

Primary Hyperparathyroidism and Celiac Disease: A Population-Based Cohort Study

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Context: Celiac disease (CD) has been linked to several endocrine disorders, including type 1 diabetes and thyroid disorders, but little is known regarding its association to primary hyperparathyroidism (PHPT).

Objective: The aim of the study was to examine the risk of PHPT in patients with CD.

Design and Setting: We conducted a two-group exposure-matched nonconcurrent cohort study in Sweden. A Cox regression model estimated hazard ratios (HR) for PHPT.

Participants: We identified 17,121 adult patients with CD who were diagnosed through biopsy reports (Marsh 3, villous atrophy) from all 28 pathology departments in Sweden. Biopsies were performed in 1969–2008, and biopsy report data were collected in 2006–2008. Statistics Sweden then identified 85,166 reference individuals matched with the CD patients for age, sex, calendar period, and county.

Main Outcome Measure: PHPT was measured according to the Swedish national registers on inpatient care, outpatient care, day surgery, and cancer.

Results: During follow-up, 68 patients with CD and 172 reference individuals developed PHPT (HR = 1.91; 95% confidence interval = 1.44–2.52). The absolute risk of PHPT was 42/100,000 person-years with an excess risk of 20/100,000 person-years. The risk increase for PHPT only occurred in the first 5 yr of follow-up; after that, HR were close to 1 (HR = 1.07; 95% confidence interval = 0.70–1.66).

Conclusions: CD patients are at increased risk of PHPT, but the absolute risk is small, and the excess risk disappeared after more than 5 yr of follow-up. (*J Clin Endocrinol Metab* 97: 897–904, 2012)

Primary hyperparathyroidism (PHPT), a common endocrine disorder characterized by overproduction of PTH, is most frequently caused by a benign parathyroid adenoma (1). Diagnosis often follows incidental discovery of hypercalcemia because a large proportion of individuals with PHPT are asymptomatic (2, 3).

Celiac disease (CD) is an immune-mediated disease characterized by small intestinal inflammation and villous

atrophy (VA) in genetically predisposed individuals (4). It occurs in approximately 1% of the Western population (5) and has previously been linked to common endocrine disorders such as type 1 diabetes (6) and thyroid disease (7). In a single-center observational study, Maida *et al.* (8) reported a PHPT prevalence of 2.3% in patients with CD (seven of 310). Although this study had no comparison group, it raises the possibility of an association between

CD and PHPT, even if the magnitude of such an association is difficult to estimate because the reported incidence of PHPT has varied widely with calendar period and geographic area. In addition to the Maida *et al.* (8) study, an association between CD and PHPT has been suggested in several case reports (9, 10). However, in the absence of studies of larger patient populations, the findings have been inconclusive. The aim of the current study was therefore to examine the risk of PHPT in a large nationwide cohort of patients with biopsy-verified CD.

Subjects and Methods

Through the personal identity number (PIN), we linked nationwide biopsy report data on CD with PHPT data with national registers on inpatient care, outpatient care, day surgery, and cancer. For this we used a two-group exposure-matched nonconcurrent cohort study design.

Celiac disease

We collected data from small intestinal biopsy reports performed in 1969–2008 from all Swedish pathology departments ($n = 28$) (Table 1). We defined CD as having VA (equivalent to Marsh grade 3; see Supplemental Data, published on The Endocrine Society's Journals Online web site at <http://jcem.endojournals.org>) (11). Although positive CD serology was not

a requirement for CD diagnosis, 88% of a random subset of patients with available CD serology at the time of biopsy were serologically positive (12).

Information technology personnel at each pathology department searched computerized databases for biopsy reports and sent the following information to us: dates of the biopsies, personal identity number of the patient (13), morphology according to the Swedish SnoMed classification codes (see Supplemental Data for a translation into international classification systems), and topography (duodenum and jejunum). The restriction to computerized data explains why most patients in our study had been biopsied from 1990 and later (Table 1).

