Season of birth in a nationwide cohort of coeliac disease patients

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ABSTRACT

Background and objective Genetic factors alone cannot explain the risk of developing coeliac disease (CD). Children born in summer months are likely to be weaned and introduced to gluten during winter when viral infections are more frequent. Earlier studies on birth season and CD are limited in sample size and results are contradictory.

Method Case–control study. We used biopsy reports from all 28 Swedish pathology departments to identify individuals with CD, defined as small intestinal villous atrophy (n=29 096). The government agency Statistics Sweden then identified 144 522 controls matched for gender, age, calendar year and county. Through conditional logistic regression we examined the association between summer birth (March–August) and later CD diagnosis (outcome measure).

Results Some 54.10% of individuals with CD versus 52.75% of controls were born in the summer months. Summer birth was hence associated with a small increased risk of later CD (OR 1.06; 95% CI 1.03 to 1.08; p<0.0001). Stratifying CD patients according to age at diagnosis, we found the highest OR in those diagnosed before age 2 years (OR 1.17; 95% CI 1.10 to 1.26), while summer birth was not associated with a CD diagnosis in later childhood (age 2–18 years: OR 1.02; 95% CI 0.97 to 1.08), but had a marginal effect on the risk of CD in adulthood (age ≥18 years: OR 1.04; 95% CI 1.01 to 1.07).

Conclusions In this study, summer birth was associated with an increased risk of later CD, but the excess risk was small, and general infectious disease exposure early in life is unlikely to be a major cause of CD.

INTRODUCTION

Coeliac disease (CD) occurs in approximately 1–2% of the Western population[1] and is characterised by small intestinal inflammation with villous atrophy (VA). CD is strongly associated with human leukocyte antigen (HLA) DQ2.5 (DQA1*05/DQB1*02)[2] and DQ8 (DQA1*03,DQB1*03:02).[3] Although the CD concordance rate is high in monozygotic twins (above 70%),[4] HLA alone is not sufficient to predict future CD. Only one out of 30 DQ2+ individuals develop CD.[5] In recent years, a number of other potentially important genes have been linked to CD. Still, these genetic factors cannot entirely determine the risk of developing CD, nor can they explain the marked rise in CD seroprevalence that has occurred in recent decades.[6]

The most important environmental factor in CD is gluten, present in wheat, rye and barley. However, other nutritional factors such as short duration of breastfeeding have also been implicated

What is already known on this topic

- ▶ Environmental factors play a role in the aetiology of coeliac disease.
- ▶ There is little knowledge about non-nutritional environmental factors in coeliac disease.

WHAT THIS STUDY ADDS

- ▶ Birth in the summer months was a risk factor for coeliac disease.
- ▶ Summer birth as a risk factor was most prominent for children diagnosed with coeliac disease before age 2.
- ▶ Seasonal differences in coeliac disease risk were small.

in the pathogenesis of CD,[7] although recent studies are contradictory.[8]

There is a paucity of research on non-dietary environmental risk factors in CD. Most[9][10] but not all[11] studies have found an inverse relationship between smoking and adult-onset CD. In 1987, Kagnoff et al suggested that adenovirus may play a role in the pathogenesis of CD,[12] and prior rotavirus infection increases the risk of developing CD[13] but not active infection.[14] A recent German study found that earlier gastrointestinal disease (including both infections and non-infectious disease) increased the risk of later CD,[15] while our group found a non-significantly increased risk of CD in children with an infection at the time of gluten introduction.[8] Recently we also showed that elective caesarean section is associated with later CD.[16] One potential explanation for the association with elective caesarean section involves changes in the individuals' microbiota.

Month of birth could potentially affect both the microbiota and the innate immune system of individuals at risk of CD through different exposures to infectious disease. We know of five studies on birth season and CD,[13][17–20] but only one of these studies included more than 500 patients with CD[18] and all studies were restricted to CD diagnosed in childhood or adolescence.

