

# Journal Pre-proof

Psychiatric disorders in patients with a diagnosis of celiac disease during childhood from 1973 to 2016

Benjamin Lebwohl, MD, MS, Linnea Haggård, MD, Louise Emilsson, MD, PhD, Jonas Söderling, PhD, Bjorn Roelstraete, PhD, Agnieszka Butwicka, MD, Peter HR. Green, MD, Jonas F. Ludvigsson, MD, PhD



PII: S1542-3565(20)31127-7  
DOI: <https://doi.org/10.1016/j.cgh.2020.08.018>  
Reference: YJCGH 57432

To appear in: *Clinical Gastroenterology and Hepatology*  
Accepted Date: 6 August 2020

Please cite this article as: Lebwohl B, Haggård L, Emilsson L, Söderling J, Roelstraete B, Butwicka A, Green PH, Ludvigsson JF, Psychiatric disorders in patients with a diagnosis of celiac disease during childhood from 1973 to 2016, *Clinical Gastroenterology and Hepatology* (2020), doi: <https://doi.org/10.1016/j.cgh.2020.08.018>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 by the AGA Institute

## Psychiatric disorders in patients with a diagnosis of celiac disease during childhood from 1973 to 2016

Benjamin Lebwohl, MD, MS<sup>1,2</sup>, Linnea Haggård, MD<sup>3</sup>, Louise Emilsson, MD, PhD<sup>3,4,5,6</sup>, Jonas Söderling, PhD<sup>3</sup>, Bjorn Roelstraete PhD<sup>3</sup>, and Agnieszka Butwicka, MD<sup>3,7,8</sup>, Peter HR Green, MD<sup>1</sup>, Jonas F. Ludvigsson, MD, PhD<sup>1,3,9</sup>

### Affiliations:

<sup>1</sup> Celiac Disease Center, Department of Medicine, Columbia University Medical Center, New York NY, USA

<sup>2</sup> Department of Epidemiology, Mailman School of Public Health, Columbia University, New York NY, USA

<sup>3</sup> Department Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

<sup>4</sup> Department of general practice, Institute of Health and Society, University of Oslo, Oslo, Norway

<sup>5</sup> Vårdcentralen Årjäng and Centre for Clinical Research, County Council of Värmland, Värmland, Sweden.

<sup>6</sup> Faculty of Medicine and Health, Örebro University, SE 701 82, Örebro, Sweden

<sup>7</sup> Child and Adolescent Psychiatry Stockholm, Stockholm Health Care Services, Region Stockholm, Sweden

<sup>8</sup> Department of Child Psychiatry, Medical University of Warsaw, Warsaw, Poland

<sup>9</sup> Department of Pediatrics, Örebro University Hospital, Örebro University, Örebro, Sweden

### Correspondence:

Jonas F Ludvigsson, MD, PhD  
Dept. of Medical Epidemiology and Biostatistics  
Karolinska Institutet  
Stockholm, Sweden  
P: +46 (0) 8-524 823 56  
jonasludvigsson@yahoo.com

**Grants and Financial Support:** BL: Celiac Disease Foundation Young Investigator Research Grant Award; The Louis and Gloria Flanzer Philanthropic Trust. JFL: Karolinska Institutet

**Running title:** Childhood Celiac disease and Psychiatric disorders

**Word Count:** 3180

**Number of Figures:** 1

**Number of Tables:** 4

**Number of Supplementary Tables:** 15

**Disclosures:** Dr Ludvigsson coordinates a study on behalf of the Swedish IBD quality register (SWIBREG). This study has received funding from Janssen corporation. All other authors declare that they have no conflicts of interest and nothing to declare.

**Abbreviations**

ADHD, attention-deficit hyperactivity disorder; CD, celiac disease; CI, confidence interval; ESPRESSO, Epidemiology Strengthened by histoPathology Reports in Sweden; HR, hazard ratio; ICD, International Classification of Diseases; IQR, interquartile range; LISA, The longitudinal integrated database for health insurance and labour market studies; ; NPR, the National Patient Register; OR, odds ratio; SD, standard deviation; SNOMED CT-System, Systematized Nomenclature of Medicine Clinical Terms.

**Contributors**

LH wrote the first draft of the paper. All authors conceived and designed the study. JFL and BL supervised the project. PG and JFL funded the study. JS carried out the statistics. All authors interpreted the data and contributed to the writing of the paper. All authors revised and approved the final version.

JFL takes responsibility for the integrity of the data and the accuracy of the data analyses. JFL is the guarantor of the data.

**Competing interest:** JFL coordinates a study on behalf of the Swedish IBD quality register (SWIBREG). This study has received funding from Janssen corporation.

**Disclaimer:** This manuscript represents the views of the authors.

**Funding and Role of the funding sources:** Karolinska Institutet. The funders did not influence the study or the decision to submit the study.

**Details of ethics approval:** This project (2014/1287-31/4) was approved by the Research Ethics Committee in Stockholm, Sweden on August 27, 2014.

**Data sharing**

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

**Transparency**

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.

Journal Pre-proof

**ABSTRACT**

**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 ESPRESSO 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 time 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 (older than 18 years: 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 was also 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 were also more common prior to diagnosis of celiac disease (odds ratio, 1.56; 95% CI, 1.39–1.76).

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

**KEY WORDS:** depression, ADHD, psychiatry, epidemiology, comorbidity

Journal Pre-proof

## Introduction

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

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

## Methods

### Celiac disease

The ESPRESSO cohort consists of 6.1 million gastrointestinal biopsy reports from 2.1 million individuals. Biopsy reports were classified according to the SNOMED CT-System (Systematized Nomenclature of Medicine Clinical Terms), and originated from 1965-2017 from Sweden's 28 pathology departments. Data collection took place between Oct 12, 2015 and April 10, 2017. Through a computerized search of the ESPRESSO cohort (see **Supplementary Table S1** for topography codes equivalent to the duodenum and jejunum; and for relevant SNOMED codes) we identified individuals with villus atrophy (Marsh III, in this study equivalent to celiac disease). An earlier patient chart validation found that 108/114 (95%) of patients with villus atrophy had celiac disease.<sup>12</sup> Since that validation was performed on individuals biopsied up until 2008, we (JFL) re-reviewed the free text of 100 randomly selected biopsy reports with villus atrophy originating from 2009-2017. 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, JFL, March 23, 2020).

Since our outcome measure was any psychiatric disorder, we restricted our study to patients diagnosed during the years spanning 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.<sup>13</sup> None of the reference individuals had celiac disease at matching date, and if they developed celiac disease their follow-up was censored at the date of diagnosis.



