THE CANADIAN MEDICAL ASSOCIATION JOURNAL

LE JOURNAL DE L'ASSOCIATION MÉDICALE CANADIENNE

Volume 98 • Number 9 • March 2, 1968

Diabetes in the Families of Diabetics

NANCY E. SIMPSON, Ph.D.,* *Kingston, Ont.*

RIMOIN[1] has critically reviewed the various concepts that have been proposed to explain the inheritance of diabetes and has indicated that no one genetic hypothesis is universally accepted. It is clear, however, that the risk of becoming diabetic is greater for relatives of diabetics than for individuals of the same age and sex in the general population. Relatives of diabetics would like to know their risk of developing the disease. The purpose of this paper is to present estimates of risks from data on the first-degree relatives of 6600 diabetics that will be useful for genetic counselling. A more detailed account of the data and its genetic interpretation will be published elsewhere.

Family Data

Over the past six years information regarding the diabetic status of first-degree relatives (parents, sibs and children) of Canadian families has been collected for the Family Tree Research Program of the Canadian Diabetic Association. The data presented here are an extension of those reported earlier by Simpson.[2]

Criteria for defining diabetes are variable. Because of the method of collecting data the simplest criteria have been used, that is, the diagnosed diabetic taking insulin, oral drugs or on diet or any combination of the three treatments. Most diabetics can be expected to have this much information about their first-degree relatives. The questionnaires were returned voluntarily by the diabetics. The diabetic respondent is referred to as the proband. During the six years two attempts were made to up-date the family information through follow-up forms.

There are better ways of collecting this kind of information, but in order to obtain a large sample the questionnaire was used. Klimt *et al.*[3] point out the pitfalls of this approach. On the other hand, it is possible from this type of data to make estimates of the risk or "liability" of becoming a diagnosed diabetic.

Control Data

It is well known that the onset of diabetes varies with age and sex and, therefore, frequencies of diabetes in relatives of diabetics are more useful if compared with a random control group. The control for the present study consisted of the frequency of known diabetics in the population of the province of Prince Edward Island by sex and decade of age (Tables I and II). The population base was taken from the 1964 vital statistics in which there were 54,700 males and 52,300 females. The diabetics were taken from provincial records up to December 1966. The number of diabetics was reasonably complete since all diabetics in the province register to receive free insulin or oral drugs with no means test. The control may not be entirely comparable to relatives of Canadian diabetics but its completeness makes it the best one available.

In all cases only known diabetics were recorded, but since this was true for both first-degree relatives of diabetics and the controls comparisons were probably valid.

Method of Analysis

The data were divided by age at onset of probands; 0-19, 20-39 and $\geq$ 40 years for males and females, making a total of six groups. The numbers of living diabetic relatives (designated

From the Departments of Pediatrics and Biology, Queen's University, Kingston, Ontario.
*Queen Elizabeth II Scientist.

Reprint requests to: Dr. Nancy E. Simpson, Associate Professor, Department of Pediatrics, Queen's University, Kingston, Ontario.

Canad. Med. Ass. J.
Mar. 2, 1968, vol. 98

TABLE I.—FREQUENCY OF DIABETES IN MALE CONTROLS IN THE PROVINCE OF PRINCE EDWARD ISLAND

Age	*% diabetic*	*Number in population*
0 - 9	0.053	13,100
10 - 19	0.128	11,700
20 - 29	0.268	6700
30 - 39	0.320	5300
40 - 49	0.500	5600
50 - 59	1.940	5000
60 - 69	2.621	3700
70 - 79	3.807	2600
80 - 89	4.333	900
90+	4.000	100
Total		54,700

TABLE II.—FREQUENCY OF DIABETES IN FEMALE CONTROLS IN THE PROVINCE OF PRINCE EDWARD ISLAND

Age	*% diabetic*	*Number in population*
0 - 9	0.031	12,600
10 - 19	0.150	11,300
20 - 29	0.196	6100
30 - 39	0.500	5000
40 - 49	0.750	5600
50 - 59	2.477	4400
60 - 69	4.600	3500
70 - 79	6.038	2600
80 - 89	5.800	1000
90+	3.500	200
Total		52,300

as "a" in the formula below) and living non-diabetic relatives (designated as "b") were tabulated. Fathers, mothers, brothers, sisters, sons and daughters were counted separately by decade of birth for each of the above six groups of probands. The same count was made for male and female diabetics "c" and non-diabetics "d" in the controls (see Tables I and II). Living relatives only were used, since there were only living diabetics in the controls.

