Metabolic Syndrome and Cardiovascular Disease in Older People: The Cardiovascular Health Study

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OBJECTIVES: To assess the prospective association between metabolic syndrome (MetS) and cardiovascular disease (CVD) in older people and to evaluate the effect of lowering the threshold for impaired fasting glucose (IFG) on the prevalence of IFG and MetS and the risk of CVD.

DESIGN: Prospective cohort study.

SETTING: Four field centers in U.S. communities.

PARTICIPANTS: Three thousand five hundred eighty-five subjects in the Cardiovascular Health Study free of diabetes mellitus and CVD at baseline (mean age 72, 62% female, 14% black).

MEASUREMENTS: Baseline measures of MetS components and adjudicated incident CVD events. MetS (2001) was defined first using the original criteria from the Third Adult Treatment Panel Report of the National Cholesterol Education Program ($\geq$3 of the following: large waist circumference (women $>$88 cm, men $>$102 cm), elevated triglycerides ($\geq$1.70 mmol/L), low high-density lipoprotein cholesterol (men $<$1.04 mmol/L, women $<$1.30 mmol/L), elevated fasting glucose (6.1–6.9 mmol/L), and high blood pressure ($\geq$130/85 mmHg or self-reported use of medications for hypertension). Subjects were also classified according to the revised definition of the MetS (2005) that applies the lower threshold for fasting glucose (5.6–6.9 mmol/L).

RESULTS: During follow-up (median 11 years), 818 coronary heart disease (CHD), 401 stroke, and 554 congestive heart failure (CHF) events occurred. Age- and race-adjusted hazard ratios (HRs) for CHD, stroke, and CHF were 1.30 (95% confidence interval (CI) = 1.07–1.57), 0.94 (95% CI = 0.73–1.21), and 1.40 (95% CI = 1.12–1.76) for women and 1.35 (95% CI = 1.10–1.66), 1.51 (95% CI = 1.08–2.12), and 1.47 (95% CI = 1.14–1.90) for men, respectively. Overall, women and men with MetS (2005) were 20% to 30% more likely to experience any CVD event than subjects without MetS (2005). Using the lower cut-point for IFG resulted in a near tripling in IFG prevalence (16% to 46%) and an additional 9% classified with MetS (2005) but HRs similar to those estimated from the original MetS (2001) criteria. High blood pressure was the component most strongly associated with incident CHD.

CONCLUSION: Results from this study of an elderly, population-based cohort provide support for earlier investigations in primarily middle-aged populations that link the presence of MetS with the development of CVD and further underscore the importance of recognizing and treating its individual components, particularly high blood pressure.
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Metabolic syndrome (MetS) is a term used to explain the co-occurrence of several conditions related to central obesity and insulin resistance that also includes impaired glucose metabolism, dyslipidemia, and high blood pressure.[1] Nearly 45% of Americans aged 50 and older have MetS[2] as originally defined by the National Heart, Lung, and Blood Institute (NHLBI) in its Third Adult Treatment Panel Report (ATP-III) of the National Cholesterol Education Program.[3] Recently, the American Diabetes Association[4] recommended that the lower limit for impaired fasting glucose (IFG) be changed from 6.1 to 5.6 mmol/L. Although the NHLBI[5] has officially adopted this lower threshold for fasting glucose as part of its revised definition of MetS (2005), the effect of this modification on the population prevalence of IFG and MetS has not been fully elucidated.[6]

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Furthermore, several population-based studies[7–13] have reported that ATP-III-defined MetS (2001) is associated with approximately twice the risk of cardiovascular disease (CVD), although these studies were conducted primarily in middle-aged populations, and as such, their findings may not be applicable to elderly populations. A recent analysis[14] using data from the Cardiovascular Health Study (CHS), a prospective investigation of elderly men and women, reported a strong association between ATP-defined MetS and incident CVD, although that analysis included subjects with prevalent diabetes mellitus but excluded those taking antihypertension or lipid-lowering medications. Thus, its conclusions may have limited generalizability, because treatment for hypertension and hypercholesterolemia is common in older age. The present study was designed to estimate the association between MetS and CVD in CHS participants initially free of diabetes mellitus and CVD using the revised definition of MetS that includes the new IFG criterion.

