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Record-high incidence of Type I (insulin-dependent) diabetes mellitus in Finnish children

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Abstract

Aims/hypothesis. In Finland, the incidence of Type I (insulin-dependent) diabetes mellitus in children aged 14 years or under is the highest in the world and the trend in incidence has been increasing. Our aim was to determine the most recent trends in incidence and the age distribution at diagnosis of Type I diabetes.

Methods. Data on the incidence of Type I diabetes in Finland nationwide were obtained from two sources: for the period 1965 to 1986 from the Central Drug Registry of the Social Insurance Institution and for the period 1987 to1996 from the prospective childhood Type I diabetes registry. The annual incidence was calculated per 100000 people. The increase and the trend in incidence were estimated by fitting the linear regression model with the annual incidence data.

Results. During 1987 to 1993 the incidence of Type I diabetes seemed to be rather stable at 36 per 100000 per year. The incidence has continued to increase thereafter and reached 45 per 100000 per year in 1996. The analysis of the long-term trend in incidence between 1965 and 1996 showed an absolute incidence increase of 0.67 per year on average being 3.4 % compared with the incidence in 1965. The increase from 1987 to 1996 was highest in very young children 1–4 years old at diagnosis.

Conclusion/interpretation. The high incidence of Type I diabetes in Finnish children has thus far not levelled off but is increasing further. If the trend continues, the predicted incidence in Finland will be approximately 50 per 100 000 per year in the year 2010. [Diabetologia (1999) 42: 655–660]

Keywords Diabetes, Type I (insulin-dependent) diabetes mellitus, incidence, Finland.

The incidence of Type I insulin-dependent diabetes mellitus in children aged 14 years or under is known to have been the highest in the world in Finland during the last two decades [1–4]. The first nationwide study of Type I diabetes in 1953 showed an incidence of 12 per 100000 person years [5]. This incidence has gradually increased and in the late 1980s it was 36 per 100000 person years [6]. From 1987 to 1992 the incidence of Type I diabetes did not show any apparent trend and the average incidence remained at 36 per 100000 person years (37 for boys and 32 for girls). This led even to speculation that the increase might have levelled off, probably as a result of some environmental changes. Peaks in incidence were seen previously in 1986 (38 per 100000 person years) and 1991 (39 per 100000 person years) [2, 4, 6].

Our previous analysis of age-period-birth cohort effects on the increasing trend in Type I diabetes during the period 1965–1984 showed that the increase was mainly related to the time period and that all age groups were similarly affected [7]. Between 1988 and 1992, however, the differences in the age-specific incidence started to diminish since the increase in in-

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Table 1. The incidence of Type I diabetes (per 100000 person years) in children aged 14 years or under in Finland from 1987 to 1996 according to age, and year

Incidence per 100000 person years							
Year		Age at diagnosis (years)					(95% confidence interval)
		< 1	1–4	5–9	10–14	All 0–14 years age-adjusted	
1987	Incidence	1.7	33.0	38.5	40.2	35.1	(31.49; 39.13)
	No.	1	83	124	127	335	
1988	Incidence	7.9	27.4	43.3	35.2	33.9	(30.57; 38.07)
	No.	5	68	141	114	328	
1989	Incidence	0.0	34.9	35.8	45.7	36.8	(32.86; 40.61)
	No.	0	86	117	149	352	
1990	Incidence	9.2	37.2	36.4	36.9	35.1	(31.32; 38.89)
	No.	6	92	119	120	337	
1991	Incidence	1.5	36.0	40.7	47.0	39.2	(35.10; 43.08)
	No.	1	91	132	152	376	
1992	Incidence	7.5	32.1	38.6	37.5	34.5	(30.80; 38.29)
	No.	5	83	123	122	333	
1993	Incidence	6.2	30.6	41.2	35.0	33.9	(30.33; 37.76)
	No.	4	80	130	115	329	
1994	Incidence	4.6	43.0	46.5	40.8	40.8	(36.91; 45.05)
	No.	3	113	146	135	397	
1995	Incidence	6.4	40.1	47.1	40.6	40.2	(36.44; 44.54)
	No.	4	105	149	134	392	
1996	Incidence	13.2	41.2	48.3	50.1	44.8	(40.69; 49.23)
	No.	8	107	155	164	434	

cidence was larger among the younger, 1–4 year-old children, than older ones [7].

