

# Metabolic Syndrome

## Risk factor distribution and 18-year mortality in the Multiple Risk Factor Intervention Trial

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**OBJECTIVE** — To examine the long-term association of metabolic syndrome with mortality among those at high risk for cardiovascular disease (CVD).

**RESEARCH DESIGN AND METHODS** — A total of 10,950 Multiple Risk Factor Intervention Trial (MRFIT) survivors were followed for mortality an additional median 18.4 years (1980–1999). Proportional hazards models examined multivariate-adjusted risks associated with Adult Treatment Panel III–defined metabolic syndrome conditions, with BMI substituted for waist circumference.

**RESULTS** — At MRFIT annual visit 6, 4,588 (41.9%) men, mean age ( $\pm$ SD) 53.0  $\pm$  5.9 years, had metabolic syndrome and 6,362 did not. Comparing men with metabolic syndrome to men without, adjusted hazard ratios (HRs) were 1.21 (95% CI 1.13–1.29), 1.49 (1.35–1.64), and 1.51 (1.34–1.70) for 18-year total, CVD, and coronary heart disease mortality, respectively. Among men with metabolic syndrome, elevated glucose (1.54 [1.34–1.78]) and low HDL cholesterol (1.45 [1.17–1.54]) were most predictive of CVD mortality, followed by elevated BMI (1.34 [1.17–1.54]), elevated blood pressure (1.25 [0.98–1.58]), and elevated triglycerides (1.06 [0.86–1.30]). In contrast, for men without metabolic syndrome, the HR for low HDL cholesterol was 1.02 (0.86–1.22). Among metabolic syndrome men with no nonfatal CVD event, smokers with elevated LDL cholesterol showed higher CVD mortality (1.79 [1.22–2.63]) compared with nonsmokers without elevated LDL cholesterol; this additional risk was even greater for metabolic syndrome men with a nonfatal CVD event (2.11 [1.32–3.38]).

**CONCLUSIONS** — Metabolic syndrome is associated with an increased risk of mortality. Among those with metabolic syndrome, risk is further increased by having more metabolic syndrome conditions, by cigarette smoking, and by elevated LDL cholesterol. Primary prevention of each metabolic syndrome condition should be emphasized, and presence of each condition should be treated in accordance with current guidelines.

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**Abbreviations:** ATP-III, Adult Treatment Panel III; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; MRFIT, Multiple Risk Factor Intervention Trial; SBP, systolic blood pressure.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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**M**etabolic syndrome is a clustering of major cardiovascular disease (CVD) risk factors. The Adult Treatment Panel III (ATP-III) (1) of the National Cholesterol Education Program defines metabolic syndrome as the occurrence of three or more of the following conditions: low HDL cholesterol, elevated triglycerides, elevated blood pressure, elevated fasting glucose or impaired glucose tolerance, and central adiposity; alternate definitions exist (2–4). Metabolic syndrome prevalence is on average 20–25% among U.S. adults but varies widely by age, race/ethnicity, adiposity, and definition used (5–13). Similar or lower prevalences have been seen in Canadian and European (6,14–20) and Asian (6,21–25) cohorts. Rising obesity and diabetes in the U.S. (26) and elsewhere (27,28) will likely increase the prevalence of metabolic syndrome (29,30).

The metabolic syndrome mortality risk among those with CVD, or elevated CVD risk (e.g., LDL cholesterol), has only been briefly studied. Metabolic syndrome prevalences up to 84% have been found in cohorts with elevated CVD risk or prior CVD (31–37). Research examining cardiovascular outcomes following metabolic syndrome (34,38–43) generally had limited follow-up. We examined the associations of metabolic syndrome and its underlying conditions with 18-year total, CVD, and coronary heart disease (CHD) mortality in men at above-average risk of CHD who were randomized into the Multiple Risk Factor Intervention Trial (MRFIT). The long follow-up and large cohort allowed examination of the association of metabolic syndrome with mortality for specific subgroups and of having additional risk factors such as smoking and elevated LDL cholesterol.

