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An Exploratory Analysis of Criteria for the Metabolic Syndrome and Its Prediction of Long-term Cardiovascular Outcomes

The Hoorn Study

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Studies have shown an increased risk of cardiovascular outcomes with the metabolic syndrome, but information on predictive properties of the National Cholesterol Education Program Adult Treatment Panel 3 (NCEP) criteria is sparse. The authors used data from the Hoorn population-based study in the Netherlands including 2,484 participants aged 50–75 years examined in 1989 and followed for cardiovascular morbidity and mortality through 2000 to assess NCEP criteria, excluding known diabetes or cardiovascular disease. Cluster analyses explored whether NCEP identifies a mixture of heterogeneous groups. For each gender, participants meeting NCEP criteria seemed to be divided into clusters distinguished primarily by triglycerides or high density lipoprotein cholesterol. Cutpoints for components predicting cardiovascular events using classification and survival tree methodology varied by endpoint and gender, but Cox model hazards ratios were relatively comparable regardless of cutpoints (range: 1.3–2.5). Clear gradation in risk of cardiovascular outcomes was evident with increasing number of components, with statistically elevated risk for $\geq$3 (NCEP) components in men but for $\geq$2 components in women. Exploratory analyses of alternative metabolic syndrome criteria suggest cardiovascular risk estimates comparable to those derived by using NCEP, but criteria evaluating risk on more of a continuum would potentially allow consideration of alternative definitions by gender or for patients with other risk factors.

cardiovascular diseases; metabolic syndrome X; morbidity; mortality

Abbreviations: CART, classification and regression tree; HDL, high density lipoprotein; NCEP, National Cholesterol Education Program Adult Treatment Panel 3; WHO, World Health Organization.

Metabolic syndrome has received a great deal of attention over the past few years, fueled in part by increasing recognition of the syndrome and a proposed definition published in the National Cholesterol Education Program Adult Treatment Panel 3 (NCEP) guidelines (1). Although many publications assessing the prevalence of the syndrome and its association with cardiovascular morbidity and mortality appeared previously, such research applied at least 10 different definitions of the syndrome (2), including those proposed by the World Health Organization (WHO) in 1998 (3) and 1999 (4), the European Group for the Study of Insulin Resistance (EGIR) group in 2002 (5, 6), and the American Association of Clinical Endocrinologists (7). The recently proposed definitions have been quickly embraced by researchers who have published on the prevalence of metabolic syndrome nationally in the United States (8–11), in American women (12), in special ethnic populations in the United States (13–16) and Canada (17), in Mexico (18), and in European (6, 19–21) and Asian (22) countries. In addition, investigators have recently reported on the association of the metabolic syndrome with incident diabetes (14, 15, 23–25) and cardiovascular morbidity and mortality (11, 16, 19, 24–29).

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This research is further supported by work associating the metabolic syndrome with carotid atherosclerosis (30, 31) or coronary artery calcification (29, 32, 33).

Several investigators have compared the NCEP definition with the WHO or a modified WHO definition (9, 13, 20, 23, 33–35). Estimates of prevalence using different definitions have varied substantially by ethnic subgroup and culture, and discordance in groups of individuals identified by WHO and NCEP has been reported in some studies (13). The few reports that have compared predictive properties of the NCEP and WHO definitions for incident diabetes or coronary heart disease have been somewhat inconsistent. The clear variation among different definitions even within similar populations, as well as the heterogeneity of the population meeting such criteria, leads to the question of which definition is most appropriate for predicting risk, particularly if risk is a continuum. To our knowledge, none of the definitions derived by the expert panels used empirical multivariate data to formulate criteria that would maximize predictive properties for identifying patients at greatest risk of cardiovascular events.

We used data from the Hoorn population-based study in the Netherlands (34, 36, 37) to assess the effect of varying cutpoints for the NCEP metabolic syndrome components and their association with cardiovascular morbidity and mortality using classification tree, survival tree, and hierarchical and nonparametric clustering techniques. We also explored alternative approaches that may better characterize risk as a continuum.

