METABOLIC SYNDROME AND RELATED DISORDERS
Volume 10, Number 1, 2012

Pp. 47–55
DOI: 10.1089/met.2011.0087

A Gender-Stratified Comparative Analysis of Various Definitions of Metabolic Syndrome and Cardiovascular Risk in a Multiethnic U.S. Population

Pawan Hari, M.D.,[1] Kamalakar Nerusu, M.D.,[1] Vikas Veeranna, M.D.,[2] Rajeev Sudhakar, M.D.,[1] Sandip Zalawadiya, M.D.,[2] Krithi Ramesh, M.D.,[3] and Luis Afonso, M.D., FACC[2]

Abstract

Introduction: We sought to evaluate the ability of various metabolic syndrome definitions in predicting primary cardiovascular disease (CVD) outcomes in a vast multiethnic U.S. cohort.
Methods: This study included 6,814 self-identified men and women aged 45–84 years enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA) study. Gender-stratified analyses were performed to calculate hazard ratios of CVD, stroke, and mortality associated with various metabolic syndrome definitions and their individual constructs.
Results: The hazard ratios [95% confidence interval (CI)] for all-cause CVD in men were 2.90 (2.18–3.85), 2.64 (1.98–3.51), 2.16 (1.62–2.88), 2.56 (1.91–3.44), 1.82 (1.35–2.46), and 2.92 (2.15–3.95) for the National Cholesterol Education Program (NCEP), American Heart Association (AHA), World Health Organization (WHO), International Diabetes Federation (IDF), European Group for the Study of Insulin Resistance (EGIR), and the newly defined consensus criteria. Hazard ratios in women were 2.11 (1.41–3.15), 2.17 (1.45–3.27), 2.04 (1.37–3.06), 1.91 (1.27–2.88), 1.85 (1.23–2.79), and 2.08 (1.37–3.14), respectively. Metabolic syndrome was strongly associated with stroke risk only in males. In men, all constitutive metabolic syndrome components were continuously and strongly associated with CVD. In women, high-density lipoprotein and triglycerides did not appear to be associated with short term CVD risk.
Conclusion: We found the newly defined consensus criteria for metabolic syndrome to be similarly predictive of cardiovascular events when compared to existing definitions. Significant gender differences exist in the association between metabolic syndrome, its individual components, and CVD.

Introduction

Metabolic syndrome has been shown to be associated with increased cardiovascular disease (CVD) morbidity and mortality in previous studies.[1,2] In the last decade, there has been a deluge of metabolic syndrome definitions proposed by various international bodies, including the National Cholesterol Education Program (NCEP),[3] American Heart Association (AHA),[4] World Health Organization (WHO),[5] International Diabetes Federation (IDF),[6] European Group for the Study of Insulin Resistance (EGIR),[7] and the American Association of Clinical Endocrinologists. More recently, these bodies met to resolve differences between definitions and proposed a common consensus metabolic syndrome criteria.[8] Because the primary utility of metabolic syndrome in clinical practice is to predict CVD events, including mortality, the various metabolic syndrome definitions are graded by their ability to forecast the same.

Prior studies have compared definitions in predominantly homogeneous populations, but little is known about the prognostic value of the newer "consensus "criteria. To our knowledge, this is the first study to compare and contrast the newly proposed metabolic syndrome definition in a vast multiethnic community–based cohort of healthy U.S. adults with no prior history of CVD.

The aims of this study were to: (1) Ascertain the prevalence of and correlation between seven currently used metabolic syndrome definitions; (2) assess the ability of these definitions to predict various cardiovascular end points in a gender-stratified analysis, the primary end point being all-cause CVD (CVDA); (3) explore the association between

[1]Department of Internal Medicine, [2]Division of Cardiology, [3]Division of Endocrinology, Wayne State University/Detroit Medical Center, Detroit, Michigan.

individual metabolic syndrome components (introduced as continuous variables) and various study end points, and examine how these associations differ by gender.

Methods

Study population

Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter, longitudinal cohort study designed to investigate the risk factors and progression of sudden cardiac arrest (SCA) in a population free of CVD at baseline. A total of 6,814 asymptomatic, self-identified men and women (52.85%) aged 45–84 years, including Caucasians, Chinese, African Americans, and Hispanics, were enrolled between July, 2000, and August, 2002, from six U.S. communities. Details of the study design, recruitment, and cohort examination procedures have been published elsewhere.[9] This study was approved by our Institutional Review Board and performed on the limited-access dataset of MESA obtained from the National Heart Lung and Blood Institute.

All participants with baseline measures of waist circumference (WC), body mass index (BMI), blood pressure, fasting blood sugar, serum insulin, triglycerides, high-density lipoprotein (HDL), and antihypertensive and hypoglycemic medication use were included in the analysis. A total of 44 subjects with missing information were excluded. Thus, the final analysis comprised of 6,770 healthy individuals with no history of CVD.

Data collection

Information about age, gender, ethnicity, and medical and medication history were obtained using questionnaires. Smoking and alcohol use was defined as current, previous, or never use. Total intentional exercise was presented as the number of MET-hours (metabolic equivalent tasks) per week. A complete physical exam was performed for anthropometric measurements. This included measurement of the body mass index (BMI) using the formula weight (kg)/height^2 (mt^2). The WC and hip circumference were measured using a Gulick II anthropometric tape at the level of the umbilicus and the maximum circumference of buttocks, respectively, with the participant standing. Blood pressure was measured three times using the Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, FL); the last two measurements were averaged for analysis. Blood was drawn at the baseline visit to measure the fasting lipid panel, glucose, and insulin; details of methods are provided elsewhere.[10] The homeostatic model assessment (HOMA) method was used to quantify insulin resistance (IR) using the formula[11]: Insulin (mU/mL)$\times$glucose (mg/dL)/405. Studies in the past have varied with regard to inclusion of diabetics. In our primary analysis, we included diabetics, but repeated secondary analysis after excluding individuals with clinical diabetes mellitus ($n=677$, 10%).

