

Increasing incidence of early onset Type 1 (insulin-dependent) diabetes mellitus: a study of Danish male birth cohorts

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Summary. To provide information of the incidence trends of Type 1 (insulin-dependent) diabetes mellitus we performed a cohort study of a series of Danish male birth cohorts. All male livebirths in Denmark between 1 January 1949 and 31 December 1964, were investigated regarding the development of Type 1 diabetes during the first 20 years of life using the files of the Danish Conscript Board, supplemented by a search in the Danish National Registry of Deaths. Diagnosis was verified and clinical information obtained from medical records. The material is estimated to be more than 95% complete. A total of 1705 diabetic subjects were identified of whom 23 were not representative of idiopathic Type 1 diabetes. The cumulative rate of Type 1 diabetes develop-

ment during the first 20 years of life increased from 2.37 to 2.90 per 1000 for the first eight and last eight birth cohorts, respectively. A log-linear analysis of the incidence revealed significantly increasing incidence rates, independent of age effects, with a maximum in the late 1970's. About 75% of the cases presented short duration of symptoms prior to diagnosis, and only very few cases were diagnosed incidentally. Cases were diagnosed relatively less frequently during summer months than during winter months.

Key words: Type 1 (insulin-dependent) diabetes mellitus, incidence, trends, seasonality, duration of symptoms.

The incidence of Type 1 (insulin-dependent) diabetes has been increasing at least in some parts of Europe during the last decades [1–8], occasionally with the character of an epidemic [9]. Furthermore, the incidence varies considerably throughout Europe [10–12]. These results strongly substantiate the existence of an environmental contribution to the aetiology of Type 1 diabetes [13]. We have previously demonstrated a gradual increase in Type 1 diabetes incidence among eight Danish male birth cohorts, observed with respect to the development of Type 1 diabetes during the first 20 years of life [3]. This analysis suggested that the increase in incidence plateaued during the mid-1970's. Because knowledge of incidence trends may provide clues to an understanding of the aetiology of Type 1 diabetes, we have extended the previously reported study to include a total of 16 male birth cohorts.

Subjects and methods

Ascertainment and verification of cases

According to the Danish constitution all male citizens must appear before a Conscript Board for a clinical examination and assessment prior to military or civil service. Subjects with a diagnosis of

diabetes will inevitably be rejected with diabetes listed as the reason. Normally, the examination takes place at age 18–19 years but may, upon request, be postponed to age 26 years at the latest. However, it has been shown that persons with chronic diseases such as diabetes tend to be examined on the earliest possible occasion [14]. For persons who develop diabetes after the Conscript Board Examination but before completing the military or civil service a re-examination is performed and the records are filed in the Conscript Registry. Accordingly, the registry provides data on patients with the diagnosis established up to age 20 years and in many instances higher ages.

From the files of the Danish National Conscript Registry we identified all males who were (1) born in Denmark between 1 January 1949 and 31 December 1964, and (2) were rejected by the Conscript Board due to a diagnosis of definite or possible diabetes. A supplementary search was performed in the Danish National Registry of Deaths to identify anyone from these birth cohorts who had died with diabetes being mentioned as a cause of death prior to Conscript Board examination.

For all cases hospital records were traced and scrutinized to verify and establish the time of diagnosis of diabetes; in three cases, this information was obtained from general practitioners. From the medical records, information was obtained on the duration of symptoms before diagnosis as well as on treatment and – whenever possible – conditions to which diabetes might be secondary.

As a diagnostic criterion for diabetes we required a clinical diagnosis of diabetes to be established by a physician. Patients treated permanently with insulin at latest 1 year after diagnosis and for

Table 1. Overview of the study material

	Cohort		
	1949–1956	1957–1964	Total
Liveborn males, <i>n</i>	320162	318556	638718
Initial study material	884	1031	1915
Exclusion criteria			
Not diabetes	28	42	70
Born outside Denmark	10	11	21
Diagnosed after age 20 years	77	42	119
Sub total	769	936	1705
Excluded from analysis			
Not permanent insulin treatment	7	8	15
Diabetes secondary to steroid treatment	1	3	4
Diabetes secondary to other conditions	2	2	4
Final study material	759	923	1682
Cumulative incidence (0–20 years), per 1000	2.37	2.90	2.63
1 SEM	0.09	0.10	0.06

