Children born in the summer have increased risk for coeliac disease

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Coeliac disease, also called permanent gluten sensitive enteropathy, is being recognised as a widespread health problem. 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. 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. 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, and after a 10 year high incidence period it has since been questioned. 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 environmental exposures in the aetiology of the disease. We therefore analysed if the risk for coeliac disease varies with month of birth.

METHOD
Case ascertainment
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).
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. 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) (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 person is registered with a unique personal identification number. The population is 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 and SPSS were used for basic calculations, and EGRET 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

![Table 1 Number of coeliac disease cases and population size by time period, age at diagnosis, and season of birth](http://jech.bmj.com/)

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<td>Number of cases</td>
<td>0–1.9 years</td>
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<tr>
<td>Winter</td>
<td>105 (42)</td>
<td>522 (41)</td>
<td>43 (35)</td>
<td>670 (41)</td>
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<td>Summer</td>
<td>145 (58)</td>
<td>738 (59)</td>
<td>81 (65)</td>
<td>964 (59)</td>
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<tr>
<td>Total</td>
<td>250</td>
<td>1260</td>
<td>124</td>
<td>1634</td>
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<td>2.0–14.9 years</td>
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<tr>
<td>Winter</td>
<td>21 (49)</td>
<td>151 (47)</td>
<td>75 (49)</td>
<td>247 (48)</td>
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<tr>
<td>Summer</td>
<td>22 (51)</td>
<td>170 (53)</td>
<td>78 (51)</td>
<td>270 (52)</td>
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<tr>
<td>Total</td>
<td>43</td>
<td>321</td>
<td>153</td>
<td>517</td>
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<td>Population per 1000</td>
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<tr>
<td>0–1.9 years</td>
<td>179</td>
<td>311</td>
<td>73</td>
<td>563</td>
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<tr>
<td>Winter</td>
<td>203</td>
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<td>86</td>
<td>647</td>
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<tr>
<td>Summer</td>
<td>382</td>
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<td>159</td>
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<td>1239</td>
<td>1829</td>
<td>538</td>
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<tr>
<td>Winter</td>
<td>1389</td>
<td>2089</td>
<td>615</td>
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<td>Summer</td>
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<td>124</td>
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<tr>
<td>Total</td>
<td>2628</td>
<td>3918</td>
<td>1153</td>
<td>7699</td>
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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.
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) (table 2). Despite these large variations in incidence rates, the relative seasonal 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 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. Diagnostic criteria were based on evaluation of the morphology of the small intestinal mucosa 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 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—when the likelihood of becoming infected is greatest. The immunological cross reactivity between adenovirus (serotype 12) and A-gliadin is one possible mechanism. 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. 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 if gluten containing foods are introduced into the infant’s diet.
in small amounts while breast feeding is still ongoing. 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, 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.²

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.³ 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 study³ 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.¹ There is increasing evidence that environmental events early in life, for example, viral infections, influence the risk of developing diabetes.⁶ Congenital rubella infection clearly increases the risk,⁷ and enteroviral infection during pregnancy has also been suggested as causal.⁸,⁹ 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 Netherlands¹⁰ and Great Britain,¹¹ but is absent in many other populations.¹² However, in most populations the incidence of diabetes is increased during the winter¹³ and environmental factors, for example, viral infections, have been suggested to precipitate clinical onset.¹⁴

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.

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REFERENCES