Metabolic syndrome

Seven existing definitions of metabolic syndrome were used, including the old NCEP,[12] AHA,[4] WHO,[5] IDF,[6] EGIR,[7] and the recently published consensus criteria[8] with IDF or AHA cutoffs for europids. The last two definitions are referred to as consensus (Con)-IDF and Con-AHA criteria in the manuscript. Details have been tabulated in Table 1. It is worth noting that the IDF and consensus criteria provide a lower race-specific cutoff for the Chinese (men >90 cm and women >80 cm) compared to higher cutoff for whites and African Americans (men >94 cm and women >80 cm). IDF also suggests lower cutoffs (90/80 cm) for ethnic Central and South American populations, but makes no specific recommendation for Hispanics in the United States. Given the dearth of data for this population, we used these lower cutoffs for the Hispanics included in this study. The top most quartile of HOMA (cutoff, 8 mU/L) and fasting insulin (cutoff, 1.837) in the nondiabetic population were used to describe IR for the WHO definition and EGIR definition, respectively. Specific treatment for dyslipidemia associated with metabolic syndrome was defined as the use of fibrates or niacin but not statins.

Clinical end point assessment

Participants were contacted by a telephone interviewer every 9–12 months in addition to the three MESA follow-up visits to obtain information about hospitalizations, cardiovascular events, or deaths. Self-reported end points were verified by obtaining medical records. In the case of outpatient deaths, next-of-kin interviews were conducted and death certificates were reviewed. Hospital records were obtained for an estimated 98% of hospitalized cardiovascular events and 96% of outpatient diagnoses. Clinical end points used for analysis included: (1) CVDA, a composite of myocardial infarction (MI), resuscitated cardiac arrest (RCA), definite angina, probable angina (if followed by revascularization), stroke, stroke death, coronary heart disease (CHD) death, other atherosclerotic and cardiovascular death; (2) all-cause coronary heart disease (CHDA), including MI, RCA, definite angina, probable angina, and CHD death; (3) stroke; and (4) all-cause mortality (ACM).

Statistical analysis

All covariates were tested for normality by visual inspection using frequency distribution curves and Q-Q plots. Normal variables (Table 2) are presented as mean and standard deviation (SD), and variables with skewed distribution as median and interquartile ranges. Categorical variables, such as the prevalence of various metabolic syndrome definitions (Table 3), are presented as percentages.

Agreement between the various metabolic syndrome definitions was determined using the kappa (κ) statistic.[13] The level of agreement was classified based on the κ as follows: <0.20 poor, 0.20–0.40 fair, 0.40–0.60 moderate, 0.60–0.80 substantial, and >0.80 very good.

All analyses were gender stratified. Effect modification by race and age (continuous) was examined using interaction terms. Univariate and multivariate Cox proportional-hazards regression analyses[14] were performed to test the association between individual metabolic syndrome components and cardiovascular outcomes (Table 4). Metabolic syndrome components were treated as continuous variables, and hazard ratios (HRs) were calculated for each SD rise in the component. Confounding variables were identified by a literature search. Three statistical models were devised to test the effect of each set of cofounding variables on association with outcomes: (1) The crude model; (2) model 1 was adjusted for demographic factors (age and race), health behaviors (smoking and voluntary activity), and socioeconomic

Table 1. Metabolic Syndrome Definitions

	Old NCEP	*Revised NCEP*	*WHO*	*IDF*	*EGIR*	*Consensus IDF**
Metabolic syndrome definition	Any three of the following five	Any three of the following five	↑Fasting glucose or >75th percentile HOMA + two of the following	Abdominal obesity + two of the following	Fasting insulin >75th percentile + any two of the following	Any three of the following five
Abdominal obesity/BMI	Waist >102/88 cm	Waist >102/88 cm and >90/80 cm in Chinese	WHR >0.9/0.85 in males/females and/or BMI >30	Race specific cutoffs†	Waist >94/80 cm in all races	Race specific cutoffs†
Hypertension	BP ≥135/80 mmHg or treatment	BP ≥135/80 mmHg or treatment	BP ≥140/90 mmHg or treatment	BP ≥140/90 mmHg or treatment	BP ≥140/90 mmHg or treatment	BP ≥135/80 mmHg or treatment
Triglycerides	≥150 mg/dL	≥150 mg/dL or treatment	≥150 mg/dL or treatment	≥150 mg/dL or treatment	≥177.1 mg/dL or treatment and/or	≥150 mg/dL or treatment
HDL	<40/50 mg/dL (M/F)	<40/50 mg/dL (M/F) or treatment	<35/40 mg/dL (M/F) or treatment	<40/50 mg/dL in (M/F) or treatment	<40 mg/dL or treatment	<40/50 mg/dL (M/F) or treatment
Fasting glucose	≥110 mg/dL	≥100 mg/dL	≥110 mg/dL	≥100 mg/dL	100–126 mg/dL	≥100 mg/dL
Fasting insulin	—	—	—	—	>8 mU/L	—
HOMA-IR	—	—	>1.837	—	—	—
UAC ratio	—	—	≥30 mg/g	—	—	—

†Waist >94/80 cm in caucasians and African-American (M/F), 90/80 cm in Chinese and Hispanics (M/F).
*Consensus AHA same as consensus IDF except higher cutoffs for caucasians (>102/88 cm).
NCEP, National Cholesterol Education Program; WHO, World Health Organization; IDF, International Diabetes Federation; EGIR, European Group for the Study of Insulin Resistance; HOMA, homeostasis model assessment; BMI, body mass index; WHR, waist-to-hip ratio; BP, blood pressure; HDL, high-density lipoprotein; M, male; F, female; IR, insulin resistance; UAC, urine albumin–creatinine ratio.

