Seasonality of birth in patients with childhood Type I diabetes in 19 European regions

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Abstract

Aims/hypothesis. Differences in seasonality of birth patterns between the general population and the group who develop Type I (insulin-dependent) diabetes mellitus indicate that environmental factors operating around the antenatal and perinatal period could be important. We investigated whether the same unusual patterns in seasonality of birth observed in children with Type I diabetes in Great Britain could also be found in other European populations.

Methods. Population-based incidence cohorts of children diagnosed with Type I diabetes under 15 years of age from 1989 onwards were analysed. Previously reported data sets from Great Britain were also included together with data on children diagnosed over an additional 5 year period (1988–1992). To assess the role of seasonality in diabetes, we used the method of Walter and Elwood to examine monthly birth figures for each country or region.

Results. Outside of Great Britain, no seasonality of birth was seen for any single or combination of Euro-

pean countries. Significant sinusoidal patterns were observed in Scotland, Yorkshire and Leicester, although the peak for Leicester appeared around autumn rather than spring. There was little evidence that sex or age at diagnosis played a part in differences in seasonal patterns, either overall or for any individual country.

Conclusions/interpretation. We found no uniform seasonal pattern of birth in childhood diabetes patients across European populations, either overall or according to sex and age. This study provides no consistent evidence that environmental factors, which vary from season to season, have any influence on the fetal or neonatal life to determine the onset of Type I diabetes. However, a study of seasonality that takes into account possible changes both over time and over geographical areas could provide more insights. [Diabetologia (2001) 44 [Suppl 3]: B 67–B 74]

Keywords Childhood Type I diabetes, seasonality of birth, Europe.

Season of birth appears to be associated with the development of many diseases, including conditions not generally thought to be season-dependent [1].

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The experiences of the growing fetus and neonate are thought to affect future susceptibility to diseases [2]. Systematic cyclical variations in the patterns of births could reflect environmental factors which also have cyclical variations.

The cause of childhood Type I (insulin-dependent) diabetes mellitus is still not clear. Genetic susceptibility accounts for only a small proportion of the possible determinants [3] and non-genetic factors therefore play an important role. After analysing sets of data from different countries, several studies have identified a number of environmental risk factors for the development of Type I diabetes, particularly

around the time of birth [4–8]. Geographical and temporal variations in the seasonality of birth of children with Type I diabetes indicate that an environmental factor with features of an epidemic could be linked to the development of diabetes. Clustering by place and time of birth of diabetic patients has been observed in Sweden [9] but not in the United Kingdom [10, 11]. In 1996, an investigation of a large cohort of children with Type I diabetes from Scotland, Yorkshire and England and Wales in Great Britain found a statistically significant asymmetry in the monthly birth patterns of children who develop Type I diabetes compared with the monthly birth patterns of the background population [12]. Seasonality of birth has also been observed in Sweden [13], in Israel, among Jews [14], and in the Netherlands where differences between males and females have been found [15].

To see whether these same patterns of births exist in other populations in Europe, both overall and according to age and sex, a follow-up study was carried out using data from the EURODIAB cohorts of children with diabetes [16]. Our study includes data from the original studies in Great Britain [12], extended by a 4-year period of observation [17], as well as from 2 other regions in Great Britain and 14 other regions of Europe.

Methods and materials

Study population. Our study included data on 15 246 patients from 19 separate geographical regions in Europe, some of which were entire countries. All 26 contributors to the EURODIAB population-based incidence register [16] were invited to participate and 14 regions (or entire countries) contributed data. The EURODIAB register provided information on subjects diagnosed after 1989. It included only those subjects who developed Type I diabetes before the age of 15 and who had been born between 1974 and 1994 (data for years 1974 and 1993–1994 were not available for some regions, see Table 1). Data from three regions in Great Britain (Scotland, Yorkshire and England and Wales) have been included in a previous report [12] together with data on additional subjects for the years 1988–1992 for Yorkshire and Scotland.

Reference birth population. To allow for fluctuations in the birth rate of the general population, the number of subjects with Type I diabetes *observed* for each month of each year was compared with the number of subjects *expected* for each region or country. The expected number was derived from data provided by the participating centres on the total number of births by month, year and sex (when available) either for each region or for each country as a whole.

The expected numbers of subjects with Type I diabetes varied, being fewer near the beginning and near the end of the study period that began in 1974 and ended in 1992. The expected numbers were fewer at the beginning of the study period because many centres provided data only from 1989 onwards so that patients born in the beginning of the study period who developed diabetes relatively early in their life were not included. The expected number of subjects with Type I diabetes were also fewer at the end of the study period because some of the children born to-

wards the end of the study (up to 1992) who might be expected to develop diabetes later in life were not included.

