Incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005–20: a multicentre prospective registration study

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Summary

Background The incidence of type 1 diabetes in children younger than 15 years is increasing. Prediction of future incidence of this disease will enable adequate fund allocation for delivery of care to be planned. We aimed to establish 15-year incidence trends for childhood type 1 diabetes in European centres, and thereby predict the future burden of childhood diabetes in Europe.

Methods 20 population-based EURODIAB registers in 17 countries registered 29 311 new cases of type 1 diabetes, diagnosed in children before their 15th birthday during a 15-year period, 1989–2003. Age-specific log linear rates of increase were estimated in five geographical regions, and used in conjunction with published incidence rates and population projections to predict numbers of new cases throughout Europe in 2005, 2010, 2015, and 2020.

Findings Ascertainment was better than 90% in most registers. All but two registers showed significant yearly increases in incidence, ranging from 0·6% to 9·3%. The overall annual increase was 3·9% (95% CI 3·6–4·2), and the increases in the age groups 0–4 years, 5–9 years, and 10–14 years were 5·4% (4·8–6·1), 4·3% (3·8–4·8), and 2·9% (2·5–3·3), respectively. The number of new cases in Europe in 2005 is estimated as 15 000, divided between the 0–4 year, 5–9 year, and 10–14 year age-groups in the ratio 24%, 35%, and 41%, respectively. In 2020, the predicted number of new cases is 24 400, with a doubling in numbers in children younger than 5 years and a more even distribution across age-groups than at present (29%, 37%, and 34%, respectively). Prevalence under age 15 years is predicted to rise from 94 000 in 2005, to 160 000 in 2020.

Interpretation If present trends continue, doubling of new cases of type 1 diabetes in European children younger than 5 years is predicted between 2005 and 2020, and prevalent cases younger than 15 years will rise by 70%. Adequate health-care resources to meet these children's needs should be made available.

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Introduction

Wide variation in incidence of type 1 diabetes in children younger than 15 years has been well characterised by registry reports from the EURODIAB study group within Europe[1] and the DIAMOND project group worldwide.[2] The DIAMOND project also analysed trends by continent in the period 1990–99, and showed increases in every region except Central America and the West Indies. In Europe, where numbers of cases are large enough to enable useful comparisons of rises in incidence in different age-groups, evidence shows that increases in incidence were highest in the youngest age-group.[3] Furthermore, analysis of EURODIAB registration data for 1989–98 in regions within Europe shows that rates of increase differed significantly and were highest in central and eastern European countries.[1]

The emergence of type 2 diabetes in children and adolescents has received much attention, but this issue should not be allowed to overshadow the rapid rises in type 1 diabetes in this age-group. Although in a few countries most cases in children will be type 2 diabetes,[4] in most European countries type 1 diabetes is, and will probably remain, the predominant form of this disease.[5] Prediction of future numbers is important to facilitate plans for the delivery of care and treatment of complications that might arise in early adulthood in these children. We aim to document trends in incidence of childhood type 1 diabetes in Europe during 1989–2003, and to use this information to predict the future burden of this disease in European children.

Methods

Inclusion criteria and region selection

Case inclusion criteria were as previously described for the EURODIAB registers[6]—new diagnoses of type 1 (insulin-dependent) diabetes mellitus in children younger than 15 years who were usually resident in the geographically defined region. Completeness of registration was estimated separately for three 5-year periods by capture-recapture methods,[7] for which independent primary and secondary sources of ascertainment are needed. In most centres, the primary sources of ascertainment were hospital records or notifications by paediatricians and family doctors, whereas secondary sources varied depending on local circumstances, and included social insurance schemes, diabetes associations,

