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ORIGINAL ARTICLE

Month of birth and the risk of developing type 1 diabetes among children in the Swedish national Better Diabetes Diagnosis Study

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Abstract

Aim: Previous studies have reported an association between month of birth and incidence of type 1 diabetes. Using population-based data, including almost all newly diagnosed children with type 1 diabetes in Sweden, we tested whether month of birth influences the risk of type 1 diabetes.

Methods: For 8761 children diagnosed with type 1 diabetes between May 2005 and December 2016 in the Better Diabetes Diagnosis study, month of birth, sex and age were compared. Human leucocyte antigen (HLA) genotype and autoantibodies at diagnosis were analysed for a subset of the cohort ($n = 3647$). Comparisons with the general population used data from Statistics Sweden.

Results: We found no association between month of birth or season and the incidence of type 1 diabetes in the cohort as a whole. However, boys diagnosed before 5 years were more often born in May ($p = 0.004$). We found no correlation between month of birth and HLA or antibodies.

Conclusion: In this large nationwide study, the impact of month of birth on type 1 diabetes diagnosis was weak, except for boys diagnosed before 5 years of age, who were

Abbreviations: BDD, Better Diabetes Diagnosis; GADA, glutamic acid decarboxylase antibodies; HLA, human leukocyte antigen; IA2A, insulinoma antigen 2 antibodies; IAA, insulin antigen antibodies; ZnT8A, zink transporter 8 antibodies, type R, Q, W.

more likely born in May. This may suggest different triggers for different subgroups of patients with type 1 diabetes.

KEYWORDS
autoantibodies, birth pattern, HLA-DQ alleles, seasonality, type 1 diabetes

1 | INTRODUCTION

Type 1 diabetes is considered to be an autoimmune disease, where destruction of the beta cells leads to insulin deficiency.[1] The underlying mechanism is unknown, but it is known that the risk of developing type 1 diabetes depends on both genetic and environmental factors.[2] The majority of the genetic risk depends on the Human leucocyte antigen (HLA) genotype and the HLA genotype DQ2 (A1*0501-B1*0201)-DQ8 (A1*0301-B1*0302) constitutes the highest risk for type 1 diabetes.[3]

More than 90% of patients diagnosed with type 1 diabetes have one or more autoantibodies at diagnosis.[4] These are antigen-specific antibodies to glutamic acid decarboxylase (GADA), insulinoma antigen 2 (IA2A), insulin (IAA) or Zink transporter 8 types W, R and Q (ZnT8WA, ZnT8RA and ZnT8WQA).[2,5]

It has been hypothesised that viral exposure in the womb plays a role in the initiation the beta cell destruction.[6–10] Some studies have shown that enteroviral infection during pregnancy may increase risk of type 1 diabetes in the offspring,[6,7] while others have not found this association.[9–11] Maternal respiratory infections and gastroenteritis during pregnancy have been identified as risk factors for type 1 diabetes in the offspring.[12,13]

In high incidence areas, such as Finland, Sweden and Sardinia, studies have demonstrated differences in birth month when comparing children with and without type 1 diabetes.[14–18] This suggests that viruses or nutritional factors may play a role as triggers for the autoimmune process. In low incidence countries such as Japan and China, these associations have not been seen.[19,20]

The aim of this study was to determine whether month of birth influences the risk of type 1 diabetes in a Swedish cohort. Furthermore, we wanted to explore potential patterns between month of birth, age and type of autoantibodies at diagnosis. These findings were also related to sex and HLA type because such factors may influence the response to environmental exposure.

We hypothesised that children diagnosed with type 1 diabetes at young ages more often are born during late summer and early fall because their first months in life would have coincided with the winter season and the highest rates of infections. We also hypothesised that different HLA genotypes differentially influence the susceptibility to environmental exposures.