The increase of diabetes in relatives of diabetics compared to that in controls was calculated in the following manner as described by Woolf:[4] x—proportion of diabetes in relatives (a/b) divided by proportion in controls (c/d) by each decade of age.

$y = \text{Log}_e$ of x

$$\text{weight} = 1/\text{ variance or } \frac{1}{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$$

$$Y = \Sigma wy/\Sigma w$$

The antilog of Y is X, which is the mean increase of diabetes in relatives compared to controls weighted by the number of individuals in each decade of age. X will be referred to as "the increased risk for relatives compared to controls".

For example, for male probands whose age at onset was in the interval 0-19 years there were 12 diabetic living fathers (a) and 255 non-diabetic fathers (b); for male controls there were 97 male diabetics (c) and 4903 non-diabetics (d) who were between 50 and 59 years of age. Then, x for the age interval is 12/255 divided by 97/4903 = 2.38; x's were converted to $\log_e$ designated as y. The mean X was then calculated for all fathers of male probands with early age at onset by summing the weights (1/variance) times y's for each age interval and dividing the sum by the sum of the weights, which gives Y. The antilog of Y is X, which is expressed for the example as a twofold increase of risk for fathers compared to controls in Table III.

RISKS

Increased Risk for Relatives Compared to Controls

Under the heading "Per cent Diabetic", Table III shows the absolute risk for fathers and mothers becoming diabetic. The risks are given for the six groups of probands (males and females for the three different ages at onset). It is obvious that as the age at onset of the proband increases, the absolute risk for parents also increases since there are more older parents of probands whose age at onset was 40 years and over. The increased risk for parents compared to the general population, however, is similar for all parents and ranges from a twofold to fourfold increase. This means that the risk for parents remains constant when compared to controls, but the risk for controls increases with age.

TABLE III.—INCREASED RISK FOR DIABETES AMONG LIVING PARENTS OF DIABETICS COMPARED TO RISK FOR CONTROLS

Proband		*Fathers*		*Increased risk for parents compared to controls**
Sex	*Age at onset*	*Number*	*% diabetic*	
Male	0 - 19	879	2.7	x 2
	20 - 39	355	5.1	x 2
	≥ 40	155	14.8	x 4
Female	0 - 19	987	3.3	x 3
	20 - 39	355	7.6	x 3
	≥ 40	152	8.6	x 3
Total		2883	4.8	
		Mothers		
Male	0 - 19	909	0.9	x 2
	20 - 39	456	7.7	x 2
	≥ 40	277	14.4	x 3
Female	0 - 19	1045	2.3	x 2
	20 - 39	434	7.4	x 2
	≥ 40	257	9.7	x 2
Total		3378	4.8	

*This value is a weighted mean of the proportion of diabetes in relatives/proportion in control by sex for each decade of birth.

TABLE IV.—INCREASED RISK FOR DIABETES AMONG LIVING SIBS OF DIABETICS COMPARED TO RISK FOR CONTROLS

Proband		*Brothers*		*Increased risk for sibs compared to controls**
Sex	*Age at onset*	*Number*	*% diabetic*	
Male.....	0 - 19	1236	2.5	x 14
	20 - 39	995	4.0	x 5
	≥ 40	1820	8.0	x 4
Female.....	0 - 19	1382	2.2	x 11
	20 - 39	1125	3.2	x 4
	≥ 40	2272	7.1	x 3
Total.....		8830	5.1	
		Sisters		
Male.....	0 - 19	1142	1.8	x 10
	20 - 39	982	3.4	x 4
	≥ 40	1935	5.0	x 2
Female.....	0 - 19	1308	3.1	x 13
	20 - 39	1107	4.2	x 4
	≥ 40	2518	6.8	x 2
Total.....		8992	4.5	

*This value is a weighted mean of the proportion of diabetes in relatives/proportion in control by sex for each decade of birth.

