Diabetologia (1999) 42: 1055–1059

Diabetologia

Short communication

Temporal, seasonal, and geographical incidence patterns of Type I diabetes mellitus in children under 5 years of age in Germany

J. Rosenbauer[1], P. Herzig[1], R. von Kries[2], A. Neu[3], G. Giani[1]

[1] Department of Biometrics and Epidemiology, Diabetes Research Institute at the Heinrich-Heine-University of Duesseldorf, Germany
[2] Institute of Social Paediatrics and Adolescent Medicine, Ludwig-Maximilians-University, Munich, Germany
[3] Children's Hospital, University of Tuebingen, Germany

Abstract

Aims/hypothesis. To estimate the national incidence of Type I (insulin-dependent) diabetes mellitus in children under 5 years of age in Germany and to analyse temporal, seasonal, and geographical patterns of the diabetes incidence.
Methods. During 1993–1995 newly diagnosed subjects were prospectively registered by the hospital-based 'German Paediatric Surveillance Unit' with monthly inquiries in all paediatric departments in Germany. Level of ascertainment was estimated by capture-recapture-analysis using two independent regional data sources.
Results. During 1993–1995 the national incidence was 8.10 (95 %-CI: 7.61, 8.61) per 100 000 person-years, ranging in-between lower rates in west European countries and higher rates in northern Europe. Degree of ascertainment was about 85 %. Male to female ratio was 1.11 (95 %-CI: 0.98, 1.25). Compared with results of previous regional studies in the east and the south-west of Germany a 3- and 1.3-fold incidence increase was observed, respectively. Multivariate Poisson regression analysis showed season, geographical region, and interactions of age at onset with sex and calendar year to be independent significant predictors of the incidence. Incidence variation by age was different between boys and girls. A significant incidence increase by calendar year was found in 3- and 4-year-old children only. In summer and fall the incidence was higher than in winter and springtime, in the northern parts of the country higher than in the southern parts.
Conclusion/interpretation. This study reports first national incidence data of Type I diabetes in children under the age of 5 years in Germany. Observed marked temporal, seasonal, and geographical incidence variations strongly support the causal role of environmental factors in disease aetiology. [Diabetologia (1999) 42: 1055–1059]

Keywords Type I diabetes mellitus in childhood, epidemiology, active surveillance, incidence, age and sex distribution, time trend, geographical variation, seasonality.

Received: 4 March 1999 and in revised form: 6 May 1999

Corresponding author: J. Rosenbauer, Diabetes Research Institute at the Heinrich-Heine-University of Duesseldorf, Department of Biometrics and Epidemiology, Auf'm Hennekamp 65, D-40225 Duesseldorf, Germany

J. Rosenbauer and P. Herzig contributed equally to this study.

Abbreviations: p_L, p_W, p_D, p-value based on the likelihood ratio, the Wald, and the deviance statistic, respectively; R^2, generalized coefficent of determination.

In the last two decades world-wide epidemiological research has shown a large geographical variation in the incidence of Type I diabetes mellitus in childhood. The widest range of intracontinental variation has been observed in Europe [1, 2]. Further, numerous studies reported a secular increase of the incidence [1, 3].

In Germany, data on the national incidence of Type I diabetes in childhood have not been available up to now. In eastern Germany diabetes incidences had been reported for the years 1960 to 1989 from the national diabetes register of the former German

Democratic Republic (GDR) [4]. In western Germany the incidence of Type I diabetes has recently been investigated in two regional studies [5, 6], which both found substantially higher incidence rates in the age-group 0–15 years than reported previously from the GDR.

This nation-wide survey during 1993 to 1995 aimed at estimating the actual national incidence of Type I diabetes in children under 5 years of age in Germany and at analysing temporal, seasonal, and geographical patterns of the diabetes incidence.

Subjects and methods

Population at risk. The number of children under 5 years of age in 1993, 1994, and 1995 was 4 328 150, 4 190 591, and 4 038 175, respectively (data from national bureau of statistics).

Definition of study subjects. New subjects with diabetes were included in the study if they had been diagnosed as Type I diabetic during 1993 to 1995, had received their first insulin injection before the age of 5 years, and were permanent residents in Germany at the time of diagnosis.

