Metabolic Syndrome and Mortality in Older Adults

The Cardiovascular Health Study

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Background: The utility of metabolic syndrome (MetS) for predicting mortality among older adults, the highest-risk population, is not well established. In addition, few studies have compared the predictive utility of MetS to that of its individual risk factors.

Methods: We evaluated relationships of MetS (as defined by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III (ATPIII)], International Diabetes Foundation [IDF], and World Health Organization [WHO]) and individual MetS criteria with mortality between 1989 and 2004 among 4258 US adults 65 years or older and free of prevalent cardiovascular disease (CVD) in the Cardiovascular Health Study, a multicenter, population-based, prospective cohort. Total, CVD, and non-CVD mortality were evaluated. Cox proportional hazards models were used to estimate the mortality hazard ratio (relative risk [RR]) predicted by MetS.

Results: At baseline (mean age, 73 years), 31% of men and 38% of women had MetS (ATPIII). During 15 years of follow-up, 2116 deaths occurred. After multivariable adjustment, compared with persons without MetS, those with MetS had a 22% higher mortality (RR, 1.22; 95% confidence interval [CI], 1.11-1.34). Higher risk with MetS was confined to persons having elevated fasting glucose level (EFG) (defined as ≥110 mg/dL [≥6.1 mmol/L] or treated diabetes mellitus) (RR, 1.41; 95% CI, 1.27-1.57) or hypertension (RR, 1.26; 95% CI, 1.15-1.39) as one of the criteria; persons having MetS without EFG (RR, 0.97; 95% CI, 0.85-1.11) or MetS without hypertension (RR, 0.92; 95% CI, 0.71-1.19) did not have higher risk. Evaluating MetS criteria individually, we found that only hypertension and EFG predicted higher mortality; persons having both hypertension and EFG had 82% higher mortality (RR, 1.82; 95% CI, 1.58-109). Substantially higher proportions of deaths were attributable to EFG and hypertension (population attributable risk fraction [PAR%], 22.2%) than to MetS (PAR%, 6.3%). Results were similar when we used WHO or IDF criteria, when we evaluated different cut points of each individual criterion, and when we evaluated CVD mortality.

Conclusion: These findings suggest limited utility of MetS for predicting total or CVD mortality in older adults compared with assessment of fasting glucose and blood pressure alone.

Arch Intern Med. 2008;168(9):969-978

METABOLIC SYNDROME (MetS) has been identified as a potential risk factor for poor outcomes.[1] The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATPIII])[2] defines 5 criteria for clinical identification of MetS, including abdominal obesity, hypertriglyceridemia, low level of high-density lipoprotein cholesterol (HDL-C), hypertension, and altered glucose metabolism, with diagnosis requiring 3 or more components. The International Diabetes Federation (IDF) and World Health Organization (WHO) use similar criteria emphasizing obesity and insulin resistance, respectively.[2,3] In predominantly middle-aged populations, the presence of MetS predicts poor outcomes,[4-13] including total mortality,[4-8,12] which is arguably the most relevant adverse outcome for any individual. However, the overall predictive utility of MetS has been questioned,[11,13-15] and the ability of MetS to identify mortality risk in older adults, the fastest growing segment of the population and the group at highest risk, is not clearly established.

Several factors may limit the utility of MetS for predicting mortality among individuals examined late in life. First, competing risks from noncardiovascular disease (non-CVD) mortality[16] and blunted associations of some measures, such as adi-

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Group Information: For a full list of Cardiovascular Health Study investigators and institutions, see "Principal Investigators and Study Sites" at http://www.chs-nhlbi.org.

posity, with death late in life[17,18] may render MetS less predictive of death in older adults. Furthermore, some MetS components—eg, systolic blood pressure (BP), fasting glucose level, and HDL-C level—may predict higher CVD risk in older adults, but other MetS components—eg, hypertriglyceridemia and diastolic BP—are not clearly related to adverse outcomes late in life.[19,20] Additionally, the dichotomization of risk factors or chosen cut points may not be optimal for identifying older adults at higher risk, since these distributions were often characterized in predominantly middle-aged populations.[21] Finally, the MetS concept may be no more important than its individual risk factors,[15] but the utility of MetS, compared with its individual risk factors, for predicting mortality in older adults is not established. To determine whether MetS predicts mortality among older men and women, and whether different individual criteria or cut points are most predictive, we evaluated relationships of MetS and individual MetS criteria with mortality in the Cardiovascular Health Study (CHS).[22,23]

METHODS

STUDY POPULATION

The CHS is a prospective, multicenter cohort study of determinants of CVD risk among older adults.[22,23] A total of 5888 noninstitutionalized, non–wheelchair-bound men and women 65 years or older were contacted and enrolled from Medicare eligibility lists in 4 US communities in 1989-1990 and 1992-1993. Compared with those ineligible or declining to participate (42.7%), participants were younger, more educated, more often married, and less likely to report activity limitations.[23] Each center's institutional review committee approved the study, and all subjects gave informed consent. Mean age at enrollment was 73 years (range, 65-100 years); 58% were women, and 16% were black. Baseline evaluations included standardized clinical examinations, laboratory evaluations, and questionnaires on health status, medical history, and risk factors.[22-24] We excluded 1320 participants with known CVD at baseline[24] (already at known high risk and for whom aggressive secondary prevention measures were already appropriate) and 310 participants with missing information on MetS criteria, leaving 4258 participants for this analysis. We also performed sensitivity analyses adding back the 1216 individuals with prevalent CVD at baseline (excluding 104 with missing MetS data).

