Parental History of Diabetes in a Population-Based Study

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OBJECTIVE — To evaluate the relative frequency of parental history of diabetes in a population-based study of younger- and older-onset groups of individuals with diabetes and a comparison group of individuals without diabetes.

RESEARCH DESIGN AND METHODS — Study participants were queried about a family history of diabetes. The frequencies of positive responses for parents and siblings were compared between younger- and older-onset groups.

RESULTS — At least one parent had diabetes in 18.6% of the families of younger-onset individuals and in 38.6% of the families of older-onset individuals. For those of younger-onset diabetes, 9.1% of fathers, 8.3% of mothers, and 1.3% of both parents had diabetes; the corresponding percentages for those of older-onset diabetes were 11.5, 23.5, and 3.6%, respectively. The difference between frequencies in mothers and fathers was significant ($P < 0.001$) in the older-onset group. In the nondiabetic comparison group, for those of similar ages to the younger- and older-onset groups, the corresponding frequencies were 6.2 and 9.0% and 7.7 and 9.8% for fathers and mothers, respectively. The greater frequencies of diabetes in mothers of older-onset diabetic individuals were not accounted for by maternal age. In younger-onset individuals, the relative risk (RR) of diabetes in a sibling if the father had diabetes was 1.22 (95% CI, 0.72–2.05); if the mother had diabetes, the RR was 2.39 (95% CI, 1.64–3.48); and, if both parents had diabetes, the RR was 5.61 (95% CI, 3.37–9.34). In the older-onset individuals, the corresponding RR values were 1.69 (95% CI, 1.35–2.13) for fathers, 1.72 (95% CI, 1.44–2.06) for mothers, and 2.42 (95% CI, 1.81–3.25) for both parents.

CONCLUSIONS — These data confirm a familial influence on the frequency of diabetes. The excess of cases in mothers of older-onset diabetic individuals is compatible with both environmental and genetic influences.

Family clustering has been observed in both IDDM and NIDDM. In IDDM, monozygotic twins are more likely to be concordant than dizygotic twins (1). The risk of IDDM in dizygotic cotwins is higher than for nontwin siblings (1). This is probably explained in part by the identical age of twins, since age is a factor in concordance with diabetes. However, environmental exposures are likely to influence risk (2). Differences in the rates of the disease in the siblings of individuals with IDDM vary by sex and age. These differences have been thought to be attributable to environmental factors (3). With regard to parental diabetes, some investigators have reported that fathers were at greater risk than mothers (4,5).

There is a consensus in the literature that NIDDM is also a familial disease with a genetic component (6–8). Concordance is higher for those with NIDDM than for IDDM (9). However, no simple genetic model explains the familial pattern (9–11). Doria and Warram (12) reported greater maternal than paternal influence on the family clustering of NIDDM from respondents to a survey at the Joslin Clinic in Boston. Even if consistent from generation to generation, this observation does not exclude the possibility of important environmental effects. We evaluated the family clustering of diabetes and the relative importance of maternal and paternal disease in data from a population-based epidemiological study.

RESEARCH DESIGN AND METHODS

— A population-based prevalence cohort of 10,135 individuals with diabetes was identified during the period 1979–1980 from an 11-county area of southern Wisconsin (13,14). Of our sample population, 2,990 individuals were asked to participate in the examination phase. This included all 1,210 individuals who were diagnosed with diabetes before 30 years of age and were taking insulin (younger-onset) and a probability sample, stratified by duration of diabetes, of individuals diagnosed at or after 30 years of age (n = 1,780, older-onset). During the period 1980–1982, 996 of the younger-onset (13) and 1,370 of the older-onset individuals participated (14). Four years later, 891 of the younger-onset (15) and 987 of the older-onset individuals (16) were seen for a follow-up examination. In addition, 12 selected younger-onset individuals and 20 selected older-onset individuals who had not participated in the baseline examination participated in the follow-up examination for a total of 903 younger- and 1,007 older-onset diabetic individuals. However, in the younger-onset group, there were 12 sibling or parent-offspring pairs where both the individuals had diabetes and were part of the younger-onset group. One member of each of these pairs was randomly excluded, leaving 891 younger-onset individuals. In addition, 20 younger-onset individuals and 84 older-onset individuals were missing information about parental history of diabetes. Thus, 871 younger- and 923 older-onset individuals remained for analysis. As a comparison group, spouses and children from a well child clinic were evaluated with procedures identical to the subjects with diabetes. Data for family members of the nondiabetic comparison group are given in Table 1. For purposes of this pa-

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ANOVA, analysis of variance; RR, relative risk.

