Long-Term Patterns in Seasonality of Insulin-Dependent Diabetes Mellitus Diagnosis in Austrian Children

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ABSTRACT. The analysis of the seasonal pattern of incidence of childhood insulin-dependent diabetes mellitus in Austria was carried out among cases where the child was under the age of 15 when diagnosed between 1979 and 1993. The cases are registered in the nationwide population-based Austrian insulin-dependent diabetes mellitus registry. Seasonal variation was compared between boys and girls and between three 5-year age groups. We also tested whether the seasonal pattern changed over the 15-year observation period.

We found a significant seasonal variation among boys aged 10-14 and girls aged 5-14, while in the 0-4 years age group no seasonal pattern could be demonstrated. Two peaks in incidence were identified during a calendar year (February-March and September-October) for girls aged 5-14. For boys aged 10-14, a yearly cycle was found with a peak in January and October. An extension of the Poisson regression model for testing seasonality by Jones et al. was developed to allow for estimation of a time-dependent amplitude of the seasonal component.

The annual incidence rate increased by 36% during the observation period, but no significant change in seasonal pattern could be demonstrated. Copyright © 1997 Elsevier Science Inc. J CLIN EPIDEMIOL 50;2:159-165, 1997.

KEY WORDS. Diabetes mellitus, incidence, epidemiology, seasonality, Poisson regression, nationwide population-based

INTRODUCTION

In many northern European countries, a significant non-linear increase in incidence of childhood insulin-dependent diabetes mellitus has been observed in the past decades [1-4]. In only a few central European countries, long-term insulin-dependent diabetes mellitus incidence data are available. Using a retrospective study design, for 1978-1987, a rising incidence was found in Hungarian children younger than 15 years [5]. In Austria we have recently reported a significant non-linear increase of 36% for 1979-1993 [6].

In addition to the long-term time trend, a seasonal cyclic pattern of insulin-dependent diabetes mellitus occurrence has been observed in many, but not in all, countries [7]. Although it has been commonly stated that the incidence of insulin-dependent diabetes mellitus is high during cold seasons and low during warm seasons, only a few attempts have been made to test this with appropriate methods. The aim of our study was to analyze the seasonal patterns of insulin-dependent diabetes mellitus incidence in Austria by the method of Jones et al. [8] and to extend their model to allow for the estimation of a possible change in the amplitude of the seasonal variation during a 15-year study period.

Several investigators have evaluated seasonal patterns of the onset of insulin-dependent diabetes mellitus, but thus far there have been no reports where possible temporal changes in seasonality have been assessed. We tested the hypothesis whether the seasonality became more pronounced during a 15-year period when the overall incidence of insulin-dependent diabetes mellitus in Austria increased significantly.

MATERIALS AND METHODS

Children in Austria who had been newly diagnosed as diabetic between January 1979 and December 1993 were included in this analysis. Methods of case-ascertainment have been described in more detail elsewhere [9]. The completeness of the case-ascertainment was 93-94% [10,11]. The year 1985 was not included, as the registry was not active in that year. Since 1989, the Austrian incidence data are
included in the Eurodiab ACE study [11]. Yearly population data were obtained from the National Population Registry which is updated continuously.

The data were grouped with regard to sex and age at diagnosis (0–4, 5–9, and 10–14 years). Age- and sex-specific average annual incidence rates were calculated per 100,000 of the population per year.

A non-linear Poisson regression model, such as described by Jones et al. was used for tests and estimation of the cyclic behavior in the incidence of insulin-dependent diabetes mellitus [1].

Plotting the incidence rate against time, reveals a slight increase in the mean and in the amplitude of the harmonics in the age group 10–14 years (Fig. 1). An increase in the amplitude can be expected, as the variance of a Poisson distributed variable equals its expectation. It is proposed here to extend the model of Jones et al. [1] by using an interaction term between time and each of the harmonics in order to test if the observed increase is due to the aforementioned dependency or if there is an independent additional increase in the amplitude. Therefore, in our model the probability of manifestation of insulin-dependent diabetes mellitus in a small interval at time $t$ for group $i$ is described by

$$
\lambda_i(t) = a \left[ 1 + b(t - T/2) + \sum_{h=1}^{H} \left( \alpha_h \cos(2 \pi ht/P) + \beta_h \sin(2 \pi ht/P) \right) + t \sum_{h=1}^{H} \alpha_h \cos(2 \pi ht/P) \right] + \beta_h \sin(2 \pi ht/P) \right]
$$