## RESEARCH DESIGN AND METHODS

### MRFIT procedures

Previous reports detail MRFIT (44–48), a primary prevention trial of a CHD mortality intervention among men aged 35–57 years at increased risk but without

clinical CHD. At screen 1 (1973–1976), 361,662 men at 22 clinical centers in 18 U.S. cities were scored for CHD risk (based on serum cholesterol, diastolic blood pressure [DBP], and cigarette smoking). Men in the top 10–15% of the risk distribution, but with no history of heart attack, treatment for diabetes, DBP  $\geq 115$  mmHg, or serum cholesterol  $\geq 350$  mg/dl, were invited to screen 2. Screen 2 excluded men with extreme obesity, clinical evidence of CVD or other serious disease, untreated symptomatic diabetes, diets incompatible with the MRFIT intervention (including excessive alcohol intake), treatment with certain medications (e.g., hypoglycemic or lipid-lowering agents), DBP  $\geq 120$  mmHg, or refusal to consider quitting smoking. At screen 3, 12,866 men were randomized to special intervention (SI group;  $n = 6,428$ , dietary counseling to lower cholesterol, smoking cessation counseling, and antihypertension medication) or usual care (UC group;  $n = 6,438$ , referred to their usual physicians). All participants were asked to return to their clinical center annually for at least 6 years (follow-up  $>90\%$  at each) for comprehensive evaluation, risk factor assessment, and medical history update including medications.

This study's cohort included 11,490 participants who attended annual visit 6 (1980–1982). Of the 1,376 participants who did not, 430 were during-trial decedents. Analyses excluded men missing data for three or more metabolic syndrome conditions ( $n = 133$ ) or for adjusting variables ( $n = 407$ , primarily alcohol use and lipid fractions), leaving 10,950 men. Baseline for this study is annual visit 6.

### Definition of metabolic syndrome

Metabolic syndrome at annual visit 6 was defined from ATP-III (1) by three or more conditions including BMI  $\geq 30$  kg/m<sup>2</sup> (waist circumference was not measured), triglycerides  $\geq 150$  mg/dl, HDL cholesterol  $<40$  mg/dl, systolic blood pressure (SBP)  $\geq 130$  mmHg (or DBP  $\geq 85$  mmHg or using antihypertensives), and fasting glucose  $\geq 110$  mg/dl (or using insulin or hypoglycemic agents). We counted men on lipid-lowering drugs ( $n = 26$ ) as meeting the triglycerides and HDL cholesterol criteria, even if their measures while on medication were  $<150$  and  $\geq 40$  mg/dl, respectively.

### Data collection

Race/ethnicity, education, and parental histories of CVD (heart attack, hypertension, stroke, or other CHD) and diabetes were self-reported at screening. At annual visit 6, disrobed height and weight were recorded, and 12-h fasting blood samples were centrally analyzed for serum glucose, cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol (49,50). Blood pressure was the average of two measurements according to a standard protocol by certified observers (51). Antihypertensive use was from trial prescription and/or self-report. Participants self-reported cigarette use (usual number smoked per day), alcohol use (number of drinks consumed per week), and physical activity (equal to or more than others their age).

During-trial nonfatal CVD was defined by any of the following: coronary bypass surgery, stroke, clinical myocardial infarction, or silent myocardial infarction on resting electrocardiogram at or before annual visit 6 (49,52). Annual visit 6 resting electrocardiogram abnormalities were recorded from any of the following: Q wave findings, ST-segment elevations and depressions, negative T waves, high R waves, conduction defects, frequent ventricular premature beats, complete atrioventricular and bundle-branch block, supraventricular tachycardia, and left axis deviation. Morbidity data were not collected posttrial.

### Mortality end point definition

Total, CVD, and CHD mortality were primary end points. For decedents through 31 December 1990, vital status was determined by clinical center staff (through 28 February 1982) or by matching identifying information with National Death Index or Social Security Administration coded cause-specific mortality based on death certificates using ICD-9; a third nosologist adjudicated disagreements. For 1991–1999, dates and causes of death were obtained using National Death Index Plus (58–61). CVD mortality was ICD-9 350–459 and ICD-10 I00-I99 and CHD mortality was ICD-9 410–414 and 429.2 and ICD-10 I20-I25.

