Diabetes, Other Risk Factors, and 12-Yr Cardiovascular Mortality for Men Screened in the Multiple Risk Factor Intervention Trial

JEREMIAH STAMLER, MD
OLGA VACCARO, MD
JAMES D. NEATON, PHD
DEBORAH WENTWORTH, MPH
FOR THE MULTIPLE RISK FACTOR INTERVENTION TRIAL RESEARCH GROUP

OBJECTIVE — To assess predictors of CVD mortality among men with and without diabetes and to assess the independent effect of diabetes on the risk of CVD death.

RESEARCH DESIGN AND METHODS — Participants in this cohort study were screened from 1973 to 1975; vital status has been ascertained over an average of 12 yr of follow-up (range 11–13 yr). Participants were 347,978 men aged 35–57 yr, screened in 20 centers for MRFIT. The outcome measure was CVD mortality.

RESULTS — Among 5163 men who reported taking medication for diabetes, 1092 deaths (603 CVD deaths) occurred in an average of 12 yr of follow-up. Among 342,815 men not taking medication for diabetes, 20,867 deaths were identified, 8965 ascribed to CVD. Absolute risk of CVD death was much higher for diabetic than nondiabetic men of every age stratum, ethnic background, and risk factor level—overall three times higher, with adjustment for age, race, income, serum cholesterol level, sBP, and reported number of cigarettes/day ($P < 0.0001$). For men both with and without diabetes, serum cholesterol level, sBP, and cigarette smoking were significant predictors of CVD mortality. For diabetic men with higher values for each risk factor and their combinations, absolute risk of CVD death increased more steeply than for nondiabetic men, so that absolute excess risk for diabetic men was progressively greater than for nondiabetic men with higher risk factor levels.

CONCLUSIONS — These findings emphasize the importance of rigorous sustained intervention in people with diabetes to control blood pressure, lower serum cholesterol, and abolish cigarette smoking, and the importance of considering nutritional-hygienic approaches on a mass scale to prevent diabetes.

FROM THE DEPARTMENT OF PREVENTIVE MEDICINE, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, CHICAGO, ILLINOIS; THE DEPARTMENT OF INTERNAL MEDICINE AND METABOLIC DISEASES, SECOND FACULTY OF MEDICINE, UNIVERSITY OF NAPLES, NAPLES, ITALY; THE DIVISION OF BIOSTATISTICS, SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF MINNESOTA, MINNEAPOLIS, MINNESOTA; AND THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE, BETHESDA, MARYLAND.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO JEREMIAH STAMLER, MD, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, DEPARTMENT OF PREVENTIVE MEDICINE, 680 NORTH LAKE SHORE DRIVE, SUITE 1102, CHICAGO, IL 60611–4402.

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MRFIT, MULTIPLE RISK FACTOR INTERVENTION TRIAL; CVD, CARDIOVASCULAR DISEASE; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; CHD, CORONARY HEART DISEASE; BP, BLOOD PRESSURE; sBP, SYSTOLIC BLOOD PRESSURE; dBP, DIASTOLIC BLOOD PRESSURE; ICD-9, INTERNATIONAL CLASSIFICATION OF DISEASE, NINTH REVISION; RR, RELATIVE RISK; NHANES, NATIONAL HEALTH AND NUTRITION SURVEY; CI, CONFIDENCE INTERVAL.

Several clinical and epidemiological studies have addressed the problem of mortality and survival in populations consisting predominantly or exclusively of people with NIDDM. Because of the great variation in data collection and study design and the problem of different diagnostic criteria, comparison between studies is not straightforward. However, the data consistently show an excess risk of mortality in diabetic individuals of both sexes in all age-groups (1–6). Generally, CVD accounts for the majority of these deaths, diabetes being an independent risk factor for both CVD and CHD death (7–12). Much less information is available on the influence of other established cardiovascular risk factors on mortality in people with diabetes (12–19). The relatively small size of previously studied cohorts—ranging from 200 to 497 individuals with diabetes in the cited studies—has limited analyses of this problem. Clarification of the problem, however, has relevance for both theoretical and practical reasons. Optimal approaches to reducing cardiovascular risk in people with diabetes is an issue of major importance given their inordinate risk.

This study takes advantage of the large cohort—361,662 men—screened for MRFIT (20) and compares the relationships of sBP, serum total cholesterol, and cigarette smoking to CVD mortality in men with and without diabetes. The increased risk of CVD mortality associated with diabetes is also estimated.

RESEARCH DESIGN AND METHODS

Cohort and baseline assessment

The study cohort consisted of the 361,662 men aged 35–57 yr who were seen as potential participants at the initial screening visit of MRFIT (20–22).

Examinations took place between 1973 and 1975 at 20 screening centers in 18 U.S. cities. Participation in screening

for MRFIT was essentially on a voluntary basis; the most common recruitment procedure was to offer screening to employee groups or communities. Details on recruitment procedures have been described previously (22).

