Risk Factors for the Development of Type II Diabetes Among Men Enrolled in the Usual Care Group of the Multiple Risk Factor Intervention Trial

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OBJECTIVE — To study the association between selected risk factors and the subsequent incidence of type II diabetes over a 5-yr period.

RESEACH DESIGN AND METHODS — Between 1973 and 1976, a cohort of men from 22 clinical centers throughout the U.S. enrolled in the Usual Care group of the Multiple Risk Factor Intervention Trial. The men (5420 white, 428 black, 56 Asian, 70 Hispanic, and 26 other) were nondiabetic at baseline, were in the upper 15% of risk for coronary heart disease, and had at least two annual follow-up visits for fasting glucose measurements. The average age was 46 yr and average body mass index was 27.6 kg/m^2. Incidence of diabetes was defined as use of insulin or hypoglycemic agents, fasting glucose ≥140 mg/dl on two consecutive annual visits, or fasting glucose ≥140 mg/dl followed the next year by insulin or hypoglycemic use. Observations were taken annually over a 5-yr period.

RESULTS — Cumulative incidence of diabetes over 5 yr was 4.1%, with 247 incident cases. Development of diabetes was directly associated with race (blacks higher than non-blacks), reported parental history of diabetes, and with baseline levels of body mass index, fasting glucose, and glucose 1 h after a 75-g oral glucose load. These associations were statistically significant in both univariate and multivariate models. A significant interaction was observed between race and reported parental history of diabetes in development of diabetes, particularly within black men who reported a parental history. These individuals had higher than expected rates of diabetes development.

CONCLUSIONS — The data from men in the Usual Care group enrolled in the Multiple Risk Factor Intervention Trial confirm previous findings regarding the associations between the development of diabetes and baseline glucose levels, obesity, race, and parental history of diabetes. The identification of these risk factors provides very powerful tools to identify individuals at high risk of diabetes mellitus who may be amenable to intervention, thereby reducing their risk of developing the disease and its complications.

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Type II diabetes, non-insulin-dependent diabetes mellitus; CVD, cardiovascular disease; MRFIT, Multiple Risk Factor Intervention Trial; CHD, coronary heart disease; SI, special intervention; BP, blood pressure; dBP, diastolic blood pressure; sBP, systolic blood pressure; UC, usual care; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; WHO, World Health Organization; NDDG, National Diabetes Data Group; CI, confidence interval; type I diabetes, insulin-dependent diabetes mellitus; NHANES, National Health and Nutrition Examination Survey; RR, relative risk.

Type II diabetes is a common disorder, prevalent in ~6% of white and 10% of black U.S. citizens 20–74 yr of age (1). Prevention of the disease could substantially decrease morbidity and mortality in the community, especially that related to renal disease, peripheral vascular disease, and CVD. Although the genetic contribution to the etiology of type II diabetes is strong, epidemiological studies have uncovered risk relationships that have important implications for the possibility of prevention (2).

Factors associated with the incidence of type II diabetes in individuals with initially normal levels of glucose tolerance have been studied in ethnically distinct populations. These populations include: the Pima Indians in Arizona (3–5); the Nauruans in Micronesia (6–7); whites in Paris, France (8–9), Iceland (10), and Sweden (11–12); Japanese Americans (13). In addition, studies have been conducted on populations residing in a single community or nation such as San Antonio, TX (14), former college students (15), Framingham, MA (16), Israel (17–19), participants in the Lipid Research Clinics Prevalence Study in Rancho Bernardo, CA (20), working men in Oslo, Norway (21), Tecumseh, Michigan (22), men in Uppsula, Sweden (23), and the Zutphen Study in the Netherlands (24). Studies of ethnically distinct populations with high rates of type II diabetes, such as the Pima Indians of Arizona (3–5) or the Nauruans of the South Pacific (6–7), have the advantage that the high incidence of diabetes facilitates identification of risk factors of the disease, the disadvantage being that results may not be generalizable to other populations. Community-based studies may be generalizable, at least to similar communities, but because rates of type II diabetes may be low, a great many subjects are required for studying possible risk factors. Furthermore, in both types of studies, the number of incident cases generally has been low (63 cases in Paris

[8–9], 28 in San Antonio [14], 44 in Oslo [21], 58 in Zutphen [24]), either because of small, high-risk populations or low rates within normal populations.

