
ORIGINAL ARTICLES

Diabetes and Cardiovascular Risk Factors: The Framingham Study

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SUMMARY The impact of cardiovascular disease was compared in non-diabetics and diabetics in the Framingham cohort. In the first 20 years of the study about 6% of the women and 8% of the men were diagnosed as diabetics. The incidence of cardiovascular disease among diabetic men was twice that among non-diabetic men. Among diabetic women the incidence of cardiovascular disease was three times that among non-diabetic women.

Judging from a comparison of standardized coefficients for the regression of incidence of cardiovascular disease on specified risk factors, there is no indication that the relationship of risk factors to the subsequent development of cardiovascular disease is different for diabetics and non-diabetics.

This study suggests that the role of diabetes as a cardiovascular risk factor does not derive from an altered ability to contend with known risk factors.

THE DISCOVERY OF INSULIN in 1921 and the later availability of the oral hypoglycemic agents has shifted the problem of diabetes from the acute metabolic consequences of ketoacidosis and coma resulting in early death, to the cardiovascular sequelae in later life. Despite the availability of effective hypoglycemic agents and more sensitive diagnostic methods allowing earlier treatment, physicians continue to encounter an excessive incidence of coronary heart disease, strokes, renal failure, retinopathy, neuropathy, and congestive heart failure among their diabetic patients. There is a need to explore further the details of the relation of diabetes to the development of cardiovascular disease (CVD).

In this report we examine the relationship of the evidence of diabetes to subsequent CVD in the presence of other cardiovascular risk factors. In particular, the question of interaction between diabetes and other cardiovascular risk factors is explored.

Methods

The Framingham Study has been in continuous operation for 25 years, following a cohort of 5209 men and women aged 30–62 years at initial examination biennially to learn in what areas those who develop CVD differ from those who remain free of it. At each biennial examination each participant was given a thorough standardized cardiovascular examination which also elicited information concerning their physical characteristics, living habits, blood chemistry and other characteristics suspected of contributing to

the occurrence of CVD.¹ This was supplemented by information on cardiovascular illness and death from daily surveillance of hospital admissions to the only hospital in town, attending physician's and medical examiner's reports, information from the spouse and other extra-clinic sources.²

Details of the laboratory methods and clinical criteria used are available elsewhere.¹ Clinical cardiovascular end points were established from biennial clinical examinations confirmed by two physician examiners, panel review of hospital protocols and death certificates, ECG findings and cardiac enzymes.

A description of the method of measurement of risk factors and the precise criteria for a definition of diabetes may be found elsewhere.¹ A person was diagnosed as having diabetes mellitus if he or she was under treatment for diabetes or had elevated casual blood glucose determinations at two successive examinations.

Follow-up of the cohort has been reasonably complete, with 3% lost to follow-up for cardiovascular mortality in 20 years. For each examination there was an 85% participation level. The rest were examined at less frequent intervals, with 69% total population participation over all examinations up to and including the tenth biennial examination or until the time of their death. Few cardiovascular events were unaccounted for, since we arranged later examinations for those missed, had daily hospital surveillance and obtained other ancillary information.

Statistical Methods

Prevalence of diabetes as reported here is a weighted average of prevalence over the period of follow-up. The prevalence at any exam was weighted by the number of persons taking the exam.

It has been shown in previous reports^{1, 2} that diabetics have a higher risk of CVD at any level of risk factors. The question in the present report is whether

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Received November 21, 1977; revision accepted August 30, 1978.
Circulation 59, No. 1, 1979.

the impact of risk factors on the development of CVD is the same for diabetics and non-diabetics. In terms of statistical hypotheses, this is the hypothesis of no second order interaction. The no second order interaction hypothesis, when applied to several 2×2 contingency tables, is expressed in terms of the equality of odds ratios. A model which is easily applied to testing the no second order interaction hypothesis is the logistic model. Testing the equality of logistic coefficients is equivalent to testing the no second order interaction hypothesis.