Key notes

- In his large population-based study of Swedish children with type 1 diabetes, we aimed to determine whether month of birth affected the incidence of diabetes and the presence of autoantibodies at diagnosis.
- Young boys (<5 years) were more often born in May, otherwise we could not confirm a strong link between month and incidence.
- There is a heterogeneity in type 1 diabetes, where boys and girls may differ in triggers.

2 | MATERIALS AND METHODS

2.1 | Study population

In Sweden, all children with diabetes are cared for at paediatric specialist clinics. The Better Diabetes Diagnosis (BDD) study is a prospective national cohort study that has included virtually all children and adolescents (<18 years) diagnosed with any type of diabetes in Sweden since 2005.[21] The study is ongoing and now includes data on more than 12 000 individuals. The study is divided into BDD 1, from May 2005 to December 2010, and BDD 2, from January 2011 and ongoing. At the time of diagnosis, blood tests are analysed for HLA genotype and islet cell antibodies as well as for C-peptide.[22]

This study is based on data from the first 8946 children included in the BDD database until December 2016. We studied children in the BDD registry diagnosed with type 1 diabetes and thus excluded those diagnosed with type 2 diabetes, monogenic diabetes, secondary diabetes and a few cases of unclassified diabetes. The American Diabetes Association (ADA) diagnostic criteria for classification of type 1 diabetes were applied.[1] The final study cohort was 8761 patients, including 4811 boys (55%) and 3950 (45%) girls. For the antibody and HLA analyses, we only used data from BDD1, which after exclusions had a total of 3647 patients (Figure 1).