Table 2. Regression analysis of incidence (log scale). Model: $\ln(\text{incidence}) = \text{constant} + \text{age effect} + \text{time effect}$

Variable	Estimated effect	Standard error
Constant	-11.497	0.577
Age		
0–3 years	(0)	–
4–7 years	0.361	0.102
8–11 years	0.413	0.106
12–15 years	0.690	0.109
16–19 years	0.283	0.121
Calendar time		
1949–1952	(0)	–
1953–1956	1.732	0.594
1957–1960	2.006	0.587
1961–1964	2.234	0.586
1965–1968	2.285	0.586
1969–1972	2.429	0.588
1973–1976	2.548	0.590
1977–1980	2.594	0.592
1981–1984	2.329	0.610

whom no mention was found in the medical records of diseases or conditions to which diabetes might be secondary were considered to be representative of idiopathic Type 1 diabetes.

The methods have been described previously [3, 14] for the first eight birth cohorts, and it has been estimated that this ascertainment method is more than 95 % complete [14].

Population data

Data on the number of liveborn males from the cohorts under study were obtained from official statistical reports (Danmarks Statistik). Also, it has been possible from these sources to assess the number of deaths and emigrations at each 1-year age level in the study population. After subtraction of all subjects who have emigrated before age 20 years we have estimated the number of person-years at risk of diabetes for various age and calendar time intervals [15]. This was done to outweigh the omission of diabetic individuals who might have emigrated before the age of conscription.

Statistical analysis

The incidence was analysed in a log-linear model [16] using the GENSTAT programming language [17] to study the effects of age and calendar time. The analysis assumes constant incidences within cells of age and calendar time intervals of 4-year lengths. The full model including all possible interaction terms between age and calendar time was reduced to a model with only main effects of age and time using the likelihood ratio test statistic. Subsequently, seasonality of diagnosis and symptom duration were also included in the analysis, and the distribution of seasonality and symptom duration within age intervals were analysed by conventional chi-square statistics (based on the log-linear models).

Results

Overview of the study material

The initial search in the files of the Conscript Board identified a total of 1915 potential study individuals (Table 1). A total of 210 persons were excluded; 119 had diabetes diagnosed later than the 20th birthday, 21 were born outside Denmark, and 70 persons suffered from other diseases (renal glucosuria, malabsorption or other metabolic diseases belonging to the same category of rejection as diabetes). After reduction by cases not fulfilling the inclusion criteria 1705 subjects remained. However, 23 cases have been excluded from analysis since they are probably not representative of idiopathic Type 1 diabetes; the four cases believed to be secondary to other conditions represented congenital pancreas aplasia (one case), pancreatitis (two cases) and cystic fibrosis (one case). Of the remaining 1682 patients, 30 were identified exclusively from the Danish National Registry of Deaths.

Table 1 also shows the cumulative incidence rates, which can be interpreted as the risk of developing Type 1 diabetes from birth to age 20 years. It should be noted, however, that these estimates do not account for possible incidence variations over calendar time.

Regression analysis of the Type 1 diabetes incidence

In the log-linear regression analysis of the Type 1 diabetes incidence we first tested the hypothesis of reduction from the full model (including interactions between age and calendar time) to a model with independent effects of age and calendar time. This was clearly accepted, the likelihood ratio test statistic being 6.59 ($p = 0.88$ when evaluated in a chi-square distribution with 12 degrees of freedom^{df}). Further reduction was not possible. The estimated effects of calendar time and age in the final model are shown in Table 2; for example, the incidence for 12–15-year-old subjects during the period 1973–1976 is estimated as $\exp(-11.497 + 0.690 + 2.548) = 25.9$ per 100,000 person-years.

The resulting estimates of the incidences according to age intervals and calendar time are shown in Figure 1. On the natural scale, the estimated effects of calendar time demonstrates that the incidence of Type 1 diabetes doubled from the beginning of the 1950's during the next 30 years.

