

Secondary Attack Rate of Type 1 Diabetes in Colorado Families

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OBJECTIVE — Families of children diagnosed with type 1 diabetes require counseling concerning type 1 diabetes risk in nondiabetic siblings and parents. No U.S. population-specific life-table risk estimates are currently available for parents, and those for siblings (2–6% by age 20 years) are based on family studies completed before 1987.

RESEARCH DESIGN AND METHODS — We analyzed family histories of 1,586 patients in Colorado with type 1 diabetes (83% non-Hispanic white, 10% Hispanic, and 7% other) diagnosed before 16 years of age and interviewed during 1999–2002. Families of probands with type 2, undetermined, or secondary diabetes ($n = 53$) or those with incomplete data ($n = 137$) were excluded. The median age at onset of the proband was 7.1 years and the median diabetes duration 3.5 years. Cumulative risk estimates were calculated using survival analysis for 2,081 full siblings and 3,016 biological parents.

RESULTS — In siblings, the overall risk of type 1 diabetes by age 20 years was 4.4%, but it was significantly ($P < 0.0001$) higher in siblings of probands diagnosed under age 7 years than in those diagnosed later. In parents, the overall risk by age 40 years was 2.6% and higher in fathers (3.6%) than in mothers (1.7%) of probands ($P < 0.001$). Similar to siblings, the risk was also higher ($P = 0.006$) in parents of probands diagnosed <7 years of age than in those diagnosed later.

CONCLUSIONS — Current risks of type 1 diabetes in Colorado siblings and parents of type 1 diabetic probands are higher than in the 1982 Pittsburgh study but similar to contemporary European rates. Recurrence risk of type 1 diabetes is significantly higher in first-degree relatives of probands diagnosed at a young age.

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Of the U.S. general population, 0.3% develop type 1 diabetes by the age of 20 years (1). The risk among siblings of type 1 diabetic patients is 10–20% higher, up to 3–6% by age 20 years (2–4) and increases further to 10% by age 60 years (5). The cumulative risk to parents of type 1 diabetic patients is less ele-

vated than among siblings and has been reported to be between 3 and 5% by the age 40 years to lifetime (2,4,6,7).

Previously published cumulative risk estimates among first-degree relatives (FDRs) vary widely by age, ethnicity, and period of time and also likely vary due to differences in methods of ascertainment.

Currently available risk estimates for the U.S. population are mainly based on family studies completed before 1987 (2,3) and may be outdated, since the incidence of type 1 diabetes has been increasing worldwide by 3–5% annually (8).

In Europe, children with an early age of onset seem to have more siblings and parents affected by type 1 diabetes (9). In a recent U.K. study, survival analysis stratified according to the age at diagnosis of the proband gave much higher risk estimates in siblings of probands diagnosed before age 5 years (cumulative risk by age 20 years 11.7% compared with 3.6% for ages 5–9 years and 2.3% for ages 10–14 years) (4); the same difference by the proband's age at onset was also seen for parents.

The aim of the present study was to obtain contemporary risk estimates for recurrence of type 1 diabetes in Colorado families with type 1 diabetic probands and to characterize the variables that influence the recurrence risk.

RESEARCH DESIGN AND METHODS

The study population consists of 1,776 families of diabetic patients diagnosed before age 16 years and seen at the Barbara Davis Center for Childhood Diabetes in Denver between 1999 and 2002. Age, sex, diabetic status, age of onset, and treatment for diabetes were ascertained using a standardized questionnaire in all immediate family members. The proband was defined as the child affected by type 1 diabetes through whom the family was ascertained. This study has been approved by the Colorado Multiple Institutional Review Board.