MATERIALS AND METHODS

Study design

The population-based Hoorn Study was designed and initiated to study glucose abnormalities in the Hoorn community in the Netherlands, as described previously (34, 36–37). Briefly, subjects aged 50–75 years were randomly selected from a population registry for the town of Hoorn in 1989; of the 3,496 Caucasian subjects invited to participate, 2,484 (71 percent) agreed. At baseline, after informed consent was obtained, triglycerides, total cholesterol, and high density lipoprotein (HDL) cholesterol were measured from fasting blood samples by using enzymatic techniques (36). Low density lipoprotein cholesterol was estimated with the Friedewald formula when triglycerides were less than or equal to 8.0 mmol/liter. Fasting plasma glucose and insulin measures were also obtained. Duplicate measures of systolic and diastolic blood pressures were determined in the right arms of patients, after they had rested for 5 minutes in the seated position, by using a random-zero sphygmomanometer, and average values were used in the analysis. Waist circumference was measured at the iliac crest. Body mass index was calculated as body weight in kilograms divided by the square of height in meters (kg/m^2). Medical history, including prior cardiovascular disease and lifestyle habits such as smoking, alcohol intake, and physical activity, was assessed by using a standardized questionnaire. McCauley's insulin sensitivity index (38) was calculated as exp[2.63 – 0.28 ln(insulin) – 0.31 ln(triglycerides)]. Homeostatic model assessment–insulin resistance was also calculated as a measure of insulin resistance (39).

Metabolic syndrome

Metabolic syndrome was defined by using the definition proposed by NCEP (1) as being present if at least three of the following criteria were met: 1) waist circumference greater than 40 inches (102 cm) in men and greater than 35 inches (88 cm) in women, 2) systolic blood pressure 130 mmHg or higher or diastolic blood pressure 85 mmHg or higher or use of antihypertensive medications, 3) HDL cholesterol less than 40 mg/dl in men and less than 50 mg/dl in women, 4) triglycerides 150 mg/dl or higher, and 5) fasting plasma glucose concentration 110 mg/dl or higher.

Ascertainment of cardiovascular morbidity and mortality

Mortality data as of January 1, 2000, were collected by using the mortality register of the municipality of Hoorn, and cause-of-death code according to the *International Classification of Diseases*, Ninth Revision was extracted from participants' medical records and the hospital of Hoorn (34, 37). For participants who relocated outside of Hoorn during the follow-up period, vital status was obtained from their new municipality. Cardiovascular death was defined as death due to diseases of the circulatory system or sudden death with cause unknown. Information about nonfatal cardiovascular events defined as coronary heart disease, congestive heart failure, transient ischemic attack or stroke, or peripheral atherosclerotic disease was obtained from the medical records of the local hospital of Hoorn (37). About 25 percent of participants did not provide permission to access their hospital files or had moved out of Hoorn and did not have complete follow-up data, while 17 participants (0.6 percent) were lost to follow-up. Such patients were excluded from our analyses of nonfatal outcomes.

For all analyses, patients with diabetes ($n = 210$) or a history of cardiovascular disease ($n = 470$) defined by self-reported history of acute myocardial infarction, coronary bypass surgery or angioplasty, angina pectoris, transient ischemic attack or stroke, intermittent claudication, or the use of nitrates were excluded. Analyses were performed for cardiovascular mortality and a composite endpoint including cardiovascular mortality and nonfatal events (cardiovascular events).

Statistical methods

Baseline characteristics of study patients were described separately by gender. Given the putative heterogeneity in populations meeting the NCEP criteria for metabolic syndrome, cluster analysis techniques were applied to data for metabolic syndrome participants by gender to explore whether the NCEP criteria define a ''mixture'' of distinct homogeneous ''clusters'' that may confer differential cardiovascular risk. Initially, a nonparametric density estimation procedure known as the *k*th nearest neighbor approach was used (40). This technique is less prone to identifying

clusters of equal size or variance compared with other classic clustering techniques and has been shown to be more useful in detecting irregularly shaped clusters. To determine the number of clusters suggested by the data, graphic tools were used to examine where the number of clusters was constant across a wide range of k (40), an approach supported by simulations (41). Clusters identified by this technique were examined using a Wilcoxon rank test to identify which variables most distinguished the groups. A hierarchical group average clustering technique was used to corroborate results (42).

Classification and regression tree (CART) (Salford Systems, San Diego, California) methodology was used to explore variation in cutpoints, by gender and endpoint, on the factors comprising NCEP criteria for metabolic syndrome that predict risk of cardiovascular events (43). This technique uses recursive partitioning to develop hierarchical binary decision trees to predict events by considering every possible cutpoint on every variable at any particular node in the tree. Cutpoints at each node that best distinguished patients with and without cardiovascular events were determined by node impurity criteria, calculated as squared probabilities of cardiovascular events or not at that node, subtracted from 1. Details of this technique and comparison with logistic regression and neural networks have been published elsewhere (43–45).