The MRFIT, a clinical trial of the primary prevention of CHD in middle-aged men, enrolled 12,866 participants from several ethnic backgrounds in 22 clinical centers across the U.S. (25). All the men were considered high-risk candidates for developing CHD on the basis of their dBP, serum cholesterol, and cigarette smoking behavior; none had a history of angina or myocardial infarction. Of the men participating in the study, ~50% (6428) were randomized to an SI group, were invited to attend the clinics every 4 mo, and received interventions intended to lower their BP and levels of serum cholesterol, and to help them stop smoking. The other men (n = 6438) were randomized to a UC group and received no targeted interventions. These men were invited to return to the clinic once a year for a physical exam and to complete a medical history and behavioral questionnaire. Extensive and complete follow-up data are available annually for 6 yr, with clinic attendance exceeding 90% during this period.

The data from the UC men enrolled in the MRFIT provide an excellent opportunity to study the associations between baseline risk factors in an initially nondiabetic population and the subsequent development of type II diabetes. UC men received no intervention from MRFIT staff to change their risk factor profile. Therefore, any associations found between baseline levels of risk factors and subsequent development of type II diabetes are not as likely to be confounded by changes in the risk factors as would be the case with the SI men.

The goals of this study were to evaluate the risks of, primarily, type II diabetes by race (i.e., black as compared with a predominantly white group), baseline blood glucose (both fasting and 1 h after a 75-g oral glucose load), obesity as measured by BMI, and reported parental history of diabetes. The risk factors were analyzed separately for those with and without a parental history of diabetes. We also evaluated the association of cardiovascular risk factors and the development of diabetes.

RESEARCH DESIGN AND METHODS

MRFIT procedures

Detailed descriptions of the MRFIT have been published previously (25,26). Briefly, the MRFIT was a primary prevention trial to determine the effects of multifactor intervention on CHD mortality in a group of high-risk men randomly assigned either to a SI program or to their usual sources of medical care. Between December 1973 and February 1976, over 360,000 men were screened for eligibility at 22 clinical centers throughout the U.S. Of this group, 12,866 men (35–57 yr of age) were enrolled in the trial, 6428 randomized to the SI group, and 6438 randomized to the UC group.

Screening occurred at three visits. At screen 1, men were scored for their risk of CHD on the basis of their measurements for serum cholesterol, dBP, and self-reported cigarette smoking, using a multiple logistic regression equation derived from the Framingham Heart Study (27). Men who were in the upper 15% (changed to 10% after one-third of the screening was completed) of risk were invited to attend screen 2.

At screen 2, a blood sample was taken after a requested overnight fast. The blood was analyzed at a central laboratory at the Institute of Medical Sciences, San Francisco, CA, using a protocol described previously (28). Measurements were determined for serum glucose in the fasting sample and in a sample taken 1 h after a 75-g oral glucose load. Measurements also were performed for total plasma cholesterol, HDL cholesterol, LDL cholesterol, TGs, and uric acid. The methods used for lipid determination are described elsewhere (29–30).

Height and weight (disrobed) were measured at screen 2. Individuals with body weight ≥150% of desirable weight were excluded from the trial, where desirable weight was defined as 0.9 of the average for men of the same height in the 1960–1962 National Health Examination Survey (30). BMI, defined as kg/m^2, is used as the measure of relative weight in this report. Alcohol consumption was assessed by an interview at screen 2 to determine the number of drinks per week of beer, wine, or whiskey beverages the man usually consumed. Individuals believed to be consuming excessive amounts of alcohol were excluded from the trial.

BP was measured according to a standard protocol by certified observers (31). The first and fifth Korotkoff phase readings obtained with a random-zero sphygmomanometer while the participant was seated were recorded as sBP and dBP. The means of two measurements at screen 2 and two measurements at screen 3 are used as baseline BP in this report.

A participant was considered to have a parental history of diabetes if at screen 2 the male participant indicated on a self-administered medical history questionnaire that either one or both of his parents had diabetes. A parental history of no diabetes was considered if the participant indicated that neither his mother nor his father had diabetes, or if the participant was unsure.