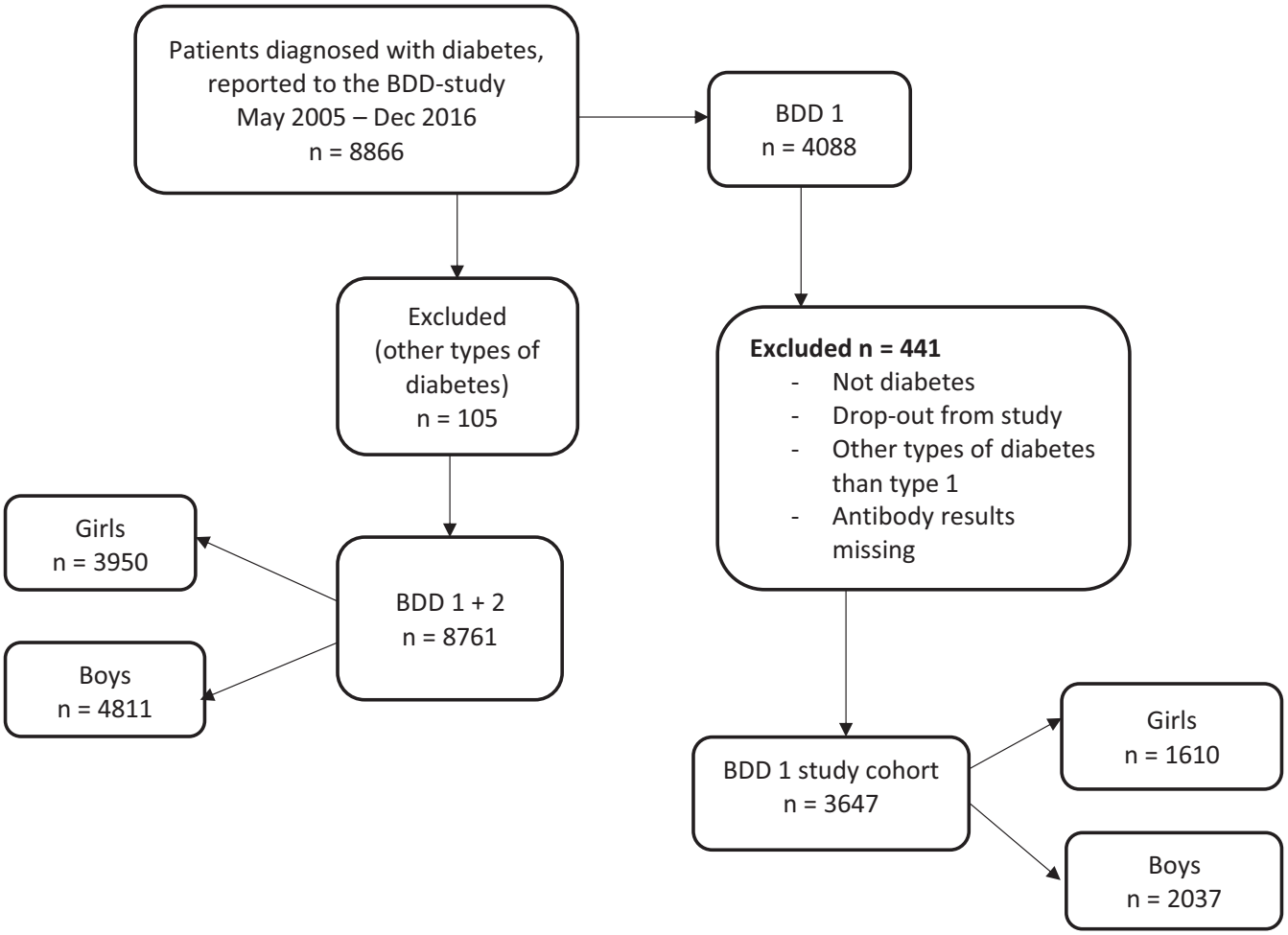

FIGURE 1 Flowchart of Better Diabetes Diagnosis 1 and Better Diabetes Diagnosis 2 participants and exclusions

2.2 | Controls

Data on the distribution of birth months for the general population were retrieved from Statistics Sweden. Comparisons between individuals in the BDD cohort and individuals from the general population were made covering all births between 1987 and 2015. The average number of births were 105 214 yearly, with a range from 88 173 to 123 985.

2.3 | Variables

From the BDD register, we collected data on date of birth (from which we extracted month of birth and season), date of diagnosis (from which we calculated age at diagnosis), sex, prevalence of autoantibodies at diagnosis and HLA type. There are limitations in comparing month of birth as a risk factor for type 1 diabetes because it is a narrow measurement that does not consider whether one is born prematurely and because being born on the last day of one month or the first of the next can affect the outcome, thus we also compared seasons of birth by categorising birth months into seasons as December–February, March–May, June–August and September–November and into warm or cold periods as April–September and October–March to catch larger periods of time.

2.4 | Autoantibodies

Blood samples for analysis of autoantibodies were taken on the first or second day after diagnosis and were analysed at the clinical research centre in Malmö, Skåne University Hospital. For the 4088 children diagnosed with type 1 diabetes during the years 2005–2010, the GADA, IAA, IA2A, and ZnT8WA, ZnT8RA and ZnT8WQA autoantibodies were analysed. The cut-off points for positive values (not including the threshold values) were IAA ≥1.0 U/ml, GADA ≥50 U/ml, IA2A >10 U/ml, ZnT8WA >75 U/ml, ZnT8RA >75 U/ml and ZnT8WQA >100 U/ml. A detailed description of the antibody analyses has been described previously.[22]

2.5 | HLA

The HLA genotypes were classified into different risk groups as follows: high risk: DQ2-DQ8, DQ8-DQ8 and DQ2-DQ2; medium risk:

DQ8-DQX; and low risk: DQ2-DQX, where X indicates all other alleles except DQ2 or DQ8. HLA genotypes were further categorised as high risk and not high risk, the latter category including both the medium-risk and low-risk HLA genotypes. More detailed information on the HLA analyses has been described previously.[22]

2.6 | Statistical analysis

Calculations were made using SPSS version 25.0–27.0 (IBM Corp). The chi-square test was used to explore differences between the groups. To take multiple comparisons into account, according to the Bonferroni, we adjusted the alpha level to 0.004 to compensate for the 12 months of comparison.