Eligibility for the trial was assessed on the basis of the individual's cardiovascular risk factor profile. Therefore, the first screening visit included measurement of BP, serum cholesterol concentration, smoking habits, and assessment of conditions that met exclusion criteria: that is, age, reported drug treatment for diabetes mellitus, and previous hospitalization of ≥2 wk for myocardial infarction (21). The need to survey hundreds of thousands of men, to recruit at least 12,000 that met MRFIT eligibility criteria, produced major logistical and cost considerations. Therefore, data collection at first screening was limited to the foregoing recruitment-related measurements. Sera were not analyzed for glucose or lipid fractions. No anthropometric measurements were made; no urinalyses were done; and no ECGs were recorded. For men reporting previous drug treatment for diabetes, no history was taken as to diet treatment, type of drug treatment, or duration of diabetes. Thus, in this study, men who indicated they were not taking medication for diabetes are identified as men without diabetes.

BP was measured according to a standardized protocol with the participant seated (23). A standard mercury sphygmomanometer was used. dBP was recorded as fifth Korotkoff sound. Three readings were taken, and the average of the second and third readings was used in the analysis. Blood was drawn for serum cholesterol determination, which was performed in 1 of 14 laboratories under the supervision of the MRFIT central laboratory in San Francisco and the Lipid Standardization Laboratory of the Centers for Disease Control in Atlanta (24).

Death ascertainment

The vital status of participants screened for MRFIT is being ascertained on an a continuing basis through the National Death Index. Prior to 1979, a data file of known deaths provided by the U.S. Social Security Administration was used. Details on the death ascertainment procedure and its validation have been published previously (25). Death certificates were obtained for 94% of identified decedents. Causes of death were coded by a trained nosologist according to ICD-9 (26). Coronary deaths were defined as ICD codes 410–414 plus 429.9, stroke as codes 430–438, and total CVD as codes 390–459. Data given are an average of 12 yr follow-up.

Data analysis

Mortality data are given as age-adjusted rates per 10,000 person-yr. Direct standardization was used to adjust for differences in age distribution between men with and without diabetes (27); the total group of men screened was used as the standard population.

The effect of cardiovascular risk factors on mortality was analyzed for men with and without diabetes across levels of serum cholesterol, sBP, and reported number of cigarettes smoked/day.

To evaluate the combined effects of the three risk factors on mortality in men with and without diabetes, and the independent influence of diabetes on risk of CVD death, participants were grouped according to serum cholesterol (<200 and ≥200 mg/dl), sBP (<120 and ≥120 mmHg, also <140 and ≥140 mmHg), and cigarette use (no or yes), yielding eight strata for comparison. In addition, age-adjusted CVD death rates for men with and without diabetes were compared according to the presence of one, two, or three risk factors.

Proportional hazards regression analyses on the relationship of diabetes and other risk factors to CVD mortality also were done, stratified by clinical center, to estimate the independent effect of diabetes on risk of CVD death and to compare the association of sBP, serum cholesterol level, and cigarettes/day with risk of CVD death for men with and without diabetes (28). To estimate RR, multivariate proportional hazards regression coefficients were exponentiated. For example, for sBP higher by 20 mmHg, for nondiabetic men, $RR = e^{0.0234 \times 20}$, where e is the base of natural logarithms (= 2.7182. . .) and 0.0234 is the multivariate regression coefficient for the relationship of sBP and time to CVD death; RR = 1.60. RR values for lower compared with higher levels of a risk factor can be regarded as estimates of relative capacity for prevention of death—e.g., $RR = e^{0.0234 \times -20} = 0.63$; i.e., CVD death rate estimated to be lower by 37%.

RESULTS

Baseline descriptive statistics

Altogether, 361,662 men aged 35–57 yr were screened in 1973–1975 for eligibility for the MRFIT. The cohort consisted of 5625 men who reported being treated at that time for diabetes mellitus; the 356,037 men free of this condition made up the cohort without diabetes; 380 men (7.2%) of the former group and 5060 (1.4%) of the latter reported a previous hospitalization for myocardial infarction and were excluded from analysis. A further 82 men with diabetes (1.6%) and 8162 men without diabetes (2.3%) were excluded because of missing sBP. Of the remaining 347,978 men serving as the basis for this study, numbers screened by the 20 MRFIT centers in 18 cities across the U.S. ranged from 11,241 (Miami) to 29,518 (Minneapolis). These large numbers and their identification across the country, along with the population-oriented approaches to recruiting them for screening, yielded a cohort with mean levels and distributions for the major risk factors similar to those recorded for U.S. middle-aged male respondents to the random sampling efforts of the U.S. National Center for Health Statistics, including NHANES I and NHANES II in the early and late 1970s (29–33).

