suicide	8 (0.1)	55 (0.1)	90,708	408,483	0.1 (0.0–0.1)	0.1 (0.1–0.2)	0.72 (0.34–1.52)
Personality disorders	108 (1.0)	392 (0.8)	90,091	406,291	1.2 (1.0–1.4)	1.0 (0.9–1.1)	1.23 (0.99–1.52)
Autism spectrum disorder	107 (1.0)	282 (0.6)	90,284	407,310	1.2 (1.0–1.4)	0.7 (0.6–0.8)	1.69 (1.35–2.12)
Any psychiatric disorder	1427 (12.7)	5833 (11.8)	83,030	378,378	17.2 (16.3–18.1)	15.4 (15.0–15.8)	1.11 (1.04–1.17)

NOTE. n celiac disease/n comparators = 11,207/49,252.
ADHD, attention-deficit hyperactivity disorder; HR, hazard ratio; PY, person-years.
[a]Conditioned on matching set (age, sex, county, and calendar period) and adjusted further for the highest education attained by parents.

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Supplementary Table 8. Comparison of Celiac Disease Patients With Siblings: Baseline Characteristics of Study Cohort

Characteristic	Celiac disease (n = 13,015)	Matched comparators (n = 18,024)
Girls, n (%)	8157 (62.7)	8831 (49.0)
Boys, n (%)	4858 (37.3)	9193 (51.0)
Age, *y*		
Mean (SD)	6.9 (4.9)	7.8 (4.7)
Median (IQR)	6.0 (2.1–10.8)	7.1 (3.9–11.4)
Range, minimum–maximum	0.0–18.0	0.0–18.0
Categories, n (%)		
<2 y	3086 (23.7)	1771 (9.8)
2 to <6 y	3400 (26.1)	5769 (32.0)
6 to <11 y	3419 (26.3)	5628 (31.2)
11 to <16 y	2518 (19.3)	3904 (21.7)
16 to <18 y	592 (4.5)	952 (5.3)
Country of birth, n (%)		
Nordic country	12,831 (98.6)	17,530 (97.3)
Other	183 (1.4)	493 (2.7)
Missing	1 (0.0)	1 (0.0)
Highest level of education attained by parents, n (%)		
≤9 y	404 (3.1)	739 (4.1)
10–12 y	5387 (41.4)	7515 (41.7)
>12 y	7218 (55.5)	9760 (54.2)
Missing	6 (0.0)	10 (0.1)
Starting year of follow-up evaluation		
1973–1989	1173 (9.0%)	1643 (9.1%)
1990–1999	3470 (26.7%)	4924 (27.3%)
2000–2009	5365 (41.2%)	7374 (40.9%)
2010–2016	3007 (23.1%)	4083 (22.7%)
Follow-up evaluation, *y*		
Mean (SD)	13.1 (8.3)	12.8 (8.5)
Median (IQR)	11.8 (6.4–19.1)	11.4 (6.0–18.9)
Range, minimum–maximum	0.0–39.0	0.0–44.0

IQR, interquartile range.

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Supplementary Table 9. Comparison of Celiac Disease Patients With Siblings: Risk of Any Psychiatric Disorder Overall and by Subgroups in Patients With Celiac Disease and Matched Sibling Comparators

