Original Article

Differential Transmission of Type 1 Diabetes from Diabetic Fathers and Mothers to Their Offspring

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We studied the incidence of type 1 diabetes in the offspring of patients with childhood- and adolescent-onset type 1 diabetes and several risk factors predicting the risk. We defined the diabetes status in the offspring of all probands who were included in the nationwide register of Finnish type 1 diabetic patients diagnosed at the age of ≤17 years from 1965 to 1979. A total of 5,291 offspring at risk contributed 72,220 person-years of follow-up between 1970 and 2003. Of them, 259 offspring developed type 1 diabetes by the end of 2003, giving a cumulative incidence of 6.7% (95% CI 5.9–7.5) by the age of 20 years. The incidence of type 1 diabetes in the offspring between the years 1980 and 2003 was 35.3, 44.6, and 44.6 per 10,000 person-years for the age-groups 0–4, 5–9, and 10–14 years, respectively. Poisson regression analyses showed a marked increase in incidence of 5.3% per year from 1983 to 2003. The greatest increase occurred in the youngest offspring, aged 0–4 years. Of the offspring of male probands, 7.8% were affected by the age of 20 years compared with 5.3% of the offspring of female probands (relative risk 1.7 [95% CI 1.3–2.2]). The young age at onset of diabetes increased the risk of type 1 diabetes in the offspring of diabetic fathers but not in the offspring of diabetic mothers. In conclusion, our findings revealed that in the offspring of type 1 diabetic patients, the increase in the recurrence risk of type 1 diabetes was not more rapid compared with that in the background population. In the multivariate analyses, statistically significant predictors of type 1 diabetes in the offspring were male sex of the diabetic parent, young age at diagnosis in the male parent, and the more recent year of birth of the offspring. *Diabetes* 55:1517–1524, 2006

The incidence of childhood type 1 diabetes has increased globally over the past decades (1,2). The risk of type 1 diabetes in the offspring of diabetic parents by the age of 20 years is ~4–5%, depending on the population where the studies have been conducted and differences in the study design (3–7). It has been suggested that the increase in the incidence of type 1 diabetes has been more rapid in the offspring of type 1 diabetic patients than in the background population (3).

The sex difference in the recurrence risk of type 1 diabetes has been detected by a number of studies: the offspring of the fathers who were affected with type 1 diabetes have an increased risk for type 1 diabetes compared with the offspring of affected mothers (3,4,6,8). Preferential cross-sex transmission has also been detected by some studies (3,9) but not by others (4,8).

Large, population-based studies with optimal study design are sparse where the ascertainment of offspring is through diabetic parents and complete. Our aim was to assess the recurrence risk of type 1 diabetes in the offspring of a Finnish population-based cohort of patients with childhood- and adolescence-onset type 1 diabetes. We also investigated possible sex-related effects in the transmission of type 1 diabetes from the diabetic parents to their offspring. In addition, we were able to study temporal trends in the incidence during 1970–2003 and characterize several variables that might have influenced the recurrence risk of type 1 diabetes in the offspring.

RESEARCH DESIGN AND METHODS

We defined the diabetes status of all offspring of all probands who are included in the nationwide register of Finnish cases with type 1 diabetes diagnosed before age of 18 years between 1965 and 1979 (n = 5,144). The cohort was originally used in the Diabetes Epidemiology Research International (DERI) mortality study (10,11). Briefly, the register was initially based on the central drug register (CDR) of the Social Insurance Institution, including patients approved to receive free-of-charge medication for certain diseases including diabetes. The case ascertainment in this cohort was virtually complete (12,13). Their offspring and the other parent of the offspring were identified through the national population register by computer linkage using the unique personal identifier that is assigned to all residents of Finland. The offspring were mainly born between 1970 and 2001, only four of them before 1970. The diabetes status of the offspring was ascertained through several sources: from the nationwide Hospital Discharge Register for years 1970–2003, from the nationwide Finnish Diabetes Register for children and young adults, and from the CDR through the record linkage using the personal identifier. The date of the diagnosis of diabetes was defined as the date of the first hospital admission due to diabetes or the approval date for free-of-charge insulin for diabetes, whichever was earlier. Practically all children with newly diagnosed diabetes are hospitalized in Finland (14). By the end of the year 2001, there were 5,291 offspring born to original DERI probands, 2,297 (43.4%) to the female probands, and 2,981 (56.4%) to the male probands, and 13 offspring had both parents as probands in the original DERI cohort. In total, 58 (1.1%) offspring had both parents with type 1 diabetes. By the end of the year 2003, a total of 259 (4.9%) offspring were affected with type 1 diabetes.

Statistical methods

Follow-up started at birth and ended at the diagnosis of type 1 diabetes, death, or the end of the year 2003. The cases and person-years at risk were split by age and calendar time (period) in 1-year classes. Poisson regression analysis was used to evaluate temporal trends in incidence. The change in incidence rates during the study period was also analyzed separately for the age-groups 0–4, 5–9, and 10–14 years. Standardized incidence ratios (SIRs) of type 1 diabetes were calculated to determine the increase in

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CDR, central drug register; DERI, Diabetes Epidemiology Research International; SIR, standardized incidence ratio.

