Cumulative Incidence of Type 1 Diabetes in 10,168 Siblings of Finnish Young-Onset Type 1 Diabetic Patients

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The aims of our analysis were to obtain the empirical risk estimates for type 1 diabetes in the siblings of a Finnish population-based cohort of childhood-onset diabetic patients and search for demographic and other factors predicting the risk of type 1 diabetes in siblings. We defined the diabetes status of all siblings of all probands who are included in the nationwide register of Finnish cases for whom type 1 diabetes was diagnosed before age 18 years between 1965 and 1979. Siblings' diabetes status was ascertained by a record search of nationwide registries through 2001, and the type of diabetes and date of its manifestation were obtained from medical records. The total number of person-years during the follow-up was 405,685. Of the 10,168 siblings at risk, 647 (6.4%) had been diagnosed with type 1 diabetes by 2001. The cumulative incidence of type 1 diabetes by ages 10, 20, 30, 40, and 50 years in all siblings was 1.5, 4.1, 5.5, 6.4, and 6.9%, respectively. A young age at diagnosis in the index case, paternal young-onset diabetes, male sex, and older parental age at delivery considerably increased the risk of type 1 diabetes for siblings. This large prospective family study of type 1 diabetes in siblings of childhood-onset diabetic patients provides reliable empirical estimates for the sibling recurrence risk. *Diabetes* 54:563–569, 2005

Type 1 diabetes is a disease that primarily affects young people. Most new type 1 diabetes cases in any population are sporadic; that is, first-degree relatives do not have diabetes at the time of the child's diabetes diagnosis. Nevertheless, siblings of childhood-onset type 1 diabetic patients are at an increased risk of developing the same disease compared with the general population (1,2), a concern that has provoked much interest. Most of the studies on this topic have been cross-sectional point estimations of the prevalence of type 1 diabetes in siblings at the time of diagnosis in the index cases or at a certain time point (3–6). The natural course of development of type 1 diabetes in siblings is more accurately reflected by follow-up studies. Such studies are, however, rare.

The range of risk of first-degree relatives developing type 1 diabetes, estimated at 4–7% by age 30 years (7–11), appears to be much less than the observed variation in the incidence of disease between populations, ranging from 0.1/100,000 per year in China and Venezuela to >35/100,000 per year in Sardinia and Finland.

Family and twin studies have been used to evaluate the role of genetic or environmental factors in the risk of the disease and to determine the age at diagnosis of type 1 diabetes (13,14). It is known that the risk for siblings depends on genetic background located primarily in the HLA region on chromosome 6 (15,16); in particular, it depends on siblings sharing the HLA haplotype with the proband (10,17). However, only a small number of genetically susceptible siblings of diabetic patients develop the disease (11,13). The aim of our study was to obtain long-term empirical estimates of the risk of type 1 diabetes among siblings of type 1 diabetic patients. In addition, we searched for the effect of several factors that might predict the risk of diabetes in siblings.

RESEARCH DESIGN AND METHODS

We defined the diabetes status of all siblings of all type 1 diabetic patients diagnosed before age 18 years in Finland between 1965 and 1979 (n = 5,144); thus, the case ascertainment in this cohort was virtually complete (18,19). The cohort was originally used in the Diabetes Epidemiology Research International Mortality Study (20,21).

All siblings born in 1990 or before and their parents were identified from the Central Population Registry (CPR) using their unique personal identifier that is assigned to every resident of Finland. To identify diabetic siblings, sibling data were linked to the National Hospital Discharge Register (HDR) data from 1970 to 2001, the Finnish Diabetes Register for Children and Young Adults, and the Social Insurance Institution Central Drug Register (CDR) using patients' identifier. The CDR was begun in 1964 and includes information on all patients receiving free-of-charge medication for chronic diseases, including diabetes. This register is virtually complete for type 1 diabetes (22). The HDR lists discharges of all hospital patients and includes each patient's identifier, dates of hospital admission and discharge, and up to four diagnoses since 1970. The vital status of the siblings, also up to 2001, was obtained by record linkage with the National Death Registry.

