The prevalence of having coeliac disease in children with type 1 diabetes was not significantly higher during the Swedish coeliac epidemic

Mara Cerqueiro Bybrant | Elsa Palmkvist | Hanna Söderström | Marie Lindgren | Hans Hildebrand | Fredrik Norström | Annelie Carlsson

Abstract

Aim: From 1986 to 1996, there was a four-fold increase in coeliac disease among young Swedish children, known as the Swedish coeliac epidemic. Children with type 1 diabetes have an increased risk of developing coeliac disease. We studied whether the prevalence of coeliac disease differed in children with type 1 diabetes born during and after this epidemic.

Methods: We compared national birth cohorts of 240 844 children born in 1992–1993 during the coeliac disease epidemic and 179 530 children born in 1997–1998 after the epidemic. Children diagnosed with both type 1 diabetes and coeliac disease were identified by merging information from five national registers.

Results: There was no statistically significant difference in the prevalence of coeliac disease among children with type 1 diabetes between the two cohorts: 176/1642 (10.7%, 95% confidence interval 9.2%–12.2%) in the cohort born during the coeliac disease epidemic versus 161/1380 (11.7%, 95% confidence interval 10.0%–13.5%) in the post-epidemic cohort.

Conclusion: The prevalence of having both coeliac disease and type 1 diabetes was not significantly higher in children born during, than after, the Swedish coeliac epidemic. This may support a stronger genetic disposition in children who develop both conditions.

Keywords
children and adolescents, coeliac disease, epidemiology, register study, type 1 diabetes

1 | INTRODUCTION

The prevalence of coeliac disease (CD) in children with type 1 diabetes has varied from 1.6% to 16% in studies from different parts of the world. It is around 10% in Sweden. The prevalence of CD differs in various populations. In the general population, it is around 1% in the Western world, and it ranges from 0.7% to 2.9% in Swedish children. The prevalence of CD may differ between studies, since many cases with CD go undiagnosed, due to mild or diffuse symptoms. It, therefore, depends on whether the population is screened for CD or not. In addition, the prevalence of CD has shown regional variations, for example, in Swedish children.

Abbreviations: CD, coeliac disease; CI, confidence interval; HLA, human leukocyte antigen; ICD, International Classification of Diseases; NDR, The Swedish National Diabetes Register; Swediabkids, The Swedish National Pediatric Diabetes Register.

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common in females, who account for two-thirds of patients, and in screened populations.7

Coeliac disease is caused by an immune cell-mediated reaction to gluten, which leads to small bowel mucosal damage in genetically predisposed children.4,6,10 Children diagnosed with CD or type 1 diabetes often have the same risk genes: human leukocyte antigen (HLA) DQ2 and DQ8.1 The presence of DQ2 and/or DQ8 is a prerequisite for developing CD.11 However, this genetic risk for CD, and exposure to gluten, is not always enough to develop CD.4 Other environmental triggers, such as the month the child was born, and repeated virus infections in infancy have also been studied.12

Sweden has the second highest incidence of type 1 diabetes in the world, after Finland. Type 1 diabetes diagnoses in Swedish children aged 0–15 years equate to around 40/100,000 person-years13 and, in contrast to other autoimmune diseases, it is more common in boys.14

Coeliac disease presents with no overt symptoms in the majority of children with type 1 diabetes, and most cases are diagnosed through screening.1 Since the start of the 1990s, Sweden has implemented annual screening for CD for children who have already been diagnosed with type 1 diabetes.2,3

The Swedish CD epidemic refers to the years 1984–1996,15 which saw a dramatic increase in the number of young children diagnosed with CD by paediatricians. The cumulative incidence of CD reached higher levels than previously reported, rising from one to four cases per 1000 births.6,15 This increase in incidence, especially among children under 2 years of age, was followed by an abrupt decline after 1996.15 In 1984, the national infant feeding recommendations suggested postponing the introduction of gluten from 4 to 6 months of age. At the same time, the gluten content in infant formula increased, but this was not related to the changes in the recommendations.7 In 1996, the feeding recommendations changed again and were almost the same as they were before 1984. These changes included gradually introducing gluten, preferably during breastfeeding, and reducing the gluten content in commercially available infant products.15 A rapid decrease in the incidence of CD was seen after these new recommendations were introduced, and this approached the levels before the epidemic.6,7 A national screening study was performed on 13,000 school children of 12 years of age from the general population, who were born in 1993, during the epidemic, and in 1997, after the epidemic. This screening confirmed a significantly higher prevalence of CD in the cohort born during the epidemic.9 These changes in incidence and prevalence, and our conclusions about these, prompted us to research triggers for disease development and strategies for primary prevention.16