	N (%)		Events, N (%)		Incidence rate (95% CI) per 1000 PY		
Group	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	HR[a] (95% CI)
Overall	13,015 (100)	18,024 (100)	1994 (15.3)	2411 (13.4)	11.7 (11.2–12.2)	10.4 (10.0–10.8)	1.12 (1.05–1.20)
Follow-up period, *y*							
0 to <1	13,015 (100)	18,024 (100)	94 (0.7)	90 (0.5)	7.3 (5.8–8.8)	5.1 (4.0–6.1)	1.48 (1.07–2.05)
1 to <5	12,725 (97.8)	17,331 (96.2,)	415 (3.3)	467 (2.7)	8.8 (8.0–9.7)	7.3 (6.7–8.0)	1.26 (1.09–1.46)
5 to <10	10,691 (82.1)	14,331 (79.5)	531 (5.0)	655 (4.6)	11.7 (10.7–12.7)	10.7 (9.9–11.6)	1.09 (0.95–1.24)
10 to <15	7591 (58.3)	10,194 (56.6)	437 (5.8)	591 (5.8)	14.3 (13.0–15.7)	14.4 (13.2–15.6)	0.86 (0.74–1.00)
15 to <20	4731 (36.4)	6376 (35.4)	303 (6.4)	368 (5.8)	15.9 (14.1–17.6)	14.3 (12.9–15.8)	0.96 (0.79–1.16)
≥20	3027 (23.3)	4100 (22.7)	214 (7.1)	240 (5.9)	13.6 (11.7–15.4)	10.9 (9.5–12.3)	1.07 (0.84–1.37)
Sex							
Girls	8157 (62.7)	8831 (49.0)	1259 (15.4)	1267 (14.3)	11.8 (11.2–12.5)	11.3 (10.6–11.9)	1.11 (0.99–1.24)
Boys	4858 (37.3)	9193 (51.0)	735 (15.1)	1144 (12.4)	11.4 (10.6–12.2)	9.6 (9.1–10.2)	1.27 (1.09–1.47)
Age, *y*							
<2	3086 (23.7)	1771 (9.8)	517 (16.8)	183 (10.3)	8.4 (7.7–9.1)	8.1 (7.0–9.3)	1.06 (0.60–1.86)
2 to <6	3400 (26.1)	5769 (32.0)	386 (11.4)	777 (13.5)	9.0 (8.1–9.8)	9.0 (8.4–9.6)	1.02 (0.81–1.30)
6 to <11	3419 (26.3)	5628 (31.2)	537 (15.7)	757 (13.5)	15.0 (13.7–16.2)	10.9 (10.1–11.7)	1.15 (0.93–1.41)
11 to <16	2518 (19.3)	3904 (21.7)	456 (18.1)	573 (14.7)	18.6 (16.9–20.3)	13.4 (12.3–14.5)	1.10 (0.89–1.36)
16 to <18	592 (4.5)	952 (5.3)	98 (16.6)	121 (12.7)	16.8 (13.5–20.2)	11.8 (9.7–13.9)	2.01 (0.64–6.28)
Year							
1973–1989	1173 (9.0)	1643 (9.1)	235 (20.0)	244 (14.9)	7.4 (6.4–8.3)	5.5 (4.8–6.2)	1.27 (1.01–1.60)
1990–1999	3470 (26.7)	4924 (27.3)	677 (19.5)	882 (17.9)	9.8 (9.1–10.5)	9.4 (8.7–10.0)	1.01 (0.90–1.14)
2000–2009	5365 (41.2)	7374 (40.9)	878 (16.4)	1058 (14.3)	15.2 (14.2–16.2)	13.9 (13.0–14.7)	1.08 (0.98–1.20)
2010–2016	3007 (23.1)	4083 (22.7)	204 (6.8)	227 (5.6)	16.9 (14.5–19.2)	14.2 (12.3–16.0)	1.14 (0.92–1.42)
Year, first 5 years of follow-up evaluation							
1973–1989	1173 (9.0)	1643 (9.1)	9 (0.8)	2 (0.1)	1.5 (0.5–2.6)	0.2 (0.0–0.6)	12.59 (1.19–132.91)
1990–1999	3470 (26.7)	4924 (27.3)	34 (1.0)	26 (0.5)	2.0 (1.3–2.6)	1.1 (0.7–1.5)	3.50 (1.75–6.98)
2000–2009	5365 (41.2)	7374 (40.9)	280 (5.2)	326 (4.4)	10.8 (9.5–12.0)	9.4 (8.4–10.4)	1.23 (1.03–1.47)
2010–2011	1207 (9.3)	1607 (8.9)	89 (7.4)	117 (7.3)	15.3 (12.1–18.5)	15.6 (12.7–18.4)	0.89 (0.65–1.21)
Country of birth							
Nordic	12,831 (98.6)	17,530 (97.3)	1972 (15.4)	2362 (13.5)	11.7 (11.1–12.2)	10.4 (10.0–10.8)	1.11 (1.04–1.19)
Other	183 (1.4)	493 (2.7)	22 (12.0)	49 (9.9)	14.1 (8.2–20.0)	10.9 (7.8–13.9)	1.36 (0.70–2.63)
Level of education, y							
≤9	404 (3.1)	739 (4.1)	85 (21.0)	146 (19.8)	12.1 (9.5–14.7)	12.6 (10.5–14.6)	1.08 (0.78–1.50)
10–12	5387 (41.4)	7515 (41.7)	956 (17.7)	1203 (16.0)	12.4 (11.6–13.1)	11.4 (10.7–12.0)	1.11 (1.00–1.22)
>12	7218 (55.5)	9760 (54.2)	953 (13.2)	1061 (10.9)	11.0 (10.3–11.7)	9.3 (8.8–9.9)	1.13 (1.02–1.25)