The data linkage yielded a total of 715 cases of any type of diabetes among siblings. Copies of medical records for all diabetic siblings were obtained and reviewed to verify the type of diabetes and define its manifestation date. Of the 715 cases, 647 had type 1 diabetes, 50 had type 2 diabetes, 6 had gestational diabetes, and 12 had secondary diabetes such as steroid-induced diabetes or diabetes associated with Down syndrome. Half-siblings and monozygotic twins were considered ineligible for the recurrence risk calculation. In our

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Received for publication 7 July 2004 and accepted in revised form 28 October 2004.

CDR, Central Drug Register; CPR, Central Population Registry; HDR, National Hospital Discharge Register.

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TABLE 1
Subject characteristics of study population and incidence of type 1 diabetes in siblings

	Siblings	Person-years	Incident cases of type 1 diabetes in siblings	Incidence per 10,000 person-years
Sex of the sibling				
Male	5,202	207,384	367 (7.1)	17.7 (15.9–19.6)
Female	4,966	198,301	280 (5.6)	14.1 (12.5–15.9)
Family size				
One child (682 families)	—	—	—	—
Two children (1606 families)	1,606	58,716	106 (6.6)	18.1 (14.8–21.8)
Three children (1230 families)	2,460	94,854	168 (6.8)	17.7 (15.1–20.6)
Four children (678 families)	2,034	81,012	133 (6.5)	16.4 (13.8–19.5)
Five or more children (772 families)	4,068	171,102	240 (5.9)	14.0 (12.3–15.9)
Total (4,968 families)	10,168	405,685	647 (6.4)	15.9 (14.7–17.2)
Birth year of the sibling				
<1960	5,151	239,016	259 (5.0)	10.8 (9.6–12.24
1960–1969	3,838	137,337	291 (7.6)	21.2 (18.8–23.8)
1970–1979	971	25,781	72 (7.4)	27.9 (21.9–35.2)
≥1980	208	3,550	25 (12.0)	70.4 (45.6–104.0)
Age at onset of type 1 diabetes in index case (years)				
0–4	1,306	42,498	160 (12.3)	37.6 (32.0–44.0)
5–9	2,811	104,799	213 (7.6)	20.3 (17.7–23.2)
10–14	4,156	173,738	203 (5.5)	11.7 (10.1–13.4)
≥15	1,895	84,649	71 (3.7)	8.4 (6.6–10.6)

Data are *n* (%) or *n* (95% CI).

analyses, the index case within the sibship was defined as the one that was diagnosed first chronologically.

Determining potential explanatory variables. Data on parents were also linked to the HDR and CDR, in which the onset of diabetes was defined as the date of the first hospital admission due to diabetes or the approval date for free-of-charge medication for diabetes, whichever was earlier. Parents with young-onset diabetes were defined as those who were diagnosed with diabetes by age 40 years. In all, 99 of 496 (20%) diabetic fathers and 51 of 403 (13%) diabetic mothers were considered as having young-onset diabetes.

Siblings were categorized according to the age of diabetes diagnosis in the index case: ages 0–4, 5–9, 10–14, and ≥15 years. The calendar period was categorized as the year of birth: before 1970, 1970–1979, and 1980 or later. Maternal and paternal age at delivery was calculated as the difference between the birth date of the sibling and the birth date of the mother and

TABLE 2
Estimated risk ratios (RRs) and 95% CIs for type 1 diabetes in siblings of childhood-onset type 1 diabetic patients fitting explanatory variables