Of the probands ($n = 1,723$), 97% had type 1 diabetes, defined by age at disease onset <16 years and permanent insulin treatment within 6 months of diagnosis. A total of 53 probands aged <16 years at onset were excluded for the following reasons: 44 had type 2 diabetes, 4 had diabetes secondary to other causes (cystic fibrosis or steroids), and 5 had undetermined diabetes. Another 137 families were excluded from the analyses because of incomplete data. The remain-

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Abbreviations: FDR, first-degree relative; GAA, GAD65 autoantibody; IA-2A, IA-2 autoantibody; IAA, insulin autoantibody.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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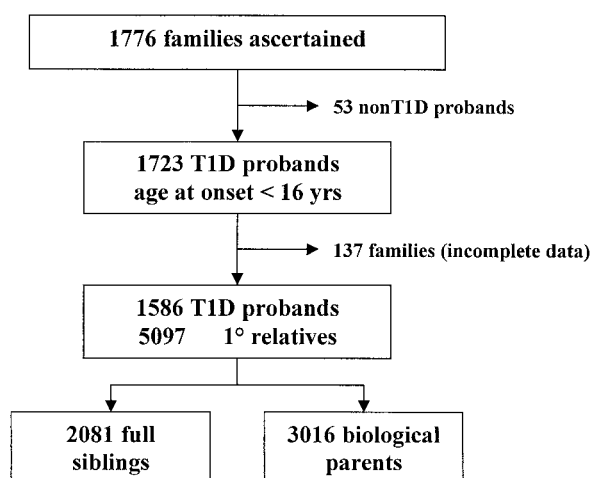


Figure 1—Barbara Davis Center Family History Study. T1D, type 1 diabetes; 1° relative, first-degree relative.

ing 1,586 type 1 diabetic probands had 5,097 FDRs, including 2,081 full siblings and 3,016 biological parents (Fig. 1). These 1,586 probands had 142 FDRs with type 1 diabetes, i.e., 8.1% of probands had at least one other FDR affected by type 1 diabetes (7.4% had one, 0.7% had two, and one proband had three affected FDRs). Diabetes in an FDR was defined as type 1 diabetes based on age at onset ≤ 35 years and permanent insulin treatment within 6 months of diagnosis ($n = 136$); a blood sample for assessment of islet autoantibodies was available for 37% ($n = 50$) and positive for at least one autoantibody in 32% ($n = 43$) of these FDRs. FDRs with age at onset > 35 years were included only if they had been on insulin treatment since the time of diagnosis and were positive for at least one autoantibody ($n = 6$).

Type 1 diabetes results from an autoimmune destruction of the β -cells of the

pancreas. Islet autoantibodies are present at diagnosis in 85–90% of the patients and in a decreasing proportion of the patients up to several years after diagnosis (10). Therefore, presence of islet autoantibodies is generally accepted as sufficient evidence for type 1a (autoimmune) diabetes, while absence of islet autoantibodies in a young insulin-dependent patient does not rule out diagnosis of type 1 diabetes. Blood samples for assessment of islet autoantibodies were obtained at least once in 62% ($n = 985$) and were positive in 50% ($n = 798$) of probands. Clinical diagnosis of type 1a (autoimmune) diabetes was confirmed if the proband was positive for at least one of the following autoantibodies: insulin autoantibody (IAA) (within 15 days of insulin treatment), GAD65 autoantibody (GAA), or IA-2 autoantibody (IA-2A). Life-table analyses were carried out for all families

and also restricted to the relatives of probands with positive islet autoantibodies.

Islet autoantibodies

Measurement of biochemical islet autoantibodies was performed in the laboratory of Dr. George Eisenbarth at the Barbara Davis Center, Denver, Colorado. We used radioimmunoassays for autoantibodies to insulin, GAD65, and IA-2. IAAs were measured by a micro-IAA assay with sensitivity of 58%, specificity of 99%, and interassay coefficient of variation (CV) of 11% (11). The combined GAA and IA-2A radioassay was done in duplicates on a 96-well filtration plate, and radioactivity was counted on a TopCount 96-well plate β -counter using methods previously described (12). In the 1995 Immunology of Diabetes Society Workshop, the GAA assay gave 82% sensitivity and 99% specificity using sera from new-onset diabetic patients aged < 30 years; the interassay CV was 6%. The IA-2A assay gave 73% sensitivity and 100% specificity, and the interassay CV was 10%. Based on 198 nondiabetic control subjects aged 0.4–67.5 years, the 99th percentile for IAA (0.01) and GAA (0.032) and the 100th percentile (single highest value) for IA-2A (0.07) were used as the cutoffs for positivity.

