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Comparison of different metabolic syndrome definitions and risks of incident cardiovascular events in the elderly

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ABSTRACT

The metabolic syndrome is associated with increased cardiovascular risk, and its prevalence increases with age. Various definitions of the metabolic syndrome exist, but whether some definitions are more predictive of future cardiovascular events in the elderly is unclear. We compared the risk of incident cardiovascular events in elderly individuals at least 65 years old from the Cardiovascular Health Study with and without the metabolic syndrome as defined by the European Group for the Study of Insulin Resistance (EGIR), National Cholesterol Education Program (NCEP)/American Heart Association (AHA), American Association of Clinical Endocrinologists, International Diabetes Federation (IDF), and modified World Health Organization (WHO) criteria (n = 3390). Participants were without baseline diabetes or cardiovascular disease. Except for EGIR, all definitions of the metabolic syndrome were significantly associated with increased risk of incident cardiovascular (coronary or cerebrovascular) events. Adjusted hazard ratios (HRs) for risk of incident cardiovascular events as defined by the modified WHO, NCEP/AHA, American Association of Clinical Endocrinologists, and IDF criteria ranged from 1.153 ($P = .045$) for NCEP/AHA to 1.314 ($P < .001$) for IDF, with 95% confidence interval (CI) ranging from 1.003 to 1.503. Adjusted HR for EGIR was 1.087 (95% CI, 0.908-1.301; $P = .362$). Similarly, all definitions of the metabolic syndrome were significantly associated with incident coronary events except for the EGIR definition. Only the modified WHO definition was associated with increased risk for cerebrovascular events (adjusted HR, 1.301; 95% CI, 1.038-1.631; $P = .022$). Although all metabolic syndrome definitions except EGIR were associated with total cardiovascular events and coronary events, only the modified WHO definition was also associated with risk of cerebrovascular events.

1. Introduction

The metabolic syndrome is a cluster of cardiovascular risk factors [1] that has been associated with increased risks of cardiovascular events [2-4]. Different definitions of the metabolic syndrome exist, including definitions from the World Health Organization (WHO) [5], the National Cholesterol Education Program Third Adult Treatment Panel (NCEP-ATPIII) [6], the European Group for the Study of Insulin Resistance (EGIR) [7], the American Association of Clinical Endocrinologists (AACE) [8],

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and the International Diabetes Federation (IDF) [9]. The NCEP-ATPIII definition has subsequently been updated by the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) [1] and most recently in a joint interim statement that serves to harmonize the definition of metabolic syndrome [10]. The core components for defining metabolic syndrome among these definitions are similar. However, cutoff values, as well as relative importance of these core components, differ among the definitions. For example, the IDF definition focuses on the importance of abdominal obesity, requiring its presence as defined by ethnic-specific waist circumferences [9].

The metabolic syndrome may be especially important in the elderly. Risk of cardiovascular events increases with age, as does the prevalence of the metabolic syndrome [11]. In a US population from the National Health and Nutrition Examination Survey III, the prevalence of the metabolic syndrome increased from 7% in the 20- to 29-year age group to 44% for those aged 60 to 69 years [12]. Most studies evaluating the relationship between the metabolic syndrome and risk of cardiovascular events have been conducted in middle-aged individuals [3,13,14]. Although recent studies indicate positive associations between the metabolic syndrome and risk of cardiovascular events in the elderly [11,15,16], these relationships are weaker than those reported in middle-aged individuals, probably because age itself is an independent predictor of cardiovascular risk. In addition, limited and conflicting data exist as to which definition of the metabolic syndrome should be used in the elderly, who are already at higher risk of cardiovascular events because of their age [17,18].

The purpose of this study is to evaluate the relationship between the metabolic syndrome, as defined by the different available criteria, and incident cardiovascular events among an exclusively elderly US population (≥65 years of age).

