Seasonality of birth in children and young adults (0–29 years) with type 1 diabetes in Ukraine

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Abstract

Aims/hypothesis Numerous epidemiological studies have shown differences in seasonality of birth patterns between the general population and the group who develop type 1 diabetes mellitus. This finding indicates that environmental factors operating during pre- and/or postnatal development could be aetiologically important. We examined whether the pattern of month of birth for type 1 diabetes patients in Ukraine differs from that for total live births.

Methods Data consist of prevalent cases of type 1 diabetes in Ukraine by the end of 2003. Cases are restricted to persons born after 1 January 1960, diagnosed with type 1 diabetes before the age of 30 years ($n=20,117$). People born during the same time in the general population ($n=29,105,560$) were the reference standard. Seasonal patterns were estimated using logistic regression with harmonic terms.

Results We found a strongly significant seasonal pattern of type 1 diabetes incidence rates ($p<0.001$), with the lowest rates in December and the highest in April. The rate ratio

between the extremes was 1.32 (95% CI 1.27–1.39). Tests for seasonal patterns in subgroups defined by sex and age or by sex and date of birth were all significant with p values less than 0.02. We found no interactions with sex ($p=0.142$) or age at diagnosis ($p=0.207$), but found a strong interaction with period of birth ($p<0.0001$).

Conclusions/interpretation The results obtained indicate that early-life factors linked to seasons may influence type 1 diabetes risk later in life.

Keywords Age cohorts · Incidence · Month of birth · Seasonality · Type 1 diabetes

Introduction

There is growing evidence that environmental factors operating in utero or early childhood may influence the risk of type 1 diabetes. The authors of studies primarily attribute the relationship to intrauterine infections, dietary intake of certain nutrients and possible toxic food components, short duration of breastfeeding, early exposure to cows' milk proteins, and vitamin D deficiency [1]. Since most of these factors vary with season, one would expect a difference in the seasonal birth pattern between the general population and those who develop diabetes. Seasonality of birth in children with type 1 diabetes mellitus has been demonstrated in populations with a high incidence: Israeli Jews, Sicily, Sardinia, Slovenia, Germany [2], Sweden [3] and the Netherlands [4]. However, no convincing seasonal trends elsewhere in Europe were seen outside Great Britain [5, 6].

Contrasting exposures in early life are predictable from seasonal climatic changes in Ukraine where seasons are well defined. Therefore, Ukraine is a suitable region for the study of the seasonally caused circumstances of human development.

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Subjects and methods

Information on date of birth, sex and year of diagnosis was extracted from the nationwide population-based Ukrainian insulin-treated diabetic patients register ($n=120,085$), created in 2000–2003 in the Institute of Endocrinology, Kiev, Ukraine. According to Public Health Ministry statistics (2004), the number of insulin-treated diabetics in Ukraine was 131,178. Therefore, the completeness of ascertainment of the register was about 92%. The reports of primary-care doctors from the entire country were used as the primary data source in creating the register.

The definition of type 1 diabetes was based on onset before 30 years of age in combination with treatment with insulin but not oral drugs. Data consisted of prevalent cases of type 1 diabetes in Ukraine by the end of 2003. Cases were classified by sex, age at diagnosis, period of birth and month of birth. Cases were restricted to persons born after 1 January 1960, diagnosed with type 1 diabetes before age 30 years (10,780 men and 9,337 women).

