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Celiac disease and Thyroid disease

## Risk of Thyroid disease in individuals with Celiac disease

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Abbreviations used in this article:

CI, Confidence Interval; DM, Diabetes mellitus; HR, Hazard ratio; ICD, International Classification of Disease [codes]; IPR, Swedish national inpatient register; SEI, Socioeconomic index.

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## **Abstract**

**Background:** It has been suggested that celiac disease is associated with thyroid disease. Earlier studies, however have been predominately cross-sectional and have often lacked controls. There is hence a need for further research. In this study, we estimated the risk of thyroid disease in individuals with celiac disease from a general population cohort.

**Methods:** 14,021 individuals with celiac disease (1964-2003) and a matched reference population of 68,068 individuals were identified through the Swedish national registers. Cox regression estimated the risk of thyroid disease in subjects with celiac disease. Analyses were restricted to individuals with a follow-up of > 1 year and with no thyroid disease prior to study entry or within one year after study entry. Conditional logistic regression estimated the odds ratio (OR) for subsequent celiac disease in individuals with thyroid disease.

**Results:** Celiac disease was positively associated with hypothyroidism (Hazard Ratio = 4.4; 95% Confidence Interval = 3.4-5.6;  $p < 0.001$ ), thyroiditis (3.6; 1.9-6.7;  $p < 0.001$ ) and hyperthyroidism (2.9; 2.0-4.2;  $p < 0.001$ ). The highest risk estimates were found in children (hypothyroidism 6.0; 3.4-10.6, thyroiditis 4.7; 2.1-10.5 and hyperthyroidism 4.8; 2.5-9.4). In post-hoc analyses, where the reference population was restricted to inpatients, the adjusted HR for hypothyroidism was 3.4 (2.7-4.4;  $p < 0.001$ ), thyroiditis 3.3 (1.5-7.7;  $p < 0.001$ ) and hyperthyroidism 3.1 (2.0-4.8;  $p < 0.001$ ).

**Conclusion:** Celiac disease is associated with thyroid disease and these associations were seen regardless of temporal sequence. This indicates shared etiology and that these individuals are more susceptible to autoimmune disease.

**Keywords:** autoimmune; celiac; coeliac; child; cohort study; hypothyroidism; hyperthyroidism; thyroiditis.

## Introduction

Celiac disease is an immune-mediated disease characterized by chronic inflammation and destruction of the villous structure of the small intestine(1). It is triggered by the ingestion of gluten. The classic clinical presentation of celiac disease includes abdominal symptoms, malnutrition and impaired growth in childhood, but many patients only have mild or no symptoms at all. Treatment consists of life-long gluten-free diet(2). Celiac disease has increasingly become considered as a multi-organ disorder, and has been linked to a number of diseases including autoimmune disorders(3, 4). About 1% of the population in the Western world is affected by celiac disease(5).

Graves' disease and different forms of thyroiditis are often referred to as autoimmune thyroid disease and have previously been suggested to be associated with celiac disease(3, 4, 6-22). The majority of earlier studies have however been cross-sectional and few of them have included children(12, 15, 19, 20). Several studies have shown a positive association between celiac disease and an increased prevalence of autoimmune thyroid antibodies(10, 19) but not clinically overt disease. Both Italian(17), and Finnish(16) data suggest an increased prevalence of hypothyroidism in individuals with celiac disease. Sategna-Guidetti et al(18) have also presented an increased risk of overall thyroid disease in individuals with celiac disease. Most other positive studies have either lacked controls(6, 9, 21) or not attained statistical significance(4, 8, 12, 20). To our knowledge no studies have until now reported a statistically significant risk increase of hyperthyroidism in celiac disease. We only know of one longitudinal study examining the risk of future thyroid disease in individuals with celiac disease(20). This study (20) showed no statistically significantly increased risk of thyroid disease in individuals with celiac disease.