ASSESSMENT OF MetS

Each MetS component was directly assessed at baseline. Seated resting BP was measured in the right arm using a habitus-appropriate cuff (Hawksley random-zero sphygmomanometer model 7076; Hawksley Sons Limited, Lancing, England). Anthropomorphic measures included weight, height, waist circumference, and hip circumference.[22] Blood was collected following 8 or more hours of fasting for measurement of plasma lipids, glucose, and insulin. Standard oral glucose tolerance testing was performed in participants without treated diabetes. MetS was diagnosed according to American Heart Association/National Heart, Lung and Blood Institute (modified ATPIII) criteria.[2] At least 3 of the following conditions had to be present: large waist circumference (men, ≥102 cm; women, ≥88 cm), elevated triglyceride level (≥150 mg/dL), low HDL-C level (men, <40 mg/dL; women, <50 mg/dL), hypertension (systolic BP, ≥130 mm Hg; diastolic BP, ≥85 mm Hg; or treated hypertension), or elevated fasting glucose level (EFG) (glucose, ≥110 mg/dL or treated diabetes); we also repeated analyses using the lower EFG cut point (≥100 mg/dL).[2] We also evaluated IDF MetS,[3] requiring obesity or large waist circumference (using the ATPIII cut points), and WHO MetS,[2] requiring the presence of insulin resistance (treated diabetes; fasting glucose level ≥110 mg/dL; 2-hour postchallenge glucose level ≥140 mg/dL; or fasting insulin level in the highest quartile among individuals with fasting glucose level <110 mg/dL [replacing hyperinsulinemic euglycemic glucose uptake in large-scale studies]) plus any 2 of hypertension (antihypertensive treatment; systolic BP, ≥140 mm Hg; or diastolic BP, ≥90 mm Hg), high triglyceride level (≥150 mg/dL), low HDL-C level (men, <35 mg/dL; women, <39 mg/dL), or obesity (body mass index [BMI] >30 [calculated as weight in kilograms divided by height in meters squared] or waist to hip ratio >0.90 in men and >0.85 in women). Urinary albumin and creatinine excretion were not measured at baseline in the CHS and were not used for MetS classification. For 477 individuals enrolled in 1992-1993 (when oral glucose tolerance tests were not administered), treated diabetes, fasting glucose level, and fasting insulin level defined WHO insulin resistance. Although treated diabetes is explicitly included in ATPIII, WHO, and IDF criteria,[2,3] we also performed analyses excluding patients with treated diabetes (n=305), a subgroup at known high risk.

To convert triglycerides to millimoles per liter, multiply by 0.0113; cholesterol to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555.

ASCERTAINMENT OF MORTALITY

Participants were observed during annual examinations and interim 6-month telephone contacts through 1999 and 6-month telephone contacts thereafter.[25] Deaths were confirmed by a mortality review committee using information from hospital records, death certificates, autopsy and coroner reports, insurance records, obituaries, and interviews with physicians or next of kin. Cause of death was adjudicated as CVD (due to coronary heart disease, cerebrovascular disease, heart failure, or peripheral vascular disease) or non-CVD. By these methods, together with interviews of contacts and proxies, mortality follow-up was complete for 100% of participants.

STATISTICAL ANALYSIS

Cox proportional hazards models were used to estimate the mortality hazard ratio (relative risk [RR]) predicted by MetS, censoring on the last day of adjudicated follow-up (June 30, 2004). Analyses using Schoenfeld residuals indicated little evidence against the proportionality assumption (global test, $P=.50$). Given ontologic concern that a syndrome based on the presence of 3 of 5 risk factors might not reveal true relations of risk factors with disease, we also evaluated risk associated with each criterion individually and with MetS in the presence or absence of specific criteria. Because dichotomization of risk factors or chosen cut points might not be optimal for older adults, we also evaluated whether different risk factor cut points might be more predictive. To test the concept of MetS to predict mortality, rather than to infer causation, evaluation of other factors for potential confounding was not a primary concern. We investigated the independent predictive ability of MetS, adjusted for age and sex, and of each individual MetS criteria further adjusted for the other criteria. We also investigated the independent predictive ability of MetS and MetS criteria above and beyond other demographic and lifestyle factors, including race, education, smoking status, smoking history, physical activity, and alcohol use. Absolute risk differences (RDs) per 1000 person-years were derived from reference group incidence rates

and multivariable-adjusted hazard ratios (incidence rate [IR] × [relative risk [RR] – 1]). Population attributable risk fractions (PAR%s) for MetS were calculated using multivariable-adjusted risks ([RR – 1]/RR × P[E], where P[E] indicates prevalence of exposure). Effect modification by prespecified strata of sex, age, race, and C-reactive protein (CRP) level was evaluated using likelihood ratio testing comparing nested models with and without a multiplicative interaction term. Because some MetS components could be affected by smoking or presence of underlying disease (reverse causation), we performed sensitivity analyses excluding smokers, individuals with cancer (except nonmelanoma skin cancer) or chronic pulmonary disease, and deaths during the first year. *P* values were 2-tailed ($\alpha = .05$). Analyses were performed using Stata software, version 9.2 (Stata Corp, College Station, Texas).

Table 1. Baseline Prevalence of Metabolic Syndrome and Individual Components Among 4258 Older Adults

Characteristic	Subjects, No. (%)	
	Women (n=2593)	Men (n=1665)
Metabolic syndrome[a]	980 (38)	508 (31)
Abdominal obesity (waist circumference ≥88 cm in women or ≥102 cm in men)	1507 (58)	529 (32)
High triglyceride levels (≥150 mg/dL)	799 (31)	485 (29)
Low high-density lipoprotein cholesterol levels (<50 mg/dL for women or <40 mg/dL for men)	713 (28)	403 (24)
Hypertension (blood pressure ≥130/85 mm Hg or undergoing treatment with blood pressure medication)[b]	1882 (73)	1198 (72)
Elevated fasting glucose levels (≥110 mg/dL or undergoing treatment with diabetes medication)[c]	658 (25)	541 (32)

SI conversions: To convert triglycerides to millimoles per liter, multiply by 0.0113; cholesterol to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555.

[a] At least 3 of the 5 individual National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults[2] criteria.

[b] Criterion met based on use of blood pressure medication in 1103 women (59%) and 608 men (51%).

[c] Criterion met based on use of diabetes medication in 158 women (24%) and 147 men (27%).

RESULTS

At baseline (mean [SD] patient age, 73 [5] years), 31% of men and 38% of women had MetS. Among different MetS criteria, hypertension was the most common, followed by abdominal obesity, EFG, high triglyceride level, and low HDL-C level (**Table 1**). Levels of the individual risk factors according to presence or absence of MetS are listed in **Table 2**.