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the risk of type 1 diabetes in the offspring of the type 1 diabetic parents compared with that in the background population for the period 1985–2003 for each of 5-year periods. The expected numbers of cases were derived by applying the age-specific incidence rates for ages 0–4, 5–9, and 10–14 years of type 1 diabetes observed at the same time in the background population, i.e., in Finland nationwide. The data on the newly diagnosed type 1 diabetes cases nationwide were derived from the CDR.

In all the analyses addressing the question of the transmission of type 1 diabetes from a diabetic parent to the offspring, all families with both parents with type 1 diabetes were excluded. Kaplan-Meier analysis was used to estimate the cumulative incidence of type 1 diabetes. The analyses were also carried out stratifying the data by the age at diagnosis of type 1 diabetes in the parent and the birth year of the offspring, separately in the offspring of type 1 diabetic fathers and mothers. The cumulative incidence is always presented up to the age of 20 years when the estimates were stable enough; otherwise the determination of the cumulative incidence was finished at an earlier age.

To assess the effect of several independent risk factors on the risk of type 1 diabetes among the offspring, univariate and multivariate regression analyses of the data were performed using the Cox proportional hazards modeling. The assumptions of proportional hazards were confirmed graphically by plotting the log cumulative hazard function over time and checking the parallelism of the curves. All proportionality assumptions were found appropriate. Model fitting was conducted to the data comprising all families and separately by the sex of the diabetic parent. Interaction between the sex of the type 1 diabetic parent and other variables was tested for. In addition to the sex of the type 1 diabetic parent, the predictors studied were the sex of the offspring, year of birth of the offspring, age at diagnosis of the parent, the parental age at delivery, and birth order. The offspring were categorized according to the age at onset of diabetes in the type 1 diabetic parent: 0–4, 5–9, 10–14, and 15–17 years. The birth year, i.e., the period, was categorized as follows: 1984 or earlier, 1985–89, 1990–1994, and 1995 or after. Maternal and paternal ages at delivery were categorized into: ≤24, 25–29, and ≥30 years. The reason for the limited number of groups of the age at delivery was that the number of the offspring in the age-group ≥35 years was limited, and the mean duration of the follow-up in this group was only 7.5 years. Birth order was defined as first, second, and third or higher born.

A possible problem of colinearity among the variables was evaluated using condition indexes before multivariate modeling. A condition index value >15 indicates potential colinearity problems. Indicator variables were created for the subcategories of variables and included in the model to test nonlinearity of those variables. If the statistical significance was not reached for a categorized variable, the association for the variable was tested as a continuous one to find out if the effect of the variable was linear and because the categorizing of a continuous variable usually increases the error term and consequently reduces the power to detect true effects.

In stage 1, univariate analyses were used to identify variables individually predictive of the development of type 1 diabetes. Those found to be statistically significant at the 5% level were then fitted in the multivariate model (stage 2). A variable that was statistically the least significant one at each step was then successively excluded. This procedure was continued until the exclusion of any variable that would have resulted in a significant change in model fit ($P < 0.05$, as defined by the change in −2logL). Variables excluded after stage 1 were then added to the multivariate model to assess whether they, in the presence of the other significant variables, contributed significantly to the model. Finally, interaction terms between the sex of the type 1 diabetic parent and other variables included in the multivariate model were tested. Because we found interaction between the age at onset of diabetes in the parent and the sex of the type 1 diabetic parent, risk ratios were estimated separately by the sex of the type 1 diabetic parent.

RESULTS

Of the 5,144 probands, 2,369 had no children; the rest of the 2,775 probands had 5,291 children. More female probands (57.7%) than male probands (50.9%) had children. On average, female probands had 1.0 ± 1.05 and male probands 1.1 ± 1.27 children. In male probands with progeny, the average number of offspring was 2.1 ± 1.02 compared with 1.7 ± 0.82 in female probands (Table 1). A total of 61 (1.15%) offspring were deceased before reaching the age of 1 year. The death rate during the 1st year of life among the children of type 1 diabetic women was 19.6/1,000 (95% CI 13.9–25.6), which was 2.4 times higher than that of the Finnish background population (8.1/1,000) (15). Among the offspring of type 1 diabetic men, it was much lower (5.4/1,000 [3.1–8.7]) than in type 1 diabetic women and not different from that expected in the population.

