# Increased Risk of Childhood Type 1 Diabetes in Children Born After 1985

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**OBJECTIVE** — The incidence rate of childhood type 1 diabetes is thought to be increasing; however, Danish studies have not confirmed this. Using a national diabetes register initiated in 1996 and two previous regional incidence studies, we studied the age-specific incidence of type 1 diabetes over 30 years. Here, we describe the incidence rates of type 1 diabetes in Danish children from 1996 to 2000 and evaluate trends in age-specific incidence rates from 1970 to 2000.

**RESEARCH DESIGN AND METHODS** — A nationwide registration of all newly diagnosed cases of type 1 diabetes among children under the age of 15 years was established in Denmark in 1996. Incidence rates of type 1 diabetes in Denmark were obtained from this register. Age-specific incidence rates were compared with data collected from 1970 to 1976 and from 1980 to 1984, both population-based studies using existing national routine registration of hospitalizations within the survey areas. Population data were obtained from Statistics Denmark.

**RESULTS** — During the study period, 1,421 Danish children developed type 1 diabetes before the age of 15 years. The incidence rates by age-groups were: 12.7, 19.4, and 26.3 for the 0–4, 5–9, and 10–14 years age-groups, respectively, and 19.5 for the 0–14 years age-group per 100,000 in the period 1996–2000. An age-period-cohort analysis showed a modest drift effect (yearly increase) of 1.2% (0.7–1.8) from 1970 to 2000, and a significant birth cohort effect with an increased risk for children born after 1985 was observed.

**CONCLUSIONS** — The incidence rate of type 1 diabetes is rising in children living in Denmark. The steep increase in the youngest age-group was explained by the increased risk for cohorts born at the beginning of the 1980s.

There is a wide geographical variation in the incidence of type 1 diabetes. The highest incidence is found in northern Europe and America, although the polar-equatorial gradient in the incidence rates is not as clear-cut as originally assumed (1). The incidence rates of childhood diabetes have increased globally over the past 50 years (2,3). The incidence rates are the highest among children between 10 and 14 years of age in most populations; nevertheless, some populations have nearly the same rates in all age-groups (0–4, 5–9, and 10–14 years of age) (1). Denmark belongs to a high-incidence area; however, studies analyzing time trends have shown both an increase and an unchanged incidence rate (4,5).

A change in incidence rates can be described by either a period effect simultaneously affecting all age-groups or a cohort effect affecting age-groups at different times. Age-period-cohort models quantify the separate effects of the factors age, period, and cohort (6,7): age is the child's age on diagnosis, period is the date of diagnosis, and cohort is the date of birth of the child. We describe the incidence in Denmark from 1996 to 2000 and evaluate trends in age-specific incidence rates from 1970 to 2000 using the age-period-cohort model.

**RESEARCH DESIGN AND METHODS** — This study was based on data collected during three periods (1970–1976, 1980–1984, and 1996–2000). In the Danish health care system, all children aged 0–14 years with suspected diabetes are referred to a hospital. Since 1 January 1996, all hospitalized incident cases have been reported on a special form containing information about the patient's personal identification number, sex, county of residence, place of birth, nationality, and date of diagnosis (i.e., the day when the first insulin injection was given). Data were validated against the national discharge register. For all cases found in the national registration, the original hospital records were checked to establish the correct diagnosis. During the first 5 years of the registration, 32 cases that did not appear from the national discharge register were registered in the diabetes register, whereas 7 (correctly diagnosed children with diabetes) were found in the national discharge register but not in the Danish Childhood Diabetes Register. In the first 5 years, 839 cases were found. The completeness of case ascertainment was estimated using these two independent sources and matching by personal identification numbers. The ascertainment rate was 99.2%.

The study from 1980 to 1984 was based on local and central registries of the medical and pediatric departments in a survey area comprising 28% of the Danish population. The registries were used to identify hospital discharges with the diagnosis of diabetes (ICD-8, 249.00, 250.00, and subclasses) for children between 0 and 14 years of age from 1980 to 1984. All records were reviewed, and dates of the initial insulin injections and diabetes clas-

**Table 1—***Incidence rates of diabetes in Denmark per 100,000 person-years*

| Age (years) | Year | | | Annual increase (%) | Trend test (P) |
|---|---|---|---|---|---|
| | 1970–1976 | 1980–1984 | 1996–2000 | | |
| 0–4 | 7.59 | 8.95 | 12.73 | 1.96 | 0.0004 |
| 5–9 | 12.47 | 13.58 | 19.36 | 1.03 | 0.0002 |
| 10–14 | 22.07 | 21.27 | 26.21 | 0.27 | 0.11 |
| 0–14* | 14.03 | 14.58 | 19.4 | 1.23 | 0.0000 |
| Boys* | 14.6 | 15.9 | 20.2 | 1.20 | 0.0008 |
| Girls* | 13.5 | 13.0 | 18.7 | 1.28 | 0.0009 |