Monitoring the incidence of Type I diabetes has continued in Finland nationwide and here we report the most recent data showing a further drastic increase in incidence in the mid-1990s. We will also attempt to find out the mode of increase in incidence and predict the incidence trend until the next millennium.

Subjects and methods

Study subjects. Between 1987 and 1996 the number of children newly diagnosed with Type I diabetes at age 14 year or under was 3613 (Table 1). For the period from 1965 to 1986 the data about newly diagnosed subjects with Type I diabetes were obtained from the Central Drug Registry of the Social Insurance Institution as described earlier [1, 6, 7]. In Finland, all children with Type I diabetes are treated in a hospital at the time of diagnosis [8]. The diabetes nurses in the paediatric wards of all hospitals treating diabetic children record the necessary information on standardized forms and send them to the Diabetes and Genetic Epidemiology Unit of the National Public Health Institute in Helsinki. We have earlier shown that case ascertainment is virtually 100% complete. Details of the procedures in case ascertainment have been described previously elsewhere [8]. Currently, the collection of incidence data continues as a part of the WHO DIAMOND (DIAbetes MONDiale) Project [9]. Population data were obtained from the National Population Registry, which is updated continuously. The Finnish population aged 14 years or under varied from 1239103 to 971770 during the period 1965 to 1996.

Statistical methods. The incidence rates were calculated per 100000 people per year. The 95% confidence intervals (CI) were estimated assuming Poisson distribution of the cases. Age adjustment of the rates was done using 5-year intervals (0–14 years) with the yearly mean of the Finnish population aged 14 years or under in 1980 as a standard. Since there were only 37 children (1.0%) diagnosed with Type I diabetes before their first birthday, age group specific analyses were carried out using the age range 1–4 years for the youngest age group. Difference in the median age at diagnosis between 1965 and 1996 were compared using Wilcoxon rank-sum test.

We modeled the expected value of the number of patients with Type I diabetes in Finland with an additive absolute (i.e. excess) risk model, which is a special case of a generalized linear model and thus a natural choice when studying disease rates in relation to time. We divided time intervals from 1965 to 1996 in one year intervals at time points t_0,. .,t_{31}, starting on January 1, 1965. Let $t_0 = 0$, $t_1 = 1$,. ., $t_{31} = 31$. A model for the expected values $E(Y(t_i)$, of the number of cases $Y(t_i)$ in year $1965 + t_i$ with $i = 0$,. .,31 can be written as $g(E(Y(t_i))) = \lambda_i N_i = (\alpha + \beta \cdot t_i)N_i$, where link function g(.) is the identity function, λ_i is the intensity of Type I diabetes at time segment i, N_i is the number of people at risk in the time segment i, α and β are regression variables to be estimated corresponding to the expected number of cases of Type I diabetes in 1965 ($t_0 = 0$) and slope. We made the following assumptions: 1) the number of cases at each time interval was statistically independent, 2) the intensity (λ_i) within time segment was constant, 3) the number of cases in each time interval followed Poisson distribution with the mean $\lambda_i N_i$. We used the S-plus program (S-plus 4.0, Mathsoft Inc., Seattle, USA) to obtain maximum likelihood estimates of the model parameters and their standard errors.