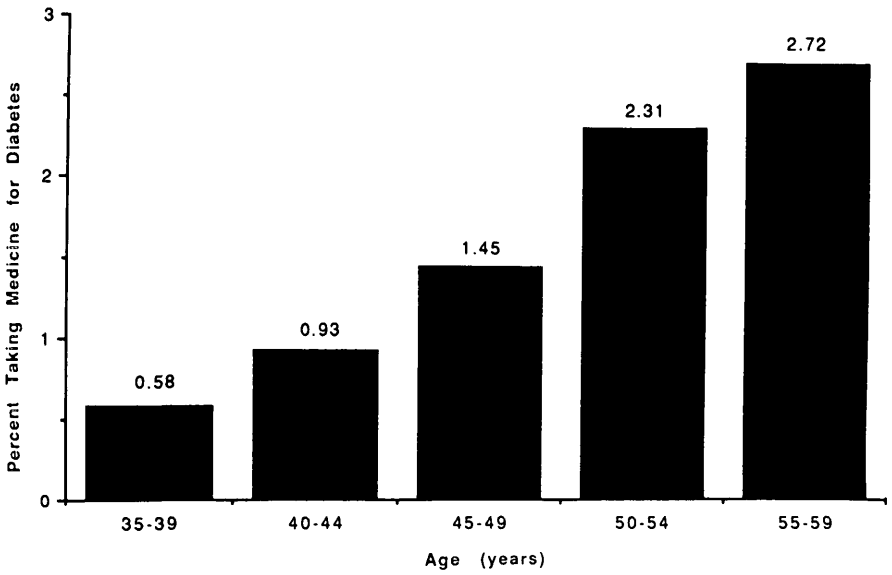

Figure 1—*Percent (by age-group) of men screened for MRFIT taking medication for diabetes.*

For the defined cohort of 347,978 men, the percentage who reported then-current treatment for diabetes was progressively higher with age (Fig. 1). Table 1 lists the characteristics for men with and without diabetes at the initial screening visit. Those with diabetes were on average 3 yr older and had higher sBP (5.8 mmHg greater on average); a smaller difference was observed for dBP (1.9 mmHg). The higher mean BPs for diabetic compared with nondiabetic men remained with adjustment for age. Serum cholesterol level and number of cigarettes/day were similar in the two groups of men; however, a slightly higher percentage of men with diabetes compared with those without diabetes reported smoking of cigarettes. Among men without diabetes, 10% were nonwhite; among those with diabetes, 18% were nonwhite. This difference in proportion of nonwhite participants was primarily the result of an excess of blacks in the diabetes group.

Overall mortality data

Deaths in the average 12-yr follow-up period numbered 1092 (160.1/10,000 person-yr) among men with diabetes and 20,867 (53.2/10,000 person-yr) among men without diabetes. Distribution of CVD causes of death is given in Table 2. Mortality from CVDs, particularly coronary disease, largely accounted for the excess mortality observed in men with diabetes. Cardiovascular deaths represented 55% of total deaths in men with diabetes and 43% in men without diabetes.

Crude CHD and CVD death rates were approximately five times higher in men with diabetes compared with men without diabetes. After adjustment for age, race, sBP, serum cholesterol level, and cigarettes/day, RR estimates for CHD and CVD were 3.2 ($P < 0.0001$) and 3.0 ($P < 0.0001$), respectively. A significant independent association of diabetes with CVD mortality ($P < 0.0001$) over and above the effects of the other risk factors was present for each of five age-groups (35–39, 40–44, 45–49, 50–54, and 55–57 yr) (Table 3). Multivariate-adjusted RR estimates for diabetic compared with nondiabetic men ranged from 2.4 (age 45–49 yr) to 3.3 (age 50–54 yr); these RR were not significantly different from each other ($P = 0.84$). Absolute excess risk of CVD death was progressively higher with age for diabetic compared with nondiabetic men—26.2 (age 35–39 yr), 39.8 (age 40–44 yr), 51.5 (age 45–49 yr), 97.7 (age 50–54 yr), and 124.4 (age 55–57 yr) per 10,000 person-yr.

With stratification by ethnicity, risk of CVD death again was consistently

Table 1—***Age, ethnicity, and risk factor levels for men with and without diabetes at initial screening for the MRFIT***

	Men with diabetes (N = 5163)	Men without diabetes (N = 342,815)
Age (yr)*	49.1 ± 5.7	45.8 ± 6.4
Ethnicity* (%)		
White	82.0	90.1
Black	13.6	6.4
Hispanic	2.5	1.9
Asian	1.4	1.2
American Indian	0.2	0.1
Other	0.4	0.4
Serum cholesterol (mg/dl)	213.2 ± 39.5	214.5 ± 49.7
sBP (mmHg)*	135.8 ± 19.2	130.0 ± 15.8
dBP (mmHg)*	85.8 ± 11.7	83.9 ± 10.7
Cigarette smokers (%)*	39.0	36.7
Cigarettes/day	25.7 ± 14.7	25.8 ± 13.2

Data are means ± SD or %.
*$P < .0001$ for differences between men with and without diabetes.