2. Methods

2.1. Data source

We used data from the Cardiovascular Health Study (CHS), which is a population-based prospective cohort study conducted by NHLBI to evaluate risk factors associated with cardiovascular disease and stroke in adults 65 years and older. The design and purpose of the CHS have been reported previously [19]. The CHS participants were randomly chosen from a list of Medicare-eligible individuals in 4 US locations: Allegheny County, Pennsylvania; Forsyth County, North Carolina; Sacramento County, California; and Washington County, Maryland [20]. Subjects in the initial cohort were recruited between 1989 and 1990 and consisted of 5201 men and women. Subjects were eligible for the study if they were (1) 65 years or older, (2) noninstitutionalized individuals, (3) expected to remain in the area for at least 3 years, and (4) able to give informed consent. Between 1992 and 1993, 687 African American subjects were added to the original cohort. During each participant's interview and examination at baseline, demographic data, current medications, blood pressure, history of medical conditions, lifestyle habits, fasting blood chemistry, echocardiography, electrocardiography, and carotid ultrasonography were obtained. Anthropometric measurements were also obtained for each patient that included weight, height, and waist and hip circumferences. Standing height was measured as the distance from the sole of the feet to the top of the head with the participant standing erect and looking straight ahead. Weight was measured with the participant wearing underwear and examination suit, but no shoes, minus the weight of the suit. Waist circumference was measured at the level of the umbilicus, and hip circumference was measured at the level of maximum protrusion of the gluteal muscles, with the participant standing. Self-reported physical activity over the previous 2 weeks was assessed using the modified Health Interview Survey [21]. Physical activity intensity was classified as (1) no exercise, (2) light activity (walking at a casual pace at <2 mph), (3) moderate intensity (physical activity at <6 metabolic equivalent tasks), and (4) high intensity (physical activity at >6 metabolic equivalent tasks). Alcohol use and smoking history were assessed by standardized CHS questionnaires. The University of Vermont's Central Blood Analysis Laboratory analyzed each participant's blood chemistry, which was based on blood drawn in the morning after an overnight fast. Further details on laboratory and blood sampling procedures, examinations, and quality assurance protocols have been published previously [19,20,22,23]. Subjects were followed with annual clinic visits and interim 6-month phone calls for a total of 11 years, followed by telephone follow-ups only from years 11 to 15. For this analysis, we used only the first 11 years of validated event data, as data for cardiovascular events after year 11 were obtained from telephone self-report without validation from medical records. The CHS was approved by the University of Washington's Data Coordinating Center and the investigational review boards at all locations. Analysis of CHS data for the purpose of comparing definitions of metabolic syndrome in its prediction of incident cardiovascular events was approved by the Virginia Commonwealth University Institutional Review Board.

2.2. Inclusion and exclusion criteria

For the analyses in the current report, all participants with a baseline interview and examination, and follow-up or censoring information were included. Subjects were censored if they completed the follow-up observation but did not develop any cardiovascular events or if they were lost to follow-up before the observation period was complete. Individuals with the following characteristics were excluded: (1) presence of *diabetes* at baseline (as defined by a fasting glucose ≥126 mg/dL, or a 2-hour glucose of ≥200 mg/dL after a 75-g oral glucose challenge, or use of antidiabetic agents); (2) history of *coronary heart disease*, as defined by a previous occurrence of myocardial infarction (MI), coronary revascularizations, angina, or silent MI (as documented by electrocardiogram findings) reported at baseline; (3) heart failure; and (4) history of stroke or transient ischemic attack (TIA). Individuals with prevalent cardiovascular disease and diabetes were excluded because they were already at risk for cardiovascular events regardless of the presence of the metabolic syndrome.

2.3. Definitions of the metabolic syndrome

We defined the presence of the metabolic syndrome among nondiabetic individuals in the CHS cohort using the following 5

