



## **Risk of tuberculosis in a large sample of patients with coeliac disease - A nationwide cohort study**

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# Risk of tuberculosis in a large sample of patients with coeliac disease - A nationwide cohort study

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Point-by-point Response to the reviewers' and editor's comments

Professor Kane

Dear professor Kane,  
Thank you for allowing us to revise our paper. Please note that during our revision we spotted an error in the conditional logistic regression (*Prior TB and risk of subsequent CD*). We have since recalculated all our data, and only those referring to the conditional logistic regression were incorrect. In the correct analysis, the Odds ratio was 1.6 instead of 2.0 as previously reported. Our new odds ratio does not change the interpretation of our paper. The cause of the incorrect conditional logistic regression was that we had listed “excluded” controls at the wrong level (see page 2 in this response) in our flowchart, and hence the logistic regression was not based on the correct number of individuals.

Reviewer: 1

**Reviewer:** Comments for Transmission to the Authors

None.

**Authors:** OK.

Reviewer: 2

**Reviewer:** In this study, Ludvigsson, et al utilize a validated nationwide histopathologic database of patients with biopsy-proven celiac disease and compare their risk of tuberculosis to that of controls matched by age, sex, county, and calendar year. The outcome of tuberculosis was determined first via billing codes of inpatient and outpatient registrars, and further analysis restricted the definition of TB to that of patients identified by a national surveillance system, the prescription of a TB medication, and positive TB culture in one of Sweden's 5 laboratories. The authors found an increased risk of TB among patients with celiac disease (HR 2.0, 95% CI 1.3-3.0), and this association was somewhat magnified when employing the more specific definitions of TB. This is a well-written manuscript and carefully performed analysis and the authors appropriately characterize the limitations of the database.

**Authors:** We would like to thank the peer reviewer for these encouraging remarks.

**Reviewer:** - The case-control analysis examining the relationship between TB and subsequent CD is tersely described in the methods and the results (only one sentence in each). This analysis is presented almost as an afterthought-- the details need to be presented. If the patients with TB were the cases, how were the controls picked? Was matching performed? Which definition of TB was used for this analysis? What were the crude proportions of subsequent development of CD when comparing TB cases to controls? Among those patients with TB who developed CD, what was the median time to developing CD? Also, there is a typographical error in this section of the results: "2-fold increased risk of having a later diagnosis of TB" should be changed to "2-fold increased risk of having a later diagnosis of

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CD."

**Authors:** This analysis was not an afterthought but at the same time not one of our main analyses. It was performed in order to look at temporal relationships between CD and TB, since our main analyses concerned CD and subsequent risk of TB.

When recalculating our data we have noted an error in the conditional logistic regression. This error was due to us listing exclusions of individuals (Figure 1) in the wrong order (some controls with data irregularities (the n=247) were listed both in the second "level" and then in the fourth "level" of the flowchart). This did not affect the overall number of individuals in the main analysis (the main analysis of this paper is still based on 29,026 individuals with CD and 144,160 matched controls and risk of subsequent TB), but did affect the logistic regression.

We have recalculated our data and the OR for future CD is 1.6 and not 2.0 as first presented in our manuscript. We have attached the statistical output for this analysis below for the editors and peer reviewers to see.

#### LOGISTIC REGRESSION (COELIAC DISEASE: Risk of future CD in patients with TB)

	B	SE	Wald	df	Sig.	Exp(B)	95,0% CI for Exp(B)	
							Lower	Upper
logtbc	,463	,134	11,902	1	,001	1,589	1,221	2,067

			logtbc_tbc_is_negative_if_later_than_study_entry		Total
			0	1	
bps_biopserad_is_1	0	Count	144313	209	144522
		% within logtbc_tbc_is_negative_if_later_than_study_entry	83,3%	75,2%	83,2%
	1	Count	29027	69	29096
		% within logtbc_tbc_is_negative_if_later_than_study_entry	16,7%	24,8%	16,8%
Total		Count	173340	278	173618
		% within logtbc_tbc_is_negative_if_later_than_study_entry	100,0%	100,0%	100,0%

As can be seen in figure 1 in the manuscript the number of individuals with TB agrees with that of the output above. We have extended the methods section and the results section with regards to the analysis of prior TB and future CD.

In the methods section we have listed absolute numbers, type of matching, and how we defined TB.

In the results section we have added proportions, and the median duration from TB diagnosis

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to CD (10 years).

**Case-control study (Methods)**

In a case-control study we used *conditional* logistic regression to examine the relationship between prior TB and *subsequent* CD. TB was defined according to relevant ICD codes (Appendix). This analysis was based on 29,096 individuals with CD and 144,522 controls matched for sex, age, calendar period and county. We then looked at the number individuals with a prior diagnosis of TB in each group.

**Risk of subsequent CD in patients with prior TB**

Individuals with TB were at a 1.6-fold increased risk of having a later diagnosis of CD (95% CI odds ratio=1.2-2.1). Out of 29,096 individuals with CD, 69 (0.24%) had an earlier diagnosis of TB vs. 209/144,522 (0.15%). The median duration from TB to CD diagnosis was 10 years.

**Reviewer:** - While employing multiple definitions of TB demonstrates the robustness of the results, it would be ideal to show that this definition of TB is internally valid, by, for example, calculating the risk of TB among those with known risk factors. Country birth was used as a covariate in this paper, and so the authors could consider calculating and reporting the risk of TB among those with a non-nordic country of birth as compared to those with a nordic country of birth. (In the US, foreign birth is one of the strongest risk factors for developing TB.)

