Familial Risks for Type 2 Diabetes in Sweden

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OBJECTIVE — Our aim was to characterize familial risks for type 2 diabetes by the type and number of affected family members, including half-siblings, adoptees, and spouses, to quantify risks and estimate the contribution of environmental effect.

RESEARCH DESIGN AND METHODS — Families were identified from the Multigeneration Register, and type 2 diabetic patients were obtained from the Hospital Discharge Register. Standardized incidence ratios were calculated for offspring with type 2 diabetes whose family members were hospitalized for type 2 diabetes at ages >39 years compared with those lacking affected family members.

RESULTS — The number of hospitalized type 2 diabetic patients was 157,549. Among 27,895 offspring, 27.9% had a parent or sibling also hospitalized for type 2 diabetes. The familial relative risk (RR) ranged from 2.0 to >30, depending on the number and type of probands. The highest RRs of type 2 diabetes were found in individuals who had at least two siblings affected by type 2 diabetes, irrespective of the parental disease. Adoptees showed no risk from adopted parents.

CONCLUSIONS — The study, the largest yet published, showed that familial RRs varied by the number and type of affected family member. However, much of the familial clustering remains yet to be genetically explained. The high risk should be recognized in clinical genetic counseling. The data from adoptees confirmed the genetic basis of the familial associations, but those from half siblings and spouses suggested that a smaller part of familial clustering may be accounted for by environmental factors.

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Type 2 diabetes is characterized by impaired pancreatic β-cell function and insulin action. The prevalence of type 2 diabetes varies in populations, and the rate in Sweden has been ranging from 2 to 4%, with a tendency to increase (1,2). The disease is thought to be caused by environmental and inherited factors in about equal proportions (3). Many environmental risks factors are known, and they include obesity, sedentary lifestyle, small or large birth weight, stress, nutritional factors, and toxins (1,4). Family history is an important risk factor that has been shown in twins and singleton siblings (1,3,5–7). The sibling relative risk (RR) is ~3, but it may depend on the age of onset and probably on the background incidence of the disease (7–10). Some 20 genes/loci have been associated with type 2 diabetes, some of which are related to pancreatic β-cell dysfunction, obesity, insulin sensitivity, or an as yet unknown function (3,7). However, the observed RRs are very low, typically ranging between 1.1 and 1.3, and thus they explain little for the observed familial clustering (9,11). Type 2 diabetes is also manifested in rare Mendelian forms, which account for <2–5% of all cases and which are caused by a number of genes (3). Most of the Mendelian forms of type 2 diabetes are of early onset, and they would not be included in the present study population hospitalized at age >39 years for type 2 diabetes. However, latent autoimmune diabetes of the adult (LADA) could be diagnosed in some 10% of the patients (12). LADA shows familial clustering both with type 2 diabetes and type 1 diabetes; the familial RR of LADA is close to that of type 2 diabetes (13).

The specific aims of the present study were to characterize familial RRs of type 2 diabetes by the type and number of affected family members, because families with multiple affected individuals were available in this nationwide study on 157,549 patients. A sufficient number of half-siblings were also identified, which enabled estimation of familial RRs for them and comparison with full siblings. In addition, the RR of type 2 diabetes was analyzed in adoptees by a comparison with their biological and adopted parents. The study was conducted by identifying families from the Multigeneration Register, which was linked to the Hospital Discharge Register. The study is unique in being able to characterize familial RRs in many types of multiplex families, among spouses, half-siblings, and adoptees. Moreover, this is the largest family study published on type 2 diabetes with the advantage that all of the results emanate from a single population of patients with medically diagnosed diabetes in a country of high medical standards and an affordable health care system.