METHODS

The CHS is a community-based, longitudinal observational study of adults aged 65 and older at baseline to evaluate risk factors for the development and progression of CVD. The study's primary objectives and design have been reported previously.[15] Briefly, participants were randomly selected from Medicare eligibility lists in four U.S. communities. An initial cohort of 5,201 was recruited between 1989 and 1990, and an additional 687 African Americans were recruited in 1992 and 1993. Of those contacted and eligible, 57.3% were enrolled. Follow-up interviews for events consisted of annual examinations and interim 6-month telephone calls. The study received approval from investigational review boards at each site and the Data Coordinating Center at the University of Washington. All subjects gave informed consent. Self-reported health behaviors, history of disease, anthropometric measures, current medication use, seated blood pressure readings, electrocardiogram recordings, echocardiograms, and fasting blood chemistry measures were obtained during the baseline home interview or clinical examination. Blood was drawn in the morning after an overnight fast, and samples were analyzed in standardized fashion at the Central Blood Analysis Laboratory, University of Vermont. Quality assurance procedures and results for blood procurement, processing, shipping, storage, and sample analysis have been reported previously.[16]

Prevalent CVD included coronary heart disease (CHD), myocardial infarction (MI), angina pectoris, self-reported coronary artery bypass surgery (CABG), angioplasty, and stroke/transient ischemic attack. For each cardiovascular condition, self-report was confirmed using components of the baseline examination or, if necessary, using a validation protocol that included review of medical records or surveys of treating physicians.[17] Prevalent diabetes mellitus was defined according to 1997 American Diabetes Association criteria[18] (fasting glucose $\geq$7.0 mmol/L ($\geq$126 mg/dL) or use of hypoglycemic agents or insulin).

Classification of MetS

MetS was defined first using the original ATP-III[3] criteria ($\geq$3 of the following: large waist circumference (women $>$88 cm, men $>$102 cm), elevated triglycerides ($\geq$1.70 mmol/L), low high-density lipoprotein cholesterol (HDL-C) (men $<$1.04 mmol/L, women $<$1.30 mmol/L), elevated fasting glucose (6.1–6.9 mmol/L), and high blood pressure ($\geq$130/85 mmHg or self-reported use of medications for hypertension). Subjects were also classified according to the revised definition of the MetS[5] that applies the lower threshold for fasting glucose (5.6–6.9 mmol/L) to assess the effect of this change on the prevalence of IFG and MetS and its association with CVD outcomes. Unless otherwise specifically stated, all analyses reported in the current study include this revised MetS criteria recommended in 2005 by the Joint American Heart Association/National Heart, Lung, and Blood Expert Panel.[5]

Ascertainment of Incident Events

At each follow-up interview, participants were asked about cardiovascular events and hospitalizations. Discharge summaries and diagnoses were obtained for all hospitalizations. The algorithms for classification of MI and definite fatal CHD,[19] stroke,[20] and congestive heart failure (CHF)[21] have been described. For this analysis, incident CHD was defined as first occurrence of angina pectoris, MI, CABG, or angioplasty or CHD death. Incident stroke (ischemic or hemorrhagic) was ascertained according to self-report or from the Health Care Financing Administration now called Center for Medicare and Medicaid Services hospitalization patient database of *International Classification of Diseases, Ninth Revision*. Incident CHF was identified according to subject self-report of a previous physician diagnosis and confirmed by review of medical records that included physician diagnosis, patients' symptoms, x-ray findings, and treatment of heart failure (prescriptions for diuretic agents, digitalis, or a vasodilator). The CHF Events Committee reviewed and classified all cardiovascular events. This analysis included events through June 30, 2001.

Statistical Analysis

The study population for this analysis included CHS subjects who were free of diabetes mellitus and CVD at the baseline visit. Subjects with prevalent diabetes mellitus were excluded, given the considerable evidence that CVD mortality is two to four time greater[22] in this population and that current treatment guidelines in the United States (ATP-III) recommend that such patients be considered for secondary, rather than primary, prevention strategies. In preliminary analysis of the CHS cohort, 79% of individuals with diabetes mellitus at baseline met the original criteria for ATP-III-defined MetS (2001). During follow-up, the crude incidence of CHD was substantially higher in subjects with diabetes mellitus and MetS than in those with MetS alone (36% vs 26%). Hence, any analyses including participants with diabetes mellitus would likely reflect the already proven association between diabetes mellitus and more cardiovascular events. The intent was to examine the association between MetS and incident CVD independent of diabetes mellitus.

CHS participants who completed a baseline examination are included in these analyses with the following exclusions: self-reported racial background other than black or white (n = 39); prevalent diabetes mellitus (n = 945), CHD (n = 878), or stroke/transient ischemic attack (n = 172); blood drawn after less than 8 hours of fasting

(n = 207); or missing data on any component of MetS (n = 62). After applying these exclusions, 3,585 individuals remained for analysis. An additional 56 subjects with prevalent CHF at baseline were excluded in models that estimated the prospective association between MetS and incident CHF.