	Univariate analysis			Adjusted for other variables		
Variable	RR	95% CI	*P*	RR	95% CI	*P*
Sex						
Female	1.00			1.00		
Male	1.26	1.08–1.47	0.004	1.29	1.10–1.50	0.002
Diagnosis age of index case (years)						
≥15	1.00			1.00		
10–14	1.35	1.03–1.77	0.03	1.43	1.09–1.88	0.009
5–9	2.27	1.73–2.96	<0.0001	2.50	1.90–3.27	<0.0001
0–4	4.05	3.06–5.36	<0.0001	4.60	3.46–6.10	<0.0001
Test for trend			<0.0001			<0.0001
Young-onset diabetes in fathers						
No	1.00			1.00		
Yes	2.11	1.33–2.32	0.001	1.95	1.23–3.10	0.004
Maternal age at delivery (years)						
<25	1.00			1.00		
25–29	1.40	1.13–1.72	0.002	1.31	1.03–1.66	0.03
30–34	1.58	1.27–1.98	<0.0001	1.33	1.00–1.76	0.05
≥35	2.23	1.77–2.80	<0.0001	1.85	1.35–2.55	0.0002
Test for trend			<0.0001			0.02
Paternal age at delivery (years)						
<25	1.00			1.00		
25–29	1.00	0.77–1.31	0.98	0.96	0.72–1.27	0.78
30–34	1.50	1.16–1.94	0.002	1.38	1.02–1.87	0.04
≥35	1.81	1.41–2.33	<0.0001	1.50	1.07–2.11	0.02
Test for trend			<0.0001			0.002