Data collection. During 1993 to 1995 children with newly diagnosed Type I diabetes were registered by the 'German Surveillance Unit for rare paediatric diseases' (ESPED) [7]. ESPED is a nation-wide hospital-based active surveillance system requesting all paediatric departments in Germany to report cases of childhood diseases under study – including Type I diabetes in children under 5 years of age – on monthly report cards. During the study period the mean return rate of report cards to ESPED was about 90 % [7].

For all registered subjects information on sex, date of birth and diagnosis, and place of residence was recorded by the reporting paediatrician in a mailed standardized questionnaire. If necessary, information was completed through a telephone interview.

Validation of ascertainment. Completeness of ascertainment was assessed by capture-recapture analysis using data of two independent regional surveys in the western German federal states of Baden-Wuerttemberg (1993) [5] and North-Rhine-Westfalia (well defined sub-region only, 1993 to 1995) [6] comprising 14.2 % and 3.4 % of the population at risk, respectively.

Statistical analysis. Crude point and interval estimates of incidence rates were calculated assuming Poisson distributions for the observed cases. Age- and sex-standardized rates were estimated by the direct method using the national population as reference. Point and interval estimates of rate ratios associated with potential risk factors were based on univariate Poisson regression analyses. To adjust for confounding and effect modification multivariate Poisson regression models were fitted to the data by a stepwise forward procedure (p-value to enter < 0.05). Adequacy of the final Poisson model was assessed by a deviance-based goodness-of-fit χ^2-test and a likelihood-based generalized coefficient of determination (R^2) [8]. Tests were done as likelihood ratio or Wald χ^2-tests at a significance level of 0.05. To test for incidence trends, continuous terms were fitted in the respective Poisson models. Interval estimates were calculated at a confidence level of 0.95.

The study was approved by the local ethics committee and the government authorities for protection of personal information.

Results

Degree of ascertainment. Completeness of registration in the federal states of Baden-Wuerttemberg and North-Rhine-Westfalia (sub-region only) was 82.9 % (95 %-CI: 79.8, 86.3) and 85.2 % (95 %-CI: 59.0, 93.9), respectively.

Univariate analysis. During 1993 to 1995, 1017 children (548 boys) with newly diagnosed Type I diabetes had been registered. The national incidence rate was 8.10 (95 %-CI: 7.61, 8.61) per 100 000 person-years. The incidence among boys and girls was 8.51 (95 %-CI: 7.81, 9.25) and 7.67 (95 %-CI: 6.99, 8.40) per 100 000 person-years, respectively, yielding a rate ratio of 1.11 (95 %-CI: 0.98, 1.25, $p_L = 0.099$).

The incidence rate varied significantly by 'age at onset' among boys and girls. The pattern of age-specific incidences, however, differed between boys and girls (Table 1).

There was a significant seasonal variation of the diabetes incidence with highest rates during summer (June to August) and fall (September to November) and the lowest rate in spring (March to May) (Table 1).

The incidence rate decreased significantly from northern to southern Germany (Table 1). In eastern Germany the incidence appeared to be higher than in western Germany. The difference, however, did not remain significant after multivariate adjustment ($p_L = 0.228$).

The incidence per 100 000 person-years increased from 6.86 (95 %-CI: 6.10, 7.69) in 1993, to 7.85 (95 %-CI: 7.03, 8.75) in 1994, and to 9.68 (95 %-CI: 8.75, 10.69) in 1995 (test for trend: $p_L < 0.001$). This significant trend, however, was confined to children above the age of 3 years (Table 2).

Incidences standardized by age or sex or both and corresponding rate ratios (not shown) were almost identical with the crude rates in Tables 1 to 2.

In Baden-Wuerttemberg, the only federal state in western Germany with previous incidence data [5] the incidence was 8.5 (95 %-CI: 7.2, 9.9) during the study period.