Table 1—*Prevalence of diabetes in parents*

Parent with diabetes	Younger-onset	Older-onset
Families of diabetic individuals		
Neither	709 (81.4)	567 (61.4)
Father	79 (9.1)	106 (11.5)
Mother	72 (8.3)	217 (23.5)
Both	11 (1.3)	33 (3.6)
P	0.63	<0.0001
Families of individuals from the nondiabetic comparison group		
Neither	178 (84.8)	151 (82.5)
Father	13 (6.2)	14 (7.7)
Mother	19 (9.0)	18 (9.8)
Both	0 (0)	0 (0)

Data are number of families (%). *P* values are for the difference between fathers and mothers.

per, the second examination (1984–1986) phase is considered the baseline because family history data were collected for the first time during this phase.

The study evaluation covered medical history, including information on current age, age at diagnosis of diabetes, therapy for diabetes, and whether or not each parent, grandparent, and sibling had diabetes. Height and weight were measured by standard protocol. The tenets of the Declaration of Helsinki were followed, informed consent was given, and the approval of the institutional human experimentation committee was granted. SAS, a statistical analysis system, was used to compute means, proportions, χ^2 statistics, and analysis of variance (ANOVA) (17).

RESULTS— Characteristics of the subjects with diabetes, including current age, BMI, age at diagnosis of diabetes, and therapeutic regimens, reflected, in general, the usual characteristics of younger- and older-onset individuals and, in part, the selection characteristics of the study groups (13, 14). The reported history of diabetes in parents of study subjects is summarized in Table 1. A total of 17.4% of the younger-onset individuals reported diabetes in either parent, and 1.3% reported the disease in both parents. There was no difference in the frequency of diabetes in fathers compared with mothers. Older-onset individuals were more likely to report diabetes in either parent (35.0%), although 3.6% of older-onset individuals reported it in both parents. Of these subjects, mothers were more likely to have diabetes than fathers ($P < 0.0001$). The frequencies of diabetes in mothers and fathers of the nondiabetic comparison group were similar. The relative proportion of affected mothers, compared with fathers, was evaluated with regard to the sex of the related study subject. Both female and male subjects with older-onset diabetes were more likely to report that their mothers were affected than that their fathers were affected (data not shown).

Since diabetes is likely to increase in frequency with increasing age, the age of parents was compared with diabetes status (Table 2). The only significant differences occurred in the younger-onset group: fathers were older when neither parent had diabetes and when only the mother had diabetes. Thus, it does not appear that older age of mothers contributes to explaining excess frequency of diabetes in the older-onset group.

The mean age of the nondiabetic group compared with the younger-onset group was greater (42.0 ± 19.3 years) than that of the younger-onset group (32.4 ± 12.3 years); the mean age of the nondiabetic group compared with the older-onset group (57.8 ± 15.0 years) was less than that of the comparable older-onset group (68.6 ± 11.0 years). However, the attained age of fathers (61.9 ± 14.9 years) and mothers (63.9 ± 16.4 years) for those compared with the parents of younger-onset individuals and that of fathers (70.1 ± 12.7 years) and mothers (73.8 ± 12.4 years) for those compared with parents of older-onset individuals were similar to the ages of parents of subjects with diabetes (Table 2).

In older-onset individuals, the average number of cases of diabetes among siblings was slightly larger in families in which the mother or both parents had diabetes (5.8 ± 3.3 for mothers only, 5.8 ± 2.9 for both parents) than it was if neither parent or only the father had diabetes (5.1 ± 2.9 for neither parent, 5.5 ± 3.2 for fathers only) ($P = 0.053$, ANOVA). Parental diabetes had no effect on the number of siblings of those with younger-onset diabetes.

The effect of parental diabetes on the prevalence of diabetes in the siblings of study subjects is given in Table 3. This analysis suggests that siblings of younger-onset individuals were more likely to have diabetes if their mother, rather than their father or neither parent, had diabetes. The effect appears to be increased if both par-

Table 2—*Age of parents in families of subjects by parental diabetes status*

	Younger-onset			Older-onset		
Parental diabetes	Mother	Father	*P*	Mother	Father	*P*
Neither	708 (56.9 ± 12.9)	700 (58.7 ± 11.9)	<0.0001	552 (72.7 ± 16.1)	546 (71.6 ± 13.7)	0.14
Father	79 (59.5 ± 11.6)	79 (58.3 ± 12.5)	0.29	104 (74.2 ± 15.9)	105 (72.8 ± 12.6)	0.41
Mother	72 (61.8 ± 12.3)	71 (66.0 ± 12.5)	<0.01	214 (73.1 ± 11.3)	212 (73.2 ± 12.8)	0.91
Both	11 (69.3 ± 14.6)	11 (63.5 ± 10.9)	0.17	33 (74.3 ± 10.4)	33 (76.6 ± 8.5)	0.30
Total	879 (57.6 ± 13.0)	870 (59.4 ± 12.2)	<0.0001	968 (72.6 ± 15.3)	952 (71.8 ± 13.6)	0.15

Data are *n* (means ± SD).