Bivariate comparisons between MetS and demographic measures and cardiovascular risk factors are expressed using means ± standard deviations and proportions. Crude incidence rates of CVD outcomes were calculated by dividing the number of events by the person-time at risk. Cox proportional hazards regression was used to estimate the association between MetS and incident CHD, stroke, and CHF. Two-way interactions between MetS and sex, race, age, low-density lipoprotein cholesterol (LDL-C) level, and smoking and the outcomes of interest were explored. A *P*-value of ≤ 0.10 was considered statistically significant for an interaction. Sex was found to significantly modify the association between MetS and incident stroke ($P = .05$). Thus, sex-specific relative risks for MetS and each CVD outcome are presented. Statistical analysis was performed with SPSS 11.0 software for Windows (SPSS Inc., Chicago, IL).

RESULTS

The mean age of the cohort was 72 (range 65–92), 62% were female, and 14% were black. High blood pressure was the most common component within each sex-by-race subgroup, ranging from 68% to 86% (Table 1). Large waist circumference was much more prevalent in women (51–70%) than men (22–27%) of both races. Applying the new, lower limit of fasting glucose (≥ 5.6 mmol/L) nearly tripled the prevalence of IFG (from 16% to 46%) and led to an additional 9% of the total population being classified as having MetS (Table 1). Overall, the prevalence of MetS using the current (revised) ATP definition in subjects without diabetes mellitus or prior history of CVD was 39% in women and 31% in men (Table 1), with substantial differences by sex and race subgroups (low of 21% in black men to high of 40% in black women).

In bivariate analysis, men who met the revised criteria for MetS were slightly older and more likely to be white and had higher mean fasting insulin and C-reactive protein values than men without the syndrome (Table 2). In women, the presence of MetS was associated with higher mean LDL-C, higher mean fasting insulin, and higher C-reactive protein. Within each sex, no significant associations were found between MetS and smoking status ($P = .37$ in women, $P = .84$ in men) or family history of CHD or stroke (results not shown). As expected, measures that constitute the MetS criteria were more prevalent in subjects classified with MetS than those not so classified.

During follow-up (median of 11 years), 818 CHD, 401 stroke, and 554 CHF events occurred. No evidence of effect

Table 1. Baseline Prevalence of Metabolic Syndrome (MetS) and Individual Components of Cardiovascular Health Study Participants Free of Prevalent Diabetes Mellitus and Cardiovascular Disease, by Sex and Race

	Women (n = 2,229)		Men (n = 1,356)	
	Black (n = 314)	White (n = 1,915)	Black (n = 182)	White (n = 1,174)
Metabolic Syndrome and Components	%			
Individual components				
Large waist (men >102 cm, women >88 cm)	70	51	22	27
High blood pressure (≥130 systolic or ≥85 diastolic or medication use)	86	68	76	69
Low high-density lipoprotein cholesterol (men <1.03 mmol/L, women <1.30 mmol/L)	18	25	12	23
High triglycerides (≥1.70 mmol/L)	15	30	13	28
Elevated fasting glucose (6.1–6.9 mmol/L)	17	14	17	19
Impaired fasting glucose (5.6–6.9 mmol/L)	39	41	43	55
MetS				
Criteria of the Third Adult Treatment Panel Report of the NCEP*	27	31	13	23
Revised NCEP criteria†	40	39	21	33
Number of components present‡				
0	5	11	13	10
1	17	24	34	27
2	39	26	31	30
3	28	22	17	21
4	10	13	5	9
5	2	5	0	3

* Original criteria for MetS (2001) were presence of at least three of the five individual components using a fasting glucose cutpoint of 6.1 mmol/L.
† Revised criteria for MetS (2005) were presence of at least three of the five individual components using a fasting glucose cutpoint of 5.6 mmol/L.
‡ Estimated by applying the revised criteria for MetS.[5]
NCEP = National Cholesterol Education Program.

Table 2. Baseline Characteristics Associated with the Presence of the Metabolic Syndrome (MetS)* in Cardiovascular Health Study Participants Free of Prevalent Diabetes Mellitus and Cardiovascular Disease