Table 1 – Definitions of the metabolic syndrome

	NCEP-ATPIII [1]	Modified WHO [5]	EGIR [7]	AACE [8]	IDF [9]
Required	–	Required: insulin resistance[a] in top 25%; glucose ≥110 mg/dL; 2-h glucose ≥140 mg/dL	Required: insulin resistance[a] (or fasting insulin) in top 25%	"High risk for insulin resistance" or BMI >25 kg/m^2 or waist ≥102 cm (men) or ≥88 cm (women)[b]	Ethnic-based waist: European: ≥94 cm (men) or ≥80 cm (women); Asian: ≥90 cm (men) or ≥80 cm (women)
No. of abnormalities	≥3 of:	And ≥2 of:	And ≥2 of:	And ≥2 of:	And ≥2 of:
Glucose	≥100 mg/dL		≥110 mg/dL	≥110 mg/dL; 2-h glucose ≥140 mg/dL	≥100 mg/dL
HDL cholesterol	<40 mg/dL (men), <50 mg/dL (women), or on medications	<35 mg/dL (men), <40 mg/dL (women)	<40 mg/dL	<40 mg/dL (men), <50 mg/dL (women)	<40 mg/dL (men), <50 mg/dL (women), or on medications
		And/or	**And/or**		
Triglycerides	≥150 mg/dL or on medications	≥150 mg/dL	≥180 mg/dL	≥150 mg/dL	≥150 mg/dL or on medications
Obesity	Waist: ≥102 cm (men), ≥88 cm (women)	Waist to hip ratio: >0.9 (men), >0.85 (women); or BMI ≥30 kg/m^2	Waist: ≥94 cm (men), ≥80 cm (women)		
Hypertension	≥130/85 mm Hg or on medications	≥140/90 mm Hg	≥140/90 mm Hg	≥130/85 mm Hg	≥135/85 mg Hg or on medications
Other:		Microalbuminuria[c]: albumin excretion >20 μg/min			

HDL indicates high-density lipoprotein.
[a] Insulin resistance was calculated by the HOMA-IR. The upper quartile included individuals with HOMA-IR values >3.87.
[b] In this study, BMI and waist circumference cut points were used to define individuals at "high risk for insulin resistance."
[c] Microalbuminuria was not used in the definition of the metabolic syndrome in this study because it was not assessed in CHS.

definitions (Table 1): (1) modified WHO [5], (2) EGIR [7], (3) AACE [8], (4) IDF [9], and (5) NCEP as modified by AHA/NHLBI [1]. For the modified WHO criteria, we did not include microalbuminuria, which was in the original WHO definition, because microalbuminuria was not assessed at baseline in CHS (Table 1). The NCEP criteria as modified by AHA/NHLBI identified the same individuals as would the most recent harmonization criteria jointly proposed by IDF, NHLBI, AHA, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity [10]. This is due to the fact that the central obesity cutoffs for North America are the same for both the NCEP/AHA and the new harmonization criteria.

Insulin resistance was measured using the homeostasis model assessment (HOMA-IR). The upper quartile of values derived from HOMA ([fasting glucose {millimoles per deciliter}] × fasting insulin {micro–international units per milliliter}]/22.5) [7,24] among nondiabetic individuals in the CHS cohort was used as a cutoff for the definition of insulin resistance.

Body mass index (BMI) was obtained by dividing the subject's weight in kilograms by the height squared in meters. The participants were classified into 3 groups based on their BMI: those with BMIs less than 25 kg/m^2 were defined as having normal weight, those whose BMIs were between 25 and 29.9 kg/m^2 were considered overweight, and those whose BMIs of at least 30 kg/m^2 were considered obese [25,26].

2.4. *Outcomes*

The primary outcome of this study was the occurrence of any first cardiovascular event, defined as any incident MI, silent MI, TIA, stroke, angina, claudication, coronary artery bypass surgery, angioplasty, or death due to coronary disease during the 11 years of follow-up. These outcomes were adjudicated by the CHS Events Subcommittee. The algorithms for identifying claudication [27], MI [28], stroke [23], and deaths due to coronary disease [28] have been reported previously. Secondary outcomes for this report included incident coronary events and cerebrovascular events evaluated separately. For the secondary outcomes, coronary events included MI, coronary artery bypass surgery, angioplasty, angina, silent MI, and deaths due to coronary disease. Cerebrovascular events included stroke or TIA.

2.5. *Statistical analysis*

Descriptive statistics for participants with and without the metabolic syndrome as defined by the WHO (modified), EGIR, NCEP/AHA, AACE, and IDF definitions were performed. We evaluated the relationship between presence of the metabolic syndrome defined by these 5 criteria and incident cardiovascular events using Cox regression analyses. Other important risk factors for cardiovascular events were evaluated for inclusion as a covariate in the multivariate model if the univariate P values were <.2 or as a confounder if its inclusion in the multivariate model changed the hazard ratio (HR) estimate by more than 10%. Preliminary multivariate models were compared using –2 log likelihood tests before a final multivariate model was constructed. The final model included the following covariates: sex, age, race, smoking status, alcohol use, exercise intensity, income, family history of

early cardiovascular events, low-density lipoprotein (LDL) concentrations, and aspirin use. Although race was not found to be significant in the univariate analyses, it was included as a covariate in the final model, as race is an established confounder in other studies [29]. Hazard ratios and their associated 95% confidence intervals (CIs) were calculated. *P* values < .05 were considered statistically significant. All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