During 15 years of follow-up, 2116 deaths occurred. After multivariable adjustment, compared with persons not having MetS, those with MetS (ATPIII) had 22% higher mortality (RD, 9.2 deaths per 1000 person-years) (**Table 3**). The higher risk with MetS was confined to individuals having EFG or hypertension as 1 of the criteria. Compared with individuals without MetS, individuals with MetS including EFG as 1 of the criteria (hereinafter, MetS including EFG) had 41% higher mortality (RR, 1.41; 95% confidence interval [CI], 1.27-1.57) (RD, 17.1), while individuals with MetS but no EFG did not have higher risk (RR, 0.97; 95% CI, 0.85-1.11) (RD, <0). Similarly, individuals with MetS including hypertension as 1 of the criteria (hereinafter, MetS including hypertension) had 26% higher mortality (RR, 1.26; 95% CI, 1.15-1.39) (RD, 10.8), while individuals with MetS but no hypertension did not (RR, 0.92; 95% CI, 0.71-1.19) (RD, <0). The proportion of deaths in the population attributable to MetS (PAR%, 6.3%) were a result of deaths attributable to MetS including EFG (PAR%, 6.2%) or MetS including hypertension (PAR%, 6.5%), not MetS without EFG (PAR%, 0%) or MetS without hypertension (PAR%, 0%). As expected, mortality risks associated with MetS were somewhat attenuated after patients with treated diabetes were excluded, but again higher mortality and PAR% with MetS were confined to individuals having EFG or hypertension as 1 of the criteria (Table 3). Sensitivity analyses including the 1216 men and women with prevalent CVD at baseline demonstrated similar results: the multivariable RRs were 1.26 for MetS (95% CI, 1.17-1.36) (PAR%, 7.7%), 1.45 for MetS including EFG (95% CI, 1.32-1.58) (PAR%, 7.2%), 1.00 for MetS without EFG (95% CI, 0.89-1.12) (PAR%, 0%),

Table 2. Levels of the Individual Risk Factors According to Presence or Absence of MetS[a]

Characteristic	Women (n=2593)		Men (n=1665)	
	No MetS (n=1613)	MetS (n=980)	No MetS (n=1157)	MetS (n=508)
Waist circumference, cm	86.6 (13.1)	100.0 (12.2)	94.4 (9.0)	104.8 (9.4)
Triglycerides, mg/dL	110.0 (41)	182.6 (87)	111.4 (46)	188.7 (97)
HDL cholesterol, mg/dL	65.9 (14.8)	50.0 (12.1)	52.2 (12.4)	41.1 (10.5)
Systolic BP, mm Hg	134.0 (22.3)	141.1 (20.5)	134.4 (21.2)	140.6 (20.3)
Diastolic BP, mm Hg	69.3 (11.1)	71.3 (10.8)	71.9 (11.7)	75.3 (10.8)
Patients treated with antihypertensive medication	529 (33)	574 (59)	342 (30)	266 (52)
Fasting glucose, mg/dL	97.4 (15.7)	126.2 (51.3)	104.0 (24.2)	131.2 (46.2)
Patients treated for diabetes	15 (1)	143 (15)	50 (4)	97 (19)

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; MetS, metabolic syndrome.

SI conversions: To convert triglycerides to millimoles per liter, multiply by 0.0113; cholesterol to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555.

[a] Data are reported as mean (SD) values or number (percentage) of subjects. Presence or absence of MetS based on criteria of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.[2]

Table 3. Total Mortality According to Presence or Absence of the Metabolic Syndrome Among 4258 Older Adults

Characteristic[a]	No MetS	MetS	MetS With EFG[b]	MetS Without EFG[b]	MetS With HTN[b]	MetS Without HTN[b]
Patients meeting ATPIII criteria, No.[c]	2770	1488	908	580	1335	153
Deaths, No.	1326	790	522	268	721	69
Person-years, No.	31 788	16 380	9565	6814	14 545	1835
Mortality rate per 1000 person-years	41.7	48.2	54.6	39.3	49.6	37.6
Age- and sex-adjusted HR (95% CI)	1 [Reference]	1.31 (1.19-1.43)	1.51 (1.36-1.67)	1.03 (0.90-1.18)	1.32 (1.21-1.45)	1.16 (0.91-1.48)
Multivariable HR (95% CI)	1 [Reference]	1.22 (1.11-1.34)	1.41 (1.27-1.57)	0.97 (0.85-1.11)	1.26 (1.15-1.39)	0.92 (0.71-1.19)
PAR%	1 [Reference]	6.3	6.2	<0	6.5	<0
Patients meeting ATPIII criteria excluding those treated for diabetes, No.[d]	2705	1248	668	580	1117	131
Deaths, No.	1284	629	361	268	573	56
Person-years, No.	31 186	14 166	7352	6814	12 551	1615
Mortality rate per 1000 person-years	41.2	44.4	49.1	39.3	45.7	34.7
Age- and sex-adjusted HR (95% CI)	1 [Reference]	1.22 (1.10-1.34)	1.38 (1.23-1.55)	1.05 (0.92-1.19)	1.23 (1.11-1.35)	1.11 (0.85-1.46)
Multivariable HR (95% CI)	1 [Reference]	1.16 (1.05-1.28)	1.33 (1.17-1.50)	0.98 (0.86-1.13)	1.19 (1.07-1.32)	0.90 (0.67-1.19)
PAR%	1 [Reference]	4.4	4.2	<0	4.5	<0
Patients meeting IDF criteria, No.[e]	3035	1,222	732	490	1087	135
Deaths, No.	1483	633	407	226	574	59
Person-years, No.	34 606	13 547	7805	5742	11 907	1640
Mortality rate per 1000 person-years	42.9	46.7	52.1	39.4	48.2	36.0
Age- and sex-adjusted HR (95% CI)	1 [Reference]	1.26 (1.15-1.38)	1.43 (1.28-1.60)	1.03 (0.90-1.19)	1.28 (1.16-1.41)	1.07 (0.82-1.39)
Multivariable HR (95% CI)	1 [Reference]	1.17 (1.06-1.29)	1.32 (1.18-1.49)	0.96 (0.83-1.11)	1.21 (1.09-1.34)	0.85 (0.64-1.12)
PAR%	1 [Reference]	4.2	4.2	<0	4.4	<0
Patients meeting IDF criteria excluding those treated for diabetes, No.[d]	2934	1018	528	490	903	115
Deaths, No.	1411	502	276	226	454	48
Person-years, No.	33 723	11 614	5872	5742	10 173	1441
Mortality rate per 1000 person-years	41.8	43.2	47.0	39.4	44.6	33.3
Age- and sex-adjusted HR (95% CI)	1 [Reference]	1.19 (1.07-1.32)	1.32 (1.16-1.51)	1.05 (0.91-1.21)	1.21 (1.09-1.35)	1.02 (0.77-1.37)
Multivariable HR (95% CI)	1 [Reference]	1.11 (1.00-1.24)	1.26 (1.10-1.44)	0.98 (0.84-1.13)	1.15 (1.03-1.29)	0.83 (0.61-1.13)
PAR%	1 [Reference]	2.6	2.8	<0	3.0	<0
Patients meeting WHO criteria, No.[f]	2458	1798	1798	NA	1521	277
Deaths, No.	1127	987	987	NA	858	129
Person-years, No.	28 431	19 724	19 724	NA	16 489	3236
Mortality rate per 1000 person-years	39.6	50.0	50.0	NA	52.0	39.9
Age- and sex-adjusted HR (95% CI)	1 [Reference]	1.26 (1.16-1.37)	1.26 (1.16-1.37)	NA	1.29 (1.18-1.41)	1.07 (0.89-1.28)
Multivariable HR (95% CI)	1 [Reference]	1.22 (1.11-1.33)	1.22 (1.11-1.33)	NA	1.26 (1.15-1.39)	0.96 (0.79-1.16)
PAR%	1 [Reference]	7.6	7.6	NA	7.4	<0
Patients meeting WHO criteria excluding those treated for diabetes, No.[d]	2403	1548	1548	NA	1304	244
Deaths, No.	1087	824	824	NA	717	107
Person-years, No.	27 929	17 412	17 412	NA	14 495	2917
Mortality rate per 1000 person-years	38.9	47.3	47.3	NA	49.5	36.7
Age- and sex-adjusted HR (95% CI)	1 [Reference]	1.20 (1.10-1.31)	1.20 (1.10-1.31)	NA	1.23 (1.12-1.35)	1.02 (0.83-1.24)
Multivariable HR (95% CI)	1 [Reference]	1.18 (1.07-1.29)	1.18 (1.07-1.29)	NA	1.22 (1.11-1.35)	0.93 (0.76-1.15)
PAR%	1 [Reference]	6.0	6.0	NA	6.0	<0