Tables IV and V summarize the absolute risks and increased risks for sibs and children of diabetic probands compared to the general population. Since the increased risk for sibs and children of diabetics whose onset was less than 20 years of age was markedly greater than the risk for sibs and children of diabetics whose age at onset was 20 years and over (Tables IV and V), similar risks by sex and decade of age were calculated for developing diabetes at less than 20 years compared to controls who developed diabetes before 20 years of age (Table VI). Although the increased risk compared to controls was intermediate for age at onset of 20 to 39 years compared to the other two groups of ages at onset, it was closer to the group with age at onset of 40 years and over. For simplification in counselling, only risks for two groups with ages at onset less than 20 years and 20 years and over are given in Table VI.

TABLE V.—INCREASED RISK FOR DIABETES AMONG LIVING CHILDREN OF DIABETICS COMPARED TO RISK FOR CONTROLS

Proband		*Sons*		*Increased risk for children compared to controls**
Sex	*Age at onset*	*Number*	*% diabetic*	
Male.....	0 - 19	116	2.6	x 40
	20 - 39	662	1.5	x 13
	≥ 40	1479	0.7	x 3
Female.....	0 - 19	145	1.4	x 29
	20 - 39	614	0.7	x 6
	≥ 40	2146	1.4	x 3
Total.....		5162	1.1	
		Daughters		
Male.....	0 - 19	118	2.5	x 41
	20 - 39	657	0.6	x 7
	≥ 40	1400	0.9	x 2
Female.....	0 - 19	175	1.1	x 18
	20 - 39	646	1.2	x 9
	≥ 40	2149	0.7	x 1
Total.....		5145	0.9	

*This value is a weighted mean of the proportion of diabetes in relatives/proportion in control by sex for each decade of birth.

TABLE VI.—SUMMARY OF INCREASED RISKS FOR DIABETES IN RELATIVES OF DIABETICS COMPARED TO CONTROLS

		Increased risk for relative compared to controls*	
		Age at onset	
Age of proband at onset	*Relative*	*<20 yrs. (a)*	*≥ 20 yrs. (b)*
0 - 19.....	Parents	x 5	x 2
	Sibs	x 15	x 8
	Children	x 22	No data
≥20.....	Parents	No data	x 2
	Sibs	x 7	x 3
	Children	x 5	x 2

*Risks are weighted means of the proportion of diabetes in relatives/proportion in control by sex for each decade of birth.

Sex of the proband and of his relative did not contribute as much as their ages at onset to differences in the increased risk for relatives compared to controls. Table VI, therefore, combines data for male and female probands and their male and female relatives. The increased risks for relatives compared to controls (a and b) in Table VI are means weighted for their age and compared with their appropriate male and female controls as described in "Method of Analysis".

Risks for Children When Both Parents are Diabetic

The risks for children in Tables V and VI were estimated from families in which the diabetic proband was married to a non-diabetic spouse. Table VII summarizes frequencies of diabetes in living children of two types of families: when the diabetic proband was married to a non-diabetic spouse and when the proband was married to a diabetic spouse. There were 76 families in which the diabetic proband had at least one child and was married to a diabetic and there were seven diabetics among their 246 children (3%). The data were too few to weight by age and sex as was done for the children when one parent was diabetic. There were no diabetics among the 24 children in the 10 families in which at least one of the two parents

Canad. Med. Ass. J.
Mar. 2, 1968, vol. 98

TABLE VII.—LIVING CHILDREN OF DIABETIC PROBANDS WHEN MARRIED TO DIABETIC AND NON-DIABETIC SPOUSES

Diabetes in parents	*Age at onset (years)*	*Number of families**	*Children*			*Increased risk†*
			*D***	*N****	*% diabetic*	
One diabetic	<40	1294	36	3097	1.15	
Both diabetic	at least one <40	10	0	24	0	
One diabetic	≥40	2339	67	7107	0.93	
Both diabetic	both ≥40	66	7	215	3.15	3.4
One diabetic	any age	3633	103	10,204	0.99	
Both diabetic	any age	76	7	239	2.85	2.9

*Number of families which have at least one child.
**D—diabetic
***N—non-diabetic.
†Increased risk for children when both parents are diabetic compared to that when one parent is diabetic.