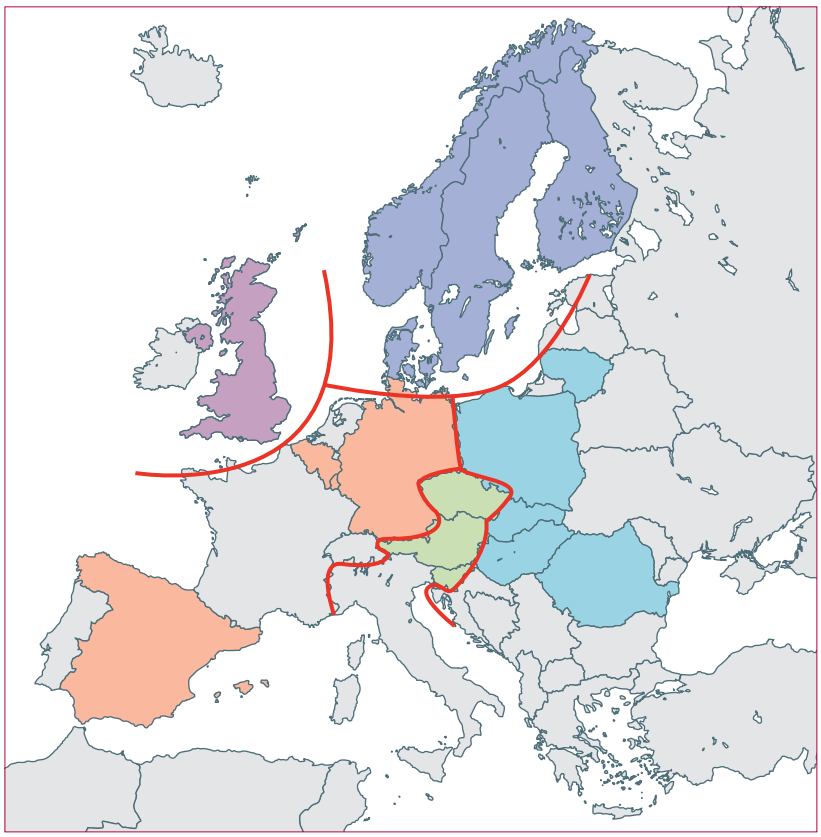


Figure 1: **20 EURODIAB centres in 17 countries split into regions with homogeneous incidence rates**
Purple=north region, four centres and 4717 cases. Pink=north west region, three centres and 5167 cases. Orange=west region, five centres and 6673 cases. Green=central region, three centres and 6198 cases. Blue=east region, five centres and 6556.

and prescription data. In common with many uses of capture-recapture methods in epidemiology, neither the assumption of source independence nor the assumption of equal probability of capture of each case by any given source is easily verifiable, so our estimates can provide only an imperfect estimate of completeness. Likely to be less sensitive to these assumptions is the comparison of each centre's completeness estimate during the three 5-year periods, which is especially important when incidence trends are being investigated.

Annual estimates of population in each centre's geographically defined area were used as denominators for calculation of standardised incidence rates. Standardisation was 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 years, 5–9 years, and 10–14 years) and sex. To provide appropriate numbers of cases for the estimation of trends in each of these six subgroups, Europe was divided into five regions. Regions were defined by three factors—geography, incidence rate, and numbers of registered cases. The Scandinavian centres (Denmark, Finland, Norway, and Sweden) formed a natural north region of very high incidence, and the three UK centres formed a northwest region of high incidence. An arbitrary target figure of about 5000 registered cases for each centre was chosen. Construction of the three other regions—each of countries with roughly homogeneous incidence rates—was largely guided by results from our previous report, which included data from 44 centres representing most countries of Europe.[3] The west region consisted of Spain, Luxembourg, Belgium, and two German centres; the central region comprised the Czech Republic, Austria, and Slovenia; and the East region consisted of Lithuania, Poland, Slovakia, Hungary, and Romania (figure 1).

Statistical analysis

Poisson regression was used to investigate trends in incidence within centres. This method specifies that factors have an additive effect on a logarithmic incidence scale (or equivalently, a multiplicative effect on the incidence scale). For each centre, a base model with terms for age-group (0–4 years, 5–9 years, and 10–14 years), sex, and age-group by sex interaction was fitted. Addition of a linear term for calendar year to this model provided a test for trend with time in the centre that took account of any changes in population age structure during the period, and gave an estimate of the annual percentage rise together with 95% confidence limits. A test for departure from log-linear time trend (ie, a check for deviation from linearity) was obtained by a likelihood-ratio test comparing the linear trend model with a general model that allowed for any pattern of difference between the years. Further models incorporating interaction terms were used to test for differences in linear time trends between sexes and between age-groups within each centre.

Furthermore, Poisson regression was used to compare trends in incidence in the five regions. For this analysis, the base model contained terms for sex, age-group, region, and all possible interactions. This base model, therefore, specified different age and sex-specific incidence rates in each region. Addition of a linear term in calendar year provided a test for time trends that took the form of a single annual percentage rise common to both sexes and all age-groups and regions. Interactions of this term with sex, age, and region tested for different time trends in the sexes, in different age-groups, and regions, respectively. High order interactions between these terms and the linear term in calendar year provided tests for patterns of further complexity (eg, the age by sex by year interaction tested for different patterns of age-specific rises in incidence in boys and girls). Likelihood-ratio χ^2 tests were used to compare fit of nested models with tests undertaken at the 5% significance level. Akaike's information criterion was also used to aid model selection. A goodness-of-fit test, obtained as a likelihood-ratio test comparing the fit of each model with that of a saturated model that perfectly predicted observed numbers of cases, was used to assess model fit and to

check for overdispersion. A significant goodness-of-fit test shows that a model fits the data poorly. All models were fitted by use of Stata 8.

Estimates of new cases in 2005 and predictions for future new cases were made by extrapolation of base-year incidence rates, with the annual percentage increase in incidence in each age-group in the five regions estimated from the Poisson regression analysis. Prevalence figures were derived from cumulated incidence rates. Extrapolated rates were then applied to the EUROSTAT 2005 population estimates[8] and the UN medium variant 2010, 2015, and 2020 population projections.[9] This approach assumes that future annual rates of increase are equal to those derived from the Poisson regression analysis of EURODIAB centre rates in 1989–2003. Base-year incidence rates used for the extrapolation in each country were published rates for the most recently available 5-year period (webappendix p 1). Nationwide estimates were used when available. When the reported rates were based on fewer than 150 cases in the 5-year period, a period of 10 years or 15 years was preferred to obtain more stable rates on which to base extrapolations.

