RESEARCH REPORT

Children born in the summer have increased risk for coeliac disease

A Ivarsson, O Hernell, L Nyström, L Å Persson

See end of article for authors' affiliations
....

Correspondence to:
Dr A Ivarsson, Department of Public Health and Clinical Medicine, Epidemiology, Umeå University, SE-901 87 Umeå, Sweden;
Anneli.Ivarsson@epiph.umu.se

Accepted for publication 28 February 2002
....

Study objective: Coeliac disease, also called permanent gluten sensitive enteropathy, is being recognised as a widespread health problem. Defining the possible role of environmental factors in its aetiology might open doors to primary prevention. This study therefore analysed if the risk for coeliac disease varies with month of birth as a proxy for a seasonal pattern for possible causal environmental exposure(s).

Design: A population based incidence register of coeliac disease in children below 15 years of age covering the period from 1973 to 1997. Incidence rates were calculated by month of birth, stratified for age at diagnosis. Poisson regression analyses were used to estimate the relative risk for coeliac disease for children below 2 years of age by season of birth, also taking into account gender and time period of diagnosis.

Setting: Sweden.

Participants: All 2151 children in the study base with verified coeliac disease.

Main results: The risk for coeliac disease was significantly higher if born during the summer as compared with the winter (RR=1.4, 95% CI 1.2 to 1.7), but only in children below 2 years of age at diagnosis. This relative seasonal risk pattern prevailed during a 10 year epidemic of coeliac disease, although incidence rates varied threefold. The incidence was constantly higher among girls as compared with boys, but boys showed a more pronounced seasonal variation in risk than girls.

Conclusions: An increased coeliac disease risk in children born in the summer compared with the winter reflects causal environmental exposure(s) with a seasonal pattern. Infections might be the exposure of importance, either by means of a direct causal role and/or through interaction with other exposures, for example, gluten intake. However, non-infectious exposures should also be explored as possible contributing causal factors.

C oeliac disease, also called permanent gluten sensitive enteropathy, is being recognised as a widespread health problem.[1][2] This is of concern because gluten containing cereals are an important part of the diet in many countries. Furthermore, if not treated, the disease is associated with a number of complications related to malabsorption, for example, diarrhoea and growth retardation in infancy, and depression, osteoporosis, and malignancies later in life. Intolerance to gluten is life long. If, however, wheat gluten proteins and related proteins from rye and barley are excluded from the diet, the disease processes resolve.

The aetiology of coeliac disease is not fully understood.[3][4] Genetic susceptibility is a prerequisite, although the genes involved still remain to be identified. Moreover, coeliac disease has an immunological pathogenesis with many similarities to autoimmune diseases, albeit strictly dependent on exposure to gluten proteins. Coeliac disease most probably has a multifactorial aetiology.[3][5] If so, complex interactions between genetic predisposition and environmental exposures probably modulate the immune system—possibly beginning during fetal life—thereby determining whether gluten exposure results in oral tolerance to gluten or coeliac disease. Thus, exploring the possible contribution of environmental factors to the aetiology might provide direction with respect to primary prevention.

In the mid-1980s the incidence rate of coeliac disease in Swedish children below 2 years of age increased threefold within a few years, and after a 10 year high incidence period it equally rapidly returned to the previous level.[6] This epidemic incidence pattern is indicative of changes in causal environmental exposures, as it can definitely not be explained by genetic changes in the population. Recent estimates suggest that about half of the coeliac disease cases during the epidemic could be explained by unfavourable infant dietary patterns.[6][7]

The possible role of environmental exposures in coeliac disease aetiology, other than the mere presence of gluten in the diet and infant dietary practices, is essentially unexplored. In the 1980s it was suggested that infection with adenovirus (serotype 12) could contribute through its immunological cross reactivity with A-gliadin,[8] although the relevance of this has since been questioned.[9] However, as the pathogenesis of coeliac disease clearly involves immunological processes, there must also be other mechanisms by which infectious diseases could contribute. A seasonal incidence pattern is characteristic for many infectious diseases. A possible causal role of infectious diseases during fetal life or in infancy might therefore be reflected in a seasonal variation in disease risk in relation to month of birth. To our knowledge, no studies have explored this possibility.

The population based incidence register of coeliac disease in Swedish children diagnosed from 1973 to 1997 covers a period of large variations in incidence, and provides a unique opportunity to explore the possible contribution of environmental exposures in the aetiology of the disease. We therefore analysed if the risk for coeliac disease varies with month of birth as a proxy for a seasonal pattern for possible causal environmental exposure(s).