**Authors:** The reason why we did not do this initially was because the number of study participants born outside the Nordic countries was small in our study. There were only 944 individuals with CD born outside the Nordic countries and 7 of these developed TB. This corresponded to a HR of 3.6 (95%CI=0.9-14.4; i.e. of borderline statistical significance p=0.072). Since individuals born outside the Nordic countries only made up 3.2% of all participants this risk increase had little effect of the summary estimate of our study.

Among the 28,078 individuals born in the Nordic countries who had CD, the HR for TB was 2.1; 95%CI=1.3-3.4.

As can be noted, the HR in this subset of individuals was higher than the summary estimate (2.0; 1.3-3.0). This because in this stratified analysis, a number of reference individuals from Non-Nordic countries were excluded and this drove up the risk estimates (to 2.1). Strata were not matched for nationality.

In the revised manuscript, we have added the following lines (italicised):  
Moreover, results were similar when we adjusted for country of birth (HR=2.2; 95% CI=1.4-3.3), or restricted our analysis to individuals born in the Nordic countries (HR=2.1; 95%CI=1.3-3.4).

**Reviewer:** - It would be of interest to report the HR of developing TB among those with inflammation and those with positive serologies and negative biopsy, compared to controls.

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(We can infer that these groups have an increased risk of TB compared to the general population as their risk of TB was similar to the CD group.) Given the increased mortality rates reported in these groups by Dr. Ludvigsson previously, especially among those with inflammation, further analysis of morbidity in these groups would be valuable.

**Authors:** Below is the output of the main analysis, now including individual estimates for “inflammation” (bpsgr0123(2)) and normal mucosa but positive CD” (bpsgr0123(1)) as requested by the peer reviewer.  
(bpsgr0123(3)) = Coeliac disease

	B	SE	Wald	df	Sig.	Exp(B)	95,0% CI for Exp(B)	
							Lower	Upper
bpsgr0123			17,229	3	,001			
bpsgr0123(1)	,571	,491	1,351	1	,245	1,770	,676	4,633
bpsgr0123(2)	,638	,250	6,500	1	,011	1,892	1,159	3,090
bpsgr0123(3)	,688	,214	10,355	1	,001	1,990	1,309	3,027

We have added the following text to our manuscript:

### Methods

*In a second post-hoc analysis we also estimated the risk of TB, defined as having a relevant ICD-code (Appendix) in individuals with either inflammation (Marsh 1-2) or normal mucosa (Marsh 0) and positive CD serology compared to that in age- and sex-matched reference individuals.*

### Results

*In a second post-hoc analysis we also estimated the risk of TB in individuals with either inflammation without VA or normal mucosa but positive CD serology compared to that in age- and sex-matched reference individuals. The risk of TB was increased in both groups, although only in inflammation (HR=1.9; 95%CI=1.2-3.1) was the risk increase statistically significant (normal mucosa but positive CD serology: HR=1.8; 95%CI=0.7-4.6).*

\*\*\*\*\*

Please note that HRs seem highest (2.0) in patients with CD (inflammation 1.9; normal mucosa but positive CD serology: 1.8). That the internal comparison found that patients with CD were at a slightly lower risk of TB than other individuals undergoing biopsy is due to different age- sex- and calendar period-distribution among patients undergoing biopsy (for this we refer to our paper in JAMA). For the convenience of the peer reviewer we have added Table 1 from that paper.



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MORTALITY RISK IN CELIAC DISEASE

Table 1. Characteristics of Study Participants

Characteristics	Celiac Disease (n = 29 096)	Inflammation (n = 13 306)	Latent Celiac Disease (n = 3719) <sup>a</sup>
Age at study entry, median (range), y	30 (0-95)	49 (0-99)	36 (0-91)
0-19	11 802 (40.6)	1226 (9.2)	941 (25.3)
20-39	5312 (8.3)	3456 (26.6)	1150 (30.9)
40-59	6477 (22.3)	4149 (31.2)	1064 (28.6)
≥60	5505 (18.9)	4385 (33.0)	564 (15.2)
Follow-up, median (range), y <sup>b</sup>	8.8 (0-39.1)	7.2 (0-33.3)	6.7 (0-18.4)
Follow-up, mean (SD), y <sup>b</sup>	10.1 (6.4)	8.6 (6.6)	7.4 (4.3)
Male, No. (%)	11 091 (38.1)	5809 (43.7)	1409 (37.9)
Calendar period			
≤1989	4105 (14.1)	1961 (14.7)	0
1990-1999	12 059 (41.4)	5164 (38.8)	1387 (27.3)
≥2000	12 932 (44.4)	6181 (46.4)	2332 (62.7)
Entry year, median (range)	1998 (1969-2008)	1999 (1970-2008)	2001 (1990-2007)

**Reviewer:** - Please comment on why there appeared to be no increased risk of TB among those diagnosed with CD pre-1990 (table 3). Is this a power issue or do you suspect that to be diagnosed of CD in the pre-serology era carried with it a different clinical profile?

**Authors:** We believe this is mostly a power issue. We observed 5 cases of TB vs. 4 expected. If, by chance we had seen another 2 individuals (n=7) this would have resulted in a HR of around 1.7-1.8 instead.

**Reviewer:** - Would rephrase the sentence in the results "The overall risk of TB in CD was 1.5 in women..." This is referring to a ratio, not an absolute risk.

