Variation and trends in incidence of childhood diabetes in Europe

*EURODIAB ACE Study Group**

Summary

Background To study the epidemiology of childhood-onset type 1 insulin-dependent diabetes in Europe, the EURODIAB collaborative group established in 1988 prospective geographically-defined registers of new cases diagnosed under 15 years of age. This report is based on 16 362 cases registered during the period 1989–94 by 44 centres representing most European countries and Israel and covering a population of about 28 million children.

Methods Multiple sources of ascertainment were used in most centres to validate the completeness of registration by the capture-recapture method. Trends in incidence during the period were analysed by Poisson regression, the data from centres within each country being pooled.

Findings The standardised average annual incidence rate during the period 1989–94 ranged from 3·2 cases per 100 000 per year in the Former Yugoslav Republic of Macedonia to 40·2 cases per 100 000 per year in two regions of Finland. By pooling over all centres, the annual rate of increase in incidence was 3·4% (95% CI 2·5–4·4%), but in some central European countries it was more rapid than this. Pooled over centres and sexes, the rates of increase were 6·3% (4·1–8·5%) for children aged 0–4 years, 3·1% (1·5–4·8%) for 5–9 years, and 2·4% (1·0–3·8%) for 10–14 years.

Interpretation The results confirm a very wide range of incidence rates within Europe and show that the increase in incidence during the period varied from country to country. The rapid rate of increase in children aged under 5 years is of particular concern.

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Introduction

Type 1 insulin-dependent diabetes is generally believed to be due to an immune destruction of pancreatic β cells in genetically susceptible individuals exposed to environmental risk factors. There has been a rapid increase in the incidence of type 1 diabetes in many European countries in the past few decades.[1–4] This increase, in conjunction with the lack of complete concordance in monozygotic twin pairs,[5–7] points to the importance of environmental factors.

Useful clues about these environmental factors may be obtained by studying geographical variation in incidence in relation to the characteristics of different countries. Fundamental to such analyses are high-quality incidence data uniformly collected via a standard protocol from population-based registers. We have previously reported data for the years 1989–90 from 26 registries in the EURODIAB Study Group, and have established that there is a wide range of incidence rates within Europe.[8] The network has since expanded to include 44 registries, with representation from most European countries and Israel. Incidence data for the 6-year period 1989–94 are presented in this paper.

Differences in the trends in incidence between countries or age-groups may also provide important clues about environmental factors. Some recent reports suggest a higher rate of increase among children under 5 years of age compared with the age groups 5–9 and 10–14 years,[9,10] which suggests that the environmental factors responsible for the increase may operate early in life. We address this issue in our analysis of the EURODIAB registry data.

Methods

The establishment of the EURODIAB collaborative group of childhood diabetes registers has been described in detail.[8,11] Briefly, in 1988, prospective registers of new cases of insulin-dependent type 1 diabetes mellitus among children aged under 15 years were established in 26 geographically-defined centres in Europe and Israel. Type 1 diabetes was defined on the basis of a clinical diagnosis of idiopathic diabetes made by a physician. Cases secondary to other conditions (having cystic fibrosis or high-dose steroid treatment) were excluded. Date of onset was taken as the date of the first insulin injection. Anonymous data were submitted to a central coordinating office in Odense, Denmark, for data processing and analysis.

Other centres whose registries met the same quality criteria have since joined the group, which now comprises 44 centres. Many of the new participants are from central and eastern Europe, and most European countries are now represented. For the analysis of trends the 40 centres with data for all 6 years in the study period were grouped into countries.