METHOD

Case ascertainment

Sweden's national child health programme—with almost complete coverage (>99%)—is implemented through child health clinics and school health services throughout the

Table 1 Number of coeliac disease cases and population size by time period, age at diagnosis, and season of birth

Characteristics	Time period			
	1973–84 n (%)	1985–95 n (%)	1996–97 n (%)	1973–97 n (%)
Number of cases				
0–1.9 years				
Winter	105 (42)	522 (41)	43 (35)	670 (41)
Summer	145 (58)	738 (59)	81 (65)	964 (59)
Total	250	1260	124	1634
2.0–14.9 years				
Winter	21 (49)	151 (47)	75 (49)	247 (48)
Summer	22 (51)	170 (53)	78 (51)	270 (52)
Total	43	321	153	517
Population per 1000				
0–1.9 years				
Winter	179	311	73	563
Summer	203	358	86	647
Total	382	669	159	1210
2.0–14.9 years				
Winter	1239	1829	538	3606
Summer	1389	2089	615	4093
Total	2628	3918	1153	7699

country. When coeliac disease is suspected, the child is referred to the closest paediatric department for further examination.

A central register of coeliac disease cases in children below 15 years of age was organised based on reporting from paediatric departments throughout the country.[6] At five departments, information on all coeliac disease cases diagnosed from 1973 to 1990 was extracted retrospectively from local registers. These five, as well as an additional nine departments, prospectively reported all incident cases from 1991 to 1997. The retrospective and prospective parts of the register cover 15% and 40%, respectively, of all children in the country.

A total of 2151 cases fulfilled the European Society for Paediatric Gastroenterology, Hepatology and Nutrition diagnostic criteria for coeliac disease (ESPGHAN)[10] (table 1), which are based on assessment of the morphology of the small intestinal mucosa. All information reported by 31 December 1998 was considered.

Population data
Population data were obtained from Statistics Sweden (table 1). The national population register is complete, and each paediatric department has a well defined geographical catchment area. In 1973 the study area comprised 258 683 children (five clinics) and in 1991 there were 623 439 children (14 clinics), including all children below 15 years of age. This resulted in a study base of 4 408 816 and 4 500 685 person years for the retrospective and prospective parts of the study, respectively, taking the variation in population over the years and the follow up period into account.

Definitions
Month of birth was arbitrarily classified into winter season, also including autumn—that is, September to February—and summer season, also including spring—that is, March to August. These periods are characterised by differences in living conditions related to climate, for example, in Stockholm the mean difference between the periods with respect to outdoor temperature was 8°C, and the mean difference in daily hours of sunlight was six hours (Swedish Meteorological and Hydrological Institute).

Age at diagnosis was defined as the age when the first small intestinal biopsy was performed. Children were divided into the age groups 0–1.9 years and 2.0–14.9 years at diagnosis, as Sweden has experienced an epidemic of coeliac disease that only affected the younger age group.[6]

Based on variations in incidence rates over time in children below 2 years of age, the study period was divided into: (1) the *pre-epidemic period*—that is, the low incidence period from 1973 to 1984, (2) the *epidemic period*—that is, the high incidence period from 1985 to 1995, and (3) the *post-epidemic period*—that is, the medium to low incidence period from 1996 to 1997.[6]

Statistical analyses
Average incidence rates of coeliac disease were calculated by month of birth and age group (0–1.9 and 2.0–14.9 years), and reported per 100 000 person years. This was done by dividing the number of new cases diagnosed by the number of person years of follow up. The sum of the number of children living in the study area on 31 December for two consecutive years, divided by two, was used to estimate the number of person years of follow up for that year.

Poisson regression models were used to estimate the relative risk of coeliac disease before two years of age considering season of birth (winter and summer), gender, and time period of diagnosis (1973–1984, 1985–1995, and 1996–1997). Bivariate analyses were followed by multivariate analyses, keeping interaction terms with a p value <0.1 in the final model. Statistical significance was defined as relative risks (RR) with 95% confidence intervals (CI) excluding 1.0.

EXCEL[11] and SPSS[12] were used for basic calculations, and EGRET[13] was used for Poisson regression analyses.

Ethics
The Swedish Data Inspection Board and the Research Ethics Committees of all Swedish Medical Faculties approved the study. Informed consent was obtained from the families.