Table 2—*Number of deaths by cause and age-adjusted death rate for men with (n = 5163) and without (n = 342,815) diabetes at initial screening for the MRFIT*

	Men with diabetes		Men without diabetes		
	Deaths (*n*)	Rate (per 10,000 person-yr)	Deaths (*n*)	Rate (per 10,000 person-yr)	Adjusted RR for diabetic/nondiabetic* (95% CI)
Cause of death (ICD-9 code)					
CVD (390–459)	603	85.13	8965	22.88	3.0 (2.8–3.3)
CHD (410–414, 429.2)	469	65.91	6681	17.05	3.2 (2.9–3.5)
Stroke (430–438)	48	6.72	685	1.75	2.8 (2.0–3.7)
Other CVD	86	12.49	1599	4.08	2.3 (1.8–2.9)
All deaths	1092	160.13	20,867	53.20	2.5 (2.4–2.7)

*Adjusted for age, race, income, serum cholesterol level, sBP, and number of cigarettes/day.

higher for diabetic compared with nondiabetic men, with RR ranging from 1.8 (Hispanic) to 4.1 (other); these risks were significantly different from each other ($P < 0.001$) (Table 3). For three of the four ethnic groups (whites, blacks, other) the higher multivariate-adjusted RR for diabetic compared with nondiabetic men was statistically significant. (The other strata include American Indian, 6%; Asian, 71%; and other, 23%; deaths among these groups were too few for separate analyses.) Absolute excess risks for diabetic compared with nondiabetic men were 45.8 (Hispanic), 52.9 (black), 62.5 (white), and 95.7 (other) per 10,000 person-yr.

Baseline risk factors and mortality—univariate analyses

Serum cholesterol. A significant positive relationship of serum cholesterol to CVD mortality was observed for both diabetic and nondiabetic men (Table 4). CVD death rates increased markedly from lowest (<180 mg/dl) to highest (≥280 mg/dl) serum cholesterol levels for both cohorts. At every level of serum cholesterol, CVD death rate was several times higher for diabetic than nondiabetic men, and the increase in CVD mortality rate with higher serum cholesterol level tended to be disproportionately greater—i.e. steeper—for diabetic than nondiabetic men. Therefore, higher serum cholesterol level was associated with greater absolute excess risk of CVD death for diabetic compared with nondiabetic men; absolute excess risk for diabetic men ranged from 47.9/10,000 person-yr with serum cholesterol <180 mg/dl to

Table 3—*Age-specific CVD death rates and age-adjusted CVD death rates by ethnicity for men with and without diabetes at initial screening for MRFIT*

	Men with diabetes			Men without diabetes			
	men (*n*)	deaths (*n*)	Rate (per 10,000 person-yr)	men (*n*)	deaths (*n*)	Rate (per 10,000 person-yr)	Adjusted RR for diabetic/nondiabetic (95% CI)
Age (yr)							
35–39	422	16	33.0	72,144	576	6.8	3.0 (1.8–5.0)
40–44	713	43	52.9	76,060	1174	13.1	3.0 (2.2–4.0)
45–49	1195	99	73.9	81,079	2113	22.4	2.4 (1.9–3.0)
50–54	1857	264	132.1	78,687	3114	34.4	3.3 (2.9–3.8)
55–57	976	181	174.8	34,845	1988	50.4	3.0 (2.6–3.5)
Ethnicity							
White	4233	508	85.0*	308,760	8007	22.5*	3.2 (2.9–3.5)
Black	702	72	84.2*	21,769	729	31.3*	2.2 (1.7–2.8)
Hispanic	130	10	65.9*	6381	128	20.1*	1.8 (0.9–3.6)
Other	98	13	109.7*	5905	101	14.0*	4.1 (2.3–7.6)

*Age adjusted.

Table 4—*Age-adjusted CVD death rates by serum cholesterol level for men with and without diabetes at initial screening for MRFIT*

	Men with diabetes			Men without diabetes				
	Men (*N*)	CVD deaths (*N*)	Rate (per 10,000 person-yr)	Men (*N*)	CVD deaths (*N*)	Rate (per 10,000 person-yr)	RR for diabetic/nondiabetic	Absolute excess risk for diabetic minus nondiabetic/(per 10,000 person-yr)
Serum cholesterol level (mg/dl)								
<180	1105	96	61.72	62,448	859	13.84	4.46	47.88
180–199	972	101	76.67	64,363	1223	17.27	4.44	59.40
200–219	1038	128	84.79	75,122	1750	20.19	4.20	64.60
220–239	823	96	80.94	60,386	1767	24.53	3.30	56.41
240–259	529	68	91.99	40,090	1411	29.02	3.17	62.97
260–279	343	58	139.34	22,802	983	35.53	3.92	103.81
≥280	353	56	130.43	17,604	972	46.12	2.83	84.31
Coefficient*		0.0030 ± 0.0007			0.0061 ± 0.0002			

*From proportional hazards regression model stratified by clinical center and with covariates corresponding to age, race, income, serum cholesterol level, sBP, and cigarettes/day.