Definition of diabetes

UC men were invited to return to the clinical center once a year for an examination and to complete a behavioral and medical history questionnaire, which had been mailed to them previously. The men were requested to arrive at their annual visits in the morning after an overnight fast. A blood sample was taken at each annual visit, and serum glucose concentration was measured. In the annual medical history questionnaire, the men were asked if at any time in the previous 12 mo, a physician had told him he had diabetes. They also were asked if they were using insulin or oral

Table 1—*Yearly and cumulative incidence of diabetes for MRFIT UC men*

Year	Diagnosed with diabetes (*n*)*	Yearly incidence†	Cumulative diagnosed (*n*)	Cumulative incidence‡
1	30	0.51	30	0.50
2	35	0.61	65	1.08
3	51	0.91	116	1.93
4	54	0.99	170	2.83
5	77	1.44	247	4.12

*Defined as use of insulin or oral hypoglycemic agents, or two successive years with fasting glucose ≥140 mg/dl or fasting glucose ≥140 mg/dl followed by insulin or hypoglycemic drug use.
†Yearly incidence is the percentage of those who developed diabetes that year compared with those at risk that year.
‡Cumulative incidence is the percentage of those who developed diabetes by that year compared with 6000 men at risk at baseline. See METHODS for exclusions.

hypoglycemic agents either currently or within the past 12 mo.

Three successively less stringent criteria for defining diabetes were initially considered and later restricted to a single criterion. Under the most stringent criterion, type II diabetes was defined as occurring in the year in which the participant first reported the use of insulin or hypoglycemic drugs either currently or within the previous 12 mo (drug use). Under the next criterion, type II diabetes was defined as occurring either in the year in which drugs were first reportedly used, or in the first of two consecutive years in which fasting glucose was ≥140 mg/dl (7.77 mM), or in the year when fasting glucose was ≥140 mg/dl (7.77 mM) followed the next year by insulin or hypoglycemic drug use (hard criterion). Under the final criterion, diabetes was diagnosed when any of the circumstances described above were met or in the first year when the male participant reported that a physician had told him he had diabetes (soft criterion).

Of the three criteria considered, the hard criterion was chosen as the definition of diabetes and was the end point for subsequent analyses. Compared with our other criteria, this one most closely matched the diagnostic criteria recommended by WHO (32) and the NDDG (33). Use of the hard criterion to define diabetes required two successive glucose values ≥140 mg/dl (7.77 mM); because the sixth visit was the final visit for ~50% of the participants, it was not possible to determine who had a high glucose value at yr 6 and also at yr 7. For this reason, this study considers the incidence of type II diabetes through the first 5 yr of the trial only.

Exclusions

The MRFIT attempted to exclude known diabetic individuals from the trial. Individuals using insulin or hypoglycemic drugs were excluded, as were those who were not being treated but who exhibited clinical symptoms of hyperglycemia (26). Despite these exclusion criteria, the UC group included 115 men with baseline fasting glucose of ≥140 mg/dl. It also included 26 men whose glucose 1 h after a 75-g oral glucose load was ≥300 mg/dl (16.65 mM) and an additional 297 men with <2 fasting glucose readings throughout the trial. These men were excluded from the present analysis, leaving 6000 UC men classified as nondiabetic who were at risk of developing diabetes over the next 5 yr.

Statistical analysis

Differences in baseline risk factors between men who did and did not develop type II diabetes were assessed using the Student's *t* test statistic for continuous variables and the χ^2 test for discrete variables. Multivariate associations were assessed with Cox proportional hazards regression models, using time to the first diagnosis of diabetes as the dependent variable. Interactions were assessed by including cross-product terms in the regression models, and all models were stratified by clinical center.

RESULTS — Table 1 shows the yearly and cumulative incidence of diabetes for UC men. The cumulative incidence of diabetes for SI men during the same period was 3.95% (239 cases out of 5905 at risk at baseline), with an age-adjusted risk relative to the UC group of 0.97 (95% CI 0.81–1.16). The nature of the intervention offered to men in this group affected many of the risk factors under study (BMI, BP, cholesterol, and smoking); thus the analysis was restricted to the UC men to more closely stimulate an observational study.