**Authors:** We agree. The sentence has been re-written.

Reviewer: 3

**Reviewer:** Your data show that TB Prevalence is increased ONLY IN MALES CD, but NOT IN FEMALES. This message is not clear as it should be in the title, in the results and in the discussion.

**Authors:** We agree that the difference in risk estimates in men and women are interesting.

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Still, the difference was not statistically significant when tested. We have discussed this specifically with Editor Professor Kane who suggested us to add that had we had access to a larger dataset we might have been able to show a difference according to sex.

We have added the following lines to the revised manuscript:

*Although the HR for TB in men with CD (2.9) was higher than in women with CD (1.5), this difference was not statistically significant. However, we cannot rule out that in a larger dataset than ours, men may with CD be at a higher risk of TB than women with CD.*

**Reviewer:** You should also comment, in the discussion, that the number of observed/expected cases is very small and may not be a big public health issue, as it may appear. Other health problems, in the celiacs, are more prevalent.

**Reviewer:** Anyway TB cases have to be screened for CD: this is important.

**Authors:** We agree and have added the following sentences to the discussion:

*Still we admit that the number of observed/expected cases of TB is limited in this study, and consequently absolute risks are low. Other health problems than TB may be of greater concern for the CD community. Nevertheless, the increased ORs for CD in individuals who first had a diagnosis of TB signal that screening for CD may be considered in patients with TB and gastrointestinal symptoms.*



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coeliac disease - A nationwide cohort study**

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**Running head:** Tuberculosis in coeliac disease

**Abbreviations used in this article:** CD, Coeliac disease; CI, Confidence Interval;  
HR, Hazard Ratio; Mtb, Mycobacterium Tuberculosis; TB, Tuberculosis; VA, Villous  
atrophy.

**Manuscript version:** December 23, 2010.

**Word count:** 3,106. **Abstract:** 227. **Tables:** 3. **Figures:** 1

**Details of ethics approval:** This project (2006/633-31/4) was approved by the Research Ethics Committee of the Karolinska Institute, Sweden on June 14<sup>th</sup>, 2006.

**Copyright license statement:**

Copyright transfer agreements (CTAs) have emailed to APT and originals sent by mail.

**Guarantor:** JFL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

**Conflicts of interest/Disclosure requirement**

All authors declare that they have no conflicts of interest and therefore nothing to declare

**Writing Assistance:** None.

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**Independence (role of the sponsors):** None of the funders had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

**Abstract**

**Background** Research suggests a positive association between coeliac disease (CD) and tuberculosis (TB), but that research has often been limited to inpatients and small sample size. We examined the relationship between TB and CD.

**Methods** We collected biopsy data from all pathology departments in Sweden (n=28) to identify individuals who were diagnosed with CD between 1969 and 2007 (Marsh 3: villous atrophy; n=29,026 unique individuals). Population-based sex- and age-matched controls were selected from the Total Population Register. Using Cox regression, we calculated hazard ratios (HRs) for TB from data in the Swedish national health registers.

**Results** Individuals with CD were at increased risk of TB (HR=2.0; 95% CI=1.3-3.0) (during follow-up, 31 individuals with CD and 74 reference individuals had a diagnosis of TB). The absolute risk of TB in patients with CD was 10/100,000 person-years with an excess risk of 5/100,000. Risk estimates were highest in the first year. Restricting our outcome to a diagnosis of TB confirmed by (I) a record of TB medication (HR=2.9; 95% CI=1.0-8.3), (II) data in the National Surveillance System for Infectious Diseases in Sweden (HR=2.6; 95% CI=1.3-5.2) or (III) positive TB cultivation (HR=3.3; 95% CI=1.6-6.8) increased risk estimates. The positive association between CD and TB was also observed before the CD diagnosis (odds ratio=1.6; 95% CI=1.2-2.1).

**Conclusions** We found a moderately increased risk of TB in patients with CD.

**Abstract word count:** 227

**Keywords:** autoimmunity, coeliac, inflammation, tuberculosis

## INTRODUCTION

Coeliac disease (CD) is an immune-mediated disease occurring in 1% of the Western population<sup>1</sup>. The disease is triggered by gluten exposure in HLA-DQ2+ and DQ8+ individuals, resulting in chronic inflammation of the small intestine. Many patients suffer from extraintestinal manifestations, such as type 1 diabetes<sup>2</sup>, reproductive disorders<sup>3</sup>, irritable bowel syndrome<sup>4</sup> and sepsis<sup>5</sup>.

Mycobacterium tuberculosis (TB) infects about one third of the world's population, although active TB is less common<sup>6</sup>. TB can affect any part of the body but most often occurs in the lungs, where it causes tissue destruction.

Several studies and case reports have indicated a positive association between CD and TB<sup>7-12</sup>. In 2007, our research group found that patients with a CD inpatient diagnosis were at a 4-fold increased risk of developing TB in the future. However, that study may have overestimated the risk of TB in CD since individuals with CD were identified using the Swedish inpatient register and not all individuals with CD require hospital admission. Furthermore, in that study<sup>13</sup> we were not able to confirm TB against external data.

In this study we examined the association between biopsy-verified CD and TB. In subanalyses we also calculated the risk of TB (1) with a record of TB medication, (2) confirmed through the Swedish national surveillance system for infectious diseases or (3) through positive cultivation. Finally, we explored whether the increased risk of TB in CD was restricted to individuals with villous atrophy (VA) or independent of small intestinal histopathology.