103.8 for diabetic men in the 260–279 mg/dl range.

RR of CVD mortality for diabetic compared with nondiabetic men ranged from 2.83 to 4.46 at varying levels of serum cholesterol (Table 4). Unlike absolute excess risk, RR was lower at higher serum cholesterol levels.

For nondiabetic men, absolute excess risk of CVD death with the highest compared with the lowest serum cholesterol level was 32.28/10,000 person-yr (46.12 − 13.84); for diabetic men, it was 68.71 (130.43 − 61.72) or more than double (Table 4). RR of CVD death for men in the highest compared with men in the lowest serum cholesterol level was 3.33 for nondiabetic (46.12/13.84) and 2.11 for diabetic (130.43/61.72) participants.

The greater RR for nondiabetic than diabetic men with higher serum cholesterol is also evident from the proportional hazards regression coefficients cited at the bottom of Table 4; the coefficient is approximately twice as large for men without diabetes compared with men with diabetes (0.0061 vs. 0.0030). Based on these coefficients, with a serum cholesterol higher by 40 mg/dl (e.g. 250 compared with 210 mg/dl), RR of CVD death was 1.28 for nondiabetic and 1.13 for diabetic men. Again, because absolute CVD death rates were much higher for diabetic than nondiabetic men at every level of baseline serum cholesterol, the lower RR for diabetic compared with nondiabetic men translated into a much higher (approximately twofold) absolute excess risk.

Alternatively, as an estimate of the potential for CVD prevention, RR with a 40 mg/dl lower serum total cholesterol can readily be estimated: 0.78 for nondiabetic and 0.89 for diabetic men. Again, given the much higher CVD death rates for diabetic than nondiabetic men, these RRs translate into a greater estimated potential for preventing deaths over a specified time for diabetic than nondiabetic men.

sBP. sBP was positively related to risk of CVD death with a significant trend in both cohorts ($P < 0.001$) (Table 5). Thus, for men with diabetes, CVD death rates increased from 53.6 to 242.6 deaths/10,000 person-yr, and for men without diabetes, from 12.2 to 128.7. As with serum cholesterol, at every level of sBP, CVD death rate was much greater for diabetic than nondiabetic men. With higher sBP, CVD mortality rate increased more steeply for diabetic than nondiabetic men, hence absolute excess risk tended to be greater for diabetic men the higher their sBP (113.96/10,000 person-yr with sBP ≥200 mmHg compared with 41.42 with sBP <120 mmHg).

RR for diabetic compared with nondiabetic men at varying sBP levels ranged from 1.89 to 4.40, with lower RR at higher sBP levels (Table 5).

Absolute excess risk of CVD death for men in the highest compared with those in the lowest sBP stratum was 116.46/10,000 person-yr for nondiabetic and 189.00/10,000 person-yr for diabetic participants, i.e., 1.62 times greater for the latter (Table 5). RR for men in the highest compared with those in the lowest sBP stratum was 4.52 for diabetic and 10.55 for nondiabetic participants. Correspondingly, based on the multivariate regression coefficients, a 20 mmHg higher sBP was associated with an RR of 1.60 for nondiabetic men and 1.41 for diabetic men; a 20 mmHg lower sBP, with an RR of 0.63 and 0.71, respectively. Given the high absolute risks and absolute excess risks for diabetic men with sBP levels above optimal, the lower RR with lower sBP translates into a large estimated absolute potential for preven-

Table 5—*Age-adjusted CVD death rates by sBP level for men with and without diabetes at initial screening for MRFIT*

	Men with diabetes			Men without diabetes				
	Men (*N*)	CVD deaths (*N*)	Rate (per 10,000 person-yr)	Men (*N*)	CVD deaths (*N*)	Rate (per 10,000 person-yr)	RR for diabetic/nondiabetic	Absolute excess risk for diabetic minus nondiabetic (per 10,000 person-yr)
sBP level (mmHg)								
<120	757	52	53.61	86,702	1112	12.19	4.40	41.42
120–139	2316	203	65.47	175,826	3745	19.07	3.43	46.40
140–159	1421	206	108.15	64,444	2794	34.18	3.16	73.97
160–179	494	102	158.71	12,827	952	56.47	2.81	102.24
180–199	131	27	155.65	2356	253	79.27	1.96	76.38
≥200	44	13	242.61	660	109	128.65	1.89	113.96
Coefficient*		0.0172 ± 0.0019			0.0234 ± 0.0005			

* From porportional hazards regression model stratified by clinical center and with covariates corresponding to age, race, income, serum cholesterol level, sBP, and cigarettes/day.

tion of CVD death by control of elevated sBP, greater for diabetic than nondiabetic men.