Cross-validation techniques (split sample approach using a random two thirds of observations to develop a model, a random one third to test; and v-fold cross-validation techniques) were used to reduce bias in the misclassification error rate and as a tool for pruning. Results presented in this paper are based on the v-fold cross-validation technique, for which the full data set is randomly divided into $k = 10$ subsets, with model development and pruning conducted iteratively omitting each of k subsets, to reduce the potential bias in the data-driven technique. CART methodology was performed on each variable individually as well as by considering all variables simultaneously, mainly as a tool to assess variation in cutpoints in predicting different endpoints by gender, rather than developing a specific tree algorithm with predictive properties.

Because CART considers the variables only hierarchically and does not consider later splits in the tree when determining appropriate binary splits at a given node, multivariate adaptive regression splines models were used to support these results (46, 47). This technique fits spline regression models and determines the location of ''knots'' (cutpoints) where the slope of the regression line may change. The technique considers all variables simultaneously, although variables are not modeled if they do not contribute significantly to predicting the outcome. To account for time to event in such analyses, a survival tree function (*tssa*) was also implemented by using an S-PLUS function to corroborate these results (48).

Using approximate cutpoints derived from the CART and multivariate adaptive regression splines results, proportional hazards regression models described the relation of various combinations of components of the metabolic syndrome with cardiovascular events. In addition, to allow a gradation of risk, analyses of the number of components present, as well as a weighted score derived from models including individual components of the metabolic syndrome, were conducted.

RESULTS

Approximately 55 percent of the participants were female, and the average age was 61 years (table 1). Mean waist circumference was larger in men (94.3 (standard deviation, 9.1) cm) than in women (85.8 (standard deviation, 9.8) cm), as expected, while average systolic and diastolic blood pressures were comparable across genders. HDL cholesterol levels were higher on average in women (57.7 (standard deviation, 14.0) mg/dl) than in men (46.6 (standard deviation, 12.1) mg/dl), and median triglyceride levels were 124 mg/dl (quartiles: 88.6, 159.4) in men and 106.3 (quartiles: 79.7, 150.6) in women. Fasting plasma glucose concentrations were slightly higher in men (99.1 (standard deviation, 9.1) mg/dl) than in women (96.0 (standard deviation, 9.6) mg/dl).

Exploratory, nonparametric clustering techniques applied to participants' data meeting NCEP criteria suggested two clusters (figure 1), and significant differences were apparent between clusters regarding all metabolic syndrome components except for waist circumference in men and for waist circumference and blood pressures in women, suggesting that the clusters were separable. The identified clusters differed on homeostatic model assessment–insulin resistance for only men but were statistically different for McCauley's index (38) for both genders. The variable showing the most distinction between clusters was triglycerides for both genders, with differences of 43–49 percent. Group average hierarchical clustering identified primary clusters distinguished mainly by triglycerides and HDL cholesterol for both genders. Triglycerides had the greatest coefficient of variation of the metabolic syndrome components.

Interestingly, binary regression trees on cross-sectional data to distinguish those with and without the metabolic syndrome also chose triglycerides or HDL cholesterol as the first binary split of the tree for both genders, suggesting that these individual components are the most discriminating for the NCEP criteria. The variables selected next in the binary tree to distinguish those with and without the metabolic syndrome varied by gender. Such analyses suggest that all components may not be equally weighted, as did hierarchical tree model analyses considering all components simultaneously.

When the individual metabolic syndrome components were used separately, cutpoints identified by regression tree techniques to predict cardiovascular events as well as cardiovascular mortality varied by gender and by endpoint but in general were comparable to the NCEP criteria (table 2). For example, cutpoints for diastolic and systolic blood pressures generally ranged from 62 to 83 mmHg and from 139 to 158 mmHg, respectively. Cutpoints for fasting plasma glucose ranged from 87 to 104 mg/dl, while waist circumference cutpoints were 73–78 cm for women and 101 cm for men. For HDL cholesterol, cutpoints ranged from 52 to 57 mg/dl for women and from 44 to 67 mg/dl for men, and

TABLE 1. Characteristics of the Hoorn cohort without diabetes or coronary heart disease at baseline, the Netherlands, 1989–2000*