Characteristic	Women (n = 2,229)		Men (n = 1,356)	
	MetS (2005) (n = 874)	No MetS (n = 1,355)	MetS (2005) (n = 429)	No MetS (n = 927)
Age, mean ± SD	72.0 ± 5.1	72.1 ± 5.3	72.6 ± 5.1	73.2 ± 6.0†
White, %	86	86	91	85†
Smoking status, %				
Current	12	14	13	12
Former	31	30	55	56
Never	57	56	32	32
Low-density lipoprotein cholesterol, mmol/L, mean ± SD	3.60 ± 0.95	3.37 ± 0.90‡	3.25 ± 0.91	3.21 ± 0.83
Lipid-lowering medication, %	6	4	4	3
Fasting insulin, pmol/L, mean ± SD	117.37 ± 62.51	77.09 ± 31.95‡	119.45 ± 56.25	80.56 ± 35.42‡
Body mass index, kg/m^2, mean ± SD	29.0 ± 4.9	24.7 ± 4.4‡	28.3 ± 3.6	25.1 ± 3.0‡
CRP, mean ± SD	2.34 ± 2.8	1.50 ± 2.0‡	1.90 ± 2.3	1.37 ± 1.9‡
Measures for ascertainment of MetS				
Hypertension, %§	73	44‡	67	45‡
Systolic BP, mmHg, mean ± SD	141.1 ± 20.7	132.3 ± 21.9‡	138.8 ± 18.8	133.5 ± 21.1‡
Diastolic BP, mmHg, mean ± SD	71.3 ± 10.9	69.1 ± 10.9‡	74.3 ± 10.4	72.1 ± 11.7‡
Anti-hypertensive medication, %	55	29‡	50	26‡
Triglycerides, mmol/L, mean ± SD	1.90 ± 0.81	1.23 ± 0.47‡	2.02 ± 1.02	1.20 ± 0.42‡
HDL-C, mmol/L, mean ± SD	1.36 ± 0.33	1.73 ± 0.39‡	1.10 ± 0.29	1.37 ± 0.32‡
Fasting glucose, mmol/L, mean ± SD	5.79 ± 0.53	5.25 ± 0.45‡	5.92 ± 0.45	5.46 ± 0.50‡
Waist circumference, cm, mean ± SD	98.5 ± 12.2	85.3 ± 12.6‡	103.2 ± 9.5	93.8 ± 8.6‡

* MetS (2005) presence of three of five of the following: large waist circumference (women >88 cm, men >102 cm); triglycerides ≥1.70 mmol/L; low high-density lipoprotein cholesterol (HDL-C; men <1.04 mmol/L, women <1.30 mmol/L); high fasting glucose (5.6–6.9 mmol/L); and high blood pressure (BP; ≥130/85 mmHg or self-reported use of medications for hypertension).
‡P<.0001, †P<.01; t-test for continuous variables, Kruskal-Wallis for C-reactive protein (CRP), chi-square for categorical variables.
§ Systolic/diastolic BP ≥140/90 mmHg or use of antihypertensive medications.
SD = standard deviation.

modification of the relative risk between MetS and CVD outcomes was detected by race, LDL-C level, or smoking (P>.10). However, age modified the association between MetS and incident CHD (interaction P=.09) but not CHF or stroke. In age-stratified analyses, MetS was significantly associated with incident CHD in the subgroup aged 65 to 74 at baseline that constituted 70% of study participants (hazard ratio (HR) = 1.44, 95% confidence interval (CI) = 1.21–1.72) but not in the remaining 30% of the population aged 75 and older (HR = 1.00, 95% CI = 0.79–1.27).

Age- and race-adjusted HRs for the association between the revised MetS criteria and incident CHD and CHF were 1.30 (95% CI = 1.07–1.57) and 1.40 (95% CI = 1.12–1.76), respectively, in women, whereas no association was detected for incident stroke (Table 3). For men, age- and race-adjusted HRs for CHD, CHF, and stroke were 1.35 (95% CI = 1.10–1.66), 1.47 (95% CI = 1.14–1.90), and 1.51 (95% CI = 1.08–2.12), respectively. Using a composite endpoint that included the first incidence of CHD, CHF, or stroke, the HRs associated with MetS were 1.21 (95% CI = 1.04–1.41) in women and 1.32 (95% CI = 1.10–1.57) in men. Further adjustment for established CVD risk factors (LDL-C, smoking, alcohol use, caloric intake, family history of CHD, and use of lipid-lowering medication) resulted in minimal changes in the magnitude of the associations between MetS and CVD outcomes (data not shown). Excluding subjects taking lipid-lowering medication at baseline from analyses made no difference in the results. Furthermore, age- and race-adjusted HRs for CVD estimated from the ATP-III criteria for MetS (2001) that used the 6.1 mmol/L to 6.9 mmol/L range for the elevated fasting glucose component differed less than 7% from HRs estimated using the revised MetS (2005) criteria (results not shown).