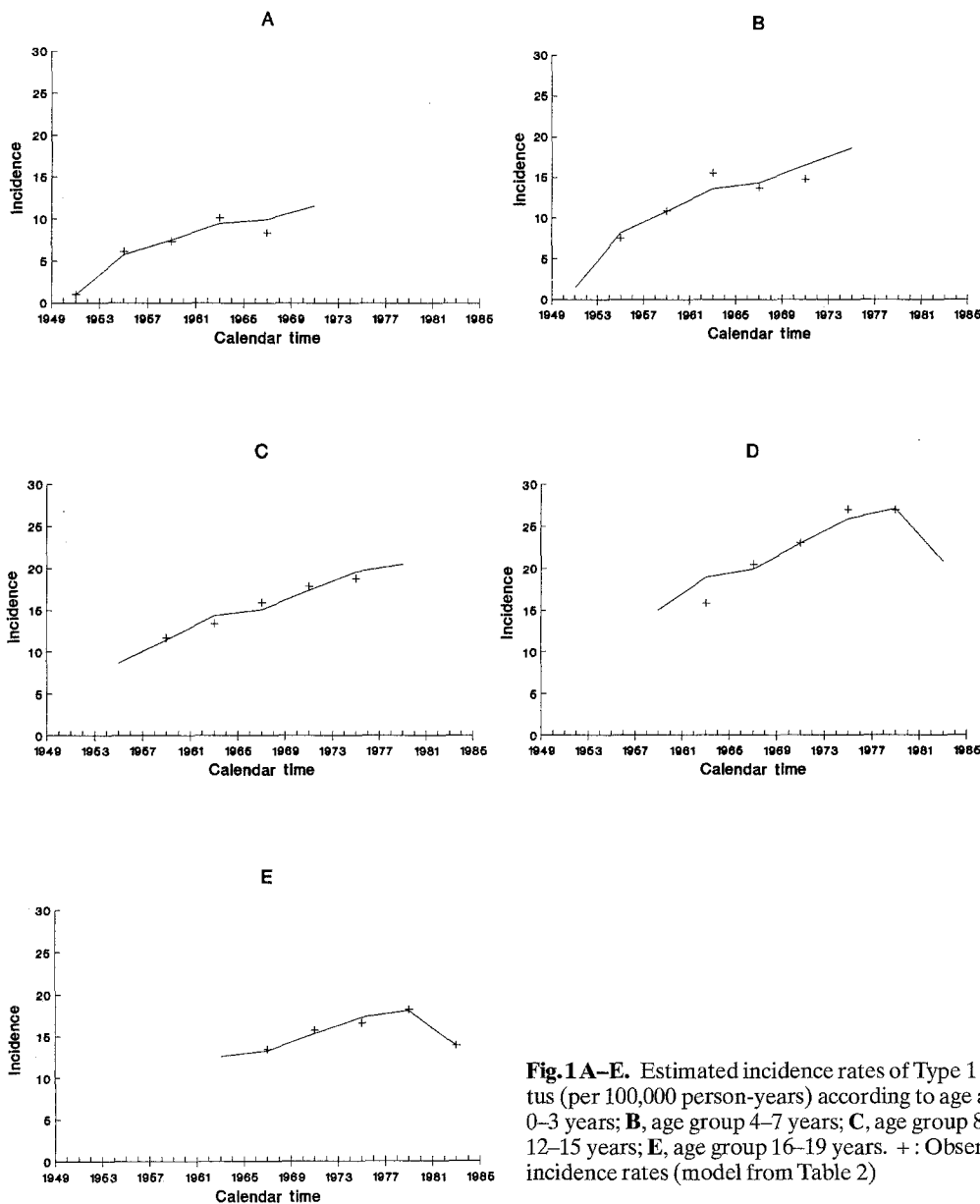


Fig. 1 A-E. Estimated incidence rates of Type 1 (insulin-dependent) diabetes mellitus (per 100,000 person-years) according to age and calendar time. **A**, age group 0-3 years; **B**, age group 4-7 years; **C**, age group 8-11 years; **D**, age group 12-15 years; **E**, age group 16-19 years. + : Observed incidence rates; —: Estimated incidence rates (model from Table 2)

Analysis of seasonal variation at diagnosis

The distribution of seasonality at diagnosis of Type 1 diabetes is shown in Table 3, specified according to age at diagnosis. The distribution of seasonality differed between the four age groups by borderline statistical significance only (chi-square: 15.36, $df = 9$, $p = 0.08$). However, whereas the youngest age groups revealed no statistically significant seasonal variation, when analysed separately both the age groups 10-14 and 15-19 years showed significant variations with relatively fewer cases diagnosed during summer ($p < 0.00001$ and $p < 0.025$, respectively).