### *Secondary reference individuals*

In a separate analysis we compared 13,015 individuals with celiac disease with their non-celiac 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 ICD 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 S2**). Psychiatric disorder data were obtained through the National Patient Register. For selected psychiatric disorders, this register has a positive predictive value of 85-95%.<sup>14 15</sup>

While data on suicide attempt were retrieved from the Patient Register, data on suicide were obtained from the Cause of Death Register. ADHD was defined as having a relevant ADHD medication in the Prescribed Drug Register.<sup>16</sup>

### **Statistics**

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

Cox proportional hazard model estimated hazard ratios (HRs) and 95% confidence intervals (Cis) for psychiatric disorder. Stratified analyses were performed according to years of follow-up (<1, 1<5,

5<10, 10<20, ≥20 years), age at celiac disease diagnosis (<2, 2-<6, 6-<, 11-<16, 16-<18) sex, level of parental education (≤9, 10-12 years, ≥13 years) and country of birth (Nordic, other). We repeated the analysis, now restricting the outcome definition to those with a prescription for a psychiatric drug in the Prescription Drug Register (for a list of included drugs see **Supplementary Table S3**). Since the Prescribed Drug Register started on July 1, 2005, this sensitivity analysis was carried out in celiac patients diagnosed from July 1, 2006 or later. In separate analyses we examined the risk of psychiatric disorders in celiac disease versus 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<sup>17</sup> and osteoporotic fracture,<sup>18</sup> we compared those children who had persistent villus atrophy to those whose villi healed in the subset of subjects who underwent 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 (18 years) during follow-up. 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 due to an underlying intellectual disability (triggering celiac testing and predisposing to a psychiatric disorder), we excluded anyone with a diagnosis of 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 since this was a strict register-based study.

Journal Pre-proof

## Results

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

### Baseline characteristics of main study cohort

The mean age at the time of celiac disease diagnosis was 6.6 years (SD 5.2 years) with almost 30% being diagnosed <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 elevated risk within the first year after celiac diagnosis (HR=1.70 95%CI=1.41-2.05). Restricting follow-up 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 S4**).

The risks of each psychiatric disorder in celiac disease patients versus controls are listed in **Table 3**.

Children with celiac disease were at an elevated risk of developing mood disorders, anxiety disorders, eating disorders, ADHD, and autism spectrum disorder.

### Follow-up from age 18 years

In analyses of adults ( $\geq 18$  years) 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 S5**). 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 S6**).

Adults with childhood celiac disease had an elevated risk later for mood disorders, ADHD, and autism spectrum disorder (**Supplementary Table S7**). When repeating the analysis, now including all subjects regardless of whether they had been diagnosed with psychiatric disease prior to celiac disease diagnosis or prior to 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 diagnosis of intellectual disability prior to study entry (n celiac=19,101; n controls=93,612) the positive association with psychiatric disorders remained (HR = 1.18; 95%CI, 1.14-1.23).

### Sibling comparisons

We repeated the above analyses using celiac-free siblings as comparators (n=18,024) restricting our cohort to 13,015 children with celiac disease and at least one sibling (**Supplementary Table S8** 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 psychiatric disorder compared to 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 S9**). Sibling comparisons found a

positive association between celiac disease and mood disorders, anxiety disorders, eating disorders, and autism spectrum disorder (**Supplementary Table S10**).

### **Mucosal healing and psychiatric disorder**

During follow-up, 2,604 children with celiac disease had a follow-up biopsy (mucosal healing: n=2,071, 79.5%); persistent villus atrophy: n=533, 20.5%)(**Supplementary Table S11**). We found no association between mucosal healing and subsequent psychiatric disorder (HR=1.21; 95%CI=0.95-1.53; **Table S12**).

### **Sensitivity analyses**

In a sensitivity analyses we defined psychiatric disorder as having a prescription for a psychiatric drug (**Table S3**). Due to the construction of the Swedish Prescribed Drug Register, this analysis was restricted to children diagnosed between July, 2006 and December, 2016 (**Supplementary Table S13**). 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 S14**). The HR for any psychiatric disorder was 1.34 (95%CI=1.24-1.43) (**Supplementary Table S14**).

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, see **Supplementary Table S15**).

### **History of psychiatric disorder preceding celiac disease CD**

In children with celiac disease a *prior* history of a psychiatric disorder (preceding the diagnosis of celiac disease) was more common compared to 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 1973-2016. During follow-up, 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.<sup>19 20</sup>

The overall risk for psychiatric disorder was highest in the first year after diagnosis. This may in part be due in part to surveillance bias, but it is also possible that the systemic inflammatory response is mediating this relationship. In addition to these purported mechanisms, the psychosocial stress associated with adapting to the gluten-free diet may be accounting for the early rise in risk of psychiatric disorders. Unlike most chronic medical conditions that are managed via pharmaceutical 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<sup>21</sup> may lead to maladaptive eating patterns<sup>22</sup> and hypervigilance, with attendant diminished

quality of life.<sup>23</sup> 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 due to the gluten-free diet alone, since we also observed an increased risk of psychiatric disorders preceding the diagnosis of celiac disease, possibly related to the systemic inflammatory response described above.

#### *Specific psychiatric disorders*

The specific psychiatric disorders found to be increased in this study of childhood-diagnosed celiac 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.<sup>24</sup> Eating disorders<sup>25</sup> have likewise been linked to celiac disease, though autism has not,<sup>11</sup> despite the popular use of a gluten-free diet among children with this condition.<sup>26</sup>

#### *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 through 2016. This compares to 10,903 children followed through 2010 in a previous population-based study in Sweden.<sup>9</sup> This expanded sample size and follow-up allowed us to evaluate additional outcomes including long-term adult-onset psychiatric disease; to our knowledge, ours is the first study to examine the development of psychiatric disorder particularly in adults with celiac disease diagnosed in childhood. The large sample size and long-term follow-up (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 were also able to perform sensitivity analyses including a comparison to 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 has some limitations. The ICD-codes and thus the criteria used for psychiatric diagnoses (**Supplementary Table S1**) have changed throughout the years, and this might influence the rates of psychiatric diagnosis. As 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 diagnosis is associated with lower adherence to the gluten-free diet.<sup>27</sup> This may be due to the fact that mucosal healing is an imperfect marker of adherence, particularly given the possibility of gradual healing, i.e. persistent villus atrophy that eventually resolves with further time while maintaining the gluten-free diet.

### **Clinical implications**

This study shows that, though small in absolute magnitude, there is an elevated risk of 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.

### **Conclusion**

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 long time and into adulthood. Mental health surveillance should be integral in the care of celiac disease.

Journal Pre-proof

**Figure 1** Flow chart of identified patients and their matched comparators

Journal Pre-proof

**Table 1** Baseline characteristics of study cohort

<b>Characteristic</b>	<b>Celiac disease (n=19,186)</b>	<b>Matched comparators (n=94,249)</b>
Girls, no. (%)	12 076 (62.9%)	59 358 (63.0%)
Boys, no (%)	7 110 (37.1%)	34 891 (37.0%)
<b>Age at celiac disease diagnosis</b>		
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, min-max	0.0-18.0	0.0-18.0
<b>Categories, no. (%)</b>		
<2y	5 694 (29.7%)	27 579 (29.3%)
2 - <6y	4 545 (23.7%)	23 460 (24.9%)
6y - <11y	4 244 (22.1%)	20 944 (22.2%)
11y - <16y	3 508 (18.3%)	17 025 (18.1%)
16 - <18y	1 195 (6.2%)	5 241 (5.6%)
<b>Country of birth, no (%)</b>		
Nordic country	18 837 (98.2%)	90 009 (95.5%)
Other	348 (1.8%)	4 236 (4.5%)
Missing	1 (0.0%)	4 (0.0%)
<b>Highest attained level of education in parents, n (%)</b>		
≤9 years	659 (3.4%)	4 333 (4.6%)
10-12 years	8 371 (43.6%)	40 792 (43.3%)
>12 years	10 136 (52.8%)	48 844 (51.8%)
Missing	20 (0.1%)	280 (0.3%)
<b>Start year of follow-up</b>		
1973-1989	1 909 (9.9%)	9 504 (10.1%)
1990-1999	5 458 (28.4%)	27 113 (28.8%)
2000-2009	7 643 (39.8%)	37 524 (39.8%)
2010-2016	4 176 (21.8%)	20 108 (21.3%)
<b>Psychiatric diagnoses in family before index date (%)</b>		
Parents	2 260 (11.8%)	11 449 (12.1%)
Siblings	331 (1.7%)	1 725 (1.8%)
Any of parents or siblings	2 505 (13.1%)	12 627 (13.4%)
<b>Follow-up, years</b>		
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, min-max	0.0-42.0	0.0-44.0