To correct for that variation, the expected number of cases for each month was calculated taking into account births in each month in each year. The more subjects born in a year, the greater the influence of the seasonal pattern in that year on the total seasonality of expected births. For example, 20 subjects born with Type I diabetes in a month (20% in a year when 100 cases were born) adds more to the general seasonal pattern of birth of Type I diabetes than 2 subjects born in a month in a year in which only 10 subjects with Type I diabetes were born, even though both constitute 20%.

Thus, to compensate for variation in the overall distribution of the observed subjects with Type I diabetes, the published month-by-month birth data in the general population of each region were modified and a ‘control set of births’ was created. The numbers in the ‘control set of births’ were made equal to the total numbers of subjects with Type I diabetes and the control set of birth’s seasonal pattern was based on the expected numbers of subjects with Type I diabetes calculated for each calendar month (Details can be found in Appendix 1).

Statistical analysis. Statistical significance of the deviation of the observed number of subjects with Type I diabetes from the expected number was calculated using the test for seasonality of events described previously [18]. The null hypothesis is that a cyclic process (birth rate from month to month) can be presented as a disc with the centre of gravity in its geometrical centre. The method we used tests the statistical significance (two-sided $p < 0.05$) of the shift of the “centre of gravity” in two dimensions (2 degrees of freedom) in a model with any number of radial points with unequal distance between the radii – especially suitable for calendar months which are unequal in length.

The data were analysed for the total subject population, and then separately for each sex and age group (age at diagnosis 0–4 years, 5–9 years, 10–14 years). Data on male and female subjects was analysed separately to examine whether gender plays a part in different seasonality of birth patterns as suggested by a study in the Netherlands [15].

Results

The total numbers of patients, periods of observation and statistical significance are presented in Table 1 (Observed and expected birth data month by month for each region are available on request). Statistically significant seasonal variation in births among patients with childhood onset diabetes was found only in the regions of Scotland, Yorkshire and Leicester (Table 1). It is worth noting that the seasonal pattern in Leicester was opposite to the ones in Scotland and Yorkshire, although the size of the data sample in Leicester was too small to counterbalance the Scotland-Leeds trend that showed a peak in spring and trough in winter. This previously reported pattern [12] was confirmed as statistically significant by an analysis of the extended total population of Great Britain (Table 1, Fig. 1). No significant seasonality was found for any of the 14 European regions taken as a whole or in any one individual European region [Total Europe (outside GB) in Table 1]. The peak of

Table 1. Numbers of diabetes subjects and statistical significance of seasonal deviation from the expected numbers for nineteen European regions.

Region	Years of births	Number of subjects	χ^2	<i>p</i>
<i>Great Britain</i>				
Scotland ^a	1974–1992	2408	8.88	0.01
Yorkshire ^a	1974–1992	1232	8.34	0.02
England & Wales ^a	1974–1992	1270	4.90	0.09
Oxford	1974–1992	758	5.21	0.07
Leicester	1974–1992	329	7.16	0.03
Total Great Britain		5997	10.15	0.01
<i>Other European countries</i>				
Austria	1974–1994	895	0.43	0.81
Czech Republic	1974–1994	1512	3.01	0.22
Denmark (4 counties)	1974–1994	296	3.33	0.19
Germany (Baden-Wuerttemberg)	1974–1994	1303	1.42	0.49
Italy (Lazio)	1974–1994	471	1.89	0.39
Italy (Sardinia)	1974–1994	886	1.73	0.42
Lithuania	1974–1994	486	0.79	0.67
Luxembourg	1974–1994	72	4.67	0.10
Northern Ireland	1974–1994	462	1.75	0.42
Poland (Gliwice)	1975–1994	448	0.36	0.84
Romania (Bucharest)	1974–1994	185	2.38	0.30
Slovak Republic	1974–1994	889	2.97	0.23
Spain (Catalunya) ^b	1975–1993	914	1.63	0.44
Sweden (Stockholm)	1974–1994	520	0.31	0.86
Total other European countries		9339	4.92	0.09
Grand Total		15336	9.87	0.01

^a these sets include data from Rothwell et al (1996) report [12], ^b data from Spain exclude patients born on the 1st of January as that date was over-represented in the set and we assume that it was used to substitute the missing value for date of birth

the non-significant trend observed in European regions was towards autumn. In combination with Great Britain's spring peak, the total data set gave a statistically significant seasonal pattern with a sloping hump in the period between spring and autumn and a trough in the winter (Fig. 1).