	Men ($n = 631$)	Women ($n = 760$)
Age (years)	60.75 (7.08)	60.93 (7.34)
Waist circumference (cm)	94.29 (9.09)	85.83 (9.75)
Systolic blood pressure (mmHg)	134.44 (19.25)	133.64 (20.71)
Diastolic blood pressure (mmHg)	83.44 (9.55)	80.85 (10.33)
HDL† cholesterol (mg/dl)	46.62 (12.14)	57.65 (13.98)
Triglycerides (mg/dl)	124.00 (88.57, 159.43)	106.29 (79.72, 150.58)
Fasting plasma glucose (mg/dl)	99.12 (9.08)	95.96 (9.64)
Fasting insulin (μU/m)	76.35 (61.80, 96.65)	72.60 (58.40, 93.80)
HOMA-IR†	390.08 (263.01)	352.67 (211.11)
McCauley's index‡	0.93 (0.18)	0.98 (0.19)
Current smoker (%)	34.6	27.9
Cardiovascular events (fatal and nonfatal) (%)	22.7	13.1
Cardiovascular death (%)	6.8	3.6

* Data followed by values in parentheses are presented as mean (standard deviation), except for triglycerides and fasting insulin, where the median (quartile 1, quartile 3) is given.

† HDL, high density lipoprotein; HOMA-IR, homeostatic model assessment–insulin resistance.

‡ McCauley's index = exp[2.63 − 0.28 ln(insulin) − 0.31 ln(triglycerides)], per McCauley et al. (38).

cutpoints for triglycerides were highly variable, ranging from 66 to more than 200 mg/dl, depending on the endpoint. A survival tree function generally corroborated these results. For women, cutpoints for systolic blood pressure (138.5 mmHg) and fasting plasma glucose level (91 mg/dl) were identified; for men, analyses suggested cutpoints for systolic blood pressure (187 and 153 mmHg), waist circumference (101 cm), and fasting plasma glucose (104 mg/dl) in predicting the cardiovascular events. For mortality, systolic blood pressure (192.5 mmHg), fasting plasma glucose

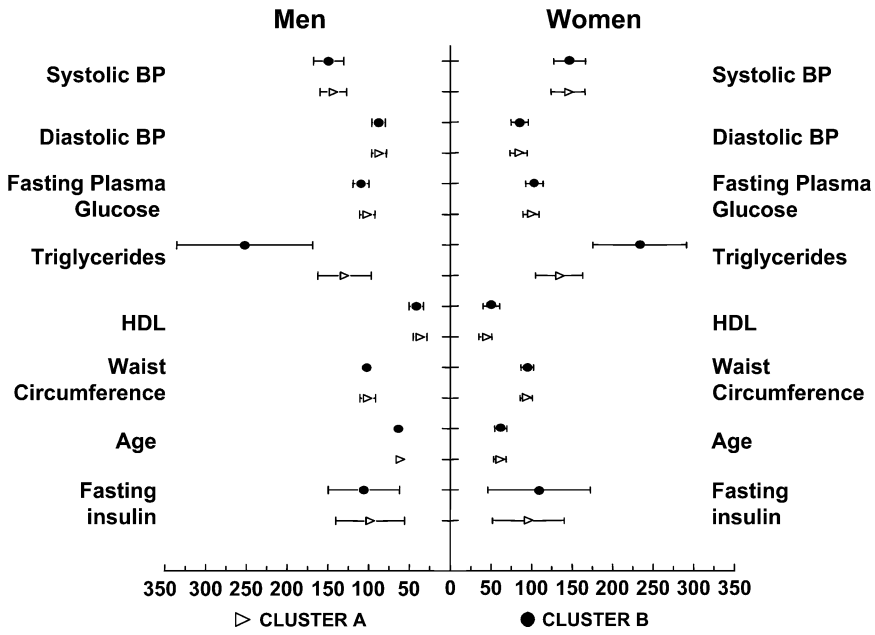

FIGURE 1. Descriptive statistics for two clusters of identified participants (arbitrarily labeled A and B) in the Hoorn population-based study initiated in the Netherlands in 1989 with follow-up through 2000, who met the National Cholesterol Education Program Adult Treatment Panel 3 criteria for metabolic syndrome, by gender. Scales extend to the left for men and to the right for women. Range for men and women is the maximum across all variables; the range for most variables is narrower. BP, blood pressure; HDL, high density lipoprotein (cholesterol).