Capture-recapture methodology,[12] which assumes the availability of independent primary and secondary sources of ascertainment, was used when possible to estimate the completeless of registration. In most centres the primary source of ascertainment was through hospital records or notifications by paediatricians and family doctors. Secondary sources varied, being dependent on local circumstances, but 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

Country	Region	Number of cases	Standardised incidence rate (95% CI) per 100 000*	Completeness of ascertainment (period)
Austria	Whole nation	753	9·1 (8·5–9·8)	99·7% (1991–94)
Belgium	Antwerp	112	11·6 (9·4–13·7)	98·7% (1989–94)
Bulgaria	Western	303	9·6 (8·5–10·7)	99·9% (1989–94)
	Eastern	218	6·8 (5·9–7·7)	99·9% (1989–94)
Croatia	Zagreb	83	6·8 (5·3–8·3)	100% (1989–94)
Czech Republic	Whole nation	1144	8·9 (8·3–9·4)	100% (1989–94)
Denmark	Four counties	221	16·0 (13·9–18·1)	99·2% (1991–94)
Estonia	Whole nation	206	10·3 (8·9–11·7)	100% (1989–94)
Finland	Two regions	425	40·2 (36·4–44·1)	100% (1992–93)
France	Four regions	837	8·3 (7·8–8·9)	99·0% (1991–94)
Germany	Düsseldorf†	111	14·0 (11·4–16·6)	92·9% (1993–94)
	Baden-Württemberg	1101	11·3 (10·6–12·0)	96·5% (1989–94)
Greece	Attica	333	9·5 (8·5–10·5)	100% (1993–94)
	Five northern regions	49	6·2 (4·5–8·0)	100% (1989–94)
Hungary	18 counties	822	8·9 (8·2–9·5)	99·6% (1989–94)
Iceland	Whole nation	52	13·5 (9·8–17·2)	100% (1989–94)
Israel‡	Whole nation	433	5·9 (5·3–6·4)	100% (1993)
Italy	Lombardia	530	7·0 (6·4–7·6)	NSSA
	Lazio	396	8·1 (7·3–8·9)	100% (1993–94)
	Sardinia	675	36·6 (33·9–39·4)	85·2% (1991–94)
	Eastern Sicily	150	11·4 (9·5–13·2)	98·3% (1991–94)
Latvia	Whole nation	221	6·6 (5·8–7·5)	99·7% (1993–94)
Lithuania	Whole nation	368	7·4 (6·6–8·1)	100% (1989–94)
Luxemboug	Whole nation	49	12·1 (8·7–15·5)	100% (1993–94)
Macedonia	Whole nation	93	3·2 (2·5–3·8)	100% (1989–94)
Netherlands	Five regions	421	13·0 (11·8–14·3)	95·9% (1991–94)
Norway	Eight counties	491	21·2 (19·3–23·1)	99·9% (1992–94)
Poland	Eight western provinces	542	6·7 (6·2–7·3)	100% (1991–94)
	Three cities	312	6·1 (5·4–6·8)	100% (1989–94)
	Gliwice	316	5·4 (4·8–6·0)	NSSA
	Bialystok§	31	5·5 (3·5–7·4)	100% (1994)
Portugal	Madeira	24	6·9 (4·1–9·6)	100% (1993–94)
	Portalegre	25	19·0 (11·5–26·5)	94·0% (1989–94)
	Algarve	51	13·6 (9·8–17·3)	85·1% (1991–94)
Romania	Bucharest	138	5·0 (4·1–5·8)	100% (1989–94)
Slovakia	Whole nation	656	8·4 (7·7–9·0)	100% (1989–94)
Slovenia	Whole nation	186	7·6 (6·5–8·7)	100% (1992–94)
Spain	Catalonia	839	12·3 (11·4–13·1)	98·4% (1991–94)
Sweden	Stockholm county	451	25·8 (23·4–28·2)	100% (1993–94)
Switzerland‖	Whole nation	353	7·9 (7·1–8·7)	NSSA
United Kingdom	Northern Ireland	462	19·6 (17·8–21·4)	98·6% (1989–94)
	Oxford	542	17·6 (16·1–19·1)	NSSA
	Leicester	169	15·9 (13·5–18·3)	100% (1989–93)
	Leeds	668	15·7 (14·5–16·9)	97·6% (1989–94)

NSSA=no secondary source of ascertainment. *Standardised for age and sex. †1993–94 only. ‡1989–93 only. §1994 only. ‖1991–94 only.