Role of the funding source

The funding source played no part in the study design, collection, analysis, and interpretation of data, writing of the report, or in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Table 1 shows the total numbers of cases registered during 1989–2003 in each of the 20 centres and the age-standardised incidence rates in the three 5-year periods. Most centres maintained greater than 90% completeness of ascertainment in all three periods, with many achieving in excess of 95%. For all but two centres, the estimated annual increases in incidence were significant. Use of a log linear trend to summarise these data was considered appropriate because the test for departure from linear trend reached significance in only one of the 20 centres. Figure 2 shows an inverse association (Spearman rank correlation, r_s=–0·52, p=0·02) between the rise in incidence rate during the 15-year period and the average rate during the same period.

Further Poisson regression modelling of interactions provided little evidence of any difference in rates of increase between the sexes, the comparison reaching significance in only one of 20 centres. By contrast, in six centres (Austria, Czech Republic, Finland, Baden Württemberg in Germany, Poland, and Yorkshire in the UK) (table 1) rates of increase differed significantly between age-groups—in every case the lowest rate of increase was recorded in the oldest age-group. Many other centres showed the same pattern though the comparison between age-groups did not attain significance.

	Region	Number of cases	Standardised incidence* per 100 000 (P1; P2; P3†)	Completeness of ascertainment (P1; P2; P3)	Increase per year (95% CI)‡
Austria	Whole nation	2215	9·0; 9·9; 13·3	99·6%; 100%; 97·6%	4·3% (3·3 to 5·3)
Belgium	Antwerp	318	10·9 ; 12·9; 15·4	99·2%; 97·9%; 94·8%	3·1% (0·5 to 5·8)
Czech Republic	Whole nation	3479	8·7; 11·7; 17·2	100%; 99·8%; 98·7%	6·7% (5·9 to 7·5)
Denmark	Four counties	657	17·0; 16·3; 22·9	99·8%; 99·5%; 100%	3·2% (1·4 to 5·1)
Finland	Two regions	1306	39·9; 50·0; 52·6	100%; 100%; 100%	2·7% (1·4 to 4·0)
Germany	Baden Württemberg	3362	11·0; 13·0; 15·5	95·6%; 98·3%; 100%	3·7% (2·9 to 4·5)
Germany	Düsseldorf	922	12·5; 15·3; 18·3	92·8%; 97·9%; 95·4%	4·7% (3·1 to 6·3)
Hungary	18 counties	2152	8·8; 10·5; 11·5	97·9%; 94·9%; 95·5%	2·9% (1·9 to 3·9)
Lithuania	Whole nation	996	7·3; 8·2; 10·3	100%; 100%; 100%	3·8% (2·2 to 5·3)
Luxembourg	Whole nation	148	11·4; 12·3; 15·5	100%; 100%; 100%	2·4% (–1·4 to 6·3)
Norway	8 counties	1380	21·1; 20·5; 24·6	100%; 100%; 100%	1·3% (0·1 to 2·6)
Poland	Katowice	1156	5·2; 7·9; 13·0	··; 99·9%; ··	9·3% (7·8 to 10·8)
Romania	Bucharest	378	4·7; 6·1; 11·3	100%; 100%; 100%	8·4% (5·8 to 11·0)
Slovakia	Whole nation	1874	8·2; 10·3; 13·6	100%; 100%; 100%	5·1% (4·0 to 6·3)
Slovenia	Whole nation	504	7·9; 9·2; 11·1	100%; 100%; 100%	3·6% (1·5 to 5·7)
Spain	Catalonia	1923	12·4; 13·6; 13·0	93·5%; 84·6%; 97·6%	0·6% (–0·4 to 0·6)
Sweden	Stockholm county	1374	25·8; 25·6; 34·6	100%; 100%; 100%	3·3% (2·0 to 4·6)
UK	Northern Ireland	1435	20·0; 24·7; 29·8	98·8%; 99·9%; 99·6%	4·2% (3·0 to 5·5)
UK	Oxford	1615	17·1; 21·7; 22·4	··; 95·3%; 90·2%	2·2% (1·1 to 3·4)
UK	Yorkshire	2117	16·0; 19·7; 23·3	99·3%; 99·5%; 99·7%	3·6% (2·6 to 4·6)

··=data not available. *Standard population has six age–sex subgroups of equal size. †P1=1989–93; P2=1994–98; P3=1999–2003. ‡Derived from the coefficient for a term in the Poisson regression model representing year.

Table 1: **Summary information for 20 EURODIAB centres with registration data**

The overall annual increase for all centres was estimated as 3·9% (95% CI 3·6–4·2), with corresponding rises in the 0–4 year, 5–9 year, and 10–14 year age ranges of 5·4% (4·8–6·1), 4·3% (3·8–4·8), and 2·9% (2·5–3·3), respectively. To help characterise geographical differences in these patterns, the 20 centres were aggregated into five regions (giving a dataset of 2 sexes×3 age-groups ×5 regions×15 years=450 observations). Poisson regression analyses of this dataset are summarised in table 2. First, the base model was fitted (line 1), defining a separate set of six age-specific and sex-specific rates in each region but assuming that these rates did not change in the 15 years. A single log linear term for year, representing a common trend between sexes, age-groups, and regions was highly significant (line 2), but the resultant model failed to provide an adequate fit to the data (goodness-of-fit test p<0·0001). When this trend was allowed to differ between age groups through addition of a term representing an interaction between year and age group (line 3), the likelihood-ratio test for the added term was significant (p<0·0001), indicating different rates of change over time in different age-groups.