The CD cohort used here was based on the 29,096 individuals with CD in our recent paper on mortality in CD (14). For each individual with CD, Statistics Sweden identified up to five reference individuals. Reference individuals were matched exactly to patients with CD for sex, age, county, and calendar period ($n = 144,522$). For instance, a woman born in 1960, diagnosed with CD in the county of Halland in 1983 was matched to five other women born in 1960 and living in Halland in 1983. None of the reference individuals had a diagnosis of CD at the time of matching. Reference individuals were identified from the total population register (15). The total population register includes information on the personal identity number, area of residence, sex, age, civil status, and dates of emigration in all Swedish residents. We then excluded study participants who had been diagnosed with PHPT before study entry and CD diagnosis (Fig. 1) and study participants whose reference individuals/index individuals had been excluded for any reason. Because uremia is associated with CD (16) and may cause secondary or tertiary hyperparathyroidism, we also excluded patients who had a diagnosis of uremia at some stage in their life (17). Finally, we restricted our dataset to adults aged 20 yr or older. This restriction was enforced because we had insufficient follow-up to study the risk of future PHPT in individuals diagnosed with CD in childhood. A detailed description of exclusions is given in Fig. 1. The final sample consisted of 17,121 individuals with CD and 85,166 in the age- and sex-matched comparison cohort.

For the purpose of comparison, we also identified individuals undergoing small intestinal biopsy but without VA [inflammation (Marsh 1–2); $n = 13,306$] and individuals with normal mucosa but positive IgA/IgG gliadin or endomysium or tissue transglutaminase antibodies ($n = 3,719$; most of these had tested positive for IgA gliadin). These two cohorts were identical to those in our earlier paper on mortality in CD (14). We then excluded anyone with a prior diagnosis of PHPT. We used individuals undergoing small intestinal biopsy but without VA as secondary reference individuals.

Primary hyperparathyroidism

PHPT was defined using relevant International Classification of Disease (ICD) codes. The following codes and registers were used to identify patients with PHPT: *National Patient Register*, which included day surgery—diagnostic codes, ICD-7, 271.0, and ICD-8, 252.0 (hyperparathyroidism); ICD-9, 252A, and ICD-10, E21.0 (PHPT); surgery codes, 0851, 0852, 0853, BBA30, BBA40, and BBA50 (Swedish surgical codes for removal of single or multiple parathyroid glands or subtotal parathyroidectomy); and *Cancer Register*, ICD-7, 195.1 (adenoma originating in the parathyroid gland). Initially this study included 241 cases of parathyroid adenoma, but after linkage to histopathol-

TABLE 1. Characteristics of the study participants

	Matched reference individuals	CD patients
n	85,166	17,121
Age at study entry, yr (median; range)	50; 20–95	50; 20–95
Attained age, yr (median; range)	62; 21–105	61; 21–100
Ages 20–39, n (%)	26,350 (30.9)	5,289 (30.9)
Ages 40–59, n (%)	32,110 (37.7)	6,419 (37.5)
Ages ≥60, n (%)	26,706 (31.4)	5,413 (31.6)
Entry year (median; range)	1999; 1969–2008	1999; 1969–2008
Follow-up, yr (median; range) ^a	9; 0–40	8; 0–35
Follow-up, yr (mean ± SD) ^a	9.8 ± 6.1	9.5 ± 6.1
Females, n (%)	52,116 (61.2)	10,470 (61.2)
Males, n (%)	33,050 (38.8)	6,651 (38.8)
Calendar year, n (%)		
1989	11,089 (13.0)	2,217 (12.9)
1990–1999	35,111 (41.2)	7,061 (41.2)
2000	38,966 (45.8)	7,843 (45.8)
Type 1 diabetes, n (%)	232 (0.3)	198 (1.2)
Autoimmune thyroid disease, n (%)	315 (0.4)	187 (1.1)

Ages were rounded to the nearest year.

^a Follow-up time until diagnosis of PHPT, death, emigration, or December 31, 2008. In reference individuals, follow-up can also end through small intestinal biopsy.