HR, hazard ratio; PY, person-years.
[a]Conditioned on matching set (within family) and adjusted further for age and sex.

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Supplementary Table 10. Comparison of Celiac Disease Patients to Siblings: Risk of Psychiatric Disorders in Patients With Celiac Disease and Matched Sibling Comparators

	Events, N (%)		Time at risk, *y*		Incidence rate (95% CI) per 1000 PY		
Group	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	HR[a] (95% CI)
Psychotic disorders	42 (0.3)	62 (0.3)	182,804	245,134	0.2 (0.2–0.3)	0.3 (0.2–0.3)	1.24 (0.79–1.95)
Mood disorders	774 (5.9)	839 (4.7)	179,127	240,967	4.3 (4.0–4.6)	3.5 (3.2–3.7)	1.22 (1.09–1.37)
Anxiety disorders	977 (7.5)	1 175 (6.5)	178,017	239,219	5.5 (5.1–5.8)	4.9 (4.6–5.2)	1.12 (1.01–1.23)
Eating disorders	219 (1.7)	172 (1.0)	181,713	244,557	1.2 (1.0–1.4)	0.7 (0.6–0.8)	1.59 (1.24–2.05)
Psychoactive substance misuse	448 (3.4)	559 (3.1)	180,260	242,014	2.5 (2.3–2.7)	2.3 (2.1–2.5)	1.14 (0.99–1.31)
Behavioral disorders	50 (0.4)	56 (0.3)	182,753	245,176	0.3 (0.2–0.3)	0.2 (0.2–0.3)	1.19 (0.79–1.80)
ADHD	545 (4.2)	651 (3.6)	180,452	242,462	3.0 (2.8–3.3)	2.7 (2.5–2.9)	1.12 (0.99–1.28)
Suicide attempt	183 (1.4)	212 (1.2)	181,654	244,109	1.0 (0.9–1.2)	0.9 (0.8–1.0)	1.22 (0.97–1.52)
Suicide	9 (0.1)	14 (0.1)	183,084	245,518	0.0 (0.0–0.1)	0.1 (0.0–0.1)	2.62 (0.76–9.06)
Personality disorders	95 (0.7)	139 (0.8)	182,522	244,787	0.5 (0.4–0.6)	0.6 (0.5–0.7)	0.82 (0.60–1.13)
Autism spectrum disorder	272 (2.1)	263 (1.5)	181,547	244,173	1.5 (1.3–1.7)	1.1 (0.9–1.2)	1.59 (1.31–1.92)
Any psychiatric disorder	1994 (15.3)	2411 (13.4)	170,810	231,138	11.7 (11.2–12.2)	10.4 (10.0–10.8)	1.12 (1.05–1.20)

NOTE. n celiac disease/n comparators = 13,015 /18,024.
ADHD, attention-deficit hyperactivity disorder; HR, hazard ratio; PY, person-years.
[a]Conditioned on matching set (within family) and further adjusted for age and sex.