RESULTS
Seasonality in coeliac disease risk
The incidence rate of coeliac disease in children below 2 years of age was higher if they were born during the summer as compared with the winter (fig 1), with a RR of 1.4 (95% CI 1.2 to 1.7) (table 2). No such seasonality in incidence rates was found in children diagnosed between 2 and 15 years of age (fig 1), illustrated by a RR of 0.96 (95% CI 0.81 to 1.1).

Gender difference
The RR for coeliac disease before 2 years of age was twice as high for girls as for boys (RR=2.1) (table 2). The seasonal pattern was, however, less pronounced in girls than in boys, as
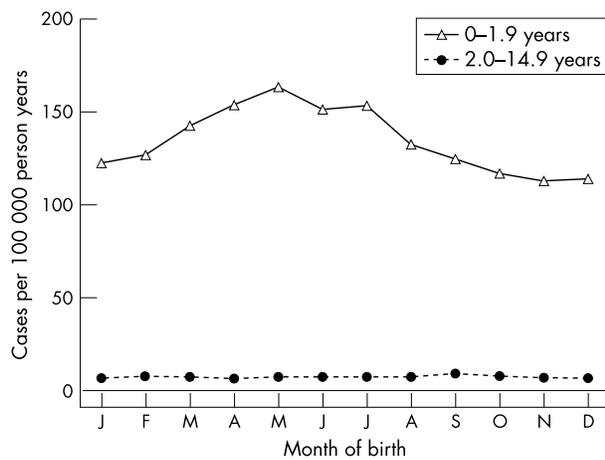
Figure 1　Average incidence rate of coeliac disease by month of birth and age at diagnosis for the time period from 1973 to 1997.

Table 2　Risk for coeliac disease before 2 years of age by season of birth, gender, and time period

Background variables	Bivariate analyses* RR (95% CI)‡	Multivariate analysis† RR (95% CI)
Season of birth		
Winter	1.0	1.0
Summer	1.3 (1.1 to 1.4)	1.4 (1.2 to 1.7)
Gender		
Boys	1.0	1.0
Girls	1.9 (1.7 to 2.1)	2.1 (1.8 to 2.5)
Time period		
1973–1984	1.0	1.0
1985–1995	2.9 (2.5 to 3.3)	2.9 (2.5 to 3.3)
1996–1997	1.2 (1.0 to 1.5)	1.2 (1.0 to 1.5)
Season of birth: Gender§		
Boys		1.0
Girls		0.83 (0.68 to 1.0)
Season of birth: Time period		Excluded from the model
1973–1984		1.0
1985–1995		1.0 (0.77 to 1.3)
1996–1997		1.3 (0.85 to 2.1)

*Poisson regression analyses based on 1634 cases and 1 210 104 person years of follow up. †Likelihood ratio statistics (LRS) on 6 degrees of freedom (DF)=3 147, p<0.001. ‡Relative risk (95% confidence intervals). §, Interaction term.

illustrated by a significant interaction between the variables season of birth and gender (RR=0.83, 95% CI 0.68 to 1.0) (table 2).

The epidemic

The period from 1985 to 1995 stands out as having a three times higher incidence rate of coeliac disease in children below 2 years of age compared with both the preceding years (1973 to 1984) and the years that followed (1996 to 1997)[6] (table 2). Despite these large variations in incidence rates, the relative seasonal risk pattern was largely constant, as illustrated by the absence of significant interaction between the variables season of birth and time period (table 2). In absolute numbers, the difference in incidence rates between the summer and winter periods was larger during the epidemic compared with both the preceding years and the years that followed.

DISCUSSION

The risk of developing coeliac disease in children below 2 years of age was significantly higher if they were born during the summer as compared with the winter. This relative seasonal

Key points

- Coeliac disease is being recognised as a widespread health problem.
- The risk for developing coeliac disease is higher for children born in the summer as compared with the winter.
- This suggests causal environmental exposure(s) with a seasonal pattern.
- Primary prevention might be possible if these causal exposures are identified.

risk pattern prevailed during a 10 year epidemic of coeliac disease, when incidence rates varied threefold.

We are confident that virtually all diagnosed cases of coeliac disease in children in the study area were reported to the register.[6] Diagnostic criteria were based on evaluation of the morphology of the small intestinal mucosa[10] and were largely unchanged during the study period. Moreover, there is no reason to expect differences in reporting to the register or in evaluation of the mucosal specimens with respect to month of birth. The incidence register was mainly based on cases diagnosed as a result of symptoms, and not a general screening approach.