3. Results

3.1. *Demographics of the cohort*

Of the original 5888 subjects in the CHS cohort, a total of 3390 subjects were included for analyses. Reasons for exclusion included diabetes (n = 1327); history of coronary heart disease (n = 1123), heart failure (n = 262), stroke (n = 244), and TIA

Table 2 – Baseline characteristics among 3390 nondiabetic elderly individuals with the metabolic syndrome as defined by the NCEP/AHA, modified WHO, EGIR, AACE, and IDF criteria

	NCEP/AHA	Modified WHO	EGIR	AACE	IDF
No. of subjects with MetS	1170	1171	543	1126	1330
Sex: male	398 (34%)	494 (42%)	212 (39%)	429 (38%)	473 (36%)
Age (y)	73 ± 5	73 ± 5	72 ± 5	73 ± 5	73 ± 5
65-74	944 (80%)	923 (79%)	448 (82%)	907 (81%)	1060 (80%)
75-84	195 (17%)	207 (18%)	85 (16%)	183 (16%)	231 (17%)
≥ 85	31 (3%)	41 (3%)	10 (2%)	36 (3%)	39 (3%)
Race					
White	1027 (88%)	1056 (90%)	479 (88%)	1040 (92%)	1174 (88%)
Black	136 (11%)	107 (9%)	61 (11%)	79 (7%)	147 (11%)
Other	7 (1%)	8 (1%)	3 (1%)	7 (1%)	9 (1%)
BMI (kg/m^2)	29 ± 4	28 ± 4	29 ± 4	29 ± 3	28 ± 4
Normal, <25	224 (19%)	287 (25%)	66 (13%)	101 (9%)	250 (19%)
Overweight, 25-29	565 (48%)	541 (46%)	273 (50%)	695 (62%)	697 (52%)
Obese, >30	380 (33%)	341 (29%)	204 (37%)	330 (29%)	382 (29%)
TG (mg/dL)	172 ± 79	159 ± 78	172 ± 80	164 ± 76	160 ± 70
HDL (mg/dL)	48 ± 13	51 ± 14	48 ± 12	50 ± 13	50 ± 14
LDL (mg/dL)	137 ± 36	135 ± 35	133 ± 34	138 ± 35	137 ± 36
SBP (mm Hg)	140 ± 20	141 ± 20	138 ± 19	140 ± 20	141 ± 19
DBP (mm Hg)	72 ± 11	72 ± 11.0	72 ± 11	72 ± 11	72 ± 11
Fasting glucose (mg/dL)	104 ± 9	104 ± 9	104 ± 9	103 ± 10	104 ± 9
Family Hx of MI	331 (31%)	334 (31%)	150 (30%)	313 (30%)	369 (30%)
Aspirin use[a]	344 (29%)	349 (30%)	162 (30%)	333 (30%)	392 (30%)
Smoking:					
Never	576 (49%)	559 (48%)	255 (47%)	553 (49%)	637 (48%)
Former	444 (38%)	481 (41%)	227 (42%)	447 (40%)	527 (40%)
Current	148 (13%)	129 (11%)	61 (11%)	124 (11%)	164 (12%)
Exercise intensity					
No exercise	103 (9%)	93 (8%)	44 (8%)	90 (8%)	114 (9%)
Low intensity	585 (50%)	579 (50%)	277 (51%)	552 (49%)	651 (49%)
Moderate Intensity	374 (32%)	379 (32%)	170 (31%)	373 (33%)	428 (32%)
High Intensity	108 (9%)	119 (10%)	52 (10%)	110 (10%)	137 (10%)
Alcohol					
0 drink/d	578 (50%)	546 (47%)	286 (53%)	538 (48%)	634 (48%)
<1 drink/d	435 (38%)	438 (38%)	194 (36%)	421 (38%)	495 (38%)
<2 drinks/d	58 (5%)	69 (6%)	18 (3.5%)	64 (6%)	66 (5%)
<3 drinks/d	40 (3%)	44 (4%)	22 (4%)	41 (4%)	60 (4%)
>3 drinks/d	47 (4%)	61 (5%)	18 (3.5%)	49 (4%)	63 (5%)
Income					
<$5000	49 (4%)	56 (5%)	26 (5%)	41 (4%)	55 (4%)
$5000-$7999	107 (10%)	101 (9%)	46 (9%)	93 (9%)	113 (9%)
$8000-$11 999	131 (12%)	124 (11%)	73 (14%)	124 (12%)	146 (12%)
$12 000-$15 999	180 (16%)	159 (14%)	76 (15%)	165 (15%)	205 (16%)
$16 000-$24 999	229 (21%)	227 (20%)	99 (19%)	223 (21%)	252 (20%)
$25 000-$34 999	182 (16%)	175 (15%)	88 (17%)	178 (16%)	205 (16%)
$35 000-$49 999	106 (10%)	119 (11%)	49 (9%)	109 (10%)	124 (10%)
>$50 000	133 (12%)	152 (14%)	64 (12%)	138 (13%)	162 (13%)