### Statistical methods

Participant characteristics, including prevalences of each metabolic syndrome condition, were summarized by annual visit 6 metabolic syndrome presence or absence. Mortality from annual visit 6

through 1999 was compared between metabolic syndrome groups using age-adjusted death rates.

Multivariate-adjusted proportional hazards models (62), stratified by clinical center, tested risk associated with metabolic syndrome and with an increasing number of metabolic syndrome conditions. Adjusting variables were SI/UC groups, age, African American or not, years of education, parental histories of CVD and diabetes, during-trial nonfatal CVD event, cigarette smoking status at screening, and annual visit 6 smoking status, cigarettes per day, alcoholic drinks per week, physical activity, fasting total cholesterol, LDL cholesterol, and resting electrocardiogram abnormalities.

Because cholesterol treatment guidelines are written for LDL cholesterol (1), and goals depend on additional risk factors such as smoking, we examined metabolic syndrome mortality risk for prespecified subgroups: age, African American or not, nonfatal CVD event, smoking status, and LDL and total cholesterol levels. We examined the mortality risk independently associated with each metabolic syndrome condition, adjusting for the other conditions. Lastly, we examined the mortality risk associated with having other risk factors in addition to metabolic syndrome, including nonfatal CVD event, smoking, and elevated LDL cholesterol. *P* values given throughout are two tailed; no adjustments for multiple comparisons were made.

## RESULTS

### Cohort characteristics

Risk factors were reduced at the end of MRFIT active intervention: average blood pressure after 6 years went from 136/91 mmHg at screening to 124/80 mmHg among SI men and from 135/91 to 127/84 mmHg among UC men, and average cholesterol went from 240 to 228 mg/dl and from 240 to 233 among SI and UC men, respectively. Neither total nor cause-specific mortality differed between SI and UC subjects (45).

Of 10,950 men, 4,588 (41.9%) had metabolic syndrome at annual visit 6, while 6,362 (58.1%) did not (Table 1). Metabolic syndrome men were more likely to have a parent with diabetes; were less likely to be African American; had on average fewer years of education and higher glucose, triglycerides, SBP, DBP, total cholesterol, and BMI and lower HDL

Table 1—Participant characteristics according to metabolic syndrome presence at this study's baseline (annual visit 6)

	With metabolic syndrome	Without metabolic syndrome	P value for group difference
n (%)	4,588 (41.9)	6,362 (58.1)	
Characteristics at screening			
African American (%)	5.9	8.2	<0.0001
Education (years)	13.8 ± 2.9	14.0 ± 2.9	<0.0001
Parental history of CVD (%)	77.0	75.5	0.06
Parental history of diabetes (%)	21.6	17.1	<0.0001
SI group (%)	50.0	51.0	0.21
Metabolic syndrome markers at annual visit 6			
Fasting glucose (mg/dl)	115.3 ± 37.4	97.7 ± 15.3	<0.0001
Fasting triglycerides (mg/dl)	270.8 ± 207.0	139.6 ± 72.9	<0.0001
Fasting HDL cholesterol (mg/dl)	35.2 ± 8.0	46.5 ± 11.8	<0.0001
SBP (mmHg)	125.7 ± 14.2	122.6 ± 14.4	<0.0001
DBP (mmHg)	83.4 ± 8.5	80.9 ± 8.6	<0.0001
BMI (kg/m <sup>2</sup> )	29.5 ± 3.9	26.3 ± 3.0	<0.0001
Metabolic syndrome conditions at annual visit 6			
Elevated glucose or drug use* (%)	44.3	7.7	<0.0001
Elevated triglycerides or drug use† (%)	88.9	30.0	<0.0001
Low HDL cholesterol or drug use† (%)	82.5	27.0	<0.0001
Elevated blood pressure or drug use‡ (%)	91.3	61.6	<0.0001
Elevated BMI (%)	45.2	8.9	<0.0001
Characteristics at annual visit 6			
Age (years)	53.0 ± 5.9	53.0 ± 5.9	0.66
Smoker (%)	34.3	41.2	<0.0001
Cigarettes per day among smokers	28.2 ± 15.1	29.0 ± 15.1	0.07
Alcohol drinker (%)	82.5	86.1	<0.0001
Drinks per week among drinkers	10.8 ± 11.4	12.4 ± 12.9	<0.0001
Physical activity more than peers (%)	70.6	79.5	<0.0001
Fasting total cholesterol (mg/dl)	232.4 ± 38.6	229.0 ± 36.3	<0.0001
Fasting LDL cholesterol (mg/dl)	145.6 ± 35.5	154.7 ± 33.4	<0.0001
Fasting LDL cholesterol ≥130 mg/dl (%)	68.0	77.8	<0.0001
During-trial nonfatal CVD (%)	23.3	18.8	<0.0001
Resting electrocardiogram abnormality (%)	33.3	33.9	0.49
Mortality			
Total number of deaths (rate)§	1,660 (228.5)	1,963 (189.6)	<0.0001
Number of CVD deaths (rate)§	899 (123.7)	846 (81.6)	<0.0001
Number of CHD deaths (rate)§	633 (86.9)	585 (55.9)	<0.0001

