Prognostic Impact of Metabolic Syndrome by Different Definitions in a Population With High Prevalence of Obesity and Diabetes

The Strong Heart Study

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OBJECTIVE — This study analyzed which definition of the metabolic syndrome is more predictive of cardiovascular events in both diabetic and nondiabetic members of a population-based sample.

RESEARCH DESIGN AND METHODS — A 10-year, longitudinal follow-up of the Strong Heart Study cohort has been evaluated. The analysis included 3,945 participants (2,384 female) with complete data (1,700 with diabetes and 1,468 with arterial hypertension) for evaluation of metabolic syndrome. Those with prevalent cardiovascular disease were excluded ($n = 287$, of whom 127 were female). Prevalence of metabolic syndrome was assessed based on the World Health Organization (WHO), the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III, and International Diabetes Federation (IDF) definitions. The main outcome was 10-year incidence of combined fatal and nonfatal cardiovascular events, including stroke, coronary heart disease, and congestive heart failure.

RESULTS — Fatal and nonfatal cardiovascular events occurred in 1,120 participants. After adjusting for age, sex, and diabetes, metabolic syndrome by all definitions was significantly associated with higher incidence of cardiovascular events (all $P < 0.0001$). In nondiabetic individuals, incident cardiovascular event rates were about 30–40% higher in those with metabolic syndrome, without a significant difference among definitions ($0.03 < P < 0.001$), and remained significant in WHO and NCEP ATP III definitions even after further adjustment for obesity, hypertension, and low HDL cholesterol. In the diabetic group, metabolic syndrome risk for cardiovascular events was greatest using the WHO definition ($P < 0.002$ vs. other models).

CONCLUSIONS — In individuals without diabetes, metabolic syndrome is associated with incident cardiovascular disease, especially with WHO and NCEP ATP III definitions. Metabolic syndrome also predicts higher cardiovascular event rates in diabetic participants, a prediction that is greatest using the WHO definition.

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The metabolic syndrome represents clusters of cardiovascular risk factors, assuming that cardiovascular risk is amplified more than is expected from the effect of single risk factors (1). Many studies support the utility of this definition (2,3), but others have questioned the incremental utility of this approach (4).

An element of potential confusion concerning the real prognostic utility of defining metabolic syndrome is the availability of several definitions (5–9), reflecting different strategies, either identifying a main characteristic as a necessary factor (5,7,9) associated with other variable risk factors or accepting varied combinations of characteristics (6,8). Other differences may also be important, including partition values and methods to define abnormalities.

At present, few data exist comparing the correlates and prognostic significance of the definitions of metabolic syndrome in the same population. Accordingly, we compared the ability of the most used definitions of metabolic syndrome to predict cardiovascular events in the Strong Heart Study (SHS) cohort.

RESEARCH DESIGN AND METHODS

— The SHS is a population-based cohort study of cardiovascular risk factors and disease in 4,549 American Indians from three communities in Arizona, seven in Southwestern Oklahoma, and three in South and North Dakota, as extensively described (10–14). Participants seen during the baseline exam, in 1989–1992, were representative of the source population (15).

For the present analysis, individuals with prevalent cardiovascular disease

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Abbreviations: HOMA, homeostasis model assessment; IDF, International Diabetes Federation; NCEP ATP, National Cholesterol Education Program Adult Treatment Panel; SHS, Strong Heart Study; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Definition of metabolic syndrome according according to the WHO, NCEP ATP III, and IDF*

Factor	WHO (main criterion + 2 factors)*	ATP III (any combination of 3 factors)	IDF (main criterion + 2 factors)
BMI (kg/m^2)	>30	—	—
Abdominal obesity (men/women)	Waist-to-hip ratio >0.9/0.85	Waist >102/88 cm	**Waist >94/80 cm†**
Triglycerides (mg/dl)	≥150	≥150	≥150
HDL cholesterol (mg/dl) (men/women)	<35/39	<40/50	<40/50
Blood pressure (mmHg)	≥140/≥90	≥130/≥85	≥140/>90 or >130/>85
HOMA‡	**>4.3**	—	—
Type 2 diabetes	**Present**	—	Present
Fasting glucose (mg/dl)	**≥110**	≥110	≥100
Fasting insulin	—	—	—
Urinary albumin excretion	≥20 μg/min or ≥30 mg/g creatinine	—	—