**Table 2** Risk of any psychiatric disorder overall and by subgroups in patients with Celiac disease and matched general population comparators

Group	N (%)		N events (%)		Incidence rate (95% CI) per 1000 PY		HR* (95%CI)
	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	
<b>Overall</b>	19 186 (100%)	94 249 (100%)	3 174 (16.5%)	13 286 (14.1%)	12.2 (11.8-12.7)	10.3 (10.2-10.5)	1.19 (1.14-1.23)
<b>Follow-up</b>							
0-<1y	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-<5y	18 762 (97.8%)	92 140 (97.8%)	629 (3.4%)	2 260 (2.5%)	9.0 (8.3-9.7)	6.6 (6.3-6.9)	1.38 (1.26-1.51)
5-<10y	15 909 (82.9%)	78 384 (83.2%)	791 (5.0%)	3 188 (4.1%)	11.6 (10.8-12.4)	9.5 (9.1-9.8)	1.24 (1.15-1.34)
10-<15y	11 474 (59.8%)	56 869 (60.3%)	690 (6.0%)	3 135 (5.5%)	14.7 (13.6-15.8)	13.5 (13.0-14.0)	1.11 (1.02-1.21)
15-<20y	7 379 (38.5%)	36 593 (38.8%)	541 (7.3%)	2 584 (7.1%)	17.9 (16.4-19.4)	17.2 (16.5-17.9)	1.02 (0.93-1.12)
≥20y	4 885 (25.5%)	24 236 (25.7%)	375 (7.7%)	1 702 (7.0%)	14.6 (13.1-16.1)	13.3 (12.6-13.9)	1.10 (0.98-1.23)
<b>Sex</b>							
Girls	12 076 (62.9%)	59 358 (63.0%)	2 027 (16.8%)	8 772 (14.8%)	12.5 (11.9-13.0)	11.0 (10.7-11.2)	1.14 (1.08-1.20)
Boys	7 110 (37.1%)	34 891 (37.0%)	1 147 (16.1%)	4 514 (12.9%)	11.8 (11.2-12.5)	9.3 (9.1-9.6)	1.28 (1.20-1.37)
<b>Age</b>							
<2y	5 694 (29.7%)	27 579 (29.3%)	1 001 (17.6%)	4 408 (16.0%)	8.9 (8.3-9.4)	8.2 (7.9-8.4)	1.06 (0.98-1.13)
2y - <6y	4 545 (23.7%)	23 460 (24.9%)	578 (12.7%)	2 691 (11.5%)	10.0 (9.2-10.8)	8.9 (8.6-9.3)	1.11 (1.01-1.22)
6y - <11y	4 244 (22.1%)	20 944 (22.2%)	707 (16.7%)	2 753 (13.1%)	16.1 (14.9-17.3)	12.5 (12.0-13.0)	1.32 (1.21-1.44)
11y - <16y	3 508 (18.3%)	17 025 (18.1%)	668 (19.0%)	2 655 (15.6%)	19.9 (18.4-21.4)	15.7 (15.1-16.3)	1.28 (1.17-1.39)
16 - <18y	1 195 (6.2%)	5 241 (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)
<b>Year</b>							
1973-1989	1 909 (9.9%)	9 504 (10.1%)	405 (21.2%)	1 760 (18.5%)	7.8 (7.0-8.6)	6.8 (6.5-7.1)	1.15 (1.03-1.28)
1990-1999	5 458 (28.4%)	27 113 (28.8%)	1 140 (20.9%)	5 052 (18.6%)	10.4 (9.8-11.1)	9.4 (9.1-9.6)	1.12 (1.05-1.19)
2000-2009	7 643 (39.8%)	37 524 (39.8%)	1 303 (17.0%)	5 352 (14.3%)	15.9 (15.0-16.8)	13.3 (12.9-13.6)	1.22 (1.14-1.29)
2010-2016	4 176 (21.8%)	20 108 (21.3%)	326 (7.8%)	1 122 (5.6%)	19.4 (17.3-21.6)	13.7 (12.9-14.5)	1.43 (1.26-1.62)
<b>Year – First 5 years of follow-up</b>							
1973-1989	1 909 (9.9%)	9 504 (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	5 458 (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	7 643 (39.8%)	37 524 (39.8%)	408 (5.3%)	1 525 (4.1%)	11.0 (9.9-12.1)	8.4 (8.0-8.8)	1.32 (1.19-1.48)
2010-2011	1 707 (8.9%)	8 300 (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)
<b>Country of birth</b>							
Nordic	18 837 (98.2%)	90 009 (95.5%)	3 121 (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%)	4 236 (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)
<b>Level of education</b>							
≤9 years	659 (3.4%)	4 333 (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 years	8 371 (43.6%)	40 792 (43.3%)	1 604 (19.2%)	6 676 (16.4%)	13.1 (12.4-13.7)	11.4 (11.1-11.6)	1.17 (1.09-1.25)
>12 years	10 136 (52.8%)	48 844 (51.8%)	1 419 (14.0%)	5 817 (11.9%)	11.3 (10.7-11.9)	9.2 (9.0-9.5)	1.20 (1.13-1.29)
<b>Psychiatric diagnoses in family</b>							
Parents or sibling	2 505 (13.1%)	12 627 (13.4%)	582 (23.2%)	2 505 (19.8%)	24.8 (22.8-26.8)	20.6 (19.8-21.5)	1.28 (1.08-1.52)

\*Conditioned on matching set (age, sex, county, and calendar period) and further adjusted for highest attained education in parents

**Table 3** Risk of psychiatric disorders in patients with Celiac disease and matched general population comparators  
(n celiac disease/n comparators = 19,186/94,249)

Group	N events (%)		Time at risk (years)		Incidence rate (95% CI) per 1000 PY		HR* (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)

\*Conditioned on matching set (age, sex, county, and calendar period) and further adjusted for highest attained education in parents

ADHD, Attention Deficit Hyperactivity Disorder

**Table 4:** Risk of psychiatric disorders in patients with celiac disease and matched general population comparators before start of follow-up (n celiac disease/n comparators = 19,583/97,362)

Group	N events (%)		Odds ratio* (95%CI)
	Celiac disease	Comparators	
Any psychiatric disorder	397 (2.0%)	1 301 (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)