Statistical analysis

All analyses were performed using SAS software, version 8.2. The cumulative risk of development of type 1 diabetes in siblings and parents was estimated by life-table analysis. Follow-up time was defined as the age at disease diagnosis for diabetic family members and age at last interview for nondiabetic family members. The log-rank test was used to test

Table 1—Characteristics of probands by availability of islet autoantibody results

	All probands ($n = 1,586$)	Confirmed type 1a diabetes ($n = 798$)	Type 1 diabetes: autoantibody status unknown ($n = 788$)*
Sex (% male)	50%	50%	51%
Ethnicity (% non-Hispanic white)†	83%	83%	82%
Family size	4.0 (4.0–5.0)	4.0 (4.0–5.0)	4.0 (4.0–5.0)
Age at onset (years)	7.1 (3.8–10.6)	8.3 (4.8–11.2)	6.1 (3.0–9.4)
Full siblings (n)	2,081	1,061	1,020
Biological parents (n)	3,016	1,530	1,486
FDRs with type 1 diabetes (n)	142	65	77

Data are median (interquartile range) unless otherwise indicated. *Includes 52 probands negative for autoantibodies to insulin, GAD, and IA-2 at onset of diabetes (up to 15 days after initiation of insulin therapy) and 135 probands that were negative for autoantibodies to GAD and IA-2 measured > 15 days after initiation of insulin therapy. †Ethnicity information missing for 264 probands.

differences in cumulative risk among subgroups (13). Multivariate analysis used Cox proportional hazards modeling to assess the contribution of the FDR's relationship to the proband and family size, as well as the proband's ethnicity, sex, age at diabetes onset, and duration of diabetes.

RESULTS — The median age at type 1 diabetes onset among the 1,586 informative probands was 7.1 years (25–75%, interquartile range 3.8–10.6) and the median type 1 diabetes duration was 3.5 years (25–75%, 0.8–7.2). The majority of the probands (83%) were non-Hispanic whites, 10% were Hispanic, and 7% were of other ethnic backgrounds. Most pro-

bands (92%) had between 3 and 6 first-degree full-blood relatives; the family size varied from 2 to 12. Characteristics of the probands are summarized in Table 1.

Probands with confirmed type 1a diabetes did not differ with regard to sex, ethnicity, and family size from those for whom islet autoantibody status was unknown. Confirmed type 1a probands were older at onset because older children are more often screened for autoantibodies to rule out type 2 diabetes. Cumulative risk analyses using Kaplan-Meier survival curves were calculated for the whole study population of 2,081 full siblings and 3,016 biological parents. Analyses restricted to the relatives of probands with

confirmed type 1a diabetes gave similar results (data not shown).

The cumulative risk of type 1 diabetes by age 20 years was higher ($P < 0.0001$) for siblings at 4.4% (95% CI 3.1–5.7) than for parents at 1.7% (1.3–2.2) (Fig. 2A). The risk was significantly higher ($P < 0.0001$) in siblings of probands diagnosed under the age of 7 years than in those diagnosed later (Fig. 2B). The cumulative risk by age 40 years was 3.6% (2.7–4.6) in fathers compared with 1.7% (1.0–2.4) in mothers ($P < 0.001$) (Fig. 3A); none of the mothers were diagnosed with type 1 diabetes after age 35 years in this dataset. Similar to siblings, the risk was also higher ($P = 0.006$) in parents of probands diagnosed under the age of 7 years than in those diagnosed later (Fig. 3B).