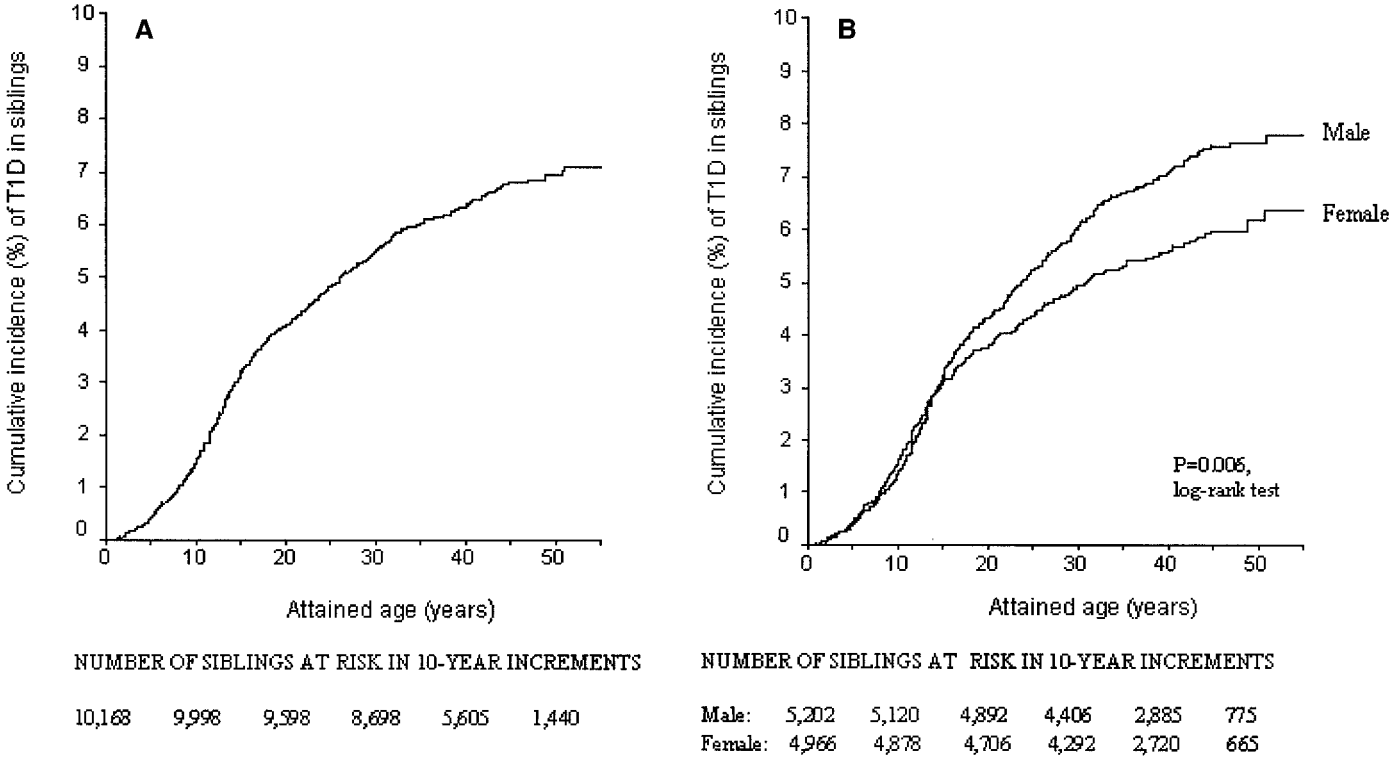


FIG. 1. Cumulative incidence (%) of type 1 diabetes (T1D) in siblings of childhood-onset type 1 diabetic patients all together (*A*) and by sex (*B*).

father and categorized in 5-years bands: ≤24, 25–29, 30–34, 35–39, and ≥40 years.

Statistical methods. Kaplan-Meier analyses were used to provide the long-term cumulative risk for the development of type 1 diabetes in siblings. Person-years were calculated from birth to the date of diagnosis of type 1 diabetes until death or until the end of follow-up at the end of 2001. We also performed analyses according to sex, age of diabetes onset in the index case, the birth-year cohort, and maternal and paternal age at delivery.

The effect of several independent risk factors on the risk of type 1 diabetes for the siblings was evaluated by a Cox regression analysis using a forward selection procedure. The censoring date for siblings without type 1 diabetes was 31 December 2001; for deaths, the date of death; and for siblings with type 2 or secondary diabetes, the date of onset. The predictors studied were sex of the sibling, sex of the proband, diagnosis age in the proband, parental history of young-onset diabetes, birth year, number of offspring in the family as a continuous variable, and parental age at delivery. The effect modification (i.e., if the effect of a variable on the risk of type 1 diabetes in siblings varied according to the level of another covariate) was controlled for by adding corresponding interaction terms to the regression model. Interaction was tested between sex and diagnosis age in the proband and between maternal and paternal age at delivery. Model selection was based on likelihood ratio tests. Relative risks were calculated with a univariate analysis and with the best fitting multivariate model.