Addition of an interaction between year and sex was not significant (line 4), but interaction between year, age, and sex was significant (line 5; p=0·03), which suggests

See Online for webappendix

	Model	Likelihood ratio test for last term (p value)	AIC	Goodness of fit (p value)
1	Base model*		4095·2	<0·0001
2	Base model+Y	<0·0001	3298·5	<0·0001
3	Base model+Y+Y•A	<0·0001	3253·9	0·0007
4	Base model+Y+Y•A+Y•S	0·53	3255·5	0·0006
5	Base model+Y+Y•A+Y•S+Y•A•S	0·03	3252·8	0·0010
6	Base model+Y+Y•A+Y•S+Y•A•S+Y•R	<0·0001	3171·6	0·37
7	Base model +Y+Y•A+Y•S+Y•A•S+Y•R+Y•R•A	0·13	3175·0	0·43
8	Base model+Y+Y•A+Y•S+Y•A•S+Y•R+Y•R•A+Y•R•S	0·79	3181·3	0·39
9	Base model+Y+Y•A+Y•S+Y•A•S+Y•R+Y•R•A+Y•R•S +Y•R•A•S	0·94	3194·4	0·33

Trends for data from 20 centres grouped into 5 regions. Model 6 is the most parsimonious model providing a reasonable fit, and it also has the smallest AIC value. AIC=Akaike Information Criterion. Model terms are: A=terms for age-groups 0–4, 5–9, and 10–14 years; S=term for sex; R=terms for region (or centre group); Y=term for linear trend across the 15 years; A•S=terms for the interaction between age-group and sex. *Base model=A+S+A•S+R+A•R+S•R+A•S•R.