The classification of period of birth and age at diagnosis is illustrated in Fig. 1. For each of the subsets of the Lexis diagram (Fig. 1) we computed the length of exposure to type 1 diabetes diagnosis (risk time) of the persons born in a particular month and year, assuming 0 mortality. This is necessary because among persons registered in the triangular subsets of the diagram (the rightmost subsets), those born in January will on average have 11 months' longer exposure to diagnosis than those born in December. These hypothetical risk times were then multiplied by the number of births for that particular month (and year) and aggregated within the

Fig. 1 The layout of the study. Persons in the study are those diagnosed inside the triangular grid and alive at the end of 2003. Persons dying before the end of 2003 are not in the database. Each subset of the grid is further subdivided in 12 subgroups by month of birth for analysis of seasonality. Male: blue, female: red

sets to form the effective population size for each unit of analysis, but they cannot be used as proper risk time in a cohort study, because they do not take mortality of the population into account. Furthermore, we have not registered all cases diagnosed, but only those surviving until the end of 2003. Thus, in relation to a detailed follow-up we have overestimated person-years and underestimated cases and these errors depend on age, period of birth and sex. Therefore we can only interpret effects of seasonality, not the effects of age, period of birth or sex; these are only in the model to correct for the bias introduced by calculations. This approach assumes that neither population mortality nor patient mortality depends on month of birth [7].

As the study is a study of diabetes prevalence in groups of persons who have survived until 2003 we analysed it with logistic regression, using the hypothetical risk times as proxies for the potential number of persons susceptible. The monthly birth figures for boys ($n=14,995,768$) and girls ($n=14,109,792$) were extracted from demographic year-books published annually by the Ukraine Department of Statistics for the period 1960–2003. The details of the statistical analyses can be found in the [Electronic supplementary material](#).

Results and discussion

In our study, similarly to those reported in other European countries [8], there is a male excess in incidence of type 1 diabetes after age 15 (Fig. 1). We found a strongly significant seasonal pattern of type 1 diabetes incidence rates (likelihood ratio $\chi^2[4]=143.47$, $p<0.0001$). Reduction to a model with only first-order harmonic terms was strongly significant ($\chi^2[2]=32.15$, $p<0.0001$); extension to a model with third-order harmonic terms was also significant ($\chi^2[2]=12.84$, $p=0.002$), but with a smaller test statistic. Due to large number of cases in the study and small changes in the shape of the estimated curve we decided to use the second-order description. We found the minimum to be at 29 December (95% CI 20 December–7 January) and the maximum at 29 April (95% CI 20 April–8 May); the distance between peak and nadir was 3.9 months (95% CI 3.7–4.3), and the amplitude of the seasonal variation was a rate ratio of 1.32 (95% CI 1.27–1.39). Tests for seasonal patterns in subgroups defined by sex and age or by sex and date of birth were all significant with p values less than 0.02. We found no interactions with sex ($\chi^2[4]=6.84$, $p=0.142$) or age at diagnosis ($\chi^2[20]=24.86$, $p=0.207$), but found a strong interaction with period of birth ($\chi^2[32]=67.07$, $p<0.0001$). The latest-born generations (1990+) showed a slightly aberrant pattern with a later time of lowest incidence (February for females and March for males), and the highest level in June for both sexes (Fig. 2, bottom

right-hand panel). This alone accounted for 40.23 of the χ^2 statistic, but only for 4 *df*. The latter findings are, however, somewhat uncertain and may be due to the rather small number of cases, being dependent on the particular choice of model.

The temporal changes in the incidence rates of type 1 diabetes cannot be assessed from the present data without further strong assumptions about the mortality rates among the general population and in the type 1 diabetes population, so therefore the present study is restricted to the study of seasonal patterns.

The classically used Walter and Elwood test for seasonality [9] is a test in a model with one harmonic term, i.e. in a model that forces the two extremes to be exactly 6 months apart. It has been the tradition to use this as a test for seasonality and report the peak incidence-based graphical displays with no formal estimation of the peak and nadir. We have chosen a harmonic with two terms (i.e. four parameters) in order to avoid this restriction in the analysis, which in this case turned out to be untenable. We found that the extremes were only 4 months apart and that type 1 diabetes was some 30% more common among persons born in April than among persons born in December.