Abbreviations: ATPIII, National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)[2]; CI, confidence interval; EFG, elevated fasting glucose level; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; HTN, hypertension; IDF, International Diabetes Federation[2,3]; MetS, metabolic syndrome; NA, not applicable; PAR%, population attributable risk fraction; WHO, World Health Organization.[2,3]

[a] Multivariable HRs and corresponding PAR%s are adjusted for age (5 groups), sex, race (black, nonblack), education (<high school, high school, or >high school), smoking status (never, former, current), smoking history (lifetime pack-years), physical activity (kilocalories per week), and alcohol use (never, former, <1 drink/wk, 1 to <7 drinks/wk, 7 to <14 drinks/wk, or ≥14 drinks/wk).

[b] MetS with or without the specific risk factor of hypertension or EFG (or for WHO criteria, insulin resistance) as 1 criterion compared with those without MetS as the reference group.

[c] At least 3 of the 5 following conditions must apply: large waist circumference, hypertension, high triglyceride levels, low HDL-C level, or EFG (glucose ≥110 mg/dL or treated diabetes) (to convert to millimoles per liter, multiply by 0.0555).

[d] Excluding 305 individuals with treated diabetes.

[e] Similar to the ATPIII criteria but requiring adiposity (either obesity or large waist circumference) as 1 criterion; excluding 1 individual with missing data on body mass index.

[f] Insulin resistance (treated diabetes, fasting glucose level ≥110 mg/dL, 2-hour postchallenge glucose level ≥140 mg/dL, or fasting insulin level in the highest quartile among individuals with fasting glucose levels <110 mg/dL) plus any 2 of obesity, hypertension, high triglyceride levels, or low HDL-C levels; excluding 2 individuals with missing data on blood pressure medication use or waist circumference.

1.30 for MetS including hypertension (95% CI, 1.20-1.40) (PAR%, 7.9%), and 0.92 for MetS without hypertension (95% CI, 0.73-1.15) (PAR%, <0%).

Results using IDF criteria were similar to those for ATPIII criteria, although RR and PAR% estimates were about 20% to 30% lower (Table 3). Relative risks pre-

Table 4. Risk of Mortality According to Individual MetS Criteria

MetS Criterion	Criterion Absent	Criterion Present, Hazard Ratio (95% CI)		
		Age- and Sex-Adjusted	Multivariable[a]	Adjusted Multivariable[b]
Abdominal obesity (waist ≥102 cm for men or ≥88 cm for women)				
Overall	1 [Reference]	1.06 (0.97-1.16)	0.97 (0.89-1.07)	0.94 (0.85-1.03)
Men	1 [Reference]	1.16 (1.01-1.33)	1.04 (0.90-1.19)	0.96 (0.83-1.12)
Women	1 [Reference]	1.00 (0.89-1.13)	0.93 (0.82-1.05)	0.95 (0.84-1.08)
High triglyceride levels (≥150 mg/dL)				
Overall	1 [Reference]	1.03 (0.94-1.14)	0.94 (0.85-1.04)	0.92 (0.82-1.02)
Men	1 [Reference]	1.18 (1.03-1.35)	1.05 (0.91-1.22)	1.08 (0.92-1.26)
Women	1 [Reference]	0.93 (0.82-1.06)	0.86 (0.75-0.98)	0.79 (0.69-0.92)
Low HDL cholesterol levels (<40 mg/dL for men or <50 mg/dL for women)				
Overall	1 [Reference]	1.11 (1.01-1.22)	1.06 (0.96-1.18)	1.00 (0.90-1.12)
Men	1 [Reference]	1.16 (1.00-1.34)	1.07 (0.91-1.25)	1.00 (0.85-1.18)
Women	1 [Reference]	1.07 (0.95-1.22)	1.06 (0.92-1.22)	1.01 (0.87-1.16)
Hypertension (BP ≥130/85 mm Hg or undergoing medical BP treatment)				
Overall	1 [Reference]	1.31 (1.18-1.45)	1.26 (1.14-1.40)	1.32 (1.18-1.47)
Men	1 [Reference]	1.32 (1.14-1.53)	1.27 (1.09-1.47)	1.26 (1.08-1.47)
Women	1 [Reference]	1.29 (1.12-1.48)	1.26 (1.09-1.45)	1.39 (1.19-1.61)
EFG (glucose ≥110 mg/dL or undergoing treatment with diabetes medications)				
Overall	1 [Reference]	1.45 (1.32-1.59)	1.42 (1.29-1.57)	1.39 (1.26-1.53)
Men	1 [Reference]	1.54 (1.35-1.76)	1.48 (1.29-1.69)	1.44 (1.25-1.67)
Women	1 [Reference]	1.38 (1.22-1.57)	1.38 (1.21-1.58)	1.36 (1.18-1.56)

Abbreviations: CI, confidence interval; EFG, elevated fasting glucose level; HDL, high-density lipoprotein; MetS, metabolic syndrome.