Data are means ± SD, unless otherwise indicated. Numbers of deaths (death rates) are over a median of 18.4 years. P values shown are from general linear model F tests, logistic model  $\chi^2$  tests, or log-rank tests, as appropriate. Drug use includes \*insulin/hypoglycemic agents, †lipid-lowering agents, or ‡antihypertensive agents. §Rates are age-adjusted death rates per 10,000 person-years.

cholesterol; and rated themselves as less physically active than their peers. Metabolic syndrome men were also less likely to be smokers or drinkers of alcohol and had lower average drinks per week, cigarettes per day, and LDL cholesterol.

Among those with metabolic syndrome, 57.9% had three conditions, 32.3% had four, and 9.9% had all five. Elevated blood pressure, elevated triglycerides, and low HDL cholesterol were most common (many MRFIT participants had elevated blood pressure and/or cholesterol at trial's onset) followed by elevated BMI and elevated glucose, similar for those without metabolic syndrome.

Among those with metabolic syndrome, the most common combination of the three or more conditions was elevated blood pressure, elevated triglycerides, and low HDL cholesterol, with 29.6%. Those three plus elevated glucose accounted for 13.3%, those three plus elevated BMI accounted for 13.1%, and all five accounted for 9.9%. Each other combination accounted for <7%.

#### Mortality associated with metabolic syndrome

Median mortality follow-up was 18.4 years, with 3,623 deaths, including 1,745 CVD and 1,218 CHD deaths. Age-

adjusted total, CVD, and CHD death rates per 10,000 person-years were higher among those with metabolic syndrome than those without (all log-rank test  $P < 0.0001$ ) (Table 1).

Proportional hazards models showed highly significant differences between men with and without metabolic syndrome (Table 2). Multivariate-adjusted hazard ratios (HRs) were 1.21 (95% CI 1.13–1.29), 1.49 (1.35–1.64), and 1.51 (1.34–1.70) for total, CVD, and CHD mortality, respectively. After further adjustment for annual visit 6 levels of glucose, HDL cholesterol, triglycerides, SBP, and BMI, HRs decreased to 1.11 (1.02–

Table 2—Relative mortality for those with metabolic syndrome compared with those without and for those with the specified number of metabolic syndrome conditions compared with those with no conditions (annual visit 6)