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Supplementary Table 11. Characteristics of Children With Celiac Disease Who Underwent a Follow-Up Biopsy

Characteristic	Mucosal healing (n = 2071)	Persistent villus atrophy (n = 533)
Girls, n (%)	1 280 (61.8)	330 (61.9)
Boys, n (%)	791 (38.2)	203 (38.1)
Age, *y*		
Mean (SD)	7.0 (4.8)	6.5 (4.8)
Median (IQR)	5.1 (2.9–10.6)	4.3 (2.7–9.6)
Range, minimum–maximum	1.0–18.0	1.1–18.0
Categories, n (%)		
<2 y	82 (4.0)	39 (7.3)
2 to <6 y	1 084 (52.3)	291 (54.6)
6 to <11 y	415 (20.0)	91 (17.1)
11 to <16 y	372 (18.0)	77 (14.4)
16 to <18 y	118 (5.7)	35 (6.6)
Country of birth, n (%)		
Nordic country	2 044 (98.7)	525 (98.5)
Other	27 (1.3)	8 (1.5)
Highest level of education attained by parents, n (%)		
≤9 y	67 (3.2)	37 (6.9)
10–12 y	950 (45.9)	272 (51.0)
>12 y	1 054 (50.9)	223 (41.8)
Missing	0	1 (0.2)
Start year of follow-up evaluation		
1973–1989	127 (6.1%)	72 (13.5%)
1990–1999	729 (35.2%)	258 (48.4%)
2000–2009	995 (48.0%)	167 (31.3%)
2010–2016	220 (10.6%)	36 (6.8%)
Psychiatric diagnoses in family before index date, n (%)		
Parents	188 (9.1)	49 (9.2)
Siblings	36 (1.7)	14 (2.6)
Any of parents or siblings	217 (10.5)	62 (11.6)
Duration since diagnosis, *y*		
Mean (SD)	1.7 (0.9)	1.8 (1.0)
Median (IQR)	1.4 (1.1–2.0)	1.4 (1.1–2.1)
Range, minimum–maximum	0.5–5.0	0.5–5.0
Follow-up period, *y*		
Mean (SD)	14.4 (7.2)	17.3 (7.9)
Median (IQR)	13.6 (9.4–20.0)	17.8 (10.9–23.3)
Range, minimum–maximum	0.0–34.0	0.0–39.0

IQR, interquartile range.

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Supplementary Table 12. Risk of Any Psychiatric Disorder Overall and by Subgroups in Patients With Celiac Disease and Mucosal Healing Vs Persistent VA

