Diabetologia (2012) 55:2142–2147
DOI 10.1007/s00125-012-2571-8

SHORT COMMUNICATION

Trends in childhood type 1 diabetes incidence in Europe during 1989–2008: evidence of non-uniformity over time in rates of increase

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Received: 30 December 2011 / Accepted: 2 April 2012 / Published online: 26 May 2012

Abstract
Aims/hypothesis The aim of the study was to describe 20-year incidence trends for childhood type 1 diabetes in 23 EURODIAB centres and compare rates of increase in the first (1989–1998) and second (1999–2008) halves of the period.
Methods All registers operate in geographically defined regions and are based on a clinical diagnosis. Completeness of registration is assessed by capture–recapture methodology. Twenty-three centres in 19 countries registered 49,969 new cases of type 1 diabetes in individuals diagnosed before their 15th birthday during the period studied.
Results Ascertainment exceeded 90% in most registers. During the 20-year period, all but one register showed statistically significant changes in incidence, with rates universally increasing. When estimated separately for the first and second halves of the period, the median rates of increase

Electronic supplementary material The online version of this article (doi:10.1007/s00125-012-2571-8) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

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were similar: 3.4% per annum and 3.3% per annum, respectively. However, rates of increase differed significantly between the first half and the second half for nine of the 21 registers with adequate coverage of both periods; five registers showed significantly higher rates of increase in the first half, and four significantly higher rates in the second half.
Conclusions/interpretation The incidence rate of childhood type 1 diabetes continues to rise across Europe by an average of approximately 3–4% per annum, but the increase is not necessarily uniform, showing periods of less rapid and more rapid increase in incidence in some registers. This pattern of change suggests that important risk exposures differ over time in different European countries. Further time trend analysis and comparison of the patterns in defined regions is warranted.

Keywords Epidemiology · Incidence · Temporal change · Trends · Type 1 diabetes

Introduction

Recent incidence rate trends in childhood type 1 diabetes have been well characterised in publications by the EURODIAB registries in Europe [1] and by the DIAMOND (Diabetes Mondiale) Project Group worldwide [2]. The DIAMOND report described increasing trends in nearly every continent in the 1990s, whereas in Europe there was clear evidence that relative increases were highest in central and eastern European countries and in the under-5-year age group during the period 1989–2003.

More recent analyses from Norway [3] and Finland [4] suggest that rates of increase were lower in the 1980s, with a subsequent acceleration in the 1990s. The same pattern is evident in data from Sweden [5], and that analysis additionally raises the possibility that the rapid increase in the 1990s may soon be reversed, a reduction in rates having been observed beginning with the 2000 birth cohort.

The EURODIAB group has maintained registers of childhood diabetes in a range of European countries since 1989 using standardised methodology and with validation of completeness of ascertainment, and these observations from Scandinavia led us to compare incidence rates in the first half of the 20-year registration period (1989–1998) with those in the second half (1999–2008).

Methods

Case inclusion criteria were as previously described for the EURODIAB registers [6]: new diagnoses of type 1 (insulin-dependent) diabetes mellitus among children aged under 15 years resident in the geographically defined region. The

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completeness of registration was estimated separately in each of the 10-year periods using capture–recapture methodology [7], which requires that independent primary and secondary sources of ascertainment are available. In most centres, the primary source of ascertainment was through hospital records or notifications by paediatricians and family doctors, whereas secondary sources varied depending on local circumstances and included social insurance schemes, diabetes associations and prescription data.

Annual estimates of the population resident in each centre's geographically defined area were used as denominators for the calculation of directly standardised incidence rates using a standard population consisting of equal numbers of children in each of six subgroups defined by age group (0–4, 5–9 and 10–14 years) and sex.

Poisson regression was used to estimate the trends in incidence rate within centres. For each centre, a model with terms for age group, sex and an age group × sex interaction was first fitted. Then either a categorical variable representing the 5-year subperiods or a linear term testing for trend across individual years was added to the model to provide comparisons of incidence rates over time that took account of changes in the age structure of the population. For three centres whose registers changed coverage during the period, separate estimates of trend were fitted for each 10-year subperiod, and the two estimates were compared by likelihood ratio test. For the remaining centres, a similar model was fitted but with the added constraint that the fitted lines should meet between 1998 and 1999. Models were fitted using Stata Release 11 (Stata, College Station, TX, USA).