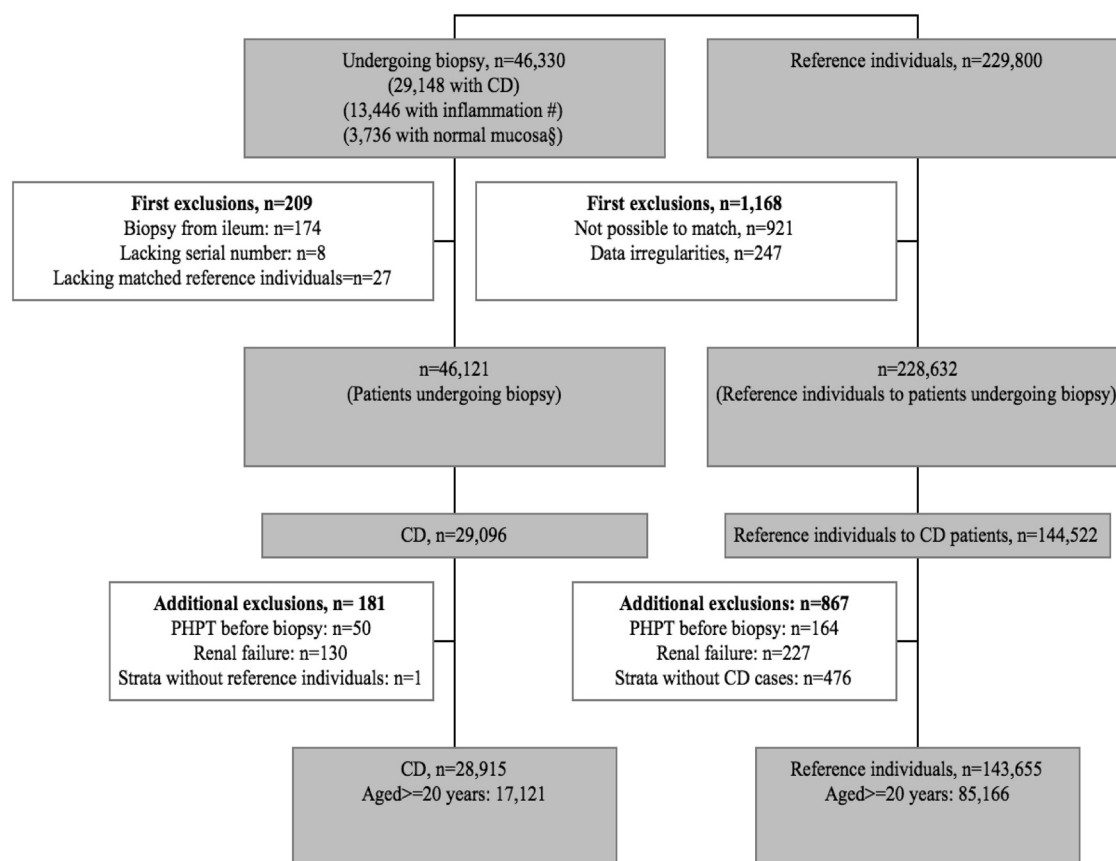


FIG. 1. Flowchart of study participants. #, Inflammation (intraepithelial lymphocytosis) equals Marsh 1–2; §, normal mucosa with positive IgA/IgG endomysium, transglutaminase, or gliadin antibodies.

ogy codes of the Cancer Registry, one of these suffered from malignant carcinoma (histopathology code “096”) in the parathyroid gland and was not counted as PHPT. Because of the low incidence of PHPT in young individuals and because of the increased incidence of multiple endocrine neoplasia in younger patients with PHPT (18), we considered only incident PHPT cases in patients aged 45 yr and older in our analysis.

Covariates

Type 1 diabetes and autoimmune thyroid disease were identified through the Swedish Patient Register (see Supplemental Data for ICD codes). CD has been associated with both type 1 diabetes (19) and thyroid disease (7). Although reports of increased incidence of these conditions in PHPT (20–22) may reflect ascertainment bias, we adjusted for these factors as well. Education was defined according to seven predefined categories. Data on country of birth (Nordic and non-Nordic countries) were obtained from Statistics Sweden.