Group	N (%)		Events, N (%)		Incidence rate (95% CI) per 1000 PY		
	Mucosal healing	Persistent VA	Mucosal healing	Persistent VA	Mucosal healing	Persistent VA	HR[a] (95% CI)
Overall	2071 (100.0)	533 (100.0)	375 (18.1)	90 (16.9)	12.6 (11.3–13.9)	9.8 (7.7–11.8)	1.21 (0.95–1.53)
Follow-up period, *y*							
0 to <1	2071 (100.0)	533 (100.0)	19 (0.9)	3 (0.6)	9.2 (5.1–13.4)	5.7 (0.0–12.1)	1.15 (0.34–3.90)
1 to <5	2045 (98.7)	527 (98.9)	70 (3.4)	10 (1.9)	9.0 (6.9–11.1)	4.8 (1.8–7.8)	1.48 (0.76–2.89)
5 to <10	1845 (89.1)	500 (93.8)	94 (5.1)	19 (3.8)	11.1 (8.9–13.4)	8.2 (4.5–11.9)	1.13 (0.68–1.88)
10 to <15	1495 (72.2)	422 (79.2)	104 (7.0)	27 (6.4)	17.5 (14.2–20.9)	14.5 (9.1–20.0)	1.14 (0.74–1.75)
15 to <20	886 (42.8)	325 (61.0)	60 (6.8)	23 (7.1)	17.4 (13.0–21.8)	17.0 (10.1–24.0)	1.01 (0.62–1.65)
≥20	517 (25.0)	222 (41.7)	28 (5.4)	8 (3.6)	13.7 (8.7–18.8)	7.3 (2.2–12.3)	1.89 (0.85–4.19)
Sex							
Girls	1280 (61.8)	330 (61.9)	220 (17.2)	59 (17.9)	11.9 (10.4–13.5)	10.4 (7.7–13.0)	1.02 (0.76–1.37)
Boys	791 (38.2)	203 (38.1)	155 (19.6)	31 (15.3)	13.7 (11.6–15.9)	8.8 (5.7–11.9)	1.53 (1.03–2.27)
Age, *y*							
<2	82 (4.0)	39 (7.3)	16 (19.5)	5 (12.8)	9.3 (4.7–13.8)	5.5 (0.7–10.3)	1.89 (0.65–5.55)
2 to <6	1084 (52.3)	291 (54.6)	176 (16.2)	54 (18.6)	9.5 (8.1–10.9)	9.4 (6.9–11.9)	1.02 (0.74–1.39)
6 to <11	415 (20.0)	91 (17.1)	73 (17.6)	14 (15.4)	15.1 (11.7–18.6)	11.0 (5.2–16.7)	1.19 (0.66–2.14)
11 to <16	372 (18.0)	77 (14.4)	84 (22.6)	10 (13.0)	23.7 (18.6–28.7)	11.0 (4.2–17.7)	1.69 (0.86–3.34)
16 to <18	118 (5.7)	35 (6.6)	26 (22.0)	7 (20.0)	23.2 (14.3–32.1)	18.0 (4.7–31.4)	1.39 (0.59–3.28)
Year							
1973–1989	127 (6.1)	72 (13.5)	26 (20.5)	12 (16.7)	7.9 (4.9–10.9)	6.2 (2.7–9.7)	1.32 (0.66–2.66)
1990–1999	729 (35.2)	258 (48.4)	143 (19.6)	48 (18.6)	10.0 (8.3–11.6)	9.1 (6.5–11.7)	1.11 (0.80–1.55)
2000–2009	995 (48.0)	167 (31.3)	180 (18.1)	28 (16.8)	16.1 (13.7–18.4)	15.1 (9.5–20.7)	1.21 (0.81–1.83)
2010–2016	220 (10.6)	36 (6.8)	26 (11.8)	2 (5.6)	29.8 (18.3–41.2)	13.5 (0.0–32.2)	2.28 (0.53–9.68)
Year, first 5 years of follow-up evaluation							
1973–1989	127 (6.1)	72 (13.5)	0	0	0	0	–
1990–1999	729 (35.2)	258 (48.4)	9 (1.2)	4 (1.6)	2.5 (0.9–4.1)	3.1 (0.1–6.2)	0.76 (0.23–2.49)
2000–2009	995 (48.0)	167 (31.3)	58 (5.8)	7 (4.2)	12.0 (8.9–15.1)	8.6 (2.2–14.9)	1.60 (0.72–3.54)
2010–2011	91 (4.4)	18 (3.4)	11 (12.1)	2 (11.1)	25.8 (10.6–41.1)	23.6 (0.0–56.3)	0.92 (0.20–4.33)
Country of birth							
Nordic	2044 (98.7)	525 (98.5)	369 (18.1)	90 (17.1)	12.5 (11.3–13.8)	9.9 (7.8–11.9)	1.18 (0.93–1.49)
Other	27 (1.3)	8 (1.5)	6 (22.2)	0	21.7 (4.3–39.1)	0	–
Level of education, *y*							
≤9	67 (3.2)	37 (6.9)	14 (20.9)	9 (24.3)	13.3 (6.3–20.3)	14.6 (5.1–24.2)	1.02 (0.42–2.52)
10–12	950 (45.9)	272 (51.0)	194 (20.4)	47 (17.3)	13.5 (11.6–15.4)	9.3 (6.6–11.9)	1.30 (0.94–1.80)
>12	1054 (50.9)	223 (41.8)	167 (15.8)	34 (15.2)	11.7 (9.9–13.5)	9.6 (6.4–12.8)	1.13 (0.78–1.64)
Psychiatric diagnoses in family							
Parents or sibling	217 (10.5)	62 (11.6)	60 (27.6)	12 (19.4)	25.9 (19.4–32.5)	15.7 (6.8–24.6)	1.61 (0.85–3.04)

HR, hazard ratio; PY, patient-years; VA, villous atrophy.

[a]Adjusted for age, sex, start year of follow-up evaluation, duration since diagnosis, highest education attained by parents, and Nordic country of birth.