SI conversions: To convert triglycerides to millimoles per liter, multiply by 0.0113; cholesterol to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555.

[a] Adjusted for age (5 groups), sex, and each of the other metabolic syndrome criteria.

[b] Adjusted for all characteristics listed in footnote a and further adjusted for other demographic and lifestyle factors listed in Table 3, footnote a.

dicted by WHO MetS were also similar to those predicted by ATPIII MetS, although PAR% was modestly higher for WHO MetS (PAR%, 7.6%) than for ATPIII MetS (PAR%, 6.3%) owing to more individuals being classified with MetS using WHO criteria (42%) than ATPIII criteria (35%). Interestingly, the multivariable RRs for the overall ATPIII definition and the WHO definition were identical (RR, 1.22), but each was only half that predicted by ATPIII MetS when EFG was present (RR, 1.41; 95% CI, 1.27-1.57), indicating that requiring EFG in the ATPIII criteria increased prediction of mortality in these older adults.

In sex-stratified analyses, MetS predicted higher relative risk of mortality in men than in women ($P = .03$ for interaction), but results were otherwise qualitatively similar: MetS predicted mortality among both men and women, but higher risk was confined to individuals having EFG or hypertension as 1 MetS criterion (data not shown). Interaction by age, race, or CRP was not evident ($P \geq .30$).

When each MetS criterion was evaluated individually, only hypertension and EFG independently predicted higher mortality (**Table 4**). After multivariable adjustment, individuals with hypertension had 32% higher mortality (RR, 1.32; 95% CI, 1.18-1.47) than those without hypertension, while individuals with EFG had 39% higher mortality (RR, 1.39; 95% CI, 1.26-1.53) than those without EFG. Findings were similar in men and women (Table 4). Evaluated as individual criteria, the proportion of deaths attributable to hypertension (PAR%, 17.5%) or EFG (PAR%, 7.9%) was higher than the proportion attributable to MetS (PAR%, 6.3%).

We evaluated sex-specific quintiles of each criterion to assess whether different cut points might alter results (**Figure 1**). Across quintiles, neither larger waist circumference, higher plasma triglyceride level, nor lower HDL-C level was significantly associated with higher mortality. Individuals with either treated diabetes or fasting glucose level above approximately 110 mg/dL, but not fasting glucose level in lower ranges (less than about 110 mg/dL), had significantly higher mortality (supporting use of the higher EFG cut point in our primary analyses). Individuals with either treated hypertension or systolic BP greater than approximately 150 mm Hg had higher mortality. Diastolic BP was not significantly associated with mortality (adjusted RR comparing extreme quintiles of 1.08 in men [95% CI, 0.82-1.43] and 1.25 in women [95% CI, 0.97-1.60]), and relations of pulse pressure with mortality were similar to those of systolic BP (adjusted RR comparing extreme quintiles of 1.51 in men [95% CI, 1.16-1.97] and 1.32 in women [95% CI, 1.01-1.71]).

We also evaluated the separate and combined associations of hypertension, EFG, and MetS with mortality (**Figure 2**). Individuals having MetS including EFG or MetS including hypertension had incrementally higher RRs than those having EFG alone (Figure 2A) or hyper-

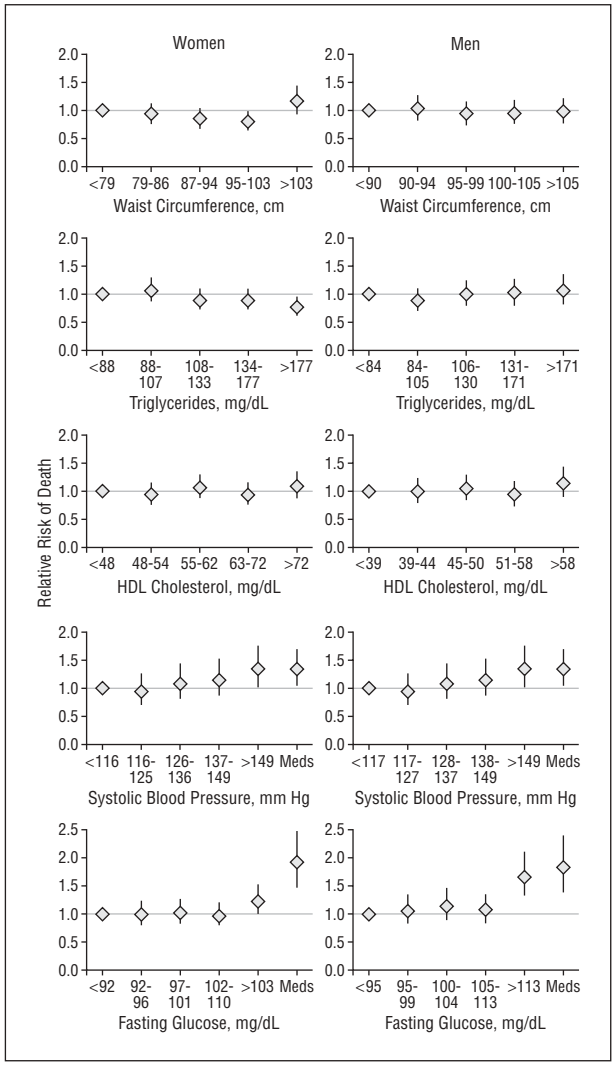

Figure 1. Relative risk of death according to individual metabolic syndrome criteria among 4258 older adults. Each criterion is evaluated in sex-specific quintiles adjusted for age, each of the other metabolic syndrome criteria, and other demographic and lifestyle risk factors as detailed in Table 3, footnote a. For evaluation of blood pressure and fasting glucose levels, individuals treated with medications for hypertension (n=1711) or diabetes (n=305) are included in separate categories (Meds). Shaded diamonds represent relative risks; vertical lines extending from the diamonds represent 95% confidence intervals. HDL indicates high-density lipoprotein. For SI conversion factors, see Table 1 footnote.

tension alone (Figure 2B). However, individuals having both EFG and hypertension had the highest RRs (Figure 2C), with 82% higher mortality (RR, 1.82; 95% CI, 1.58-2.09) (PAR%, 10.4%) compared with individuals having neither hypertension nor EFG. In sum, the total proportion of deaths attributable to hypertension and EFG was 22.2%, substantially higher than the deaths attributable to MetS (PAR%, 6.3%) (Table 3). Total mortality was also evaluated according to all possible combinations of EFG, hypertension, and MetS (**Figure 3**).