	Smoking and age adjusted		Multivariate adjusted	
	HR (95% CI)	P value	HR (95% CI)*	P value
<b>Total mortality</b>				
Metabolic syndrome (yes versus no)	1.26 (1.18–1.35)	<0.0001	1.21 (1.13–1.29)	<0.0001
One condition versus none	1.10 (0.95–1.28)	0.22	1.06 (0.92–1.24)	0.42
Two conditions versus none	1.14 (0.98–1.32)	0.09	1.09 (0.94–1.27)	0.25
Three conditions versus none	1.22 (1.05–1.42)	0.008	1.16 (1.00–1.34)	0.06
Four conditions versus none	1.50 (1.29–1.76)	<0.0001	1.41 (1.20–1.66)	<0.0001
Five conditions versus none	2.19 (1.82–2.64)	<0.0001	1.96 (1.62–2.38)	<0.0001
Linear trend with number of conditions	1.13 (1.10–1.16)	<0.0001	1.11 (1.08–1.14)	<0.0001
<b>CVD mortality</b>				
Metabolic syndrome (yes versus no)	1.58 (1.43–1.73)	<0.0001	1.49 (1.35–1.64)	<0.0001
One condition versus none	1.14 (0.90–1.46)	0.28	1.09 (0.86–1.39)	0.48
Two conditions versus none	1.40 (1.10–1.77)	0.005	1.29 (1.02–1.63)	0.04
Three conditions versus none	1.66 (1.32–2.10)	<0.0001	1.51 (1.19–1.92)	0.0006
Four conditions versus none	2.15 (1.69–2.75)	<0.0001	1.98 (1.55–2.53)	<0.0001
Five conditions versus none	3.34 (2.53–4.40)	<0.0001	2.98 (2.24–3.95)	<0.0001
Linear trend with number of conditions	1.25 (1.21–1.30)	<0.0001	1.23 (1.18–1.28)	<0.0001
<b>CHD mortality</b>				
Metabolic syndrome (yes versus no)	1.60 (1.43–1.80)	<0.0001	1.51 (1.34–1.70)	<0.0001
One condition versus none	1.18 (0.88–1.58)	0.31	1.12 (0.84–1.51)	0.44
Two conditions versus none	1.45 (1.09–1.93)	0.01	1.32 (0.99–1.76)	0.06
Three conditions versus none	1.76 (1.32–2.34)	0.0001	1.59 (1.19–2.11)	0.002
Four conditions versus none	2.20 (1.64–2.96)	<0.0001	2.01 (1.49–2.72)	<0.0001
Five conditions versus none	3.56 (2.56–4.96)	<0.0001	3.18 (2.26–4.47)	<0.0001
Linear trend with number of conditions	1.26 (1.21–1.32)	<0.0001	1.24 (1.18–1.30)	<0.0001

\*Adjusting variables: SI/UC group, age, race/ethnicity (African American or not), education, parental histories of heart disease and diabetes, participant during-trial nonfatal CVD event, smoking status (cigarette smoker, yes versus no) at screening, and annual visit 6 measures of smoking status, cigarettes per day, alcoholic drinks per week, physical activity, fasting total cholesterol, LDL cholesterol, and resting electrocardiogram abnormality.

1.20), 1.23 (1.09–1.38), and 1.20 (1.04–1.39). Adjustment instead for trial-averaged values decreased HRs further to 1.02 (0.94–1.11), 1.11 (0.99–1.25), and 1.11 (0.96–1.28). Results were similar when the 2005 International Diabetes Federation definition of metabolic syndrome (4) was used: 1.21 (1.12–1.31) for total, 1.48 (1.33–1.66) for CVD, and 1.48 (1.30–1.69) for CHD mortality.

An increasing number of metabolic syndrome conditions was associated with higher mortality, up to CHD mortality more than three times higher for five conditions compared with none (Table 2). Significant linear trends with number of conditions were observed for total, CVD, and CHD mortality (HR 1.11, 1.23, and 1.24, respectively, all  $P < 0.0001$ ). When triglycerides and HDL cholesterol conditions did not incorporate lipid-lowering drug use, 26 men were no longer considered as having metabolic syndrome. Multivariate-adjusted metabolic syndrome HRs were then nearly identical: 1.21 (95% CI 1.13–1.30) for total, 1.49 (1.35–

1.65) for CVD, and 1.51 (1.34–1.70) for CHD mortality.