The hypothesis of a different increase in incidence of Type I diabetes in children aged 1–4 years from that in children aged

Table 2. Parameter estimates (per 100000 person years) of additive model for the annual increase in the incidence of Type I diabetes in Finland from 1965 to 1996

Parameter	Estimate	(standard error)	Wald test	df	p-value
Constant	19.88	(0.50)	39.6	1	< 0.0001
Slope	0.67	(0.032)	21.1	1	< 0.0001

5–14 years was tested using two models where indexes $j = 1$ and $j = 2$ correspond to the age group 1–4 years and the age group 5–14 years respectively.

Model 1: $E(Y_{ij}) = \alpha_j + \beta \cdot t_i$, $i = 0,. .,31$ and $j = 1,2$ and

Model 2: $E(Y_{ij}) = \alpha_j + \beta_j \cdot t_i$, $i = 0,. .,31$ and $j = 1,2$, where Y_{ij} is the number of cases of Type I diabetes in age group j in the year $1965 + t_i$. Model 1 has a common slope for all children aged 1–14 years and model 2 has two separate slopes for the two age groups. The models are nested, therefore we compared these two models by calculating the difference of the residual deviances (Likelihood ratio test).

Results

During the ten-year-period from 1987 to 1996 the age-standardized incidence of Type I diabetes in Finnish children aged 14 years or under was 37 per 100000 person years. From 1987 to 1993 the incidence was fairly stable, 36 per 100000 person years, but since 1994 the incidence exceeded 40 per 100000 person years for the first time with a record high of 45 per 100000 person years in 1996. From 1987 to 1996 there was a slight male excess in incidence, with the male to female ratio 1.08 (95% CI 0.98; 1.16).

The average annual increase in the incidence of Type I diabetes from 1965 to 1996 among children aged 14 years or under was 0.67 per 100000 person years (Table 2). This is equal to an annual incidence increase of 3.4% of the incidence in 1965, calculated from the additive model as $(0.67/19.88) \cdot 100$, where 19.88 per 100000 person years is the estimated incidence in 1965 (Fig. 1). The age-at-onset of Type I diabetes has become younger. The median age of diagnosis of Type I diabetes decreased from 10 years in 1965 to 8 years in 1996 (Wilcoxon rank sum test statistics $Z = 5.06$, $p < 0.0001$).

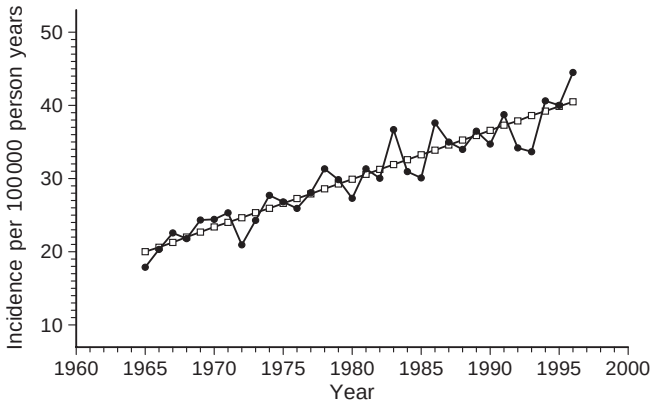

Fig. 1. The trend in the incidence of Type I diabetes in Finnish children aged 1–14 years. Linear regression line is shown for the years 1965–1996. ● Observed, □ Linear

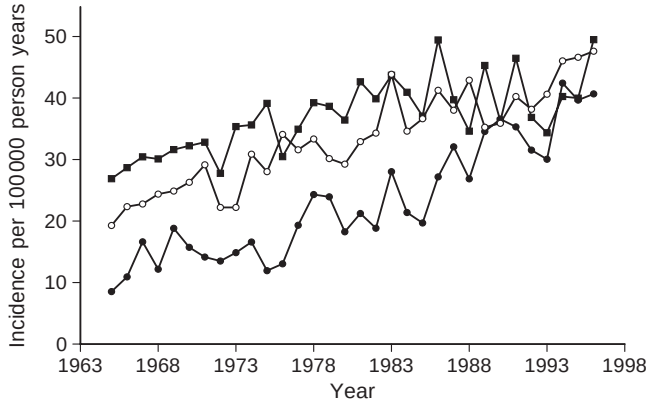

Fig. 2. The age-specific annual incidence of Type I diabetes per 100 000 Finnish children aged 1–14 years between 1965 and 1996. ● 1–4 years, ○ 5–9 years, ■ 10–14 years