Table 2: **Summary of Poisson regression analyses of incidence trends**

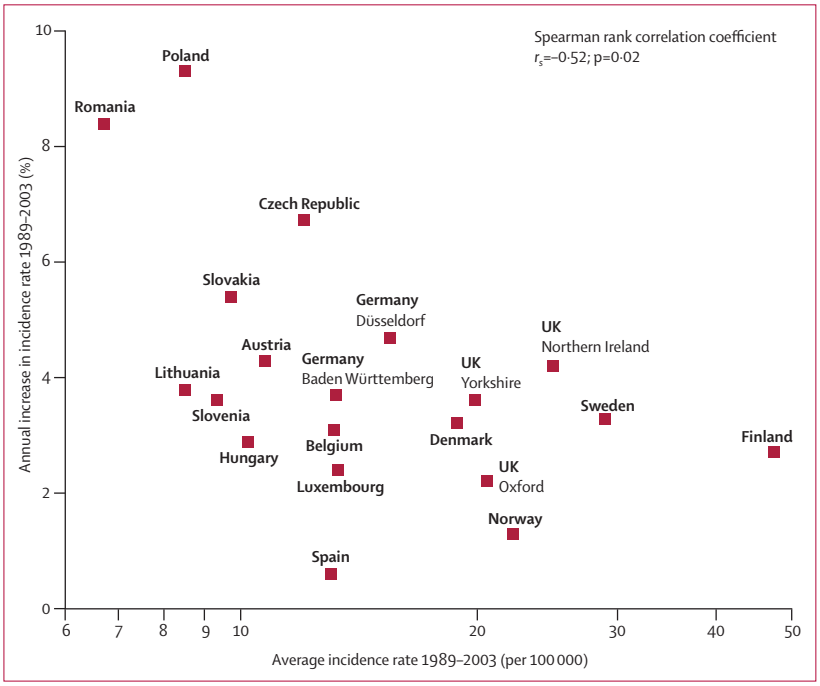


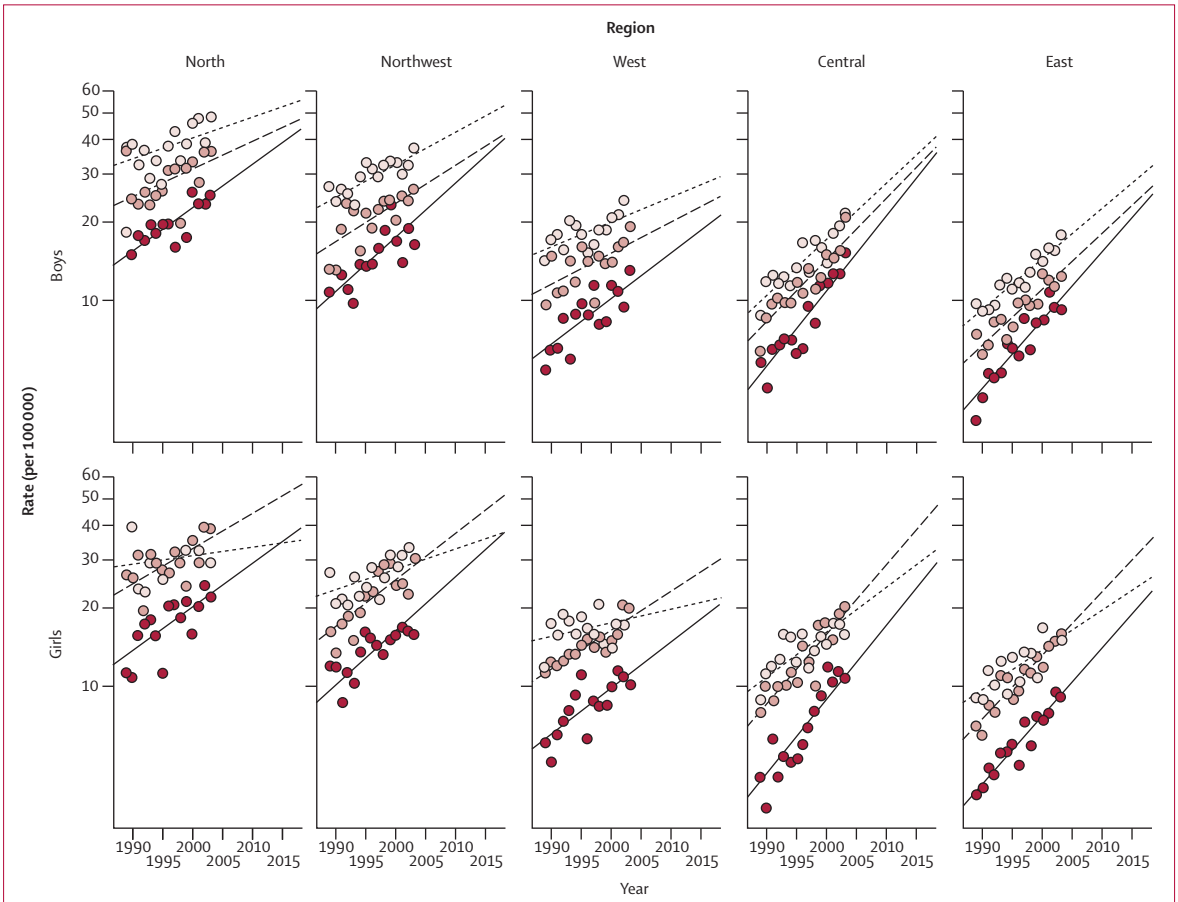
Figure 2: **Inverse association between rate of incidence increase and average incidence**
Incidence rate on horizontal axis, plotted on a logarithmic scale. Spearman rank correlation coefficient r_s=–0·52, p=0·02.

that differences in trends between age-groups depended on sex. Girls showed faster rates of increase in incidence of type 1 diabetes in the 5–9 year age-group and slower rates in the 10–14 year age-group than did boys. When the trend was allowed to differ between regions through addition of a year by region interaction (line 6), this interaction was significant (p<0·0001), showing differing rates of rise in incidence in different regions. The goodness-of-fit tests show that line 6 was the simplest model, that provided an adequate fit to the data with no evidence of overdispersion. Since this model also gave the lowest Akaike information criterion, it was selected for prediction purposes. Further models specifying differences in trends between regions that varied between sexes and age groups (lines 7, 8, and 9) had non-significant likelihood-ratio tests.

The log linear trends obtained from the model in line 6 (table 2) are summarised in figure 3. The rapid rise of type 1 diabetes in the youngest age-group in regions in central and east Europe (figure 1) are especially striking. Of note is the tendency for rates in the different age-groups to converge over time in many regions. Smaller rises in incidence in girls compared with in boys aged 10–14 years were also observed.

Some countries, mainly in the eastern fringes of Europe, had no published age-specific incidence rates for type 1 diabetes available. Belarus, the Russian Federation, Ukraine, Moldova, and Albania were, therefore, omitted from analysis of estimated new cases in 2005 and predicted numbers in 2010, 2015, and 2020. Predicted numbers were calculated by application of rates of increase (figure 3) to the base rates (webappendix p 1). Results are summarised by age-group and sex in figure 4 (country by country data in webappendix p 3). The estimated number of new cases of type 1 diabetes in Europe in 2005 is 15 000, and this total is divided between the 0–4 years, 5–9 years, and 10–14 years age-groups in the ratio 24%, 35%, and 41%, respectively.

By 2020, the predicted number of new cases is 24 400, but this change is not shared evenly between the age groups, with incidence of type 1 diabetes in the youngest age group expected to double in both sexes compared with a factor of 1·6 in boys and 1·3 in girls in the oldest age-group. On the basis of our predictions, we suggest that in 2020 the percentage distribution of new cases across the three age-groups will be more uniform at 29% (0–4 years), 37% (5–9 years), and 34% (10–14 years), with the excess of new cases in the 5–9 year age range being most apparent in girls. Prevalent cases under age 15 years are expected to rise from 94 000 in 2005, to 160 000 in 2020 (country by country data in webappendix p 4).