Multivariate regression analysis. 'Season', 'geographical region' (northern, central, and southern Germany), and interactions of 'age at onset' with 'sex' and 'calendar year' were shown to be independent significant predictors of the diabetes incidence ($p_L < 0.05$). The final Poisson model including these significant terms fitted the incidence data very well (Goodness-of-fit test: $p_D = 0.384$, $R^2 = 38\,\%$). The age related incidence variation was proven to be significantly different between boys and girls. The incidence increase during the study period was shown to vary significantly between age-groups. Multivariate adjusted estimates and tests (not shown) confirmed the results in Tables 1 and 2.

Table 1. Crude incidence rates of Type I diabetes and rate ratios by age at onset and sex, season, and geographical region in children under the age of 5 years in Germany from 1993 to 1995

Risk factor	No of cases	Person-years at risk	Incidence rate[a] (95%-CI)	p_L[b]	Incidence rate ratio[c] (95%-CI)	p_w[d]
Age at onset in male				< 0.001		
0 yr	19	1198724	1.59 (0.95, 2.48)		1	
1 yr	119	1230304	9.67 (8.01, 11.57)		6.10 (3.76, 9.90)	< 0.001
2 yrs	139	1272413	10.92 (9.18, 12.90)		1.13 (0.88, 1.44)	0.330
3 yrs	136	1343155	10.13 (8.50, 11.98)		0.93 (0.73, 1.17)	0.529
4 yrs	135	1397407	9.66 (8.10, 11.43)		0.95 (0.75, 1.21)	0.699
Age at onset in female				< 0.001		
0 yr	28	1135919	2.46 (1.64, 3.56)		1	
1 yr	70	1166879	6.00 (4.68, 7.58)		2.43 (1.57, 3.77)	< 0.001
2 yrs	101	1208610	8.36 (6.81, 10.15)		1.39 (1.03, 1.89)	0.033
3 yrs	148	1275837	11.60 (9.81, 13.63)		1.39 (1.08, 1.79)	0.011
4 yrs	122	1327668	9.19 (7.63, 10.97)		0.79 (0.62, 1.01)	0.057
Season[e]				0.006		
Spring	216	3139229	6.88 (5.99, 7.86)		1	
Summer	283	3139229	9.01 (8.00, 10.13)		1.31 (1.10, 1.56)	0.003
Fall	279	3139229	8.89 (7.88, 9.99)		1.29 (1.08, 1.54)	0.005
Winter	239	3139229	7.61 (6.68, 8.64)		1.11 (0.92, 1.33)	0.281
Region 1[e,f]				0.023[g]		
North	207	2273149	9.11 (7.91, 10.43)		1	
Central	474	5650014	8.39 (7.65, 9.18)		0.92 (0.78, 1.09)	0.325
South	336	4633753	7.25 (6.50, 8.07)		0.80 (0.67, 0.95)	0.010
Region 2[e,h]				0.051		
West	864	10931592	7.90 (7.39, 8.45)		1	
East	153	1625324	9.41 (7.98, 11.03)		1.19 (1.00, 1.41)	0.046

[a] per 100000 person-years
[b] likelihood ratio χ^2-test of homogeneity of incidence rates across respective categories
[c] current vs previous age-group regarding age at onset, current vs first category regarding season, region 1, and region 2
[d] Wald χ^2-test of the hypothesis: 'rate ratio equals 1'
[e] crude estimates are almost identical to sex- and age-standardized estimates (not shown)
[f] grouping of German federal states according to their geographical site into a northern, central and southern region of Germany
[g] likelihood ratio χ^2-test for trend: $p_L = 0.007$
[h] grouping of German federal states according to former East and West Germany

Discussion

This prospective survey provides first national incidence data of Type I diabetes in children under 5 years of age in Germany, the ascertainment level was 83–85%. The incidence adjusted for the ascertainment level (9.53, 95%-CI: 8.95, 10.13 per 100 000 person-years) ranges in-between lower rates in west European countries and higher rates in northern Europe [1, 2]. The finding of a slightly higher incidence among boys is consistent with previous European studies [1, 2, 4, 5].