Table 2. Baseline Characteristics Stratified by Gender

Characteristic	*Entire population*	*Males*	*Females*
Number (%)	6770 (100%)	3197 (47.22%)	3573 (52.78%)
Age (years)	62.16 (10.23)	62.19 (10.21)	62.12 (10.25)
Smoking	878 (13.01%)	462 (14.5%)	416 (11.68%)
Alcohol	3727 (55.45%)	1996 (62.83%)	1731 (48.84%)
BMI (kg/m^2)	28.33 (5.42)	27.86 (4.40)	28.74 (6.16)
Waist circumference (cm)	98.16 (14.39)	99.31 (12.21)	97.14 (16.02)
Hip circumference (cm)	105.61 (11.44)	103.49 (9.15)	107.5 (12.86)
WHR	0.93 (0.08)	0.96 (0.07)	0.90 (0.08)
Exercise (≥5 MET-h of intentional exercise/week)	70%	72.85%	67.45%
Fasting blood glucose	97.35 (30.24)	100.18 (32.84)	94.83 (27.47)
Fasting insulin (mU/L)	5.4 (3.5–8.5)	5.4 (3.5–8.5)	5.4 (3.6–8.5)
HOMA	1.24 (0.76–2.08)	1.28 (0.80–2.15)	1.21 (0.75–2.03)
Systolic blood pressure	126.59 (21.48)	126.03 (19.32)	127.09 (23.24)
Diastolic blood pressure	71.91 (10.26)	75.03 (9.4)	69.11 (10.19)
Triglyceride levels	131.69 (88.91)	135.47 (95.48)	128.32 (82.45)
HDL level	50.95 (14.83)	45.04 (11.77)	56.24 (15.27)
LDL level	117.20 (31.43)	116.63 (30.93)	117.7 (31.87)
Family history of heart attacks	42.71%	39.21%	45.80%
Income (>$30,000 a year)	62.55%	69.19%	56.60%
Education (>high school)	82.92%	83.77%	80.26%

BMI, body mass index; WHR, waist-to-hip ratio; HOMA, homeostasis model assessment for insulin resistance; MET, metabolic equivalent tasks; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

factors such as income and education which are known powerful confounders based on previous studies; (3) model 2 was adjusted in addition for the remaining metabolic syndrome components, however, there was evidence of multicollinearity in this model. Association between metabolic syndrome definitions and outcomes were tested in a similar fashion. The final model presented in Table 6 (below) was adjusted for age, race, income, education, physical activity, cigarette smoking, and low-density lipoprotein (LDL). Two-tailed P values <0.05 were considered statistically significant. All statistical procedures were performed using Statistical Analysis Systems version 9.1 (SAS Institute, Cary, NC) statistical software package.

Results

Baseline data

The study population consisted of 6,770 healthy individuals (52.78% female). Participants were followed for an average period of 4.1 years. During this period, a total of 322 CVDA events, 232 CHDA, 89 strokes, and 224 ACM events were noted. Of these deaths, only 46 (20.5%) were attributed to cardiovascular causes.

The prevalence of metabolic syndrome in this population, which also included diabetics, ranged from 24.52% as defined by the EGIR definition to 42.54% according to the consensus IDF criteria. Gender- and race-stratified prevalence of individual metabolic syndrome definitions is provided in Table 3. It is worth noting that abdominal obesity as defined by the IDF criteria had a prevalence of 86.87% in women, whereas the WHO cutoff (based on waist-to-hip ratio) similarly identified 84.11% of men as centrally obese. These numbers appear to be higher as compared to previous studies, but are not surprising given that the mean WCs were 99.31 cm and 97.14 cm in males and females respectively (Table 2). The higher prevalence of metabolic syndrome as defined by IDF and the consensus criteria can be explained by the lower cutoffs for abdominal obesity.

Correlation among metabolic syndrome definitions

Correlational analysis as defined by the κ statistic showed that EGIR and WHO definitions correlated moderately with

Table 3. Gender- and Race-Stratified Prevalence of Various Metabolic Syndrome Definitions

			Males					*Females*			
Definitions	*All*	*All males*	*Caucasians*	*Chinese*	*African American*	*Hispanics*	*All females*	*Caucasians*	*Chinese*	*African American*	*Hispanics*
NCEP	33.10%	29.23%	28.67%	18.86%	29.34%	35.64%	36.56%	31.36%	31.31%	36.72%	48.25%
AHA	37.82%	33.87%	31.79%	33.85%	34.85%	38.97%	40.43%	33.88%	41.99%	41.47%	51.49%
WHO	31.58%	34.13%	27.43%	30.75%	37.96%	43.13%	29.30%	19.73%	26.39%	36.46%	38.03%
EGIR	24.52%	23.21%	22.65%	16.28%	27.90%	33.98%	22.08%	15.52%	16.95%	30.27%	31.31%
IDF	41.22%	39.58%	37.11%	25.84%	39.52%	51.32%	42.68%	35.77%	39.47%	44.29%	54.33%
Con-IDF	42.54%	42.04%	38.04%	33.59%	42.16%	53.40%	42.99%	35.99%	41.89%	44.39%	53.95%
Con-AHA	40.89%	39.51%	31.58%	33.59%	42.16%	53.40%	42.12%	33.70%	41.89%	44.39%	53.95%

NCEP, National Cholesterol Education Program; AHA, American Heart Association; WHO, World Health Organization, IDF, International Diabetes Federation; EGIR, European Group for the Study of Insulin Resistance; Con, consensus.