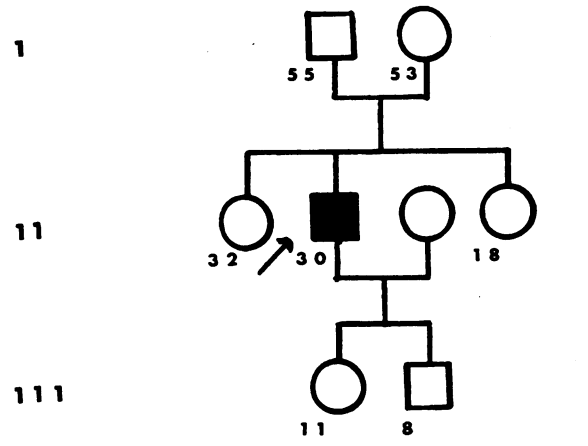
developed diabetes before the age of 40 years. There were seven diabetics among the 222 children (3%) from conjugal diabetic parents who both developed diabetes at 40 years and over, compared to 67 among 7174 children (1%) from one diabetic parent whose age at onset was 40 years and over: a threefold increase of risk for diabetic children from conjugal matings compared to that for children from one diabetic parent. The increased risk given in Table VII was not changed by including the few dead children from the conjugal matings. The risks for children becoming diabetic of 1% when one parent was diabetic and 3% when both parents were diabetic appear low. It must be emphasized that these are absolute risks, not the increased risks for children over that in the population, and that the mean age of the children is about 33 years. Reference to Table V also points out that the children of parents whose age at onset was 40 years and over have the lowest increased risk compared to controls. As they become older, since the population risk will increase, their absolute risk will increase.

Cooke *et al.*[5] have shown that the risk for children from conjugal matings in which at least one parent developed diabetes before 40 years of age was about 12% compared to 3% when both parents developed diabetes at 40 years and over. The risks of 3% in the published sample and 3% in the present one for children from parents with the older age at onset are comparable. The risks of 12% in the published sample when at least one parent had an early onset of diabetes was based on a sample of 57 children, and finding no diabetics among our 24 children could be a chance observation. In any case, it is clear that the risk for children from conjugal matings is at least three times that for children when only one parent is diabetic, and may be more when at least one of the conjugal pair developed diabetes early. In fact, the increased risk when at least one parent was diabetic in conjugal matings noted by Cooke *et al.*[5] is not surprising when the risk for diabetes is increased for children in families in which the age at onset of one parent is early (compared to late) and the other parent is non-diabetic (Table V). The threefold increased risk for children of conjugal matings must also be taken into account when counselling these uncommon families.

Application of Risks to Examples

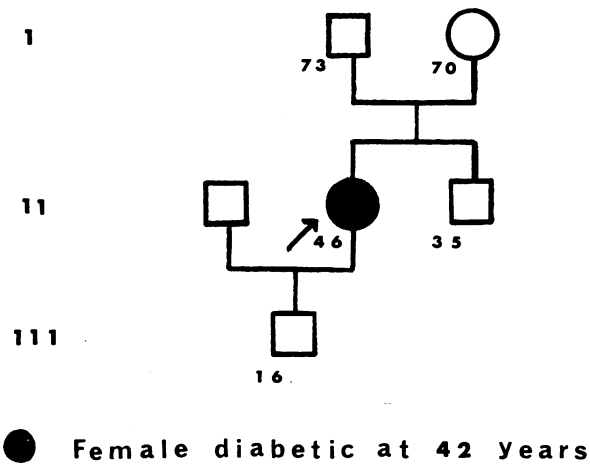
From the data it is possible to estimate the risk for a first-degree relative developing diabetes for each decade of his life. The risk is dependent on the age at onset of the known diabetic in the family. The risk for the relative differs according to his relationship to the proband, the age of onset of the proband and the age and sex of the relative in question. Use of Tables I, II and VI to estimate risks for specific cases is illustrated by two hypothetical families (Figs. 1 and 2).