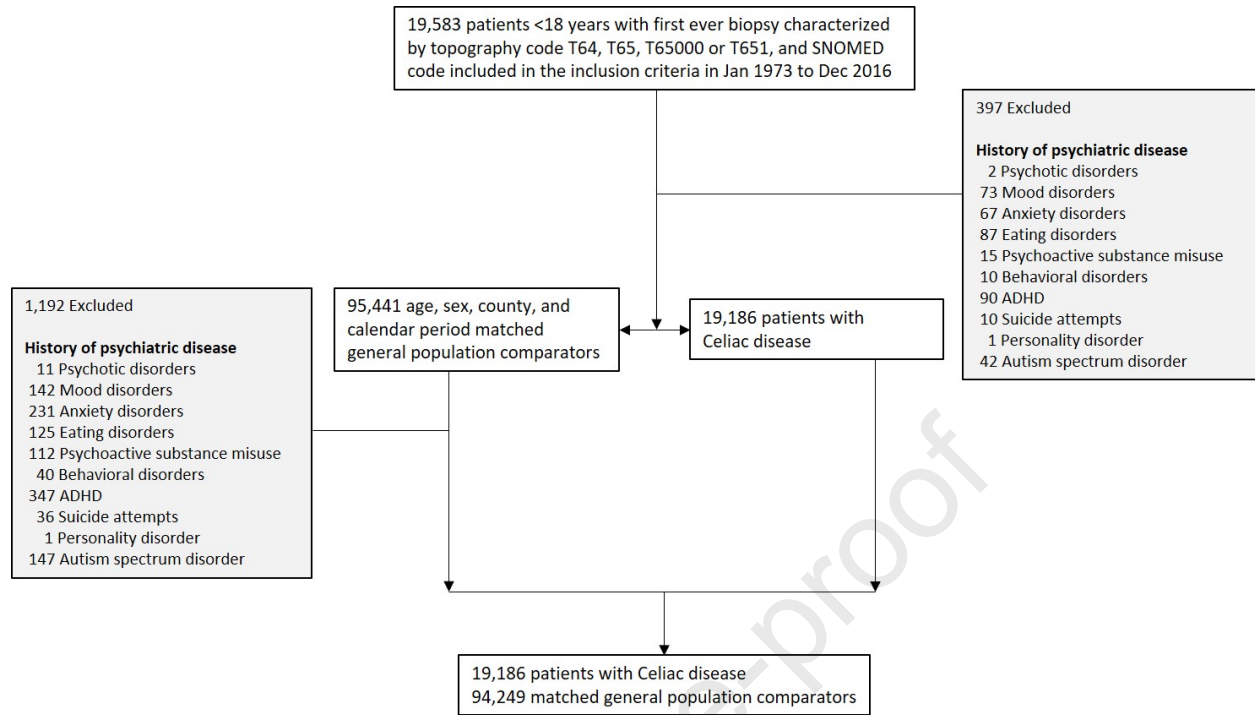
\*Conditioned on matching set (age, sex, county, and calendar period) and further adjusted for highest attained education in parents  
ADHD, Attention Deficit Hyperactivity Disorder

## References

- <sup>1</sup> Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH, Hadjivassiliou M, Kaukinen K, Kelly CP, Leonard JN, Lundin KE, Murray JA, Sanders DS, Walker MM, Zingone F, Ciacci C. The Oslo definitions for coeliac disease and related terms. *Gut*. 2013 Jan;62(1):43–52.
- <sup>2</sup> Ludvigsson JF, Green PH. Clinical management of coeliac disease. *J Intern Med* 2011;269:560-71.
- <sup>3</sup> Lebwohl B, Sanders DS, Green PHR. Coeliac disease. *Lancet* 2018; 391:70-81.
- <sup>4</sup> Mustalahti K, Catassi C, Reunanen A, et al, for the Coeliac EU Cluster, Project Epidemiology. The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. *Ann Med* 2010;42:587–95.
- <sup>5</sup> Siniscalchi M, Iovino P, Tortora R, Forestiero S, Somma A, Capuano L, et al. Fatigue in adult coeliac disease. *Aliment Pharmacol Ther* 2005;22:489- 94.
- <sup>6</sup> Ludvigsson JF, Zingone F, Tomson T, Ekbom A, Ciacci C. Increased risk of epilepsy in biopsy-verified celiac disease: a population-based cohort study. *Neurology* 2012;78:1401-7.
- <sup>7</sup> Lionetti E, Francavilla R, Pavone P, Pavone L, Francavilla T, Pulvirenti A, et al. The neurology of coeliac disease in childhood: what is the evidence? A systematic review and meta-analysis. *Dev Med Child Neurol* 2010;52:700-7.
- <sup>8</sup> Ludvigsson JF, Reutfors J, Osby U, Ekbom A, Montgomery SM. Coeliac disease and risk of mood disorders: a general population-based cohort study. *J Affect Disord* 2007;99:117-26.
- <sup>9</sup> Butwicka A, Lichtenstein P, Frisén L, Almqvist C, Larsson H, Ludvigsson JF. Celiac disease is associated with childhood psychiatric disorders: a population-based study. *J Pediatr* 2017;184:87-93.
- <sup>10</sup> Pynnönen PA, Isometsä ET, Aronen ET, Verkasalo MA, Savilahti E, Aalberg VA. Mental disorders in adolescents with celiac disease. *Psychosomatics* 2004;45:325-35.
- <sup>11</sup> Ludvigsson JF, Reichenberg A, Hultman CM, Murray JA. A nationwide study of the association between celiac disease and the risk of autistic spectrum disorders. *JAMA Psychiatry* 2013;70:1224-30.
- <sup>12</sup> Ludvigsson JF, Brandt L, Montgomery SM, Granath F, Ekbom A. Validation study of villous atrophy and small intestinal inflammation in Swedish biopsy registers. *BMC Gastroenterol*. 2009 Mar 11;9:19.
- <sup>13</sup> Ludvigsson JF, Almqvist C, Bonamy AK, Ljung R, Michaëlsson K, Neovius M, Stephansson O, Ye W. Registers of the Swedish total population and their use in medical research. *Eur J Epidemiol*. 2016 Feb;31(2):125-36.
- <sup>14</sup> Sellgren C, Landén M, Lichtenstein P, Hultman CM, Långström N. Validity of bipolar disorder hospital discharge diagnoses: file review and multiple register linkage in Sweden. *Acta Psychiatr Scand*. 2011 Dec;124(6):447-53.
- <sup>15</sup> Christian Rück, K Johan Larsson, Kristina Lind, Ana Perez-Vigil, Kayoko Isomura, Amir Sariaslan, Paul Lichtenstein, and David Mataix-Cols. Validity and reliability of chronic tic disorder and obsessive-compulsive disorder diagnoses in the Swedish National Patient Register. *BMJ Open*, 22 Jun 2015, 5(6):e007520.
- <sup>16</sup> Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, Persson I, Sundström A, Westerholm B, Rosén M. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf*. 2007 Jul;16(7):726-35.
- <sup>17</sup> Lebwohl B, Granath F, Ekbom A, Smedby KE, Murray JA, Neugut AI, Green PH, Ludvigsson JF. Mucosal healing and risk for lymphoproliferative malignancy in celiac disease: a population-based cohort study. *Ann Intern Med*. 2013 Aug 6;159(3):169-75.
- <sup>18</sup> Lebwohl B, Michaëlsson K, Green PH, Ludvigsson JF. Persistent mucosal damage and risk of fracture in celiac disease. *J Clin Endocrinol Metab*. 2014 Feb;99(2):609-16.
- <sup>19</sup> Smith DF, Gerdes LU. Meta-analysis on anxiety and depression in adult celiac disease. *Acta Psychiatr Scand* 2012;125:189-93.
- <sup>20</sup> Zingone F, Swift GL, Card TR, Sanders DS, Ludvigsson JF, Bai JC. Psychological morbidity of celiac disease: A review of the literature. *United European Gastroenterol J*. 2015 Apr;3(2):136-145.