In age- and race-adjusted analyses performed separately for each component of MetS (Table 4), high blood pressure and fasting glucose (6.1–6.9 mmol/L) were significantly associated with an approximate 60% to 80% and 30% to 45% increase in CHD, respectively. Women and men who met the revised criteria for IFG (5.6–6.9 mmol/L) were 8% to 28% more likely to experience a CHD event than those with normal glucose (<5.6 mmol/L), although this association was statistically significant only in men. The remaining components were less strongly associated with CHD and achieved statistical significance only for elevated triglycerides (men) and low HDL-C (women). When all five of the components of the revised MetS were included in a single Cox model, the HR for high blood pressure was attenuated slightly but still exhibited the strongest association with CHD of all of the components (results not shown).

To examine the association between the number of components and incident CHD, sex-specific models were fit

Table 3. Absolute Rates and Relative Risks of Cardiovascular Events Associated with Metabolic Syndrome (MetS) in Cardiovascular Health Study Participants Free of Diabetes Mellitus and Cardiovascular Disease at Baseline

	Women (n = 2,229)			Men (n = 1,356)		
	MetS (2005)*			MetS (2005)*		
	Yes	No		Yes	No	
Cardiovascular Event	Incidence Rate/1,000 Person-Years (Number of Events/Person-Years at Risk)		HR (95% CI)†	Incidence Rate/1,000 Person-Years (Number of Events/Person-Years at Risk)		HR (95% CI)†
Coronary heart disease	23.5 (190/8,081)	18.1 (229/12,629)	1.30 (1.07–1.57)	43.1 (147/3,414)	33.0 (252/7,637)	1.35 (1.10–1.66)
Stroke	11.4 (96/8,442)	12.2 (159/13,068)	0.94 (0.73–1.21)	14.9 (57/3,819)	10.6 (89/8,394)	1.51 (1.08–2.12)
CHF‡	17.3 (142/8,191)	12.5 (161/12,914)	1.40 (1.12–1.76)	26.0 (96/3,689)	19.2 (155/8,082)	1.47 (1.14–1.90)

* Presence of three of five of the following: large waist circumference (women > 88 cm, men > 102 cm); high triglycerides ≥1.70 mmol/L; low high-density lipoprotein cholesterol (men <1.04 mmol/L, women <1.30 mmol/L); high fasting glucose (5.6–6.9 mmol/L); and high blood pressure (≥130/85 mmHg or self-reported use of medications for hypertension).[5]
† Adjusted for age and race.
‡ After excluding prevalent congestive heart failure (CHF) at baseline, n = 2,192 women, and n = 1,337 men.
HR = hazard ratio; CI = confidence interval.

with categories representing the presence of one, two, three, and four or more components with zero components as the referent (Table 5). Women and men with four to five components were 2.2 and 2.4 times as likely to experience a CHD event as subjects with zero components. Furthermore, the presence of any two components was positively associated with CHD (women: HR = 1.84, 95% CI = 1.19–2.84; men: HR = 2.14, 95% CI = 1.39–3.28). When blood pressure was removed as a component (Table 5), the magnitude of the association between each number of remaining components and CHD was attenuated, although subjects with three or four components were still approximately 1.5 times as likely to experience incident CHD.

DISCUSSION

Several population-based studies[7,9–14] have investigated prospectively the link between ATP-III-defined MetS and fatal CVD or a combined fatal and nonfatal CVD endpoint. The majority of these studies were conducted in middle-aged populations and thus may not be applicable to elderly individuals. With the exception of the Strong Heart Study,[9] all other studies reported significantly higher risks of CVD according to the presence of MetS after multivariate adjustment for established risk factors.

In an analysis of the publicly available data from the CHS, one study[14] reported that the age- and sex-adjusted HR of fatal and nonfatal CVD associated with the ATP-III MetS was 2.12 (95% CI = 1.77–2.52), which remained significant after adjustment for established risk factors, including the individual MetS components (HR = 1.38, 95% CI = 1.06–1.79). The follow-up time for that analysis was truncated to a median of 4 years, because the public-use files do not contain the most current CHD and stroke-ascertainment information. In contrast, the current study examined the association over a much longer follow-up period (median of 11 years). In addition, because the previous study[14] included subjects with diabetes mellitus at baseline but excluded all subjects taking antihypertensive or cholesterol-lowering medications, the generalizability of their findings to elderly subjects (who are commonly treated for hypertension or hypercholesterolemia) is limited. For example, in the present study, in the subpopulation of CHS participants initially free of diabetes mellitus and CVD, removing those taking antihypertension medications alone would have excluded 37% (n = 1,333) of the study population, a subgroup that, under current guidelines from the NHLBI,[5] would be classified as meeting the high blood pressure component of MetS.

