

Letter to the Editor

Celiac disease confers a 1.6-fold increased risk of asthma: A nationwide population-based cohort study*To the Editor:*

Celiac disease (CD) is a chronic immune-mediated disease that occurs in about 1% to 2% of individuals in Western Europe. Although the classic form of CD involves gastrointestinal symptoms, it has become increasingly recognized that extragastrointestinal symptoms and complications occur.¹ Asthma is a respiratory disorder characterized by airflow obstruction and inflammation with a prevalence of 6% to 8% in Swedish children and adults.² Most earlier research has indicated a positive relationship between CD and asthma or airflow obstruction, but relative risk estimates have varied widely from 1.0 to 7.26, and studies have generally suffered from small numbers.³ Through the personal identity number,⁴ we matched nationwide data on small intestinal biopsies with the Swedish National Patient Register (containing both inpatient care and hospital outpatient care) to examine the risk of asthma in patients with CD. Through linkages with the Medical Birth Register and the Prescribed Drug Register, we also had access to information on education, cesarean section, body mass index, smoking, and asthma medication in a subcohort.

The exposure of this cohort study was CD according to small intestinal biopsy (defined as villous atrophy, histopathology stage Marsh 3; see this article's [Table E1](#) in the Online Repository at www.jacionline.org). We originally collected data on 351,403 biopsy reports representing 287,586 unique individuals. Biopsies took place from 1969 to 2008. Details on biopsy data collection have been published elsewhere.^{1,5} In all, this study was based on

28,281 individuals with CD and 140,295 general population reference individuals matched for sex, age, and calendar period of study entry. We defined asthma according to relevant International Classification of Disease (ICD) codes in the Swedish National Patient Register (see this article's [Table E2](#) in the Online Repository at www.jacionline.org). Cox regression estimated hazard ratios (HRs) for subsequent asthma (excluding patients with a diagnosis of asthma before study entry), whereas we used conditional logistic regression to examine the risk of previous asthma in CD. The study was approved by the Regional Ethical Review Board of Karolinska Institutet.

The median age at first asthma diagnosis was 15 years in patients with CD and 16 years in reference individuals, with a median duration from study entry (and diagnosis of CD) to asthma of 6 years in both cohorts. During follow-up, 1118 individuals with CD and 3379 reference individuals had a subsequent diagnosis of asthma. Detailed results are given in this article's [Table E3](#) in the Online Repository at www.jacionline.org.

The risk of asthma was increased in CD (HR, 1.61; 95% CI, 1.50-1.72; [Table I](#)), with a risk increase remaining 5 years after CD diagnosis. This risk estimate did not change after adjusting for the covariates type 1 diabetes and education. Risk estimates did not differ by sex or calendar period ([Table I](#)). When we required individuals to have had an asthma diagnosis on at least 2 occasions, the HR was 1.77 (95% CI, 1.62-1.94). Adjusting for smoking, body mass index, and cesarean section, CD was still positively associated with asthma. Restricting our outcome to a diagnosis of asthma (1) with a record of asthma medication, (2) with at least 1 more atopic disorder (allergic rhinitis, allergic conjunctivitis, or eczema), and (3) where study participants had no previous

TABLE I. CD and risk of asthma and other atopic disorders

Subgroup	Observed events, n	Expected events, n	HR; 95% CI	P value	Absolute risk/ 100,000 PYAR	Excess risk/ 100,000 PYAR	Attributable percentage
Asthma							
All	1118	696	1.61; 1.50-1.72	<.001	390	147	38
Year <1	172	86	2.01; 1.69-2.39	<.001	617	310	50
Year 1-4.99	332	236	1.41; 1.25-1.59	<.001	335	97	29
Year 5+	614	375	1.64; 1.49-1.79	<.001	384	149	39
Sex							
Male	438	261	1.68; 1.51-1.87	<.001	410	166	40
Female	680	435	1.56; 1.43-1.70	<.001	378	136	36
Age							
<20 y	711	429	1.66; 1.52-1.80	<.001	560	222	40
20-39 y	118	65	1.80; 1.47-2.22	<.001	222	99	45
40-59 y	177	108	1.64; 1.39-1.94	<.001	263	103	39
60+ y	112	96	1.17; 0.95-1.44	.148	285	41	14
Calendar period							
1989 and before	194	124	1.56; 1.33-1.84	<.001	243	88	36
1990-1999	586	347	1.69; 1.54-1.85	<.001	407	166	41
2000 and after	338	224	1.51; 1.34-1.70	<.001	538	181	34
Other atopic disease							
Allergic conjunctivitis	228	132	1.72; 1.48-2.00	<.001	77	32	42
Allergic rhinitis	816	475	1.72; 1.59-1.86	<.001	277	116	42
Eczema	532	302	1.76; 1.60-1.94	<.001	180	78	43

PYAR, Person-years at risk.