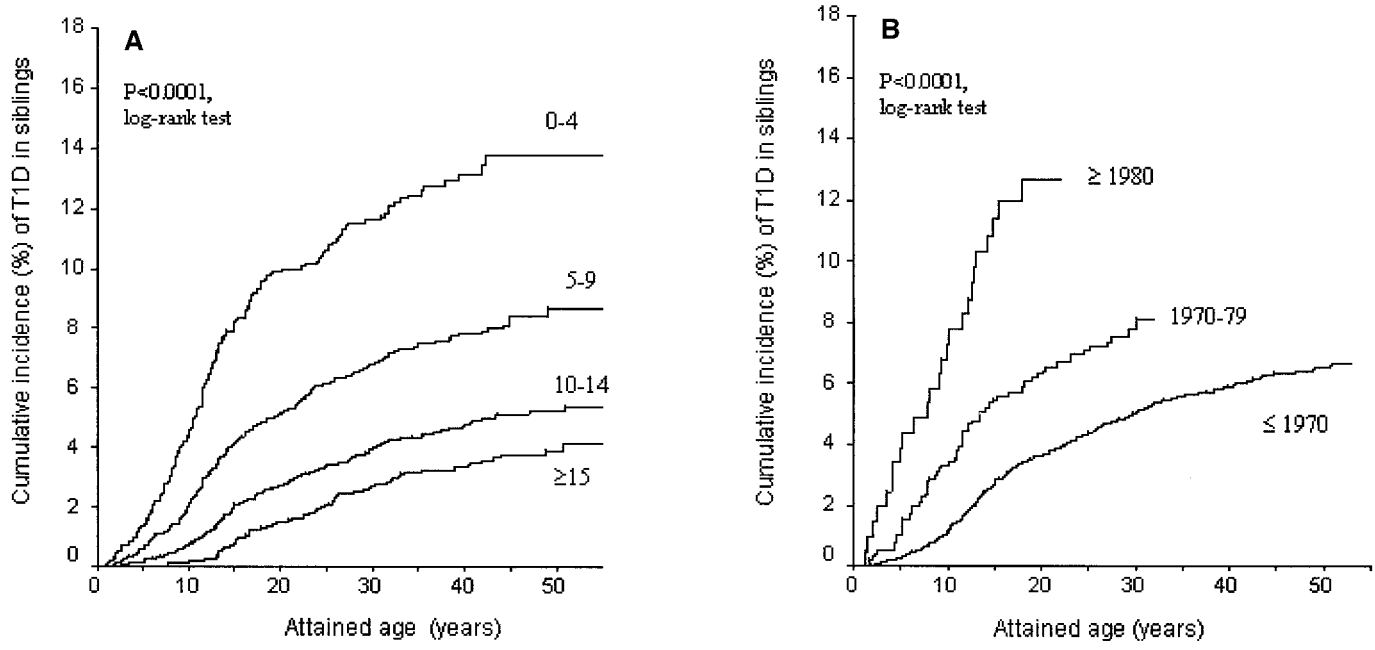
RESULTS

The total number of person-years accumulated in this follow-up study was 405,685. Of the 10,168 siblings at risk, 647 (6.4%) were diagnosed with type 1 diabetes by 2001. In 484 families there were two cases with type 1 diabetes; in 67 families, three cases; in 7 families, four cases; and in 2 families, five cases. Of the families with more than one child, 11% had at least two affected type 1 diabetes siblings. The median age at diagnosis among the siblings was 15.1 years (range 0.8–56 years). Of nondiabetic living siblings, 99% were ≥20 years of age at the end of the follow-up in 2001, and all had reached ≥11 years of age. There was a male predominance, with 57% of the siblings with type 1 diabetes being male.

The descriptive statistics of the study population of 10,168 siblings and the crude incidences in each stratum are presented in Table 1. A young age at diagnosis of diabetes in the index case was the strongest predictor of the risk of type 1 diabetes in siblings. In addition, sex, young-onset diabetes in fathers, and maternal and paternal age at delivery were statistically significant predictors. The birth-year cohort effect was significant in the univariate analyses, but when adjusted for other variables, its significance disappeared. No first-order interactions were found. Table 2 shows the risk ratios for these variables in univariate and multivariate analyses. The effect of maternal and paternal age at delivery was attenuated when other variables were included in the model. The association between age at diabetes onset in the index case and the risk of type 1 diabetes became stronger after adjusting for other variables.

The cumulative risk of type 1 diabetes up to ages 10, 20, 30, 40, and 50 years in all siblings was 1.5 (95% CI 1.3–1.8), 4.1 (3.7–4.4), 5.5 (5.1–5.9), 6.4 (5.9–6.8), and 6.9% (6.4–7.4), respectively (Fig. 1*A*). The sex of the index case did not influence risk by age, but the sex of the sibling did. Up to age 14 years, no sex difference was seen in the risk for the siblings (male/female ratio 1.0), but thereafter brothers had a progressively higher risk compared with sisters. The relative risk for brothers compared with sisters increased from 1.06 at age 15 years to 1.23 at age 50 years (Fig. 1*B*).

The age at diagnosis in the index case considerably influenced the risk of type 1 diabetes for siblings (Fig. 2*A*). By age 10 years, the type 1 diabetes risk for a sibling was 21.5 times higher when the index case was diagnosed at ≤4 years of age compared with siblings in the families where the index was diagnosed at ≥15 years of age. This gap decreased during follow-up, and the overall risk ratio



NUMBER OF SIBLINGS AT RISK IN 10-YEAR INCREMENTS

0-4:	1,306	1,242	1,102	822	375	50
5-9:	2,811	2,745	2,613	2,236	1,233	241
10-14:	4,156	4,120	4,023	3,833	2,601	669
≥15:	1,895	1,890	1,860	1,807	1,396	488

NUMBER OF SIBLINGS AT RISK IN 10-YEAR INCREMENTS

≥1980:	208	189	64			
1970-79:	971	933	904	273		
≤1970:	8,989	8,876	8,630	8,425	5,605	1440