Table 3—*Prevalence of diabetes in siblings of subjects by parental diabetes status*

	Younger-onset				Older-onset			
Parental diabetes	No. of siblings	Diabetes prevalence (%)	RR	95% CI	No. of siblings	Diabetes prevalence (%)	RR	95% CI
Neither	2243	5.1	1.00	—	2306	10.4	1.00	—
Father	240	6.2*	1.22	0.72, 2.05	477	17.6†	1.69	1.35, 2.13
Mother	254	12.2*	2.39	1.64, 3.48	1023	17.9†	1.72	1.44, 2.06
Both	42	28.6	5.61	3.37, 9.34	159	25.2	2.42	1.81, 3.25

The *P* values refer to the indicated comparison. *$P = 0.023$; †$P = 0.90$. RR, relative risk.

ents had diabetes. The siblings of older-onset individuals were more likely to have diabetes if either parent or both parents had diabetes than if neither had diabetes, but the evidence of a specific maternal influence is lacking.

CONCLUSIONS— The analyses confirm a familial influence on the frequency of diabetes in our population. This study had data on family history from a nondiabetic group with which to compare the frequencies of positive family histories. In this group, the frequency of diabetes in their parents was similar to that of the U.S. population (~8%) (18). Because the nondiabetic comparison group consisted of a casual sample of individuals and was not population based, we have not presented a formal statistical analysis of those data in the tables. There appeared to be a difference in the frequency of diabetes between mothers of the older-onset group and mothers of the appropriate comparison subjects (i.e., in the groups with diabetes, frequencies in parents were higher). Parents of individuals with younger-onset diabetes were, on average, younger than parents of individuals with older-onset diabetes. It is possible that, as parents of younger-onset individuals age, the frequency of diabetes approaches that of parents of older-onset individuals as the prevalence of diabetes, in general, increases with increasing age (11). It may be that the pattern of maternal excess of diabetes that we found in parents of older-onset subjects could emerge in the parents of younger-onset individuals. However, it may be that familial influences on diabetes differ between younger- and older-onset diabetes.

Not only do the absolute frequencies of diabetes in parents differ between younger- and older-onset groups, but the relative difference in rates between fathers and mothers also differs. Mothers of individuals with older-onset diabetes were disproportionately burdened in our study, as it has been in others (19,20). One explanation for the maternal influence is the effect of environment. An excess in frequency of diabetes in siblings is compatible with this hypothesis, especially since there is a difference in excess by a specific parent. In the younger-onset group, we find that the siblings of our subjects were more likely to have diabetes if their mother had diabetes than if their father had the disease (the RR of diabetes in the siblings of younger-onset individuals for mothers versus fathers was 1.97 [95% CI, 1.09–3.56]; not previously shown). However, salient environmental influences are unknown. It may be that the number of such factors, as well as ranges of exposures to them, may differ between siblings. Important environmental influences may not be specific for parents' sex, but may be related to usual, although not universal, gender role patterns (e.g., mothers usually, but not always, prepare meals). A larger study would be needed to sort out the relevant environmental patterns, and we cannot exclude the possibility of genetic effects.

In studies such as this one, we must always be aware of the possibility of other explanations of the findings. There may be bias in recalling whether or not a parent or both parents had the disease, as well as in recalling the specific type of diabetes. Since older-onset diabetes is much more common than younger-onset diabetes, an unexpected imbalance in the relative frequency of either condition in the parents of either group is likely to bias our findings to the null. Selective mortality of affected fathers could also have influenced our findings. It is possible that some of the parental influence may reflect greater surveillance for diabetes in parents and may be greater in parents of children with younger-onset diabetes than in parents of adult children with older-onset diabetes.

Our findings are in concert with those of Thomas et al. (21) who report that mothers were about twice as likely to have diabetes than fathers in the CODIAB study, although Mitchell et al. (22) found no maternal effect. It may be that ethnic differences in environmental and genetic patterns may explain the apparent disparities between these and other studies of this phenomenon.

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