Cigarette smoking. A significant, graded increase in CVD mortality also was observed in men across increasing levels of cigarettes smoked/day for both groups (Table 6). As with serum cholesterol and sBP, at every level of cigarette use CVD death rate was several times higher for diabetic than nondiabetic men. With cigarette smoking, the CVD mortality rate increased more steeply for diabetic than nondiabetic men, hence absolute excess risk was greater for diabetic heavy smokers than diabetic nonsmokers (89.64/ vs. 56.28/10,000 person-yr).

RR for diabetic compared with nondiabetic men ranged from 2.38 (smokers of 16–25 cigarettes/day) to 4.56 (nonsmokers) (Table 6).

The absolute excess risk of CVD death for men with the greatest daily cigarette use compared with nonsmokers was 26.16/10,000 person-yr for nondiabetic and 59.52 for diabetic participants, i.e., more than double for diabetic men (Table 6). RR was 2.65 for nondiabetic heavy smokers and 1.83 for diabetic heavy smokers. Correspondingly, the regression coefficient for cigarettes/day for those without diabetes was approximately twice the size of that estimated for men with diabetes (0.0230 vs. 0.0127). Based on these coefficients, for smokers of 20 cigarettes/day compared with nonsmokers, risk of CVD death was 1.58 times higher for nondiabetic men and 1.29 times higher for diabetic men; for nonsmokers compared with smokers of one pack/day, RR was 0.63 for nondiabetic men and 0.78 for diabetic men. Because CVD mortality rates and absolute excess risks were high for men with

Table 6—*Age-adjusted CVD death rates by reported number of cigarettes/day for men with and without diabetes at initial screening for MRFIT*

	Men with diabetes			Men without diabetes				
	Men (*N*)	CVD deaths (*N*)	Rate (per 10,000 person-yr)	Men (*N*)	CVD deaths (*N*)	Rate (per 10,000 person-yr)	RR for diabetic/nondiabetic	Absolute excess risk for diabetic minus nondiabetic (per 10,000 person-yr)
Cigarettes per day								
0	3284	347	72.11	218,068	4112	15.83	4.56	56.28
1-15	472	59	100.00	26,237	733	25.87	3.87	74.13
16-25	587	67	85.40	42,294	1639	35.81	2.38	49.59
≥26	820	130	131.63	56,216	2481	41.99	3.13	89.64
Coefficient*		0.0127 ± 0.0024			0.0230 ± 0.0006			

*From proportional hazards regression model stratified by clinical center and with covariates corresponding to age, race, income, serum cholesterol level, sBP, and cigarettes/day.

Table 7—*Baseline major risk factors and age-adjusted CVD mortality in men and without diabetes at initial screening for MRFIT*

Major risk factors			Men (*n*)		CVD deaths (*n*)		Age-adjusted death rate (per 10,000 person-yr)			
Serum cholesterol (mg/dl)	Cigarettes/ day	sBP (mmHg)	Men with diabetes	Men without diabetes	Men with diabetes	Men without diabetes	Men with diabetes	Men without diabetes	RR for diabetic/ nondiabetic	Absolute excess risk for diabetic minus nondiabetic (per 10,000 person-yr)
<200	No	<120	216	25,517	9	144	30.68	6.02	5.10	24.66
<200	No	120+	1093	56,395	94	827	60.33	12.96	4.66	47.37
<200	Yes	<120	137	13,262	10	178	57.12	14.33	3.99	42.79
200+	No	<120	240	30,189	17	343	52.17	9.99	5.22	42.18
Any	one only		1470	99,846	121	1348	58.82	12.21	4.82	46.61
<200	Yes	120+	631	31,637	84	933	102.71	28.50	3.60	74.21
200+	No	120+	1735	105,967	227	2798	87.03	20.59	4.23	66.44
200+	Yes	<120	164	17,734	16	447	86.01	23.48	3.66	62.53
Any	two only		2530	155,338	327	4178	90.87	22.41	4.05	68.46
200+	Yes	120+	947	62,114	146	3295	125.23	47.38	2.64	77.85

diabetes for each stratum of smokers, this latter RR translates into a large potential for prevention of CVD death through cessation of smoking.

Baseline risk factors and mortality—multivariate analyses

As described in METHODS, participants with and without diabetes were stratified according to baseline serum cholesterol, sBP, cigarette use, and diabetes status. The cutoff point of 120 mmHg was used for sBP in these analyses because risk of CVD death was greater for men at every higher level (Table 5). Analyses with sBP dichotomized at 140 mmHg or with dBP dichotomized at 80 or 90 mmHg yielded qualitatively similar results (data not shown). The nonsmokers with sBP <120 mmHg and serum cholesterol <200 mg/dl made up a small proportion of both cohorts—4.2 and 7.4%, respectively (Table 7). Most men screened had one or more risk factors. For men both with and without diabetes, only one of the three risk factors was present in 28 and 29%, respectively; 49 and 45% had a combination of any two of these traits, and 18% in both groups had all three.