Table 4. Hazard Ratios of Various Clinic Outcomes in Males Associated for Each Standard Deviation Increase in Individual Tenets of the Metabolic Syndrome Definition

	CVD (N = *206*)	*CHD* (N = *164*)	*Stroke* (N = *40*)	*Mortality* (N = *130*)
Waist circumference (crude)	1.29 (1.11–1.51)†	1.21 (1.02–1.44)*	1.51 (1.10–2.06)†	1.06 (0.87–1.29)
Model 1	1.29 (1.11–1.50)†	1.21 (1.02–1.45)*	1.50 (1.09–2.07)*	0.93 (0.74–1.17)
Model 2	1.15 (0.97–1.36)	1.11 (0.91–1.34)	1.37 (0.95–1.97)	0.93 (0.73–1.19)
Log HOMA (crude model)	1.33 (1.17–1.52)‡	1.32 (1.14–1.52)†	1.55 (1.16–2.06)†	1.02 (0.85–1.21)
Model 1	1.37 (1.20–1.57)‡	1.34 (1.15–1.56)‡	1.56 (1.16–2.09)†	1.00 (0.83–1.2)
Model 2	1.18 (1.00–1.40)	1.19 (0.99–1.44)	1.25 (0.87–1.79)	1.03 (0.82–1.29)
Triglycerides (crude model)	1.09 (1.01–1.18)*	1.1 (1.01–1.19)*	1.10 (0.94–1.30)	0.90 (0.74–1.10)
Model 1	1.12 (1.05–1.20)†	1.13 (1.05–1.21)†	1.14 (0.96–1.34)	1.01 (0.85–1.21)
Model 2	1.06 (0.96–1.17)	1.07 (0.97–1.18)	1.08 (0.86–1.36)	1.03 (0.86–1.24)
HDL (crude model)	0.79 (0.65–0.95)*	0.76 (0.61–0.95)*	0.82 (0.54–1.26)	1.10 (0.90–1.36)
Model 1	0.73 (0.60–0.88)†	0.71 (0.57–0.89)†	0.78 (0.51–1.20)	1.00 (0.81–1.25)
Model 2	0.81 (0.65–0.99)*	0.77 (0.61–0.98)*	0.94 (0.61–1.47)	1.00 (0.78–1.27)
Systolic blood pressure (crude)	1.65 (1.45–1.88)‡	1.46 (1.25–1.70)‡	2.44 (1.87–3.18)‡	1.37 (1.15–1.63)†
Model 1	1.49 (1.29–1.71)‡	1.31 (1.11–1.55)†	2.17 (1.63–2.90)‡	1.05 (0.87–1.26)
Model 2	1.45 (1.25–1.68)‡	1.29 (1.09–1.53)†	2.05 (1.52–2.77)‡	1.05 (0.87–1.27)
Log UAC (crude model)	1.48 (1.35–1.63)‡	1.36 (1.21–1.52)‡	1.86 (1.57–2.21)‡	1.54 (1.38–1.73)‡
Model 1	1.40 (1.26–1.55)‡	1.27 (1.12–1.44)†	1.77 (1.47–2.13)‡	1.37 (1.20–1.56)‡
Model 2	1.26 (1.12–1.41)‡	1.15 (1.00–1.32)*	1.49 (1.21–1.84)†	1.37 (1.20–1.56)‡

Model 1, race, age, cigarette smoking (current, ever, never), exercise (> 5 METS/h every week), income and education; model 2, model 1 + other metabolic syndrome components (WC, HOMA, HDL, Trig, SBP).

*$P < 0.05$.

†$P < 0.01$.

‡$P < 0.001$.

CVD, all cardiovascular disease events; CHD, all coronary heart disease events; UAC, urine albumin–creatinine ratio; MET, metabolic equivalent; WC, waist circumference; HOMA, homeostasis model assessment; HDL, high-density lipoprotein; Trig, triglycerides; SBP, systolic blood pressure.

other definitions ($\kappa = 0.40$–0.60). Correlation amongst the remaining definitions (AHA, NCEP, IDF, consensus IDF, and consensus AHA) ranged from 0.69 to 0.98, and in general ranked in the "very good" range ($\kappa > 0.80$). The IDF criteria was strongly associated with the AHA and NCEP criteria (0.69 and 0.78 in males; 0.85 and 0.93 in females), most likely secondary to predominance of central obesity in the MESA cohort. Con-AHA and Con-IDF correlated well with the IDF criteria in men (0.89, 0.94) and women (0.96, 0.98) and with the NCEP (0.77 and 0.72 in men; 0.87 and 0.86 in women) and AHA criteria (0.87 and 0.82 in men; 0.95 and 0.94 in women).

Outcomes

CVDA/CHDA. CVDA and CHDA trended in the same direction for a majority of analyses given that CHDA constituted a majority of events in the broader CVDA outcome and are therefore presented together.

Males. As shown in Table 4, all metabolic syndrome components including microalbuminuria showed significant associations with CVDA/CHDA in crude and adjusted analyses. The adjusted risk of CVDA and CHDA rose consistently with each SD rise in WC (29% and 21%), log HOMA (37% and 32%), triglycerides (12% and 13%), systolic blood pressure (49% and 31%), and log urine albumin–creatinine ratio (UAC) (40% and 27%) in men. HDL, on the other hand, was associated with a 27% and 29% decrease in CVDA and CHDA risk, respectively, with each SD increase. When adjusted in addition for other metabolic syndrome components, only HDL (inversely), systolic blood pressure (SBP), and log UAC appeared to be significantly associated with CVDA/CHDA, whereas WC and log HOMA showed a trend toward association. However, this model needs to be assessed cautiously because there was evidence of collinearity between the various components of metabolic syndrome.

As shown in Table 6 (below), AHA, NCEP, IDF, and the consensus criteria showed similar adjusted HRs with respect to CVDA and CHDA outcomes [odds ratio (OR) = 2.5–3). The WHO and EGIR definitions, on the other hand, appeared to be weaker predictors in comparison.

The unadjusted areas under the curve (AUCs) for CVDA as defined by the NCEP, AHA, IDF, Con-IDF, and Con-AHA definitions (0.619, 0.617, 0.613, 0.626, and 0.624, respectively) were similar to each other but significantly higher than the WHO, EGIR-defined metabolic syndrome (0.595, 0.562). Likewise, the AUCs for CHDA were similarly lower for WHO-metabolic syndrome and EGIR-metabolic syndrome.