- <sup>21</sup> Shah S, Akbari M, Vanga R, et al. Patient perception of treatment burden is high in celiac disease compared with other common conditions. *Am J Gastroenterol* 2014;109:1304-11.
- <sup>22</sup> Cadenhead JW, Wolf RL, Lebwohl B, et al. Diminished quality of life among adolescents with coeliac disease using maladaptive eating behaviours to manage a gluten-free diet: a cross-sectional, mixed-methods study. *J Hum Nutr Diet* 2019;32:311-320.
- <sup>23</sup> Wolf RL, Lebwohl B, Lee AR, et al. Hypervigilance to a Gluten-Free Diet and Decreased Quality of Life in Teenagers and Adults with Celiac Disease. *Dig Dis Sci* 2018;63:1438-1448.
- <sup>24</sup> Sainsbury K, Marques MM. The relationship between gluten free diet adherence and depressive symptoms in adults with coeliac disease: A systematic review with meta-analysis. *Appetite*. 2018 Jan 1;120:578-588.
- <sup>25</sup> Mårild K, Størdal K, Bulik CM, Rewers M, Ekbohm A, Liu E, Ludvigsson JF. Celiac Disease and Anorexia Nervosa: A Nationwide Study. *Pediatrics*. 2017 May;139(5).
- <sup>26</sup> Blackett JW, Shamsunder M, Reilly NR, Green PHR, Lebwohl B. Characteristics and comorbidities of inpatients without celiac disease on a gluten-free diet. *Eur J Gastroenterol Hepatol*. 2018 Apr;30(4):477-483.
- <sup>27</sup> Nachman F, Planzer de Campo M, Gonzalez A, et al. Long-term deterioration of quality of life in adult patients with celiac disease is associated with treatment noncompliance. *Dig Liver Dis* 2010;42:685-91.



**Supplementary Table S1** 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

**Supplementary Table S2** ICD-codes used for outcomes

Comorbidity	ICD8 (1969-1986)	ICD9 (1987-1996)	ICD10 (1997-)
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

**Supplementary Table S3** ATC-codes used for outcomes

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

**Supplementary Table S4** Risk of any psychiatric disorder overall and by subgroups in patients with Celiac disease and matched general population comparators, with follow-up ending at age 18 years.

Group	N (%)		N events (%)		Incidence rate (95% CI) per 1000 PY		HR* (95%CI)
	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	
<b>Overall</b>	19 186 (100%)	94 249 (100%)	1 747 (9.1%)	6 861 (7.3%)	9.9 (9.4-10.4)	7.9 (7.7-8.1)	1.26 (1.20-1.33)
Follow-up							
0-<1y	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-<5y	18 180 (94.8%)	89 819 (95.3%)	492 (2.7%)	1 764 (2.0%)	7.7 (7.0-8.4)	5.6 (5.3-5.8)	1.40 (1.26-1.55)
5-<10y	13 656 (71.2%)	67 406 (71.5%)	525 (3.8%)	1 994 (3.0%)	9.7 (8.9-10.5)	7.5 (7.1-7.8)	1.31 (1.19-1.45)
10-<15y	8 467 (44.1%)	41 719 (44.3%)	456 (5.4%)	2 038 (4.9%)	14.1 (12.8-15.3)	12.7 (12.2-13.3)	1.10 (0.99-1.22)
15-<20y	4 671 (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%)	1 094 (9.1%)	4 463 (7.5%)	9.8 (9.2-10.4)	8.1 (7.9-8.4)	1.22 (1.14-1.30)
Boys	7 110 (37.1%)	34 891 (37.0%)	653 (9.2%)	2 398 (6.9%)	10.0 (9.2-10.8)	7.4 (7.1-7.7)	1.35 (1.23-1.47)
Age							
<2y	5 694 (29.7%)	27 579 (29.3%)	526 (9.2%)	2 210 (8.0%)	6.2 (5.7-6.7)	5.5 (5.2-5.7)	1.10 (0.99-1.21)
2y - <6y	4 545 (23.7%)	23 460 (24.9%)	387 (8.5%)	1 726 (7.4%)	8.4 (7.5-9.2)	7.2 (6.9-7.5)	1.16 (1.03-1.30)
6y - <11y	4 244 (22.1%)	20 944 (22.2%)	463 (10.9%)	1 677 (8.0%)	15.2 (13.9-16.6)	11.1 (10.6-11.6)	1.40 (1.25-1.55)
11y - <16y	3 508 (18.3%)	17 025 (18.1%)	324 (9.2%)	1 157 (6.8%)	22.6 (20.1-25.0)	16.3 (15.4-17.3)	1.41 (1.24-1.60)
16 - <18y	1 195 (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	1 909 (9.9%)	9 504 (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	5 458 (28.4%)	27 113 (28.8%)	506 (9.3%)	2 130 (7.9%)	7.0 (6.4-7.6)	5.9 (5.7-6.2)	1.17 (1.06-1.29)
2000-2009	7 643 (39.8%)	37 524 (39.8%)	872 (11.4%)	3 461 (9.2%)	14.1 (13.2-15.1)	11.4 (11.0-11.7)	1.26 (1.17-1.36)
2010-2016	4 176 (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							
1973-1989	1 909 (9.9%)	9 504 (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	5 458 (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	7 643 (39.8%)	37 524 (39.8%)	327 (4.3%)	1 206 (3.2%)	9.7 (8.7-10.8)	7.3 (6.8-7.7)	1.37 (1.21-1.55)
2010-2011	1 707 (8.9%)	8 300 (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%)	1 718 (9.1%)	6 643 (7.4%)	9.8 (9.4-10.3)	7.8 (7.6-8.0)	1.25 (1.19-1.32)
Other	348 (1.8%)	4 236 (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							
≤9 years	659 (3.4%)	4 333 (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 years	8 371 (43.6%)	40 792 (43.3%)	872 (10.4%)	3 411 (8.4%)	10.6 (9.9-11.3)	8.7 (8.4-9.0)	1.24 (1.13-1.36)
>12 years	10 136 (52.8%)	48 844 (51.8%)	808 (8.0%)	3 097 (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	2 505 (13.1%)	12 627 (13.4%)	348 (13.9%)	1 487 (11.8%)	20.7 (18.5-22.9)	17.3 (16.4-18.2)	1.36 (1.10-1.67)

\*Conditioned on matching set (age, sex, county, and calendar period) and further adjusted for highest attained education in parents

**Supplementary Table S5** Analysis limited to those with available follow-up starting at age 18 years: baseline characteristics of study cohort