Within each stratum homogeneous for cardiovascular risk, CVD mortality was considerably higher for those with diabetes, including for the stratum with optimal profile of the three CVD risk factors (Fig. 2 and Table 7). Age-

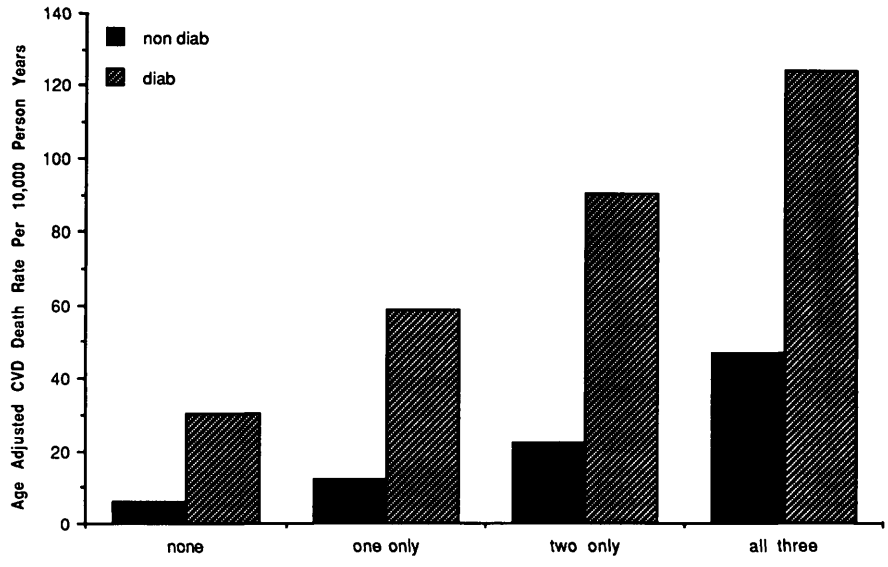

Figure 2—*Age-adjusted CVD death rates by presence of number of risk factors for men screened for MRFIT, with and without diabetes at baseline.*

adjusted CVD death rates progressively increased with increasing number of the three major risk factors, in men with diabetes from 30.7 to 125.2/10,000 person-yr, and in men without diabetes from 6.0 to 47.4. Presence of risk factors singly or in combination (any two or all three) was associated with steeper increase in CVD mortality for diabetic than nondiabetic participants; hence, absolute excess risk for diabetic compared with nondiabetic men was progressively greater with more adverse risk factor status—24.7/10,000 person-yr for men with none of the three risk factors, 46.6 for those with any one only, 68.5 for those with any two only, and 77.8 for those with all three. On average, mortality rates increased in men with diabetes more than expected based on an additive effect of diabetes and the other risk factors.

Age-adjusted RR for men with diabetes compared with those without diabetes ranged from 2.6 to 5.2 (Table 7). RR estimates associated with increasing number of risk factors were less for men with diabetes than men without diabetes, but these translated into much greater absolute excess risks given the much higher CVD mortality rates for diabetic compared with nondiabetic participants.

Based on the data in Table 7, estimates can be made of the proportion of CVD deaths that are excess deaths attributable to diabetes, elevated serum cholesterol and sBP, and cigarette use. If the 5163 men with diabetes had a CVD death rate of 6.02/10,000 person-yr (the rate for nonsmoking men without diabetes and without elevated serum cholesterol and sBP), one would have observed ~37 CVD deaths in 12 yr, instead of 603, or 94% fewer. If all those with diabetes had a CVD death rate of 30.68/10,000 person-yr (the rate for nonsmoking men with diabetes and without elevated serum cholesterol and sBP), one would have observed 190 CVD deaths instead of 603, or 68% fewer.

Similar calculations for the 342,815 men without diabetes in the MRFIT cohort yield the estimate that ~70% of all CVD deaths among them were excess deaths attributable to elevated serum cholesterol, sBP, and cigarette use recorded for most of them at baseline.

CONCLUSIONS— The findings of MRFIT confirm that diabetes is a strong, independent risk factor for CVD mortality over and above the effect of serum cholesterol, BP, and cigarette use. In addition, the MRFIT results clearly indicate that serum cholesterol, sBP, and cigarette smoking are significant, strong, independent predictors of mortality in men with and without diabetes. Previous studies on this issue have yielded inconsistent results for people with diabetes (12–19), probably because of small sample size and thus low statistical power to detect these relationships: in contrast to the 5163 men with diabetes in the MRFIT cohort, other investigations have involved 200–497 diabetic individuals. Although the MRFIT findings, based on men 35–57 yr of age with a history of drug treatment for diabetes, cannot be extrapolated directly in a quantitative way to other groups (e.g., persons with presumptively milder diabetes, women, older persons with diabetes), it is a reasonable inference that the pattern of relationships reported here is generalizable qualitatively. The MRFIT data collection did not include information that would permit classification into IDDM and NIDDM. However, it has been estimated from surveys of representative U.S. population samples that >90% of diabetic individuals ≥35 yr of age are likely to be non-insulin-dependent (34).