Table 2 shows the baseline values of selected characteristics for UC men with and without a diagnosis of diabetes. Compared with men who were not diagnosed, men who were diagnosed had higher average age, sBP, uric acid, TGs, BMI, and fasting and 1-h postload glucose. In addition, a higher percentage of those diagnosed were black and reported a parental history of diabetes. However, lower values were observed for plasma HDL and LDL cholesterol in those diagnosed with diabetes. Also, the percentage reporting smoking and number of alcoholic drinks per week were lower in the men diagnosed with diabetes.

Table 3 presents the age-adjusted and fully adjusted relative risks of developing diabetes, using proportional hazards models for the risk factors under study. After adjusting only for age, the risk of developing diabetes increased significantly ($P < 0.05$) with being black; higher levels of BMI, fasting glucose, glucose 1 h after a 75-g oral glucsoe load; and reported parental history of diabetes.

After adjusting for all risk factors except glucose (but including sBP, uric acid, TGs, alcoholic drinks per week,

Table 2—*Baseline values of selected clinical characteristics for MRFIT UC men with and without a diabetes diagnosis*

	Nondiabetic men	Diabetic men	*P* value
n	5753	247	
Age (yr)	46.2	48.0	<0.01
sBP (mmHg)	134.8	139.9	<0.01
Plasma uric acid (mg/dl)	6.8	7.1	<0.01
Plasma TGs (mM/mg/dl)	4.89/189.1	6.01/232.6	<0.01
BMI (kg/m^2)	27.6	29.6	<0.01
Reported number of alcoholic drinks/wk	12.6	10.9	0.03
Plasma HDL cholesterol (mM/mg/dl)	1.09/42.3	1.00/38.8	<0.01
Plasma LDL cholesterol (mM/mg/dl)	4.16/160.7	4.03/155.7	0.03
Cigarette smokers (%)	63.8	53.4	<0.01
Plasma fasting glucose (mM/mg/dl)	5.40/97.2	6.18/111.3	<0.01
Plasma glucose 1 h after 75-g load (mM/mg/dl)	9.05/163.1	12.21/219.9	<0.01
Black (%)	7.0	11.3	<0.01
Reporting parental history of diabetes (%)	18.0	31.6	<0.01
One diabetic parent (%)	17.0	29.1	<0.01
Two diabetic parents (%)	1.0	2.4	

Data are means.

HDL and LDL cholesterol, and smoking status), race, BMI, age, and parental history of diabetes were all significant predictors of subsequent diabetes. Controlling additionally for glucose weakened the associations between diabetes, BMI, and parental history and strengthened the associations between diabetes and race. However, the differences in the associations were not large, and all risk factors were statistically significant in both models.

The associations noted in Table 2 between diabetes and uric acid, TGs, alcohol consumption, and LDL cholesterol were no longer statistically significant in the adjusted model. However, a statistically significant positive association remained between diabetes and sBP, and a statistically significant negative association remained between diabetes, HDL cholesterol, and smoking.

Table 4 shows the characteristics of black and non-black men who did and did not develop diabetes. As with non-blacks, blacks who developed diabetes had significantly higher levels of BMI, fasting glucose, and 1-h postload glucose; they were also more likely to report a parental history of diabetes. Unlike non-blacks, for whom averages of all other variables differed significantly when those who developed diabetes were compared with those who did not, no statistically significant differences in the averages for other variables were found in blacks.

For both blacks and non-blacks, a parental history of diabetes was associated with an increased risk of developing the disease, but the risk was nearly twice as great for blacks (Table 5). Similarly, race was a significant predictor of diabetes among men who both did and did not report a parental history, but showed a stronger association among those with such a history (adjusted RR for being black = 5.11, 95% CI 2.22–11.72 for men with a parental history; adjusted RR = 2.22, 95% CI 1.27–3.90 for men without a parental history of diabetes).

Except for race, the other risk factors examined showed similar associations with the development of diabetes for men who did and did not report a parental history of diabetes (Fig. 1).