FIG. 2. Cumulative incidence (%) of type 1 diabetes (T1D) in siblings of childhood-onset type 1 diabetic patients by the onset age of diabetes in the index case (*A*) and birth cohort (*B*).

was 4.1 (95% CI 3.1–5.4). The cumulative risk of type 1 diabetes by age 20 years for siblings whose index case was diagnosed at 0- 4, 5–9, 10–14, and ≥15 years of age was 9.9 (8.4–11.3), 5.1 (4.3–5.9), 2.7 (2.2–3.2), and 1.5% (0.9–2.0), respectively ($P < 0.0001$, log-rank test). The corresponding rates by age 40 years were 13.2 (11.4–14.8), 7.8 (6.9–8.8), 4.7 (4.1–5.3), and 3.4% (2.6–4.2) (Fig. 2*A*).

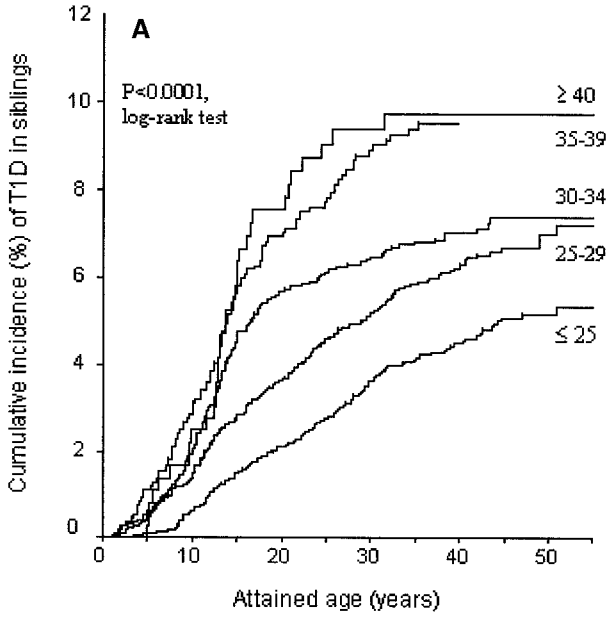
Figure 2*B* shows the Kaplan-Meier curves stratified by year of birth. Of siblings born in 1980 or after, 11.4% (95% CI 7.4–15.2) had developed type 1 diabetes by age 15 years, whereas only 5.5% (4.1–6.8) of those who were born in 1970–79 had and only 2.7% (2.4–3.0) of those who were born before 1970 had ($P < 0.0001$, log-rank test).

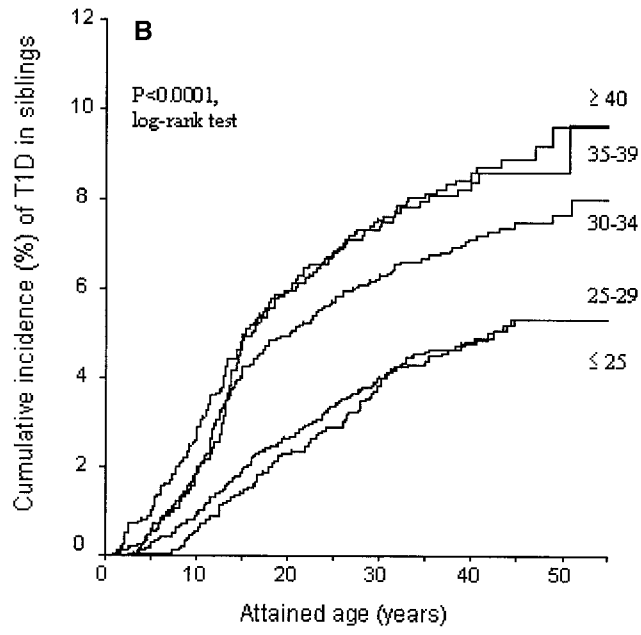
Figure 3 shows the cumulative risk curves by parental age at delivery. The risk of type 1 diabetes in siblings increased with increasing maternal and paternal age at delivery (log-rank test, $P < 0.0001$). In fathers, the impact of age began to increase after age 30 years, whereas each 5-year increase from age 25 to 35 years in maternal age enhanced the risk of diabetes. In both mothers and fathers, the effect of their age at delivery on the risk of diabetes in siblings of the index case did not increase after age 35 years.