We carried out a multivariate analysis of several variables that might influence the cumulative risk of type 1 diabetes in FDRs using the Cox proportional hazard model (Table 2). These analyses revealed that the relation to the proband (sibling versus parent) and the proband's younger age at onset were the two most important factors influencing type 1 diabetes risk. Smaller family size and longer duration of diabetes in probands also increased the risk of type 1 diabetes in FDRs. The proband's sex and ethnicity were not statistically related to recurrence of type 1 diabetes.

A subanalysis including only one affected FDR per family (in addition to the proband) led to similar results. The Cox proportional hazard model showed the same variables significantly associated with recurrence of type 1 diabetes in FDR: relation to proband (hazard ratio 2.48, 95% CI 1.54–3.98; $P = 0.0002$), proband age at onset (2.24, 1.48–3.41; $P = 0.0002$), family size (0.72, 0.59–0.87; $P = 0.0005$) and duration of diabetes (1.03, 1.01–1.06; $P = 0.011$).

CONCLUSIONS — The clinic-based data of this study were obtained for families of 1,586 type 1 diabetic probands with age at disease onset <16 years, creating the largest family history study of type 1 diabetes in the U.S. Current risks of type 1 diabetes in Colorado siblings and parents of type 1 diabetic probands are higher than in the 1982 Pittsburgh study (2) but similar to contemporary Danish (5) and U.K. (4) rates. The 1982 Pittsburgh study ($n = 1,128$) ascertained pro-

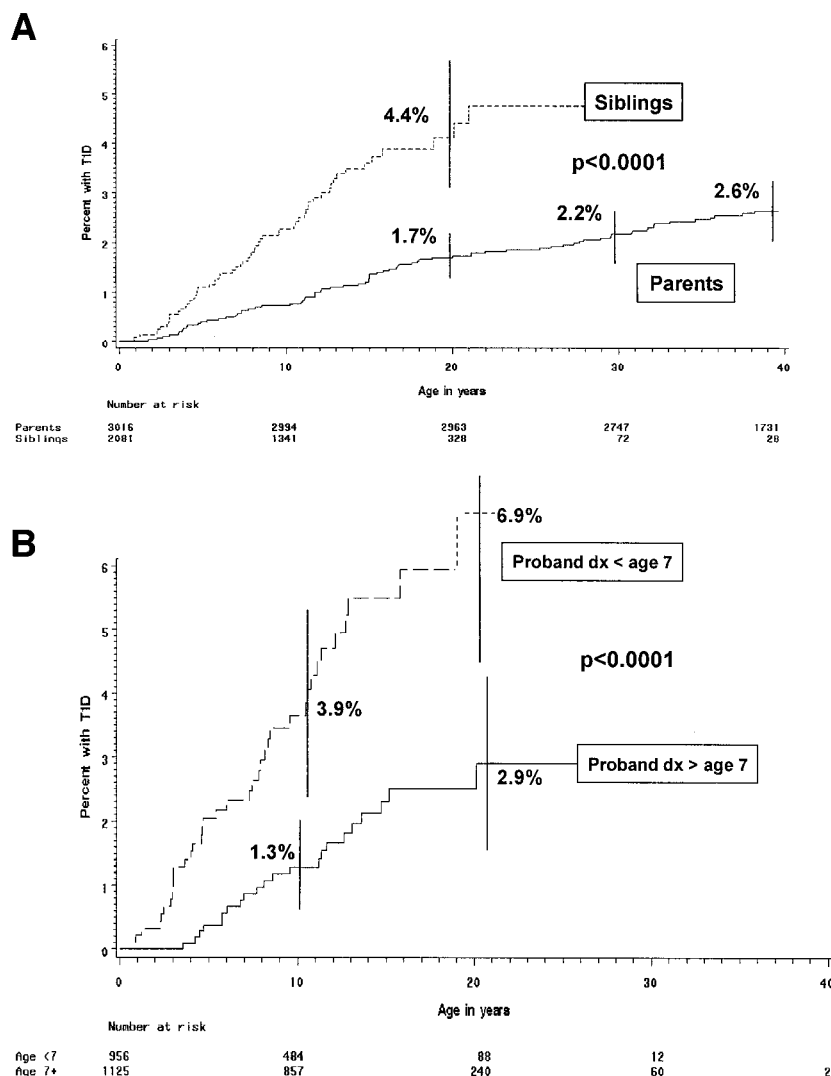


Figure 2—A: Cumulative incidence of type 1 diabetes in siblings and parents: point estimates and 95% CI by age 20, 30, and 40 years. B: Cumulative incidence of type 1 diabetes in siblings according to proband age at diagnosis: point estimates and 95% CI by age 10 and 20 years. T1D, type 1 diabetes.