Boys age group	Annual increase (95% CI)				
10–14 years	1·8% (0·9 to 2·6)	2·7% (1·9 to 3·6)	2·2% (1·4 to 2·9)	5·1% (4·3 to 5·9)	4·6% (3·8 to 5·4)
5–9 years	2·4% (1·4 to 3·3)	3·4% (2·5 to 4·3)	2·8% (1·9 to 3·6)	5·7% (4·8 to 6·6)	5·2% (4·4 to 6·1)
0–4 years	3·9% (2·8 to 4·9)	4·9% (3·8 to 5·9)	4·3% (3·3 to 5·3)	7·3% (6·2 to 8·3)	6·8% (5·8 to 7·8)
Girls age group	**Annual increase (95% CI)**				
10–14 years	0·8% (–0·1 to 1·6)	1·7% (0·9 to 2·6)	1·2% (0·4 to 2·0)	4·1% (3·2 to 4·9)	3·6% (2·8 to 4·4)
5–9 years	3·0% (2·1 to 3·9)	4·0% (3·1 to 4·9)	3·5% (2·6 to 4·3)	6·4% (5·5 to 7·3)	5·9% (5·1 to 6·8)
0–4 years	3·9% (2·8 to 5·0)	4·9% (3·8 to 6·0)	4·3% (3·3 to 5·4)	7·3% (6·2 to 8·3)	6·8% (5·7 to 7·9)

Figure 3: **Incidence rate increases by region**
Points=observed annual rate. Lines=trends in rates predicted by the best fitting Poisson regression model.

Discussion

From review of worldwide epidemiology of childhood type 1 diabetes,[10] we noted that Europe provides the most informative data about present incidence trends; European estimates of age-group-specific annual increases have narrower CIs than do estimates from other continents, indicating greater precision. We have extended the analysis of European trends to confirm that the highest rates of increase, at least in relative terms, arise in the youngest age-groups. The most striking changes over time are observed in central and eastern European countries. These increases in countries with lower incidence result in a tendency for incidence rates in Europe to converge.

Although cohort effects have been examined,[11–16] results have been equivocal. Incorporation of cohort effects in our model might have improved our ability to predict rates in the future, but a 15-year period is rather short for such an analysis, and the difficulties in separation of period and cohort effects when the predominant pattern of change is one of linear increase are well recognised.[17] Notably, incidence of type 1 diabetes in young adults over age 15 years shows little evidence of rising,[18,19] but a higher incidence in men than in women is widely reported in this age range.[20] If type 1 diabetes really is shifting toward a younger age at diagnosis, lower incidence rates in women 15 years or older might help to explain the low rates of increase in girls in the 10–14 year age range seen in all five regions.

Our extrapolation of rates to predict numbers of new cases in future years assumes that log linear trends fitted to age-specific incidence rates in the EURODIAB register data for 1989–2003 will continue into the future. Although we found no evidence of systematic departures from log linear trends, either in our centre-by-centre analysis or