During 72,220 person-years of observation, 259 offspring, 121 girls and 138 boys, were affected with type 1 diabetes by the end of the year 2003, of which 236 were diagnosed at the age of ≤14 years. Of the 58 (22.4%) offspring who have both parents with diabetes, 13 were affected. The first cases of type 1 diabetes occurred in the year 1983; no cases were seen during 1970–1982. During this period, 971 offspring were born. Table 2 lists the incidence per year and age-groups. The overall incidence in all offspring of one or both parents with type 1 diabetes in the age-group of ≤14 years was 40.8 per 10,000 person-years (95% CI 35.7–46.3) during 1980–2003. It was 40.0 (33.0–48.1) in girls and 41.5 (34.4–49.5) in boys. The incidence was equal in the offspring aged 5–9 and 10–14 years (44.6), but in the age-group 0–4 years it tended to be somewhat lower (35.3). However, during 2000–2003 the

TABLE 1
Descriptive data of the study population

Characteristics	Female proband	Male proband	All probands
Number of probands	2,313	2,831	5,144
Number of probands with offspring	1,335 (57.7%)	1,440 (50.9%)	2,775 (53.9%)
Number of offspring	2,310	2,994	5,291 (13)*
Girls	1,157	1,444	2,595 (6)*
Boys	1,153	1,550	2,696 (7)*
Year of birth of the offspring			
<1970	3	1	4
1970–79	253	269	522
1980–89	906	1,124	2,028 (2)*
1990–99	1,032	1,416	2,438 (10)*
2000–01	116	184	299 (1)*
Offspring with diabetes	86 (3.7%)	177 (5.9%)	259 (4)*
Girls	36 (3.1%)	87 (6.0%)	121 (2)*
Boys	50 (4.3%)	90 (5.8%)	138 (2)*

*Both parents belonging to the original DERI cohort, and probands are shown in parentheses.

TABLE 2
Age-group– and time period–specific incidence of type 1 diabetes in the offspring per 10,000 person-years

Age (years)	Year						Annual increase (%)	Trend test (*P*)
	1980–1984	1985–1989	1990–1994	1995–1999	2000–2003	1980–2003		
0–4	—	18.0	41.3	42.0	69.1	35.3	7.3	<0.001
5–9	40.8	26.9	38.6	48.9	57.1	44.6	4.7	0.04
10–14	—	41.8	34.0	52.0	46.5	44.6	1.7	0.5
0–14	11.3	24.0	38.9	47.3	56.3	40.8	5.3	<0.001

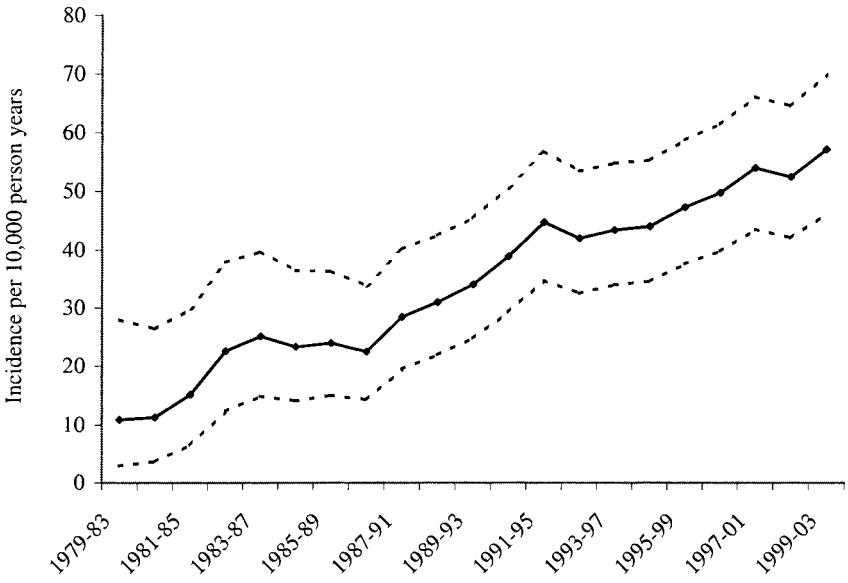

FIG. 1. Five-year moving averages of the incidence of type 1 diabetes per 10,000 person-years in the offspring of type 1 diabetic parents. The age of diagnosis of type 1 diabetes was age ≤14 years. Dotted lines represent 95% CIs.

incidence of type 1 diabetes in the offspring aged 0–4 years (69.1) exceeded the incidence in the 5–9 years age-group (57.1).

Figure 1 shows the time trend in the incidence of all age-groups combined. During 1980–2003 the overall incidence of type 1 diabetes in the offspring showed an average increase of 5.3% ($P < 0.001$) per year. In the offspring aged 0–4 years at diagnosis the annual increase was 7.3% ($P < 0.001$), while in the offspring aged 5–9 and 10–14 years it was 4.7 ($P = 0.04$) and 1.7% ($P = 0.5$), respectively (Table 2).

The offspring of patients with type 1 diabetes had an ~10-fold excess risk compared with the type 1 diabetes incidence in the general population of Finland. SIRs in 5-year time periods were 9.7 (95% CI 8.5–11.0) during 1985–2003. In the first period, during 1985–1989, it was 7.6 (4.9–11.3) and remained fairly stable during the subsequent years.