#### CVD mortality associated with metabolic syndrome for subgroups

The association of metabolic syndrome with CVD mortality did not vary significantly across subgroups for SI/UC group, age, African American or not, nonfatal CVD, smoking, LDL cholesterol, and total cholesterol (Table 3). Among those with metabolic syndrome, there was little evidence of increased risk at higher LDL or total cholesterol levels (Table 3); similar results were found for those without metabolic syndrome. In contrast, among those with metabolic syndrome, smokers had substantially higher risk of CVD mortality than never smokers (HR 2.05 [95% CI 1.61–2.62]), while former smokers showed only marginally higher risk than never smokers (1.18 [0.96–1.45]); similar results were seen among those without metabolic syndrome. Having nonfatal CVD was associated with similarly higher risk for both those with metabolic syn-

drome (1.63 [1.42–1.87]) and those without metabolic syndrome (1.60 [1.38–1.87]).

#### CVD mortality associated with each metabolic syndrome condition

Among men with metabolic syndrome, elevated glucose and low HDL cholesterol were most predictive of CVD mortality (Table 4), while elevated blood pressure and elevated BMI were less so. (Many MRFIT participants had elevated blood pressure at trial's onset, and extremely obese men were excluded.) After adjusting for other risk factors and the other conditions, among men with metabolic syndrome, the HR for CVD mortality comparing those with elevated glucose with those without was 1.54 (95% CI 1.34–1.78), those with low HDL cholesterol to those without was 1.45 (1.18–1.77), those with elevated BMI to those without was 1.34 (1.17–1.54), those with elevated blood pressure to those without was 1.25 (0.98–1.58), and those with elevated triglycerides to those without was

Table 3—Cardiovascular mortality associated with metabolic syndrome (annual visit 6) for various subgroups of men

	With metabolic syndrome: comparison of subgroups			Without metabolic syndrome: comparison of subgroups			Within subgroups: comparison of metabolic syndrome (with versus without)	P§
	n*	Rate†	HR (95% CI)‡	n*	Rate†	HR (95% CI)‡	HR (95% CI)‡	
Age at annual visit 6								
<50 years	1,486	76.3	0.53 (0.45–0.62)	2,090	50.0	0.50 (0.43–0.60)	1.54 (1.25–1.89)	0.68
≥50 years	3102	142.7	1.00	4272	90.5	1.00	1.47 (1.31–1.64)	
Race/ethnicity								
African American	272	97.2	0.73 (0.53–1.01)	519	87.5	0.98 (0.76–1.26)	1.13 (0.76–1.67)	0.15
Other	4,316	125.0	1.00	5,843	81.2	1.00	1.52 (1.37–1.68)	
Randomized MRFIT group								
SI group	2,292	122.5	1.07 (0.94–1.23)	3,256	78.8	1.03 (0.89–1.18)	1.52 (1.33–1.75)	0.63
UC group	2,296	125.1	1.00	3,106	84.7	1.00	1.45 (1.27–1.67)	
During-trial nonfatal CVD								
Yes	1,070	194.7	1.63 (1.42–1.87)	1,195	128.6	1.60 (1.38–1.87)	1.50 (1.27–1.78)	0.89
No	3,518	103.7	1.00	5,167	70.9	1.00	1.48 (1.32–1.67)	
Annual visit 6 smoking status								
Current	1,574	171.2	2.05 (1.61–2.62)	2,624	109.2	2.11 (1.62–2.75)	1.50 (1.30–1.73)	0.93
Former	2,255	106.8	1.18 (0.96–1.45)	2,843	68.3	1.25 (0.99–1.57)	1.47 (1.26–1.70)	
Never	759	90.3	1.00	895	55.6	1.00	1.54 (1.17–2.03)	
Annual visit 6 LDL cholesterol								
≥160 mg/dl	1,575	122.0	0.98 (0.81–1.18)	2,758	85.7	1.16 (0.92–1.44)	1.40 (1.20–1.63)	0.43
130–159 mg/dl	1,545	130.8	1.10 (0.93–1.30)	2,192	83.6	1.24 (1.02–1.52)	1.46 (1.24–1.71)	
<130 mg/dl	1,468	117.9	1.00	1,412	70.3	1.00	1.65 (1.35–2.02)	
Annual visit 6 total cholesterol								
≥240 mg/dl	1,866	117.8	0.98 (0.77–1.23)	2,360	85.8	1.12 (0.88–1.44)	1.40 (1.20–1.64)	0.52
200–239 mg/dl	1,889	132.0	1.11 (0.91–1.35)	2,677	82.9	1.16 (0.95–1.42)	1.54 (1.34–1.79)	
<200 mg/dl	833	118.7	1.00	1,325	71.6	1.00	1.62 (1.29–2.03)	