Sine qua nonfactors are in bold. *According to the WHO, either BMI or abdominal obesity represents one criterion. †Ethnic group waist circumference (as measure of central obesity): Europid men ≥94 and women ≥80 cm; South Asian men ≥90 and women ≥80 cm; Chinese men ≥90 and women ≥80 cm; and Japanese men ≥85 and women ≥90 cm. Ethnic South and Central American populations use South Asian recommendations until more specific data are available. Sub-Saharan African populations use European data until more specific data are available. Eastern Mediterranean and Middle East (Arab) populations use European data until more specific data are available. ‡According to the WHO, HOMA, type 2 diabetes, and fasting glucose are alternatives, fulfilling one criterion.

(n = 287, 127 of whom were female) were excluded. Prevalent and incident cardiovascular events (cardiovascular death, stroke, congestive heart failure, myocardial infarction, and coronary heart disease [coronary angiography, combination of typical symptoms with positive treadmill tests or abnormal imaging stress test, or revascularization procedures]) were confirmed by the SHS mortality and morbidity committees, using specified criteria for causes of fatal and nonfatal cardiovascular events (16).

Diabetic participants were included; participants with fasting triglyceride levels >750 mg/dl were excluded. Thus, 3,945 participants (2,384 women) without prevalent cardiovascular disease and available data (1,700 with diabetes and 1,468 with hypertension) were included in the analysis.

Laboratory tests and definitions of metabolic syndrome

Fasting plasma glucose and lipid profile were measured by standard methods (12). Diabetes (fasting plasma glucose ≥126 mg/dl or antidiabetes treatment) and impaired fasting glucose (≥110 mg/dl) were diagnosed by 1997 American Diabetes Association recommendations (17). Obesity was classified based on the 1998 National Institutes of Health guidelines (18) (BMI ≥30 kg/m^2). Central fat distribution was based on waist circumference and defined in relation to sex-specific cutoff points used in the different definitions examined in this study (Table 1). For the International Diabetes Federation (IDF) definition, the values proposed for Europids have been adopted. A random urine sample was used to measure albumin and creatinine (11).

Table 1 shows the criteria used to define metabolic syndrome by three guidelines: those by the World Health Organization (WHO) (5,9), the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III (6), and the IDF (9). Insulin-glucose homeostasis for the WHO definition was estimated by the homeostasis model assessment (HOMA) equation (19). Based on the WHO recommendation, a partition value for HOMA index was arbitrarily determined in the nondiabetic SHS participants as the lower boundary of the highest tertile (4.3). Thus, insulin resistance status was defined as the presence of type 2 diabetes or fasting glucose ≥110 mg/l or HOMA index >4.3. Hypertension was defined by Joint National Committee VII criteria (blood pressure ≥140/90 mmHg or use of antihypertensive treatment).

Statistical analysis

Data were analyzed using SPSS (version 12.0; SPSS, Chicago, IL). Data are expressed as means ± SD. All variables deviating from normal distribution were log transformed before parametric statistics. The urinary albumin-to-creatinine ratio is presented as median (interquartile range). An indicator variable was included for the three field centers: Arizona, South and North Dakota, and Oklahoma. Participants were categorized into groups according to the presence of metabolic syndrome, defined by each definition.

The 10-year relative risk of combined fatal and nonfatal cardiovascular events

Table 2—*Metabolic syndrome by different definitions (see Table 1): concordance and differences in blood pressure and urinary albumin-to-creatinine ratio*

			Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)		Urinary albumin/creatinine ratio	
Prevalence of metabolic syndrome	Men	Women	No MetS	MetS	No MetS	MetS	No MetS	MetS
WHO	48	53	122 ± 16	133 ± 20	75 ± 9	79 ± 10	6.60 (3.40–12.5)	28.18 (7.62–153.74)
ATP III	44	63	121 ± 17	132 ± 20	75 ± 9	78 ± 10	6.96 (3.57–15.73)	16.55 (6.38–82.58)
IDF	59	73	120 ± 16	131 ± 19	74 ± 9	78 ± 10	6.90 (3.59–15.94)	13.62 (5.54–62.25)

Data are means ± SD, percentages, or median (interquartile range). MetS, metabolic syndrome.