Reference is general population comparison cohort.

diagnosis of sarcoidosis, tuberculosis, or pneumonia did not change the HRs. Individuals with CD were also at a 1.7-fold increased risk of allergic conjunctivitis, allergic rhinitis, and eczema.

There was also a positive association between CD and asthma before the CD diagnosis in the entire study population (odds ratio, 1.44; 95% CI, 1.34-1.56).

This is the first large population-based study of asthma in patients with biopsy-verified CD. We found a small but statistically significant increased risk of asthma in CD both before and after diagnosis. We used biopsy data to ascertain CD. This may explain why we found lower risk estimates for asthma than many other studies using inpatient data on CD.³ Biopsy data with villous atrophy has a high sensitivity for diagnosed CD as well as a high specificity.

In CD, gluten occurring in wheat, barley, and rye is deamidated by transglutaminase 2 and then presented in the form of peptides to T cells by antigen-presenting cells in the gut. Activated CD4⁺ T cells produce mainly T_H1 cytokines, including IFN- γ , whereas asthma has a T_H2-type cytokine profile. Regulatory T (Treg) cells, both so-called “natural” forkhead box protein 3⁺ Treg cells and induced, IL-10 producing Treg cells, have been implicated in the control of T_H2 as well as T_H1 responses. However, there is evidence that the Treg-cell function is deficient in patients with allergic and asthmatic disease.⁶

The positive association between CD and asthma may be a result of malnutrition, because some 60% to 70% of patients with CD have low levels of 25-(OH) vitamin D,⁷ often several years after diagnosis.⁸ Vitamin D affects immune cells, in particular Treg cells, through direct effects of calcitriol on effector T cells, such as inhibition of proliferation and IL-2 production, or through a Treg-cell-promoting effect of calcitriol on T cells, either directly or indirectly via dendritic cells.⁹ Therefore, vitamin D deficiency as seen in CD could lead to a reduced suppressive capacity of Treg cells, and the resulting inability to control T-cell responses could contribute to the development of asthma. Alternative explanations for the positive association between CD and asthma include shared genetics and high antioxidant levels. Of note, shared risk factors are consistent with our findings that there was a positive association between CD and asthma, also before CD diagnosis.

This study has several limitations. We had no data on spirometry, IgE levels, or nitric oxide levels in patients with asthma. In addition, we had no information on dietary adherence in patients with CD and thus cannot rule out that a gluten-free diet reduces the excess risk of asthma in patients with CD who comply with this dietary recommendation.

In conclusion, this study found a positive association between CD and asthma. We propose that this association may be a result of vitamin D deficiency and subsequently insufficient Treg-cell capacity, or shared risk factors.

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MAIN FINDINGS: SUMMARY

During follow-up, 1118 individuals with CD and 3379 reference individuals developed asthma. Hence, patients with CD were at increased risk of subsequent asthma (HR, 1.61; 95% CI, 1.50-1.72). The absolute risk of asthma in patients with CD was 390 per 100,000 person-years with an excess risk of 147 per 100,000.

Risk estimates for asthma did not change with adjustment for type 1 diabetes or education or in a subset of participants with adjustment for smoking, body mass index, or cesarean section. Nor did risk estimates change when we restricted our outcome to those with both a diagnosis of asthma and a record of asthma medication, or asthma plus at least 1 more atopic disorder (allergic rhinitis, conjunctivitis, or eczema).

In this study, a previous asthma diagnosis increased the risk of having a later CD diagnosis (odds ratio, 1.44; 95% CI, 1.34-1.56).

SUBANALYSES

The following 2 subanalyses were not based on the complete dataset:

- CD-asthma taking smoking and body mass index into account: women with CD, $n = 2485$; reference women, $n = 11,937$.
- CD-asthma, taking cesarean section into account: we had data on delivery mode in 12,228 patients with CD (both males and females) and 59,304 reference individuals.

ATC CODES IN THE SWEDISH PRESCRIBED DRUG REGISTER

We examined the risk of having a diagnosis of asthma and a record of medication for asthma according to relevant *Anatomic Therapeutic Chemical classification system* (ATC) codes. We then used the following ATC codes:

- Inhaled β_2 -agonist: R03AC
- Inhaled corticosteroids including those with long-acting β_2 -agonists: R03BA and R03AK
- Leukotriene receptor antagonists: R03DC

The Swedish Prescribed Drug Register contains all prescribed drugs dispensed to Swedish residents at pharmacies in Sweden

since July 1, 2005, and has an almost 99% coverage excluding drugs in ambulatory care.