We hypothesised that summer birth (children would then be weaned in winter time with heavy exposure to viral infections at time of gluten introduction) would be associated with later CD. This was based on the rationale that children born in

summer months are more likely to have initial exposure to gluten during winter months, when concurrent viral infection is more probable. Another potential cause of seasonal variations in CD is lack of vitamin D. Low levels of vitamin D predisposes to certain immune-mediated diseases.[21] For example, individuals born in summer months are at increased risk of multiple sclerosis, perhaps due to lower levels of vitamin D during foetal development (in wintertime).[22]

To test this hypothesis we examined birth season in a nationwide cohort of CD patients and in their age- and gender-matched controls.

METHODS
We linked data on patients with biopsy-verified CD identified through Sweden's 28 pathology departments. Controls matched for age, gender, calendar period and county were identified from the Swedish national Total Population Register, from which we also obtained data on birth date.

Collection of biopsy data
We collected data on small intestinal biopsies (duodenum and jejunum) performed between July 1969 and February 2008 from all Swedish pathology departments. The data collection took place in 2006–2008. We searched computerised registers for data on arrival date of the biopsies, the personal identity number,[23] and morphology according to SnoMed classification codes. Most pathology departments were computerised in the 1990s and hence most biopsy reports originated after 1990. Initially we collected data on both (VA, Marsh 3), but also milder histopathology (Marsh 0–2).[24] In this study, we equated VA with CD. Later patient chart reviews of a random sample of 114 patients with VA found that 108 (95%) had CD,[25] and a manual review by two independent researchers of more than 1500 biopsy reports with VA or Marsh 1–2 found that diagnoses other than CD were very rare in Swedish patients with VA (the most common non-CD diagnosis was inflammatory bowel disease, which occurred in 0.3% of all patients with VA).[25] We did not require a positive CD serology for a diagnosis of CD, but in the above sample, 88% of patients undergoing patient chart validation and with available data on CD serology at time of biopsy had a positive serology.[25]

Cases and controls
We initially collected data on 351 403 biopsy reports (in 287 586 unique individuals); 29 148 of these had CD. After exclusion of patients where the biopsy could potentially have been obtained in the ileum, patients without matched controls, and patients who could not be matched by the government agency Statistics Sweden, there remained 29 096 patients with CD. Statistics Sweden then identified up to five controls for each individual with CD (total n=144 522). Controls were matched on gender, age, calendar year and county.

Seasonality data
The dates of birth of all CD patients and matched controls were obtained from the Swedish Total Population Register, and birth season was dichotomised a priori into summer births (1 March to 31 August) and winter births (1 September to 29 February). This season cut-off definition is the same as the two other studies that dichotomised birth season.[18 19]

Statistical analyses
The primary outcome of interest was the proportion of summer births among CD patients as compared to controls. We used conditional logistic regression to compare CD patients to controls, who were matched by age, gender and calendar period. We also tested whether the association between CD and birth season varied by age of diagnosis of CD (<2, 2–18, ≥18), gender, and calendar period of diagnosis (≤1989, 1990–1999, ≥2000). We used the Breslow–Day test for homogeneity of ORs. All p values reported are two sided. All statistical calculations were performed with SAS V.9.2.

Ethics
The study was approved by the Research Ethics Review Board, Stockholm, Sweden. Since none of the participants was contacted and individual information was anonymised prior to the analyses, informed consent was not required.

RESULTS
Background
We used the same set of 29 096 individuals with CD and 144 522 controls matched for age, gender and calendar period as in our previous study on mortality in CD.[26] Sixteen per cent of CD patients were diagnosed <2 years of age (table 1). Most study participants were female (62%), and the majority were diagnosed after year 1990.

Main results
A total of 54.10% of individuals with CD versus 52.75% of controls were born in the summer months (table 1). Summer birth was hence associated with a small increased risk of later CD (OR 1.06; 95% CI 1.03 to 1.08; p<0.0001).