TABLE 2. Results of classification and regression tree analyses exploring thresholds for components of the metabolic syndrome to predict cardiovascular events and mortality in the Hoorn Study, the Netherlands, 1989–2000

Parameter	Cardiovascular events		Cardiovascular mortality	
	Men	Women	Men	Women
Components univariately				
Diastolic blood pressure (mmHg)	76	62	75.75	82.75
Systolic blood pressure (mmHg)	152	138.5	138.5	157.5
Triglycerides (mg/dl)	385/164*,†	146	66.4	120
HDL‡ cholesterol (mg/dl)	67	56.7	44	51.6
Fasting plasma glucose (mg/dl)	104	87.4	103.6	87.4
Waist circumference (cm)	100.7	73	101.4	77.9
All components simultaneously§				
Diastolic blood pressure (mmHg)	70.5_4	—¶	83.5_2	—¶
Systolic blood pressure (mmHg)	153.5_2	138.5_1; 128.5_4	122_6	157.5_1; 107.5_4; 170_6
Triglycerides (mg/dl)	—¶	—¶	—¶	190_5
HDL cholesterol (mg/dl)	58.8_3	52_3; 62_5	44_4	52_2; 44_3
Fasting plasma glucose (mg/dl)	—¶	91_2	—¶	92.8_7
Waist circumference (cm)	100.7_1; 92.65_5	—¶	101.4_1; 80.8_3; 91.4_5	—¶

* Significant nonlinearity in relation to the endpoint.
† The value following / was a secondary cut.
‡ HDL, high density lipoprotein.
§ Subscripts for models with all components considered simultaneously (bottom half of the table) refer to order of entry in the tree-based model.
¶ Not entered into the model (cutpoint not identified).

(104 mg/dl), and waist circumference (112 cm) were again most predictive for men. However, for women, the resulting survival tree for mortality was more complex, involving waist circumference (112 cm), systolic blood pressure (158 or 170 mmHg), triglycerides (146 mg/dl), diastolic blood pressure (87 or 97 mmHg), and HDL cholesterol (59 or 53 mg/dl), depending on the branch of the tree.

When all components of the metabolic syndrome were considered simultaneously, however, some failed to enter the hierarchical tree and no cutpoints were identified, again suggesting unequal weighting of components in predicting cardiovascular events. When cutpoints were identified, the actual thresholds varied by endpoint and gender but, for the most part, did not dramatically differ from those identified by considering individual variables univariately. Application of multivariate adaptive regression spline models showed inconsistent results in terms of variables entering the model, cutpoints, and nonlinearity in predicting cardiovascular events. When the survival function was used and all components were fitted simultaneously, cutpoints generally ranged from 90 to 108 mmHg for diastolic blood pressure; 152 to 192 mmHg for systolic blood pressure; 90 to 104 mg/dl for fasting plasma glucose; and, for waist circumference, 87 to 112 cm for women and 99.5 to 101 cm for men. Cutpoints for triglycerides varied widely for men but fluctuated around 146 mg/dl for women. However, in most cases, the sensitivity and specificity in predicting cardiovascular events were not much better than 0.5.

Estimates using NCEP-like definitions that applied the different thresholds suggested by CART and multivariate adaptive regression splines showed age-adjusted hazard ratios for cardiovascular events in the range of 1.3 to 2.2 for men, with most of the estimates in the same general range as those for NCEP. For women, estimates applying different thresholds were generally higher (2.2–2.5) than those using the NCEP criteria.

Simultaneous testing of dummy variables for one, two, three, and four or five components relative to no components in proportional hazards models suggested statistically significant elevations in risk for all but two components (borderline for one component) in men and for all but one component in women (table 3). Hence, the number of components associated with elevated cardiovascular risk varied by gender, but the risk increased with increasing number of components ($p < 0.001$) for both genders (figure 2).

Proportional hazards models including dichotomous components of the metabolic syndrome as covariates suggested that obesity and hypertension in men and hypertension and HDL cholesterol in women might be weighted nearly twofold higher in a scoring algorithm than the other components. However, a categorical score weighted accordingly was not materially better than the simple unweighted number of components in predicting outcomes for either gender (table 3). In proportional hazards models with all components included simultaneously as continuous variables, only blood pressures in men and blood pressures and HDL cholesterol ($p = 0.07$) in women were significant in predicting cardiovascular events after adjusting for age and smoking.

Finally, a score that incorporated several risk categories for each metabolic syndrome component was statistically

TABLE 3. Proportional hazards model results in predicting cardiovascular events* for various definitions of the metabolic syndrome and traditional risk scores in the Hoorn Study, the Netherlands, 1989–2000