Females. In contrast to men, triglycerides and HDL did not appear to be associated with CVDA or CHDA; even when trends were observed, the effect sizes were modest at best. The risk of CVDA and CHDA rose considerably with each SD rise in WC (25% and 25%), log HOMA (26% and 28%), SBP (38% and 24%), and log UAC (40% and 27%). In the final model, when adjusted for all components of metabolic syndrome, only SBP and log UAC appeared to be significantly associated with CVDA/CHDA (Table 5).

In women, metabolic syndrome appeared to be less predictive of CVDA (adjusted HR, 1.85–2.20) and CHDA (adjusted HR, 1.63–2.43) as compared to men (Table 6). EGIR-metabolic syndrome was least predictive of both CVDA and CHDA in women. The unadjusted AUCs for the NCEP, AHA, WHO, IDF, Con-IDF, and Con-AHA definitions in females were not statistically different (0.609, 0.619, 0.607, 0.605, 0.612, and 0.612, respectively), but were

Table 5. Hazard Ratios of Various Clinic Outcomes in Females Associated for Each Standard Deviation Increase in Individual Tenets of the Metabolic Syndrome Definition

	CVD (N = *116*)	*CHD* (N = *68*)	*Stroke* (N = *49*)	*Mortality* (N = *94*)
Waist circumference (crude)	1.29 (1.11–1.51)†	1.30 (1.07–1.58)†	1.24 (0.98–1.57)	1.17 (0.99–1.40)
Model 1	1.25 (1.05–1.49)*	1.25 (1.00–1.57)*	1.13 (0.85–1.50)	1.19 (0.97–1.46)
Model 2	1.18 (0.98–1.43)	1.19 (0.93–1.52)	1.03 (0.76–1.41)	1.16 (0.94–1.45)
Log HOMA (crude model)	1.28 (1.08–1.53)†	1.29 (1.02–1.62)*	1.32 (1.01–1.73)*	1.18 (0.97–1.44)
Model 1	1.26 (1.04–1.53)*	1.28 (1.00–1.65)	1.33 (1.00–1.79)*	1.14 (0.92–1.41)
Model 2	1.11 (0.88–1.40)	1.14 (0.84–1.55)	1.26 (0.88–1.81)	1.06 (0.82–1.37)
Triglycerides (crude model)	1.10 (0.96–1.27)	1.12 (0.95–1.32)	1.10 (0.89–1.35)	0.97 (0.77–1.22)
Model 1	1.13 (0.94–1.34)	1.17 (0.96–1.42)	1.18 (0.88–1.57)	0.94 (0.72–1.23)
Model 2	1.07 (0.85–1.35)	1.15 (0.90–1.46)	1.08 (0.74–1.58)	0.84 (0.61–1.17)
HDL (crude model)	0.88 (0.73–1.06)	0.93 (0.74–1.19)	0.83 (0.62–1.12)	0.90 (0.74–1.11)
Model 1	0.85 (0.69–1.04)	0.87 (0.67–1.14)	0.82 (0.60–1.14)	0.91 (0.73–1.14)
Model 2	0.92 (0.73–1.16)	0.99 (0.74–1.32)	0.89 (0.62–1.27)	0.90 (0.70–1.17)
Systolic blood pressure (crude model)	1.69 (1.47–1.95)‡	1.48 (1.22–1.80)‡	1.91 (1.55–2.36)‡	1.40 (1.18–1.65)
Model 1	1.38 (1.17–1.63)‡	1.24 (0.99–1.56)	1.48 (1.15–1.91)†	1.10 (0.91–1.33)
Model 2	1.36 (1.15–1.61)†	1.19 (0.95–1.50)	1.48 (1.14–1.91)†	1.10 (0.90–1.33)
Log UAC (crude model)	1.61 (1.41–1.85)‡	1.56 (1.30–1.87)‡	1.70 (1.40–2.07)‡	1.75 (1.52–2.01)‡
Model 1	1.44 (1.23–1.69)‡	1.42 (1.15–1.74)†	1.51 (1.20–1.89)†	1.57 (1.33–1.84)‡
Model 2	1.31 (1.11–1.55)†	1.33 (1.06–1.66)*	1.33 (1.04–1.71)*	1.62 (1.36–1.94)‡

Model 1, race, age, cigarette smoking (current, ever, never), exercise (>5 METS/h every week), income, and education; model 2, model 1 + other metabolic syndrome components (WC, HOMA, HDL, Trig, SBP).

*$P < 0.05$.

†$P < 0.01$.

‡$P < 0.001$.

CVD, all cardiovascular disease events; CHD, all coronary heart disease events; UAC, urine albumin–creatinine ratio; MET, metabolic equivalent; WC, waist circumference; HOMA, homeostasis model assessment; HDL, high-density lipoprotein; Trig, triglycerides; SBP, systolic blood pressure.

uniformly higher than EGIR-metabolic syndrome (0.575). AUCs for CHDA followed a similar trend.