RESEARCH DESIGN AND METHODS

— The research database used for this study is a subset of the national MigMed 2 datasets at the Center for Primary Health Care Research, Malmö, Lund University. The MigMed database was compiled using data from several nationwide Swedish registers provided by Statistics Sweden, including the Multigeneration Register in which persons (second generation) born in Sweden in 1932 and thereafter are registered shortly after birth and are linked to their parents (first generation). Sibships could be defined for the second generation. National Census Data (1960–1990) and the Swedish population register (1990–2001) were incorporated into the database to obtain information on individuals' socioeconomic status. Dates of hospitalization

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Table 1—*Sex-specific familial RRs for type 2 diabetes according to probands*

	Men		Women		All		
Proband	O	SIR (95% CI)	O	SIR (95% CI)	Person-years	O	SIR (95% CI)
Singleton siblings							
Men	698	2.68 (1.76–4.09)	372	2.63 (1.67–4.12)	572,318	1,070	2.66 (1.77–4.00)
Women	335	2.83 (1.79–4.46)	278	3.20 (2.00–5.09)	293,157	613	2.99 (1.95–4.57)
All	1,033	2.73 (1.81–4.10)	650	2.85 (1.86–4.35)	865,475	1,683	2.77 (1.87–4.11)
Parents							
Father	1,586	1.96 (1.86–2.06)	905	1.99 (1.86–2.13)	2,045,048	2,491	1.97 (1.89–2.05)
Mother	2,314	2.01 (1.93–2.10)	1,423	2.17 (2.06–2.28)	2,706,561	3,737	2.07 (2.00–2.14)
All	3,900	1.99 (1.93–2.05)	2,328	2.10 (2.01–2.18)	4,751,609	6,228	2.03 (1.98–2.08)

O, observed number of cases.

for type 2 diabetes were obtained from the Swedish Hospital Discharge Register for years 1964–2007; this Register was started in 1964, and it reached nationwide coverage in 1987. Patients registered for hospitalization stayed at least 1 night in the hospital, usually in wards with specialists; the Register does not include outpatients in hospitals or health care centers. Diagnoses were reported according to the different versions of the ICD. The codes for type 2 diabetes and type 1 diabetes were first separated in ICD-10 (1997 onward), and we thus only included patients aged >39 years at hospitalization; this age limit is the same as that used by the National Swedish Diabetes Registry (14). All linkages were performed using the national 10-digit civic identification number that is assigned to each person in Sweden for his or her lifetime. This number was replaced by a serial number for each person to provide anonymity and to check that each individual was only entered once, for his or her first hospitalization for type 2 diabetes. More than 11.8 million individuals in >3.5 million families were included in this database; 8.9 million individuals belonged to the second generation, who had reached age 75 years at the end of the follow-up, which spanned from 1972 to 2007 (15). The population was not static over the 44 years of follow-up: in year 1972 the second generation, reaching age 40 years was made up of 15,542 men and 15,749 women compared with 1,841,858 men and 1,764,906 women by year 2007. Parental diagnoses were covered from 1964.

Person-years were calculated from start of follow-up on 1 January 1972 (i.e., when the second generation reached age 40), until hospitalization for type 2 diabetes, death, emigration, or closing date, 31 December 2007. Standardized incidence ratios (SIRs) were calculated as the ratio of observed to expected number of cases. The expected number of cases was calculated for age (5-year groups), sex, period (5-year groups), region, and socioeconomic status-specific standard incidence rates derived from offspring lacking an affected family member; person-years at risk for the familial population are shown in the tables. For each type of familial analysis a specific reference population was used. Familial RRs were calculated for type 2 diabetes in men and women with parents, singleton siblings, half-siblings, adoptees, and spouses, compared with men and women whose relatives were not affected by type 2 diabetes, using the cohort method as described (16). In this method all siblings in families with two or more affected sibling contribute cases, and they are compared with single case families using the described person-year calculation. In families in which more than two siblings were affected, each was counted as an individual patient. CIs (95% CI) were calculated assuming a Poisson distribution, and they were adjusted for dependence between the sibling pairs (16). For the estimation of interactions for parental probands, the additive model considered data as $2 \times SIR - 1.0$; the multiplicative model was fitted as SIR × SIR (17); SIR is the familial RR in offspring when one parent was affected. We note that the results are only approximations because SIRs cannot be formally compared when different reference populations were used. Yet, the use of SIR as an effect measure is useful because the indirect standardization is efficient in dealing with small numbers of cases.