\*Number of men. †Rates are age-adjusted CVD death rates per 10,000 person-years. ‡Adjusting variables (not including the corresponding subgroup variable for each subgroup analysis): SI/UC group, age, race/ethnicity (African American or not), education, parental histories of heart disease and diabetes, participant during-trial nonfatal CVD event, smoking status (cigarette smoker, yes versus no) at screening, and annual visit 6 measures of smoking status, cigarettes per day, alcoholic drinks per week, physical activity, fasting total cholesterol, LDL cholesterol, and resting electrocardiogram abnormality. §P values correspond to likelihood ratio tests for interactions of metabolic syndrome with each subgroup.

1.06 (0.86–1.30). Results were similar among men without metabolic syndrome except for low HDL cholesterol (1.02 [0.80–1.22]). Dividing the blood pressure condition into very high risk (SBP ≥140 or DBP ≥90, regardless of antihypertensive drug use) and high risk (130 ≤ SBP < 140 or 85 ≤ DBP < 90 or antihypertensive drug use) yielded higher HRs for very high risk than high risk (Table 4).

#### CVD mortality associated with additional risk factors

Among men with metabolic syndrome, we examined mortality risk associated with having additional risk factors: nonfatal CVD, cigarette smoking, and LDL cholesterol ≥130 mg/dl. For those without nonfatal CVD, CVD mortality was substantially higher with both smoking and elevated LDL cholesterol (HR 1.79 [95% CI 1.22–2.63]) relative to men with

neither. For those with nonfatal CVD, CVD mortality was even more elevated with both (2.11 [1.32–3.38]) compared with neither. Among all men, considering seven conditions (five metabolic syndrome conditions, smoking, and elevated LDL cholesterol), CVD mortality risk increased with more conditions: relative to men with none, HRs were 1.53 (0.56–4.21) for one condition, 1.92 (0.71–5.16) for two, 2.19 (0.82–5.89) for three, 2.62 (0.98–7.05) for four, 3.43 (1.27–9.24) for five, 4.71 (1.73–12.80) for six, and 5.68 (1.97–16.41) for all seven.

**CONCLUSIONS**— Metabolic syndrome in the MRFIT survivors was associated with higher 18-year total, CVD, and CHD mortality even after adjusting for SI/UC group, age, African American or not, education, physical activity, and other CVD risk factors. The association

increased with number of metabolic syndrome conditions present, up to total mortality twice as high and CVD and CHD mortality almost three times as high among those with all five conditions compared with those with none. Elevated glucose and low HDL cholesterol were most predictive of CVD mortality among those with metabolic syndrome. In contrast, low HDL cholesterol was not predictive among men without metabolic syndrome. Lastly, mortality among men with metabolic syndrome was higher for smokers with elevated LDL cholesterol, regardless of nonfatal CVD status.

Our work is unique for its large sample size and long mortality follow-up but limited by lack of posttrial morbidity, restriction to men, and exclusion of during-trial decedents. The MRFIT age range and exclusion criteria, such as for severe disease (e.g., cancer) or factors thought likely

Table 4—Importance of each metabolic syndrome condition in predicting cardiovascular mortality, separately for the 4,588 men with and 6,362 men without metabolic syndrome (annual visit 6)