This survey found a significant 3.5- and 1.3-fold incidence increase in eastern Germany and the southwest German federal state of Baden-Wuerttemberg, respectively, compared with results of previous regional studies [4, 5] [9.4 vs 2.7 (1988) and 8.5 vs 6.4 (1987–1993) per 100 000 person-years, respectively, $p_L < 0.001$]. Since the degree of ascertainment in both previous studies (eastern Germany: 98%, Baden-Württemberg: 96,2%) was higher than in this survey, the observed incidence increase may not be attributed to different methods of data collection. Therefore, the findings are likely to reflect a real time trend in accordance with previous observations in other European countries [1, 3]. This time trend has been reported to be most distinctive in children under 5 years of age [3].

The observed coincidence of changes in the living conditions in eastern Germany during the reunification process since 1989 and a threefold incidence increase within a 7-year-period could particularly be regarded as another piece of ecological evidence for the substantial influence of environmental factors in the development of Type I diabetes [1].

From 1993 to 1995 the incidence among children 3 or 4 years of age increased significantly. The absence of a time trend among younger children is possibly due to their more limited exposure to peer-contact and infectious diseases [1]. Further studies are needed to validate these findings and to identify potential causal factors for interactions between age at onset and time trends.

In Germany a significant geographical variation statistically in the incidence of diabetes was found, which is in accordance with observations in other

Table 2. Crude annual incidence rates of Type I diabetes and rate ratios of successive calendar years in 0- to 4-year-old children in Germany from 1993 to 1995

Age at onset	Calendar year	No of cases	Person-years at risk	Incidence rate[a] (95 %-CI)	p_L[b]	Incidence rate ratio[c] (95 %-CI)	p_w[d]
0 yr	1993	21	799,022	2.63 (1.63 4.02)	0.243	1	
	1994	11	769,617	1.43 (0.71 2.56)		0.54 (0.26, 1.13)	0.102
	1995	15	766,004	1.96 (1.10 3.23)		1.37 (0.63, 2.98)	0.428
1 yr	1993	59	818,846	7.21 (5.48 9.29)	0.691	1	
	1994	66	802,816	8.22 (6.36 10.46)		1.14 (0.80, 1.62)	0.462
	1995	64	775,521	8.25 (6.36 10.54)		1.00 (0.71, 1.42)	0.983
2 yrs	1993	79	850,783	9.29 (7.35 11.57)	0.725	1	
	1994	77	822,359	9.36 (7.39 11.70)		1.01 (0.74, 1.38)	0.958
	1995	84	807,881	10.40 (8.29 12.87)		1.11 (0.82, 1.51)	0.507
3 yrs	1993	84	936,040	8.97 (7.16 11.11)	0.042[e]	1	
	1994	93	855,019	10.88 (8.78 13.33)		1.21 (0.90, 1.63)	0.201
	1995	107	827,933	12.92 (10.59 15.62)		1.19 (0.90, 1.57)	0.224
4 yrs	1993	54	932,459	5.85 (4.39 7.63)	< 0.001[e]	1	
	1994	82	940,780	8.72 (6.93 10.82)		1.49 (1.06, 2.10)	0.023
	1995	121	860,836	14.06 (11.66 16.80)		1.61 (1.22, 2.13)	0.001

[a] per 100 000 person-years, crude estimates are almost identical to sex-standardized estimates (not shown)
[b] likelihood ratio χ^2-test of homogeneity of incidence rates across all calendar years
[c] current vs previous calendar year
[d] Wald χ^2-test of hypothesis: 'rate ratio equals 1'
[e] likelihood ratio χ^2-test for trend: $p_L = 0.012$ and $p_L < 0.001$, respectively

countries [1, 2]. These regional differences in Germany are not likely due to genetic factors and therefore possibly corroborate the importance of environmental exposures in the aetiology of Type I diabetes.

This survey found the age-specific incidence pattern to be different among boys and girls. Both different age-specific incidence patterns have been reported previously [4, 5, 9]. If confirmed in other studies, the observed sex-specific incidence variation with age might help to generate new hypotheses on the aetiology of diabetes.

Seasonal variation with peaks during winter and early spring is a frequently reported incidence pattern in childhood [1, 2, 9]. In children younger than 5 years of age, however, the seasonal variation has been observed to be less clear or absent [2, 5]. The opposite seasonal pattern observed in this study with high rates in summer and fall possibly supports the hypothesis of a different pathogenesis of Type I diabetes in younger and older children. Further, the observed seasonality in Germany might be related to HLA, for a summer peak of diabetes onset was observed in HLA-DR4 positive children [10].