Analyses of month of birth were made comparing the general population with individuals in the BDD cohort, both in total and grouped by sex and by age at diagnosis (5 years and older or less than 5 years). This was done comparing observed values (BDD data) with expected values (calculated from the general population) for the current month and comparing each month to all other months using the chi-square test. First, we compared birth month, and then we compared seasons and warm or cold periods.

For the autoantibody and HLA analyses, we could not use the general population for comparison because there are no data on HLA and autoantibodies. We therefore compared the antibody presence at diagnosis per group for a specific month to other months for the same group and performed a chi-square test. Similarly, for HLA we compared the high-risk group to the other groups for the different months and for age at diagnosis and sex.

3 | RESULTS

For demographic data, see Figure 1. In the general population, there was no difference in monthly distribution of births comparing boys and girls, but there was an observed seasonal variability with higher total numbers of births between March and May and fewer in November and December. No significant difference was seen in the distribution of birth months ($p = 0.76$) when comparing the general population with the BDD cohort (Figure 2). We studied observed cases of type 1 diabetes in the whole BDD cohort in relation to expected cases based on monthly distribution and divided by sex. The risk of type 1 diabetes did not differ with birth month in either sex (girls $p = 0.29$, boys $p = 0.21$). In children diagnosed with type 1 diabetes before 5 years of age, boys were more likely to be born in May ($p = 0.004$). No differences among girls were seen (Figures 2 and 3).

With respect to season of birth, no significant difference was observed for either of the age groups or sexes. Birth during the warmer half of the year, as compared to the colder half, did not influence the risk of type 1 diabetes.

Because a larger proportion of boys diagnosed with type 1 diabetes before the age of 5 were born in May, we compared the pattern of autoantibodies for individuals with type 1 diabetes born in May with those born in other months and found that ZNT8RA was slightly more common in boys born in May compared with children born in other months ($p = 0.01$), but the difference was not significant (Figure 4). For girls, we found no differences.

When looking at the distribution of birth months for the different HLA risk groups compared with the general population, we found a weak overrepresentation of children born in August with high-risk HLA, although this was not significant ($p = 0.02$). No differences were seen between the sexes.

4 | DISCUSSION

In this large population-based study, consisting of almost all children diagnosed with diabetes during the period, boys diagnosed with type 1 diabetes before the age of 5 years were more likely to be born in May compared with sex-matched controls.

Our results are in line with data from the SEARCH for Diabetes in Youth study, which reported that children with type 1 diabetes were more likely to be born in May and less likely to be born between November and February, also among younger children, although they did not report any sex differences.[14] In contrast, Songini et al. showed that children in Sardinia with type 1 diabetes had a different pattern of birth month than the general population, with a higher frequency of children with type 1 diabetes born during the summer months.[18] However, theirs was a smaller study, and they did not compare by sex. Similarly, an older Swedish study by Samuelsson et al. showed that it was more likely for children with type 1 diabetes to be born during the summer months and less likely to be born in October, specifically for children aged 10–15 years at diagnosis.[17]

We did not find any clear association between HLA genotype and birth month. Badenhoop et al. did find that birth month differed with HLA genotype in individuals with type 1 diabetes,[23] but they did not look at different age groups. Pöllänen et al. compared patients with

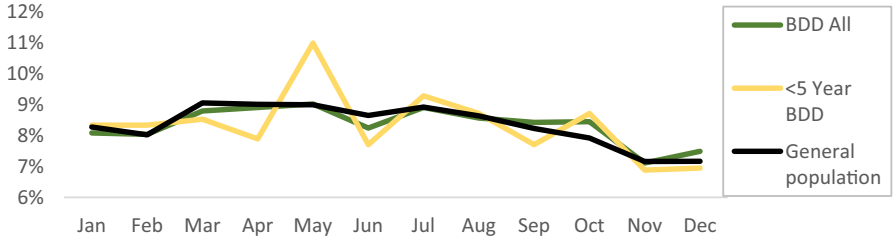

FIGURE 2 Month of birth distribution shown for the general population, the entire Better Diabetes Diagnosis cohort and Better Diabetes Diagnosis children <5 years, in %