**METHODS**

Through the personal identity number<sup>14</sup>, we linked nationwide data on small intestinal histopathology with data on Swedish national TB registers. We defined CD as having a record of VA at small intestinal biopsy (see Table A1 in the appendix.).

Tuberculosis was defined according to relevant international classification of disease (ICD) codes, in the Swedish outpatient and inpatient registers (appendix).

**Collection of biopsy data**

We collected data from duodenal/jejunal biopsy reports with VA (Marsh stage 3 and equal to CD)<sup>15</sup> from all pathology departments in Sweden (n=28). Data collection took place between October 2006 and February 2008 while the biopsies had been performed between 1969 and 2008 (Table 1). Each individual undergoing biopsy was matched with up to five reference individuals by age, sex, county and calendar year through the Total Population Register.

For comparative reasons (secondary reference groups), we also collected data on patients with inflammation without VA (Marsh 1-2) and normal mucosa but positive CD serology (Marsh 0 with positive IgA/IgG for antigliadin, endomysial (EMA) or tissue transglutaminase (TTG))<sup>16</sup>. More information on that data collection has been published in two validation papers<sup>15, 16</sup>.

When examining TB in patients with CD, we used the same dataset as in our paper on overall mortality in CD<sup>17</sup>. This dataset consisted of 29,096 individuals with CD.

Additional exclusions among patients with CD and their reference individuals are shown in Figure 1.

## Outcome

Our main outcome was a diagnosis of TB (appendix). In subanalyses we restricted our outcome to individuals with a TB diagnosis confirmed by a second independent data source: (1) a record in the Swedish national surveillance system for infectious diseases (appendix), (2) a record of TB medication according to relevant ATC codes (J04A) in the Swedish Prescribed Drug Register (appendix) and (3) positive TB cultivation in one of Sweden's five TB labs specialized in TB.

## Statistics

We used internal stratified Cox regression to estimate Hazard ratios (HRs) for TB.

The internal stratification means that the index individual was only compared with his or her reference individuals within the same stratum and then a summary risk estimate was calculated. The proportional hazards assumption was tested through plotting log minus log curves. Follow-up started on the date of the first biopsy with VA and the corresponding date in matched reference individuals. Follow-up ended with TB diagnosis, death, emigration or on Dec 31, 2008, whichever happened first.

In *a priori* subanalyses we examined the risk of TB by follow-up period, sex, age and calendar year at CD diagnosis. We calculated incidence rates as the number of first recorded TB diagnoses divided by person-years at risk.

In separate analyses we adjusted for type 1 diabetes mellitus, education and country of birth (Nordic country vs. non-Nordic country). In a post-hoc analysis we examined the risk of TB in individuals with CD compared with the risk in secondary reference groups. In a second post-hoc analysis we also estimated the risk of TB, defined as

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3 having a relevant ICD-code (Appendix) in individuals with either inflammation  
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5 (Marsh 1-2) or normal mucosa (Marsh 0) and positive CD serology compared to that  
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8 in age- and sex-matched reference individuals.  
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14  
15 **Case-control study**  
16

17 In a case-control study we used conditional logistic regression to examine the  
18  
19 relationship between prior TB and subsequent CD. TB was defined according to  
20  
21 relevant ICD codes (Appendix). This analysis was based on 29,096 individuals with  
22  
23 CD and 144,522 controls matched for sex, age, calendar period and county. We then  
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26 looked at the number individuals with a prior diagnosis of TB in each group.  
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32 We used SPSS 18.0 to perform all analyses. HRs with 95% CIs that did not include 1  
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34 were regarded as statistically significant.  
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39 **Ethics**  
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41 The study was approved by the Research Ethics Committee of Karolinska Institutet.  
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50 *Additional details on the method are provided in the appendix.*  
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## RESULTS

### Background data

This study included 29,026 individuals with CD and 144,160 general population reference individuals. Secondary reference groups consisted of 13,261 individuals with inflammation and 3710 individuals with normal mucosa but positive CD serology.

The majority of the study participants were females (Table 1). The median age was 30 years at study entry with 40% undergoing biopsy in childhood. Most individuals were biopsied after 1990 (Table 1).

### Coeliac disease and subsequent TB

During follow-up, 31 individuals with CD and 74 reference individuals developed TB. The HR for TB was 2.0 (95% CI=1.3-3.0). HRs decreased with follow-up (Table 2). When we excluded the first year of follow-up, the risk of TB was 1.7 (95% CI=1.1-2.8).

The overall HR for TB in CD was 1.5 in women (95% CI=0.8-2.7) and 2.9 in men (95% CI=1.6-5.3)(Table 3). The difference between women and men with CD was not statistically significant ( $p=0.104$ ).

TB was uncommon in children and only in middle-aged and elderly people was the association between CD and TB statistically significant (Table 3). The age differences in HRs for TB, however, were only of borderline significance ( $p=0.058$ ).

Adjustment for type 1 diabetes (HR=2.1; 95% C=1.4-3.2) or education (HR=2.1; 95% C=1.3-3.4) did not change the risk estimates. Moreover, results were similar when we adjusted for country of birth (HR=2.2; 95% CI=1.4-3.3), or restricted our analysis to individuals born in the Nordic countries (HR=2.1; 95%CI=1.3-3.4).