Statistics

We used Cox regression analysis to estimate hazard ratio (HR) for PHPT. Our Cox regression model was internally stratified for age, sex, county, and calendar year. Accordingly, each individual with CD was only compared with his or her reference individuals regarding future PHPT; age, sex, county, and calendar year had no influence on our risk estimates for PHPT.

Follow-up time began on the date of the first biopsy with VA and on the corresponding date in matched reference individuals.

For example, if a patient with CD entered the study in 1983 (year of biopsy), then the reference individuals in his/her stratum also began their follow-up in 1983. Follow-up ended with a diagnosis of PHPT (in any of the national registers on cancer, day care surgery, inpatient care, or hospital-based outpatient care), death, emigration, or on December 31, 2008, whichever occurred first.

We also evaluated the risk of PHPT according to follow-up time (<1 yr, 1–<5 yr, and ≥5 yr), sex, age at CD diagnosis (20–39, 40–59, and ≥60 yr at first biopsy), and calendar period of the first biopsy with CD (1989 and earlier, 1990–1999, and 2000). Incidence rates were calculated using the number of first PHPT events divided by the number of person-years at risk. Attributable risks (percentage) were calculated as $(1 - 1/HR)$. We also examined the risk of PHPT after adjusting for type 1 diabetes, autoimmune thyroid disease, education, and country of birth.

Secondary analyses

In a prespecified secondary analysis, we first examined the association between CD and PHPT as diagnosed exclusively through the cancer register. This was done because a parathyroid adenoma diagnosis in this register is likely to have a high positive predictive value (PPV).

We also compared the risk of PHPT in biopsy-proven CD *vs.* that in individuals without VA [inflammation (Marsh 1–2), (11), $n = 11,920$; and normal mucosa (Marsh 0), (11), with positive serology to gliadin, endomysium, or tissue transglutaminase antibodies, $n = 2,762$]. This latter analysis was not internally strat-

ified, but instead we adjusted for age, sex, and calendar period. In a final secondary analysis, we excluded anyone with a diagnosis of Zollinger-Ellison syndrome, hyperprolactinemia, hypophyseal adenoma, or endocrine pancreatic cancer. We used relevant ICD codes to identify these individuals through the National Patient Register (Supplemental Data). These conditions can all be associated with PHPT in multiple endocrine neoplastic syndromes.

Because PHPT is a disease in which over half of all affected patients are postmenopausal women, in a *post hoc* analysis we examined the risk of PHPT in women diagnosed with CD before or after assumed menopause (≤ 50 yr *vs.* ≥ 51 yr) (23).

Statistical significance was defined as 95% confidence intervals (CI) for risk estimates not including 1.0. SPSS 18.0 software (SPSS Inc., Chicago, IL) was used for the statistical analysis.

Ethics

This project (2006/633-31/4) was approved by the Research Ethics Committee of the Karolinska Institute, Sweden (June 14, 2006).

Results

Background data

Most adults with CD were female (Table 1), with equal proportions undergoing biopsy when aged 20–39 yr, 40–59 yr, and ≥ 60 yr of age. Almost 90% of the individuals had been biopsied in 1990 or later.

PHPT was diagnosed in 240 individuals (68 patients with CD and 172 reference individuals). The median age at incident PHPT diagnosis was 64 yr in patients with CD (range, 46–89) and 69 yr in reference individuals (range, 45–91). The median duration from study entry until PHPT diagnosis was 4 yr in CD patients and 7 yr in reference individuals. The follow-up time was similar in CD patients and in reference individuals (Table 1).

Main results

Patients with CD were at an increased risk of PHPT (HR = 1.91; 95% CI = 1.44–2.52; Table 2). This risk did not change materially with adjustment for type 1 diabetes, autoimmune thyroid disease, country of birth, or educa-

tion (data not shown). Excluding the first year of follow-up when there is risk of ascertainment bias, the HR for PHPT remained elevated (HR = 1.80; 95% CI = 1.35–2.42). The increased risk of PHPT was, however, only present in the first 5 yr of follow-up (Table 2); after that period, the excess risk disappeared, and the HR was close to unity.