Between 1987 and 1996 the incidence of Type I diabetes increased in the youngest age group (1–4 years of age) which was a more pronounced increase than among the older (5–14 years) children ($p < 0.0007$) (Table 3, Fig. 2). The increase became striking at the beginning of the 1990s and the incidence in young

Table 3. Parameter estimates (per 100000 person years) of additive model of the annual incidence of Type I diabetes in Finland from 1987 to 1996 according to age group

	Constant (standard error) Age-at-diagnosis		Slope (standard error)		Residual deviance	df
	1–4 years	5–14 years				
Model 1	11.5 (0.63)	24.2 (0.57)	0.74 (0.033)		113.69	61
Model 2	9.9 (0.77)	25.4 (0.67)	0.87 (0.052)	0.65 (0.042)	102.18	60

Difference between residual deviances 11.5, 1 df., $p < 0.0007$

Model 1: $E(Y_{ij}) = \alpha_j + \beta \cdot t_i$, $i = 0,. . .,31$ and $j = 1,2$ and

Model 2: $E(Y_{ij}) = \alpha_j + \beta_j \cdot t_i$, $i = 0,. . .,31$ and $j = 1,2$, where Y_{ij} is the number of Type I diabetic cases in age group j in the year $1965 + t_i$

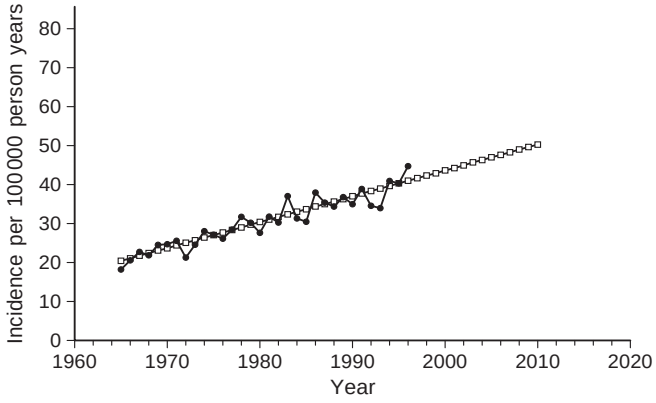

Fig. 3. Predicted linear trend in the incidence of Type I diabetes until the year 2010 in Finnish children aged 1–14 years. ● Observed; □ Linear

children reached that among older children during the first half of the 1990s.

An additive risk model was fitted for Type I diabetes incidence data for the period 1965 to 1996. On the basis of the observed trend, we extrapolated the incidence to the future years (Fig. 3, Table 2). The predicted incidence based on the linear trend showed that the incidence would be 50.1 per 100000 person years in 2010, if the trend remains the same as it has been over almost the last 40 years.

Discussion

The incidence of Type I diabetes in Finland is now a record-high of 45 per 100000 person years in 1996. This is approximately four times higher than that in the first nationwide study in 1953 [5]. The good fit of the linear regression for the long-term trend in incidence and the long observation period of over 40 years ensure that this linear trend is true.

Increases in the incidence of Type I diabetes have also been reported from other populations, e.g. from Sweden [10], Norway [11], Holland [12], Austria [13], Hungary [14], England [15, 16]. Also outside of Europe a recent report from Kuwait indicated a major increase in incidence [17]. In keeping with our results, the recent findings from the Oxford region of England also show a dramatic 11% increase in Type I diabetes incidence in children aged under 5 years during the period 1985 to 1996 [16]. Such long-term data as we have in Finland, are not available from any other population. It is, however, obvious from our present data that it is very difficult and sometimes misleading to speak about temporal trends in the incidence of Type I diabetes where the time span is less than 10 years.