The logistic function assumes that the probability of a person developing disease in some specified time frame, given the values of several baseline characteristics x_1, \dots, x_r is:

$$P(\text{event}/x_1, \dots, x_r) = 1/(1 + \exp(-\alpha - \beta_1 x_1 - \dots - \beta_r x_r))$$

where α and $\beta_1 \dots \beta_r$ are unknown parameters. Given the baseline characteristics and the subsequent disease experience of a population, maximum likelihood estimates of α and β can be obtained using a Newton-Raphson iterative procedure as suggested by Walker and Duncan.³

In order to assure roughly equivalent follow-up for all participants and to obtain maximal use of the data, the data from all 10 biennial exams were pooled. At any exam all persons at risk of CVD at the exam are classified according to the values of the characteristics being considered. A person is considered at risk of CVD if he has not previously been diagnosed as having either CVD or rheumatic heart disease. A person remains at risk according to this classification until the next biennial exam, when he or she is reclassified according to his new values for the characteristics of interest. Thus, a person might contribute follow-up to more than one age group and would be considered a non-diabetic until diagnosed as being a diabetic. The method of pooling is analogous to using person years in that each person contributes 2 years of experience at each examination.

The logistic function may be used for two purposes. First, it may be used to model the occurrence of CVD given the values of specified risk factors. Secondly, preliminary models can be tested in order to analyze the relationship of antecedent factors to the incidence of CVD. It is for the latter purpose that the logistic function was used in the present report. Earlier reports have indicated that diabetics have a higher risk of CVD at any level of risk factors. The question here is whether the impact, e.g., of an elevated blood pressure, is different in diabetics and non-diabetics; that is, whether there is interaction between diabetes and blood pressure. In terms of the logistic function, this is the question of whether, if we estimate univariate logistic coefficients for diabetics and non-diabetics, the β associated with blood pressure is the same in diabetics and non-diabetics. If no interaction is found, the best estimates of the β s would be those derived from pooling diabetics and non-diabetics and using a model

including a term for diabetics status. For this reason the coefficients presented here should be viewed as analytic tools rather than part of predictive equations; thus, only β s are presented.

An issue not directly related to interaction, but of interest, is whether the relative impact of the risk factors is the same for diabetics and non-diabetics. To judge this, the coefficients must be transformed so that they refer to the same scale. This was accomplished by calculating standardized coefficients, i.e., each estimated coefficient was multiplied by the standard deviation of the variable with which it was associated. The magnitude of these standardized coefficients can then be compared for the different risk factors.

Before proceeding further with the analysis of interaction, we had to decide how to handle age. First, we considered the question of an age and diabetes interaction. Although the impact of diabetes appeared to wane with age, the trend was not statistically significant, and hence, in the succeeding analysis we made the assumption of no age and diabetes interaction. Two methods of accounting for age were available. First, age could have been included in the model and coefficients estimated over the age range. Secondly, the analysis could be done within age ranges and the results summarized. Although both methods were done and basically identical results achieved, the latter method was selected for presentation because we believed the majority of readers would prefer to see age-specific results.

Given two independent estimates of β , and their standard errors, the difference may be tested using an approximately normal statistic. That is, since the β s are asymptotically normal, the difference divided by the standard error of the difference is asymptotically normal under the hypothesis that the β s are equal. One further decision was necessary. Should the differences be tested age-specific or in some summary form? Here, we are faced with a multiple comparisons problem. We would be making 24 age-sex-specific comparisons, and thus would expect one or two significant results on a random basis. We felt that the safest inferences were to be made on a summary basis. To summarize the results, an average β and its standard error for each sex-specific diabetic group was calculated. The average β was calculated as the weighted average of the three β s, the weights being the inverse of the associated variances. Given an average coefficient and its standard error for the diabetic and non-diabetic groups, the hypothesis that the two are equal may be tested in the same manner as described previously.

Age adjustment was accomplished using the logistic function by first estimating the coefficients for a model, including age and diabetes as risk variables. A probability of developing an event was calculated for each person according to his or her true diabetic status, but adjusting to age 60 years. These assigned probabilities were summed within sex and diabetic status categories. The resulting sums can be viewed as the expected number of cases if everyone were age 60 years.