<b>Characteristic</b>	<b>Celiac disease (n=11,207)</b>	<b>Matched comparators (n=49,252)</b>
Girls, no. (%)	6 958 (62.1%)	30 266 (61.5%)
Boys, no (%)	4 249 (37.9%)	18 986 (38.5%)
<b>Age</b>		
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, min-max	18.0-18.0	18.0-18.0
<b>Country of birth, no (%)</b>		
Nordic country	11 025 (98.4%)	47 181 (95.8%)
Other	182 (1.6%)	2 070 (4.2%)
Missing	(0.0%)	1 (0.0%)
<b>Highest attained level of education in parents, n (%)</b>		
≤9 years	476 (4.2%)	2 524 (5.1%)
10-12 years	5 365 (47.9%)	23 098 (46.9%)
>12 years	5 360 (47.8%)	23 581 (47.9%)
Missing	6 (0.1%)	49 (0.1%)
<b>Start year of follow-up</b>		
1973-1989	83 (0.7%)	385 (0.8%)
1990-1999	782 (7.0%)	3 744 (7.6%)
2000-2009	4 985 (44.5%)	22 484 (45.7%)
2010-2016	5 357 (47.8%)	22 639 (46.0%)
<b>Psychiatric diagnoses in family before index date (%)</b>		
Parents	2 063 (18.4%)	9 237 (18.8%)
Siblings	962 (8.6%)	4 066 (8.3%)
Any of parents or siblings	2 712 (24.2%)	11 997 (24.4%)
<b>Follow-up, years</b>		
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, min-max	0.0-35.4	0.0-35.7

**Supplementary Table S6** Analysis limited to those with available follow-up starting at age 18 years: risk of any psychiatric disorder overall and by subgroups in patients with celiac disease and matched general population comparators

Group	N (%)		N events (%)		Incidence rate (95% CI) per 1000 PY		HR* (95%CI)
	Celiac disease	Comparators	celiac disease	Comparators	Celiac disease	Comparators	
<b>Overall</b>	11 207 (%)	49 252 (%)	1 427 (12.7%)	5 833 (11.8%)	17.2 (16.3-18.1)	15.4 (15.0-15.8)	1.11 (1.04-1.17)
Follow-up							
0-<1y	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-<5y	10 405 (92.8%)	45 959 (93.3%)	680 (6.5%)	2 662 (5.8%)	19.4 (18.0-20.9)	17.0 (16.4-17.7)	1.14 (1.04-1.24)
5-<10y	7 024 (62.7%)	31 802 (64.6%)	349 (5.0%)	1 497 (4.7%)	14.8 (13.2-16.3)	13.8 (13.1-14.5)	1.09 (0.96-1.23)
10-<15y	2 870 (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-<20y	1 003 (8.9%)	4 895 (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)
≥20y	355 (3.2%)	1 815 (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	6 958 (62.1%)	30 266 (61.5%)	933 (13.4%)	3 901 (12.9%)	18.2 (17.0-19.3)	17.0 (16.4-17.5)	1.06 (0.99-1.15)
Boys	4 249 (37.9%)	18 986 (38.5%)	494 (11.6%)	1 932 (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%)	3 744 (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	4 985 (44.5%)	22 484 (45.7%)	782 (15.7%)	3 415 (15.2%)	16.6 (15.4-17.7)	15.9 (15.4-16.5)	1.05 (0.97-1.14)
2010-2016	5 357 (47.8%)	22 639 (46.0%)	466 (8.7%)	1 807 (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							
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%)	3 744 (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	4 985 (44.5%)	22 484 (45.7%)	447 (9.0%)	1 868 (8.3%)	19.0 (17.3-20.8)	17.6 (16.8-18.4)	1.08 (0.97-1.20)
2010-2011	2 078 (18.5%)	8 954 (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%)	1 403 (12.7%)	5 575 (11.8%)	17.2 (16.3-18.0)	15.3 (14.9-15.7)	1.11 (1.04-1.18)
Other	182 (1.6%)	2 070 (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							
≤9 years	476 (4.2%)	2 524 (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 years	5 365 (47.9%)	23 098 (46.9%)	732 (13.6%)	2 978 (12.9%)	18.0 (16.7-19.3)	16.4 (15.8-17.0)	1.08 (0.98-1.19)
>12 years	5 360 (47.8%)	23 581 (47.9%)	611 (11.4%)	2 447 (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	2 712 (24.2%)	11 997 (24.4%)	507 (18.7%)	1 947 (16.2%)	32.3 (29.5-35.1)	26.5 (25.3-27.6)	1.25 (1.08-1.46)

\*Conditioned on matching set (age, sex, county, and calendar period) and further adjusted for highest attained education in parents

**Supplementary Table S7** Analysis limited to those with available follow-up starting at age 18 years: risk of psychiatric disorders in patients with celiac disease and matched general population comparators (n celiac disease/n comparators = 11,207/49,252)

Group	N events (%)		Time at risk (years)		Incidence rate (95% CI) per 1000 PY		HR* (95%CI)
	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	
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%)	2 334 (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%)	3 401 (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%)	1 660 (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	1 427 (12.7%)	5 833 (11.8%)	83 030	378 378	17.2 (16.3-18.1)	15.4 (15.0-15.8)	1.11 (1.04-1.17)

\*Conditioned on matching set (age, sex, county, and calendar period) and further adjusted for highest attained education in parents

ADHD, Attention Deficit Hyperactivity Disorder

**Supplementary Table S8: Comparison of celiac disease patients to siblings: baseline characteristics of study cohort**

<b>Characteristic</b>	<b>celiac disease (n=13,015)</b>	<b>Matched comparators (n=18,024)</b>
Girls, no. (%)	8 157 (62.7%)	8 831 (49.0%)
Boys, no (%)	4 858 (37.3%)	9 193 (51.0%)
<b>Age</b>		
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, min-max	0.0-18.0	0.0-18.0
<b>Categories, no. (%)</b>		
<2y	3 086 (23.7%)	1 771 (9.8%)
2y - <6y	3 400 (26.1%)	5 769 (32.0%)
6y - <11y	3 419 (26.3%)	5 628 (31.2%)
11y - <16y	2 518 (19.3%)	3 904 (21.7%)
16 - <18y	592 (4.5%)	952 (5.3%)
<b>Country of birth, no (%)</b>		
Nordic country	12 831 (98.6%)	17 530 (97.3%)
Other	183 (1.4%)	493 (2.7%)
Missing	1 (0.0%)	1 (0.0%)
<b>Highest attained level of education in parents, n (%)</b>		
≤9 years	404 (3.1%)	739 (4.1%)
10-12 years	5 387 (41.4%)	7 515 (41.7%)
>12 years	7 218 (55.5%)	9 760 (54.2%)
Missing	6 (0.0%)	10 (0.1%)
<b>Start year of follow-up</b>		
1973-1989	1 173 (9.0%)	1 643 (9.1%)
1990-1999	3 470 (26.7%)	4 924 (27.3%)
2000-2009	5 365 (41.2%)	7 374 (40.9%)
2010-2016	3 007 (23.1%)	4 083 (22.7%)
<b>Follow-up, years</b>		
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, min-max	0.0-39.0	0.0-44.0



**Supplementary Table S9: Comparison of celiac disease patients to siblings: risk of any psychiatric disorder overall and by subgroups in patients with celiac disease and matched sibling comparators**