Our new finding of variation in coeliac disease risk with season of birth suggests causal environmental exposure(s) that change during the year. In Sweden, the most obvious seasonal variations are related to climate, with large changes in outdoor temperatures and hours of sunlight over the year. This results in profound seasonal differences in living conditions. These variations might have a direct effect on the immune system, but in many respects they also indirectly cause changes in the exposure of the population with respect to both infectious and non-infectious exposures.

The incidence rate of coeliac disease with respect to month of birth changed gradually over the year (fig 1). The multivariate analysis, however, was only possible provided that months of birth were aggregated into only a few groups. We then arbitrarily divided the year into only two parts defined as winter and summer, respectively, as a more detailed analysis, for example, dividing the year into four parts also including spring and autumn, would require a larger sample size. As Sweden extends all the way from a latitude of 55° to a latitude of 69°, with large differences in climate within the country, a south to north gradient in coeliac disease risk, and the risk associated with a certain month of birth, could be expected. However, such analyses require a larger sample size.

Children born during the summer, when there is an increased risk for coeliac disease, have been in utero mainly during the winter when there is the greatest risk for infections in the mother. Furthermore, children born in the summer are introduced to dietary gluten and also frequently weaned off the breast during the winter—that is, at about six months of age[7]—when the likelihood of becoming infected is greatest. The immunological cross reactivity between adenovirus (serotype 12) and A-gliadin is one possible mechanism.[8] However, given the complexity of the immune system there are also other possible paths by which infectious diseases could contribute.

We found that the relative seasonal risk pattern of coeliac disease was largely constant despite the epidemic entailing large variations in incidence rates over time.[6] This means that the changes in incidence rates were larger in children born during the summer as compared with those born in the winter, both during the increase and later during the decrease in incidence rates. Thus, it is most likely that exposure(s) with a seasonal pattern contributed to the Swedish epidemic of coeliac disease, either directly or by interaction with other exposures, for example, gluten intake.

Our recent results support a reduced risk for coeliac disease if gluten containing foods are introduced into the infant's diet

in small amounts while breast feeding is still ongoing.[5–7] Thus, if infant feeding practices vary with the season, this could be an explanation for seasonality in coeliac disease risk. However, according to our recent case-referent study,[7] Swedish infant feeding practices with respect to breast feeding duration and amount of gluten consumed do not vary with the season (data not shown).

Furthermore, we found that the seasonality in coeliac disease risk was absent in children diagnosed at an older age—that is, between 2 and 15 years of age. It therefore seems as if the causal seasonal exposure(s) only exhibit their effect during the very first years of life. This supports our previous conclusion that the causal pattern of coeliac disease, at least with respect to some exposures, differs between younger and older children.[7]

The seasonal risk pattern for coeliac disease was less pronounced in girls than in boys. The reasons for this are unknown. However, it has been clearly shown that immune responses differ between females and males.[14] Thus it is reasonable to speculate that the effect of the seasonal environmental exposure(s), for example, infectious diseases, differs between girls and boys. If infections early in life are part of the causal pattern, another possibility would be that boys are exposed more to these. However, according to our recent case-referent study[7] this is not the case (data not shown).

Coeliac disease and insulin dependent diabetes mellitus have several features in common. The immune system has a key function in the pathogenesis of both diseases, and there is an increased risk for coeliac disease in persons with diabetes.[15] There is increasing evidence that environmental events early in life, for example, viral infections, influence the risk of developing diabetes.[16] Congenital rubella infection clearly increases the risk,[17] and enteroviral infection during pregnancy has also been suggested as causal.[18 19] An increased risk for diabetes in children born during the summer, as is the case for coeliac disease, has been reported from some populations, for example, the Netherlands[20] and Great Britain,[21] but is absent in many other populations.[21] However, in most populations the incidence of diabetes is increased during the winter[22 23] and environmental factors, for example, viral infections, have been suggested to precipitate clinical onset.

In summary, this population based longitudinal study reveals increased coeliac disease risk in children born in the summer as compared with the winter. This suggests causal environmental exposure(s) with a seasonal pattern. Infections might be the exposure of importance, either by means of a direct causal role and/or through interaction with other exposures, for example gluten intake. However, non-infectious exposures should also be explored as possible contributing causal factors.

ACKNOWLEDGEMENTS

. . . .