In Fig. 1 the diabetic proband had an age at onset of 15 years and is now 30 years of age. The ages of other members of the family (i.e., his parents, sibs and children) are shown. The increased risks for early (a) and late (b) ages at onset for the relative in question is read from Table VI and the risk for the general population is read from Table I or II depending on the age and sex of the individual; this is indicated as "population risk for age and sex" in Fig. 1. The per cent risk is then "a" or "b" times the population risk. For example, the 55-year-old father (individual I, 1 in Fig. 1) of the proband has a twofold risk of becoming diabetic (Table VI) and the population risk for males between 50 and 59 years of age is 1.94 (Table I); therefore his risk is $2 \times 1.94 = 3.9\%$. Since the proband in this pedigree developed his diabetes before the age of 20 years, members of the family who still had not reached the age of 20 are probably even more concerned about the risk of becoming a diabetic at an early age. By multiplying the increased risk for becoming dia-



Relative in pedigree	a or b from Table VI		Population risk for age and sex	% risk for diabetes
I, 1	2	x	1.940	3.9
I, 2	2	x	2.477	5.0
II, 1	8	x	0.500	4.0
II, 4	15	x	0.150	2.3
III, 1	22	x	0.128	2.8
III, 2	22	x	0.053	1.2

Fig. 1.—Numbers under males and females in the pedigree indicate their present ages.



Relative in pedigree	a or b from Table VI		Population risk for age and sex	% risk for diabetes
I, 1	2	x	6.038	12.1
I, 2	2	x	3.807	7.6
II, 3	3	x	0.320	1.0
III, 1	5	x	0.128	0.6

Fig. 2.—Numbers under males and females in the pedigree indicate their present ages.

betic at less than 20 years from Table VI (a) by the population risk for their sex from Tables I or II, the per cent risk can be calculated. Therefore, his son of 11 years of age has a risk of $22 \times .128 = 3\%$ for developing diabetes before the age of 20 years.

The risk for the 16-year-old son (III,1) of the woman who developed diabetes at 42 years of age in Fig. 2 would be $5 \times 0.128 = 0.6\%$ for developing diabetes before he is 20 years of age. After he reaches 20 years of age (b) from Table VI would be applied to the appropriate population risk.

COMMENTS

The risks for relatives of diabetics developing diabetes which have been presented are estimates of risks of becoming a diagnosed diabetic because of the nature of the data from which the risks are derived. If family members and physicians have sought to detect diabetes in relatives by glucose tolerance tests and other methods not applied to the population as a whole, the risks are overestimated. According to Klimt *et al.*,[3] relatives of diabetics do not make special efforts to be diagnosed, and it is assumed that this is so for the Canadian families. It may even be possible to predict diabetes in some members of the family by presence of synalbumin[6] or sluggish insulin response.[7, 8]

It was not possible from the data to estimate lifetime risks but only risks for the decade of age in which the relative happens to be. It is also possible to predict his chances of developing diabetes for each subsequent decade of his life. The risks presented will be guidelines for the counsellor of diabetic families. It should be noted that the risks are not as large as the Mendelian genetic risks of 25% and 50% from which the genetic counsellor more often makes his predictions.

Recently, several authors have proposed that diabetes is a result of several genes[2, 9-13] rather than a single recessive gene[14, 15] and that there are more genetic factors responsible for the early age at onset type[2, 12, 13] than for the development of diabetes in later life. Data from the Family Tree Research Program have supported the multifactorial hypothesis with more genetic factors for early age at onset of diabetes.[2, 13] Analysis of the 4000 families additional to the 2600 previously reported[2] still supports the above hypothesis. One of the strongest arguments for the multifactorial hypothesis is the observed threefold increase in the proportion of affected children from conjugal diabetic parents compared to that for children of one

Canad. Med. Ass. J.
Mar. 2, 1968, vol. 98

affected parent (a twofold increase would be expected from the recessive hypothesis). It should be noted that Falconer[13] has estimated that the heritability (the contribution of genes to the liability of being a diabetic) is 70 to 80% for people under 10 years of age and 30 to 40% for people over 50 years of age from the 2600 families.[2]

Only when the individual genes are identified can the genetic contribution to diabetes be satisfactorily settled. The discoveries of a biochemically different insulin in young diabetics[16] and excess of synalbumin in most diabetics[6, 17] may be steps to identify two of these genes.