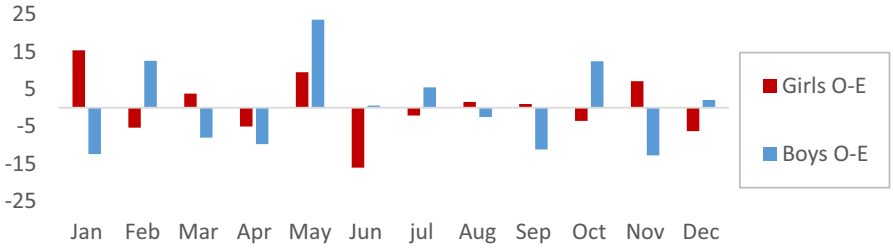

FIGURE 3 Month of birth for boys and girls in the Better Diabetes Diagnosis cohort <5 years old at diagnosis compared with the general population. The difference between observed cases (O) and expected cases (E) is shown

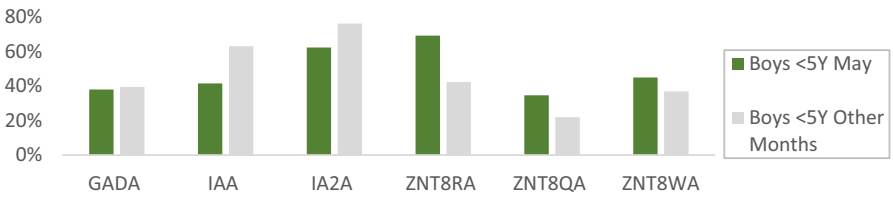

FIGURE 4 Presence of the different autoantibodies in boys under 5 years of age at diagnosis born in May compared with boys of the same age born other months

different HLA genotypes and showed that slow progressors to type 1 diabetes were more likely to be born during the fall while more rapid progressors were more often born during the spring, although their results were unrelated to age or sex.[24]

We found no major differences in HLA genotype or antibodies present at diagnosis depending on month of birth. Lewy et al.[25] showed that there is a different seasonal pattern among GADA-positive patients of both sexes compared with the healthy population, but they did not divide their population into different age groups and had a generally older cohort. Several studies have shown a correlation between HLA-haplotype and type of autoantibodies present at diagnosis,[26–28] but no study has investigated this in relation to month of birth.

The incidence of type 1 diabetes has increased, both in Sweden and globally, during the second half of the 20th century and especially among younger children.[29,30] We can only speculate whether our different results are influenced by the increasing incidence with a different population with diabetes that may also have different triggers that are less influenced by month of birth. Contrary to our hypothesis, this study only shows an increased risk for boys born in May who acquired the disease earlier in life, which may support a difference in susceptibility depending on sex.

A strength of this study is the large, population-based sample size of 8761 individuals with type 1 diabetes, which reduces the risk of selection bias. However, a limitation is that there were numerous analyses done in this study, with subgroups and several variables, and scattered significances will be found when looking at enough variables and analyses. We have tried to compensate for this to some extent by lowering the statistical threshold for significance to $p < 0.004$.

5 | CONCLUSION

In this large, population-based study, the impact of month of birth on type 1 diabetes diagnosis was weak, with the one exception of boys diagnosed before 5 years of age being more likely to have been born in May. These results might reflect the heterogeneity of type 1 diabetes with different environmental triggers for different subgroups of individuals with type 1 diabetes.

CONFLICT OF INTEREST

None of the authors have any conflicts of interest to declare.

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