Metabolic syndrome predicted CVD (RR, 1.51; 95% CI, 1.29-1.76) but not non-CVD (RR, 1.08; 95% CI, 0.96-1.21) mortality (**Figure 4**). For CVD deaths, higher risk was present only among individuals having MetS including EFG or MetS including hypertension as 1 of the criteria (Figure 4A). Non-CVD mortality was also slightly higher among individuals with MetS including EFG (RR, 1.21; 95% CI, 1.05-1.39) than among those without MetS. The proportion of CVD mortality attributable to MetS (PAR%, 11.8%) was largely a result of deaths attributable to MetS including EFG (PAR%, 9.6%) or MetS including hypertension (PAR%, 11.3%) rather than MetS without EFG (PAR%, 1.1%) or MetS without hypertension (PAR%, 0.2%). Compared with assessment of MetS, assessment of EFG and hypertension alone provided better stratification of CVD mortality risk (Figure 4B). A much higher proportion of CVD deaths was attributable to EFG and hypertension (PAR%, 44.6%) than to MetS (PAR%, 11.8%).

Current smoking and prevalent chronic disease could affect MetS components (eg, waist circumference) and mortality risk. Thus, we performed sensitivity analyses excluding current smokers (n=537), those with prevalent (prior 5 years) chronic pulmonary disease or cancer except nonmelanoma skin cancer (n=247), and (to minimize effects of undiagnosed prevalent disease at baseline) deaths during the first year (n=30). Findings for MetS and each individual MetS criterion were very similar to the main analyses. For example, the multivariable RRs of mortality were 1.22 for MetS (95% CI, 1.09-1.35), 1.41 for MetS including EFG (95% CI, 1.25-1.59), 0.96 for MetS without EFG (95% CI, 0.82-1.12), 1.25 for MetS including hypertension (95% CI, 1.12-1.39), and 0.88 for MetS without hypertension (95% CI, 0.63-1.22).

Finally, we repeated the main analyses using the lower ATPIII cut point for EFG (≥100 mg/dL or treated diabetes). Prevalence of MetS increased to 46% in women and 39% in men, and associations of both MetS and EFG with mortality were attenuated. Using the lower EFG cut point, individuals with MetS had 12% higher mortality (multivariable RR, 1.12; 95% CI, 1.02-1.23) (PAR%, 4.6%) rather than the 22% higher mortality (PAR%, 6.3%) we found using the higher EFG cut point (Table 3). Individuals with EFG had 17% higher mortality (multivariable RR, 1.17; 95% CI, 1.07-1.29) (PAR%, 7.8%) rather than the 39% higher mortality (PAR%, 7.9%) we found using the higher EFG cut point (Table 4).

COMMENT

In this large population-based study of older US adults, MetS was common (38% of women, 31% of men), predicted 22% higher all-cause mortality (9.2 additional deaths per 1000 person-years), and accounted for 6.3% of all deaths. While RR differences were smaller in the present study than in prior studies of middle-aged adults, absolute risk differences were similar or larger (a common finding for risk factors with advancing age). For example, among middle-aged Finnish men free of CVD or diabetes,[4] MetS predicted an approximate 72% higher relative mortality risk (ATPIII RR, 1.67; WHO RR, 1.77) with multivariable-adjusted mortality differences of about 5.2 (ATPIII) and 5.9 (WHO) per 1000 person-years. In comparison, among individuals free of CVD or diabetes in the present study, MetS predicted about a 17% higher relative mortality risk (ATPIII RR, 1.16; WHO RR, 1.18) with multivariable-adjusted mortality differences of 6.6 (ATPIII) and 7.0 (WHO) per 1000 person-years. Al-