	With metabolic syndrome (n = 4,625)		Without metabolic syndrome (n = 6,411)		P
	n*	HR (95% CI)†	n*	HR (95% CI)†	
Conditions as originally defined					
Elevated glucose or drug use‡	2,028	1.54 (1.34–1.78)	489	1.43 (1.12–1.78)	0.52
Low HDL cholesterol or drug use§	3,787	1.45 (1.18–1.77)	1,720	1.02 (0.86–1.22)	0.006
Elevated triglycerides or drug use§	4,079	1.06 (0.86–1.30)	1,906	1.02 (0.87–1.19)	0.79
Elevated blood pressure or drug use¶	4,188	1.25 (0.98–1.58)	3,913	1.37 (1.16–1.62)	0.53
Elevated BMI	2,067	1.34 (1.17–1.54)	563	1.20 (0.94–1.55)	0.58
With blood pressure divided					
SBP ≥140 or DBP ≥90 mmHg	1,255	1.32 (1.02–1.72)	1,317	1.46 (1.19–1.79)	0.53
130 ≤ SBP < 140 or 85 ≤ DBP < 90 or antihypertensive drug use	2,933	1.21 (0.95–1.55)	2,596	1.30 (1.09–1.56)	0.67

HRs are for presence versus absence of that condition, and *P* values are for metabolic syndrome by condition interaction tests. \*Number of men with that condition. †Adjusting variables: SI/UC group, age, race/ethnicity (African American or not), education, parental histories of heart disease and diabetes, participant during-trial nonfatal CVD event, smoking status (cigarette smoker, yes versus no) at screening, and annual visit 6 measures of smoking status, cigarettes per day, alcoholic drinks per week, physical activity, LDL cholesterol, resting electrocardiogram abnormality, and each of the other metabolic syndrome conditions. Drug use includes ‡insulin/hypoglycemic agents, §lipid-lowering agents, or ¶antihypertensive agents. ||*P* values correspond to *z* tests for interactions of metabolic syndrome with each condition.

to interfere with the intervention (e.g., extreme obesity, excessive alcohol consumption), also limit the generalizability. Men randomized to MRFIT were at above-average risk for CHD (47). Other follow-up studies among high-risk groups have been of shorter duration but have also shown high prevalence of and poor prognosis following metabolic syndrome (32,34,39,40). Other studies in general populations have found lower prevalence of metabolic syndrome but similarly unfavorable prognosis of metabolic syndrome (38,41–43).

Our metabolic syndrome definition was based on ATP-III (1) but included use of certain medications, as done elsewhere (8,14–16,20,22,24,32,35,39,40). MRFIT did not collect waist circumference; we used BMI instead, as done elsewhere (12,14,15). Use of BMI may have resulted in lower estimated effects than waist circumference would have shown because BMI includes total fat mass. Waist circumference reflects visceral fat mass, more directly related to insulin resistance (63–69).

Metabolic syndrome has had multiple and changing definitions, indicating the uncertainty about a unifying pathogenesis. This is despite Reaven's (70) assertion that the "basic abnormality leading to all of these changes is resistance to insulin-mediated disposal," supported by the significant association of ATP-III–defined metabolic syndrome with measured insulin resistance among healthy adults (71) with high specificity (72). Nevertheless,

in a recent extensive review (73), the imprecision of the metabolic syndrome definition led the authors to doubt the value of using the syndrome as a marker for CVD risk and to emphasize the importance of treatment of all CVD risk factors. This view is supported by our results showing an increased risk with additional metabolic syndrome conditions, from one condition to the full complement of five, along with a further increase in risk with smoking and elevated LDL cholesterol. In a population study in the U.K., analysis of different ways of combining the conditions of metabolic syndrome showed that this clustering had no greater predictive value beyond the consideration of all of the individual risk factors (74). This held true in the MRFIT cohort as well when adjusting for trial-averaged risk factors but not for single ascertainment of risk factors. As the utility of metabolic syndrome continues to be debated, Grundy et al. (75) describe metabolic syndrome as a combination of metabolic risk factors and underlying risk factors, which give rise to the metabolic risk factors, and recognize that metabolic syndrome is not a discrete entity known to be caused by a single factor; they emphasize again its strong association with obesity.

The justification for invoking the syndrome (Mitka [76], quoting Scott Grundy, chair of ATP-III) was to garner attention and action by primary care physicians who had apparently paid scant regard to the admonition for weight reduction promulgated in ATP-II (77).

However, there is real danger that such concentration on a cluster of three of five conditions (unjustified by the additive predictiveness of all five) will distract from the need to address all risk factors including those not part of the five, namely LDL cholesterol and smoking.

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