Authors' affiliations
A Ivarsson, L Nyström, Department of Public Health and Clinical Medicine, Epidemiology, Umeå University, Umeå, Sweden
O Hernell, Department of Clinical Sciences, Pediatrics, Umeå University
L Å Persson, ICDDR,B: Centre for Health and Population Research, Dhaka, Bangladesh

REFERENCES

1 **Mäki M**, Collin P. Coeliac disease. *Lancet* 1997;**349**:1755–9.
2 **Murray JA**. The widening spectrum of celiac disease. *Am J Clin Nutr* 1999;**69**:354–65.
3 **Sollid LM**. Molecular basis of celiac disease. *Annu Rev Immunol* 2000;**18**:53–81.
4 **Schuppan D**. Current concepts of celiac disease pathogenesis. *Gastroenterology* 2000;**119**:234–42.
5 **Ivarsson A**, Persson LÅ, Hernell O. Does breast-feeding affect the risk for coeliac disease? In: Koletzko B, Michaelsen KF, Hernell O, eds. *Short and long term effects of breast feeding on child health.* New York: Kluwer Academic/Plenum Publishers, 2000:139–49.
6 **Ivarsson A**, Persson LÅ, Nyström L, *et al.* Epidemic of coeliac disease in Swedish children. *Acta Paediatr* 2000;**89**:165–71.
7 **Ivarsson A**, Hernell O, Stenlund H, *et al.* Breast-feeding protects against coeliac disease. *Am J Clin Nutr* 2002;**75**:917–21.
8 **Kagnoff MF**, Paterson YJ, Kumar PJ, *et al.* Evidence for the role of a human intestinal adenovirus in the pathogenesis of coeliac disease. *Gut* 1987;**28**:995–1001.
9 **Howdle PD**, Blair Zajdel ME, Smart CJ, *et al.* Lack of a serologic response to an E1B protein of adenovirus 12 in coeliac disease. *Scand J Gastroenterol* 1989;**24**:282–6.
10 **Walker-Smith JA**, Guandalini S, Schmitz J, *et al.* Revised criteria for diagnosis of coeliac disease. Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition. *Arch Dis Child* 1990;**65**:909–11.
11 **Microsoft Corporation 1985–99**. *EXCEL 97.* Sweden: Microsoft Corporation, 1997.
12 **SPSS**. *SPSS 9.0. Statistical Package for Social Sciences.* Chicago: SPSS Inc, 1999.
13 **Cytel Software**. *EGRET for Windows; Epidemiological GRaphics, Estimation and Testing package.* Cambridge: Cytel Software Corporation, 1999.
14 **Whitacre CC**, Reingold SC, O'Looney PA. A gender gap in autoimmunity. *Science* 1999;**283**:1277–8.
15 **Cronin CC**, Shanahan F. Insulin-dependent diabetes mellitus and coeliac disease. *Lancet* 1997;**349**:1096–7.
16 **Leslie RDG**, Elliott RB. Early environmental events as a cause of IDDM. Evidence and implications. *Diabetes* 1994;**43**:843–50.
17 **Ginsberg-Fellner F**, Witt ME, Yagihashi S, *et al.* Congenital rubella syndrome as a model for type 1 (insulin-dependent) diabetes mellitus: increased prevalence of islet cell surface antibodies. *Diabetologia* 1984;**27** (suppl):87–9.
18 **Dahlquist GG**, Ivarsson S, Lindberg B, *et al.* Maternal enteroviral infection during pregnancy as a risk factor for childhood IDDM. A population-based case-control study. *Diabetes* 1995;**44**:408–13.
19 **Hyöty H**, Hiltunen M, Knip M, *et al.* A prospective study of the role of coxsackie B and other enterovirus infections in the pathogenesis of IDDM. Childhood Diabetes in Finland (DiMe) Study Group. *Diabetes* 1995;**44**:652–7.
20 **Jongbloet PH**, Groenewoud HM, Hirasing RA, *et al.* Seasonality of birth in patients with childhood diabetes in The Netherlands. [Letter]. *Diabetes Care* 1998;**21**:190–1.
21 **Rothwell PM**, Gutnikov SA, McKinney PA, *et al.* Seasonality of birth in children with diabetes in Europe: multicentre cohort study. European Diabetes Study Group. *BMJ* 1999;**319**:887–8.
22 **Dahlquist G**, Blom L, Holmgren G, *et al.* The epidemiology of diabetes in Swedish children 0–14 years–a six-year prospective study. *Diabetologia* 1985;**28**:802–8.
23 **Lévy-Marchal C**, Patterson C, Green A. Variation by age group and seasonality at diagnosis of childhood IDDM in Europe. The EURODIAB ACE Study Group. *Diabetologia* 1995;**38**:823–30.