	Men				Women			
	HR†	95% CI†	Adjusted HR‡	95% CI	HR	95% CI	Adjusted HR‡	95% CI
NCEP† definition	1.82	1.26, 2.65	1.59	1.09, 2.34	2.14	1.41, 3.23	1.77	1.17, 2.69
No. of components§	1.30	1.12, 1.51	1.23	1.06, 1.43	1.42	1.22, 1.65	1.30	1.12, 1.51
c statistic	0.58				0.64			
1	1.76	0.99, 3.14	1.63	0.91, 2.92	1.71	0.78, 3.74	1.19	0.54, 2.62
2	1.46	0.79, 2.71	1.29	0.70, 2.41	2.78	1.31, 5.91	1.81	0.84, 3.89
3	2.30	1.22, 4.35	1.86	0.97, 3.55	3.28	1.48, 7.25	2.11	0.94, 4.70
4 or 5	4.11	1.96, 8.64	3.34	1.58, 7.06	4.97	2.23, 11.1	2.96	1.31, 6.70
Categorical score§,¶	1.11	1.05, 1.18	1.09	1.03, 1.15	1.16	1.10, 1.23	1.14	1.07, 1.20
c statistic	0.61				0.68			
Categorical score§,¶ collapsed into three categories	1.56	1.12, 2.17	1.36	0.97, 1.90	2.27	1.61, 3.21	1.36	0.97, 1.90

* Comparable results were found for cardiovascular mortality.

† HR, hazard ratio; CI, confidence interval; NCEP, National Cholesterol Education Program Adult Treatment Panel 3.

‡ Adjusted for age and smoking.

§ Hazard ratio is per-unit increase in score, except for the score collapsed into three categories, where the lowest category serves as the reference for the hazard ratio.

¶ A weighted score of the number of components, with waist circumference and hypertension in men or hypertension and high density lipoprotein cholesterol in women weighted twice as much as the other components.

significantly associated with cardiovascular events for both genders, and collapsing the score into three risk categories showed hazard ratios of 1.4–2.2 for men and 1.4–1.9 for women. However, hazard ratio estimates and *c* statistics were generally comparable to the much simpler number of categories in predicting outcomes.

DISCUSSION

Since Reaven coined the clustering of cardiovascular risk factors as ''syndrome X,'' a massive literature has accumulated. However, the lack of a universally accepted definition (1, 2) and the cultural differences in prevalence and associated long-term risk of cardiovascular morbidity, mortality, and diabetes made it difficult to interpret the diverse published studies. Publication of the recent definitions (1, 3, 6) of metabolic syndrome provided some accepted standards around a working definition, but there is still a substantial variation in how these definitions are applied and in findings across different populations.

Although the elevated risk of cardiovascular disease and diabetes associated with the clustering of cardiovascular risk factors formed the basis for establishing the metabolic syndrome criteria, few studies had prospectively established these associations in representative populations when the criteria were established (19). Recent studies have documented an increased risk of mortality (20, 26, 27), with relative risks ranging from 1.4 to 3.4 for the NCEP criteria, as well as cardiovascular events (12, 14, 16, 26), including one report on this same Hoorn cohort (34). In some studies, the increased cardiovascular risk does not appear to exceed that predicted by the individual components (11, 16, 34).

To our knowledge, classic nonparametric and hierarchical clustering techniques or tree-based methodologies have not been applied to assess the association of metabolic syndrome with cardiovascular events. Such techniques can be useful in easily identifying thresholds or algorithms to predict an outcome of interest. However, given their data-driven nature and the instability that can result with rarer events, cross-validation is critical. Many researchers have used factor analysis that generally supports two to four factors. A recent confirmatory factor analysis suggested that the metabolic syndrome was comprised primarily of the insulin/glucose and obesity factors, followed by dyslipidemia and, to a lesser extent, blood pressure (49). The association between hypertension and metabolic syndrome has been challenged, although elevated blood pressure in combination with insulin resistance may be integral to the development of cardiovascular disease (50, 51). The metabolic syndrome criteria have been limited to factors that appear to contribute the most robust evidence from prior studies, and they exclude the potential fibrinolytic, inflammatory, and procoagulant factors; hyperuricemia; and endothelial dysfunction that also have been suggested as part of the clustering. We could not conduct analyses to explore whether such factors contribute to the prediction of cardiovascular events because of a lack of such measurements in the full Hoorn cohort.