A previous retrospective study explored the effects of the Swedish CD epidemic on children and adolescents with type 1 diabetes, who were diagnosed in the Stockholm region.2 No differences in the prevalence of CD were found in birth cohorts before, during, and after the epidemic. The study had some limitations, as the post-epidemic cohort was small and had a short follow-up time.2

The aim of this study was to compare the national Swedish prevalence of CD and the age when children and adolescents were diagnosed with type 1 diabetes. To do this, we studied two different birth cohorts with equal follow-up times, one born during the Swedish CD epidemic and one born after it.

2 | MATERIALS AND METHODS

This study uses general population data from Statistics Sweden,17 which included immigration and mortality. It was analysed by sex (Table 1).

We based our study on two national birth cohorts from Statistics Sweden,17 including all children in Sweden. The first was 240,844 individuals born from 1 January 1992 to 31 December 1993 during the Swedish CD epidemic. We compared with a second cohort of 179,530 individuals born after the epidemic, from 1 January 1997 to 31 December 1998.

We compared these cohorts because children born in 1993 and 1997 had previously been screened for undiagnosed CD by the Exploring the Iceberg of Celciacs in Sweden (ETICS) study. Around 10% of Swedish children were invited to take part in this study: 75,676 (75%) of those invited had participated in the 1993 birth cohort study, and 57,126 (69%) had participated in the 1997 birth cohort study. The aim of the study was to follow up undetected CD in 12-year-old children born during and after the coeliac epidemic.5,7 Our study included children born in 1992 to the 1993 cohort and children born in 1998 to the 1997 cohort, as this created two cohorts with bigger sample sizes.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Number of children born each year in Sweden. Data collected from Statistics Sweden.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth cohort</td>
<td>Total</td>
</tr>
<tr>
<td>1992</td>
<td>122,847</td>
</tr>
<tr>
<td>1993</td>
<td>117,997</td>
</tr>
<tr>
<td>1997</td>
<td>90,502</td>
</tr>
<tr>
<td>1998</td>
<td>89,028</td>
</tr>
<tr>
<td>92 + 93</td>
<td>240,844</td>
</tr>
<tr>
<td>97 + 98</td>
<td>179,530</td>
</tr>
</tbody>
</table>

Key notes

- We used national registers to explore whether children with type 1 diabetes had an increased risk of developing coeliac disease during the Swedish coeliac epidemic.
- The sex distribution was more even among children with both conditions, unlike the general population, where girls dominated.
The incidence of type 1 diabetes is around 40 per 100,000 Swedish children below 18 years each year, and only 10% of these develop CD. We included all children diagnosed with type 1 diabetes in Sweden and used different registers to make sure we captured all those born between 1992-1993 and 1997-1998. This meant that the numbers of children with CD and type 1 diabetes were as comparable as possible.

We also chose to study cohorts that were very close to the epidemic dates of 1986–1996 to decrease the influence of time-dependent confounders.

The immigration rate was similar in both age cohorts. Mortality rates among children aged 1-19 years in the total Swedish population were 292 (0.12%) in 1993 and 275 (0.15%) in 1998. As this difference was not significant, we decided to disregard mortality.

Data on type 1 diabetes diagnoses in the two birth cohorts were collected from four different patient registers: the Swedish Diabetes Register for Children (Swediabkids), the Swedish National Diabetes Register (NDR) and the National Board of Health and Welfare inpatient and outpatient registries.

Data on CD diagnosis were retrieved from the inpatient and outpatient registers and the outpatient surgery register. These were based on the International Classification of Diseases Ninth and Tenth Edition diagnoses and used ICD-9 code 579.0 and ICD-10 code K900. The outpatient surgery register was used as it contains data about children who underwent biopsies as part of their CD diagnoses.