Stroke. Males. The adjusted risk of stroke rose significantly with each SD rise in WC (50%), log HOMA (56%), SBP (117%), and log UAC (77%) (Table 4). The wider confidence intervals seen reflect the relatively smaller number of events noted in the population. When adjusted for all metabolic syndrome components together in the final model, only SBP and abdominal obesity showed a trend toward association. In men, stroke risk was predicted to a

Table 6. Gender-Stratified Multivariate Hazard Ratios of Clinical Outcomes for Various Metabolic Syndrome Definitions

	CVD (n = *206*)		*CHD* (n = *164*)		*Stroke* (n = *40*)		*Mortality* (n = *130*)	
Males	N	*HR (95% limits)*	N	*HR (95% limits)*	N	*HR (95% limits)*	N	*HR (95% limits)*
NCEP	106	2.90 (2.18–3.85)***	84	2.87 (2.08–3.96)***	22	2.96 (1.58–5.56)**	50	1.40 (0.96–2.03)
AHA	110	2.64 (1.98–3.51)***	87	2.61 (1.89–3.60)***	23	2.74 (1.45–5.17)**	53	1.29 (0.89–1.87)
WHO	107	2.16 (1.62–2.88)***	82	1.99 (1.44–2.76)**	25	3.04 (1.58–5.85)**	57	1.23 (0.85–1.77)
IDF	125	2.56 (1.91–3.44)***	97	2.37 (1.71–3.30)***	28	3.51 (1.76–7.00)**	68	1.50 (1.04–2.16)**
EGIR	77	1.82 (1.35–2.46)**	61	1.80 (1.28–2.52)**	17	2.16 (1.14–4.10)*	41	1.20 (0.81–1.79)
Con–IDF	135	2.92 (2.15–3.95)***	107	2.88 (2.05–4.04)***	29	3.55 (1.75–7.18)**	68	1.35 (0.94–1.95)
Con–AHA	129	2.92 (2.16–3.93)***	101	2.80 (2.01–3.92)***	29	3.96 (1.95–8.05)***	63	1.29 (0.89–1.87)
Females	N	*CVDA* (n = *116*)	N	*CHDA* (n = *68*)	N	*Stroke* (n = *49*)	*N*	*Mortality* (n = *94*)
NCEP	67	2.11 (1.41–3.15)***	41	2.43 (1.43–4.16)**	26	1.65 (0.90–3.00)	36	0.89 (0.58–1.39)
AHA	72	2.17 (1.45–3.27)***	43	2.46 (1.43–4.25)**	29	1.74 (0.95–3.18)	38	0.85 (0.55–1.31)
WHO	58	2.04 (1.37–3.06)**	34	2.17 (1.27–3.70)**	25	1.98 (1.08–3.62)*	35	1.03 (0.65–1.61)
IDF	73	1.91 (1.27–2.88)**	43	2.10 (1.21–3.62)**	30	1.59 (0.87–2.92)	38	0.70 (0.45–1.08)
EGIR	44	1.85 (1.23–2.79)**	24	1.66 (0.96–2.88)	19	1.81 (0.97–3.38)	27	1.20 (0.75–1.94)
Con–IDF	75	2.08 (1.37–3.14)**	45	2.45 (1.40–4.29)**	30	1.57 (0.86–2.89)	40	0.76 (0.49–1.17)
Con–AHA	74	2.10 (1.39–3.18)**	44	2.41 (1.39–4.20)**	30	1.67 (0.90–3.07)	40	0.79 (0.51–1.22)

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.0001$.

Analysis is adjusted for age, race, income, education, activity, cigarette smoking, low-density lipoprotein cholesterol. *N* = number of index events in the metabolic syndrome group.

CVD, all cardiovascular disease events; CHD, all coronary heart disease events; HR, hazard ratio; NCEP, National Cholesterol Education Program; AHA, American Heart Association; WHO, World Health Organization, IDF, International Diabetes Federation; EGIR, European Group for the Study of Insulin Resistance; Con, consensus.

similar extent by all metabolic syndrome definitions (OR = 3—4) except for EGIR, which exhibited a weaker association (HR, 2.16) (Table 6).

Females. Each SD increase in log HOMA, SBP, and log UAC was associated with a 33%, 48%, and 51% increase in strokes, respectively (Table 5). When adjusted for other metabolic syndrome components, only SBP and log UAC were noted to be associated with stroke. Stroke in females was best predicted by the WHO (HR, 1.98) definition in this study (Table 6).

Mortality. IDF-metabolic syndrome alone was associated with a modest but significant increase in risk of death in males (HR, 1.50). None of the usual metabolic syndrome components or definitions appeared to be associated with an increased risk of ACM in males or females in this study. It is noteworthy that microalbuminuria, which is a basic tenet of the WHO criteria, was associated strongly with all outcomes including ACM (irrespective of gender), even after being adjusted for other metabolic syndrome components.

Discussion

The data presented here allow us to draw the following conclusions in a gender-stratified, healthy multiethnic U.S. population:

1. The newer consensus criteria (Con-IDF and Con-AHA) correlate very well with IDF and AHA criteria, substantially with the NCEP criteria, and moderately with the EGIR and WHO criteria in both genders.
2. In men, all constitutive metabolic syndrome components are continuously and strongly associated with CVDA/CHDA on multivariate analyses. In women, on the other hand, HDL and triglycerides did not appear to be associated with short-term CVDA/CHDA risk.
3. Stroke risk in men is continuously associated with WC, insulin resistance, and SBP. In women, this association was noted only with insulin resistance and SBP.
4. Metabolic syndrome or any of its usual components were not associated with an adjusted risk of short-term all-cause mortality in either gender. The only exception to this observation was the IDF definition in men.
5. Regardless of gender, microalbuminuria was continuously and strongly associated with CVDA, CHDA, stroke, and ACM.
6. All metabolic syndrome definitions, including the consensus criteria, are more or less similarly associated with a higher risk of CVDA and CHDA outcomes in both genders, except the EGIR and WHO definition in males and EGIR alone in females, which were less predictive of events. Metabolic syndrome was noted to be strongly associated with risk of stroke only in males; a weaker but significant association with WHO-metabolic syndrome was noted in women.