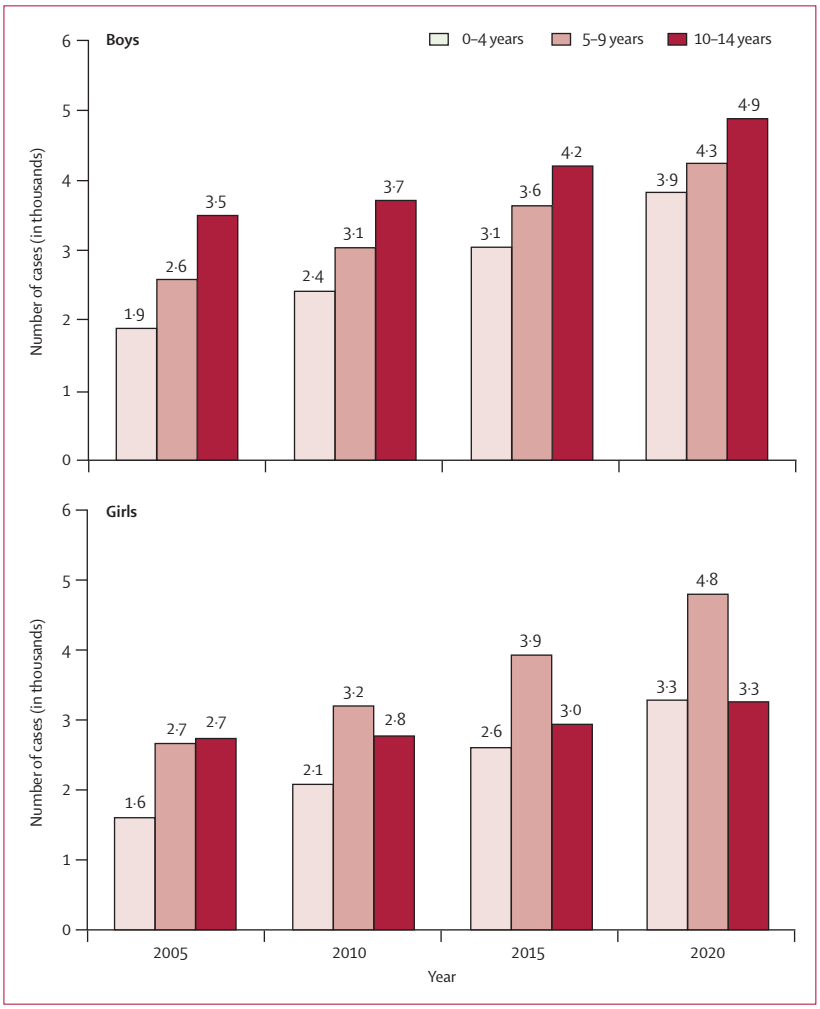


Figure 4: **Estimated (2005) and predicted cases of newly diagnosed type 1 diabetes**
Predicted new cases for future years in Europe (excluding Belarus, the Russian Federation, Ukraine, Moldova, and Albania) on the basis of the best fitting Poisson regression model.

analysis of the five regions, this absence of evidence does not provide any guarantee that our assumption will be valid; moreover, brief periods of apparent stabilisation of rates have been reported.[21,22] However, such periods appear to be transient, and the general trend in incidence continues to be upward in the long term. We have examined the likely consequences for incidence of type 1 diabetes in Europe if our assumption of a log linear increase holds, and we predict numbers of new cases in children younger than 5 years old will double between 2005 and 2020. Regional differences in European incidence rates might become less pronounced, because low-incidence countries in eastern and central Europe have the most rapid rises in rates.

Our analysis gives no explanation for the time trends we have described, but the rapid changes over time clearly cannot be attributable to changes in prevalence of susceptibility genes. One suggestion is that need for genetic susceptibility has lessened over time because of heightened environmental pressure, which results in a raised disease progression rate—especially in individuals with protective HLA genotypes.[23] Several hypotheses[24–26] based on analytical epidemiological studies have pointed to modern lifestyle habits as possible environmental factors, such as increased weight and height development,[27] and caesarean section deliveries,[28] or reduced frequency of early infections.[29] This notion accords with reported ecological associations between estimates of gross domestic product and incidence rate in European countries.[30] Faster rates of increase in countries with low incidence rate—in particular eastern European countries—might be an expression of effects of lifestyle factors, which are changing rapidly in these countries; therefore, convergence of incidence rates might reflect harmonisation of lifestyle-related risk factors in Europe.

The predicted rise in childhood type 1 diabetes in Europe during the next 20 years, and the raised proportion of cases diagnosed at younger ages than were before, could result in more cases presenting with ketoacidosis and needing hospital admission. More patients with severe diabetes complications presenting at younger ages than before are also likely, and appropriate care from diagnosis, and maintenance of good metabolic control are crucial for delay or prevention of these adverse complications.[31] In the absence of any effective means to prevent type 1 diabetes, European countries need to ensure appropriate planning of services and that resources are in place to provide high-quality care for the increased numbers of children who will be diagnosed with diabetes in future years.

Contributors
CCP undertook the statistical analysis, the review of published European incidence rates, and wrote a first draft of the report. GGD helped establish the methods used by the collaboration, advised on the content, and contributed to subsequent drafts of the report. EG maintained contact with the study centres, assembled and validated the data for analysis, and commented on drafts of the report. AG set up the collaboration in 1988, coordinated the group until 1998, established the registration methodology, and commented on drafts of the report. GS coordinated the collaboration since 1998, advised on content and contributed to subsequent drafts of the report.

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Conflicts of interest

We declare that we have no conflicts of interest.

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References

1 Green A, Patterson CC. Trends in the incidence of childhood-onset diabetes in Europe 1989–1998. *Diabetologia* 2001; **44** (suppl 3)**:** B3–8.

2 The DIAMOND Project Group. Incidence and trends of childhood Type 1 diabetes worldwide 1990–1999. *Diabet Med* 2006; **23:** 857–66.

3 EURODIAB ACE Study Group. Variation and trends in incidence of childhood diabetes in Europe. *Lancet* 2000; **355:** 873–76.

4 Kaufman FR, Shaw J. Type 2 diabetes in youth; rates, antecedents, treatment, problems and prevention. *Pediatr Diabetes* 2007; 8 (suppl 9): 4–6.

5 Soltesz G, Patterson C, Dahlquist G, Singh R, Shaw J, Zimmet P. Diabetes in the young. In: Gan D. Diabetes Atlas, 3rd edn. International Diabetes Federation, 2006: 153–207.

6 Green A, Gale EAM, Patterson CC. Incidence of childhood-onset insulin-dependent diabetes mellitus: the EURODIAB ACE study. *Lancet* 1992; **339:** 905–09.

7 Bishop YMM, Fienberg SE, Holland PW. Discrete multivariate analysis: theory and practice.-Cambridge, MA: MIT Press, 1974.

8 EUROSTAT estimates of 2005 population. http://epp.eurostat.ec.europa.eu/extraction/evalight/EVAlight.jsp?A=1&language=en&root=/theme3/demo/demo_ppavg (accessed Jan 12, 2009).