Annual increase adjusted for sex and country. *Incidence rates standardized to a uniform age distribution

sifications were checked. Ascertainment was validated by sending questionnaires to 10% of the general practitioners in the area and to all specialists in pediatrics and internal medicine and by checking death certificates. Two patients were only treated in outpatient clinics. No patients were treated only at the general practitioner's office. Ascertainment was calculated on the assumption that the 10% of the general practitioners surveyed were representative. Ascertainment was then >99%. Of the Danish population, ~28% lived within the survey area. (8)

The data from 1970 to 1976 were collected retrospectively. The study covers ~45% of the Danish population, including the area covered in the 1980–1984 study. The study was based on hospital records from the survey area. Patients with a hospital discharge diagnosis of diabetes (ICD-8, according to 1965 World Health Organization guidelines) were defined as having type 1 diabetes, and insulin treatment was instituted within 1 year of diagnosis. All patients in the age-group 0–14 years living in the survey area were included (9).

Ascertainment was calculated using the same methods as in the study of 1980–1984; 2 patients were not hospitalized, and 9 patients were found in a local registry of 792. The degree of ascertainment using this method was 98.6% in this study period (9). Population data were obtained from Statistics Denmark.

### Definition of immigrants in Denmark

All residents in Denmark have a personal identification number and are registered by place of birth and citizenship together with the parents' citizenship and place of birth in the central population register. The children were registered as immigrants if born outside Denmark and if

their parents were born outside Denmark or had foreign citizenship. The children were registered as offspring of immigrants if they were born in Denmark and if the parents were born outside Denmark or had foreign citizenship.

The first study period gives no exact information on immigrants; however, the number of immigrants was <5% in Denmark. Immigrants were included in both the denominator and the numerator. In the second and third study period, data on percentage immigrants in the background population were available at Statistics Denmark, and all patients were registered with immigrant status. Immigrants were then excluded in both the numerator and the denominator.

### Statistical analysis

The incidence rate in the age-group 0–14 years of age was adjusted to a standard population, with uniform age distribution for international comparison. The secular trends in incidence rates were estimated using the Poisson multiple regression analysis. Data were classified by age, date of diagnosis (period), and date of birth (cohort) in 1-year classes and by county and sex. The incidence rates were described as a function of age, period, cohort, sex, and county to estimate whether the rise in incidence could be explained by either a period effect simultaneously affecting all age-groups or a cohort effect affecting special birth cohorts. (6,7,10)

Incidence rates were assumed to be linear in 2.5-year spans of age and in 5-year spans of cohort and period, allowing for linear increase or decrease within these time spans. The age-period-cohort analysis fitted the regression models to the data using forward stepwise selection. In each step, the last term entered into the model was tested for significance. To test for period and cohort effect, the model

with a linear increase (drift) (6,7) was compared with the model with either period or cohort divided in these time spans.

Models were compared by likelihood ratio tests. The trend tests for the three age classes 0–4, 5–9, and 10–14 years were calculated using an interaction between the linear cohort and the three age-groups as follows: Log(Incidence rate) = $a + b_{age} + c_{age,sex} + d_{county} + f_{age-groups} \times$ cohort. The differences between the linear increases in the three age-groups were tested with likelihood ratio tests. Models were also compared by likelihood ratio test.

**RESULTS** — During the total study period, 1,474 children developed type 1 diabetes before 15 years of age; of these, 53 children were either immigrants or offspring of immigrants and consequently excluded.

Table 1 lists the incidence rates per year group and age-group with the annual increase in incidence rates. The annual increase in the age-group 0–14 years of age is the drift (linear increase). Table 2 shows the stepwise age-period-cohort modeling. When using the forward stepwise selection, where variables are included if they cause a significantly better-fitted model, the best-fitting model is model 6B (Table 2). The reporting is based on this model. The annual increase for all age-groups combined applying the same model, but including immigrants, was 1.1% (0.6–1.7). The annual increase in incidence rates differed significantly between the three age-groups (df = 3; $\chi^2$ = 24.28, $P <$ 0,001) and was the highest in the youngest age-group.

Figure 1 shows the incidence rates by age. There is a peak in puberty for both girls and boys, but the girls have a more pronounced decrease compared with boys in the older age span (12.5–15 years, $P$ = 0.0005). The difference between boys and girls in the older age span explained the significant interaction between age and sex seen in model 4.