Analysis of symptom duration

The association between duration of symptoms prior to the establishment of diagnosis and age at diagnosis is shown in Table 4. Overall, 21.4% of the cases had symp-

toms for more than 2 months whereas only 2.8% had no symptoms at all; these cases were typically detected during routine urine examinations. The distribution of symptom duration varied significantly by age group (chi-square: 19.21, $df = 6$, $p < 0.005$), the significance being caused by relatively more cases with short duration (84.5%) in the youngest age group.

Discussion

Our study has confirmed that the incidence of early onset Type 1 diabetes in Denmark is relatively high, compared with other regions in Europe [10-12]. Furthermore, we have found that in most cases the onset of diabetes is preceded by a short period with symptoms when assessed from routinely recorded data in the medical records; in only 1-2% of the patients was the diagnosis established by

Table 3. Seasonality of diagnosis of diabetes by age

Season	Age at diagnosis (years)									
	0-4		5-9		10-14		15-19		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
December-February	46	21.4	100	25.3	175	30.2	136	28.6	457	27.4
March-May	49	22.8	97	24.6	144	24.9	128	26.9	418	25.1
June-August	55	25.6	88	22.3	98	16.9	93	19.5	334	20.1
September-November	65	30.2	110	27.8	162	28.0	119	25.0	456	27.4
Unknown	5		7		4		1		17	
Total	220		402		583		477		1682	

Table 4. Distribution of symptom duration

Duration of symptoms	Age at diagnosis (years)									
	0-4		5-9		10-14		15-19		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
2 months or more	28	13.5	87	22.3	124	21.8	111	23.7	350	21.4
Less than 2 months	175	84.5	300	76.7	428	75.1	337	72.0	1240	75.8
No symptoms	4	1.9	4	1.0	18	3.2	20	4.3	46	2.8
Sub total	207		391		570		468		1636	
Unknown	13		11		13		9		46	

routine examination without clinical symptoms. We found that the diagnosis of Type 1 diabetes was established relatively more frequently in winterly than in summer, confirming results from other studies [4, 7, 18-29]. It remains to be determined whether the seasonal variation reflects higher probability of precipitation of clinical disease among susceptible individuals or whether the patients and their families are more alert to symptoms during the dark months.

The principal aims of our study were to characterize the secular trend in the incidence of Type 1 diabetes. In the analysis of the first part of these cohorts we found a curvilinear increasing trend in the Type 1 diabetes incidence with a possible plateau about the mid-1970's. This trend has been confirmed in the extended study even though it was impossible to describe the calendar time effect by a simple equation. Nevertheless, the calendar time effects clearly demonstrate that the incidence apparently reached a maximum in the late 1970's. Furthermore, our analysis has suggested that the calendar time effects apply equally to all age groups studied.

Because the present study material is delineated as a classic cohort it is impossible to determine whether the calendar time effects might be confounded by particular cohort effects. However, recent studies from Sweden [6] and Finland [8] have investigated this aspect and found no evidence of cohort effects. Both studies also identified a gradually increasing incidence without any interaction between age and calendar time, and with similar trends for both sexes. Accordingly, even though the present study has been restricted by design to males, our conclusions can probably be generalised for females as well.

The causation of the increasing trend in Type 1 diabetes incidence is unknown. Possibly, the incidence increase might be explained by increasing number of genes conferring susceptibility to Type 1 diabetes in the popula-

tions in which Type 1 diabetic patients have improved survival [30] and therefore possibly also improved reproductive capacity. This explanation is unlikely for several reasons. First, the most simple genetic models of the HLA-conferred susceptibility to Type 1 diabetes involve a disease gene with high frequency and low penetrance, implying that most gene carriers are unaffected heterozygotes [31]. Second, even in "high risk" populations, only about 10% of newly-diagnosed children with Type 1 diabetes have affected mothers or fathers [32], implying that most cases are offspring of healthy individuals. Accordingly, the additional susceptibility genes, introduced because of improved fertility and survival among patients with Type 1 diabetes, must have represented only a small and probably insignificant contribution to the pool of susceptibility genes.

No likely candidates of aetiologically important factors in the environment have so far been identified with certainty. However, the existence of both an increasing trend in incidence and of a ten-fold difference between lowest and highest recorded incidence in Europe [12] illustrates the potential value of comparative case-control studies across populations to identify the environmental determinants of Type 1 diabetes.

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