Summary This study presents estimates of the frequency of known diabetics in the population of the province of Prince Edward Island by sex and decade of age. The increased risks, according to age and sex, for the first-degree relatives of 6600 Canadian diabetics who have been diagnosed as such were compared to those of the general population of the province. This information was collected for the Family Tree Research Program of the Canadian Diabetic Association. The risks for children of parents who are both diabetics were also calculated.

The author discusses the methods employed for counselling and guiding these families, giving concrete examples.

Résumé Cette étude statistique donne, pour la population de l'Ile du Prince Edouard, la fréquence des cas de diabète chez l'homme et la femme par tranche de 10 ans de vie. L'augmentation des risques, suivant l'âge et le sexe, pour les parents en ligne directe de diabétiques qui ont été diagnostiqués comme tels, comparée aux risques encourus par l'ensemble de la population de cette province canadienne a été calculée chez 6600 familles canadiennes. Ces données ont été recueillies par le Comité de Recherches généalogiques de l'Association diabétique canadienne. On a également calculé le risque que courent les infants dont le père et la mère sont tous deux diabétiques. L'auteur expose les méthodes employées pour conseiller et guider des familles déterminées et illustre cette méthode par des exemples concrets.

The moral and financial support of the Canadian Diabetic Association and its Foundation Fund throughout the study are most gratefully acknowledged. I am particularly indebted to Mr. C. E. Praught of the Prince Edward Island provincial government for making their records of diabetics available and to the Queen's University Computer Centre for their services during analysis of the data.

The author wishes to thank Dr. H. B. Newcombe, Atomic Energy Commission, Chalk River, Canada, for his interest, encouragement and helpful suggestions.

REFERENCES

1. RIMOIN, D. L.: *Diabetes*, **16**: 346, 1967.
2. SIMPSON, N. E.: *Ibid.*, **13**: 462, 1964.
3. KLIMT, C. R. *et al.*: *Ibid.*, **16**: 40, 1967.
4. WOOLF, B.: *Ann. Hum. Genet.*, **19**: 251, 1955.
5. COOKE, A. M. *et al.*: *Brit. Med. J.*, **2**: 674, 1966.
6. VALLANCE-OWEN, J.: *Diabetologia*, **2**: 248, 1966.
7. PYKE, D. A. AND TAYLOR, K. W.: *Brit. Med. J.*, **4**: 21, 1967.
8. TAYLOR, K. W. *et al.*: *Ibid.*, **4**: 22, 1967.
9. SIMPSON, N. E.: *Ann. Hum. Genet.*, **26**: 1, 1962.
10. NEEL, J. V. *et al.*: Diabetes mellitus. *In*: Genetics and the epidemiology of chronic diseases, edited by J. V. Neel, M. W. Shaw and W. J. Schull, Public Health Service Publication No. 1163, Washington, 1965, p. 105.
11. THOMPSON, G. S.: *J. Med. Genet.*, **2**: 221, 1965.
12. MALINS, J. M. *et al.*: *Brit. Med. J.*, **1**: 960, 1965.
13. FALCONER, D. S.: *Ann. Hum. Genet.*, **31**: 1, 1967.
14. BARRAI, I. AND CANN, H. M.: *J. Med. Genet.*, **2**: 8, 1965.
15. STEINBERG, A. G.: *Ann. N.Y. Acad. Sci.*, **82**: 197, 1959.
16. ELLIOTT, R. B., O'BRIEN, D. AND ROY, C. C.: *Diabetes*, **14**: 780, 1965.
17. EHRLICH, R. M. AND MARTIN, J. M.: *Ibid.*, **15**: 400, 1966.