Because not all counties were included in all three study periods, county was included in the model. No differences were observed between the counties included in all three study periods and the counties included only in the last period. The rate ratio between counties with the highest incidence and those with the lowest incidence was ~2, but none of the counties differed significantly from the

**Table 2—***Models fitted to data on type 1 diabetes incidence rates in Denmark in ages 0–15 years in the periods 1970–1976, 1980–1984, and 1996–1999*

| No. | Model | Model | | Last term | | |
|---|---|---|---|---|---|---|
| | | df | Deviance | df | LR-test | P |
| 0 | Null model | 7,559 | 4,971.0 | — | — | — |
| 1 | Age | 7,553 | 4,750.2 | 6 | 220.8 | <0.001 |
| 2 | Age + country | 7,539 | 4,702.5 | 14 | 47.7 | <0.001 |
| 3 | Age + country + sex | 7,538 | 4,699.8 | 1 | 2.7 | 0.10 |
| 4 | Age + country + sex + sex × age | 7,532 | 4,679.2 | 6 | 20.6 | 0.002 |
| 5A | Model 4* + period (linear) | 7,531 | 4,661.2 | 1 | 18.0 | <0.001 |
| 5B | Model 4* + cohort (linear) | 7,531 | 4,661.2 | 1 | 18.0 | <0.001 |
| 6A | Model 4* + period (nonlinear) | 7,526 | 4,649.6 | 5 | 11.6 | 0.041 |
| 6B | Model 4* + cohort (nonlinear) | 7,523 | 4,641.9 | 8 | 19.3 | 0.013 |
| 7 | Model 4* + cohort (nonlinear) + period | 7,518 | 4,636.1 | 5 | 5.8 | 0.33 |
| 8 | Model 4* + cohort (nonlinear) + cohort × age | 7,522 | 4,641.0 | 1 | 0.9 | 0.34 |
| 9 | Model 4* + cohort (nonlinear) + cohort × sex | 7,522 | 4,641.9 | 1 | 0.0 | 0.92 |

LR-test, likelihood ratio statistics, referring to the last term entered in the model. These are approximately $\chi^2$ distributed. *Age + county + sex + sex × age = model 4.

mean. None of the study periods showed differences between areas with high- and low-density population.

Although incidence data are missing for some calendar years, all birth cohorts from 1955 to 2000 are represented in this study. Each birth cohort from 1960 to 1996 is represented by at least 4 years of observation. There was a significant effect of birth cohort on the incidence of diabetes ($P < 0.013$), with the incidence increasing in children born after 1980 (Fig. 2). This effect of year of birth explains the steeper increase in incidence in the youngest age-groups compared with the older age-groups, as seen in Table 2. Inclusion of immigrants in the analysis did not alter the results substantially.

**CONCLUSIONS** — This study confirms that Denmark is a high-incidence area in Europe, with an overall incidence rate of childhood diabetes of 19.5 per 100,000. The rate is similar to those found in the neighboring countries of Norway, Sweden, and the U.K., but markedly lower than that in Finland (2).

The increase in incidence rates in the Danish population over the last 30 years in children (aged 0–14 years) of 1.2% is also in accordance with the finding of a global increase in this age-group. Onkamo et al. (2) found a 3.0% increase in this age-group but also a tendency to a steeper increase in low-incidence areas compared with high-incidence areas. The Eurodiab study (11) found an average annual increase in this age-group of 3.5%

per year, but the EuroDiab study covered the years 1989–1994 only. The high-increase rate is in concordance with results for the birth cohorts after 1985 in our study.

The trend was similar in boys and girls but differed between age-groups (0–4, 5–9, and 10–14 years). The greater relative increase in incidence in those under 5 years of age confirms observations from other European studies (11,12). In our data the steeper increase in the younger age-groups compared with the older age-group is explained by the significant cohort effect, since there is no interaction between age and cohort in a model including the effect of cohort (Table 2, model 8).

The finding of a cohort effect is contrary to other studies using the age-period-cohort model (13–16) but in accordance with a study covering a later period (17). This might indicate that there is a change in the risk factors causing the increased risk of childhood diabetes from factors affecting all age-groups to factors affecting special birth cohorts. Our data on the cohort effect in the oldest age-groups were sparse, and the coming years will reveal if the incidence rates show a continuous rise, as the model predicts. There was a significant period effect seen in the age-period model, but this effect disappeared in the model including cohort (Table 2, model 7), indicating that
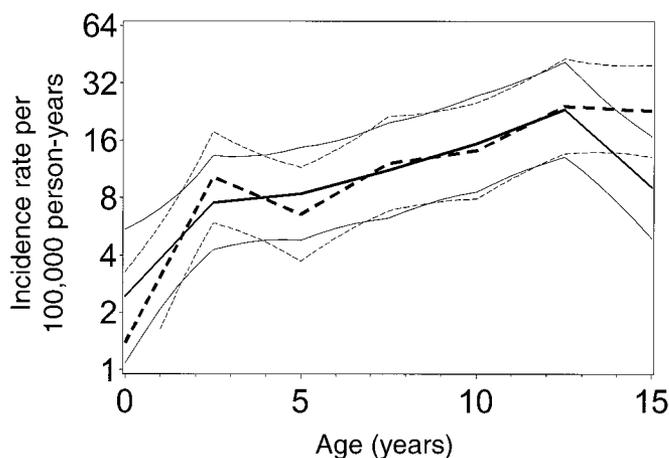