In all offspring with one type 1 diabetic parent, the overall cumulative incidence to develop type 1 diabetes by the age of 15 years was 5.6% (95% CI 4.9–6.4) and by the age of 20 years, 6.7% (5.9–7.5). It took on average 17.5, 10.1, 9.2, and 6.8 years for the offspring born in 1985 or before, 1985–1989, 1990–1994, and 1995 or later, respectively, to reach a 4% cumulative incidence of type 1 diabetes (data not shown). Of the offspring of type 1 diabetic fathers born in 1995 or after, 4.2% (2.8–5.6) had developed diabetes by age of 5 years (Fig. 2*A*), whereas only 1.5% (0.5–2.5) of those of type 1 diabetic mothers had developed diabetes (Fig. 2*B*). Each 5-year increase in the birth year until the year 1995 enhanced the risk in the offspring of type 1 diabetic mothers, whereas the offspring of type 1 diabetic fathers born between 1985 and 1989 and between 1990 and 1994 had equal cumulative risk of type 1 diabetes (Fig. 2).

In the univariate Cox regression analysis, in addition to the sex of the type 1 diabetic parent, the age at onset of type 1 diabetes in parent and the year of birth were the most significant predictors of type 1 diabetes in offspring. Also, maternal and paternal age at delivery and birth order were associated in the risk of type 1 diabetes in offspring (Table 3). When the variable selection to the multivariate model was done, only sex of the type 1 diabetic parent, the age at onset of type 1 diabetes in the parent, interaction between them, and the year of birth of the offspring were statistically significant. There was a sex difference in the probability of the parent-offspring transmission of type 1 diabetes. Diabetic fathers were more likely than diabetic mothers to transmit type 1 diabetes to their offspring. Of the offspring of the male probands, 7.8% were affected by 20 years of age compared with 5.3% of the offspring of the female probands (relative risk [RR] 1.7 [95% CI 1.3–2.2], $P < 0.0001$). This excess risk in the offspring of male fathers manifested itself through the higher risk for fathers who were young when diagnosed with type 1 diabetes. The risk of type 1 diabetes in the offspring was especially high when the father had been diagnosed at the age ≤4 years: 11.0% (6.6–15.3) of the offspring became affected during their first 10 years of life (Fig. 3*A*). The corresponding relative risk was 2.66 (1.48–4.79) compared with the offspring of fathers diagnosed at the age of ≥15 years. RR for the offspring of fathers affected at 5–9 and 10–14 years of age was 1.45 (0.90–2.33) and 1.17 (0.77–1.79), respectively (Table 4). A young age at onset of type 1 diabetes in diabetic mothers did not increase the risk of type 1 diabetes in the offspring (Fig. 3*B*, Table 4).

The interaction between the sex of type 1 diabetic parent and the age at diagnosis of diabetes can also be presented differently: the RR of type 1 diabetes for the offspring of type 1 diabetic fathers compared with that of type 1 diabetic mothers was the highest when the age at diagnosis in the parent was ≤5 years (RR 4.3 [$P = 0.002$]). Thereafter, when the age decreased the risk ratio lowered progressively being 1.9 ($P = 0.01$) and 1.5 ($P = 0.04$) for the age-groups 5–9 and 10–14 years, respectively. At the age-group 15–17 years, no statistically significant sex difference existed (RR 1.2, $P = 0.58$).

The interaction term was not statistically significant between the sex of type 1 diabetic parents and the sex of the offspring. However, the sons of female probands had a borderline significantly higher risk of type 1 diabetes than that the daughters (RR 1.55, $P = 0.06$), whereas no difference was found in the risk of type 1 diabetes between sons and daughters of the male probands (RR 0.96, $P = 0.78$) (Table 5). Six of seven