The National Board of Health and Welfare gave us permission to access the patient registries for data on children born during 1992–1993 and 1997–1998 and diagnosed with type 1 diabetes between 1 January 1992 and 31 December 2015. The first date of a visit with a CD diagnosis, as specified above. The end date of December 2015 was chosen to make sure that only children diagnosed with type 1 diabetes under 17 years of age were included. This ensured that the children had the same follow-up time in all the cohorts.

The study was approved by the Lund University Ethics Committee (Dnr 2014/476 EPN).

2.1 | Swediabkids and the Swedish National Diabetes Register

Swediabkids is an ongoing national register for children and adolescents up to 18 years of age with all types of diabetes. All diabetes clinics in Sweden report data to Swediabkids, and the coverage has been almost 100% since 2007. The NDR is the corresponding register for adults with diabetes. It was used to complement the accuracy of the data from Swediabkids, as adolescents were transferred to this when they reached 18 years of age. This meant that we were able to evaluate the accuracy of the diagnoses, by comparing the type 1 diabetes diagnoses in childhood with the adult data on the same individual in the NDR. The NDR was created in 1996 and by 2015 the reported coverage was close to 100% for patients with type 1 diabetes. The register records the date and year of type 1 diabetes diagnoses and the type of diabetes.

2.2 | Inclusion and exclusion criteria

Children included in the study had a type 1 diabetes diagnosis recorded in either the inpatient or outpatient register and in Swediabkids or the NDR. They were born in 1992-1993 or 1997–1998 and diagnosed with type 1 diabetes between 1 January 1992 and 31 December 2015.

We excluded children who were 17 years of age or more at the time of their type 1 diabetes diagnosis and those who did not have a diagnosis recorded in the inpatient or outpatient register. Children with another diabetes diagnosis than type 1 diabetes in Swediabkids, such as type 2 diabetes, secondary diabetes and other non-specified diabetes, including monogenic diabetes, were also excluded.

2.3 | Statistical methods and data analysis

SPSS Statistics, version 25 (IBM Corp.) was used for the statistical analyses. The chi-square test was used to test differences in prevalence rates. A p-value of <0.05 was considered to be statistically significant. The 95% confidence interval (CI) is presented when appropriate.

3 | RESULTS

The study comprised 3022 children (55% boys) who had been diagnosed with type 1 diabetes before 17 years of age. As shown in Figure 1, we excluded 50 children from the 1992 to 1993 cohort and 39 from the 1997 to 1998 cohort because they had received another diabetes diagnosis than type 1 diabetes.

This meant that we focused on 1642 children diagnosed with type 1 diabetes who were born during the CD epidemic of 1992–1993 and 1380 who were born during the post-epidemic period of 1997–1998.

3.1 | Type 1 diabetes and coeliac disease

We found that 337 of the 3022 children with type 1 diabetes had also been diagnosed with CD, which was an overall prevalence of 11.5% (Figure 1). Of those, 148 had a diagnosis recorded in the inpatient register, 334 patients had a diagnosis recorded in the outpatient register and nine patients had a diagnosis recorded in the outpatient surgery register.

The difference in the prevalence of CD between the two cohorts was not statistically significant, as it was 10.7% (95% CI 9.2%-12.2%) in the 176 children with type 1 diabetes born during
the 1992–1993 epidemic and 11.7% (95% CI 10.0%–13.5%) in the 161 children with type 1 diabetes born in 1997–1998 after the epidemic (Figure 1).

### 3.2 Age and sex at coeliac disease diagnosis

Overall, the children and adolescents in the 1997–1998 cohort were diagnosed with CD at a statistically significant younger age (mean of 9.4 years) than the children and adolescents born during the epidemic (11.0 years) (p = 0.003) (Table 2).

There was no statistically significant difference in the age at diagnosis of type 1 diabetes for the children with CD between the cohorts (8.3 vs. 8.5 years, p = 0.707). However, the mean age at the time of the type 1 diabetes diagnosis was statistically significantly lower in the group diagnosed with both type 1 diabetes and CD than in the children diagnosed with just type 1 diabetes (8.4 years compared with 9.8 years, p < 0.001).