Data are mean ± SD or frequency (% participants). MetS indicates metabolic syndrome; TG, triglycerides; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hx, history.

[a] Aspirin use was defined as present if use is greater than 2 days in the previous 2 weeks.

(n = 161); and lack of follow-up or censor information (n = 89). Some individuals had more than one excluding conditions. Of the individuals included for analyses, the prevalence of the metabolic syndrome as defined by NCEP/AHA, modified WHO, EGIR, AACE, and IDF were 34.5%, 34.5%, 16.0%, 33.2%, and 39.2%, respectively.

The demographic and metabolic characteristics of subjects fulfilling each definition of metabolic syndrome were similar (Table 2). For each definition, most of the participants with metabolic syndrome (approximately 80%) were between 65 and 74 years of age. They were most likely overweight (BMI between 25 and 29 kg/m^2) or obese (BMI ≥30 kg/m^2). In addition, rates and proportions of common cardiovascular and demographic factors, such as sex, ethnicity, lipid values, blood pressure, fasting glucose, family history of MI, and aspirin use, were similar among the different definitions. The majority of participants with the metabolic syndrome never smoked, exercised at a low intensity, and reported no alcohol intake. The family income for most participants was less than $25 000.

3.2. *Cardiovascular events*

The number of first cardiovascular events (including both coronary and cerebrovascular events) among individuals with and without the metabolic syndrome according to each definition is shown in Table 3. In univariate analyses, the WHO (modified), NCEP/AHA, IDF, and AACE definitions of metabolic syndrome were all significantly associated with an increased risk of incident cardiovascular events. However, the metabolic syndrome as defined by the EGIR criteria was not associated with increased risk (P = .427).

We next performed multivariate analyses to evaluate if relationships between metabolic syndrome and cardiovascular events were independent of other major cardiovascular risk factors. Results of the multivariate analyses were similar to those of univariate models. The WHO (modified), NCEP/AHA, IDF, and AACE definitions of the metabolic syndrome were all significantly associated with increased risks of incident cardiovascular event in the multivariate models. However, metabolic syndrome as defined by the EGIR criteria was not associated with increased risk (P = .785).

3.3. *Coronary and cerebrovascular events*

Univariate and multivariate HRs of coronary and cerebrovascular events were separately analyzed as secondary end points (Table 3). As in total cardiovascular events, all definitions of the metabolic syndrome, except for EGIR, were significantly associated with increased risk of incident coronary events in univariate and multivariate models. In contrast to coronary events, only the AACE and modified WHO criteria were significantly associated with cerebrovascular events in univariate analyses, with HRs of 1.275 (95% CI, 1.037-1.569; P = .022) and 1.398 (95% CI, 1.139-1.715; P = .001), respectively. After adjustments for other major cardiovascular risk factors, only the modified WHO criteria remained significant (HR = 1.301; 95% CI, 1.038-1.631; P = .022).