TABLE 1. *Number of Diabetics and Prevalence of Diabetics in Specified Age and Sex Groups*

Age (years) at exam	Men		Women	
	Number	Prevalence (%)	Number	Prevalence (%)
45-54	378	5.4	322	3.5
55-64	478	9.5	528	7.4
65-74	226	12.7	322	11.8
Total	1082	7.8	1172	6.2

Only persons free of CVD and RHD are included in the population.

Numbers and prevalence are over the period of follow-up (see text).

Abbreviations: CVD = cardiovascular disease; RHD = rheumatic heart disease. CVD includes atherosclerotic and hypertensive cardiovascular disease.

The results were normalized so that the expected total number of cases for either sex agrees with the observed number. The rates calculated from these normalized results are termed age-adjusted rates.

Results

Over the 20-year period, the prevalence of diabetes in both sexes increased with age. There was a higher prevalence of diabetes in men in the younger age groups, but the difference in prevalence between the sexes decreased in the oldest age group. The overall prevalence was 7.8% for men and 6.2% for women (table 1).

For all age groups and in both sexes the incidence of CVD was higher among diabetics than non-diabetics. Overall, the incidence of CVD among diabetic men was roughly twice that among non-diabetic men. Among diabetic women, the incidence of CVD was almost three times that among non-diabetic women (table 2). The risk ratios appear to decrease with advancing age; however, the age trend is not statistically significant.

Table 3 gives age-adjusted mean level of the cardiovascular risk factors to be considered. These means are given by diabetic status, and by whether a cardiovascular event occurred in the 2 years subsequent to the measurement. Diabetic men, both cases and non-cases, were more obese, had lower cholesterol, and smoked less than their non-diabetic counterparts.

TABLE 2. *Average Annual Incidence of Cardiovascular Disease Per 1000 Persons At Risk According to Age, Sex and Diabetic Status*

Age (years) at exam	Men		Women	
	Diabetics	Non-diabetics	Diabetics	Non-diabetics
45-54	31.7	12.3	24.8	4.3
55-64	48.1	25.1	37.9	12.6
65-74	57.5	28.4	40.4	22.4
Total	39.1	19.1	27.2	10.2

The total rate is an age-adjusted rate.

TABLE 3. *Age-Adjusted* Mean Levels of Specified Characteristics Among Diabetics and Non-Diabetics, by Sex and Whether Developed Cardiovascular Disease in 2 Years. The Framingham Study 20-Year Follow-up*

	Men			
	Diabetics		Non-diabetics	
	Cases	Non-cases	Cases	Non-cases
n	76	1092	522	12,942
SBP (mm Hg)	147.0	142.0	146.9	136.0
Chol (mg%)	238.7	229.6	244.3	232.7
Cigs (no. per day)	12.5	9.4	15.7	12.2
MRW (% of ideal weight)	126.0	126.8	122.9	120.1
	Women			
	Diabetics		Non-diabetics	
	Cases	Non-cases	Cases	Non-cases
n	72	1266	379	18,272
SBP (mm Hg)	165.3	152.4	153.8	139.6
Chol (mg %)	281.0	259.2	261.8	250.2
Cigs (no. per day)	4.9	5.6	5.7	5.3
MRW (% of ideal weight)	145.3	135.5	128.5	122.5

*Adjusted to age distribution of total population.

Abbreviations: n = number of cases studied; SBP = systolic blood pressure; Chol = cholesterol; MRW = Metropolitan relative weight.

While diabetic men who were non-cases had higher blood pressure than non-diabetics, among cases, the mean level of pressure was roughly the same. Diabetic women, both cases and non-cases, were more obese and had higher blood pressures and cholesterol, but smoked roughly the same amount as their non-diabetic counterparts.

Table 4 gives the standardized univariate logistic coefficients for systolic blood pressure in the various age-sex-diabetic status categories. It should be kept in mind when considering these coefficients for specific age groups that those for diabetics are estimated using rather small numbers (table 1). The variances of the estimated coefficients for diabetics are very large because of the small numbers involved. The coefficients displayed are standardized coefficients, so that their magnitude, and hence, the differences in their magnitude, are in general larger than for the estimated coefficients. This should be noted also when considering the coefficients for the risk factors to be considered in the following. Standardized coefficients were used to allow a comparison of the impact of the various risk factors with each other on an equal footing.