CONCLUSIONS— In this study the diagnostic criteria for incident cases of diabetes depended on fasting plasma glu-

Table 3—*Age-adjusted and fully adjusted RRs for developing diabetes by levels of selected baseline risk factors for MRFIT UC participants*

	Age adjusted RR (95% CI)	Adjusted RR without glucose (95% CI)*	Fully adjusted RR (95% CI)
Age (5 yr)	—	1.30 (1.16–1.46)	1.08 (0.95–1.22)
Race (black vs. non-black)	1.69 (1.13–2.53)	2.02 (1.33–3.07)	2.83 (1.81–4.42)
BMI (5 kg/m^2)	2.21 (1.87–2.62)	1.88 (1.57–2.24)	1.56 (1.28–1.90)
Plasma glucose after overnight fast (0.1 mM)	1.21 (1.18–1.23)	—	1.12 (1.10–1.15)
Plasma glucose 1 h after 75 g load (0.1 mM)	1.05 (1.04–1.06)	—	1.03 (1.03–1.04)
Reported parental history of diabetes (yes vs. no)	2.01 (1.54–2.64)	1.97 (1.50–2.58)	1.50 (1.11–2.01)

Covariates in fully adjusted model includes all variables listed above plus sBP, uric acid, TGs, reported number of alcoholic drinks per week, HDL and LDL cholesterol, and smoking status.

Table 4—*Baseline values of selected clinical characteristics for MRFIT black and non-black UC men with and without a diabetes diagnosis*

	Blacks			Non-Blacks*		
	Developed diabetes	Did not develop diabetes	*P* value	Developed diabetes	Did not develop diabetes	*P* value
n	28	400	—	219	5353	—
Age (yr)	46.7	45.6	0.35	48.2	46.3	<0.01
sBP (mmHg)	139.1	137.3	0.51	140.0	134.6	<0.01
Plasma uric acid (mg/dl)	6.56	6.68	0.65	7.15	6.76	<0.01
Plasma TGs (mM/mg/dl)	3.65/141.2	3.67/141.9	0.97	6.32/244.2	4.98/192.6	<0.01
BMI (kg/m^2)	29.2	27.6	0.03	29.6	27.5	<0.01
Reported number of alcoholic drinks/wk	10.1	12.2	0.37	10.9	12.7	0.04
Plasma HDL cholesterol (mM/mg/dl)	1.26/48.8	1.27/49.3	0.87	0.97/37.5	1.08/41.9	<0.01
Plasma LDL cholesterol (mM/mg/dl)	4.34/168.0	4.11/158.9	0.22	3.99/154.2	4.16/160.9	<0.01
Cigarette smokers (%)	53.6	69.8	0.07	53.4	63.4	<0.01
Plasma fasting glucose (mM/mg/dl)	6.19/111.5	5.27/95.0	<0.01	6.18/111.3	5.41/97.4	<0.01
Plasma glucose 1 h after 75 g load (mM/mg/dl)	11.9/214.3	8.5/152.4	<0.01	12.2/220.6	9.09/163.8	<0.01
Parental history of diabetes (%)	39.3	18.5	<0.01	30.6	18.0	<0.01

*Non-blacks include 5420 whites, 56 Asians, 70 Hispanics, 7 Native Americans, and 19 others.

cose values and reported use of insulin or hypoglycemic agents. Fasting venous glucose concentrations ≥140 mg/dl (7.77 mM) are considered diagnostic (32). However, because on occasion the men may not have fully complied with instructions to fast and therefore may have considerable intraindividual variability of blood glucose measurements, the more definite finding of repeat fasting values ≥140 mg/dl was used for the main analyses.

We were unable to use 2-h postload blood glucose as a criterion to identify incident cases for those whose fasting glucose was not ≥140 mg/dl (as recommended by WHO [32] and the NDDG [33]), because no such values were available. Thus, it is possible that some individuals who developed diabetes under this more stringent criterion were not identified as such by us.