The current study extends to older people previous findings of an excess risk of CVD attributable to MetS in middle-aged populations. In the CHS population free of prevalent diabetes mellitus and CVD at baseline, MetS was moderately and significantly associated with incident CHD, CHF, and in men only, incident stroke, with adjusted HRs ranging from 1.3 to 1.5. Using a composite endpoint that included first incidence of CHD, CHF, or stroke, women and men with MetS were 20% to 30% more likely to experience a CVD event than subjects without MetS. Furthermore, evidence was found to suggest that age modified the association between MetS and CHD but no such evidence for stroke and CHF outcomes. Although, subjects

Table 4. Absolute Rates and Relative Risks of Coronary Heart Disease for Each Component of Metabolic Syndrome (MetS) in Cardiovascular Health Study Participants Free of Diabetes Mellitus and Cardiovascular Disease at Baseline

	Women (n = 2,229)			Men (n = 1,356)		
	Component Present			Component Present		
	Yes	No		Yes	No	
MetS (2005) Component	Incidence Rate/1,000 Person-Years		HR (95% CI)*	Incidence Rate/1,000 Person-Years		HR (95% CI)*
High blood pressure	24.0 (133/5,540)	23.9 (205/8,560)	1.82 (1.42–2.33)	43.1 (90/2,088)	40.7 (220/5,408)	1.62 (1.28–2.05)
Low high-density lipoprotein cholesterol	25.0 (93/3,719)	21.2 (27/1,272)	1.27 (1.03–1.57)	43.3 (65/1,502)	31.9 (30/939)	1.14 (0.90–1.43)
High triglycerides	21.8 (94/4,308)	21.6 (35/1,618)	1.15 (0.93–1.41)	45.5 (76/1,671)	34.4 (40/1,163)	1.25 (1.00–1.55)
Large waist	23.8 (127/5,333)	19.3 (110/5,689)	1.16 (0.95–1.40)	46.1 (68/1,476)	33.5 (46/1,373)	1.18 (0.95–1.47)
High glucose ($\geq$6.1 mmol/L)	25.5 (60/2,354)	20.0 (12/601)	1.31 (1.02–1.68)	46.9 (56/1,194)	47.6 (37/777)	1.45 (1.15–1.83)
Impaired glucose ($\geq$5.6 mmol/L)	23.7 (139/5,876)	15.1 (40/2,641)	1.08 (0.89–1.31)	42.9 (125/2,915)	37.3 (108/2,896)	1.28 (1.05–1.57)

*Estimated from separate Cox proportional hazards models for each component, adjusted for age and race.
HR = hazard ratio; CI = confidence interval.

aged 65 to 74 had a 40% increase in the relative risk of CHD associated with MetS, no association was observed in CHS subjects aged 75 and older. This finding is consistent with previous research from the CHS[23] and other studies[24,25] indicating that lipids and obesity may be less predictive of CHD in older people, possibly due to an increased presence of competing risk factors.

The risk estimates for CVD from the current study are similar to those of several U.S. studies that have examined individuals without prevalent CVD or diabetes mellitus. Investigators using data from the Framingham Offspring Study,[10] Atherosclerosis Risk in Communities Study,[13] National Health and Nutrition Examination Survey Mortality Study,[11] and San Antonio Heart Study[12] reported relative risks of fatal or nonfatal CVD ranging from 1.5 to 2.1. Two of these studies[12,13] reported that sex modified the relationship between MetS and CVD. The relative risk of CVD mortality was significantly larger in women than men (HR = 4.7 vs 1.8, interaction $P = .03$) in the general population of the San Antonio Heart Study[12] (i.e., including subjects with and without prevalent CHD or diabetes mellitus) after adjusting for age, race, and ethnicity. In the biracial community population of the Atherosclerosis Risk in Communities Study free of diabetes mellitus and CVD at baseline, the association between MetS and combined fatal and nonfatal CHD was stronger in women than men (HR = 2.0 and 1.5, respectively, sex interaction $P = .007$) after multivariate adjustment.[13]

The current analysis did not detect a sex interaction for CHD. Although lack of statistical power to detect such an interaction cannot be excluded, it is also possible that, because the absolute incidence rate of CVD in women increases from middle to older age, the difference in the observed relative risks of CHD associated with MetS for men and women is attenuated.

Results from this study underscore the importance of recognizing and treating high blood pressure in older people as part of CVD prevention efforts.[23] Three fourths of this elderly community-based population eligible for primary prevention of CHD had high blood pressure, making it the most common of all the MetS components in African Americans and Caucasians. In addition, in this study and at least two others[12,13] that examined the associations between individual MetS components and incident CVD, high blood pressure exhibited the strongest association with incident CVD of all five components.