Prevalence of metabolic syndrome

Our study noted a higher prevalence of metabolic syndrome as compared to prior population-based studies.[15,16] A previous study using the National Health and Nutrition Examination Survey (NHANES) data (1988–1994), noted a prevalence (NCEP-metabolic syndrome) of 21.8% and 23.7% in males and females, respectively, much lower than the 29.23% and 36.56% noted in the MESA cohort. The higher prevalence can be explained by the relatively older population studied and the increasing trends in obesity and WC in the U.S. population.[17,18] In fact, the average WCs noted in our study are similar to the NHANES data for the year 2001–2002.[18] It is also interesting to note that the prevalence of metabolic syndrome was higher in females in comparison to males in this study. Previous population-based studies have shown a slightly higher prevalence of metabolic syndrome in males. Studies have shown that obesity has risen rapidly in females over the past decade, with a 61% rise in obesity incidence between 1991 and 2000.[19] The NHANES data for 1999–2001 showed an increase prevalence of metabolic syndrome in females.[20] Therefore, the higher prevalence might be indicative of a nationwide obesity epidemic affecting females disproportionately. The higher prevalence of metabolic syndrome in Hispanics, as noted our study, has been previously reported.[20,21] The Con-IDF criteria were associated with the highest prevalence of metabolic syndrome.

Correlation between definitions

The agreement between metabolic syndrome definitions noted in this study is higher as compared to prior studies. The agreement between the serum insulin/HOMA-based WHO/EGIR criteria and the NCEP/AHA/IDF criteria (which do not require serum insulin/HOMA measurements) was somewhat higher in comparison to previous studies by Dekker et al.[22] and Lin et al.[23] performed in predominantly white and Chinese populations, respectively. The newer consensus criteria appeared to have excellent correlation with other existing definitions in this multiethnic sample. Correlation between definitions was typically better in females as compared with males, which is not surprising given that the cutoff for central obesity in females has been defined as a WC of 80 cm irrespective of race for a majority of metabolic syndrome definitions due to a dearth of race-specific literature.

Gender differences in outcomes

The adjusted association between metabolic syndrome and CVDA/CHDA appeared to be somewhat stronger in males as compared with females. Studies have been divided with regard to gender differential in the association between metabolic syndrome and outcomes. Some have shown a stronger association in males,[24] whereas others in females,[25] and yet others have reported a comparable risk of CVD in both genders.[22,26] The meta-analysis of seven population-based studies by Gami et al investigated gender disparities in metaboic syndrome and noted a higher risk associated with metabolic syndrome in women compared to men [relative risk (RR) 2.63 vs. 1.98, $P = 0.09$).[27] However, the majority of included studies analyzed homogeneous populations except for the Atherosclerosis Risk in Communities (ARIC) study, which included a higher number of minorities. Metabolic syndrome, irrespective of definition, was more strongly associated with stroke in men in our study. On the other hand, only the WHO criteria were weakly predictive of stroke in females. This is in contrast to the Framingham offspring study, where both men and women with metabolic syndrome ran a higher risk of stroke, with a stronger association noted in women.[28]

Metabolic syndrome components

It is interesting to note that two of the five metabolic syndrome components (triglycerides and HDL) were not predictive of CVDA/CHDA events in females. This contrasts with the findings of the British Women's Heart and Health Study, in which all components were associated with CVDA/CHDA events.[29] HDL and triglycerides did not predict stroke risk in the MESA cohort; these findings are similar to the Northern Manhattan Cohort Study (NOMAS), which investigated an identical population without history of CVD and did not find an association with baseline lipids.[30] This may be explained in part by the use of lipid-lowering drugs in the population, as suggested by the NOMAS investigators.

Abdominal obesity, insulin resistance, and hypertension, on the other hand, are well-known risk factors for stroke.[31–34] In our study, however, WC was found to be a predictor of stroke in males but not in females when adjusted for other risk factors.

Comparison of definitions in relation to outcomes

The San Antonio Heart Study, a large multiethnic prospective study, noted that the NCEP, IDF, and WHO criteria defined similar risks for CVD outcomes.[21] The Hoorn study investigators, on the other hand, noted that the HRs of fatal and nonfatal CVD as defined by the EGIR and WHO criteria were slightly lower in comparison to the NCEP definition. In the present study, all metabolic syndrome definitions that do not require measurement of IR (NCEP, AHA, IDF, and consensus criteria) appear to be equally good at predicting CVDA/CHDA.[22] The EGIR definition, on the other hand, showed weak associations with all outcomes in both genders, whereas the WHO definition showed strong associations with CVDA, CHDA, and stroke in women but weaker associations in men. The recently proposed consensus criteria appear to perform at least as well at predicting CVDA, CHDA, and stroke events in comparison to existing definitions.

The San Antonio Heart Study investigators noted that all-cause mortality was predicted significantly by NCEP-metabolic syndrome (HR, 1.47) but not WHO-metabolic syndrome.[21] The meta-analysis by Gami et al., which included 36 studies, showed a 60% increase in deaths associated with metabolic syndrome.[27] In contrast to prevalent data, none of the metabolic syndrome definitions (except IDF in men) appeared to be predictive of short-term mortality in our study. A previous study by Sundstrom et al. showed that the mortality differential associated with metabolic syndrome became apparent only after a period of 10–15 years of follow up.[35] Therefore, the weak association noted might plausibly be due to the relatively short follow-up in this study (4.1 years).

Finally, the Botnia and Framingham offspring study investigators noted a two-fold increase in risk of stroke in individuals with metabolic syndrome.[26,28] In a gender-stratified analysis, the ARIC study investigators noted a 96% increase in risk of stroke in women and a significant but lower risk of in men with metabolic syndrome (42% increase). In contradistinction, our study noted a three- to four-fold higher risk of stroke in men, whereas in women, only the WHO criteria significantly predicted stroke risk (HR, 1.98, 1.08–3.62). This finding probably reflects the inclusion of microalbuminuria in WHO criteria, a parameter strongly associated with stroke in our study.

Limitations and strengths

Potential limitations of our study include the relatively small number of cardiovascular events in our study cohort, resulting in wider confidence intervals for outcomes such as stroke. With accrual of additional events, these associations will likely strengthen and become more evident. Likewise, the small number of events also limits our ability to make race-specific recommendations. Studies on metabolic syndrome in the past have been varied with regard to inclusion or exclusion of diabetics from the study population. In this analysis, we did not exclude individuals with clinical diagnosis of diabetes, because our primary aim was to compare the predictive value of existing and newer metabolic syndrome definitions with respect to cardiovascular risk, regardless of diabetic status, in an attempt to broaden clinical applicability to a community-based population.