$$
\alpha_h = c_h \cos(\Phi_h), \quad \beta_h = -c_h \sin(\Phi_h),
$$

where

- $a_i$ is a parameter allowing the size of the underlying population of group $i$ to be arbitrary;
- $b$ the linear time trend centered around time $T/2$;
- $h$ order of the harmonic;
- $H$ number of harmonics;
- $c_h$ the amplitude of the corresponding harmonic;
- $\Phi_h$ the phase angle describing the location of the maximum within one period;
- $P$ the fundamental period of the model, i.e., the length of the period in which a harmonic reaches its starting point.
FIGURE 2. (a) Monthly mean incidence of IDDM for boys per 100,000. Ages 0–4 (solid line); ages 5–9 (dashed line); ages 10–14 (dotted line). (b) Monthly mean incidence of IDDM for girls per 100,000. Ages 0–4 (solid line); ages 5–9 (dashed line); ages 10–14 (dotted line).
TABLE 1. Parameters and \( p \) values of the Poisson regression model with and without interaction terms

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Boys aged 10-14 years</th>
<th>Girls aged 5-14 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without interactions</td>
<td>With interactions</td>
</tr>
<tr>
<td></td>
<td>Parameter estimate</td>
<td>( p ) Value</td>
</tr>
<tr>
<td>Slope</td>
<td>0.0031 0.0013</td>
<td>0.0362 0.0013</td>
</tr>
<tr>
<td>( \Phi_1 )</td>
<td>-21.3493 0.0001</td>
<td>-31.5525 0.0001</td>
</tr>
<tr>
<td>( c_1 )</td>
<td>0.4024</td>
<td>0.4439</td>
</tr>
<tr>
<td>( \omega_1 )</td>
<td></td>
<td>0.0131</td>
</tr>
<tr>
<td>( \Phi_1 )</td>
<td>-4.4553 0.0005</td>
<td>-3.0076 0.0005</td>
</tr>
<tr>
<td>( c_2 )</td>
<td>-0.2330</td>
<td>-0.2344</td>
</tr>
<tr>
<td>( \omega_2 )</td>
<td></td>
<td>-0.0011</td>
</tr>
</tbody>
</table>

\( \Phi, c, = \) parameter describing the phase (in degrees) and amplitude of the \( i \)-th harmonic; 
\( \omega = \) interaction between time and the \( i \)-th harmonic.

Here \( \omega_h \) is a new parameter which describes a time depending amplitude of the \( h \)-th harmonic in group \( i \). A positive value of \( \omega_h \) implies an increasing amplitude of the \( h \)-th harmonic in group \( i \) over the time. In the interaction term \((t - T/2)\) has been replaced by \( t \) in order to ensure a monotone increase of the sine and cosine waves. The number of harmonics \( H \) has to be fixed by the investigator. Significance of the parameters is tested by the difference of the \( 2 \times \log \)Likelihood between two hierarchical models. Parameters \( \Phi \) are added in a hierarchical way, i.e., estimation of 2nd order harmonics always includes estimation of 1st order harmonics, 3rd order harmonics imply estimation of 1st and 2nd order harmonics.

Selection of non-hierarchical models is done by calculation of Akaike's information criterion \( AIC = 2 (\log \)Likelihood + Number of estimated parameters) and choosing the model with the minimum AIC. Tests for goodness of fit of the model are carried out by using the chi-square statistic.

The observed incidence was compared with the estimated incidence by calculating the average relative incidence adjusted for time trend. This was done by subtracting the linear trend term from the observed incidence, averaging by month and dividing by the annual mean.

In a further step we divided the period 1979–1993 into two periods, from 1979–1984 and 1986–1993. We then estimated for the subgroups resulting from the first analysis for each period a separate model to look if the pattern of the harmonics has changed.

The software package GAUSS [12] was used to estimate the model. The procedure was validated using Jones' data and the BASIC-programs TSEASON and TCOMLIN written by Jones et al. [8].

RESULTS

Figures 2, a and b depict the monthly incidence rates without correction for a possible time trend. The rate for boys aged 10–14 years shows clear peaks in January and October. For girls aged 5–9 and 10–14 years, the maximum rate is centered around March and October.