RESULTS — The number of type 2 diabetic patients aged >39 years at hospitalization was 157,549 of whom 27,895 (18,377 men and 9,518 women) belonged to the offspring generation of <76 years of age; the parental generation included 129,654 individuals. Sex-specific familial RRs for type 2 diabetes in singleton siblings and in offspring of affected parents are shown in Table 1. The familial populations, offspring with affected siblings or with affected parents, accumulated 865,475 and 4,751,609 person-years at risk, respectively; the average follow-up time was 14.8 years. The results showed that daughters of affected women and female siblings were at somewhat higher risk than any other types of offspring; however, none of the sex-specific results were significantly different from each other. We have also analyzed the effect of age at diagnosis on familial RRs. The results showed a modest age dependence; for example, for siblings in age-band 40–49 years the SIR was 2.95 compared with 2.48 in age-band 60–75 years (data not shown).

Familial RRs are shown in Table 2 by the type and number of probands in mutually inclusive groups. Also shown are the number of each type of affected families, median age of affected offspring in these families, and person-years at risk for the familial populations. The number of affected offspring was 5,662 when a parent was also affected, and 181 had both parents affected; thus, 20.3% of all offspring had a parental family history and 0.7% had bilineal history. A total of 2,116 siblings were affected, representing 7.6% of all offspring. The total familial proportion was 27.9% of all offspring. When a parent was a proband, the RR was 2.03, but it increased to 2.39 when the parental age was limited to 75 years, equal to the maximal age in the offspring generation. The RR for a singleton sibling of a sibling proband was somewhat higher at 2.77. The RRs increased markedly when the

Table 3—*Familial RRs for type 2 diabetes in half-siblings and adoptees*

	Men		Women		All		
	O	SIR (95% CI)	O	SIR (95% CI)	Person-years	O	SIR (95% CI)
Half-siblings							
By mother	30	2.35 (1.12–4.75)	16	2.15 (0.87–4.94)	29,435	46	2.28 (1.18–4.3)
By father	18	1.54 (0.64–3.45)	13	1.84 (0.69–4.47)	32,656	31	1.65 (0.79–3.32)
All	48	1.96 (1.02–3.68)	29	2.00 (0.95–4.07)	62,091	77	1.98 (1.10–3.5)
Adoptees							
By biological parents	45	2.06 (1.50–2.75)	73	2.24 (1.75–2.81)	49,749	118	2.16 (1.79–2.59)
By adopted parents	20	0.79 (0.48–1.23)	15	1.27 (0.71–2.1)	50,260	35	0.95 (0.66–1.32)

O, observed number of cases.

Table 2—*Familial RRs for type 2 diabetes in offspring according to the number of probands*

	Men		Women		All		
Proband (*n* families, median age at hospitalization of offspring)	O	SIR (95% CI)	O	SIR (95% CI)	Person-years	O	SIR (95% CI)
1. Parent, no age limitation (4,356, 51 years)	3,545	1.99 (1.93–2.06)	2,117	2.11 (2.02–2.20)	4,923,322	5,662	2.03 (1.98–2.09)
2. Parent <76 years (2,198, 50 years)	2,353	2.30 (2.21–2.40)	1,426	2.56 (2.43–2.69)	2,751,545	3,779	2.39 (2.32–2.47)
3. Two parents <76 years (109, 49 years)	98	4.99 (4.05–6.08)	65	6.02 (4.65–7.68)	51,241	163	5.35 (4.56–6.24)
4. Singleton sibling (671, 52 years)	1,033	2.73 (1.81–4.10)	650	2.85 (1.86–4.35)	865,475	1,683	2.77 (1.87–4.11)
5. Two singleton siblings (30, 52 years)	57	31.58 (16.91–57.88)	33	51.87 (25.23–103.12)	2,976	90	36.86 (20.96–64.10)
6. Three or more singleton siblings (3, 47 years)	6	22.78 (5.80–70.58)	6	69.44 (17.67–215.18)	432	12	34.31 (12.47–85.01)
7. Singleton sibling and parent <76 years (117, 50 years)	173	4.46 (3.82–5.18)	111	4.80 (3.95–5.79)	99,733	284	4.59 (4.07–5.16)
8. Singleton sibling and two parents <76 years (7, 50 years)	8	5.10 (2.18–10.10)	10	10.33 (4.92–19.07)	3,884	18	7.10 (4.20–11.24)
9. Two or more singleton sibling and parent <76 years (9, 53 years)	18	28.24 (16.70–44.71)	11	53.14 (26.38–95.41)	891	29	34.34 (22.98–49.37)
10. Spouse, no age limitation	3,296	1.31 (1.26–1.35)	3,178	1.33 (1.29–1.38)	3,490,178	6,474	1.32 (1.29–1.35)