**Linkage with other registers**

The Swedish Prescribed Drug Register was initiated in mid-2005 and therefore covered only a very small part of the study period. In our study five individuals with CD had a TB diagnosis *and* a record of TB medication (reference individuals, n=10), corresponding to a HR of 2.9 (95% CI=1.0-8.3).

Of the individuals with a TB diagnosis in either the inpatient or outpatient register, the diagnosis could be confirmed in the TB register of the National Institute for Infectious Disease Control in Sweden in 11 patients with CD (reference individuals, n=18). Thus, the HR for having a TB diagnosis confirmed in the national surveillance system was 2.6 (95% CI=1.3-5.2). Of the 11 patients with CD and TB, 8 suffered from pulmonary TB (72%), which can be compared with 15/18 reference individuals (83%) (Fisher's exact test, p=0.646).

The HR increased to 3.3 (95% CI=1.6-6.8) when we restricted our outcome to a TB diagnosis confirmed by positive TB cultivation according to the Swedish Institute for Infectious Disease Control.

### Post-hoc analyses

Individuals with CD (VA) were at no increased risk of TB when compared with individuals with inflammation without VA (adjusted HR=0.9; 95% CI=0.5-1.6) or those with normal mucosa but positive CD serology (adjusted HR=0.7; 95% CI=0.3-1.9).

In a second post-hoc analysis we also estimated the risk of TB in individuals with either inflammation without VA or normal mucosa but positive CD serology compared to that in age- and sex-matched reference individuals. The risk of TB was increased in both groups, although only in inflammation (HR=1.9; 95%CI=1.2-3.1) was the risk increase statistically significant (normal mucosa but positive CD serology: HR=1.8; 95%CI=0.7-4.6).

### Risk of subsequent CD in patients with prior TB

Individuals with TB were at a 1.6-fold increased risk of having a later diagnosis of CD (95% CI odds ratio=1.2-2.1). Out of 29,096 individuals with CD, 69 (0.24%) had an earlier diagnosis of TB vs. 209/144,522 (0.15%). The median duration from TB to CD diagnosis was 10 years.

**DISCUSSION**

This nationwide population-based study found a 2-fold increased risk of TB in patients with biopsy-verified CD. This increased risk in TB was highest in the first year of follow-up. Children with CD were at no increased risk of TB. A positive association between CD and TB was also noted before CD diagnosis.

**Main findings and comparison with previous research**

Several studies have examined the relationship between CD and TB<sup>7-13, 18</sup>. Two of these studies calculated risk estimates among patients with CD<sup>12, 13</sup> with rather high relative risks for both incident TB (HR=3.74; 95% CI=2.14-6.53)<sup>13</sup> and death from TB (standardized mortality ratio, SMR=5.9; 95% CI=1.6-15.1)<sup>12</sup>.

The slightly lower risk of TB in this study (HR=2.0) as compared with that in the two above-mentioned studies<sup>12, 13</sup> can probably be explained by our non-selected group of patients. We included patients with biopsy-verified CD throughout Sweden, whereas the two previous studies were restricted to inpatients with CD<sup>12, 13</sup>. Inpatients with CD are likely to have a more intense disease activity with more complications (including TB and other diseases) than the average patient with CD. That surveillance bias plays an important role for the association is clear from the higher risk estimates in the first year after biopsy when the HR for TB was 3.5. In contrast, the risk of TB more than five years after diagnostic biopsy with VA was only 1.6 and did not reach statistical significance.

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3 The lower risk estimate for TB in our study cannot be explained by lack of statistical  
4 power. In the study by Peters et al<sup>12</sup> the expected number of deaths from TB was only  
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6 0.7; in our study on incident TB published in 2007 (Ludvigsson et al, 2007) we  
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8 expected to find 6.4 cases with TB<sup>13</sup>. This should be compared with 16 expected cases  
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10 of TB in our current study. Still we admit that the number of observed/expected cases  
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12 of TB is limited in this study, and consequently absolute risks are low. Other health  
13  
14 problems than TB may be of greater concern for the CD community. Nevertheless,  
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16 the increased ORs for CD in individuals who first had a diagnosis of TB signal that  
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18 screening for CD may be considered in patients with TB and gastrointestinal  
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20 symptoms.  
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29 Whereas Peters et al did not separate children and adults in their study on mortality in  
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31 CD al<sup>12</sup>, our previous study<sup>13</sup> found increased risks of TB in both children (HR=3.44)  
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33 and adults (HR=3.84). This finding contrasts with the lack of association between CD  
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35 and TB in patients diagnosed 0-19 years of age or 20-39 years of age in the current  
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37 study. However, we cannot rule out the risk of type 2 errors (and that we have failed  
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39 to identify a true risk increase) in children since stratified analyses had lower power  
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41 than the all-inclusive main analysis and since the interaction between CD and age on  
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43 the risk of TB was non-significant.  
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50 Although the HR for TB in men with CD (2.9) was higher than in women with CD  
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52 (1.5), this difference was not statistically significant. However, we cannot rule out  
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54 that in a larger dataset than ours, men with CD may be at a higher risk of TB than  
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56 women with CD.  
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**Strengths and limitations**

We used biopsy reports with VA from all Swedish pathology departments (n=28) to identify CD. Biopsy reports have a high sensitivity for *diagnosed* CD<sup>15</sup>. In a questionnaire study<sup>15</sup> 96% of Swedish adult gastroenterologists and 100% of pediatric gastroenterologists reported performing small intestinal biopsy before CD diagnosis in at least 9 out of 10 patients. On average, 3 biopsies are taken<sup>16</sup>, which is likely to rule in about 95% of patients with CD<sup>19</sup>. We also reviewed patient charts and laboratory data in 114 randomly selected patients in our cohort and concluded that 108 (95%) of those with VA had CD<sup>15</sup>. Furthermore, we reviewed a large number of biopsy reports (through computerized searches followed by manual review). This review found that other diagnoses than CD were very uncommon in individuals with VA (any inflammatory bowel disease, 0.3%; *Helicobacter pylori*, 0.2% and gastric metaplasia, 0.1%)<sup>15</sup>.