Table 1: **Summary registration information for 44 EURODIAB centres**

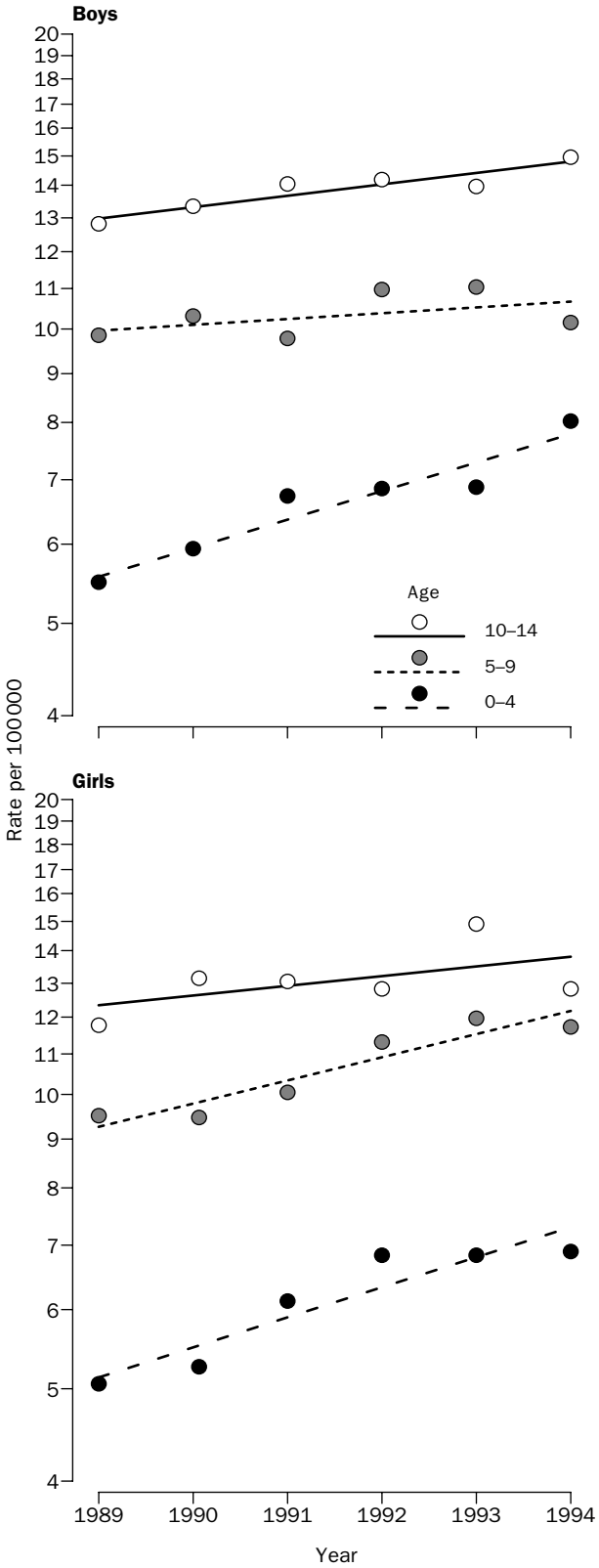
calculation of rates. Age/sex standardised incidence rates were obtained by the direct method with a standard population consisting of equal numbers of children in each of six subgroups defined by age group (0–4, 5–9, and 10–14 years) and sex.