The comprehensive head-to-head comparative assessment of all existing definitions of metabolic syndrome vis-a-vis cardiovascular risk in a large, multiethnic, representative U.S. population may be viewed as a strength of our study. The Northern Manhattan and San Antonio Heart Study populations comprised a sizeable number of Hispanics, but did not include Chinese. The availability of all parameters required to define metabolic syndrome using various criteria, the minimal attrition, and reliable definition of study end points are other important assets of this study.

Conclusions

In this large multiethnic community-based population, we found the newly defined consensus criteria for metabolic syndrome to be equally predictive of cardiovascular events when compared to existing definitions. We also noted important gender differences in the association between metabolic syndrome definitions/components and cardiovascular outcomes.

Acknowledgments

The Multi-Ethnic Study of Atherosclerosis (MESA) is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the MESA Study investigators. This manuscript was prepared using a limited access dataset obtained from the NHLBI and does not necessarily reflect the opinions or views of the MESA or the NHLBI.

Author Disclosure Statement

The authors have nothing to disclose.

References

1. 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.
2. 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.
3. 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. 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.
5. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15: 539–553.
6. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006;23:469–480.
7. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). *Diabet Med* 1999;16:442–443.
8. Alberti KG, Eckel RH, Grundy SM et al. Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 200;120: 1640–1645.
9. Bild DE, Bluemke DA, Burke GL et al. Multi-ethnic study of atherosclerosis: Objectives and design. *Am J Epidemiol* 2002;156:871–881.
10. MESA Coordinating Center. *Multi-Ethnic Study of Atherosclerosis Field Center Manual of Operations*. Seattle, WA: University of Washington, January 5, 2001.
11. Matthews DR, Hosker JP, Rudenski AS et al. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–419.
12. 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) final report. *Circulation* 2002;106:3143–3421.
13. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159–174.
14. Cox D. Regression models and lifetables. *J R Stat Soc B* 1972;34:187–220.
15. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: Findings from the third National Health and Nutrition Examination Survey. *JAMA* 2002;287:356–359.
16. Meigs JB, Wilson PW, Nathan DM et al. Prevalence and characteristics of the metabolic syndrome in the San Antonio Heart and Framingham Offspring Studies. *Diabetes* 2003;52: 2160–2167.
17. Flegal KM, Carroll MD, Ogden CL et al. Prevalence and trends in obesity among US adults, 1999–2008. *JAMA* 2010; 303:235–241.
18. Li C, Ford ES, McGuire LC et al. Increasing trends in waist circumference and abdominal obesity among US adults. *Obesity (Silver Spring)* 2007;15:216–224.
19. Steinbaum SR. The metabolic syndrome: An emerging health epidemic in women. *Prog Cardiovasc Dis* 2004;46:321–336.
20. Ford ES. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. *Diabetes Care* 2005;28:2745–2749.
21. Lorenzo C, Williams K, Hunt KJ et al. The National Cholesterol Education Program–Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. *Diabetes Care* 2007;30:8–13.
22. Dekker JM, Girman C, Rhodes T et al. Metabolic syndrome and 10-year cardiovascular disease risk in the Hoorn Study. *Circulation* 2005;112:666–673.
23. Lin CC, Liu CS, Li CI et al. The relation of metabolic syndrome according to five definitions to cardiovascular risk factors—a population-based study. *BMC Public Health* 2009;9:484.
24. Wilson PW, D'Agostino RB, Parise H et al. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation* 2005;112:3066–3072.
25. 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.
26. Isomaa B, Almgren P, Tuomi T et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001;24:683–689.
27. Gami AS, Witt BJ, Howard DE et al. Metabolic syndrome and risk of incident cardiovascular events and death: A systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol* 2007;49:403–414.
28. Najarian RM, Sullivan LM, Kannel WB et al. Metabolic syndrome compared with type 2 diabetes mellitus as a risk factor for stroke: The Framingham Offspring Study. *Arch Intern Med* 2006;166:106–111.
29. Lawlor DA, Smith GD, Ebrahim S. Does the new International Diabetes Federation definition of the metabolic syndrome predict CHD any more strongly than older definitions? Findings from the British Women's Heart and Health Study. *Diabetologia* 2006;49:41–48.
30. Willey JZ, Xu Q, Boden-Albala B et al. Lipid profile components and risk of ischemic stroke: The Northern Manhattan Study (NOMAS). *Arch Neurol* 2009;66:1400–1406.
31. Suk SH, Sacco RL, Boden-Albala B et al. Abdominal obesity and risk of ischemic stroke: The Northern Manhattan Stroke Study. *Stroke* 2003;34:1586–1592.
32. Walker SP, Rimm EB, Ascherio A et al. Body size and fat distribution as predictors of stroke among US men. *Am J Epidemiol* 1996;144:1143–1150.
33. Pyorala M, Miettinen H, Halonen P et al. Insulin resistance syndrome predicts the risk of coronary heart disease and stroke in healthy middle-aged men: The 22-year follow-up results of the Helsinki Policemen Study. *Arterioscler Thromb Vasc Biol* 2000;20:538–544.
34. Lewington S, Clarke R, Qizilbash N et al. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903–1913.
35. Sundstrom J, Riserus U, Byberg L et al. Clinical value of the metabolic syndrome for long term prediction of total and cardiovascular mortality: Prospective, population based cohort study. *BMJ* 2006;332:878–882.

Address correspondence to:
Luis Afonso, M.D., FACC
Division of Cardiology
Wayne State University
Harper University Hospital
8 Brush, 3990 John R
Detroit, MI 48201

E-mail: lafonso@med.wayne.edu