DISCUSSION

Our study was the largest population-based study that has been performed on the risk of type 1 diabetes in the siblings of patients with childhood-onset type 1 diabetes, covering 405,685 person-years at risk. It provides stable estimates on the cumulative sibling recurrence risk in families with childhood-onset type 1 diabetes in a population with the world's highest incidence of type 1 diabetes, which is increasing rapidly, particularly in the very young (23,24). Our estimates have been obtained using a prospective design as opposed to the cross-sectional approach applied by most other studies on the topic, thus providing a realistic and unbiased picture of the disease risk over time.

The cumulative incidence for type 1 diabetes in siblings of type 1 diabetic patients by age 30 years observed in this study, 5.5% on average, is similar to that of most studies where the estimate has varied from 4.9 to 6.4% (2,7–9,11). In general, the risk of type 1 diabetes for close relatives is usually quite similar (25,26). Considering the probabilities of shared HLA haplotype between siblings and the index case, the fraction of genetically susceptible siblings at risk, and consequently the fraction that has the potential to develop the disease, is expected to be the same in all populations. Deviations from such a theoretical situation can be caused by a higher or lower exposure to environmental factors affecting the etiopathogenesis of type 1 diabetes. However, a recent large European ecological study has suggested that the incidence of type 1 diabetes and the prevalence in siblings at the time of the diagnosis of a diabetic child are correlated (6). Our estimates of the recurrence risk confirm the finding that brothers are more commonly affected with type 1 diabetes after puberty than sisters (7,27). Furthermore, we found that young-onset diabetes in fathers was associated with increased risk of type 1 diabetes in siblings, which is in keeping with data





NUMBER OF SIBLINGS AT RISK IN 10-YEAR INCREMENTS

≥ 40:	366	353	311	259	111	9
35-39:	1,089	1,052	955	804	408	71
30-34:	2,184	2,136	2,018	1,775	1,079	237
25-29:	3,220	3,171	3,087	2,805	1,843	481
≤ 25:	3,309	3,286	3,227	3,055	2,164	642

NUMBER OF SIBLINGS AT RISK IN 10-YEAR INCREMENTS

≥ 40:	1,207	1,177	1,085	933	510	106
35-39:	1,529	1,484	1,385	1,200	694	191
30-34:	2,611	2,560	2,452	2,196	1,378	338
25-29:	3,080	3,048	2,984	2,760	1,891	470
≤ 25:	1,741	1,729	1,692	1,609	1,132	335

FIG. 3. Cumulative incidence (%) of type 1 diabetes (TID) in siblings of childhood-onset type 1 diabetic patients by maternal (*A*) and paternal (*B*) age at delivery.

showing that fathers with type 1 diabetes are more likely than affected mothers to transmit diabetes to their offspring (28). In the present study, we could not unequivocally determine the type of parental diabetes based on data from the HDR and CDR. At the time the CDR was established, 19% of parents were >40 years of age and could have been graded as having older-onset diabetes instead of potential type 1 diabetes in the present study. Also, parents diagnosed at a young age who died before the foundation of the CDR could not be detected; 94 parents died in or before 1964, 12 of whom belonged to the families with more than one diabetic sibling.

The higher risk of type 1 diabetes for the siblings of index cases who were diagnosed at a young age was first clearly demonstrated in the 1990s (3). Our findings support this theory. For siblings from families in which the index case was diagnosed at a very early age, the cumulative risk of type 1 diabetes is dramatically high. It can be speculated that early onset of type 1 diabetes in a child might be a risk marker for an early onset of type 1 diabetes in relatives, suggesting that genetic effects in such families may be particularly strong. Our long-term follow-up study clearly demonstrates that a young age of onset in the first child diagnosed with type 1 diabetes indicates an overall increased lifetime risk of type 1 diabetes in siblings, and that the process leading to diabetes seems to be more rapid in such siblings.