O, observed number of cases.

number of affected probands increased. The SIR was 36.86 when two singleton siblings were probands, and it was 4.59 when a sibling and a parent were probands. The SIR was also high: 34.34 when two or more siblings and a parent were probands. For SIRs >30, half or more than half of siblings were affected: row 5, 90 affected and 72 unaffected; row 6, 12 affected and 15 unaffected; and row 9, 29 affected and 25 unaffected. Female SIRs were higher than male SIRs in families of many affected siblings (e.g., rows 5 and 6), but because of a small number of cases, the 95% CIs overlapped. The median age of onset, ranging from 47 to 53 years, showed no large differences between the family types. The SIR between spouses was 1.32, which could suggest that close to one-third of the familial excess risk of 1.03 (row 1, offspring of an affected parent SIR 2.03, excess risk $2.03 - 1.00 = 1.03$) could be explained by environmental sharing (row 10, $1.32 - 1.00 = 0.32$). Interactions could be tested when one or two parents were affected. Based on row 2 of one affected parent, an additive effect of 3.78 could be calculated, compared with a calculated multiplicative effect of 5.71; according to row 3 of two affected parents, the true effects was 5.35, thus close to a multiplicative effect.

A total of 77 affected half-siblings were identified among a total of 2,777 (1,477 maternal and 1,300 paternal) half-siblings hospitalized for type 2 diabetes (Table 3), showing a familial RR of 1.98 and an excess familial risk of 0.98; this was somewhat more than one-half (55%) of the excess familial risk for full siblings (1.77) (Table 3: $2.77 - 1.00 = 1.77$). However, only the SIR of 2.28 for maternal half-siblings was significant; the excess risk of 1.28 was 72% of that of full siblings. The results for adoptees are also shown among 533 (364 men and 189 women) hospitalized patients. The risk was 2.16 for adoptees when their biological parents were probands, similar to data in Table 2. However, when the adopted parents were probands, there was no excess risk and the SIR was 0.95; the SIR was 0.79 when the adoptee was male and it was 1.27 when the adoptee was female.

CONCLUSIONS — The use of hospitalized patients offers advantages and disadvantages to etiological studies. One limitation is that all patients are not hospitalized, and there is probably a selection to severe disease presentation and complications. By extrapolation from regional rates, it has been estimated that there would be some 350,000 type 2 diabetic patients in Sweden in year 2004 (18). On the other hand, at the same time, the National Diabetes Register in Sweden only included 57,000 patients with the age of onset of >39 years (12,14). The Register figure is an underestimate because only 50% of the primary care centers and 90% of diabetes clinics have participated. Thus, the present overall figure of 157,549 patients aged >39 years who are hospitalized seems to be between The National Diabetes Register number, corrected for full coverage and the extrapolated figure for type 2 diabetic patients. When all patients are not hospitalized, selection may take place whereby family members of hospitalized patients may preferentially seek hospitalization. However, such selection should be largest among cohabiting spouses and the spouse correlation of 1.32 was well below any of the familial risk estimates. The use of hos-

pital discharge data has great advantages, such as access to a nationwide patient pool and reasonably high diagnostic accuracy because the discharge diagnoses are often delivered by specialists during extended examinations in the clinic. In Sweden, hospitalization for type 2 diabetes may be a secondary or tertiary referral step; type 2 diabetes is diagnosed in primary care centers, which refer the patients to hospital outpatient clinics or directly to inpatient clinics. Hospital clinics are directed by specialists in internal medicine or endocrinology/diabetology (14). With poor diagnostic accuracy, any effects would be expected to regress toward null, which appeared not to be the case with the present results.

In the present offspring population, with a maximal age of 75 years, 27.9% had an affected parent or sibling and 0.7% had two affected parents. These results can be compared with those of the Framingham offspring study in which 23.7% of the offspring had an affected parent (in our study 20.3%) and 1.7% had two affected parents (19).