**Figure 1—***Age-specific incidence rates per 100,000 person-years of type 1 diabetes in Denmark for 1980 birth cohort, as estimated in model 6B. Solid line, girls; dotted lines, boys.*
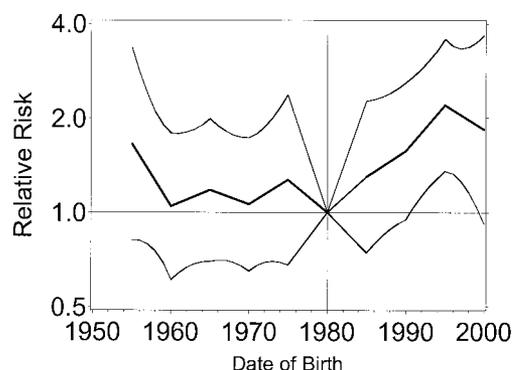
**Figure 2**—*RR by birth cohort, as estimated from model 6B, with 95% CI. 1980 is the reference year.*

the period effect can be attributed to a cohort effect.

The categorization of age differs between studies. In most studies of the incidence rates of childhood diabetes, data are divided into 5-year age-groups assuming the same incidence rates from 0–4, 5–9, and 10–14 years of age. Looking at the change in incidence by age (Fig. 1) with relatively large variation within these 5-year age-groups, this approximation might influence the results. In our study, age was stratified into 1-year age classes, and we used an age-period-cohort model allowing for linear changes within the age, period, and cohort spans to show that the rise in the youngest age-group is well explained by a cohort effect. Some age-groups are not represented in all birth cohorts. The assumption in the best-fitting model (6B) is that the cohort effect is similar in all age-groups. This assumption was tested by adding the interaction between age and cohort. Because the interaction term was insignificant, the assumption seems appropriate.

The data collected in all three study periods were based on local registration of cases of newly diagnosed diabetes, but since 1996 all incident cases have been reported to the National Childhood Diabetes Register. The older data were validated by questionnaires sent to outpatient clinics in the area. The ascertainment is high in all three study periods, so this cannot explain the cohort effect found in this study.

The background population in Denmark has changed from that of 1970–2000. The incidence of immigration is difficult to estimate; most immigrants in Denmark come from Turkey, Germany, Sweden, Norway, and Pakistan. To esti-mate the possible influence of this change, the age-period-cohort model was applied to the dataset including immigrants and offspring of immigrants; we still found an increasing trend and a significant cohort effect, indicating a limited effect of the change in population genetics.

Our analysis was based on data collected during three different periods from 1970 to 2000. Because the incidence of insulin-dependent diabetes varies substantially between years (13,18), this may cause methodological problems. If the incidence rates were especially low or high during the study periods not covered, they would alter the incidence rates and could even alter the effect from the birth cohorts. To address this problem, we studied incidence rates based on the National Discharge Register, a register independent of the Diabetes Register. We estimated the incidence rates of type 1 diabetes by year, age, and sex, based on the first registered hospitalization in the National Discharge Register. Using this method, we found that the rates in 1980–1984 did not differ from the rates in the years before or after. This indicates that the study periods covered in this study were representative.

The increase in incidence is too steep to be caused by shifts in the population gene pool due to improved survival of people with insulin-dependent diabetes. Therefore, environmental factors must be involved. Several known environmental risk factors have changed in Denmark over the last 30 years when related to birth cohorts, including birth weight (19) and maternal age (20–22), which might account for some of the cohort effects.

Breastfeeding is associated with a de-creased risk; breastfeeding until 3 months of age has increased in Denmark, from 18% in 1970 to 62% in 1990. If other environmental factors were responsible for the increasing incidence rates, the full effect of these factors could be diluted because of the beneficial effect of the changes in breastfeeding

## Conclusion

The incidence rates of type 1 diabetes in children in Denmark are increasing, with a significantly steeper increase in the youngest age-groups, attributable to an increased risk in birth cohorts born after 1980. This indicates that a future rise in incidence rates in the older age-groups can be expected, and environmental factors in early childhood may contribute to the increasing incidence rates.

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