Table 3 – Number and risk of any cardiovascular events, coronary events, and cerebrovascular events among elderly individuals with and without the metabolic syndrome as defined by various definitions

	Any cardiovascular events				Coronary events				Cerebrovascular events			
	Univariate		Multivariate[a]		Univariate		Multivariate[a]		Univariate		Multivariate[a]	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
NCEP-AHA	1.153 (1.017-1.308)	.026	1.153 (1.003-1.326)	.045	1.246 (1.061-1.463)	.007	1.273 (1.067-1.519)	.007	1.068 (0.866-1.319)	.538	1.004 (0.794-1.269)	.975
Modified WHO	1.244 (1.098-1.41)	<.001	1.197 (1.044-1.373)	.010	1.245 (1.06-1.462)	.008	1.193 (1.001-1.421)	.049	1.398 (1.139-1.715)	.001	1.301 (1.038-1.631)	.022
EGIR	1.069 (0.907-1.259)	.4268	1.087 (0.908-1.301)	.362	1.058 (0.857-1.307)	.598	1.033 (0.819-1.302)	.785	1.194 (0.919-1.553)	.185	1.207 (0.902-1.615)	.205
AACE	1.243 (1.097-1.41)	<.001	1.261 (1.098-1.449)	.001	1.285 (1.094-1.509)	.002	1.305 (1.094-1.557)	.003	1.275 (1.037-1.569)	.022	1.256 (0.998-1.581)	.053
IDF	1.300 (1.15-1.469)	<.001	1.314 (1.149-1.503)	<.001	1.355 (1.158-1.585)	<.001	1.387 (1.168-1.648)	<.001	1.196 (0.976-1.467)	.085	1.123 (0.896-1.406)	.315

[a] Adjusted for sex, age, race, smoking status, alcohol use, exercise intensity, income, family history, LDL, and aspirin use.

4. Discussion

The metabolic syndrome is highly prevalent in elderly individuals [11,12] and has been associated with future cardiovascular events [2-4]. Currently, various definitions of the metabolic syndrome exist. Whether all of these definitions equally identify individuals at risk has been seldom studied, especially among North American elderly individuals, in whom the risk of cardiovascular events is highest. We sought to compare the various definitions of the metabolic syndrome and their association with risks of future cardiovascular events, including coronary and cerebrovascular events.

In this report using data from the CHS study, the AACE, NCEP/AHA, and modified WHO definitions identified similar number of elderly individuals with the metabolic syndrome. Using the EGIR definition, less participants were identified as having the metabolic syndrome, which is consistent with prior studies suggesting that the requirement of the presence of insulin resistance in this definition leads to a conservative estimate for the prevalence of the metabolic syndrome [17,30,31]. The highest prevalence of metabolic syndrome resulted from the IDF definition. Other studies have found similar results, proposing that the difference in prevalence may come from the IDF definition's requirement of the presence of abdominal obesity rather than insulin resistance [31,32].

We found that most definitions of the metabolic syndrome (NECP/AHA, modified WHO, AACE, and IDF) except EGIR were associated with increased risk of total cardiovascular and coronary events in US elderly individuals. This finding is consistent with existing literature. In a study based on a nondiabetic Finnish elderly population, all the above definitions of the metabolic syndrome were predictive of cardiovascular mortality [18]. Our results are also similar to those of a study involving a population of British women aged 60 to 79 years, in whom the IDF, WHO, and NCEP-ATPIII definitions of the metabolic syndrome were modestly associated with coronary heart disease (age-adjusted HR of 1.32 [95% CI ,1.03-1.70; $P = .03$], 1.45 [95% CI, 1.00-2.10; $P = .04$], and 1.38 [95% CI, 1.00-1.93; $P = .05$], respectively) [33].

The EGIR definition was not associated with any increased cardiovascular risk, including coronary and cerebrovascular risk, in both the univariate and adjusted analyses. Previous conflicting findings exist for the ability of the EGIR definition to predict cardiovascular risk. For example, the Hoorn Study of Dutch men and women aged 50 to 75 years (mean, 60 years) compared the cardiovascular risk among NCEP-ATPIII, WHO, EGIR, and AACE metabolic syndrome definitions and concluded that the metabolic syndrome, regardless of the definition, was associated with a higher risk of nonfatal and fatal cardiovascular disease [30]. In this current report with a North American elderly population with a mean age of 72 years, the EGIR definition was not significantly associated with increased cardiovascular risk. Our findings corroborate results from a similar investigation involving elderly nondiabetic Finns [18]. Although EGIR in that study was initially found to be associated with increased cardiovascular disease mortality, the association disappeared after exclusion of subjects who already had cardiovascular disease at baseline, as in our study [18].