For diabetic men in the MRFIT cohort, compared with nondiabetic men, 12-yr CVD mortality rates were much higher at every level of the three major risk factors (serum cholesterol, sBP, cigarette smoking) considered singly and in combination. This was the finding also for the small stratum with optimal levels of all three risk factors. With progressively more unfavorable risk factor status, the CVD mortality rate rose much more steeply for diabetic men than for nondiabetic men, so that absolute excess risk of CVD death became progressively greater for diabetic than nondiabetic men the worse the baseline risk factors. This result, underscoring the importance and potential for prevention of premature CVD death in diabetic individuals through sustained control of the major CVD risk factors, is unequivocal in the 12-yr MRFIT data reported here. This fact merits emphasis because the MRFIT 6-yr follow-up data, previously reported, were equivocal in this regard (12,35). That is, although they clearly showed higher coronary and CVD death rates for diabetic than nondiabetic men at each level of the three risk factors considered together, and significant progressive increases in CVD death rates for both diabetic and nondiabetic men with higher risk factor levels at baseline, the 6-yr data were equivocal as to whether CVD excess risk was greater for diabetic than nondiabetic men with higher risk factor levels. With the 12-yr follow-up data—and the evidence of many more deaths—the answer on this matter is clearly affirmative.

The overall unfavorable cardiovascular risk factor profile for men with and without diabetes therefore requires particular attention and concern (35–37). Despite their current treatment for diabetes, only a small percentage (4%) of men with diabetes did not smoke and had optimal levels of serum cholesterol (<200 mg/dl) and sBP (<120 mmHg). Although it might be argued that the unfavorable serum cholesterol and BP distributions of those with diabetes may at least in part reflect metabolic problems related to the diabetic state, this notion is not relevant with regard to the 39% prevalence of then-current cigarette use in the MRFIT men when screened in 1973–1975. These and other data (4) indicate that at that time at least in the U.S., medical care for people with diabetes did not include vigorous sustained

attention to correction of unhealthy life-style choices (smoking, rich diet, physical inactivity) related to cardiovascular risk.

Although little information exists on the effects of intervention measures in people with diabetes, and judgments vary (38), the MRFIT results strongly support the concept that benefit can be expected from changing risk factors in people with diabetes, based on early detection and effective correction at least to values recommended for the general population (33,35,39–44). This concept also is supported by data from developing countries and from Japan that have shown low rates of atherosclerotic disease in people with diabetes from populations whose diets have not habitually contained high levels of cholesterol and saturated fats and who do not have high serum cholesterol levels (1,45–47). These cross-population findings are concordant with the judgment that a rich diet—through its unfavorable influences on body weight, BP, glycemia, serum lipids, and thrombogenesis (1,11,12,45–52)—needs to be viewed as a pivotal trait that adds to risk for people with diabetes, as has been emphasized in policy statements of the American Diabetes Association (35,53,54).

From the MRFIT data, it is also evident that diabetes is a strong, independent risk factor for CVD mortality over and above the effect of BP, serum cholesterol, and cigarette smoking. The RR conferred by diabetes was high among men with the best apparent baseline cardiovascular risk factor status, i.e., nonsmokers with sBP <120 mmHg and serum cholesterol <200 mg/dl, as well as among men with less favorable status. Reasons remain to be elucidated for this marked excess in CVD risk attributable to diabetes per se. Recent research has focused on the role of such wide-ranging endogenous phenomena as glycosylation of arterial wall ground substance, microalbuminuria, hypertriglyceridemia, and low levels of plasma high-density lipoprotein, the latter two attributable apparently, or at least in part, to insulin resistance and hyperinsulinemia (37,55–62). Data also are available to indicate that hyperinsulinemia with insulin resistance, common in NIDDM, may be an independent CVD risk factor (37,56,62). In efforts to resolve this important problem, it seems relevant to consider the interplay between such endogenous metabolic abnormalities and habitual life-style choices, especially those concerning nutrition.

Whatever the etiopathogenetic pathways for the markedly increased CVD risk attributable to diabetes per se, the finding underscores the importance of enhanced efforts to prevent this disease. Although much remains to be learned for this purpose, extensive data are available from population studies showing that an individual's being overweight, particularly markedly overweight, is associated with higher likelihood of having NIDDM, the common form of diabetes among middle-aged and older people (11,12,51,63,64). Data are also available on ability to favorably influence glucose intolerance by nutritional-hygienic means, including increased leisure-time isotonic exercise and fat-modified diets that are lower in calories, saturated fat, and cholesterol, and higher in fiber (64–67). Such findings point to the possibility of the primary prevention as well as the control of NIDDM on a mass scale by effective nutritional-hygienic programs that prevent and control overweight, as well as high serum cholesterol and high BP.

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