The observed familial RR of 2.03 in offspring of affected parents increased to 2.39 when parental age was limited to the maximal offspring age of 75 years. This RR was close to the risk of 2.77 for singleton siblings, leaving little space overall for recessive or childhood shared effects. The results for the familial risk were in line with those in the literature (6,10,19,20). The RR from two affected parents was 5.35, which was closer to the modeled multiplicative (5.71) than to the additive (3.78) estimate. In the Framingham and Pima Indian studies, the bilineal estimates have been close to the additive models (19). The general interpretation of the additive effect is that the underlying genes are noninteractive and influence different pathways (19,21). However, none of the models used considered the possible environmental contribution to the risk estimates, discussed later.

Sex-specific analysis in singleton siblings and in offspring of affected parents showed modest female excesses: daughters of affected women were at somewhat higher risk than any other types of offspring, similar to female siblings. Sex-specific differences were largest for sibships of multiple affected patents. However, none of the sex-specific results were significantly different from each other. The literature on sex effect is controversial, and the present data agree that the differences are not large (10,19).

With the present large sample size, we were able to define families with multiple affected individuals and high familial risks. When two or more singleton siblings were probands, the familial RR exceeded 30, irrespective of the affected parents. This level of risk was probably as high as was possible for a relatively common disease and in fact one-half or more of all siblings were affected in these families. These high-risk families accounted for 0.4% of all offspring, and they are likely to include late onset Mendelian forms of type 2 diabetes. Notably, 102 of 131 patients from the high-risk families (SIR >30) lacked affected parents, which would suggest recessive inheritance. The known monogenic forms of type 2 diabetes include maturity-onset diabetes of the young (MODY) and other very rare syndromes (22). The six genetically characterized MODY subtypes cause hyperglycemia before age 25 years, but unknown MODY loci may represent 20–50% of the cases and some of the identified high-risk families may carry these MODY-X loci (22). However, some of the families may even belong to the known MODY types, but the first hospitalizations of the family members took place before the Hospital Discharge Register was nationwide in year 1987. Considering that a familial risk of 10 can be conveyed by rare dominant or additive genes of high risk (allele frequency of ~1%, odds ratio 100) or more common recessive genes of very high risk (allele frequency of ~20%, odds ratio 200) (11), none of the recently detected low-penetrance genes alone belong to this domain of genes. However, the combinations of risk variants in rare individuals would mimic the effects of rare high-risk alleles (3). The effects would be strong if the variants interacted with each other, which, however, may not be the case with the type 2 diabetes genes detected. Accordingly, the addition of gene tests into the available clinical parameters causes a negligible improvement in prediction (23,24). Such results have been a disappointment for other diseases as well, however, not unexpectedly (25). In contrast, the present results of familial risk of >30 when two siblings have diabetes have clinical relevance. Even the risk of 5 from two affected parents or from a parent and sibling is of concern.

Many environmental and host factors predispose to type 2 diabetes, but the low spouse correlation of 1.32 suggests that these factors had a limited, yet definite, influence on the observed familial aggregation. Such an effect was not seen among adoptees, who showed no excess through adopted parents, but the case numbers were limited. The risk for adoptees from biological parents was as high as that for offspring of affected parents in the whole population. The data on half-siblings supported the contribution of environmental factors to the familial aggregation; the risks were higher for maternal than for paternal half-siblings, which may be explained by the fact that, after parental divorce, the children have usually lived with their mother in Sweden. The familial excess risk for maternal half-siblings was 72% of that for full siblings; the expectation from additive genetic effects is 50%. However, this figure is only an approximation because comparison of two SIRs may not be accurate. With such reservations, these data, together with the spouse correlation, suggest that close to one-third of the familial risk for type 2 diabetes may have an environmental origin in families of two affected individuals; in multiplex families, this proportion is likely to be less.

In summary, the present family study on type 2 diabetes, the largest one yet published, showed that in the offspring population hospitalized for type 2 diabetes between ages 40 and 75 years, 27.9% have a parent or sibling also hospitalized for type 2 diabetes. The familial risk ranged from 2 to >30, depending on the number and type of probands. Probably much of the familial clustering remains yet to be genetically explained. The high risk should be recognized in clinical genetic counseling. The data from adoptees confirmed the genetic basis of the familial associations, whereas the data from half-siblings and spouses suggested that close to one-third of familial clustering may be accounted for by environmental factors in families of two affected individuals.

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