As noted in METHODS, men who at baseline had a clinical history of diabetes,

Table 5—*Diabetes incidence by race and reported family history of diabetes for MRFIT UC men*

	Men (*n*)	Developed diabetes (*n*[%])	Adjusted RR (without glucose) for history (95% CI*)	Adjusted RR (with glucose) for history (95% CI)†
Blacks	428	28 (6.5)	3.62 (1.55–8.47)	5.99 (1.62–22.08)
Parental history	85	11 (13.0)	—	—
No parental history	343	17 (5.0)	—	—
Non-Blacks	5367	219 (3.9)	1.85 (1.38–2.48)	1.40 (1.30–1.50)
Parental history	1027	67 (6.5)	—	—
No parental history	4540	152 (3.4)	—	—

*Model adjusted for age, BMI, sBP, uric acid, TGs, number of alcoholic drinks/per week, HDL cholesterol, LDL cholesterol, and smoking status.
†Model adjusted for age, BMI, fasting glucose, glucose 1 h after a 75-g load, sBP, uric acid, TGs, number of alcoholic drinks/per week, HDL cholesterol, LDL cholesterol, and smoking status.

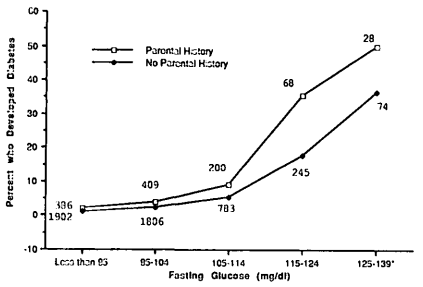

Figure 1—*Incidence of diabetes by reported parental history of diabetes and baseline levels of fasting glucose. Those with glucose ≥140 mg/dl at baseline were not included in this study. Numbers on the graph refer to the number of men in that category.*

a fasting blood glucose ≥140 mg/dl, or blood glucose ≥300 mg/dl (16.65 mM) 1 h after a 75-g glucose challenge were excluded from the study, so that incidence in an initially nondiabetic population could be examined. Despite these exclusion criteria, some men probably would have been classified as diabetic under the 2-h postload blood glucose criterion of WHO and the NDDG. Thus, not all of the cases we noted may have been true incidence cases.

The definite separation of type I diabetes from type II diabetes requires immunogenetic measures, which are rarely available in epidemiological studies (34). With diabetes onset in adult life, patients who are treated with insulin

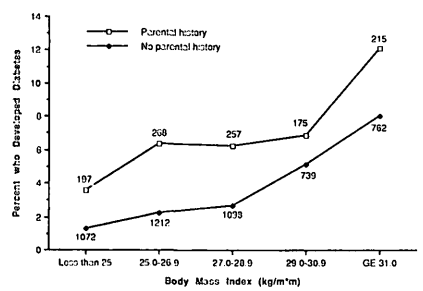

Figure 2—*Incidence of diabetes by reported parental history of diabetes and baseline levels of BMI. Numbers on graph refer to number of men in that category.*

cannot be assigned with certainty to either category (35), though Cowie et al. (36) used a combination of relative weight at onset, insulin use, and medical history to distinguish between types of diabetes mellitus. Although classification is to an extent arbitrary, epidemiological studies have consistently considered such individuals to have type II diabetes.

The average annual incidence of diabetes was 0.94%/yr among MRFIT UC men (and 0.84%/yr among MRFIT SI men), a rate that was about equal to McPhillips et al.'s (20) findings for 40- to 79-yr-old men living in Rancho Bernardo, California. This rate was slightly higher than those found by Haffner et al. (14) for 25- to 64-yr-old Mexican-American men and women and by Medalie et al. (18) for Israeli men >40 yr of age. This rate was considerably higher than rates found among other predominantly white populations in Norway, the U.S., Sweden, and France (9,11,16,21), but did not begin to approach the incidence of over 30/1000/yr found among the Pima Indians (3). Although conclusive comparison with other studies is difficult because of differing ages and diagnostic criteria, it appears that the MRFIT incidence of diabetes was higher than the incidence in predominantly white populations, but lower than the incidence in epidemic populations.