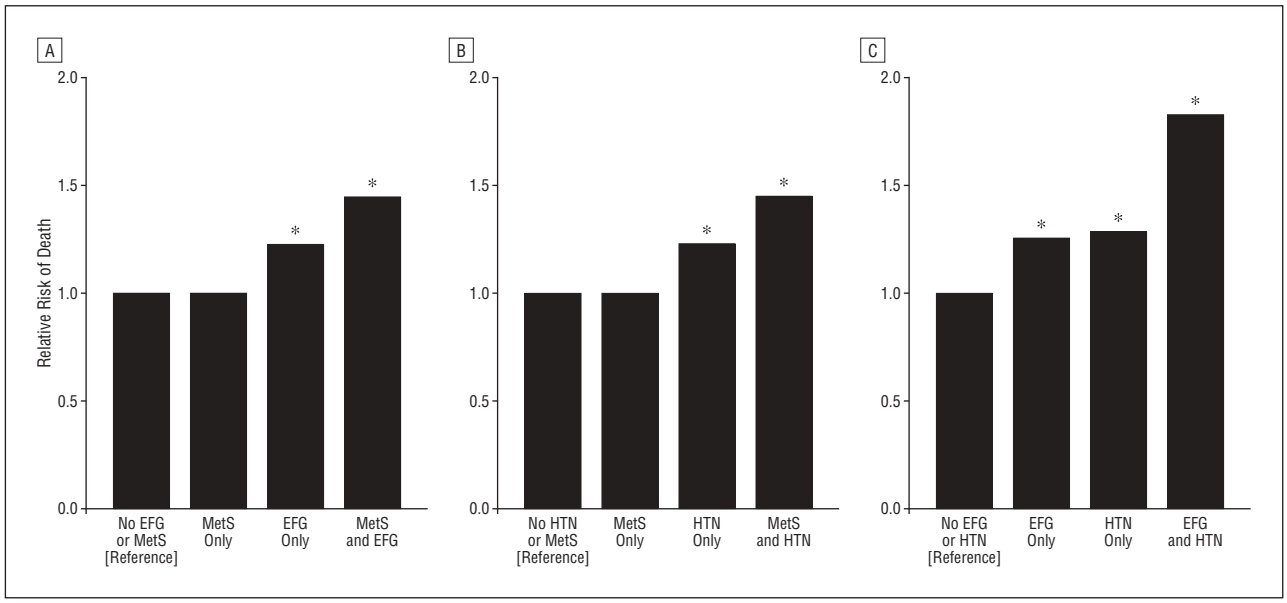

Figure 2. Separate and combined associations of elevated fasting glucose level (EFG), hypertension (HTN), and metabolic syndrome (MetS) with mortality among 4258 older adults. A, Compared with individuals having neither EFG nor MetS, individuals with EFG had higher mortality whether MetS was absent (relative risk [RR]=1.22; population attributable risk fraction [PAR%]=1.2%) or present (RR=1.44; PAR%=6.5%), but MetS did not predict higher mortality in the absence of EFG (RR=0.99; PAR%<0). B, Compared with individuals having neither HTN nor MetS, individuals with HTN had higher mortality whether MetS was absent (RR=1.27; PAR%=8.7%) or present (RR=1.47; PAR%=10.0%), but MetS did not predict higher mortality in the absence of HTN (RR=1.06; PAR%=0.2%). C, Compared with individuals having neither HTN nor EFG, individuals with HTN alone (RR=1.28; PAR%=10.8%) or EFG alone (RR=1.25; PAR%=1.0%) had higher mortality, while individuals having both HTN and EFG had the highest risk (RR=1.82; PAR%=10.4%). For each comparison, the RR of death is based on comparison with individuals having neither of the risk factors (reference group), adjusted for age, sex, the other MetS criteria (when evaluating HTN and EFG), and other demographic and lifestyle risk factors (given in Table 3, footnote a). *$P<.05$.

though CIs in the Finnish study were broad due to relatively few deaths (109 deaths compared with 2116 deaths in the present study), these findings suggest lower relative but similar absolute impact of MetS on mortality later in life.

Notably, the higher risk with MetS was largely confined to individuals having MetS and either hypertension or altered glucose metabolism (EFG and/or diabetes) as 1 of the criteria; persons with MetS in the absence of hypertension or altered glucose metabolism did not have significantly higher mortality. Furthermore, compared with the 22% higher mortality with MetS (accounting for 6.3% of all deaths), hypertension by itself predicted 32% higher mortality (accounting for 17.5% of all deaths), and altered glucose metabolism by itself predicted 39% higher mortality (accounting for 7.9% of all deaths). Presence of both hypertension and altered glucose metabolism predicted 82% higher mortality; these 2 conditions accounted for 22.2% of all deaths. These comparisons were similar using ATPIII, WHO, or IDF criteria, and including or excluding individuals with treated diabetes or prevalent CVD.

As would be expected, MetS more strongly predicted CVD than non-CVD death. As with total mortality, the higher CVD mortality with MetS was confined to individuals having EFG or hypertension as 1 of the criteria, and assessment of EFG and hypertension alone predicted the highest risk, including a higher than 3-fold greater risk of CVD death when both conditions were present. Individuals having EFG plus MetS or EFG plus hypertension also had modestly higher non-CVD mortality (perhaps due to infectious or renal risks associated with insulin resistance or high BP).

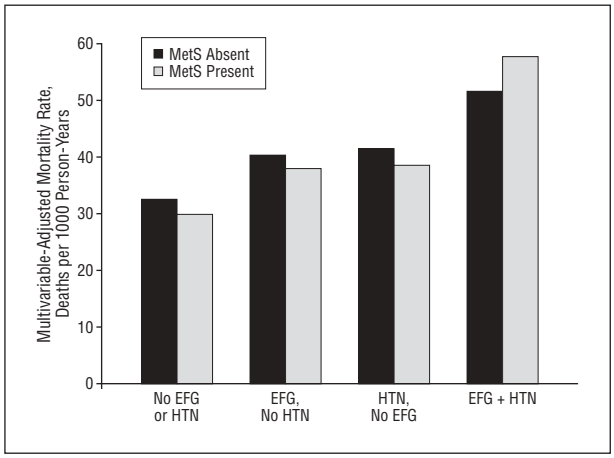

Figure 3. Mortality rates according to different combinations of presence or absence of elevated fasting glucose level (EFG), hypertension (HTN), and metabolic syndrome (MetS), adjusted for age, sex, and other demographic and lifestyle risk factors (see Table 3, footnote a). Compared with individuals without EFG or HTN, individuals having either HTN alone, EFG alone, or both HTN and EFG had higher mortality ($P<.05$ for each comparison), whether or not MetS was present. In contrast, within these same groups, individuals with MetS did not have significantly higher mortality than those without MetS ($P>.05$ for each comparison).

The comparative utility of MetS vs its individual risk factors for predicting adverse outcomes in older populations has not previously been well established. Among 70-year-old Swedish men, RRs of total and CVD mortality with MetS were similar to RRs with diabetes or hypertension alone; however, after exclusion of individuals with prevalent CVD or diabetes,[12,13] neither MetS nor any individual MetS component predicted mortality (pos-

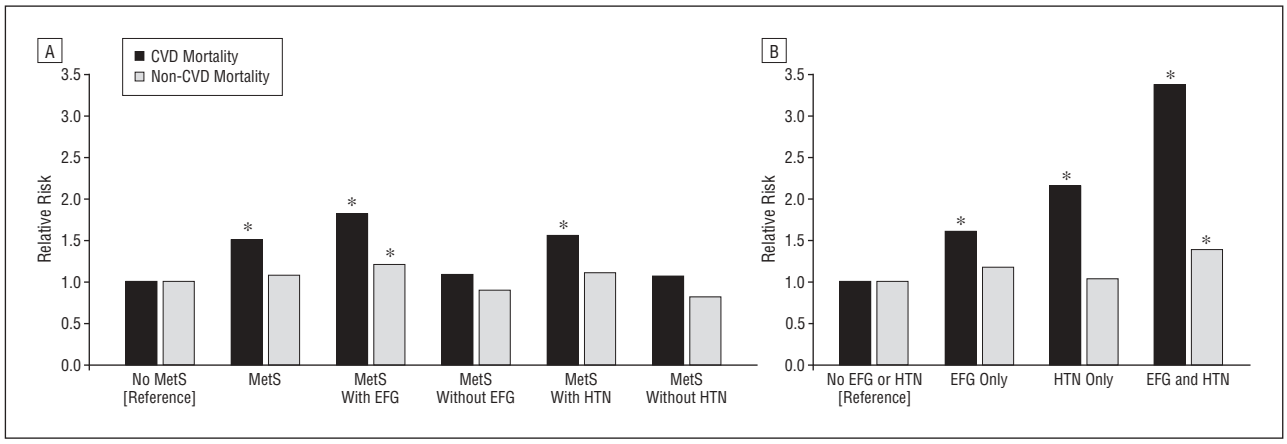

Figure 4. Relative risk of cardiovascular disease (CVD) mortality and non-CVD mortality according to presence or absence of the metabolic syndrome (MetS) overall and with or without elevated fasting glucose levels (EFG) and hypertension (HTN) (A) and according to presence or absence of EFG and HTN alone (B). Relative risks (hazards) are adjusted for age, sex, the other MetS criteria (when evaluating hypertension and EFG), and other demographic and lifestyle risk factors (given in Table 3, footnote a) and compared with individuals without MetS (A) or without EFG or HTN (B) as the reference group. *$P<.05$