The average coefficient for systolic blood pressure is smaller among diabetics than that among non-diabetics for both sexes; however, the averages do not differ significantly in either sex. Thus, the regression of incidence of CVD of blood pressure cannot be said to differ in diabetics and non-diabetics.

TABLE 4. Standardized Univariate Logistic Coefficients for Regression of Cardiovascular Disease on Systolic Blood Pressure for Specified Populations and Events

Age (years) at exam	Event: CVD in two years, persons free of CVD and RHD at exam							
	Men				Women			
	Diabetics		Non-diabetics		Diabetics		Non-diabetics	
	β	SE (β)	β	SE (β)	β	SE (β)	β	SE (β)
45-54	0.039	0.297	0.403	0.064	0.455	0.329	0.419	0.081
55-64	0.030	0.218	0.476	0.055	0.151	0.225	0.522	0.061
65-74	0.603	0.256	0.254	0.095	0.710	0.253	0.400	0.087
Average	0.216	0.145	0.414	0.038	0.410	0.150	0.464	0.043

Abbreviations: CVD = cardiovascular disease; RHD = rheumatic heart disease. CVD refers to atherosclerotic and hypertensive cardiovascular disease.

Table 5 gives the standardized univariate, logistic coefficients for serum cholesterol in the various categories. Here, also, the average coefficients for the diabetic and non-diabetic groups do not differ significantly for either sex.

Table 6 displays the standardized univariate logistic coefficients for cigarettes. Here not only are the differences in the average coefficients of diabetics and of non-diabetics non-significant, but also the absolute magnitudes are roughly the same in spite of the small numbers.

Table 7 gives the standardized logistic coefficients for Metropolitan Relative Weight for the specified categories. Although large differences in magnitude are shown, the average coefficients for diabetics and for non-diabetics do not differ significantly, nor are they consistent in direction in each age group and sex. There is no indication of a greater impact of obesity in diabetics.

Discussion

Diabetics have an increased risk of cardiovascular morbidity and mortality.⁴⁻⁸ They particularly have an increased risk of congestive failure.⁹ Diabetics in less affluent societies have fewer cardiovascular complications compared with non-diabetics in the same area and to diabetics in affluent societies.¹⁰⁻¹² This suggests that not all diabetes is the same or that other factors markedly influence its impact on health.

Diabetes mellitus was originally considered a simple consequence of a pancreas unable to produce enough

insulin, causing the blood sugar to become unduly elevated which, in turn, produced a series of disastrous metabolic alterations culminating in coma and death. Current concepts are more complex. Diabetes beginning in childhood is usually due to severe insulin deficiency; when it first appears in adult life, it is often associated with normal or increased insulin levels. In the latter case, something interfering with insulin utilization seems more likely.

The cause of hyperglycemia, which is the *sine qua non* of "diabetes," is still obscure. At times it can be traced to specific causes such as chronic pancreatitis, thyroid, adrenal or pituitary endocrine disorders and as a consequence of steroid, diuretic or oral contraceptive administration. Viruses (particularly B-4 coxsackievirus) may also play a role. However, in most cases of either adult or childhood onset diabetes, the reason for underproduction of insulin or for less effective insulin production is poorly understood. Genetic factors undoubtedly play a role, and diabetes definitely runs in families. However, the pattern of inheritance is more complex than originally thought, and it is not possible to predict accurately whether parents with diabetes will transmit the disease to their offspring.

The cardiovascular sequelae of diabetes may differ, depending on whether the diabetes is hyperinsulinemic, early or late in onset, caused by some known cause, or treated or untreated. These possibilities are not addressed in this report.

It is not clear whether, when considering cardio-

TABLE 5. Standardized Univariate Logistic Coefficients for Serum Cholesterol for Specified Populations

Age (years) at exam	Event: CVD in two years, persons free of CVD and RHD at exam							
	Men				Women			
	Diabetics		Non-diabetics		Diabetics		Non-diabetics	
	β	SE (β)	β	SE (β)	β	SE (β)	β	SE (β)
45-54	0.039	0.302	0.360	0.065	0.460	0.252	0.294	0.112
55-64	0.553	0.218	0.208	0.064	0.046	0.231	0.246	0.074
65-74	0.222	0.272	0.004	0.106	0.147	0.294	0.208	0.093
Average	0.312	0.148	0.240	0.042	0.213	0.147	0.244	0.051

Abbreviations: CVD = cardiovascular disease; RHD = rheumatic heart disease. CVD refers to atherosclerotic and hypertensive cardiovascular disease.