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Supplementary Table 13. Outcomes Restricted to Those With a Psychiatric Medication Prescription (July 2006–December 2016): Baseline Characteristics of Study Cohort

Characteristic	Celiac disease (n = 6815)	Matched comparators (n = 32,459)
Girls, n (%)	4361 (64.0)	20,827 (64.2)
Boys, n (%)	2454 (36.0)	11,632 (35.8)
Age, *y*		
Mean (SD)	8.8 (4.8)	8.6 (4.8)
Median (IQR)	8.6 (4.6–12.9)	8.4 (4.4–12.6)
Range, minimum–maximum	0.0–18.0	0.0–18.0
Categories, n (%)		
<2 y	493 (7.2)	2440 (7.5)
2 to <6 y	1851 (27.2)	9100 (28.0)
6 to <11 y	2051 (30.1)	9896 (30.5)
11 to <16 y	1818 (26.7)	8538 (26.3)
16 to <18 y	602 (8.8)	2485 (7.7)
Country of birth, n (%)		
Nordic country	6608 (97.0)	30,230 (93.1)
Other	207 (3.0)	2226 (6.9)
Missing	0	3 (0.0)
Highest level of education attained by parents, n (%)		
≤9 y	150 (2.2)	1312 (4.0)
10–12 y	2431 (35.7)	12,409 (38.2)
>12 y	4224 (62.0)	18,624 (57.4)
Missing	10 (0.1%)	114 (0.4%)
Start year of follow-up evaluation		
2006 (July)–2009	2761 (40.5%)	13,282 (40.9%)
2010–2012	2327 (34.1%)	11,112 (34.2%)
2013–2016	1727 (25.3%)	8065 (24.8%)
Psychiatric diagnoses in family before index date, n (%)		
Parents	1240 (18.2)	6099 (18.8)
Siblings	222 (3.3)	1095 (3.4)
Any of parents or siblings	1400 (20.5)	6818 (21.0)
Follow-up period, *y*		
Mean (SD)	5.5 (2.8)	5.6 (2.8)
Median (IQR)	5.7 (3.2–7.8)	5.8 (3.3–7.9)
Range, minimum–maximum	0.0–10.5	0.0–10.5

IQR, interquartile range.

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Supplementary Table 14. Outcomes Restricted to Those With a Psychiatric Medication Prescription (July 2006–December 2016): Risk of Any Psychiatric Disorder Including Drug Use Overall and by Subgroups in Patients With Celiac Disease and Matched General Population Comparators