Group	N (%)		N events (%)		Incidence rate (95% CI) per 1000 PY		HR* (95%CI)
	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	
<b>Overall</b>	13 015 (100%)	18 024 (100%)	1 994 (15.3%)	2 411 (13.4%)	11.7 (11.2-12.2)	10.4 (10.0-10.8)	1.12 (1.05-1.20)
Follow-up							
0-<1y	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-<5y	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-<10y	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-<15y	7 591 (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-<20y	4 731 (36.4%)	6 376 (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)
≥20y	3 027 (23.3%)	4 100 (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	8 157 (62.7%)	8 831 (49.0%)	1 259 (15.4%)	1 267 (14.3%)	11.8 (11.2-12.5)	11.3 (10.6-11.9)	1.11 (0.99-1.24)
Boys	4 858 (37.3%)	9 193 (51.0%)	735 (15.1%)	1 144 (12.4%)	11.4 (10.6-12.2)	9.6 (9.1-10.2)	1.27 (1.09-1.47)
Age							
<2y	3 086 (23.7%)	1 771 (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)
2y - <6y	3 400 (26.1%)	5 769 (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)
6y - <11y	3 419 (26.3%)	5 628 (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)
11y - <16y	2 518 (19.3%)	3 904 (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 - <18y	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	1 173 (9.0%)	1 643 (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	3 470 (26.7%)	4 924 (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	5 365 (41.2%)	7 374 (40.9%)	878 (16.4%)	1 058 (14.3%)	15.2 (14.2-16.2)	13.9 (13.0-14.7)	1.08 (0.98-1.20)
2010-2016	3 007 (23.1%)	4 083 (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							
1973-1989	1 173 (9.0%)	1 643 (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	3 470 (26.7%)	4 924 (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	5 365 (41.2%)	7 374 (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	1 207 (9.3%)	1 607 (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%)	1 972 (15.4%)	2 362 (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							
≤9 years	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 years	5 387 (41.4%)	7 515 (41.7%)	956 (17.7%)	1 203 (16.0%)	12.4 (11.6-13.1)	11.4 (10.7-12.0)	1.11 (1.00-1.22)
>12 years	7 218 (55.5%)	9 760 (54.2%)	953 (13.2%)	1 061 (10.9%)	11.0 (10.3-11.7)	9.3 (8.8-9.9)	1.13 (1.02-1.25)

\*Conditioned on matching set (within family) and further adjusted for age and sex

**Supplementary Table S10 Comparison of celiac disease patients to siblings:** risk of psychiatric disorders in patients with celiac disease and matched sibling comparators

(n celiac disease/n comparators = 13,015 /18,024)

Group	N events (%)		Time at risk (years)		Incidence rate (95% CI) per 1000 PY		HR* (95%CI)
	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	
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	1 994 (15.3%)	2 411 (13.4%)	170 810	231 138	11.7 (11.2-12.2)	10.4 (10.0-10.8)	1.12 (1.05-1.20)

\*Conditioned on matching set (within family) and further adjusted for age and sex

ADHD, Attention Deficit Hyperactivity Disorder

**Supplementary Table S11:** Characteristics of children with celiac disease who underwent follow-up biopsy

Characteristic	Mucosal healing (n=2,071)	Persistent villus atrophy (n=533)
Girls, no. (%)	1 280 (61.8%)	330 (61.9%)
Boys, no (%)	791 (38.2%)	203 (38.1%)
<b>Age</b>		
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, min-max	1.0-18.0	1.1-18.0
<b>Categories, no. (%)</b>		
<2y	82 (4.0%)	39 (7.3%)
2y - <6y	1 084 (52.3%)	291 (54.6%)
6y - <11y	415 (20.0%)	91 (17.1%)
11y - <16y	372 (18.0%)	77 (14.4%)
16 - <18y	118 (5.7%)	35 (6.6%)
<b>Country of birth, no (%)</b>		
Nordic country	2 044 (98.7%)	525 (98.5%)
Other	27 (1.3%)	8 (1.5%)
<b>Highest attained level of education in parents, n (%)</b>		
≤9 years	67 (3.2%)	37 (6.9%)
10-12 years	950 (45.9%)	272 (51.0%)
>12 years	1 054 (50.9%)	223 (41.8%)
Missing	0	1 (0.2%)
<b>Start year of follow-up</b>		
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%)
<b>Psychiatric diagnoses in family before index date (%)</b>		
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%)
<b>Duration since diagnosis, years</b>		
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, min-max	0.5-5.0	0.5-5.0
<b>Follow-up, years</b>		
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, min-max	0.0-34.0	0.0-39.0

**Supplementary Table S12** Risk of any psychiatric disorder overall and by subgroups in patients with Celiac disease and mucosal healing vs persistent villous atrophy (VA)

Group	N (%)		N events (%)		Incidence rate (95% CI) per 1000 PY	
	Mucosal healing	Persistent VA	Mucosal healing	Persistent VA	Mucosal healing	Persistent VA
<b>Overall</b>	2 071 (100.0%)	533 (100.0%)	375 (18.1%)	90 (16.9%)	12.6 (11.3-13.9)	9.8 (7.7-11.8)
<b>Follow-up</b>						
0-<1y	2 071 (100.0%)	533 (100.0%)	19 (0.9%)	3 (0.6%)	9.2 (5.1-13.4)	5.7 (0.0-12.1)
1-<5y	2 045 (98.7%)	527 (98.9%)	70 (3.4%)	10 (1.9%)	9.0 (6.9-11.1)	4.8 (1.8-7.8)
5-<10y	1 845 (89.1%)	500 (93.8%)	94 (5.1%)	19 (3.8%)	11.1 (8.9-13.4)	8.2 (4.5-11.9)
10-<15y	1 495 (72.2%)	422 (79.2%)	104 (7.0%)	27 (6.4%)	17.5 (14.2-20.9)	14.5 (9.1-20.0)
15-<20y	886 (42.8%)	325 (61.0%)	60 (6.8%)	23 (7.1%)	17.4 (13.0-21.8)	17.0 (10.1-24.4)
≥20y	517 (25.0%)	222 (41.7%)	28 (5.4%)	8 (3.6%)	13.7 (8.7-18.8)	7.3 (2.2-12.3)
<b>Sex</b>						
Girls	1 280 (61.8%)	330 (61.9%)	220 (17.2%)	59 (17.9%)	11.9 (10.4-13.5)	10.4 (7.7-13.0)
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)
<b>Age</b>						
<2y	82 (4.0%)	39 (7.3%)	16 (19.5%)	5 (12.8%)	9.3 (4.7-13.8)	5.5 (0.7-10.3)
2y - <6y	1 084 (52.3%)	291 (54.6%)	176 (16.2%)	54 (18.6%)	9.5 (8.1-10.9)	9.4 (6.9-11.9)
6y - <11y	415 (20.0%)	91 (17.1%)	73 (17.6%)	14 (15.4%)	15.1 (11.7-18.6)	11.0 (5.2-16.7)
11y - <16y	372 (18.0%)	77 (14.4%)	84 (22.6%)	10 (13.0%)	23.7 (18.6-28.7)	11.0 (4.2-17.7)
16 - <18y	118 (5.7%)	35 (6.6%)	26 (22.0%)	7 (20.0%)	23.2 (14.3-32.1)	18.0 (4.7-31.4)
<b>Year</b>						
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)
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)
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)
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)
<b>Year – First 5 years of follow-up</b>						
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)
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)
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)
<b>Country of birth</b>						
Nordic	2 044 (98.7%)	525 (98.5%)	369 (18.1%)	90 (17.1%)	12.5 (11.3-13.8)	9.9 (7.8-11.9)
Other	27 (1.3%)	8 (1.5%)	6 (22.2%)	0	21.7 (4.3-39.1)	0
<b>Level of education</b>						
≤9 years	67 (3.2%)	37 (6.9%)	14 (20.9%)	9 (24.3%)	13.3 (6.3-20.3)	14.6 (5.1-24.2)
10-12 years	950 (45.9%)	272 (51.0%)	194 (20.4%)	47 (17.3%)	13.5 (11.6-15.4)	9.3 (6.6-11.9)
>12 years	1 054 (50.9%)	223 (41.8%)	167 (15.8%)	34 (15.2%)	11.7 (9.9-13.5)	9.6 (6.4-12.8)
<b>Psychiatric diagnoses in family</b>						
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)