The prevalence of celiac disease is likely increased among individuals with thyroid disease(7, 10, 11, 13, 14). However, although Spadaccino et al(22) recently reported an

increased prevalence of celiac disease in Italian patients with thyroid disease, that study did not use a matched control group. In the current study, we obtained data from the Swedish national registers to conduct a longitudinal study of the risk of thyroid disease in a general population cohort of 14,021 individuals with celiac disease and an age- and sex-matched reference population of 68,068 individuals.

## Materials and methods

We used the Swedish national inpatient register (IPR) to identify all individuals with a diagnosis of celiac disease on discharge from hospital admissions between 1964 and 2003. Celiac disease was defined according to international classification of disease (ICD) codes (ICD-7: 286.00; ICD-8: 269.00, 269.98; ICD-9: 579A; ICD-10: K90.0). The IPR was also used to identify individuals with thyroid disease and DM(23). The IPR is maintained by the Swedish national board of health and welfare and was set up in 1964. All records in the IPR can be identified through a personal identity number. The personal identity number is a unique number assigned to more than 99,9% of all Swedish residents and immigrants(24). The government agency for demographic statistics, Statistics Sweden, then used the Total Population Register(25) to match each individual with celiac disease with up to five reference individuals for age, sex, calendar year and area of residence at time of celiac disease diagnosis. This register contains information on e.g. area of residence, vital status, and dates of immigration or emigration. Certain individuals with celiac disease could only be matched with three or four reference individuals due to lack of potential reference individuals with the same age and sex in smaller counties.

### Celiac disease and subsequent Thyroid disease

In the main analyses we estimated the risk of subsequent thyroid disease in a general population cohort of 14,021 (9,338 children and 4,683 adults) individuals with celiac disease and a reference population of 68,068 individuals. We also made stratified analyses of risk estimates in males, females, children and adults.

### Inclusion and exclusion criteria

We identified 15,533 individuals with celiac disease diagnosed between 1964 and 2003. Of these, 94 were excluded due to data irregularities. In the dataset consisting of 15,439 individuals with celiac disease we identified 153 (1.0%) individuals with hyperthyroidism, 370 (2.4%) with hypothyroidism, and 52 (0.3%) with thyroiditis before or after diagnosis of celiac disease. Among the 76,910 individuals in the

reference population, the corresponding figures were: hyperthyroidism: 280 (0.4%), hypothyroidism: 375 (0.5%); and thyroiditis: 52 (0.1%).

In the main analyses we then excluded all individuals with thyroid disease prior to study entry and diagnosis of celiac disease (233 individuals with celiac disease and 1386 in the reference population). Finally, 1,185 individuals with celiac disease and 7,456 in the reference population were excluded due to 1) thyroid disease within the first year of follow-up, 2) death or emigration in that time or 3) in the reference population only, exclusion of all reference individuals belonging to a stratum where the index individuals with celiac disease was excluded (since we used internal stratification).

The main analysis in this study was hence based on 14,021 individuals with celiac disease and a reference population of 68,068 individuals without a diagnosis of celiac disease (Table 1).

### Follow-up time

Follow-up started one year after study entry (equal to the date of first inpatient diagnosis of celiac disease or corresponding date in the matched reference population). Since we used Cox regression, that is a survival analysis, the length of follow up for each study participant is not known at study entry. Follow-up time ended on date of first discharge diagnosis of thyroid disease, emigration, death or end of the study period (31st December 2003), whichever occurred first.

### Socioeconomic index (SEI)

In a subset of individuals (8,642 individuals with celiac disease and 35,843 without celiac disease) Statistics Sweden had data on socioeconomic index (SEI)(26). Some 6,500 of these were children who had been assigned a socioeconomic code on the basis of the occupation of their mother.

### Statistical methods and analyses

Cox regression estimated the hazard ratios (HRs) for subsequent thyroid disease in celiac disease. These analyses were conditioned on risk-set so that an individual with celiac disease

was only compared with his/her age- and sex-matched reference individuals.