9 World Population Prospects: the 2006 Revision Population Database. http://esa.un.org/unpp/ (accessed Jan 12, 2009).

10 Soltesz G, Patterson CC, Dahlquist G, on behalf of the EURODIAB Study Group. Worldwide Childhood Type 1 Diabetes Incidence—what can we learn from epidemiology? *Pediatr Diabetes* 2007; **8** (suppl 6)**:** 6–14.

11 Bruno G, Merletti F, Biggeri A, and the Piedmont Study Group for Diabetes Epidemiology. Increasing trend of type 1 diabetes in children and young adults in the province of Turin (Italy). Analysis of age, period and birth cohort effects from 1984 to 1996. *Diabetologia* 2001; **44:** 22–25.

12 Svensson J, Carstensen B, Molbak A, et al. Increased risk of childhood type 1 diabetes in children born after 1985. *Diabetes Care* 2002; **25:** 2197–201.

13 Feltbower RG, McKinney PA, Parslow RC, Stephenson CR, Bodansky HJ. Type 1 diabetes in Yorkshire: time trends in 0–14 and 15–29 year olds, age at onset and age-period-cohort modelling. *Diabet Med* 2003; **20:** 437–41.

14 Pundziute-Lycka A, Dahlquist G, Urbonaite B, Zalinkevicius R. Time trend of childhood type 1 diabetes incidence in Lithuania and Sweden, 1983-2000. *Acta Paediatr* 2004; **93:** 1519–24.

15 Moltchanova E, Penttinen A, Karvonen M. A hierarchical Bayesian birth cohort analysis from incomplete registry data: evaluating trends in the age of onset of insulin-dependent diabetes mellitus (T1DM). *Stat Med* 2005; **25:** 2989–3004.

16 Aamodt G, Stene LC, Njolstad PR, Sovik O, Joner G, on behalf of the Norwegian Childhood Diabetes Study Group. Spatiotemporal trends and age-period-cohort modeling of the incidence of type 1 diabetes among children aged <15 years in Norway 1973–1982 and 1989–2003. *Diabetes Care* 2007; **30:** 884–89.

17 Clayton D, Schifflers E. Models for temporal variations in cancer rates. II: age-period-cohort models. *Stat Med* 1987; **6:** 469–81.

18 Weets I, De Leeuw IH, Du Caju MV, et al. The incidence of type 1 diabetes in the age group 0–39 years has not increased in Antwerp (Belgium) between 1989 and 2000: evidence for earlier disease manifestation. *Diabetes Care* 2002; **25:** 840–46.

19 Pundziute-Lyckå A, Dahlquist G, Nyström L, et al. The incidence of Type I diabetes has not increased but shifted to a younger age at diagnosis in the 0–34 years group in Sweden 1983–1998. *Diabetologia* 2002; **45:** 783–91.

20 Kyvik KO, Nystrom L, Gorus F, et al. The epidemiology of type 1 diabetes mellitus is not the same in young adults as in children. *Diabetologia* 2004; **47:** 377–84.

21 Joner G, Stene LC, Sovik O. Nationwide, prospective registration of type 1 diabetes in children aged <15 years in Norway 1989–1998. No increase but significant regional variation in incidence. *Diabetes Care* 2004; **27:** 1618–22.

22 Schober E, Rami B, Waldhoer T, and the Austrian Diabetes Incidence Study Group. Steep increase of incidence of childhood diabetes since 1999 in Austria. Time trend analysis 1979–2005. A nationwide study. *Eur J Pediatr* 2008; **67:** 293–97.

23 Hermann R, Knip M, Veijola R, et al. Temporal changes in the frequencies of HLA genotypes in patients with Type 1 diabetes—indication of an increased environmental pressure? *Diabetologia* 2003; **46:** 420–25.

24 Wilkin TJ. The accelerator hypothesis: weight gain as the missing link between type I and type II diabetes. *Diabetologia* 2001; **44:** 914–22.

25 Gale EA. A missing link in the hygiene hypothesis? *Diabetologia* 2002; **45:** 588–94.

26 Dahlquist G. Can we slow the rising incidence of childhood-onset autoimmune diabetes? The overload hypothesis. *Diabetologia* 2006; **49:** 20–24.

27 EURODIAB Substudy 2 Study Group. Rapid early growth is associated with increased risk of childhood Type 1 diabetes in various European populations. *Diabetes Care* 2002; **25:** 1755–60.

28 Cardwell CR, Stene LC, Joner G, et al. Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. *Diabetologia* 2008; **51:** 726–735.

29 McKinney PA, Okasha M, Parslow RC, et al. Early social mixing and childhood type 1 diabetes mellitus: a case-control study in Yorkshire, UK. *Diabet Med* 2000; **17:** 236–42.

30 Patterson CC, Dahlquist G, Soltész G, Green A, on behalf of the EURODIAB ACE Study Group. Is childhood-onset Type I diabetes a wealth-related disease? An ecological analysis of European incidence rates. *Diabetologia* 2001; **44** (suppl 3)**:** B9–16.

31 The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329:** 977–86.