Table 1 Age and sex standardised rates of type 1 diabetes diagnosed before 15 years of age in four five year periods for 23 EURODIAB centres from 19 countries in Europe

Centre	Region	Period	Number of cases	Standardised incidence rate per 100,000[a]			
				P1	P2	P3	P4[b]
Austria	Whole nation	1989–2008	3372	9.0	9.9	13.3	17.5
Belgium	Antwerp	1989–2008	448	10.9	12.9	15.5	15.9
Croatia	Zagreb	1989–2008	339	6.7	6.4	8.2	10.4
Czech Republic	Whole nation	1989–2008	4883	8.5	11.5	17.0	19.3
Denmark[c]	1) Four counties	1989–1998	385	17.0	16.3	–	–
	2) Whole nation	1999–2008	2402	–	–	22.6	25.1
Germany	Baden Württemberg	1989–2007	4804	11.0	13.0	15.4	21.8[d]
Germany[c]	1) Düsseldorf (seven districts)	1989–1998	595	13.3	16.8	–	–
	2) North Rhine-Westphalia	1999–2008	6331	–	–	21.3	23.7
Germany	Saxony	1998–2008	921	–	11.6[d]	15.6	20.1
Hungary	18 counties	1989–2008	3239	9.0	10.7	12.4	18.3
Lithuania	Whole nation	1989–2008	1396	7.3	8.2	10.3	14.2
Luxembourg	Whole nation	1989–2008	229	11.4	12.3	15.5	19.0
Macedonia	Whole nation	1989–2008	447	3.2	3.9	5.6	5.8
Montenegro	Whole nation	1996–2008	252	–	10.1[d]	14.0	17.5
Norway[c]	1) Eight counties	1989–2003	1380	21.1	20.5	24.6	–
	2) Whole nation	2004–2008	1504	–	–	–	32.8
Poland	Katowice	1989–2008	1719	5.2	7.9	12.9	16.5
Romania	Bucharest	1989–2008	534	4.7	6.1	11.3	14.5
Slovenia	Whole nation	1989–2008	715	7.9	9.2	11.1	14.6
Spain	Catalonia	1989–2008	2527	12.4	13.6	12.9	12.1
Sweden	Stockholm county	1989–2008	1978	25.8	25.6	34.5	36.6
Switzerland	Whole nation	1991–2008	2220	8.0[d]	8.3	11.0	13.1
United Kingdom	Northern Ireland	1989–2008	2043	20.0	24.7	29.8	33.9
United Kingdom	Oxford	1989–2008	2288	17.2	21.7	24.0	25.1
United Kingdom	Yorkshire	1989–2008	3018	16.1	19.7	23.5	25.5

[a] Standard population with six age-sex subgroups of equal size

[b] Periods denoted P1: 1989–1993, P2: 1994–1998, P3: 1999–2003, P4: 2004–2008

[c] In three registries, period 2) has extended geographic coverage compared with period 1)

[d] Rate based on registration data for only part of the period

The Joinpoint regression program (Version 3.5 – April 2011; Statistical Methodology and Applications Branch and Data Modeling Branch, Surveillance Research Program National Cancer Institute, Bethesda, MD, USA) specifically designed for surveillance of trends in cancer incidence, was also used to see how sensitive conclusions were to the arbitrary division of the period into two 10-year subperiods. Joinpoint provides greater flexibility by accommodating the fitting of two or more linear segments that join at time points that are estimated from the data. The program provides a permutation test to assess the number of linear segments and the times at which they join, while taking into account the multiple testing issues inherent in the approach. A less conservative Bayesian information criterion for model selection was also employed. In order that Joinpoint should mimic as closely as possible the Poisson regression approach, the log-linear model option was chosen, and heteroscedasticity was taken into account by using the standard error of the annual standardised rates.

Further details are provided in the electronic supplementary material [ESM] Statistical methods.

Table 2 Completeness of ascertainment and estimated annual rates of increase compared in the two 10-year periods 1989–1998 and 1999–2008 for 23 EURODIAB centres