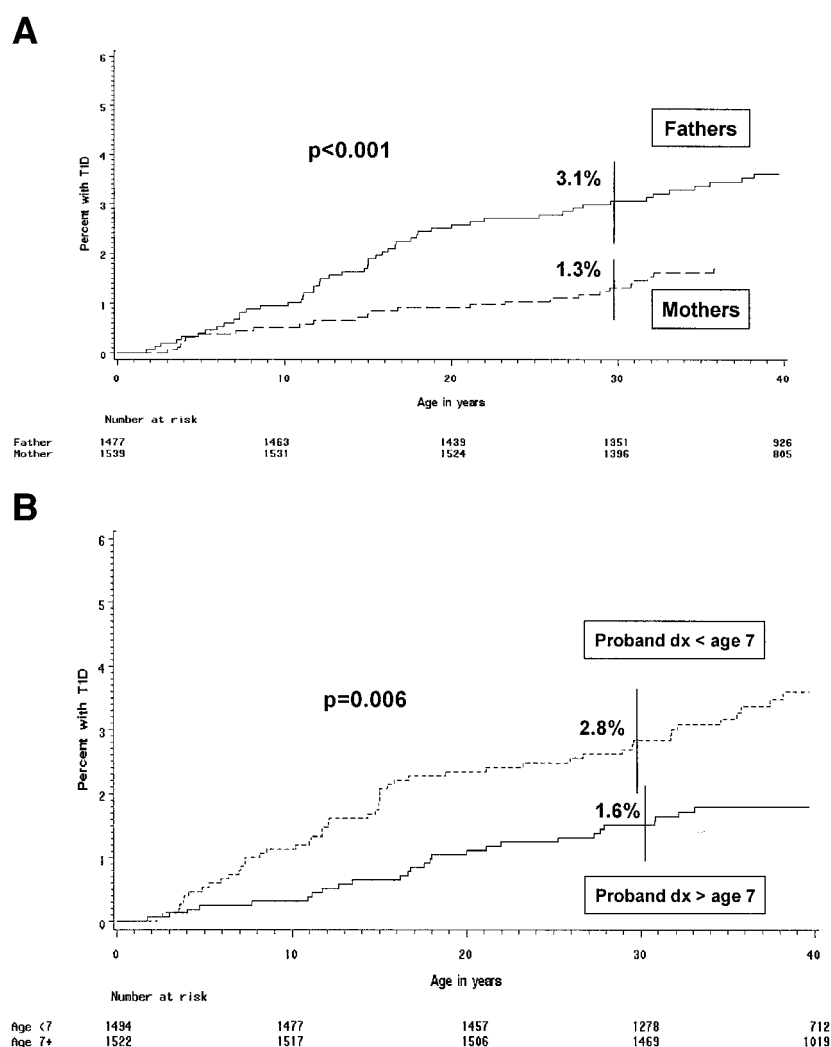


Figure 3—A: Cumulative incidence of type 1 diabetes in fathers and mothers: point estimates and 95% CI by age 30 years. **B:** Cumulative incidence of type 1 diabetes in parents according to proband age at diagnosis: point estimates and 95% CI by age 30 years. T1D, type 1 diabetes.

bands with age at onset <17 years and on insulin when discharged from the hospital; type 1 diabetes relatives were defined as those diabetic subjects taking insulin regularly. The 2002 Bart's-Oxford Study recruited 1,299 families of type 1 diabetic patients diagnosed before age 15 years; type 1 diabetes criteria for relatives were stricter: permanent insulin treatment within 6 months of diagnosis, presence of at least one islet autoantibody at study entry, or diagnosis <30 years, with permanent insulin treatment. While ascertainment differences between these studies limit direct comparison of the rates, it is quite likely that the incidence of type 1 diabetes among FDRs has increased in parallel to the reported incidence increase in the general population (8,14).