In separate analyses we stratified for sex, and age at study entry ( $\leq 15$  years,  $\geq 16$  years). In order to increase the specificity of our outcome measure, we specifically calculated I) HRs for thyroid disease when listed as main diagnosis and II) HRs for thyroid disease when the same individual had received the same thyroid diagnosis at least twice; and III) HRs for thyroid disease when the diagnosis had been recorded in departments of pediatrics, internal medicine, surgery or endocrinology since diagnostic investigations for thyroid disease are most often carried out in these departments.

We also estimated the risk of thyroid disease after adjusting for DM and after excluding all individuals who had a diagnosis of DM before the end of follow-up. We also calculated crude and adjusted risk estimates for thyroid disease in a subset of individuals with data on SEI. In a separate analysis we included the first year after study entry in the follow-up to see if this would affect the risk estimate.

In post-hoc analyses, we estimated the risk of subsequent thyroid disease in individuals with celiac disease compared with a reference population who had been admitted to hospital within less than one year before or after the first diagnosis of celiac disease in the matched individual with celiac disease. To maximize the power we included the first year of follow-up in the post-hoc analyses. This was deemed reasonable since all individuals in the post-hoc-analyses had been admitted to hospital and were therefore at risk of being investigated for thyroid disease due to hospital admission. We chose to adjust for sex, age, and calendar period instead of using internal stratification since some strata only consisted of one individual with celiac disease (and no reference individuals).

95% confidence intervals (CI) for HRs not including 1.00 were considered statistically significant.

Statistics were calculated using SPSS 11.0 (Chicago, Illinois, SPSS Inc. 2002).

### **Thyroid disease and subsequent celiac disease**

From the original cohort of 15,439 individuals with celiac disease and the corresponding reference population we used conditional logistic regression to estimate the odds ratio (OR) for celiac disease (the dependent variable) in individuals with a prior diagnosis of thyroid disease. We performed this analysis to evaluate if the positive association between celiac disease and thyroid disease was restricted to patients with celiac disease preceding thyroid disease. The end of follow-up was defined as date of first celiac disease diagnosis and the same date in the matched reference population without celiac disease. Those with one year or less between the date of first thyroid disease diagnosis and celiac disease diagnosis, and corresponding reference individuals, were excluded.

### **Power calculation**

This study had the power (80%) to detect a risk increase for hyperthyroidism at 5% significance level if the HR for hyperthyroidism exceeded 1.6. For hypothyroidism we needed a HR above 1.5 and for thyroiditis a HR above 2.2.

### **Ethics**

This study was approved by the Research Ethics Committee of the Karolinska Institutet. None of the participants was contacted. Subject information was anonymised prior to the analyses.

## Results

Characteristics of the study participants are presented in Table 1. The majority of study participants were female (58,2%) and the median (range) age at study entry (age at first recorded celiac disease diagnosis and the corresponding date in the reference population) was 2 (0-94) years. Study participants have been divided according to four calendar periods due to the potential change of diagnostic algorithms of celiac disease and thyroid disease over time.

### Celiac disease and subsequent Thyroid disease

Celiac disease was associated with hypothyroidism (HR = 4.4; 95% CI = 3.4-5.6;  $p < 0.001$ ), thyroiditis (HR = 3.6; 95% CI = 1.9-6.7;  $p < 0.001$ ) and hyperthyroidism (HR = 2.9; 95% CI = 2.0-4.2;  $p < 0.001$ ) (Tables 2-4). The highest risk estimates were found in children (hypothyroidism HR = 6.0; 95% CI = 3.4-10.6, thyroiditis HR = 4.7; 95% CI = 2.1-10.5 and hyperthyroidism HR = 4.8; 95% CI = 2.5-9.4). The risk estimates remained statistically significant when we used the following outcome measures: 1) receiving at least two hospital discharge diagnoses of thyroid disease 2) thyroid disease listed as main discharge diagnosis or 3) thyroid disease diagnosed in a department of Pediatrics, Internal Medicine, Surgery or Endocrinology (Tables 2-4). The relative risk of hypothyroidism in individuals with celiac disease was higher in males than in females (HR 11.2 vs 3.5). The same gender difference could not be seen in hyperthyroidism and thyroiditis. Adjustment for SEI, did not affect our risk estimates (data not shown). Risk estimates were similar in the different calendar periods (data not shown).