An early onset age of type 1 diabetes has been found to be associated with certain HLA haplotypes (29,30). Gillespie et al. (29), in a large family study, detected that half of the children who were diagnosed before age 5 years were heterozygous for HLA DRB1*03-DQA1*0501-DQB1*02/DRB1*04-DQA1*0301-DQB1*0302, and the frequency of that genotype decreased with an increase in the age at onset. A population-based Finnish family study did not show any increase in the effect of DR3/DR4 heterozygosity, but two high-risk HLA haplotypes were found more frequently in type 1 diabetic children diagnosed at <5 years of age (31) than in those diagnosed when older.

The correlation of onset ages between the index cases and affected siblings ($r = 0.30$) was similar to that we observed in Finnish dizygotic twins ($r = 0.38$) (13), but much weaker than suggested by earlier studies (5,14,32). Our study is unique in that the follow-up was longer than in any other study and thus the siblings had more time to develop the disease, thereby enabling a larger disease-free interval among siblings and a closer reflection of the real-life situation. The low correlation between the onset age of index cases and affected siblings has been interpreted to suggest that the effect of genetic factors on determining onset age of type 1 diabetes is relatively weak. Fava et al. (14) concluded that the onset age of type 1 diabetes was highly genetically determined. In the present study on affected sibpairs, the onset age of type 1 diabetes ranged widely, even for the siblings born closest to the diabetic index case (mean age 10.3 years, range 0.1–36.8 years). These affected siblings must share the same genetic susceptibility to type 1 diabetes. If environmental factors are responsible for determining the onset age of type 1 diabetes, the correlation should have been much

higher, as it is very likely these siblings share much of the yet unknown environmental exposures during their childhood. Our findings dispute the suggestion that the onset age of type 1 diabetes in siblings is largely controlled by similar environmental exposures within the family during a limited time period before disease onset.

The risk of type 1 diabetes in siblings increased according to the successive birth-year cohorts. The birth-year cohort effect disappeared when the onset age of type 1 diabetes in the index case, which significantly decreased by successive birth-year cohort, was included in the model. Changes in environmental risk factors may interact with diabetes susceptibility genes over time, modifying their penetrance. It is likely that enhanced gene expression leads to a more aggressive form of diabetes and may manifest itself in families in diabetes onset at a younger age, and it may also result in an increase in the overall risk of type 1 diabetes. In this observational study, we did not have any data on exposure, either genetic or environmental. The markedly increased risk for siblings born in 1980 or later is in keeping with the incidence trend data from Finland and several European countries (23,33–35). Although the data show differences in the risk of type 1 diabetes between birth cohorts, there might be some underestimation in the risk of type 1 diabetes in the earliest birth cohort. Any diabetic siblings diagnosed with type 1 diabetes and deceased before 1967, when the CPR was begun, could not be detected. However, type 1 diabetes mortality in such young people is not very high (19,21), and there have been very few cases lost.

The relation between parental age at delivery and the risk of type 1 diabetes for the child has been reported in several studies (36–41). Our results concur with studies that have found a relation between increasing parental ages at delivery and the risk of type 1 diabetes (37). The parturients have continuously become older and the proportion of primigravida age 35 years or more has increased by 50% during the past decade in Finland, to 19% in 2001 (42). Because older women tend to have children with older men, both maternal and paternal ages at delivery have increased. The increasing parental age at delivery can contribute in a small way to the increasing incidence of type 1 diabetes in Finland.

In conclusion, our large prospective study of the risk of type 1 diabetes in siblings of childhood-onset type 1 diabetic patients with a long follow-up provides reliable empirical estimates for the sibling recurrence risk. A young age at the diagnosis of type 1 diabetes in the first diabetic child in the family, male sex, young-onset diabetes in fathers, and high parental age at delivery increase the risk of type 1 diabetes for the siblings.

ACKNOWLEDGMENTS

This work has been supported by Academy of Finland Grants 46558 and 51224 and grants from the Sigrid Jusélius Foundation and the Juvenile Diabetes Research Foundation.

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