In validated patients with VA and available data on CD serology 88% had positive CD serology prior to biopsy. We did, however, not require positive CD serology for the diagnosis of CD since a study based on CD serology would have diminished our follow-up since CD serology was only introduced in routine health care in the late 1990s. In contrast, VA has been in use since the 1970s and has remained critical for the CD diagnosis ever since. The long follow-up and large number of study participants increased statistical power and allowed for important subanalyses.

In our main analysis we used both the inpatient and the outpatient registers to identify patients with TB. To our knowledge, the TB diagnosis has not yet been validated in any of these registers. Based on validations of other diseases, we expect a positive

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3 predictive value of about 80-90%<sup>20, 21</sup>. It is important to note that HRs for TB  
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5 increased when we increased the specificity through validation against independent  
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7 TB data from (1) the Swedish Prescribed Drug Register, (2) the Swedish national  
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9 surveillance system for infectious disease and (3) TB cultivation data from the five  
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11 Swedish national TB laboratories.  
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17 We did not adjust for smoking data. Smoking is a risk factor for TB, but often  
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19 inversely associated with CD. Accordingly, lack of smoking data is not likely to  
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21 explain our findings. This assumption is supported by data from the current study on  
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23 women with CD and at least one record in the Swedish Medical Birth Register where  
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25 smoking is recorded. Of 3,902 women with CD, 18.3% indicated that they were  
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27 smokers, which can be compared with 20.8% of 18,987 reference women.  
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### 34 Mechanisms

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36 There may be several mechanisms, not mutually exclusive, that could explain the  
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38 association between CD and tuberculosis. One potential explanation could be vitamin  
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40 D deficiency. CD may result in malabsorption of vitamin D and gluten-free products  
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42 are often low in vitamin D content. Low serum levels of vitamin D are associated  
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44 with increased risk of active tuberculosis, as shown by a recent meta-analysis of  
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46 previous studies<sup>22</sup>. Support for an association between vitamin D and TB is also  
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48 provided by findings that genetic variants of the vitamin D receptor have been linked  
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50 to the risk of TB infection<sup>23</sup>. Vitamin D has been found to promote the antimicrobial  
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52 activity of the innate immune system, which provides a rapid response against  
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54 invading pathogens. For example, vitamin D was shown to induce the synthesis of  
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56 nitric oxide in macrophages, resulting in suppression of *M. tuberculosis* (*Mtb*)  
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intracellular growth<sup>24</sup>. Other mechanisms have recently been elucidated, including the role of vitamin D together with IL-15 to mediate the effect of pathogen-induced stimulation of the pattern-recognition receptor TLR2 to induce expression of the antimicrobial peptide cathelicidin in macrophages<sup>25</sup>.

Furthermore, increased frequency of Foxp3+ CD25+ regulatory T-cells has been demonstrated in the blood of CD patients<sup>26</sup>. An increased Treg frequency could dampen the response of effector T-cells needed to combat *M. tuberculosis* with a subsequent higher risk to develop clinical TB. Increased numbers of Foxp3+ CD25+ Treg cells, capable of suppressing *Mtb*-specific T-cell cytokine production, have been demonstrated in the blood from patients with active TB<sup>27</sup>. The clinical relevance of Treg represents an intense field of research and the cytokine Interleukin-17 (IL-17A) may be instrumental in deciding the fine balance between protective immune responses and autoimmunity. TGFβ and Il-6 differentiate precursor T-cells to IL-17-producing Th17 cells, TGFβ alone induces Treg cells and both cells have common stages in their development<sup>28</sup>. The discovery of human IL-17+ Foxp3+ T-cells underlines the common nature of these cells<sup>29</sup>. Autoimmunity appears to be driven, in part, by IL-17 immune responses and overt IL-17-positive immune responses may, depending on the frequency of exposure to mycobacterial species, be detrimental in the orchestrated immune response to *Mtb*.<sup>30</sup> Thus, the nature of Tregs along with IL-17-producing cells may shape an environment facilitating CD (increased Th17 response and Tregs) as well as clinical active TB; both of these conditions are characterized by increased Treg frequency and Th17-associated immune responses<sup>31</sup>