Individuals with celiac disease were also at increased risk of later hyperthyroidism requiring surgery of the thyroid gland (HR = 2.4; 95% CI = 1.4-4.3;  $p = 0.002$ ; based on 19 individuals with celiac disease and 37 reference individuals).

Incidence rates (per 100,000 person-years) for thyroid disease were consistently higher in individuals with celiac disease than in matched reference individuals: hypothyroidism: 67 vs.

20; thyroiditis: 9 vs. 3; and hyperthyroidism: 25 vs. 10 (Table 5).

In post-hoc analyses, we restricted our reference population to individuals who had been admitted to hospital at the time of study entry. This did not influence our risk estimates more than marginally (Tables 2-4).

### Thyroid disease and subsequent celiac disease

Conditional logistic regression showed an increased risk of celiac disease in individuals with prior hypothyroidism (Odds Ratio = 3.8; 95% CI = 2.8-5.2;  $p < 0.001$ ), thyroiditis (OR = 4.0; 95% CI = 2.2-7.2;  $p < 0.001$ ) and hyperthyroidism (OR = 2.0; 95% CI = 1.5-2.8;  $p < 0.001$ ) (Table 6).

## Discussion

We found a statistically significantly increased risk of hypothyroidism, thyroiditis and hyperthyroidism in individuals with celiac disease. Our study is the largest longitudinal study of the risk of thyroid disease in individuals with celiac disease up to date. The large number of individuals with celiac disease and the fact that we used a matched reference population enabled us to calculate reliable risk estimates. Part of this association may be due to surveillance bias. However, surveillance bias is unlikely to fully explain the positive association between celiac disease and thyroid disease, since the association was seen in all strata (males, females, children and adults), and did not vanish after adjustment for potential confounders including the presence of DM. The positive association also remained when we excluded the first year of follow up in order to minimize the risk of surveillance bias during the first year after study entry. The sex differences in the association of thyroid disease type with celiac disease may be due to chance, alternatively these differences may reflect sex-specific variation in the phenotypes of autoimmune disease.

The association between celiac disease and thyroid disease probably reflects the general increase of autoimmune disease seen in celiac disease(4, 23) and might be explained by the presence of shared genetic traits. Both HLA DQ2 (HLA-DQA1\*05-DQB1\*02) and DQ8 (HLADQA1\*03-DQB1\*0302) are common both in thyroid disease(21, 27) and celiac disease(28), and patients with overlapping disease are often HLA DQ2-positive(3, 15). In a recent study by Hadithi et al, 53 out of 104 consecutive patients with Hashimoto's thyroiditis were HLA DQ2-positive(21). We have previously examined celiac disease and the risk of type 1 diabetes mellitus(23) in this cohort. After excluding the first year after celiac disease diagnosis, the risk of later DM in individuals with celiac disease (and no prior DM) was similar to that in any HLA-DQ2-positive individual(29). Considering that a vast majority of individuals with celiac disease are HLA DQ2-positive(28), we suggest that shared HLA is a plausible explanation also for the increased risk of thyroid disease in celiac disease. Another potential explanation may be

found in the increased expression of T lymphocyte-associated antigen 4 (CTLA4). CTLA4 is a T cell surface molecule involved in control of T cell proliferation. An increased expression of CTLA4 has been seen in both Graves' disease(30, 31) and hypothyroidism(30); as well as other autoimmune diseases such as DM(32). CTLA4 is also more common in celiac disease(33, 34). The presence of shared genetic risk factors might hence explain the positive association between celiac disease and thyroid disease.