Although the risk of PHPT was higher in women with CD (HR = 2.00) than in men with CD (HR = 1.42), this difference was not statistically significant (*P* for interaction = 0.378) (Table 3). HR for PHPT did not differ according to age at CD diagnosis (*P* for interaction = 0.533) or with calendar period (*P* for interaction = 0.205).

Secondary analyses

Restricting our outcome to PHPT with an adenoma diagnosis in the National Cancer Register, the HR was 2.53 (95% CI = 1.60–4.01).

In comparison with individuals undergoing small intestinal biopsy but not having VA, individuals with CD were at no increased risk of PHPT (*vs.* inflammation, HR = 1.03, 95% CI = 0.67–1.51; and *vs.* normal mucosa with positive CD serology, HR = 1.30, 95% CI = 0.56–3.03).

In the main analyses we only accepted a diagnosis of PHPT if the individuals were at least 45 yr of age. Six patients with CD and seven reference individuals had a PHPT diagnosis before the age of 45 yr (see the Supplemental Data for their exact age distribution). When we included those patients with PHPT with onset before age 45 yr as a positive outcome, the HR for PHPT in CD was 1.99 (95% CI = 1.52–2.60).

When we excluded anyone with Zollinger-Ellison syndrome, hyperprolactinemia, pituitary adenoma, or endocrine pancreatic cancer, the HR for PHPT in CD was 1.80 (95% CI = 1.35–2.39). (This analysis was based on 17,054 individuals with CD and 84,974 reference individuals.)

In a first *post hoc* analysis, we restricted our analysis to PHPT occurring in 1987 or later (because ICD coding

TABLE 2. Risk of PHPT based on follow-up time in individuals with CD

Follow-up	Observed events	Expected events ^b	HR; 95% CI	P-value	Follow-up time (yr)	Absolute risk/100,000 PYAR	Excess risk/100,000 PYAR	Attributable percentage
All	68	36	1.91; 1.44–2.52	<0.001	162,356	42 ^a	20	48
Year <1	7	2	3.70; 1.47–9.35	0.006	16,811	42	30	73
Years 1–4.99 yr	36	11	3.29; 2.18–4.96	<0.001	59,215	61	42	70
Years ≥ 5	25	23	1.07; 0.70–1.66	0.754	86,330	29	2	7

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

^a Incidence in reference individuals was 22/100,000 person-years.

^b Expected number of events in patients with CD was derived from the observed number of events divided by the HR.

TABLE 3. Risk of PHPT in relation to characteristics of patients with CD

Subgroup	Observed events	Expected events ^a	HR; 95% CI	P value	Follow-up time (yr)	Absolute risk/100,000 PYAR	Excess risk/100,000 PYAR	Attributable percentage
Sex								
Males	8	6	1.42; 0.65–3.13	0.381	61,826	13	4	30
Females	60	30	2.00; 1.49–2.70	<0.001	100,530	60	30	50
Age								
20–39 yr	2	2	0.93; 0.21–4.16	0.924	54,243	4	0	–8
40–59 yr	31	16	1.96; 1.30–2.97	0.001	68,222	45	22	49
≥60	35	18	1.98; 1.34–2.93	0.001	39,891	88	43	49
Calendar period								
1989	15	10	1.52; 0.84–2.77	0.166	40,385	37	13	34
1990–1999	33	20	1.68; 1.14–2.50	0.009	81,638	40	16	41
2000–2008	20	7	3.06; 1.79–5.20	<0.001	40,333	50	33	67

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

^a Expected number of events in patients with CD was derived from the observed number of events divided by the HR.

before that year was less certain). The HR was then 1.77 (95% CI = 1.33–2.36). Our second *post hoc* analysis found that HR for PHPT were higher in women diagnosed with CD after assumed menopause (HR = 2.14; 95% CI = 1.52–3.01) than in women diagnosed earlier in life (HR = 1.59; 95% CI = 0.85–2.96). The difference in HR was, however, nonsignificant (*P* for interaction = 0.398).