	N (%)		Events, N (%)		Incidence rate (95% CI) per 1000 PY		
Group	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	HR[a] (95% CI)
Overall	6815 (100)	32,459 (100)	1016 (14.9)	3757 (11.6)	26.9 (25.3–28.6)	20.5 (19.8–21.2)	1.34 (1.24–1.43)
Follow-up period, *y*							
0 to <1	6815 (100)	32,459 (100)	150 (2.2)	412 (1.3)	22.6 (19.0–26.3)	13.0 (11.7–14.2)	1.73 (1.43–2.09)
1 to <5	6424 (94.3)	30,817 (94.9)	535 (8.3)	1903 (6.2)	25.5 (23.3–27.7)	18.7 (17.9–19.6)	1.38 (1.25–1.53)
5 to <10	3898 (57.2)	19,081 (58.8)	326 (8.4)	1423 (7.5)	32.3 (28.8–35.9)	28.7 (27.2–30.2)	1.15 (1.01–1.30)
Sex							
Girls	4361 (64.0)	20,827 (64.2)	663 (15.2)	2503 (12.0)	27.6 (25.5–29.7)	21.3 (20.5–22.2)	1.30 (1.19–1.42)
Boys	2454 (36.0)	11,632 (35.8)	353 (14.4)	1254 (10.8)	25.8 (23.1–28.5)	19.0 (17.9–20.0)	1.42 (1.26–1.60)
Age, *y*							
<2	493 (7.2)	2440 (7.5)	38 (7.7)	128 (5.2)	11.4 (7.8–15.0)	7.8 (6.5–9.2)	1.29 (0.87–1.90)
2 to <6	1851 (27.2)	9100 (28.0)	125 (6.8)	513 (5.6)	11.5 (9.5–13.5)	9.6 (8.8–10.5)	1.29 (1.05–1.58)
6 to <11	2051 (30.1)	9896 (30.5)	286 (13.9)	953 (9.6)	26.8 (23.7–29.9)	18.1 (17.0–19.3)	1.52 (1.32–1.74)
11 to <16	1818 (26.7)	8538 (26.3)	410 (22.6)	1607 (18.8)	41.8 (37.7–45.8)	33.5 (31.9–35.2)	1.28 (1.14–1.43)
16 to <18	602 (8.8)	2485 (7.7)	157 (26.1)	556 (22.4)	51.7 (43.6–59.7)	42.3 (38.8–45.8)	1.26 (1.05–1.52)
Year							
2006 (July)–2009	2761 (40.5)	13,282 (40.9)	582 (21.1)	2291 (17.2)	26.8 (24.7–29.0)	21.7 (20.8–22.5)	1.27 (1.15–1.39)
2010–2012	2327 (34.1)	11,112 (34.2)	314 (13.5)	1119 (10.1)	25.9 (23.0–28.7)	19.0 (17.9–20.1)	1.37 (1.21–1.56)
2013–2016	1727 (25.3)	8065 (24.8)	120 (6.9)	347 (4.3)	30.5 (25.0–36.0)	18.6 (16.6–20.5)	1.66 (1.34–2.05)
Country of birth							
Nordic	6608 (97.0)	30,230 (93.1)	987 (14.9)	3521 (11.6)	26.8 (25.2–28.5)	20.5 (19.8–21.1)	1.32 (1.22–1.42)
Other	207 (3.0)	2226 (6.9)	29 (14.0)	236 (10.6)	30.2 (19.2–41.1)	20.9 (18.3–23.6)	1.80 (0.57–5.70)
Level of education, *y*							
≤9	150 (2.2)	1312 (4.0)	28 (18.7)	191 (14.6)	39.0 (24.6–53.5)	27.7 (23.8–31.6)	0.33 (0.03–3.20)
10–12	2431 (35.7)	12,409 (38.2)	449 (18.5)	1743 (14.0)	33.1 (30.0–36.1)	24.4 (23.3–25.6)	1.23 (1.08–1.41)
>12	4224 (62.0)	18,624 (57.4)	537 (12.7)	1813 (9.7)	22.9 (21.0–24.9)	17.3 (16.5–18.1)	1.30 (1.17–1.45)
Psychiatric diagnoses in family							
Parents or sibling	1400 (20.5)	6818 (21.0)	292 (20.9)	1149 (16.9)	42.4 (37.5–47.2)	33.0 (31.1–34.9)	1.46 (1.18–1.80)

HR, hazard ratio; PY, person-years.

[a]Conditioned on matching set (age, sex, county, and calendar period) and adjusted further for the highest attained education by parents.

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Supplementary Table 15. Outcomes Restricted to Those With a Psychiatric Medication Prescription (July 2006-December 2016): Risk of Psychiatric Disorders in Patients With Celiac Disease and Matched General Population Comparators

	Events, N (%)		Time at risk, *y*		Incidence rate (95% CI) per 1000 PY		
Group	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	HR[a] (95% CI)
Any psychiatric disorder	1016 (14.9)	3757 (11.6)	37,750	183,287	26.9 (25.3–28.6)	20.5 (19.8–21.2)	1.34 (1.24–1.43)
Antidepressants	841 (12.3)	3070 (9.5)	38,377	185,733	21.9 (20.4–23.4)	16.5 (15.9–17.1)	1.35 (1.25–1.46)
Anxiolytics, hypnotics, and sedatives	947 (13.9)	3526 (10.9)	37,975	183,989	24.9 (23.3–26.5)	19.2 (18.5–19.8)	1.32 (1.23–1.42)
Antipsychotics	714 (10.5)	2610 (8.0)	38,735	186,995	18.4 (17.1–19.8)	14.0 (13.4–14.5)	1.34 (1.23–1.46)

NOTE. n celiac disease/n comparators = 6,815 /32,459.
HR, hazard ratio; PY, person-years.
[a]Conditioned on matching set (age, sex, county, and calendar period) and adjusted further for the highest education attained by parents.

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