The currently proposed consensus panel definitions dichotomize continuous variables, count the components present, and apply an algorithm (presence of three of five, or insulin resistance plus two components) to define the metabolic syndrome criteria. The cutpoints for individual components appear to have been established by expert

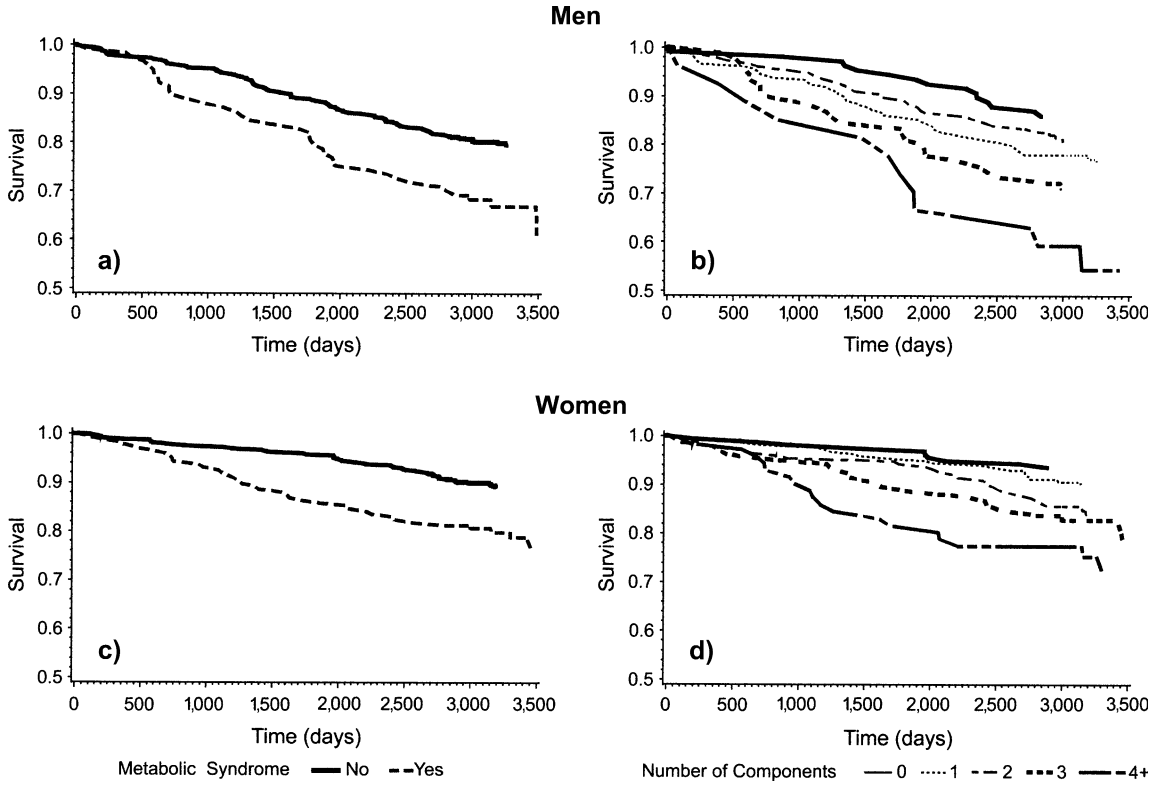

FIGURE 2. Kaplan-Meier survival curves for the composite cardiovascular endpoint: a) men by metabolic syndrome (no/yes), b) men by number of components of the syndrome (0, 1, 2, 3, 4+), c) women by metabolic syndrome (no/yes), and d) women by number of components of the syndrome (0, 1, 2, 3, 4+), Hoorn population-based study initiated in the Netherlands in 1989 with follow-up through 2000.

consideration of components individually, without necessarily accounting for intercorrelations among them; published empirical analysis assessing which cutpoints and definitions predict risk have been lacking. The predictive properties of these definitions may depend on the nature and severity of the population being studied, the outcomes being predicted, the culture-specific prevalence of various components, the appropriateness of cutpoints for the specific population, and the pathophysiologic relation of the components to atherosclerosis. Based on this cohort, our analyses within gender showed variable cutpoints across the endpoints assessed and with different statistical techniques, and, in some cases, no cutpoint was readily apparent because of risk being a continuum. In many cases, cutpoints seemed intuitive and fairly comparable to NCEP's, although rarely were the cutpoints entirely consistent across endpoints and techniques. For fasting plasma glucose, cutpoints were generally lower than the 110 mg/dl originally used to define impaired fasting glucose levels for both men and women, supporting the recent lowering of the threshold from 110 to 100 mg/dl (52, 53). The thresholds for waist circumference were surprisingly close to the 102 cm (men) and 88 cm (women) proposed, particularly in light of the known cultural differences and variability with such measurements. Diastolic blood pressure cutpoints were generally 75–90 mmHg for men and 85–90 mmHg for women, while systolic blood pressure cutpoints varied from 130 mmHg upward and, in some cases, were not at all clear.