There are two main shortcomings of this survey, namely the geographically limited validation procedure and the only moderately high ascertainment level, both possibly causing bias in incidence estimation. Since the ascertainment levels in the two validation regions were quite similar and there were no substantial regional variations in the response rates in the surveillance system [7], the regionally estimated ascertainment level is assumed to be representative for the whole country. Attaining high ascertainment is a particular problem for nation-wide studies in countries with a non-centralized health care system. Higher ascertainment rates than in this study could mainly be achieved in regional European registers [2].

Nevertheless, the incidence estimate corrected for the degree of ascertaiment in this study possibly still underestimates the true rate in Germany and the observed geographical differences in incidence have to be interpreted with care.The observed incidence increase during the study period might also be influenced by increasing response rates in the surveillance system (1993: 82 %, 1994: 93 % and 1995: 95 %) [7]. Presented rate ratios related to sex, age, and season, however, are unlikely to be biased due to the mentioned shortcomings, because registration of new subjects with diabetes can be assumed to be independent of these factors.

In conclusion, this study reports first national incidence data of Type I diabetes in children under the age of 5 years in Germany, which serve as a base for future analysis of temporal trends. The observed incidence patterns strongly support the important role of environmental factors as determinants of Type I diabetes in young children. The increasing time trend observed so far is an important public health issue. An effective and cost efficient tool to monitor the time trend of the Type I diabetes incidence in childhood is active surveillance of patients admitted to the hospital.

Acknowledgements. We thank all physicians and diabetes nurses in the participating hospitals and practices for supporting our study.

This study was supported by the Deutsche Forschungsgemeinschaft (HE 234/1–1) and the European Community Concerted Action EURODIAB ACE (Contract BMH1-CT92–0043) and EURODIAB TIGER (Contract BMH4-CT96–0577).

References

1. Karvonen M, Tuomilehto J, Libman I, LaPorte R for the World Health Organization DIAMOND Project Group (1993) A review of the recent epidemiological data on the worldwide incidence of Type I (insulin-dependent) diabetes mellitus. Diabetologia 36: 883–892
2. Levy-Marchal C, Patterson C, Green A on behalf of the EURODIAB ACE Study Group (1995) Variation by age group and seasonality at diagnosis of childhood Type I diabetes in Europe. Diabetologia 38: 823–830
3. Gardner SG, Bingley PJ, Sawtell PA, Weeks S, Gale EA (1997) Rising incidence of insulin dependent diabetes in children aged under 5 years in the Oxford region: time trend analysis. The Bart's-Oxford Study Group. BMJ 315: 713–717
4. Michaelis D, Jutzi E, Heinke P (1993) 30 jähriger Inzidenz- und Prävalenztrend des juvenilen Typ-I-Diabetes in der ostdeutschen Bevölkerung. Diab Stoffw 2: 245–250
5. Neu A, Kehrer M, Hub R, Ranke MB (1997) Incidence of Type I diabetes in German children aged 0–14 years. Diabetes Care 20: 530–533
6. Rosenbauer J, Icks A, Giani G (1998) Typ 1-Diabetes bei Kindern und Jugendlichen – prospektive Inzidenzstudie in der Region Düsseldorf. Kinderärztliche Praxis 1: 15–25
7. Giani G, Helwig H, Herzig P et al. im Auftrag des ESPED-Beirates (1996) ESPED-Jahresbericht 1995. Monatsschr Kinderheilkd 144: 967–973
8. Nagelkerke NJD (1991) A note on a general definition of the coefficient of determination. Biometrika 78: 691–692
9. Goday A, Castell C, Treserras R et al. (1992) Incidence of Type I (insulin-dependent) diabetes mellitus in Catalonia, Spain. Diabetologia 35: 267–271
10. Ludvigsson J, Samuelsson U, Deschamps I et al. (1986) HLA-DR3 is associated with a more slowly progressive form of Type I (insulin-dependent) diabetes. Diabetologia 29: 207–210