The recent recommendation by the Expert Committee on the Diagnosis and Classification of Diabetes[4] to change the lower limit of IFG from 6.1 mmol/L to 5.6 mmol/L has engendered considerable debate.[6,26] Critics of this modification cite the lack of consistent findings of a higher risk of CVD attributable to glycemic levels once other established risk factors are taken into account and the substantial number of Americans who will be classified as having "prediabetes" but who will never develop diabetes mellitus. An analysis of the 1999/2000 National Health and Nutrition Examination Survey data[6] indicates that, in Americans aged 65 and older, the effect of applying the lower glucose threshold will increase the prevalence from 18% to 44%.[6]

In the current analysis, lowering the cutpoint of fasting glucose from 6.1 mmol/L to 5.6 mmol/L nearly tripled the

Table 5. Number of Metabolic Syndrome (MetS) (2005)* Components and Risk of Coronary Heart Disease in Cardiovascular Health Study Participants Free of Diabetes Mellitus and Cardiovascular Disease at Baseline

	Women (n = 2,218)		Men (n = 1,350)	
MetS Components	Hazard Ratio (95% Confidence Interval)†			
All 5 components				
4–5	2.16	(1.38–3.37)	2.36	(1.47–3.78)
3	1.92	(1.24–2.98)	2.26	(1.45–3.52)
2	1.84	(1.19–2.84)	2.14	(1.39–3.28)
1	1.48	(0.95–2.32)	1.54	(0.99–2.39)
0	1.00		1.00	
All components except blood pressure				
3–4	1.32	(1.00–1.75)	1.69	(1.22–2.34)
2	1.11	(0.84–1.47)	1.46	(1.08–1.97)
1	0.92	(0.70–1.21)	1.47	(1.12–1.92)
0	1.00		1.00	

* Presence of three of five of the following: large waist circumference (women >88 cm, men >102 cm), high triglycerides (≥ 1.70 mmol/L), low high-density lipoprotein cholesterol (men <1.04 mmol/L, women <1.30 mmol/L), high fasting glucose (5.6–6.9 mmol/L), and high blood pressure ($\geq 130/85$ mmHg or self-reported use of medication for hypertension).[5]
† Adjusted for age and race.

prevalence of subjects classified as having IFG, from 16% to 46%, and resulted in an additional 9% of the population meeting the criteria for MetS. In models that estimated the relative risk of each component of MetS, using the lower glucose cutpoint resulted in relative risks of CHD associated with IFG that were 12% to 18% lower than those estimated when the original threshold of 6.1 mmol/L was applied. However, when the lower threshold for IFG was included as part of the MetS criteria, the strength of the association between the revised MetS and CHD did not materially differ from the original criteria. Further research is needed to determine whether the lower IFG threshold, in isolation or as a component of MetS, is useful for identifying elderly patients at high cardiovascular risk that traditional mechanisms do not identify.

Several limitations of the data should be recognized. First, dichotomous representations of truly continuous measures such as those constituting the MetS criteria decrease available information and can result in misclassification of exposure. This is especially true for measures with known biological variability and thus may account for the weak association detected between low HDL-C and incident CHD observed in this study. In a previous analysis of the CHS,[27] a 1–standard deviation difference in HDL-C was strongly and consistently associated with MI even after multivariate adjustment that included other lipid factors. It may be that a cutpoint of 1.30 mmol/L in men and 1.03 mmol/L in women does not optimally define the risk associated with low HDL-C and CVD in this population. However, the purpose of the study was to investigate the associations between CVD and MetS and its individual components as defined using ATP-III, in which specific threshold values have been recommended.

Second, the associations observed in this study may be due to survival bias (i.e., that data on individuals most at risk for CHD outcomes associated with the presence of the MetS were not included, because such individuals died before reaching the eligibility age for the study). Although it can be surmised that the absence of such individuals would only dilute the true association between MetS and incident CVD (bias towards the null), this cannot be confirmed using the CHS data. Third, the CHS is limited to community-living adults. It excludes those in nursing homes or those too frail to attend clinic visits at baseline. These criteria may have excluded many with MetS at high risk for CVD and thus may have also diminished the strengths of association.

Lastly, the present analysis excluded CHS subjects with diabetes mellitus at baseline. Given that the preliminary analysis found that 79% of these subjects met the criteria for MetS, the prevalence figures that are presented are undoubtedly an underestimation of the prevalence of MetS in the combined CHS population of subjects with and without diabetes mellitus. However, the primary aim of the current study was to estimate the association between MetS and incident CVD outcomes. Because current clinical guidelines from the NHLBI[3] for the prevention of CHD and treatment of high LDL-C consider prevalent diabetes mellitus to be a "CHD-risk equivalent" and diabetes mellitus would likely drive any association between the MetS and CHD, subjects with baseline diabetes mellitus were not included.