Males compared with females. The results of the analyses for male and female subjects with Type I diabetes are presented in Table 2 (Observed and expected numbers month by month by region for males and females are available on request). We found evidence for statistically significant seasonality for males in two individual regions – Great Britain (England and Wales) and Luxemburg – as well as in the combined data of 5 regions in Great Britain and in the overall male population (significant trends are presented in Fig. 1. Peaks and troughs for other regions appeared to be scattered at random). For females significant seasonality was found in Scotland only (Table 2). A direct comparison between observed male and female subjects with Type I diabetes was used as an additional tool to investigate the different seasonal patterns of each sex. Differences between the seasonal pattern of birth of male and female subjects with Type I diabetes were found in three regions: Great Britain: England and Wales, Sweden and Sardinia where there was raised male-to-female ratio for subjects with Type 1 diabetes (1.56:1).

Age groups. The results of the analysis of age groups is presented in Table 3 (Data comparing observed subjects with Type I diabetes with expected subjects with Type I diabetes are available on request). Table 3 illustrates the presence of significant seasonal variation in some subgroups; in the 0–4 years age group in two regions, in the 5–9 years age group in two individual regions and in the total data from Great Britain as well as the 10–14 years age group for four regions and for Europe as a whole. There was no consistent trend in seasonal distribution between those regions.

Discussion

Analysis of the entire data set confirmed significant seasonality in two of five regions of Great Britain, that had been previously studied [12], that is in Scotland and Yorkshire with peaks in spring and early summer. However, in the present study, which extended the period of observation of the previous study by 4 years (from 1972–88 to 1972–92), statistically significant trends disappeared in the third region in England and Wales. Of the other two regions in Great Britain only Leicester showed statistically significant seasonality with a pattern opposite to the other regions in Great Britain with a trough in spring and a peak in autumn. Our search for significant sea-

Total Great Britain

Total other European countries

Total

1) All ages (0-14), both sexes

2) Males vs control subjects

3) Females vs control subjects

4) 0-4 years

5) 5-9 years

6) 10-14 years

Fig. 1. Seasonal patterns of observed to expected ratios of births in diabetic patients for total GB, total Europe (outside GB) and overall total for males and females and age groups at diagnosis (Plotted line is 3-month moving average of the observed to expected ratios)

sonality of birth in populations of patients with childhood onset Type I diabetes in 14 European regions outside of Great Britain failed to find any evidence of a seasonal pattern. The grouping of countries into areas of high, medium and low incidence did not show any degree of seasonal effect [17] although differences between high and low incidence groups have been observed in Israel [14].

Explanations for the differences in patterns of seasonality of birth of Type I diabetic subjects between Great Britain and other European regions are not immediately obvious. One reason why we were not able to detect statistically significant trends in patterns of seasonality of birth of Type I diabetic subjects might have been the small study cohort of some of the regions but even when we pooled the data on all the subjects with Type I diabetes across Europe we were not able to find a trend.

The relatively short periods covered by the study of the EURODIAB cohorts could have obscured the presence of patterns in the seasonality of birth for subjects with Type I diabetes which have been seen in longer time periods by investigators in the Slovak Republic [19] and Sweden [13]. We chose our statistical method of analysis partly to allow comparison with previous studies but mainly to adjust for the patterns of seasonality of births in the underlying population: it must be added, however, that the Walter and Elwood test is of limited use for small populations [20, 21] and also fails to provide confidence bounds to p values. The Walter and Elwood test in sub group analyses failed to find any significant or systematic patterns of seasonality and therefore correcting for multiple tests was not warranted.

The peak of births for children with diabetes which occurs in spring in the UK contrasts with continental Europe, and could be a reflection of a reduced exposure to sunlight and hence of reduced vitamin D production during a critical time of gestation or neonatally. Vitamin D is vital for a properly functioning immune system and dietary vitamin D supplementation in early life has been shown to reduce the risk of diabetes in childhood [22]. Seasonality of birth implies an effect of seasonally occurring widespread expo-

Table 2. Numbers of diabetic subjects and statistical significance of seasonal deviation from the expected number for twelve European regions for males and females (when separate data for sex were available)