Our study confirms the positive association between celiac disease and thyroid disease. Although, earlier studies have suggested a positive association between celiac disease and thyroid disease(3, 4, 6-17, 19-22), the majority of these studies have either been cross-sectional(3, 4, 6-17, 19, 21, 22), lacked controls(6, 9, 21, 22) or failed to attain statistical significance(4, 8, 12). In 2005 Viljamaa et al(20) conducted a longitudinal study of thyroid disease in a cohort of individuals with celiac disease. This study indicated an increased incidence of thyroid disease in celiac disease but results did not reach statistical significance. To the best knowledge of the authors, our study is the first study to present a statistically significant risk increase of hyperthyroidism in individuals with celiac disease.

The study participants were identified through the national inpatient register (IPR). Misclassification of celiac disease is uncommon in the IPR (>85% of individuals with IPR diagnoses of celiac disease and concomitant lymphoma, were correctly classified with regards to celiac disease)(35) due to the well-established practice to carryout a small-bowel biopsy prior to the celiac disease diagnosis(36). This has been done in an inpatient setting during most of the study period and still does in small children who often need general anaesthesia during endoscopy. Not all individuals with celiac disease will be identified through a hospital-based register but this should be no major drawback since we nevertheless had access to morbidity data in more than 14,000 individuals with celiac disease. There is also a risk that individuals with celiac disease

identified through a hospital-based register have more severe disease than the average individual with celiac disease and are therefore at increased risk of any disease. However, the positive association between celiac disease and subsequent thyroid disease remained statistically significant when we restricted our reference population to inpatients. This means that ascertainment bias due to hospital admission in individuals with celiac disease is unlikely to explain the positive association between celiac disease and thyroid disease. Although, we cannot rule out the risk of misclassification, this should only be a concern if it differs between those with celiac disease and the reference population (i.e. differential misclassification). To our knowledge there are no validation studies of thyroid disease in the IPR. Nilsson et al (37) in their systematic analysis of the reliability of diagnosis of ICD 8 in the IPR, however found that 88-90% of listed main diagnoses were correct. In ICD 9 and 10 this percentage should be even higher and incorrect diagnoses are also likely to result in conservative risk estimates. To reduce the risk of differential misclassification we also validated our diagnosis through estimating the risk of having at least two hospital discharge diagnoses of thyroid disease and receiving the diagnosis in departments of pediatrics, internal medicine, surgery or endocrinology (where misclassification is

supposed to be low). Restricting our outcome measure in this way did not influence our risk estimates. The highest risk estimates of thyroid disease in individuals with celiac disease were seen in children. A possible explanation for this might be that autoimmune thyroid disease dominates in children whereas in adults non-autoimmune causes of thyroid disease are common. However, we cannot rule out that children with thyroid disease were more likely to be admitted to hospital than adults and that this partly accounts for the age-specific differences in the risk of thyroid disease. A protective effect of gluten free-diet in celiac disease has previously been reported by Ventura et al(4). This could not be confirmed in the current study where risk estimates were similar both prior to and subsequent to diagnosis and presumed gluten introduction.

This study concludes that celiac disease is associated with hypothyroidism and thyroiditis as well as hyperthyroidism. These associations were seen regardless of temporal sequence, and we therefore suggest that the increased risk of thyroid disease in celiac disease is an expression of a more general increase in autoimmunity that characterizes many individuals with celiac disease. The positive association between celiac disease and thyroid disease may be due to shared genetic or immunological traits.

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**Table 1** Characteristics of participants with at least one year of follow-up\*

Characteristics	Reference population (No celiac disease) (%)	Celiac disease (%)
Total	68,068	14,021
Age at first recorded diagnosis of celiac disease (years)		
0-15		9,338 (66.6)
≥16		4,683 (33.4)
Age at end of follow-up (years)		
0-15	18,050 (26.5)	3,659 (26.1)
≥16	50,018 (73.5)	10,362 (73.9)
Sex		
Male	28,473 (41.8)	5,861 (41.8)
Female	39,595 (58.2)	8,160 (58.2)
Calendar Period		
1964-1973	2,396 (3.5)	493 (3.5)
1974-1983	18,972 (27.9)	3,885 (27.7)
1984-1993	30,028 (44.1)	6,169 (44.0)
1994-2003	16,672 (24.5)	3,474 (24.8)
Socioeconomic index		
I	7,097 (10.4)	1,469 (10.5)
II	9,020 (13.6)	2,100 (15.0)
III	19,726 (29.0)	5,073 (36.2)
Missing data	32,225 (47.3)	5379 (38.4)
Median age at first thyroid disease (range)	67 (2-96)	56 (2-93)
Median duration until first thyroid disease (range)	9 (1-31)	6 (1-31)
Diabetes Mellitus	1,840 (2.7)	876 (6.2)