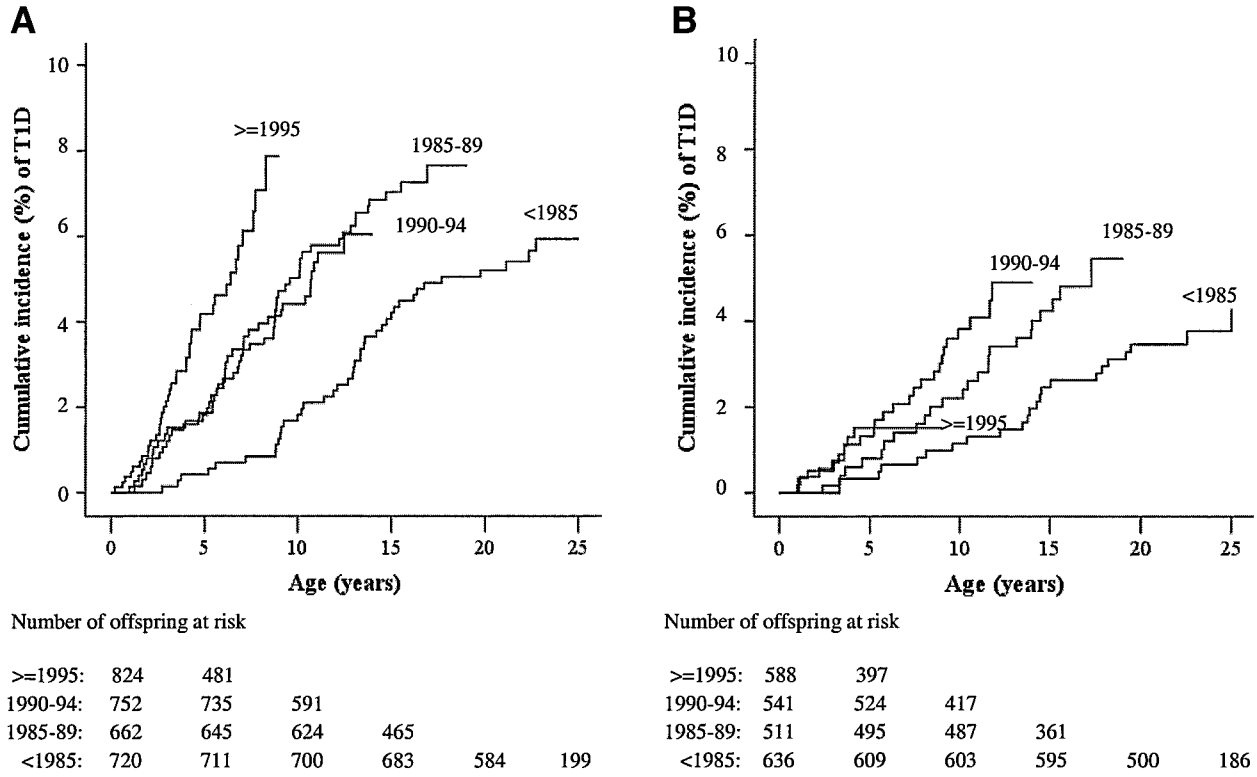

FIG. 2. Cumulative incidence of type 1 diabetes in the offspring of childhood-onset type 1 diabetic fathers (*A*) and mothers (*B*) according to the year of birth of the offspring.

affected offspring of the type 1 diabetic mothers diagnosed at ≤4 years were boys.

Univariate analyses showed that the impact of both maternal and paternal age at delivery began to increase after the age of 30 years (Table 3). The effect of maternal age was statistically significant only when the mother was diabetic, and the risk increased linearly by 6% (95% CI 1–11%) for each increasing year at delivery (Table 5). Neither reached the paternal age at delivery statistical significance when the father was diabetic, but, however, there was light increase after the age of 30. Instead, increasing paternal age at delivery enhanced the risk of type 1 diabetes in the offspring of type 1 diabetic mothers. Although the significant effects of the parental age at delivery were seen in the univariate analysis, they were not statistically significant in the multivariate model. Neither was the birth-order effect.

DISCUSSION

We have collected thus far unique information about the development of type 1 diabetes in the offspring of a large population-based cohort of probands with childhood-onset type 1 diabetes in the country where the incidence of the disease is highest in the world (2). This study had an optimal study design to avoid ascertainment bias, which has been a common problem with most of the previous studies. Our approach was to ascertain the study families through the diabetic parents, not through the affected offspring. The cumulative risk of type 1 diabetes in the offspring of the parents with type 1 diabetes was 6.7% by age 20 years. It is higher than reported by earlier studies, most of them not being population-based (3,4,6,8,16). The fact that Finland has the highest incidence of childhood-onset type 1 diabetes in the world (2) may be reflected also in the risk in the offspring of parents with type 1 diabetes. Such a correlation between the incidence of type 1 diabetes in the population and prevalence of type 1 diabetes in the first-degree relatives at the time of diagnosis of the diabetic child was seen in the EURODIAB family study (17).

Our study confirmed the repeatedly shown phenomenon that men with type 1 diabetes are more likely to transmit diabetes to their offspring than women with type 1 diabetes. The risk of type 1 diabetes in the offspring of the type 1 diabetic fathers was 1.7 times higher than that in the offspring of the type 1 diabetic mothers. In addition, daughters of female type 1 diabetic probands had some reduced risk to be affected compared with sons.

Guo and Tuomilehto (18) have described many bias-causing factors that can lead to an apparent preferential transmission, for example misclassification of gestational diabetes as type 1 diabetes, coupled with a fecundity difference between two sexes and the birth-order effect. In this study we avoided those sources of bias. First, we ascertained the recurrence risk through parents with type 1 diabetes and not through offspring. Moreover, both the cohort of type 1 diabetic parents and their offspring had a virtually complete case ascertainment. Second, a reduction of fecundity in diabetic females was only 5.6% as compared with men, but there was a difference in infant mortality between type 1 diabetic men and women. The predicted ratio of type 1 diabetes incidence in the offspring born to type 1 diabetic fathers and mothers taking into account differences of fecundity between sexes and a possible birth-order effect (18) would be only 1.006; meanwhile, the observed ratio was substantially higher (1.7). Third, there was no significant birth-order effect. Finally,

TABLE 3
Univariate Cox regression analysis for the factors influencing the risk for type 1 diabetes in all offspring of one parent with type 1 diabetes