Discussion

CD is classically associated with evidence of vitamin D deficiency and calcium malabsorption, both causes of secondary hyperparathyroidism. Although the constellation of CD and elevated PTH levels are therefore expected, the association of CD with hypercalcemia and subsequent diagnosis of PHPT is not. After prior anecdotal reports of the coexistence of these conditions, this report sought to validate (or repudiate) the association. Using a large population-based sample, the current study found a 2-fold increased risk of PHPT in patients with CD. Exclusion of a diagnosis of PHPT in the first year of follow-up, when ascertainment bias is most likely to increase the HR, did not affect the risk estimate.

Data on the association of PHPT and CD are sparse. A British study found PHPT in seven of 310 patients with CD (2.3%) (8). Interestingly, most of their PHPT cases were diagnosed 1–5 yr after CD, the “delay” being explained by the low or low-normal vitamin D levels in these patients at the time of CD diagnosis (8). Of the seven patients with PHPT, three had substantial vitamin D improvement after treatment of PHPT. Therefore, Maida *et al.* (8) suggest that PHPT may be considered in CD patients not improving on dietary treatment. Wu *et al.* (10) recently reported two cases of individuals with both CD and PHPT. One

woman had severe osteomalacia, whereas the other suffered from generalized weakness, anxiety, and depression.

We used biopsy reports to ascertain CD. Biopsy reports with VA have a high PPV for CD (95%), and nearly all (96–100%) gastroenterologists and pediatricians in Sweden perform a biopsy in at least nine of 10 patients with suspected CD before diagnosis (12). The median number of specimens obtained at each biopsy in our study was three, which should identify approximately 95% of all CD cases (24). Although we know of no validation study of PHPT in Swedish registers, the PPV for most disorders in the Swedish Inpatient Register is about 85–95% (25). In our study, the overall incidence of PHPT was 22/100,000 person-years in the nonceliac control group. This is virtually identical to U.S. data (26). The age- and gender-adjusted incidence of PHPT, as determined by Wermers *et al.* (26) in the Rochester Epidemiology Project, was 21.6/100,000 person-years. In an older Swedish paper, the incidence of PHPT was 28/100,000 person-years (27).

We cannot definitively rule out the possibility that part of the risk increase for PHPT is due to bias in the sense that the highest risk estimates were found in the first year after diagnosis when surveillance of CD patients is more intense. We lack information on how PHPT was diagnosed in individual patients and cannot rule out the possibility that investigation of suspected PHPT differed among CD patients and reference individuals. An alternative explanation for the higher HR in the first year is that treatment for CD may have “unmasked” PHPT. Severe vitamin D deficiency could have depressed serum calcium levels into the normal range before diagnosis. Subsequent treatment of CD would then allow improved absorption of calcium and vitamin D, emergence of hypercalcemia, and subsequent diagnosis of PHPT. Thus, treatment with a gluten-

free diet may unmask PHPT by means of repletion of vitamin D stores. It is also possible that small intestinal inflammation with increased autoantibody levels trigger PHPT. The excess risk of PHPT might then gradually vanish after introduction of a gluten-free diet and the healing of the mucosa.

The risk of PHPT in CD did not differ from that in other individuals undergoing small intestinal biopsy but not having VA. This lack of association may be due to insufficient power in this subanalysis because patients with VA had a 30% (nonsignificantly) higher risk than individuals with a normal mucosa. An alternative explanation is that biopsied patients with a normal mucosa may receive a more intensive follow-up, similar to that of CD patients. Due to the lack of data on individual patients, we were unable to restrict this subanalysis to CD patients and secondary reference individuals with gastrointestinal symptoms.