Additional studies may be needed to confirm our finding of the inability of the EGIR definition to predict cardiovascular risk. It is possible that, with increased age, risk factors other than insulin resistance and fasting insulin, which are required components in the EGIR definition, may play a more important role in cardiovascular risk among the elderly. Although the WHO definition also requires the presence of insulin resistance, presence of abnormal fasting or 2-hour glucose (Table 1) also satisfies this requirement. Impaired fasting glucose alone has been reported to carry a higher risk of cardiovascular events than the combined components of metabolic syndrome [34]; and this may explain why the modified WHO, but not the EGIR definition, is significantly associated with increased cardiovascular risk in this study. It is also possible that fasting insulin concentrations, a component of HOMA-IR used to assess insulin resistance in this study, may not be important in predicting cardiovascular risk in the elderly. Indeed, we performed sensitivity analyses using the upper 25th percentile of fasting insulin levels in lieu of insulin resistance for the EGIR definition (data not shown). Results of the sensitivity analysis did not alter the conclusion of the lack of relationship between the EGIR definition and any incident cardiovascular, coronary, or cerebrovascular events.

Only the metabolic syndrome as defined by the modified WHO criteria also predicted increased risk of cerebrovascular events in our study. Several prospective studies have evaluated the value of different metabolic syndrome definitions to predict stroke, but they varied with respect to the characteristics of the study population. In an elderly nondiabetic Finnish population, the WHO, EGIR, NCEP-ATPIII, and IDF definitions, but not the AACE criteria, significantly predicted stroke (HR range, 1.49-1.80) [35]. However, persons with previous MIs were included in the aforementioned analysis. In a nondiabetic middle-aged (mean age, 58 years) Swedish population without history of coronary or cerebrovascular events, the NCEP, but not the EGIR or IDF definitions, was associated with increased risk of stroke after adjusting for age and sex [17]. Hence, the contribution of metabolic syndrome as defined by various definitions to the risk of stroke may depend on the demographics of the population studied.

The strengths of this study included a prospective follow-up design, length of follow-up, validated methods for defining cardiovascular events, and the fact that participants were closely followed. Importantly, this study evaluated a distinctly elderly population from the United States. This added to the translational potential of this work by addressing a practical knowledge gap. Currently, most studies evaluating the risk of cardiovascular events conferred by the metabolic syndrome involve middle-aged individuals. Risk estimates reported in these studies cannot be readily used in the elderly, as age itself is also an independent predictor of cardiovascular risk and may dilute the risk associated with the metabolic syndrome in this age group. By studying an elderly US population, we were able to provide risk estimates of different metabolic syndrome definitions in this distinct population whose risk for cardiovascular events is already high independent of the presence of the metabolic syndrome.

There are several limitations in this present study. One limitation is that the CHS participants only included Medicare-eligible subjects that are noninstitutionalized. The exclusion of older adults living in nursing homes may underestimate the prevalence of the metabolic syndrome and subjects at risk for incident cardiovascular events. Furthermore, this also decreased the number of individuals older than 85 years that could be included in the analyses. Another limitation is that a modified WHO definition was used. We were not able to include microalbuminuria in the WHO criteria, as microalbuminuria assessments were not performed in CHS. In addition, the euglycemic clamp to measure insulin resistance was used in the original WHO criteria; in our study, we used HOMA-IR. Nonetheless, HOMA-IR has been found to closely resemble the glucose clamp technique in assessing insulin sensitivity and was reliable when used in large-scale studies with fasting blood samples to measure insulin sensitivity [36].

In summary, the results of the present study show that all metabolic syndrome definitions with the exception of EGIR are associated with increased risks of cardiovascular events in elderly subjects. Only the modified WHO definition significantly predicts all 3 end points: total cardiovascular events, coronary events, and cerebrovascular events. Further studies will be required to confirm whether the modified WHO definition is more clinically useful than other definitions in classifying the presence of the metabolic syndrome in the elderly.

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Conflicts of Interest

All authors have nothing to declare.

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