Variable	RR (95% CI)	*P* value
Male sex of offspring vs female sex	1.12 (0.87–1.44)	0.37
Male sex of the type 1 diabetic parent vs. female sex	1.70 (1.30–2.23)	<0.0001
Year of birth		
<1985	1.00 (—)	
1985–89	1.70 (1.19–2.43)	
1990–94	2.08 (1.41–3.05)	
≥1995	3.39 (2.19–5.26)	<0.0001
Birth order		
First	1.00 (—)	
Second	0.97 (0.73–1.29)	
Third or higher	1.51 (1.06–2.12)	0.05
Mother's age at delivery (years)		
<25	1.00 (—)	
25–29	1.02 (0.76–1.38)	
≥30	1.51 (1.09–2.08)	0.02
Mother's age at delivery (continuous)	1.03 (1.00–1.06)	0.05
Father's age at delivery (years)		
<25	1.00 (—)	
25–29	1.15 (0.82–1.62)	
≥30	1.46 (1.04–2.05)	0.07
Father's age at delivery (continuous)	1.03 (1.00–1.05)	0.03
Parent's age at onset of diabetes (years)		
0–4	2.21 (1.37–3.58)	
5–9	1.50 (1.03–2.19)	
10–14	1.17 (0.83–1.65)	
15–17	1.00 (—)	0.005

there was no misclassification of mothers with gestational diabetes: all probands have been diagnosed with type 1 diabetes at the age of ≤17 years. This study clearly shows that there must be other reasons than bias behind the observed sex-related preferential transmission of type 1 diabetes. Though with this observational study we cannot explain the reasons for this, we can show the existence of the preferential transmission.

The effect of the parental age at onset of diabetes has been previously reported, but only few studies have distinguished this between maternal and paternal effects (4,6,19). We found that the risk of type 1 diabetes in the offspring was associated with the paternal but not with maternal age at onset of diabetes. The younger the age at onset of diabetes in the type 1 diabetic father the greater the risk of type 1 diabetes was in the offspring of type 1 diabetic fathers. The risk was 2.7 times higher if the diabetic father had been diagnosed at the age of ≤4 years compared with the risk in the offspring of fathers whose diabetes was diagnosed at the age of 15–17 years. This pattern was not seen in the offspring of diabetic mothers. Conversely, the offspring born to mothers who were diagnosed with type 1 diabetes at ≤4 years had the lowest recurrence risk, and in this age-group there was almost complete absence of affected daughters. Predominance of the affected sons may be due to chance, but any mechanism leading to this must be properly addressed in future studies. The quality of the data and the power of an observational study in another population with a lower incidence of type 1 diabetes might, however, cause certain difficulties in confirming these results.

There are some, though only few, earlier observations that paternal but not maternal age at onset of diabetes has an impact on the recurrence risk of diabetes in their children (4,6). Observations from the Joslin Diabetes Clinic reported that the 20-year recurrence risk of type 1 diabetes in the offspring was 9.3% if the father had been diagnosed with type 1 diabetes under the age of 11, compared with 4% of the others. Also an increased risk of type 1 diabetes in the offspring of mothers with younger onset diabetes was observed, but among them the sex-difference for the risk in the offspring did not reach a level of statistical significance (6). The phenomenon was previously seen only in a Danish study that reported an over twofold increased risk of type 1 diabetes in the offspring of fathers diagnosed before the age of 17 years compared with that of older ages, but no such relation was found in the maternal offspring (4). However, another study conducted in the Joslin Diabetes Clinic reported contrary results: the mothers who developed diabetes before age 8 years transmitted diabetes at the same rate as fathers who had type 1 diabetes (7).

The observed sex difference in the type 1 diabetes transmission can be partly explained by a decreased transmission rate in mothers who have been diagnosed with diabetes at a very young age, but the mechanism that might be responsible for this remains unclear. Several hypotheses can be proposed. The rate of miscarriage among diabetic women is higher than that among the general population, reported to be 15–30% (20–23). Selective loss of fetuses bearing type 1 diabetes susceptibility genes in women with diabetes could appear in a lower prevalence of type 1 diabetes in the offspring of women than men. An early age at onset of type 1 diabetes has been found to be associated with certain HLA haplotypes. Those high-risk HLA haplotypes were found more frequently in type 1 diabetic children diagnosed under the age of 5 years than in those diagnosed when older (24,25). One study, which included early spontaneous abortions using a sensitive β-chain human chorionic gonadotropin radioimmunoassay for the detection of pregnancy before clinical detection, reported that the age at onset of diabetes is associated with the risk of spontaneous abortions (20). The rate of spontaneous abortions was the highest, 45%, if mother's "White class" was D, where the age at onset of diabetes is ≤10 years. It might be possible that fetuses bearing high-risk HLA haplotypes associated with early-onset diabetes are more frequently lost in mothers than in fathers carrying type 1 diabetes susceptibility HLA haplotypes. This is only speculative at the moment. The main reason for the spontaneous abortions in diabetic patients has been detected to be hyperglycemia at conception and early pregnancy (26,27). More studies are needed to evaluate the outcome of diabetic pregnancies in their early stage, in particular, because two-thirds of all fetal losses seem to occur before the clinical detection of pregnancy (28).