Nearly all researchers who have assessed the metabolic syndrome in association with cardiovascular events have weighted the individual components equally. Our analyses support unequal weighting of the individual components of the metabolic syndrome in terms of predicting cardiovascular events, as others have reported (11, 14, 16). The different weighting of components and cutpoints suggested by gender may be driven partially by gender differences in nonfatal versus fatal events and the underlying association of the metabolic components with such events. However, an NCEP-like score giving greater weight to certain components yielded results comparable to those obtained when the unweighted definition was used. Derivation of the appropriate weights for a weighted score could vary by outcome considered, study, and culture, making application of such weighted scoring impractical. A categorical score that summed categories instead of dichotomies of each component gives greater weight to more severe measures on each component but also showed comparable predictive properties. Such scores appeared to be fairly insensitive to cutpoints applied. Scores substituting body mass index for waist circumference were comparable in predicting cardiovascular events.

The increasing risk of both cardiovascular events and diabetes with increasing number of components of the

metabolic syndrome has been shown by several studies (12, 16, 24, 28, 34, 54) and is intuitive, because risk is a continuum and not dichotomous. Prior investigators have found that combinations of three or more components tend to occur more commonly than expected by chance (55, 56). Our results further suggest that the elevation in risk may differ by gender (statistically significant for men with three or more and for women with two or more components). Hence, using the number of components to reflect a gradation in risk may be more useful for clinicians in evaluating patients and considering therapeutic alternatives and lifestyle changes, as previously suggested (34), and may allow different criteria to be applied for women or patients with other risk factors, if warranted.

The dichotomous metabolic syndrome criteria were not intended to be used to monitor patients' health status over time, nor have the reproducibility and reliability of the criteria been reported to our knowledge. The expert panels establishing these criteria appeared to focus on criteria to help detect patients at higher cardiovascular risk, who may not be identified by using more traditional risk tools. However, the metabolic syndrome criteria have been shown to be even more strongly predictive of diabetes (15, 23, 25), and insulin resistance is thought to underlie these criteria, despite the lack of a more direct measure of insulin resistance or hyperinsulinemia in the NCEP criteria. Direct measures of insulin resistance are not practical on a routine basis, although surrogates such as homeostatic model assessment–insulin resistance are becoming increasingly well accepted. One study showed that the components most strongly associated with insulin resistance, according to a modified insulin suppression test (55), were obesity (body mass index) and triglycerides, whereas the component with the weakest association was fasting plasma glucose concentration followed by systolic blood pressure, a finding supported by our previous analyses (34). Reilly et al. (33) recently showed that measures of insulin resistance significantly contributed beyond metabolic syndrome in explaining the variation in coronary calcification. This finding questions whether a surrogate measure of insulin resistance should be part of the definition (as in the WHO definition) or whether a definition should be derived by simultaneously predicting cardiovascular events and insulin resistance in various population-based studies. However, the WHO definitions that incorporate insulin resistance have not consistently shown a stronger relation to cardiovascular outcomes. Finally, whether other factors should be included as part of the NCEP criteria warrants further study.

Consensus expert panels might be informed by epidemiologic and statistical analyses of multiple databases in forming consensus-panel definitions, with an evidence-based approach analogous to that applied to evaluating interventions. Although currently proposed definitions of the metabolic syndrome are reasonable, a consortium of researchers in the relevant field with prospective data could provide empirical analyses from multiple sources to help guide expert panels in formulating definitions, with attention to practical issues; predictive properties for key outcomes; and treatment implications for targeting therapy.

Analyses presented in this paper were based on a cohort of subjects from the Hoorn region of the Netherlands, who were followed for 10–12 years regarding cardiovascular morbidity and mortality. The number of subjects in the cohort who would now meet the metabolic syndrome criteria is not known but, given the rise in obesity, diabetes, and metabolic syndrome worldwide, is likely underestimated. Our techniques assessed cutpoints associated with cardiovascular events and not their ''appropriateness.'' In some cases, it may be more helpful to identify cutpoints at an earlier stage. Although the homogeneous nature of this population could be considered a strength of our study in assessing associations of the metabolic syndrome with cardiovascular events, caution should be used in generalizing these results to other populations and cultures with different characteristics and lifestyles, especially given that sedentary lifestyle and obesity presumably play a strong role in the etiology of this syndrome.

In conclusion, alternative criteria to NCEP's for the metabolic syndrome are associated with an elevated risk of cardiovascular morbidity and mortality, with hazard ratios in the same general range as NCEP's but varying by gender, outcome, and definition. Criteria evaluating the risk of metabolic syndrome on more of a continuum would potentially allow consideration of alternative definitions by gender or for patients who have other risk factors.

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