Region	Male vs general population			Females vs general population			Males vs females	
	<i>n</i>	χ^2	<i>p</i>	<i>n</i>	χ^2	<i>p</i>	χ^2	<i>p</i>
<i>Great Britain</i>								
Scotland ^a	1265	4.07	0.13	1143	6.81	0.03	3.59	0.17
Yorkshire ^a	642	5.30	0.07	589	3.52	0.17	1.51	0.47
England & Wales ^a	650	9.64	0.01	620	1.90	0.39	12.0	0.01
Oxford ^a	171	3.87	0.14	158	1.58	0.45	0.43	0.81
Leicester ^{a, b}	429	2.51	0.29	338	5.83	0.05	1.50	0.47
Total Great Britain	3148	7.45	0.02	2848	3.39	0.18	1.51	0.47
<i>Other European countries</i>								
Austria	481	0.95	0.62	414	0.41	0.81	1.70	0.43
Czech Republic ^c	731	4.55	0.10	720	0.95	0.62	4.37	0.11
Denmark (4 counties)	166	0.46	0.79	130	5.54	0.06	4.12	0.13
Germany (Baden-Wuerttemberg)	677	0.37	0.83	626	1.23	0.54	0.30	0.86
Italy (Lazio) ^a	239	1.01	0.60	232	1.27	0.53	0.81	0.67
Italy (Sardinia) ^a	540	5.51	0.06	346	0.88	0.64	7.72	0.02
Lithuania	248	0.21	0.90	238	2.83	0.24	4.23	0.12
Luxembourg	34	7.75	0.02	38	2.23	0.33	3.18	0.20
Northern Ireland	240	2.21	0.33	222	0.29	0.87	1.45	0.48
Poland (Gliwice)	245	0.79	0.67	203	0.14	0.93	1.05	0.59
Romania (Bucharest)	88	0.03	0.99	97	4.69	0.10	4.10	0.13
Slovak Republic	445	0.55	0.76	444	3.08	0.21	1.25	0.54
Spain (Catalunya)	474	0.42	0.81	440	1.42	0.49	0.35	0.84
Sweden (Stockholm)	271	3.28	0.19	249	3.41	0.18	12.38	0.01
Total other European countries	4879	4.7	0.10	4399	1.01	0.60	1.40	0.50
Grand Total	8027	6.74	0.03	7247	3.38	0.18	0.36	0.84

^a the incidence of diabetes in males and females was compared with total birth rates as no separate birth rates were available for UK, Spain and Romania; and it was available only for years 1974–1979 for Italy, ^b Leicester. No record of sex for 1 patient (born in May '86), ^c Czech data: 61 patients born in 1992–1994

are not presented in this table as we did not have access for births rates separately for males and females born in those years

n = number of subjects

Table 3. Numbers of cases of diabetes and statistical significance of seasonal deviation from the expected number for nineteen regions of Europe grouped by age at the time of diagnosis

Region	Age at diagnosis								
	0–4 years			5–9 years			10–14 years		
	<i>n</i>	χ^2	<i>p</i>	<i>n</i>	χ^2	<i>p</i>	<i>n</i>	χ^2	<i>p</i>
<i>Great Britain</i>									
GB-Scotland	767	2.35	0.31	877	5.40	0.07	764	2.23	0.33
GB-Yorkshire	365	10.69	0.01	418	7.38	0.02	448	0.05	0.98
GB-England & Wales	338	0.95	0.62	432	3.38	0.18	500	1.52	0.47
GB-Oxford	177	0.55	0.76	243	7.26	0.03	338	2.08	0.35
GB-Leicester	94	5.89	0.05	125	0.00	1.00	110	8.83	0.01
Total Great Britain	1741	4.16	0.12	2095	7.58	0.02	2160	0.65	0.72
<i>Other European countries</i>									
Austria	178	1.42	0.49	328	1.29	0.52	389	2.35	0.31
Czech Republic	170	12.16	0.01	483	4.13	0.13	859	8.71	0.01
Denmark (4 counties)	51	0.35	0.84	96	3.33	0.19	149	3.12	0.21
Germany (Baden-Wuerttemberg)	320	1.14	0.57	450	1.77	0.41	533	2.08	0.35
Italy (Lazio)	120	2.75	0.25	179	2.99	0.22	172	0.91	0.63
Italy (Sardinia)	186	3.13	0.21	329	1.06	0.59	371	4.05	0.13
Lithuania	85	5.05	0.08	183	0.23	0.89	218	1.51	0.47
Luxembourg	18	2.32	0.31	21	1.72	0.42	33	22.27	0.01
Northern Ireland	92	1.73	0.42	166	0.01	1.00	204	10.39	0.01
Poland (Gliwice)	53	0.86	0.65	147	1.08	0.58	248	3.02	0.22
Romania (Bucharest)	24	1.30	0.52	76	5.18	0.08	85	0.17	0.92
Slovak Republic	196	1.43	0.49	296	2.39	0.30	397	1.58	0.45
Spain (Catalunya ^a)	96	1.34	0.51	283	4.23	0.12	535	4.76	0.09
Sweden (Stockholm)	145	3.30	0.19	191	0.29	0.87	184	2.27	0.32
Total other European countries	1734	1.07	0.59	3228	0.28	0.87	4173	8.83	0.01

^a data from Spain exclude patients born on the 1st of January as that date was overrepresented in the set and we assumed that it was used to substitute the missing value for date of birth

n = number of subjects

sure and candidates for this could be cyclical patterns of infections. However, the prevalence and patterns of infectious diseases in Great Britain and all other European regions might not be sufficiently different to explain the differences in seasonality observed.