Other possible explanations for the observed preferential transmission have been put forward, such as protective environment of diabetic mothers during pregnancy or fathers' facility to transfer disease susceptibility genes in higher frequency, but so far they have remained controversial and not proven (8,29).

One of the main highlights of this study was that although the increase in incidence of type 1 diabetes in the

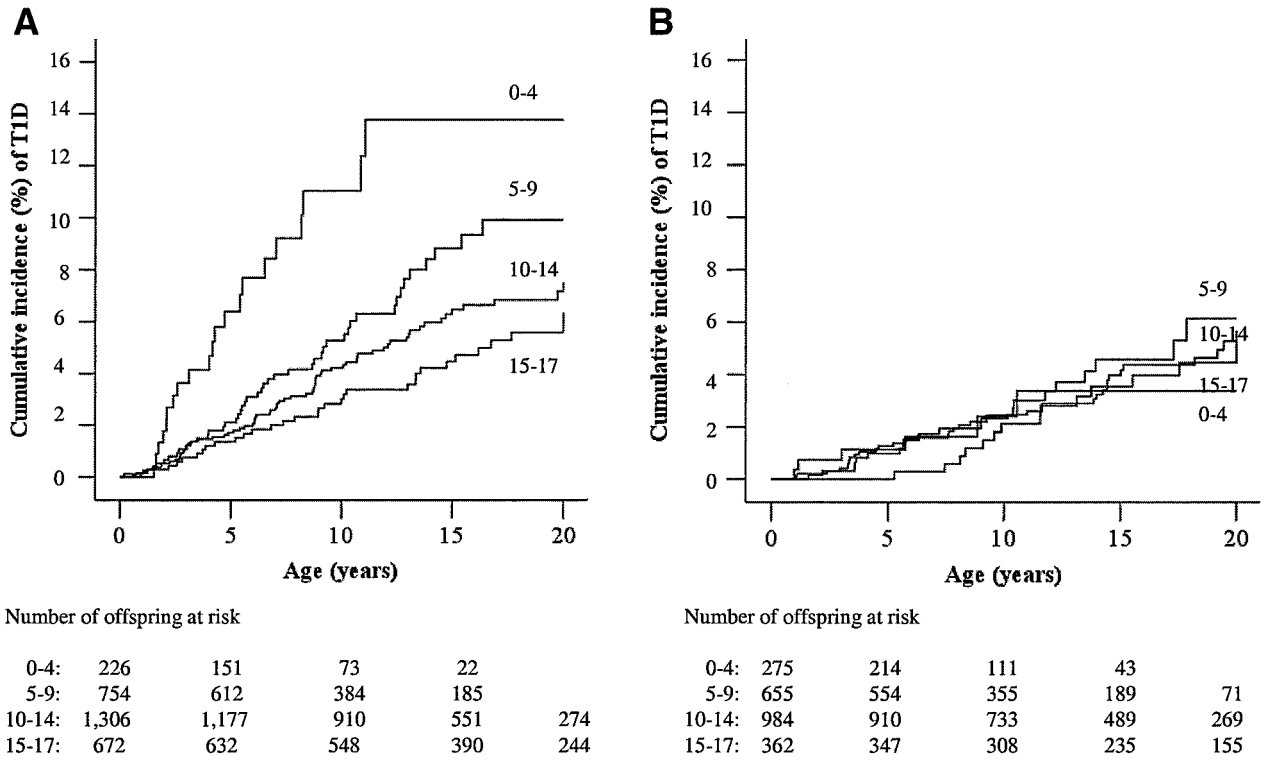

FIG. 3. Cumulative incidence of type 1 diabetes in the offspring of childhood-onset type 1 diabetic patients according to the age at onset of diabetes in type 1 diabetic fathers (*A*) and mothers (*B*).

offspring of parents with type 1 diabetes was substantial, it was not faster compared with that in the background population. The SIRs have remained quite stable throughout the follow-up. Only in the first 5-year period was SIR less than (but not significantly) in the subsequent periods, possibly a result of instability of the incidence of type 1 diabetes in the offspring due to a small number of person-years and type 1 diabetes cases. It is noteworthy that there were no cases diagnosed with type 1 diabetes in the offspring before the year 1983, but after that the increase in incidence was remarkable. This increase in incidence was almost exclusively among the offspring at the age of ≤4 years, in which it was 7% annually.

Using survival analysis we were able to reveal differences in the progress to type 1 diabetes in different birth cohorts of children born to parents with type 1 diabetes. Because the follow-up time in the youngest birth cohort was relatively short, it was impossible as yet to draw any conclusions, whether in the offspring of type 1 diabetic parents the risk of type 1 diabetes is actually higher over the lifetime or whether there is only a shift toward a younger age at onset of type 1 diabetes, reflecting a more aggressive form of the disease. The markedly increased risk of type 1 diabetes in later-born offspring is in keeping with the incidence trend data from Finland and several other countries (17,30,31). In addition, the age at onset of type 1 diabetes has shifted to younger ages not only in Finland (30) but worldwide (32,33).