\*Individuals with at least one year of follow-up after celiac disease diagnosis or corresponding date in matched individuals. See also text.

Socioeconomic index. "I" is highest category. See also text.

For reference population we have given the number of individuals who constituted the basis for the Cox regression. We actually had data on socioeconomic index in another 6,297 individuals in the reference population; but these individuals were not part of the internally stratified calculations due to missing values on socioeconomic index in the matched individual with celiac disease. Adding the 6,297 reference

individuals to those presented above, the proportion of missing values was similar among individuals with celiac disease and the reference population.

**TABLE 2.** Celiac disease and risk of subsequent Hypothyroidism

<b>Outcome</b>	<b>Positive events in reference population*</b>	<b>Positive events in celiac disease *</b>	<b>HR#, 95% CI</b>	<b>p-value</b>
Thyroid disease	191	127	4.4; 3.4-5.6	<0.001
Adjusting for DM	191	127	4.1; 3.2-5.3	<0.001
<i>Subgroups</i>				
Diagnosis of celiac disease in childhood	22	27	6.0; 3.4-10.6	<0.001
Diagnosis of celiac disease in adulthood	169	100	4.1; 3.1-5.4	<0.001
Male	30	37	11.2; 6.0-20.8	<0.001
Female	161	90	3.5; 2.7-4.7	<0.001
≥2 diagnoses of Hypothyroidism	86	66	5.2; 3.6-7.4	<0.001
Hypothyroidism is main diagnosis	20	11	3.0; 1.4-6.8	0.006
Dept. of pediatrics, internal medicine, surgery or endocrinology	88	71	4.9; 3.5-6.8	<0.001
<i>First year included</i>				
Hypothyroidism	238	261	8.5; 6.9-10.5	<0.001
Compared with inpatients				
Hypothyroidism	87	261	3.4; 2.7-4.4	<0.001

DM = Diabetes mellitus. # HR = Hazard ratio.

\* Number of positive events among individuals with celiac disease and among the reference population. E.g. in the main analyses 191 reference individuals and 127 individuals with celiac disease had a subsequent diagnosis of hypothyroidism.

**TABLE 3.** Celiac disease and risk of subsequent Thyroiditis

<b>Outcome</b>	<b>Positive events in reference population*</b>	<b>Positive events in celiac disease *</b>	<b>HR#, 95% CI</b>	<b>p-value</b>
Thyroid disease	24	17	3.6; 1.9-6.7	<0.001
Adjusting for DM	24	17	2.7; 1.3-5.5	0.007
<i>Subgroups</i>				
Diagnosis of celiac disease in childhood	12	12	4.7; 2.1-10.5	<0.001
Diagnosis of celiac disease in adulthood	12	5	2.2; 0.8-6.5	0.146
Male	3	1	2.3; 0.2-25.6	0.493
Female	21	16	3.7; 1.9-7.1	<0.001
≥2 diagnoses of Thyroiditis	2	6	14.2; 2.9-70.4	0.001
Thyroiditis is main diagnosis	7	4	2.7; 0.8-9.4	0.108
Dept. of pediatrics, internal medicine, surgery or endocrinology	23	16	3.5; 1.8-6.8	<0.001
<i>First year included</i>				
Thyroiditis	25	27	5.5; 3.1-9.6	<0.001
Compared with inpatients				
Thyroiditis	7	27	3.3; 1.5-7.7	<0.001

DM = Diabetes mellitus. # HR = Hazard ratio.