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3 However, another study found evidence for reduced Treg function in CD<sup>32</sup>, and even  
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5 if Treg cells are increased in CD, they do not seem to prevent CD from being  
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7 associated with many autoimmune diseases.  
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12 Co-infection or 'co-disease' may lead to a chronic inflammatory process with a  
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14 concomitant increased CTLA-4 and PD-1 expression on immune cells, which is  
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16 associated with decreased Th17 and Th1 responses. Blockage of PD-1 restored IFN-  
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18 gamma responses and blockage of CTLA-4 restored both Th1 and Th17 responses<sup>33</sup>.  
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20 We could hypothesize that CD represents such a 'chronic inflammatory situation',  
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22 which may be associated with reduced immune responsiveness (defined by increased  
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24 PD-1 and CTLA-4 expression on T-cells). This situation may facilitate *Mtb* infection  
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26 because of the reduction of, in particular, Th1 responses, which are crucial to contain  
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28 or fight off *Mtb*.  
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36 Finally, one possible way in which bacterial infection (such as TB) could promote the  
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38 development of CD is via the induction of fever since that could lead to the increased  
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40 transport of gluten-derived peptides across the intestinal epithelium, which, in turn,  
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42 enhances the sensitization to gluten peptides<sup>34</sup>. Even at physiologically relevant  
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44 temperature increases, the permeability of intestinal epithelium is increased<sup>35</sup>.  
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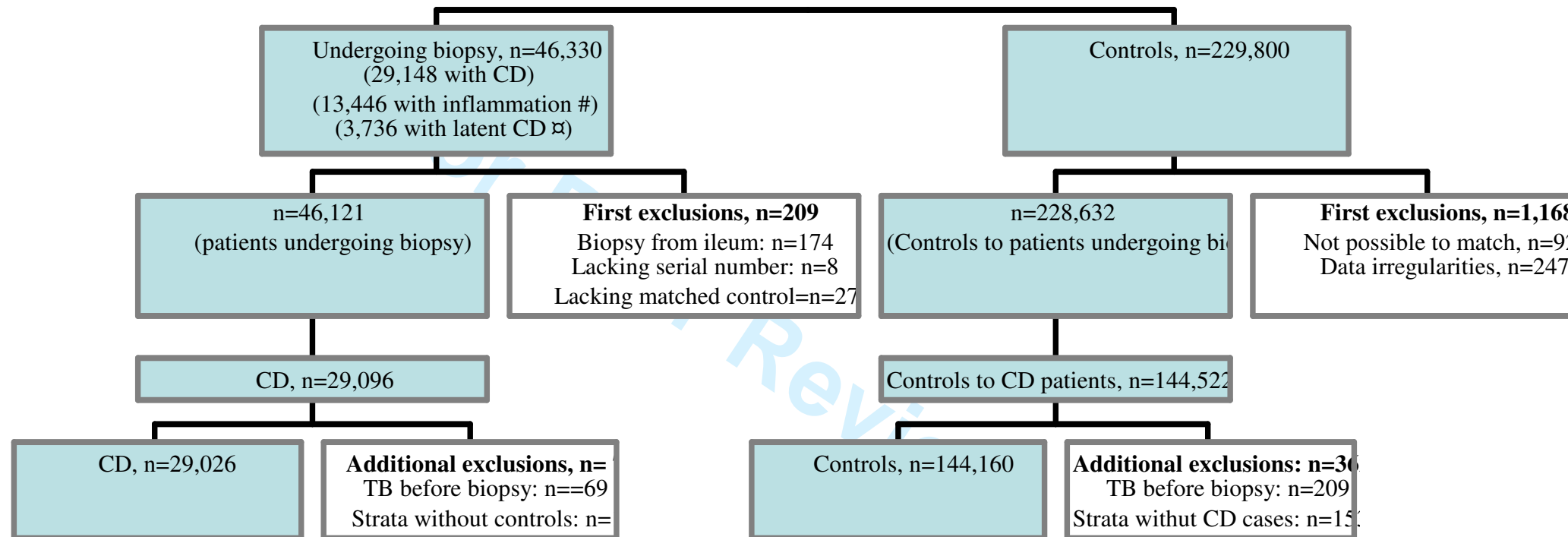
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51 We cannot rule out that some individuals with TB were identified as part of the  
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53 investigations for CD. The highest risk estimates were seen in the first year after  
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55 diagnosis even if the HR for TB remained statistically significant thereafter.  
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57 Compared with individuals undergoing small intestinal biopsy but not having VA,  
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59 individuals with CD (with VA) were at no increased risk of TB. This observation  
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suggests that severe histopathological changes may not be a prerequisite for later TB in patients with CD.

In conclusion, we found a positive association between CD and TB, both before and after diagnosis of CD. This finding suggests shared risk factors or an increased risk of TB in patients with undiagnosed CD.

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**Figure 1: Flow chart of study participants**

CD, Celiac disease

\*153 controls were excluded because their matched individual undergoing biopsy had been excluded (and all analyses were matched on strata, see methods).

# Marsh pathology grade 1-2.

§ Marsh pathology grade 0 in individuals with positive CD serology (antigliadin, antiendomysial or anti-transglutaminase antibodies).

**Table 1** Characteristics of study participants

	<i>Matched controls</i>	<i>Coeliac disease</i>
Total	144,060	29,026
Age at study entry, years (median, range)	30; 0-95	30; 0-95
Attained age, years (median, range)	40; 1-105	41; 1-100
Age 0-19 (%)	58,838 (40.8)	11,799 (40.6)
Age 20-39 (%)	26,347 (18.3)	5,305 (18.3)
Age 40-59 (%)	31,148 (22.3)	6,461 (22.3)
Age ≥60 (%)	26,827 (18.6)	5,461 (18.8)
Entry year (median, range)	1998; 1969-2008	1998; 1969-2008
Follow-up†, years (median, range)	9; 0-40	9; 0-40
Follow-up†, years (mean±SD)	10.4±6.4	10.3±6.4
Females (%)	89,345 (62.0)	17,967 (61.9)
Males (%)	54,815 (38.0)	11,059 (38.1)
<i>Calendar year</i>		
-1989	20,301 (14.1)	4,087 (14.1)
1990-99	59,717 (41.4)	12,032 (41.5)
2000-	64,142 (44.5)	12,907 (44.5)
<i>Country of birth</i>		
Nordic ‡	135,966 (94.3)	28,078 (96.7)
Outside the Nordic region	8,194 (5.7)	944 (3.3)

Missing data	0 (0)	4 (<0.1)
Type 1 diabetes	533 (0.4)	922 (3.2)

\*Positive coeliac disease serology 180 days before biopsy and until 30 days after biopsy.