TABLE 6. *Standardized Univariate Logistic Coefficients for Cigarettes/Day for Specified Populations*

Age (years) at exam	Event: CVD in two years, persons free of CVD and RHD at exam							
	Men				Women			
	Diabetics		Non-diabetics		Diabetics		Non-diabetics	
	β	SE (β)	β	SE (β)	β	SE (β)	β	SE (β)
45-54	0.343	0.280	0.272	0.072	-0.041	0.376	0.047	0.111
55-64	0.227	0.185	0.232	0.060	-0.094	0.249	0.007	0.076
65-74	-0.256	0.373	0.021	0.107	0.148	0.247	0.100	0.083
Average	0.186	0.143	0.206	0.042	0.016	0.159	0.049	0.050

Abbreviations: CVD = cardiovascular disease; RHD = rheumatic heart disease. CVD refers to atherosclerotic and hypertensive cardiovascular disease.

vascular disease prevention, screening for asymptomatic hyperglycemia is justified. Unlike blood pressure, where even in the absence of symptoms, treatment may be proven effective, it is not established whether treatment of mild, asymptomatic hyperglycemia will prevent damage to the heart, brain, kidney or eye. However, such information used in conjunction with other cardiovascular risk factors might help in risk assessment to indicate the urgency for other interventions of proven efficacy.

Numerous reports of risk factors in the diabetic are available, including some on the question of interaction. The elevated blood pressure of diabetics in the Framingham study has been reported previously.⁴ This finding is in accord with some findings,¹³ while it differs with others.¹⁴ The interaction between diabetes and blood pressure has also been investigated. In one study¹⁴ an interaction was found, while in another study it was not.¹⁵ Both of these studies were of mortality. In the study finding interaction, it was reported that diabetics tolerated hypertension less well than non-diabetics.

In comparisons of lipid values of diabetics and non-diabetics, diabetics have generally been found to have elevated cholesterol values.¹⁶⁻¹⁸ The female diabetics in the Framingham study have a generally higher level of serum cholesterol; the males have a lower level.

Possible differences in treatment are not taken into account in the present analysis. Other studies have indicated that diabetics who develop atherosclerotic

complications have higher cholesterol values than those who do not,¹⁹ but there does not appear to have been any previous analysis of possible interaction between cholesterol and diabetes.

Some studies of cigarette smoking among diabetics have been published.²⁰⁻²² The finding of reduced cigarette consumption among diabetic males appears to be unique to Framingham. Although the question of interaction between diabetes and cigarette smoking has been raised,²³ the present report appears to be the first formal analysis of the question. The finding of higher relative weights and no interaction between relative weights and diabetes is in accord with previous reports.^{15, 24, 25}

In general, it does not appear that diabetics cope less well with risk factors than do non-diabetics. Although the present analysis is based on a limited number of diabetics, the evidence is consistently against interaction between diabetes and cardiovascular risk factors.

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TABLE 7. *Standardized Univariate Coefficients for Metropolitan Relative Weight for Specified Populations and Events*

Age (years) at exam	Event: CVD in two years, persons free of CVD and RHD at exam							
	Men				Women			
	Diabetics		Non-diabetics		Diabetics		Non-diabetics	
	β	SE (β)	β	SE (β)	β	SE (β)	β	SE (β)
45-54	-0.170	0.318	0.199	0.075	0.599	0.335	0.301	0.090
55-64	-0.228	0.239	0.174	0.065	0.169	0.216	0.225	0.068
65-74	0.221	0.290	0.042	0.106	-0.360	0.319	0.034	0.094
Average	-0.078	0.160	0.159	0.045	0.135	0.158	0.198	0.047

Abbreviations: CVD = cardiovascular disease; RHD = rheumatic heart disease. CVD refers to atherosclerotic and hypertensive cardiovascular disease.

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