ICD CODES

The following International Classification of Disease (ICD) codes were used in this study:

- Asthma: ICD-7, 241; ICD-8 and ICD-9, 493; ICD-10, J45 and J46.
- Sarcoidosis: ICD-7, 138.0; ICD-8, 135; ICD-9, 135; ICD-10, D86.
- Tuberculosis: ICD-7, 001-019; ICD-8, 010-018; ICD-9, 010-019; ICD-10, A15-19.
- Pneumonia—not specified: ICD-7, 490, 491.10, and 491.19; ICD-8, 486; ICD-9, 486; ICD-10, J15.
- Pneumonia caused by pneumococci: ICD-8, 481; ICD-9, 481; ICD-10, J13.
- Allergic conjunctivitis: ICD-7, 370; ICD-8, 372; ICD-9, 372; ICD-10, H10.1.
- Allergic rhinitis: ICD-7, 240; ICD-8, 507; ICD-9, 477; ICD-10, J30.
- Eczema: ICD-7, 701; ICD-8, 691; ICD-9, 691; ICD-10, L20.
- Diabetes: Earlier versions of the Swedish ICD (7-9) did not distinguish between type 1 and type 2 diabetes. In this study, type 1 diabetes was defined as a relevant ICD-8-10 code (ICD-8, 250; ICD-9, 250; ICD-10, E10-14) recorded before the age of 30 years.

AGE AS TIME-SCALE IN THE COX REGRESSION

To examine whether temporal biases skewed our data, we performed an additional analysis in which we used age instead of years since biopsy/study entry as the time scale in our Cox regression. This did not influence our risk estimates, and with that model, the HR for asthma in patients with CD was 1.61 (95% CI, 1.51-1.72).

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TABLE E1. Comparison of small intestinal histopathology classifications

Classification used in this project	Villous atrophy			
Marsh classification	Type IIIa	Type IIIb	Type IIIc	
Marsh description		Flat destructive		
Corazza et al ^{E1}		Grade B1	Grade B2	
SnoMed codes	M58, D6218, M58005	M58, D6218, M58006		M58, D6218, M58007
KVAST/Alexander classification	III Partial VA	IV Subtotal VA	IV Total VA	
Characteristics				
Villous atrophy	+	++	++	
IEL	+	+	+	
Crypt hyperplasia	+	++	++	

TABLE E2. Characteristics of study participants

Characteristics	Matched controls	CD
Total, n	140,295	28,281
Age at study entry (y), median (range)	31 (0-95)	31 (0-95)
Attained age (y), median (range)	41 (1-105)	41 (1-100)
Age 0-19 y, n (%)	56,643 (40.4)	11,334 (40.1)
Age 20-39 y, n (%)	25,841 (18.4)	5,199 (18.4)
Age 40-59 y, n (%)	31,671 (22.6)	6,375 (22.5)
Age ≥60 y, n (%)	26,140 (18.6)	5,373 (19.0)
Entry year, median (range)	1997 (1969-2008)	1997 (1969-2008)
Follow-up,* (y), median (range)	9 (0-40)	9 (0-38)
Follow-up,* (y), mean ± SD	10.4 ± 6.4	10.1 ± 6.4
Females, n (%)	87,314 (62.2)	17,560 (62.1)
Males, n (%)	52,981 (37.8)	10,721 (37.9)
Calendar year		
1989 and before, n (%)	20,148 (14.4)	4,066 (14.4)
1990-1999, n (%)	58,664 (41.8)	11,808 (41.8)
2000 and after, n (%)	61,483 (43.8)	12,407 (43.9)
Type 1 diabetes, n (%)	524 (0.4)	884 (3.1)

*Follow-up time until diagnosis of asthma, death from other cause, emigration, or December 31, 2008. In reference individuals, follow-up could also end through small-intestinal biopsy.

TABLE E3. Additional results

Subanalyses: CD and risk of later asthma	HR; 95% CI
Adjustment for	
Type 1 diabetes	1.61; 1.50-1.72
Education	1.62; 1.52-1.74
Smoking and body mass index	1.65; 1.18-2.29
Cesarean section	1.64; 1.50-1.78
Exclusions	
Excluding the first year of follow-up	1.55; 1.44-1.67
Excluding individuals with a diagnosis of sarcoidosis, tuberculosis, or pneumonia	1.60; 1.49-1.72
Additional requirements for the diagnosis of asthma	
Diagnosis of asthma with a record of asthma medication	1.55; 1.43-1.67
Diagnosis of asthma and at least 1 more atopic disorder (allergic rhinitis, allergic conjunctivitis, or eczema)	1.78; 1.58-2.00