In conclusion, results from this study of an elderly, population-based cohort provide support for earlier investigations in primarily middle-aged populations that link the presence of MetS with the development of CVD and further underscore the importance of recognizing and treating its individual components, particularly high blood pressure.

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REFERENCES

1. Reaven G. Insulin resistance, compensatory hyperinsulinemia and coronary heart disease: Syndrome X revisited. In Jefferson LS, Cherrington AD, eds. Handbook of Physiology, Section 7, The Endocrine System, Vol II, The Pancreas and Regulation of Metabolism. New York: Oxford University Press, 2001, pp 1169–1197.
2. Alexander CM, Landsman PB, Teutsch SM et al. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes 2003;52:1210–1214.
3. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–2497.
4. Genuth S, Alberti KG, Bennett P et al. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;26:3160–3167.
5. Grundy SM, Cleeman JI, Daniels SR et al. Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735–2752.
6. Davidson MB, Landsman PB, Alexander CM. Lowering the criterion for impaired fasting glucose will not provide clinical benefit. Diabetes Care 2003;26:3329–3330.
7. Lakka HM, Laaksonen DE, Lakka TA et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002; 288: 2709–2716.
8. Bonora E, Kiechl S, Willeit J et al. Carotid atherosclerosis and coronary heart disease in the metabolic syndrome: Prospective data from the Bruneck study. Diabetes Care 2003;26:1251–1257.
9. Resnick HE, Jones K, Ruotolo G et al. Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease in nondiabetic American Indians: The strong heart study. Diabetes Care 2003;26:861–867.
10. Rutter MK, Meigs JB, Sullivan LM et al. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. Circulation 2004;110:380–385.
11. Malik S, Wong ND, Franklin SS et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. Circulation 2004;110:1245–1250.
12. Hunt KJ, Resendez RG, Williams K et al. National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study. Circulation 2004;110:1251–1257.
13. McNeill AM, Rosamond WD, Girman CJ et al. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. Diabetes Care 2005;28:385–390.
14. Scuteri A, Najjar SS, Morrell CH et al. The metabolic syndrome in older individuals: Prevalence and prediction of cardiovascular events: The Cardiovascular Health Study. Diabetes Care 2005;28:882–887.
15. Fried LP, Borhani NO, Enright P et al. The Cardiovascular Health Study: Design and rationale. Ann Epidemiol 1991;1:263–276.
16. Cushman M, Cornell ES, Howard PR et al. Laboratory methods and quality assurance in the Cardiovascular Health Study. Clin Chem 1995;41:264–270.
17. Psaty BM, Kuller LH, Bild D et al. Methods of assessing prevalent cardiovascular disease in the Cardiovascular Health Study. Ann Epidemiol 1995;5:270–277.
18. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183–1197.
19. Ives DG, Fitzpatrick AL, Bild DE et al. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. Ann Epidemiol 1995;5:278–285.
20. Price TR, Psaty B, O'Leary D et al. Assessment of cerebrovascular disease in the Cardiovascular Health Study. Ann Epidemiol 1993;3:504–507.
21. Gottdiener JS, Arnold AM, Aurigemma GP et al. Predictors of congestive heart failure in the elderly: The Cardiovascular Health Study. J Am Coll Cardiol 2000;35:1628–1637.
22. Geiss LS, Herman WH, Smith PJ. Mortality in Non-Insulin Dependent Diabetes Mellitus. National Diabetes Data Group: Diabetes in America, 2nd Ed. Bethesda, MD: National Institutes of Health, 1995.
23. Psaty BM, Furberg CD, Kuller LH et al. Traditional risk factors and subclinical disease measures as predictors of first myocardial infarction in older adults. The Cardiovascular Health Study. Arch Intern Med 1999;159:1339–1347.
24. Krumholz HM, Seeman TE, Merrill SS et al. Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years. JAMA 1994;272:1335–1340.
25. Dey DK, Lissner L. Obesity in 70-year-old subjects as a risk factor for 15-year coronary heart disease incidence. Obes Res 2003;11:817–827.
26. Schriger DL, Lorber B. Lowering the cut point for impaired fasting glucose: Where is the evidence? Where is the logic? Diabetes Care 2004;27:592–601.
27. Psaty BM, Anderson M, Kronmal RA et al. The association between lipid levels and the risks of incident myocardial infarction, stroke, and total mortality: The Cardiovascular Health Study. J Am Geriatr Soc 2004;52: 1639–1647.