Poisson-regression models were used to study differences in incidence rate between countries and to investigate the trends in incidence rate. Models with terms for sex, age group (0–4, 5–9, and 10–14 years), country, and calendar year were fitted. These models take account of possible differences in age/sex structure in each country's population and permit testing for any linear trend in incidence rate within a country. Further models incorporating interaction terms were used to test for differences in the linear trends between countries, between sexes, and between age groups. Likelihood-ratio χ^2 tests were used to compare the fit of nested models and to provide a test of significance for the last term added to the model. Models were fitted by the SAS GENMOD procedure. (SAS system for Windows, release 6.12, SAS Institute Inc, North Carolina, USA.)

Results

Average annual incidence rates

Table 1 summarises registration for each centre—the number of cases, the standardised average annual incidence rate, and the estimated completeness of ascertainment. Among the 40 centres validating ascertainment, all but four achieved completeness of ascertainment of over 95%. The estimates for some centres exclude the early years of the study period, but estimates for the years 1989–90 have already been published.[8] The standardised rates varied from 3·2 cases per 100 000 per year in the Former Yugoslav Republic of



Trends in childhood diabetes incidence in Europe during 1989–94 by age group and sex

Country	Risk ratio (95% CI) per year	p
Austria	1·08 (1·03–1·12)	0·0005
Belgium	1·10 (0·99–1·23)	0·09
Bulgaria (two centres)	1·05 (1·00–1·10)	0·06
Croatia	1·03 (0·91–1·17)	0·68
Czech Republic	1·08 (1·04–1·12)	0·0001
Denmark	0·91 (0·84–0·99)	0·02
Estonia	1·04 (0·96–1·12)	0·36
Finland	0·99 (0·93–1·04)	0·62
France	1·04 (1·00–1·09)	0·04
Germany	1·07 (1·03–1·10)	0·0004
Greece (two centres)	0·98 (0·93–1·04)	0·57
Hungary	1·07 (1·03–1·12)	0·0006
Iceland	0·99 (0·84–1·16)	0·88
Italy (three centres)	1·01 (0·97–1·04)	0·69
Italy (Sardinia)	1·01 (0·96–1·05)	0·78
Latvia	0·98 (0·90–1·05)	0·53
Lithuania	1·00 (0·94–1·06)	0·91
Luxembourg	1·04 (0·88–1·22)	0·68
Macedonia	1·01 (0·90–1·14)	0·84
Netherlands	1·02 (0·97–1·08)	0·47
Norway	0·99 (0·94–1·04)	0·67
Poland (three centres)	1·06 (1·03–1·10)	0·0006
Portugal (three centres)	1·13 (1·01–1·27)	0·04
Romania	1·03 (0·93–1·14)	0·57
Slovakia	1·09 (1·04–1·14)	0·0003
Slovenia	1·01 (0·93–1·10)	0·86
Spain	1·00 (0·96–1·04)	0·96
Sweden	1·03 (0·98–1·09)	0·25
United Kingdom (four centres)	1·02 (0·99–1·05)	0·14

Account has been taken of changes in age/sex structure of population.

Table 2: **Summary of Poisson-regression analyses showing the incidence trend in each country during 1989–94**

Macedonia to 40·2 cases per 100 000 in the two regions of Finland. Incidence rates were high in northern and north-western Europe and low in central, southern, and eastern Europe (figure 1). However, Sardinia was a notable exception to this pattern, with a much higher rate than any neighbouring region.

Trends in incidence

Data for each of the 6 years of the study period were available for all but four of the centres (Germany-Düsseldorf, Israel, Poland-Bialystok, and Switzerland). Poisson-regression models were fitted separately for each country, after data for the centres within each country were pooled. Sardinia, however, was retained as a centre on its own because the incidence there was much higher than for other Italian centres. There was evidence of a significant linear trend in nine of the 29 analyses, all but one showing an increase in incidence rate (table 2). For one country there was evidence of departure from linear trend (p=0·04), but this was no more than might be expected by chance and the annual rates for the country in question showed no consistent pattern. Some central and eastern European countries had rates that increased rapidly (table 2).