Table 1 shows the parameter estimates and their corresponding \( p \) values of the regression models with and without interaction terms. The values refer to the increase in the twofold logLikelihood when a parameter is added to the model. The \( p \) value beside the parameter \( \Phi \) refers to the simultaneous addition of the parameters \( \alpha \) and \( \beta \). For girls, based on AIC, the tests for pooling age groups showed that the best pooling was to present the data for two strata: the age group 0–4 years and the group 5–14 years (AIC = -32.39). The AIC value for the model, where each age group has its own parameters, was -27.47. For the 0–4 years age group, neither a linear time trend nor any of the harmonics showed a significant improvement over the null model. The model for the pooled age group 5–14 years, revealed a significant positive linear time trend (\( p = 0.0003 \)) with a harmonic of order one (\( p < 0.0001 \)) and order two (\( p = 0.0005 \)). The test for an interaction between time trend and yearly variation was not significant (harmonic one: \( p = 0.2331 \), harmonic two: \( p = 0.9578 \)). The test for goodness-of-fit was not significant (\( p = 0.39 \)).

For boys, the best age grouping was 0–9 years and 10–14 years (AIC = -35.38), which was slightly better than the model with three age groups (AIC = -34.94). The model for the age group 0–9 years revealed no significant parameters. Modeling the incidence rates for boys aged 10–14 years shows a significant trend parameter (\( p = 0.0013 \)) and a significant harmonic of order one with a \( p \) value of \( p < 0.0001 \). The test for the interaction between time and the first-order harmonic (\( p = 0.37 \)) and the chi-square test for goodness-of-fit were not significant (\( p = 0.74 \)).

Figure 3 shows the expected and the observed average relative incidence for boys aged 10–14 years and girls aged 5–14 years. For girls, the observed incidence rates fit well within the confidence interval of the estimated rate. For boys, deviations from the estimated incidence occurred at two times/points: December (downwards) and January (upwards). This can be explained by the exclusion of the 2nd and 3rd order harmonics, which were not significant with \( p \) values of 0.315 and 0.066, respectively.

Stratification of the data into the periods 1979–1984 and 1986–1993 yielded very similar results compared to the period 1979–1993. The only exception occurred in the group boys aged 10–14 years in the period 1979–1984, where the \( p \) value of the aforementioned 3rd order harmonic changed to \( p = 0.018 \).
FIGURE 3. (a) Estimated (solid line) and observed (thick line) weekly average relative incidence adjusted for trend for boys aged 10–14 years. The inner two dotted lines refer to the 95% confidence interval and the outer dashed lines refer to the 95% confidence interval for the entire curve, respectively. (b) Estimated (solid line) and observed (thick line) weekly average relative incidence adjusted for trend for girls aged 5–14 years. The inner two dotted lines refer to the 95% confidence interval and the outer dashed lines refer to the 95% confidence interval for the entire curve, respectively.
According to the model, we found in girls (5–14 years) a bicyclic yearly pattern with the nadir in June–July and peaks around February–March and October–November, whereas the rate for boys aged 10–14 years showed only one peak around January. The possible high peak in October in boys was not significant according to the full model.

In our cohort, a significant seasonal variation could not be found in the younger age groups (girls under 5 years and boys under 10 years). This may be due to the smaller number of cases in this age group as incidence is low in our country for both sexes under the age of five. On the other hand, several other studies, even in areas with incidence rates two or three times higher than in Austria; for example, England [2], Colorado [19], Sweden [16], or Finland [23] also found a significant seasonal pattern only in older age groups. The Eurodiab ACE study [24] reported the smallest relative amplitude of the seasonal distribution in the age group 0–4 years. This less pronounced seasonal pattern of onset in the younger children, could be an indication that, in this age group, seasonally varying trigger mechanisms may not be important for the manifestation of the disease. It could also be that the manifestation of insulin-dependent diabetes mellitus in young children is due to a more aggressive process that may not be modulated by environmental factors.

The temporal trend and epidemic-like outbreaks of insulin-dependent diabetes mellitus manifestations offer strong evidence that non-genetic, in all probability environmental, factors play a role in at least the manifestation of the disease in pre-diabetic individuals. Viral infections have been implicated for the seasonal pattern of insulin-dependent diabetes mellitus occurrence [3]; newly diagnosed patients, for instance, have been found to have a significantly higher prevalence of viral antibody titres [25,26]. In addition, many physiological parameters such as glucose tolerance, blood pressure, blood lipids and body weight change during the year as well as physical activity and nutritional habits. It is not clear if, and if so which, one of these seasonally changing conditions are directly involved in the pattern of insulin-dependent diabetes mellitus manifestation.

**SUMMARY**

In conclusion, our study was able to demonstrate that, in Austria, insulin-dependent diabetes mellitus incidence fluctuates significantly within a year as well as during a longer period of time. Over the 15 years, the mean annual incidence rate increased significantly in Austria but the amplitude of the seasonal pattern did not change.

**REFERENCES**


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