There was no statistically significant difference in CD prevalence by sex between the cohorts. In the epidemic birth cohort, 52.9% of the boys were diagnosed with both CD and type 1 diabetes compared with 49.1% in the post-epidemic birth cohort (Figure 1).

In contrast, the age at diagnosis showed some statistically significant differences by sex (p = 0.003). In the post-epidemic cohort, the boys were 2.1 years younger at the time of their CD diagnosis, with a mean of 9.8 years compared with 11.9 years in the epidemic cohort. This difference was statistically significant. The girls in the post-epidemic cohort were 1.1 years younger (9.1 years) than girls born during the epidemic (10.2 years), but this result was not statistically significant different (Table 2).

### 4 DISCUSSION

There was no statistically significant difference in the prevalence of CD between the two birth cohorts of children diagnosed with type 1 diabetes, during and after the Swedish CD epidemic. We found that the age at the time of the CD diagnoses was lower in the birth cohort after the epidemic. Overall, children with both diseases were younger at the time of their type 1 diabetes diagnosis in both cohorts than children without CD. There were no differences between

**FIGURE 1 Flowchart. Selection of children <17 years from data from the National Board of Health and Welfare Sweden, diagnosed with type 1 diabetes (T1D) and diagnosed with coeliac disease (CD). Two birth cohorts: born during the Swedish epidemic of CD (1992/1993) and post-epidemic (1997/1998). Patients excluded according to a more precise diabetes diagnosis in the quality registers Sweddiabkids and NDR, excluding maturity onset diabetes in young, secondary diabetes or unclassified type of diabetes.**

**TABLE 2 Prevalence and mean age at coeliac disease (CD) diagnosis in the two birth cohorts during the Swedish epidemic of CD (1992/1993) and after (1997/1998) the epidemic, and mean age divided by gender.**

<table>
<thead>
<tr>
<th>Birth cohorts</th>
<th>ALL with CD; n = 337 (51% boys)</th>
<th>1992-1993; n = 176 (53% boys)</th>
<th>1997-1998; n = 161 (49% boys)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total prevalence of CD, %</td>
<td>11.1</td>
<td>10.7</td>
<td>11.7</td>
<td>0.461</td>
</tr>
<tr>
<td>Mean age CD diagnosis, years</td>
<td>10.3</td>
<td>11.0</td>
<td>9.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Females’ mean age CD diagnosis, years</td>
<td>9.6</td>
<td>10.2</td>
<td>9.1</td>
<td>0.127</td>
</tr>
<tr>
<td>Males’ mean age CD diagnosis, years</td>
<td>10.8</td>
<td>11.9</td>
<td>9.8</td>
<td>0.003</td>
</tr>
</tbody>
</table>
the two birth cohorts in boys and girls with both type 1 diabetes and CD. Girls are much more likely to have CD than boys in the general population, but this predominance was not found in children with both CD and type 1 diabetes.

The results of this study are similar to a smaller study carried out in Stockholm.2 We could not find any other studies that compared children with type 1 diabetes and the risk of developing CD. This was because the national change in infant feeding recommendations about gluten introduction in Sweden did not appear to occur elsewhere. Our study may suggest that environmental factors, such as differences in infant gluten intake, do not affect children with type 1 diabetes in the same way as the general population. We think this may be due to the strong genetic predisposition in children with type 1 diabetes compared with the general population.

Some of the environmental changes that may influence the risk of CD are the frequency or duration of breastfeeding, the age when gluten is introduced, and the amount of gluten, and infectious diseases like gastroenteritis.19 Two randomised intervention studies of children with a genetic risk for CD, but not diabetes, focused on introducing gluten during the so-called window of opportunity for preventing CD. These failed to show if the early or delayed introduction of gluten, with or without ongoing breastfeeding, protected children from developing CD.20,21 Both studies showed that the highest risk for developing CD was found in children with HLA-DQ2, especially those with the HLA genotype DQ2/DQ2. Another study of children with DQ2/DQ8 found that the timing of introducing gluten did not affect the CD risk22 but that an additional 1 gram of gluten intake per day did increase the risk of developing CD by three years of age.23 However, another study that compared children with type 1 diabetes in Sweden and Denmark found differences in coeliac autoimmunity between the two countries, independent of HLA. This supported the suggestion that different environmental exposures had an effect.24 Future interventional studies on gluten intake may take this knowledge into account. These include other environmental factors, such as the composition of the microbiota, and vaccination schedules, which have been suggested as a possible primary intervention.16 One suggestion is to carry out intervention studies with enough power to analyse subgroups by sex, by different HLAs, such as DQ2 homozygous or heterozygous, and between individuals with or without HLA DQ8.