Stratifying CD patients according to age at diagnosis (table 2), we found the highest OR in those diagnosed before age 2 years (OR 1.17; 95% CI 1.10 to 1.26). Summer birth was not associated with a CD diagnosis in later childhood (age 2–18 years: OR 1.02; 95% CI 0.97 to 1.08), but was weakly associated with an increased risk of CD in adulthood (age ≥18 years: OR 1.04; 95% CI 1.01 to 1.07). The difference in age-specific ORs was statistically significant (Breslow–Day test for homogeneity: p=0.0017).

Stratified analysis by gender and calendar period is shown in table 3. The association between summer birth and risk of CD

Table 1 Characteristics of coeliac disease patients and controls

Characteristic	Coeliac disease (n=29096)	Controls (n=144522)	p Value
Age at diagnosis/study entry (years) Mean/median (overall: 32/30, SD 25.7) (range <1 year to 95)	32/30	32/30	0.43
<2	4589 (16)	22857 (16)	0.8857
2–18	6719 (23)	33530 (23)	
≥18	17788 (61)	88135 (61)	
Gender			0.8041
Male	11091 (38)	54978 (38)	
Female	18005 (62)	89544 (62)	
Calendar period of diagnosis			0.9970
≤1989	4105 (14)	20378 (14)	
1990–1999	12059 (41.5)	59874 (41.5)	
≥2000	12932 (44.5)	64270 (44.5)	
Birth season			<0.0001
Summer	15742 (54.10)	76230 (52.75)	
Winter	13354 (45.90)	68292 (47.25)	

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Table 2 Distribution of summer (March–August) versus winter (September–February) births in coeliac disease (CD) patients and controls, stratified by age of diagnosis

	Summer births	Winter births	OR (95% CI)	p Value
Age <2				
CD patients	2654 (58)	1935 (42)	1.17 (1.10 to 1.26)	<0.0001
Controls	12314 (54)	10543 (46)		
Age 2–18				
CD patients	3633 (54)	3,086 (46)	1.02 (0.97 to 1.08)	0.4082
Controls	17945 (54)	15585 (46)		
Age ≥18				
CD patients	9455 (53)	8333 (47)	1.04 (1.01 to 1.07)	0.0155
Controls	45971 (52)	42164 (48)		

was similarly present in boys (OR 1.08; 95% CI 1.03 to 1.12) and girls (OR 1.04; 95% CI 1.01 to 1.08). The association between summer birth and CD decreased over time, and in patients diagnosed from 2000 and onwards, the OR was 1.02 (95% CI 0.98 to 1.06).

DISCUSSION

This study found a modest increased risk of later CD in individuals born in summer months. More importantly, the upper 95% CI was 1.08, ruling out a large effect of summer birth on the risk of CD. Overall, seasonal variation in food intake and infectious disease exposures are therefore unlikely to be a major cause of CD.

Of the five earlier studies on this topic, three found a positive association between CD and summer birth in subsets of study participants with CD.[13 18 19 20]

While Ivarsson et al found a 1.4-fold increased risk of future CD in children born in the summer and aged <2 years at diagnosis, they did not see an increased risk in children diagnosed

with CD at the age of 2–15 years (relative risk=0.96; 0.81–1.1).[18] Interestingly, Lewy et al also found a seasonality pattern in girls diagnosed with CD before 24 months of age but not after,[20] and even if there was a seasonality pattern in boys with CD both before and after 24 months of age, the patterns differed.[20]

Data from a longitudinal study in Denver (54 cases with CD) found that 54% of CD cases versus 48% of controls were born April–September.[13] A study from Massachusetts, published in abstract form, examined 382 children with CD and reported an increased risk of CD in individuals diagnosed <15 years, but not in individuals diagnosed 15–19 years of age.[19] Kokkonen et al examined 226 Finnish children but observed no association between birth season and risk of CD.[17]

The main difference between our study and earlier studies lies in the number of patients with CD. Our study involved more than 29 000 patients with CD compared to 3244 patients in the five earlier studies combined.[13 17–20] This allowed for stratified analyses where we were able to detect a positive association between summer birth and CD in all age strata although only for children diagnosed <2 years, and adults diagnosed ≥18 years were these associations statistically significant. Another difference is our use of matched controls. Using a conditional logistic regression approach we could examine study participants per stratum (one individual with CD compared to his or her matched controls), and we were hence able to eliminate the effect of gender, age, calendar period and county on our risk estimates.