We have previously shown with the data from the large population-based cohort of Finnish twins that genetic effects explain 70–75% of the susceptibility to Type I diabetes, and environmental effects may explain the rest [18, 19]. Similar estimates can be derived from the recent Danish twin study [20]. This favors the hypothesis that genetic factors are also the likely reasons for the steady increase in Type I diabetes in Finnish children. This hypothesis is not easy to prove since comparisons of the genetic factors conferring susceptibly to Type I diabetes are not available for the Type I diabetic patients and birth cohorts back in the 1920s and 1930s. One of the first reports about Type I diabetes in children from Cambridge, UK, stated that between 1925 and 1933 there were only 18 patients diagnosed and admitted to the Addenbrook's Hospital [21]. In Finland, the first paper reported an incidence of 12 per 100000 people for the year 1953 [5]. Note that this rate falls exactly on the regression line derived from the years 1965 to 1996.

During recent years much attention has been paid to the identification of possible environmental factors which may initiate or trigger the process leading to Type I diabetes. Although some studies have suggested associations between environmental factors such as diet and viral infections with the risk of Type I diabetes [22–34], their causative role in the aetiology of Type I diabetes remains uncertain. It is also difficult to find evidence that putative environmental factors have increased with a steady pattern during the last decades. On the contrary, breast feeding for instance has become more common during the last 20 years. At the beginning of the 1970s only 10% of children were breast-fed until 6 months of age but now in the 1990s about 60% of children are breast-fed for 6 months [35]. Consequently, the use of supplementary foods for very young babies has not drastically increased in Finland [35].

The new MMR (measles-mumps-rubella) vaccination was introduced in the early 1980s nationwide in Finland [36]. Another vaccination programme against *Haemophilus influenzae* was initiated at the end of 1985 [37]. Whether these vaccination programmes could be related to the steep increase in Type I diabetes incidence in the youngest children after the mid-1980s needs to be explored scientifically before such a claim can be made.

Although genetic factors have a major role in the development of Type I diabetes, 85–90% of new cases occur in families with no previous history of Type I diabetes among first degree relatives. By definition a child with Type I diabetes must have inherited the Type I diabetes susceptibility genes from one or both parents. Thus, the frequency of the disease in the population is a function of the frequency of the susceptibility genes and their penetrance in the population. Because Type I diabetes is not very common in parents of a child with the disease, the number of carriers of the disease susceptibility genes must be relatively high.

We have previously shown that there is a specific HLA haplotype which is only found in Finnish Type I diabetc patients and not in any other population

[38]. This HLA-A2,Cw1,B56,w6,DR4,DQ8 haplotype was the third most common (5.5%) haplotype found in newly diagnosed children with Type I diabetes, and it was the most common haplotype transmitted from the diabetic parent to the child with Type I diabetes (17%). This haplotype is also very penetrant, the absolute risk for it is 209 per 100000 person years, i.e. six times higher than the average incidence of Type I diabetes in Finland [38] and 30 times higher than the incidence in low risk European populations [39]. This haplotype occurs more frequently in younger than older children [40] and could have contributed to the increase in the incidence and the younger onset of Type I diabetes.

Finland is the first country in the world to have a Type I diabetes incidence of greater than 40 per 100000 person years. The incidence will surpass 50 per 100000 person years around the year 2010, and around 2020 the incidence would be approximately 55 per 100000 person years. Thus far the only other population to reach a level of 30 per 100000 person year is in Sardinia [41]. The increase in Finland has been steady and no really effective intervention is in sight either for individual subjects at high risk or for the population as a whole. Meanwhile, the incidence is likely to continue to rise not only in Finland but globally. It is important to continue monitoring the Type I diabetes incidence in diverging populations to document long-term trends in what is now one of the most common childhood-onset chronic diseases.

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