We found that children born after the epidemic were younger at the time of their CD diagnosis. The 1997–1998 cohort may have been screened for CD earlier, and more often, than the older cohort at the time of their diabetes diagnosis. This is a possibility because CD screening in children with diabetes was less common at the beginning of the 1990s. In addition, awareness of the increased risk of CD in patients with type 1 diabetes increased towards the end of the decade. In contrast, the age at diagnoses of type 1 diabetes was similar in both birth cohorts. Furthermore, we also found that children with both type 1 diabetes and CD developed type 1 diabetes at a younger age than children with just type 1 diabetes. This reflected the findings of some studies,3,25 but not all.26

This study found that the sex distribution was fairly even among children with both type 1 diabetes and CD. In contrast, girls have been shown to account for two-thirds of the children with just a CD diagnosis in the general population.3,7 Girls have also dominated populations screened for CD in otherwise healthy children.7 There have been a number of studies on the sex distribution of patients with both type 1 diabetes and CD. One study found no differences.27 A study from southern Sweden, that comprised 300 children with type 1 diabetes, showed a significantly higher prevalence of CD in boys than girls, namely 19 versus 10.3 However, the previously mentioned Stockholm study found that 39 of 77 children with both diseases were boys and 38 were girls.2 Consequently, the proportion of males and females may be different, depending on the proportions of diabetes. The proportion of males to females in our cohort with type 1 diabetes and CD, 55% versus 45%, was only slightly higher, but not significantly. This suggests that boys and girls with type 1 diabetes have a similar risk of developing CD.

4.1 Strengths and limitations

A major strength of this study was that we analysed the nationwide prevalence in two population-based birth cohorts in Sweden. It also enabled us to outline this unique epidemiologic event of a high CD incidence in young children and a high overall prevalence of CD in Sweden. If this was due to changes in infant feeding recommendations, it could not be ethically reconstructed in other populations.

However, our study had limitations that could affect our results. The cohorts covered a total period of 6 years, with the earliest child born in 1992 and the youngest born in 1998. This means that they could have been exposed to differences in screening procedures for CD. In the early 1990s, endomysial autoantibodies were used to screen for CD. Around 2007, these autoantibodies were fully replaced with transglutaminase autoantibodies in Sweden. This approach was supported by the 2012 European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of CD.28 This means that different autoantibodies were used to find CD in our two cohorts. However, when the Society revised the guidelines in 2020,29 the specificity and sensitivity of both tests were considered reliable, and this means that using different methods may not have influenced our results. It is also plausible that children born after the coeliac epidemic were more likely to be screened for CD, due to increased awareness. Routine clinical screening may have also been more common in the younger type 1 diabetes cohort born in 1997–1998. Increased screening may have influenced the favourable prevalence in that cohort. Nevertheless, most Swedish children with type 1 diabetes have been repeatedly screened for CD since 2006 in Sweden and this also included the older cohort born in 1992–1993. Another factor that should be taken into account is the quality of the registration of the registries. This may have improved over time and may also favour the prevalence in the younger cohort. Altogether, changes in the screening procedure, increased awareness and better-quality registries may have influenced the
prevalence in favour of the younger cohort. Having said that, we do not believe that would have affected the results, as the maximum gap between the oldest and youngest children was only 6 years.

5 | CONCLUSION

The prevalence of CD among children with type 1 diabetes was not statistically significantly increased in the cohort born during the Swedish CD epidemic. This key finding may support a strong genetic disposition in children who develop both type 1 diabetes and CD. It could also have reduced the impact of the change in gluten recommendations introduced during the Swedish CD epidemic. We suggest that differences in HLA risk may be considered when planning intervention studies to decrease the risk of CD.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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