†Follow-up time until diagnosis of TB, death from other cause, emigration or Dec 31, 2008.

In reference individuals follow-up can end through small intestinal biopsy.

‡ Sweden, Denmark. Finland, Norway and Iceland.

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**TABLE 2.** Risk of TB based on follow-up time

Follow-up	Observed events	Expected events	HR; 95% CI	P-value	Absolute risk/ 100,000 PYAR	Excess risk/ 100,000 PYAR	Attributable percentage
All	31	16	2.0; 1.3-3.0	0.001	10	5	50
Year <1	8	2	3.5; 1.5-8.4	0.005	28	20	72
1-4.99	10	5	1.9; 0.9-3.8	0.082	10	5	47
5+	13	8	1.6; 0.8-3.1	0.164	8	3	37

PYAR, Person-years at risk.  
Reference is general population comparator cohort



**TABLE 3.** Risk of TB (subgroup analyses).

<b>Subgroup</b>	<b>Observed events</b>	<b>Expected events</b>	<b>HR; 95% CI</b>	<b>P-value</b>	<b>Absolute risk/ 100,000 PYAR</b>	<b>Excess risk/ 100,000 PYAR</b>	<b>Attributable percentage</b>
<b><i>Sex</i></b>							
Males	17	6	2.9; 1.6-5.3	0.001	15	10	65
Females	14	10	1.5; 0.8-2.6	0.205	8	2	32
<b><i>Age</i></b>							
<20 yrs	1	2	0.4; 0.1-3.2	0.399	1	-	-
20-39 yrs	3	2	1.3; 0.4-4.4	0.701	6	1	21
40-59 yrs	11	4	2.7; 1.3-5.4	0.007	16	10	62
60+ yrs	16	6	2.5; 1.4-4.8	0.004	40	24	61
<b><i>Calendar period</i></b>							
-1989	5	4	1.2; 0.4-3.3	0.719	6	1	17
1990-1999	17	7	2.4; 1.3-4.3	0.004	11	7	58
2000-	9	4	2.1; 1.0-4.5	0.048	14	7	53

PYAR, Person-years at risk.

Reference is general population comparator cohort

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APPENDIX.

Risk of tuberculosis in a large sample of patients with coeliac disease - A nationwide cohort study

Jonas F Ludvigsson, David S Sanders, Markus Maeurer, Jerker Jonsson, Johan Grunewald, Jan Wahlström

Definition of Tuberculosis

Individuals with a relevant ICD code (ICD-7: 001-019; ICD-8: 010-018; ICD-9: 010-019; ICD-10: A15-19) in the Swedish inpatient or outpatient register were defined as suffering from TB. The inpatient register began in 1964, covering all Swedish counties since 1987. The outpatient register records all hospital outpatient visits since 2001.

Description of registers used in this paper

1. *Swedish National Surveillance System for Infectious Diseases*. This register contains data on TB between 1989 and 2007 and reporting is mandatory for both clinical and laboratory physicians. There are five TB laboratories in Sweden.
2. The *Swedish Prescribed Drug Register* was established in mid-2005 and initially covered 84% of all drugs used in Sweden. This register, however, does not cover use of drugs in the wards.

### Description of covariates

*Type 1 diabetes mellitus.* Defined according to relevant ICD codes. In ICD 7, 8 and 9 there was no distinction between type 1 and type 2 diabetes. In this study we defined type 1 diabetes as having an inpatient diagnosis of diabetes before age 30 years.

*Education.* We used seven predefined levels, ranging from not completed the 9-year compulsory school to the PhD-degree. This information was obtained from the Education Register.

*Country of birth.* This information was obtained from the government agency Statistics Sweden and we used the customary division (Nordic countries vs. the rest of the world).



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**TABLE A1 - Small intestinal histopathology classifications – a comparison**

<i>Classification used in this project</i>	<i>Normal</i>	<i>Inflammation</i>		<i>Villous atrophy</i>		
Marsh Classification*	Type 0	Type 1	Type 2	Type 3a	Type 3b	Type 3c
Marsh Description	Pre-infiltrative	Infiltrative	Infiltrative-hyperplastic	Flat destructive		
Corazza et al (ref A1)	-	Grade A		Grade B1		Grade B2
SnoMed Codes	M0010, M0011	M40000, M41000, M42000, M43000, M47000, M47170		M58, D6218, M58005	M58, D6218, M58006	M58, D6218, M58007
KVAST/Alexander classification	I Normal	II Intraepithelial lymphocytosis (IEL)#		III Partial VA	IV Subtotal VA	IV Total VA
<i>Characteristics</i>						
Villous atrophy	-	-	-	+	++	++
IEL#	-	+	+	+	+	+
Crypt hyperplasia	-	-	+	+	++	++

\*We have not included Marsh type 4 in this classification since such lesions are very rare and cannot be identified through SnoMed Codes. # Increased intraepithelial lymphocyte count (often >30/100 epithelial cells).

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