It is surprising that those offspring born in the year 1995 or after and who were affected had mainly fathers with type 1 diabetes. One could speculate further that if there are selective abortions among type 1 diabetic mothers there may be a different set of high-risk genotypes among the offspring of the type 1 diabetic fathers and mothers left as a material for increasing environmental pressure.

Our large population-based study indicates that the incidence in the offspring of childhood-onset type 1 dia-

TABLE 4
Multivariate Cox regression analysis for the factors influencing the risk of type 1 diabetes in offspring of parents with type 1 diabetes

	Offspring of male proband		Offspring of female proband	
Variable	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Year of birth				
<1985	1.00 (—)		1.00 (—)	
1985–89	1.47 (0.94–2.28)		1.87 (1.01–3.49)	
1990–94	1.48 (0.91–2.41)		2.97 (1.49–5.91)	
≥1995	2.94 (1.71–5.03)	0.001	2.21 (0.86–5.69)	0.02
Age at onset of diabetes (years)				
0–4	2.66 (1.48–4.79)		0.75 (0.28–2.01)	
5–9	1.45 (0.90–2.33)		0.96 (0.48–1.92)	
10–14	1.17 (0.77–1.79)		0.94 (0.51–1.72)	
15–17	1.00 (—)	0.007	1.00 (—)	0.95

TABLE 5
Univariate Cox regression analysis for the factors influencing the risk for type 1 diabetes in offspring of parents with type 1 diabetes according to sex of type 1 diabetic parent

Variable	Offspring of male proband		Offspring of female proband	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Male sex of offspring versus female sex*	0.96 (0.71–1.30)	0.78	1.55 (0.98–2.43)	0.06
Year of birth*				
<1985	1.00 (—)		1.00 (—)	
1985–89	1.60 (1.04–1.48)		1.84 (1.00–3.41)	
1990–94	1.71 (1.07–2.75)		2.88 (1.47–5.64)	
≥1995	3.76 (2.26–6.26)	<0.0001	2.10 (0.84–5.26)	0.02
Birth order*				
First	1.00 (—)		1.00 (—)	
Second	0.91 (0.65–1.29)		0.99 (0.59–1.65)	
Third or higher	1.19 (0.79–1.79)	0.51	2.06 (1.07–4.09)	0.08
Mother's age at delivery (years)*				
<25	1.00 (—)		1.00 (—)	
25–29	1.00 (0.70–1.43)		1.14 (0.67–1.94)	
≥30	1.36 (0.93–2.00)	0.21	1.90 (1.06–3.42)	0.08
Mother's age at delivery (continuous)	1.02 (0.99–1.05)	0.30	1.06 (1.01–1.11)	0.03
Father's age at delivery (years)*				
<25	1.00 (—)		1.00 (—)	
25–29	0.94 (0.64–1.40)		1.96 (0.99–3.90)	
≥30	1.24 (0.83–1.84)	0.29	2.45 (1.23–4.87)	0.04
Father's age at delivery (continuous)	1.03 (1.00–1.06)	0.08	1.04 (1.00–1.07)	0.04
Parent's age at onset of diabetes (years)†				
0–4	3.75 (2.15–6.55)		1.05 (0.40–2.73)	
5–9	1.78 (1.13–2.82)		1.22 (0.62–2.38)	
10–14	1.29 (0.85–1.97)		1.03 (0.56–1.88)	
15–17	1.00 (—)	<0.0001	1.00 (—)	0.83

*Interaction term between the sex of type 1 diabetic parent and the variable in question was not statistically significant. †Interaction term between the sex of type 1 diabetic parent and the variable in question was statistically significant.

betic patients is 10 times higher than that in the general population. The risk of type 1 diabetes in the offspring of the young-onset cases of patients with type 1 diabetes has increased over the past few decades, but according to this study not more than the rapid increase in incidence in the background population. The risk of type 1 diabetes in the offspring seems to be especially high in the families where the proband is male and developed diabetes at an early age. Moreover, the probability to become diabetic at a young age is 3–10 times higher in the offspring of families where both parents have type 1 diabetes. By definition, in such families both parents carry type 1 diabetes susceptibility genes, and thus, the likelihood for a child to inherit at least one set of susceptibility genes is obviously very high.

In conclusion, these data demonstrate that the interplay between environmental and genetic factors is very difficult to distinguish even in a population-based study. Obviously, the expression of type 1 diabetes genes has changed to develop the disease in highly genetically susceptible children at an earlier age. Male type 1 diabetic probands diagnosed at an early age transmit type 1 diabetes to their offspring most efficiently. Our results reinforce that genetic susceptibility to type 1 diabetes might be modified somehow in diabetic pregnancies. Furthermore, the effect might be different to sons and daughters.

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