A small study ($n = 194$) in Wisconsin (1984–1987) by Allen et al. (15) found higher cumulative risks than in the Colorado population (cumulative risk 9.0% to siblings by age 20 years). The genetic pool of Wisconsin type 1 diabetic families is largely of Northern European origin, and

the higher risk of type 1 diabetes recurrence is consistent with reports from other high-risk populations (16).

Cumulative risk of type 1 diabetes in both siblings and parents of probands diagnosed under the age of 7 years was higher than that in relatives of probands diagnosed later. This was particularly significant for siblings who had a more than twofold greater risk by age 20 years if the proband was diagnosed under the age of 7 years (6.9%) compared with that if the proband was diagnosed at 7–16 years (2.9%). These results confirm that a proband's age at onset is an important predictor in familial risk of type 1 diabetes and agree with similar findings in recent European studies (4,9) and two older U.S. studies (3,15). In contrast, the older Pittsburgh study did not find any difference in risk according to age of onset (2). The overall body of evidence, however, strongly suggests that genetic or environmental factors that precipitate earlier onset of type 1 diabetes in probands are shared with the relatives and may also increase their risk of type 1 diabetes.

We found that a higher number of fathers than mothers of diabetic children develop type 1 diabetes. The increased cumulative risk in offspring of type 1 diabetic fathers (4–9%) compared with offspring of type 1 diabetic mothers (~2–3%) has been frequently observed and published (9,17–19). However, the reason for this parental sex difference is still not known, although several hypotheses have been proposed (e.g., genomic imprinting and immunologic tolerance in utero) (20–22).

This study may underestimate cumulative recurrence risk in FDRs, since type 1 diabetes criteria for FDRs are rather strict and the median proband diabetes duration is only 3.5 years. Lorenzen et al. (5) have indeed shown that 50% of sec-

Table 2—Multivariate analysis of type 1 diabetes risk in FDRs (Cox proportional hazards model)

	Hazard ratio	95% CI	P
Siblings vs. parents	2.60	1.65–4.08	<0.0001
Proband dx <7 vs. 7+	2.30	1.54–3.44	<0.0001
Family size (per person)	0.74	0.62–0.88	0.001
Duration of diabetes (per year)	1.04	1.01–1.06	0.004
Hispanic vs. non-Hispanic white	0.76	0.37–1.56	0.45
Female vs. male	0.95	0.65–1.38	0.77

ond cases among siblings were affected >10 years after the first sibling.

The multivariate analyses confirmed that type of relation and proband age at onset are the two most important predictors of type 1 diabetes recurrence risk in FDRs. Longer duration of diabetes in probands also increased the risk of type 1 diabetes in FDRs, likely due to older ages of FDRs in these families. Interestingly, when controlling for family size, the risk ratio for siblings (compared with parents) became larger. Two hypotheses might explain the fact that bigger families have a lower risk of type 1 diabetes; families with type 1 diabetes children tend to have fewer children. Although the relation of maternal age and birth order to risk of type 1 diabetes is complex and controversial (23,24), several studies found that older maternal age (22,25) and/or increasing birth order (25,26) were associated with a decreased risk of type 1 diabetes in offspring.

In summary, this analysis shows that >4% of siblings develop type 1 diabetes by the age of 20 years and 2.6% of the parents do so by the age of 40 years, with the highest risk to FDRs of probands diagnosed at a young age. These estimates may be important for counseling families affected by childhood type 1 diabetes, as well as for the design of trials to screen and prevent type 1 diabetes in FDRs.

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