Surprisingly, significant seasonal variations were found not only in children but also in adolescents and young adults aged 10–29 years at diagnosis. The autoimmune process begins many years before the clinical detection of type 1 diabetes. In some cases, a preclinical period lasts for

even more than 10 years [10]. However, for our data with many newly diagnosed cases aged 20 years or more, the early-life induction of autoimmunity does not seem a likely explanation. We hypothesise that such long-time effects are due to seasonal mismatch between fetal and postnatal environments for persons born in different months of the year. According to a recently proposed ‘predictive adaptive response’ hypothesis [11], a growing fetus takes cues from its mother to predict the postnatal environment. These processes determine the phenotype, which optimises survival chances in the predicted environment. Nutritional influences are particularly important [11]. If prediction is inappropriate, the risk of certain diseases increases. In our study, spring-born people experienced fetal life largely in the nutritionally marginal months from late autumn to early spring, and passed the first postnatal months in a season of relative plenty. These individuals were found to have an increased type 1 diabetes risk. In contrast, a lower incidence rate was seen for those who were born in autumn and early winter. In this group, fetal development in a nutritionally favourable season has been followed by early infancy in a season of relative shortage (winter–spring). Importantly, seasonality of birth of type 1 diabetics in Ukraine is more pronounced than anything previously reported in Western Europe [3–6], where dietary inadequacies are likely to be less marked. We suggest that not only level but also type of mismatch is important, and the first scenario (poor prenatal nutrition followed by improved postnatal nutrition) carries

Fig. 2 Effect of month of birth on the risk of developing type 1 diabetes. *Left-hand panel*, the overall effect with the 95% CI, controlled for sex, age at diagnosis and period of birth. The points are observed rate ratios for single months. *Right-hand panel*, analyses subdivided by sex and broad categories of date of birth. Men: *dark*; women: *light*

more risk than the opposite one. Further studies are required to determine the exact mechanisms behind the effect of seasonality on type 1 diabetes occurrence.

References

1. Akerblom HK, Vaarala O, Hyoty H, Ilonen J, Knip M (2002) Environmental factors in the etiology of type 1 diabetes. *Am J Med Genet* 115:18–29
2. Laron Z (2002) Interplay between heredity and environment in the recent explosion of type 1 childhood diabetes mellitus. *Am J Med Genet* 115:4–7
3. Samuelsson U, Johansson C, Ludvigsson J (1999) Month of birth and risk of developing insulin dependent diabetes in southeast Sweden. *Arch Dis Child* 81:143–146
4. Jongbloet PH, Groenewoud HMM, Hirasing RA, Buuren SV (1998) Seasonality of birth in patients with childhood diabetes in the Netherlands. *Diabetes Care* 21:190–191
5. Rothwell PM, Gutnikov SA, McKinney PA et al (1999) Seasonality of birth in children with diabetes in Europe: multi-centre cohort study. *Br Med J* 319:887–888
6. McKinney PA; EURODIAB Seasonality Of Birth Group. Europe and Diabetes (2001) Seasonality of birth in patients with childhood type I diabetes in 19 European regions. *Diabetologia* 44 (Suppl 3):B67–B74
7. Prener A, Carstensen B (1990) Month of birth and testicular cancer risk in Denmark. *Am J Epidemiol* 131:15–19
8. Kyvik KO, Nystrom L, Gorus F et al (2004) The epidemiology of type 1 diabetes mellitus is not the same in young adults as in children. *Diabetologia* 47:377–384
9. Walter S, Elwood J (1975) A test for seasonality of events with a variable population at risk. *Br J Prev Soc Med* 29:18–21
10. Kimpimaki T, Kulmala P, Savola K et al (2000) Disease-associated autoantibodies as surrogate markers of type 1 diabetes in young children at increased genetic risk. *J Clin Endocrinol Metab* 85:1126–1132
11. Gluckman PD, Hanson MA, Morton SMB, Pinal CS (2005) Life-long echoes—a critical analysis of the developmental origins of adult disease model. *Biol Neonate* 87:127–139