The greater incidence of diabetes among the MRFIT UC men may be attributable to the selection criteria for MRFIT, which attempted to include men at high risk for CHD on the basis of levels of serum cholesterol, BP, and smoking. Although not specifically selected for these characteristics, the MRFIT UC men under study had higher levels of BMI compared with the 40- to 77-yr-old men sampled in NHANES (29.6 vs. 26.5 kg/m^2 for diabetic subjects and 27.5 vs. 25.8 kg/m^2 for nondiabetic subjects)(37). Also based on data from NHANES (38), the mean level of HDL cholesterol among U.S. white males 35–54 yr of age was 43.4 mg/dl compared with 42.4 mg/dl for MRFIT UC men who didn't develop diabetes and 38.8 mg/dl for MRFIT UC men who did develop diabetes. Average levels of TGs for our group were considerably higher than those for men of similar age who were studied as part of the Lipids Research Clinics Prevalence Study (189.1 vs. 121.5 mg/dl) (39).

The initial defect in type II diabetes is thought to be insulin resistance and compensatory increased insulin secretion, followed by pancreatic exhaustion and subsequent decrease in insulin secretion (40,41). Insulin was not measured in this study, thus this sequence could not be examined here.

We acknowledge that the most reliable predictor of subsequent diabetes is the glucose concentration in the blood, in either a casual or fasting state and/or after being subjected to a glucose challenge (3,6,8–11,13,14,20,22). This result also has been found in populations with impaired glucose tolerance who subsequently develop diabetes (42–49). UC men enrolled in the MRFIT were no exception to this general observation. Levels of serum glucose, after both a fast and a 75-g oral glucose load, were strongly, and apparently independently, associated with the incidence of diabetes. This association was linear, with no apparent threshold effect.

It is generally agreed that diabetes is associated with obesity, although the exact nature of both the epidemiological association and the potential causal mechanisms of the association are unclear (50,54). Our study showed a strong relationship between BMI and future incidence of diabetes, with no threshold below which there is a near immunity to disease. MRFIT examinations did not include the measurement of body fat distribution, which is considered an important risk marker for diabetes, above that provided by BMI (55,56). Our study may not, therefore, be able to fully investigate or account for the influence of body composition on diabetes risk.

Race was strongly associated with developing diabetes in the MRFIT UC

men. The higher rates among blacks compared with non-blacks, even after adjusting for other risk factors, is somewhat consistent with cross-sectional data that show a higher prevalence of and mortality from diabetes among black men compared with white men. Adjusting only for age, the risk of developing diabetes in this study was 1.69 for blacks compared with non-blacks, a difference similar to that observed in the NHANES (1) for the prevalence of diabetes in the U.S. population. Unfortunately, no comparable longitudinal studies of the incidence of diabetes among blacks in the U.S. in which similar types of information regarding blood glucose, BMI, and family history are available. It is possible that the higher rates among black men are attributable to greater genetic predisposition or to their greater exposure to environmental risk factors such as diet, distribution of body weight, or fat distribution.

Our study almost certainly underestimates the effects of genetic host susceptibility (50–53), because our information on family history of diabetes was available only from the participants' self-reports of parental history and was not carefully validated by testing either parents or siblings. Despite this limitation, parental history of diabetes was a clear risk factor for developing diabetes, especially among blacks.

With data such as those available herein, it is difficult to separate the effects of both the risk factors under study and the variables used to adjust multivariate models. The levels of both fasting and 1-h postload oral glucose were significantly higher for men with parental histories of diabetes compared with men without parental histories and for nonblacks compared with blacks (data not shown). Both glucose measures increased with levels of sBP, TGs, and BMI. Postload glucose increased with higher levels of uric acid, number of alcoholic drinks per week, and plasma HDL cholesterol. Given the relatively large amount of measurement imprecision associated with glucose measurements (57), together with the status of BMI as a poor proxy for fat patterning and the potential errors identifying genuine family history of diabetes, it is not possible to come to firm conclusions about the extent to which these factors act independently of one another (58–60).

The fairly high overall incidence of diabetes (>4% over 5 yr) was probably caused by the selection criteria for the MRFIT. The combination of race, parental history of diabetes as a marker of genetic host susceptibility, obesity as measured by BMI, and blood glucose levels provide very powerful predictors of the risk of diabetes, despite the inability to assess their independent effects. It is possible, using these relatively simple measures, to identify individuals who have an extremely high risk of developing diabetes and would be potential candidates for aggressive interventions to prevent the onset of the disease.

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