sibly due to limited power: 133 total deaths). In the Health ABC study[26] (mean patient age, 74 years), MetS predicted higher risk of myocardial infarction (RR, 1.51) ($P=.001$) but not total mortality (RR, 1.06) ($P=.82$)[26]; relationships of individual MetS criteria with risk were not reported. Among older Italian adults (aged 65-84 years at baseline), MetS predicted modestly higher (12%) CVD mortality in men but not in women.[27] In prior analyses from CHS,[28,29] MetS was associated with higher risk of total combined CVD events (including fatal and nonfatal myocardial infarction, stroke, coronary revascularization, and angina), but similar or higher risks were seen for EFG alone or hypertension alone.[29] The present results are consistent with these prior reports and considerably extend the findings by evaluating total, CVD, and non-CVD mortality; population attributable risks; ATPIII, IDF, and WHO definitions; and detailed associations of each of the individual criteria—including different criterion cut points—with risk.

Our results indicate that major limitations of MetS for predicting mortality in older adults, compared with assessment of fasting glucose level and BP alone, are limited associations of waist circumference, hypertriglyceridemia, or HDL-C level with higher mortality. In predominantly middle-aged populations, risk of total or CVD mortality associated with MetS may exceed risks associated with any individual MetS component.[5,7] Conversely, in the present study, the modest mortality impact of MetS was a function of strong impact from 2 factors (hypertension and altered glucose metabolism) and little impact from the other 3 factors (waist circumference, triglyceride level, and HDL-C level). Thus, classification of older adults into a syndrome defined by any 3 of these 5 factors "diluted" the true mortality impact of hypertension and altered glucose metabolism. These findings were not related to suboptimal cut points for any individual criterion. When examined across quintiles, neither waist circumference, triglyceride level, nor HDL-C level was predictive of higher mortality. Use of the lower fasting glucose cut point (100 mg/dL) attenuated associations of EFG and MetS with mortality, suggesting that, at least for older adults, the higher cut point may be more appropriate for risk prediction.

It is not clearly established why obesity measures are less predictive of mortality later in life, but possible reasons include (1) varying loss of lean body mass with aging,[30] causing misclassification of adiposity; (2) confounding by undiagnosed chronic disease, which might reduce adiposity and increase mortality (reverse causation); and (3) a speculative protective effect of modest adiposity against some causes of death later in life. Measures of adiposity in middle-age predict higher mortality[31] and prevalent CVD later in life,[32] so our findings do not counter the public health importance of obesity prevention. It is also unclear why HDL-C and triglyceride measures may be nonpredictive; potential explanations may be similar to those for obesity measures, given physiologic colinearity of adiposity, hypertriglyceridemia, and low HDL-C level. (Nonfasting triglyceride levels may also be more predictive than fasting levels.[33,34]) Loss of predictive utility could also reflect earlier deaths of individuals vulnerable to adverse health effects of these factors (depletion of susceptible subjects). Nonetheless, our findings indicate different prognostic value of these factors for mortality when assessed later in life compared with middle-age,[17,35] supporting the need for distinct characterization (or methods of measurement) of risk profiles among older adults. The results also highlight the importance of considering individual risk factors rather than a composite syndrome; other modifiable risk factors such as smoking, physical activity, and dietary habits would also be important in predicting mortality and crafting appropriate interventions.

This analysis had several strengths. Information on MetS criteria, other risk factors, and mortality were prospectively collected using standardized methods in a large multicenter cohort of older men and women with little loss to follow-up. Large numbers of events (>2100 deaths) provided substantial statistical power and precision, allowing detection of RRs as low as 1.15. Participants were randomly selected and enrolled from Medicare eligibility lists in several US communities, providing a population-based sample of older adults. Limitations were also

present. Two WHO subcriteria (hyperinsulinemic euglycemic testing and microalbuminuria) were unavailable for analysis, although these indices are also commonly unavailable in routine clinical practice for primary prevention. Several different MetS definitions and individual risk factors were evaluated, increasing the possibility of type I error; conversely, specific hypotheses related to MetS and its individual criteria were evaluated, with varying strength of prior supporting evidence, and 95% CIs may be more informative than adjusted *P* values in this setting. These associations were observed in older US adults and may not be generalizable to younger populations or other nations.

In conclusion, among older adults, (1) MetS did not predict higher mortality in the absence of hypertension or altered glucose metabolism; (2) the mortality predicted by MetS was similar to that predicted by either hypertension or altered glucose metabolism alone; and (3) hypertension and altered glucose metabolism together predicted the highest risk and accounted for the largest proportion of deaths. These findings suggest limited utility of the MetS concept for predicting total, CVD, or non-CVD mortality in older men and women compared with assessment of fasting glucose level and BP alone.

Accepted for Publication: October 18, 2007.
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Author Contributions: Dr Mozaffarian had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Mozaffarian, Prineas, and Siscovick. *Acquisition of data:* Kamineni, Prineas, and Siscovick. *Analysis and interpretation of data:* Mozaffarian, Kamineni, Prineas, and Siscovick. *Drafting of the manuscript:* Mozaffarian and Siscovick. *Critical revision of the manuscript for important intellectual content:* Mozaffarian, Kamineni, Prineas, and Siscovick. *Statistical analysis:* Mozaffarian and Kamineni. *Obtained funding:* Mozaffarian and Siscovick. *Administrative, technical, and material support:* Prineas.
Financial Disclosure: Ms Kamineni was supported by an unrestricted educational grant from Amgen to the CHS Coordinating Center (D.S.S.) to support analyses related to diabetes.
Funding/Support: The National Institutes of Health and National Heart, Lung, and Blood Institute (NHLBI) provided support for the research reported in this article through grant K08-HL-075628 (Dr Mozaffarian) and contracts N01-HC-85079 through N01-HC-85086, N01-HC-35129, and N01-HC-15103 awarded to the CHS.
Role of the Sponsor: The funding sources had no role in study conception, conduct, or design; management or interpretation of data analysis; interpretation of results; or manuscript preparation. The NHLBI reviewed the final manuscript to ensure consistency with prior CHS publications.
Additional Contributions: We thank the CHS participants.

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