Centre	Region	Completeness of ascertainment, %	Rates of increase per annum, %[a] (95 % CI)	
		1989–1998:1999–2008	1989–1998 : 1999–2008	*p* value
Austria	Whole nation	99.8 : 97.2	3.3 (1.8,4.8) : 6.1 (4.8,7.4)	0.03*
Belgium	Antwerp	98.·6 : 94.·9	3.3 (–0.6,7.4) : 1.9 (–1.6,5.5)	0.68
Croatia	Zagreb	99.7 : 100.0	0.1 (–4.3,4.7) : 6.8 (2.7,11.0)	0.09
Czech Republic	Whole nation	99.9 : 97.4	7.6 (6.3,8.8) : 3.9 (2.9,5.0)	0.001*
Denmark[b]	1) Four counties	99.1 : —	0.5 (–2.9,4.1)[c] : —	0.56[c]
	2) Whole nation	— : 99.2[d]	— : 1.7 (0.2,3.1)[c]	
Germany	Baden Württemberg	97.2 : 100.0	2.9 (1.7,4.2) : 6.5 (5.3,7.7)[e]	0.002*
Germany[b]	1) Düsseldorf (seven districts)	94.0 : —	6.1 (3.2,9.2)[c] : —	0.01*[c]
	2) North Rhine–Westphalia	— : 98.6	— : 2.1 (1.3,3.0)[c]	
Germany	Saxony	— : 93.6[d]	— : 4.6 (2.2,7.1)	—
Hungary	18 counties	97.1 : 98.7	3.2 (1.8,4.7) : 5.8 (4.5,7.2)	0.04*
Lithuania	Whole nation	100.0 : n/a	2.1 (–0.1,4.3) : 7.2 (5.1,9.3)	0.009*
Luxembourg	Whole nation	100.0 : 100.0	0.9 (–4.7,6.8) : 5.8 (0.9,10.8)	0.32
Macedonia	Whole nation	94.9 : 100.0	6.4 (2.2,10.7) : 2.9 (–0.5,6.5)	0.33
Montenegro	Whole nation	100.0 : 100.0	— : 6.5 (1.6,11.7)	—
Norway[b]	1) Eight counties	100.0 : —	–1.2(–3.5,1.1)[c] : —	0.42[c]
	2) Whole nation	— : 92.0[d]	— : 0.5 (–3.0,4.2)[c,e]	
Poland	Katowice	99.9 : n/a	10.7 (8.3,13.1) : 5.5 (3.7,7.3)	0.006*
Romania	Bucharest	100.0 : 100.0	8.0 (4.3,12.0) : 7.8 (4.4,11.2)	0.93
Slovenia	Whole nation	100.0 : 100.0	4.1 (1.0,7.2) : 3.9 (1.1,6.8)	0.96
Spain	Catalonia	89.4 : 97.6	0.9 (–0.5,2.4) : –1.4 (–2.9,0.1)	0.09
Sweden	Stockholm county	100.0 : n/a	2.5 (0.6,4.5) : 2.5 (0.9,4.2)	0.66
Switzerland	Whole nation	91.7[d]: 91.3[d]	2.1 (–0.3,4.5)[e] : 5.4 (3.8,7.0)	0.07
UK	Northern Ireland	99.5 : 99.5	4.6 (2.7,6.5) : 2.8 (1.2,4.5)	0.27
UK	Oxford	n/a : n/a	4.0 (2.3,5.8) : 0.4 (–1.1,2.0)	0.02*
UK	Yorkshire	99.0 : 99.6	4.7 (3.1,6.3) : 1.6 (0.3,2.9)	0.02*

[a] Derived from Poisson regression model estimates of log-linear trends constraining lines to meet between 1998 and 1999 (see ESM Statistical methods)

[b] In three registries, period 2) has extended geographic coverage compared with period 1)

[c] Rates of increase in periods 1) and 2) were estimated and compared without constraining the fitted log-linear trends to meet between 1998 and 1999

[d] Estimate was obtained independently of the EURODIAB study

[e] Rate of increase was based on registration data for only part of the period

*$p<0.05$

n/a, not available

Results

Table 1 shows the total numbers of cases registered during the 20-year period 1989–2008 in each of the 23 centres, and the age- and sex-standardised incidence rates in the four 5-year subperiods 1989–1993, 1994–1998, 1999–2003 and 2004–2008. The age- and sex-specific incidence rates used in the calculations are available in ESM Table 1. Investigation of changes in incidence during the period was complicated in Denmark and Norway because the registers changed from regional to national coverage, and in Germany because of the extension of the Düsseldorf register to cover the whole North Rhine–Westphalia region. Poisson regression analysis confirmed that there were significant differences in the age-standardised rates between the four periods in all remaining centres with the exception of Catalonia (Spain), and incidence rates were universally observed to increase.