Depending on the year of diagnosis, we observed different risk increases for PHPT. No significant association was noted in persons diagnosed before 1989, whereas the risk increased in the subsequent calendar periods. In the earlier period, vitamin D measurement was more problematic, and there was little appreciation of the importance of vitamin D repletion in patients with CD. This situation may have led to less frequent repletion of vitamin D, which in turn could have prevented hypercalcemia and subsequent diagnosis of PHPT. In the last calendar period, the HR for PHPT was over 3. This relatively high ratio could be explained by greater appreciation among those caring for celiac patients for the importance of vitamin D and calcium repletion. These practice patterns may have led to more frequent treatment with calcium and vitamin D, as well as more common assessment for PHPT in the most recent calendar period. In addition, the follow-up of CD patients diagnosed after 1999 was shorter, and thus the higher risk of PHPT in the first year will play a larger role for the overall HR. Another possible contribution to the gradually increasing HR for PHPT over time may be the increased awareness over the past several decades of issues surrounding skeletal health. Patients with CD are at increased risk of osteoporosis (28, 29). Heightened public health awareness of this issue, increased availability of bone densitometry, or postfracture investigations in patients with CD could all lead to a diagnosis of PHPT.

The excess risk for PHPT vanished after 5 yr of follow-up. A decrease of HR with increasing follow-up has been observed for both mortality (14) and a number of comorbidities (30–33) in CD. One potential explanation for this decrease in risk estimates includes the beneficial effect of the gluten-free diet. It is also possible that some patients take a long period after diagnosis to become vitamin D

replete and unmask hypercalcemia. Although 5 yr seems unusually long, it could be that ascertainment bias is no longer operative after 5 yr.

One weakness in our analysis is the risk of misclassification. In their study, Stenson *et al.* (28) reported that most CD patients with osteoporosis have secondary hyperparathyroidism with vitamin D deficiency, and there is strong evidence that CD is linked to vitamin D malabsorption (34). Although we restricted our ICD codes to PHPT, some patients who were classified as having PHPT may actually have had secondary hyperparathyroidism, particularly in the case of those included under the ICD diagnostic code 252.0. However, this code was not used in Sweden after 1986 and, excluding individuals diagnosed until 1986, had only a marginal effect on the HR. Furthermore, secondary hyperparathyroidism due to vitamin D deficiency is not treated with parathyroid surgery unless associated with renal failure, and end-stage renal disease patients were excluded in our analyses. Furthermore, individuals with secondary hyperparathyroidism will not have the pathological diagnosis of parathyroid adenoma. Indeed, the highest HR in our study were observed when we restricted our outcome to PHPT in the cancer register, where causes of PHPT other than parathyroid adenoma are highly unlikely [27 of the 68 patients with CD and PHPT (40%) had a record of benign adenoma in the Swedish Cancer Register]. Hence, the HR of 1.91 in our main analysis may even be an underestimate. None of the 27 individuals with a diagnosis of parathyroid adenoma had a histopathology code of “096” (malignant carcinoma).

A major weakness is the lack of data on the biochemical hallmarks of PHPT (serum calcium and PTH levels), and the presence of vitamin D deficiency in our cohort. Still, absence of hypercalcemia may not rule out PHPT, in that patients with CD and PHPT may have normal or near-normal serum calcium levels (8) if their coexisting vitamin D deficiency decreases the calcium into the normal range (2, 3).

Finally, the data available in this study do not provide any insight into the nature of the association between CD and PHPT. We do not know whether this association is causal or whether CD and PHPT are related to another unidentified condition. Idiopathic hypoparathyroidism, rather than PHPT, is the parathyroid disorder most commonly thought to have an autoimmune basis. However, to our knowledge, there are no data on HLA DQ patterns in PHPT. Nor do we know how long CD went undiagnosed in our patients. Theoretically, long-standing undiagnosed CD could lead to parathyroid hyperplasia and ultimately to tertiary hyperparathyroidism. Although we have no specific information on the frequency of four-gland hyperplasia in our patients with PHPT, the small case series

of Maida *et al.* (8) reported that parathyroid adenoma rather than hyperplasia caused the disease in all seven of their patients.

In conclusion, this study found a moderately increased risk of PHPT in patients with CD. Future studies should focus on identifying the possible mechanisms for the link between these common yet seemingly disparate illnesses.

Acknowledgments

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Guarantor: J.F.L. 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.

Disclosure Summary: All authors declare that they have no conflicts of interest and therefore nothing to declare.

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