Investigators from the Netherlands [15] found specific seasonality of birth patterns for male but not female subjects with childhood onset diabetes. They explained the excess male seasonality of birth in winter/spring births in childhood onset diabetes with the seasonal preovulatory overripeness ovopathy hypothesis (SPrOO). This assumes that pathological conceptions occur at the transitional stage between anovulatory cycles in winter and ovulatory cycles in spring. Overall analysis of all male patients from the 19 regions in our study did indeed reveal statistically significant seasonality of birth, the highest peak being in September and lowest trough in October. As peaks and troughs for individual regions (where seasonality was not statistically significant) appeared to be scattered at random across calendar months rather than following a particular pattern, we interpret the observed overall significance of seasonality in the male population to be an artefact rather than a true trend. In addition, the seasonal pattern for males with a peak in September is the reverse of the one that would have been expected applying the seasonal

preovulatory overripeness ovopathy hypothesis (winter/spring) [15].

A real difference between seasonal pattern of birth in male and female diabetic subjects would be revealed by a comparison of seasonal patterns not only with the rate of births in the general population but also with each other. After making this comparison, we found significant seasonal difference in birth patterns of male and female subjects only in three regions (England and Wales, Sweden, Sardinia). In other words, seasonal patterns of births for male and female subjects in most regions do not differ, casting doubt on the view that there is a sex-related trend in seasonality of birth in diabetic subjects.

Previous studies [23] suggest that childhood onset Type I diabetes could be caused by environmental factors operating over a limited but critical period in early childhood. If the expression of these hypothetical environmental factors have a seasonal pattern but the time “window” for any effect is narrow, there might be seasonality of birth in subjects diagnosed at a particular age which is hidden in the total population of children with Type I diabetes. The age specific pattern of Type I diabetes incidence shows a peak between 10 and 14 years of age although there could also be a smaller pre-school peak [24]. To test this assumption we analysed separately conventional age

groups of 0–4 years, 5–9 and 10–14 years, although these categories could obscure any link with a pre-school peak [24]. No clear evidence of statistically significant seasonality in a particular age group was observed.

In conclusion, no evidence of a uniform seasonal pattern of birth incidence in patients with childhood onset diabetes has been found in European populations other than in Great Britain. Thus there is little evidence to support the hypothesis that seasonal environmental factors act during fetal or neonatal development to create a predisposition for diabetes in future life in a substantial proportion of children. Male subjects showed some significant seasonality of birth but the inconsistent pattern across regions is not compatible with the SPrOO hypothesis for childhood diabetes. These results for a specific seasonal phenomenon do not necessarily exclude the possibility that infections, either specific enteroviruses or a broad spectrum of agents, have a role to play, during fetal or perinatal development, in causing childhood onset Type I diabetes. There is still a need for further study of perinatal risk factors and further investigations using different seasonality tests might provide further insights.

Appendix 1

Let b_{ij} and n_{ij} denote, respectively, the number of (live) births and the number of children who develop diabetes born in month j ($j = 1, \dots, 12$) of year i ($i = 1974, \dots, 1994$).

Also let $n_i = \sum_j n_{ij}$ denote the number of cases in year i summed over months
 $n_{.j} = \sum_i n_{ij}$ denote the number of cases in month j summed over all years
 and $N = \sum_i \sum_j n_{ij}$ denote the total number of cases in the period.

The numbers of births in the months of year i are then weighted, with the weights $w_i = n_i/N$ chosen to reflect the proportion of the total cases occurring in that year.

The expected number of cases in month j , denoted $e_{.j}$, is then obtained by apportioning to month j an appropriate fraction of the total cases, N , according to the numbers of weighted births in the j th month, $\sum_i w_i b_{ij}$.

$$e_{.j} = N * \left(\sum_i w_i b_{ij} / \sum_j \sum_i w_i b_{ij} \right)$$

Observed ($n_{.j}$) and expected ($e_{.j}$) numbers of cases in month j are then compared using the method of Walter and Elwood (1975) with the expected numbers of cases serving as the population at risk.

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