The results of fitting Poisson-regression models to the data from all countries simultaneously are summarised in table 3. Preliminary model fitting confirmed that there were significant differences in incidence rate between countries and suggested that both sex and age effects differed from country to country. A base model incorporating terms for age, sex, and country was therefore fitted to allow for differences in age/sex specific rates from country to country. Models that specified different patterns of linear trend were then obtained by adding terms to the base model. The test of the overall trend in incidence rate shown in the second line of table 3 is highly significant, with a risk ratio estimate of 1·034 (95% CI 1·025–1·044), which indicates on average a 3·4% (2·5–4·4%) increase in incidence per year. Table 3 indicates a significant difference in the trends between countries (line 3) and a difference in the trends between age groups (line 4) with no evidence of a difference in trends between boys and girls (line 5) and no evidence that the difference in trends between age-groups varied between boys and girls (line 6). The age-specific annual rates pooled across countries are displayed for boys and girls in figure 2 with a logarithmic vertical scale. Estimates of the rates of increase in the three age groups pooled over countries and sexes were 6·3% (4·1–8·5%) for children aged 0–4 years, 3·1% (1·5–4·8%) for 5–9 years, and 2·4% (1·0–3·8%) for 10–14 years, which shows that in relative terms the highest rates of increase occurred in the youngest age group.

Discussion

This multicentre study shows a greater than 10-fold range in incidence rate of childhood diabetes in Europe. Such variation seems unlikely to be explained by genetic differences, since Europeans (except for some outlying populations) are more homogeneous compared with the indigenous populations of other continents.[13] Although the independence of primary and secondary sources of ascertainment cannot easily be verified our assessment of completeness is more thorough than in most previous studies of international variations in incidence, and underascertainment is unlikely to be a major factor in explaining the incidence variation described here.

The rapid increase in incidence is not readily explained by shifts in the frequency of susceptibility genes, and change in environmental factors is a more plausible explanation. A homogeneous pattern of increasing incidence across age groups would suggest that similar environmental exposures operate in each age group. However, our observation of a greater relative increase in incidence in those under 5 years supports the importance of exposures operating early in life.[14,15] The nature of these exposures is not yet clear, but increased perinatal infections[16,17] or a rapid growth rate in early life[18,19] could be contributing. 6 years is too short a period to investigate age-group differences in incidence trends

Model terms*	Goodness of fit			Likelihood ratio test for last term		
	χ^2	Degrees of freedom	p	χ^2	Degrees of freedom	p
1 Base model	980·59	870	0·005	. .	. .	. .
2 Base model+year	930·54	869	0·07	50·1	1	<0·001
3 Base model+year+(year×country)	875·00	841	0·20	55·5	28	0·001
4 Base model+year+(year×country)+(year×age)	865·86	839	0·25	9·14	2	0·01
5 Base model+year+(year×country)+(year×age)+(year×sex)	864·49	838	0·26	1·37	1	0·24
6 Base model+year+(year×country)+(year×age)+(year×sex)+(year×age×sex)	859·91	836	0·28	4·58	2	0·10

*Base model=constant+age+sex+age×sex+country+age×country+sex×country+age×sex×country. Age: terms for age groups 0–4, 5–9, and 10–14 years; Sex: terms for sex; Country: terms for country; Year: terms for linear trend across the 6 years; Age×sex: terms for the interaction between age-group and sex.

Table 3: **Summary of Poisson-regression analyses of incidence trends for data from 40 centres grouped into 29 countries**

within each centre. Our modelling compared age-group differences in incidence trends pooled over centres instead, which took account of the different trends in the various centres.

It is tempting to link the rapid increase in incidence rates in some central and eastern European countries with recent political changes. However, the long prediabetic phase thought to be involved in the pathogenesis of this disease[20] suggests that the factors responsible for these rapid increases may have operated earlier. It will be important to continue monitoring the incidence rate trends in these countries and to compare them with those in Romania and the republics of former Yugoslavia where increases in incidence rate are not yet apparent.

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