\* Number of positive events among individuals with celiac disease and among the reference population. E.g. in the main analyses 24 reference individuals and 17 individuals with celiac disease had a subsequent diagnosis of thyroiditis.

**TABLE 4.** Celiac disease and risk of subsequent Hyperthyroidism

<b>Outcome</b>	<b>Positive events in reference population*</b>	<b>Positive events in celiac disease *</b>	<b>HR#, 95% CI</b>	<b>p-value</b>
Thyroid disease	100	48	2.9; 2.0-4.2	<0.001
Adjusting for DM	100	48	2.9; 2.0-4.3	<0.001
<i>Subgroups</i>				
Diagnosis of celiac disease in childhood	17	17	4.8; 2.5-9.4	<0.001
Diagnosis of celiac disease in adulthood	83	31	2.4; 1.5-3.7	<0.001
Male	14	7	3.1; 1.2-8.2	0.023
Female	86	41	2.9; 1.9-4.2	<0.001
≥2 diagnoses of Hyperthyroidism	33	15	2.7; 1.4-5.1	0.003
Hyperthyroidism is main diagnosis	66	32	2.8; 1.8-4.3	<0.001
Dept. of pediatrics, internal medicine, surgery or endocrinology	81	39	2.7; 1.8-4.0	<0.001
Hyperthyroidism requiring surgery of the thyroid gland	37	19	2.4; 1.4-4.3	0.002
<i>First year included</i>				
Hyperthyroidism	118	81	4.2; 3.1-5.7	<0.001
<i>Compared with inpatients</i>				
Hyperthyroidism	27	81	3.1; 2.0-4.8	<0.001

DM = Diabetes mellitus. # HR = Hazard ratio.

\*Number of positive events among the reference population and individuals with celiac disease. E.g. in the main analyses 100 reference individuals and 48 individuals with celiac disease had a subsequent diagnosis of hyperthyroidism.

**TABLE 5.** Incidence of thyroid disease

Type	Reference population			Individuals with celiac disease	
	Stratum	Person-years	Incidence Events / 100,000 person- years	Person-years	Incidence Events / 100,000 person-years
<i>Hypothyroidism</i>	Any	191/952773	20	127/188609	67
	Child	22/695056	3	27/141082	19
	Adult*	169/257718	66	100/47527	210
	Adult end*#	225/828546	27	231/157889	146
	Female	161/550268	29	90/109430	82
	Male	30/402504	7	37/79178	47
	First Year	238/1056017	23	261/203923	128
<i>Thyroiditis</i>	Any	24/953356	3	17/189116	9
	Child	12/695066	2	12/141194	8
	adult*	12/258290	5	5/47922	10
	Adult end*#	18/829251	2	14/158934	9
	Female	21/550750	4	16/109757	15
	Male	3/402606	1	1/79360	1
	First Year	25/1056729	2	27/205025	13
<i>Hyperthyroidism</i>	Any	100/952842	10	48/188960	25
	Child	17/695082	2	17/141185	12
	adult*	83/257760	32	31/47774	65
	Adult end*#	114/828599	14	73/158644	46
	Female	86/550274	16	41/109658	37
	Male	14/402568	3	7/79301	9
	First Year	118/1056072	11	81/204716	40

\*Individuals who were adults at study entry and diagnosis of celiac disease.

# Individuals were adults at end of follow-up. These individuals may have been diagnosed with celiac disease in either childhood or adulthood. Incidence figures are based on person-years both in childhood and adulthood.

**TABLE 6.** Thyroid disease and risk of subsequent celiac disease

<b>Outcome</b>	<b>OR#, 95% CI</b>	<b>p-value</b>
Hypothyroidism	3.8; 2.8-5.2	< 0.001
Thyroiditis	4.0; 2.2-7.2	< 0.001
Hyperthyroidism	2.0; 1.5-2.8	< 0.001

# OR = Odds ratio.