\*Adjusted for age, sex, start year of follow-up, duration since diagnosis, highest attained education in parents, and Nordic country of birth

**Supplementary Table S13:** Outcomes restricted to those with a psychiatric medication prescription (July 2006-December 2016): baseline characteristics of study cohort

<b>Characteristic</b>	<b>Celiac disease (n=6,815)</b>	<b>Matched comparators (n=32,459)</b>
Girls, no. (%)	4 361 (64.0%)	20 827 (64.2%)
Boys, no (%)	2 454 (36.0%)	11 632 (35.8%)
<b>Age</b>		
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, min-max	0.0-18.0	0.0-18.0
<b>Categories, no. (%)</b>		
<2y	493 (7.2%)	2 440 (7.5%)
2y - <6y	1 851 (27.2%)	9 100 (28.0%)
6y - <11y	2 051 (30.1%)	9 896 (30.5%)
11y - <16y	1 818 (26.7%)	8 538 (26.3%)
16 - <18y	602 (8.8%)	2 485 (7.7%)
<b>Country of birth, no (%)</b>		
Nordic country	6 608 (97.0%)	30 230 (93.1%)
Other	207 (3.0%)	2 226 (6.9%)
Missing	0	3 (0.0%)
<b>Highest attained level of education in parents, n (%)</b>		
≤9 years	150 (2.2%)	1 312 (4.0%)
10-12 years	2 431 (35.7%)	12 409 (38.2%)
>12 years	4 224 (62.0%)	18 624 (57.4%)
Missing	10 (0.1%)	114 (0.4%)
<b>Start year of follow-up</b>		
2006 (July) -2009	2 761 (40.5%)	13 282 (40.9%)
2010-2012	2 327 (34.1%)	11 112 (34.2%)
2013-2016	1 727 (25.3%)	8 065 (24.8%)
<b>Psychiatric diagnoses in family before index date (%)</b>		
Parents	1 240 (18.2%)	6 099 (18.8%)
Siblings	222 (3.3%)	1 095 (3.4%)
Any of parents or siblings	1 400 (20.5%)	6 818 (21.0%)
<b>Follow-up, years</b>		
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, min-max	0.0-10.5	0.0-10.5

**Supplementary Table S14: 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**

Group	N (%)		N events (%)		Incidence rate (95% CI) per 1000 PY		HR* (95%CI)
	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	
<b>Overall</b>	6 815 (100%)	32 459 (100%)	1 016 (14.9%)	3 757 (11.6%)	26.9 (25.3-28.6)	20.5 (19.8-21.2)	1.34 (1.24-1.43)
Follow-up							
0-<1y	6 815 (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-<5y	6 424 (94.3%)	30 817 (94.9%)	535 (8.3%)	1 903 (6.2%)	25.5 (23.3-27.7)	18.7 (17.9-19.6)	1.38 (1.25-1.53)
5-<10y	3 898 (57.2%)	19 081 (58.8%)	326 (8.4%)	1 423 (7.5%)	32.3 (28.8-35.9)	28.7 (27.2-30.2)	1.15 (1.01-1.30)
Sex							
Girls	4 361 (64.0%)	20 827 (64.2%)	663 (15.2%)	2 503 (12.0%)	27.6 (25.5-29.7)	21.3 (20.5-22.2)	1.30 (1.19-1.42)
Boys	2 454 (36.0%)	11 632 (35.8%)	353 (14.4%)	1 254 (10.8%)	25.8 (23.1-28.5)	19.0 (17.9-20.0)	1.42 (1.26-1.60)
Age							
<2y	493 (7.2%)	2 440 (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)
2y - <6y	1 851 (27.2%)	9 100 (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)
6y - <11y	2 051 (30.1%)	9 896 (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)
11y - <16y	1 818 (26.7%)	8 538 (26.3%)	410 (22.6%)	1 607 (18.8%)	41.8 (37.7-45.8)	33.5 (31.9-35.2)	1.28 (1.14-1.43)
16 - <18y	602 (8.8%)	2 485 (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	2 761 (40.5%)	13 282 (40.9%)	582 (21.1%)	2 291 (17.2%)	26.8 (24.7-29.0)	21.7 (20.8-22.5)	1.27 (1.15-1.39)
2010-2012	2 327 (34.1%)	11 112 (34.2%)	314 (13.5%)	1 119 (10.1%)	25.9 (23.0-28.7)	19.0 (17.9-20.1)	1.37 (1.21-1.56)
2013-2016	1 727 (25.3%)	8 065 (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	6 608 (97.0%)	30 230 (93.1%)	987 (14.9%)	3 521 (11.6%)	26.8 (25.2-28.5)	20.5 (19.8-21.1)	1.32 (1.22-1.42)
Other	207 (3.0%)	2 226 (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							
≤9 years	150 (2.2%)	1 312 (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 years	2 431 (35.7%)	12 409 (38.2%)	449 (18.5%)	1 743 (14.0%)	33.1 (30.0-36.1)	24.4 (23.3-25.6)	1.23 (1.08-1.41)
>12 years	4 224 (62.0%)	18 624 (57.4%)	537 (12.7%)	1 813 (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	1 400 (20.5%)	6 818 (21.0%)	292 (20.9%)	1 149 (16.9%)	42.4 (37.5-47.2)	33.0 (31.1-34.9)	1.46 (1.18-1.80)

\*Conditioned on matching set (age, sex, county, and calendar period) and further adjusted for highest attained education in parents

**Supplementary Table S15: 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**  
(n celiac disease/n comparators = 6,815 /32,459)

Group	N events (%)		Time at risk (years)		Incidence rate (95% CI) per 1000 PY		HR* (95%CI)
	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	
Any psychiatric disorder	1 016 (14.9%)	3 757 (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%)	3 070 (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%)	3 526 (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%)	2 610 (8.0%)	38 735	186 995	18.4 (17.1-19.8)	14.0 (13.4-14.5)	1.34 (1.23-1.46)

\*Conditioned on matching set (age, sex, county, and calendar period) and further adjusted for highest attained education in parents

Journal Pre-proof



## **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 risks 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.