In Table 2 estimates of completeness of ascertainment obtained by the capture–recapture method are presented in the two 10-year periods 1989–1998 and 1999–2008 (for further details, see ESM Table 2). In most centres, greater than 90% ascertainment was maintained in both periods, with many achieving in excess of 95% ascertainment. The estimated annual increases (with 95% confidence intervals) in the first and second 10-year periods are given in the final columns. Comparison of these rates of increase showed a significant acceleration in the rate of increase in four centres (Austria, Germany [Baden Württemberg], Hungary and Lithuania) and a significant deceleration in the rate of increase in five centres (Czech Republic, Germany [Düsseldorf/North Rhine–Westphalia], Poland [Katowice] and the UK [Oxford and Yorkshire]). The median rates of increase over all the centres changed little, from 3.4% per annum in 1989–1998 to 3.3% per annum in 1999–2008.

Using the default permutation test settings, the Joinpoint program detected significant departures from a uniform log-linear trend with time for two of the largest centres that our analyses had identified – the Czech Republic, with a join between two log-linear segments in 2000, and Germany (Baden Württemberg), with a join in 2002. Using the alternative and less conservative Bayesian Information Criterion settings, the program detected departures from uniform log-linear trend with time in a further five of the centres identified by our analysis – Austria, Hungary, Lithuania, Poland (Katowice) and the UK (Yorkshire).

Discussion

The incidence rate of childhood type 1 diabetes continues to rise across Europe by approximately 3–4% per annum, but the increase is not necessarily uniform, with periods of less rapid and more rapid increase in incidence occurring in many registers. Although such patterns of change in incidence rate have previously been described in Scandinavian countries, our analysis suggests that the same phenomenon is also occurring in other parts of Europe.

Although our analysis may be criticised for comparing two arbitrarily selected 10-year periods, the finding of significant differences in the rates of increase in nine of the 21 centres for which the comparison was possible does suggest that these changes in rate are not an artefact, particularly since the completeness of registration was uniformly high in most of these centres. The Joinpoint program provided broad confirmation of our findings, but only when the less conservative Bayesian Information Criterion was used for model selection.

The possibility that changes in trends are affecting different age groups at different times cannot be ruled out. Use of age–period–cohort models has the potential to address this issue, but long-term data over broad age ranges are necessary for this technique to provide useful conclusions [8], and there are well-recognised difficulties in separating period and cohort effects when the predominant pattern of change is one of a log-linear increase [9].

Given the changing trends over time observed within individual centres in our analysis, forecasting future numbers of cases of type 1 diabetes in children by extrapolating past trends in a single centre or country could be misleading, and a better general strategy may be to derive trend estimates from groups of geographically adjacent countries with broadly similar incidence rates when attempting such extrapolations [1].

Our findings suggest that important environmental risk exposures are changing over time in different ways across European countries. Further time trend analysis and comparison of the patterns in different regions within Europe are warranted.

Acknowledgements The authors acknowledge the Austrian Diabetes Incidence Study Group, the Belgian Diabetes Registry (fellowship for I. Weets from the Belgian Fund for Scientific Research), the Danish Study Group of Diabetes in Childhood, the Baden-Württemberg Diabetes Incidence Registry (DIARY), the German Paediatric Surveillance Unit, Düsseldorf University and DPV Science Initiative, Ulm University, the German Competence Network Diabetes Mellitus (Federal Ministry of Education and Research, support codes 01GI0802, 01GI0859), the Saxonian Childhood Diabetes Register Group, the Hungarian Childhood Diabetes Epidemiology Group, the Norwegian Childhood Diabetes Study Group (supported by the South-Eastern Norway Regional Health Authority), the Catalan Epidemiology Type 1 Diabetes Study Group, the Swedish Childhood Diabetes Study Group (supported by the Swedish Research Council, Project number 07531), the Northern Ireland Childhood Diabetes Group, the Bart's-Oxford Study Group (supported by Diabetes UK) and the Yorkshire Register of Diabetes in Children and Young People (supported by the UK Healthcare Quality Improvement Partnership). The collaboration was supported in part by European Community Concerted Action Program grants (BMH1-CT92-0043, BMH4-CT96-0577 and IC20-CT96-0070).

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement CCP has coordinated the group since 2010, undertook the statistical analysis and wrote a first draft of the report. EG maintained contact with the study centres and assembled and validated the data for analysis. AG set up the collaboration and coordinated the group until 1998 and together with GGD established the registration methodology. GS coordinated the group from 1998 to 2009. Remaining authors established and/or maintained the registration process in the different centres, and were thereby responsible for data collection. They also validated the ascertainment level. All authors commented on a draft of the report and approved the final manuscript.

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