We used biopsy data to ascertain CD. An earlier validation study has found that 96% of all Swedish adult gastroenterologists and 100% of all paediatricians biopsy patients with CD before diagnosis.[25] Hence our study is likely to have identified a very high proportion of patients with diagnosed CD. However we did not screen the Swedish population for CD and hence we were unable to study the association between birth season and undiagnosed CD.

It is unlikely that our findings are due to chance. Of the six summer months in this study, there was a positive association with CD in five (August being the exception). Our risk estimate was highly statistically significant (OR 1.06; 95% CI 1.03 to

Table 3 Distribution of summer (March–August) versus winter (September–February) births in coeliac disease (CD) patients and controls, stratified by gender and year of diagnosis

	Summer births	Winter births	OR (95% CI)	p Value	Test for heterogeneity of ORs
Gender					0.2427
Male					
CD patients	6080 (55)	5011 (45)	1.08 (1.03 to 1.12)	0.0004	
Controls	29131 (53)	25847 (47)			
Female					
CD patients	9662 (54)	8343 (46)	1.04 (1.01 to 1.08)	0.0091	
Controls	47099 (53)	42445 (47)			
Calendar period					0.0274
≤1989					
CD patients	2245 (55)	1860 (45)	1.11 (1.04 to 1.19)	0.0028	
Controls	10624 (52)	9754 (48)			
1990–1999					
CD patients	6.605 (55)	5454 (45)	1.08 (1.04 to 1.13)	<0.0001	
Controls	31625 (53)	28249 (47)			
≥2000					
CD patients	6892 (53)	6040 (47)	1.02 (0.98 to 1.06)	0.3805	
Controls	339891 (53)	30289 (47)			

1.08, p<0.0001). Still, we urge caution when interpreting our data, as the mechanism for this small association is unknown, it did not occur in the last calendar period, and our findings should therefore not influence how parents plan their conception and pregnancy.

The positive association between summer birth and future CD was only seen in children born until 1999. We cannot explain the lack of association in children born thereafter. One potential explanation is that the lack of statistical significance here is a chance finding, just as the opposite, statistically significant associations, may occur when many comparisons are performed. It is also possible that individuals diagnosed after 1999 are phenotypically different from children born earlier, due to the advent of easily available CD screening tools such as endomysium and tissue transglutaminase antibodies. If summer birth is associated with CD primarily in children with classic symptoms, this could also explain why we saw the highest OR in children diagnosed with CD before 2 years of age (when disease onset often consists of malabsorptive symptoms).

In this study we did not have access to data on exposures to infectious disease, age at gluten introduction and breastfeeding duration. However, we speculate that children born in the summer are more exposed to viral infections at the time of gluten introduction (winter). In our recent paper on 9408 children with prospective data on nutrition and infectious disease, infection at the time of gluten introduction was associated with an increased risk of future CD although the risk estimate failed to attain statistical significance (adjusted OR=1.8, 95% CI 0.9 to 3.6).[8]

Infections (either viral or bacterial) could potentially increase the risk of CD in several ways. They may influence the microbiota, thereby compromising the mucosal barrier function.[27] Infections may also lead to the release of interferon gamma, increasing HLA expression.[28] Importantly, some infections seem to influence tissue transglutaminase release,[29] which is a crucial factor in CD.

Another possible mechanism is the effect of low vitamin D levels, either in the mother, due to lack of ultraviolet light exposure in mid-pregnancy, or in the child at the time of gluten introduction or viral infection.[22]

In conclusion, summer birth was associated with an increased risk of later CD, but the excess risk was small, largely limited to children diagnosed before age 2, and was not seen in the last calendar period. Seasonal exposures early in life, such as infectious diseases, are unlikely to be a major cause of CD. Future studies should focus on testing putative mechanisms underlying this modest association between birth season and risk of CD.

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