Table 3—*The 10-year hazard for incident fatal/nonfatal cardiovascular associated with metabolic syndrome, according to three different definitions, adjusting for age, sex, field center, and diabetes*

	Diabetes	No diabetes	*P*	−2 log likelihood
WHO	2.29 (1.97–2.67)	1.54 (1.32–1.80)	≤0.0001	15,033
ATP III	2.45 (2.12–2.84)	1.42 (1.22–1.66)	≤0.0001	15,043
IDF	2.59 (2.25–2.98)	1.37 (1.17–1.61)	≤0.0001	15,049

Data are HRs (95% CI) for metabolic syndrome. Comparison between likelihood functions has been done for 1 d.f.

was estimated for each definition. Log-cumulative hazard functions were computed by Cox regression, adjusting for age (years), field center, sex, and diabetes. Additional models were also adjusted for the other components of metabolic syndrome. Cox regression was also run separately for diabetic and nondiabetic participants.

To compare the independent prognostic effect of metabolic syndrome by the three definitions, likelihood functions were compared (20). The difference between two −2 log likelihoods has a χ^2 distribution, which, for this comparison, has 1 d.f. (20). Two-tailed $\alpha \leq 0.01$ identified significant differences among the three models.

RESULTS — Table 2 shows that the IDF definition yielded the highest prevalence of metabolic syndrome in both men and women. The WHO definition resulted in a similar proportion of metabolic syndrome in men and women, whereas NCEP ATP III and IDF showed a substantially higher prevalence in women, with the greatest sex difference by the NCEP ATP III definition (both $P < 0.0001$). The coefficient of concordance (k) among the different definitions in the recognition of metabolic syndrome status was not excellent: 0.56 and 0.59 for men and women between WHO and NCEP ATP III, 0.58 and 0.77 between NCEP ATP III and IDF, and only 0.49 and 0.50 between WHO and IDF definitions, respectively.

Table 2 also shows that, due to differing high blood pressure criteria, the WHO definition was associated with slightly higher blood pressure levels than was NCEP ATP III or IDF. Urinary albumin-to-creatinine ratio was highest in participants with metabolic syndrome by the WHO definition (including this parameter among criteria for definition), but also higher in the NCEP ATP III and IDF definitions (all $P < 0.0001$), than in participants without metabolic syndrome.

The criteria for adiposity proposed by the WHO identified 83% of participants with central fat distribution in the absence of metabolic syndrome (compared with 96% in those with metabolic syndrome). The difference between groups without (66% with central fat) vs. with metabolic syndrome (100% with central fat) was more accentuated in the IDF and maximal with the NCEP ATP III definition (50 vs. 91%, respectively). In all definitions, one-half or more of individuals free of the syndrome exhibited central fat distribution.

Table 4—*The 10-year hazard for incident fatal/nonfatal cardiovascular events in separate nondiabetic and diabetic subgroups of the SHS, in relation to presence of metabolic syndrome, according to 3 different definitions, adjusting for age, sex, and field center*

	Increase in cardiovascular risk	95% CI	*P*	−2 log likelihood
Nondiabetic				
WHO	1.28	1.03–1.59	≤0.03	5,309
ATP III	1.40	1.13–1.73	≤0.002	5,305
IDF	1.44	1.17–1.78	≤0.001	5,302
Diabetic				
WHO	1.94	1.51–2.47	≤0.0001	8,381
ATP III	1.43	1.13–1.81	≤0.003	8,404
IDF	1.26	0.99–1.62	≤0.07	8,410

Comparison between likelihood functions has been done for 1 d.f.

Cardiovascular risk in the metabolic syndrome

Over the follow-up time (119 ± 45 months), 1,157 cardiovascular events were adjudicated, including 176 strokes, 299 myocardial infarctions, 226 other clinical manifestations of coronary heart disease, 394 cases of congestive heart failure, and 62 sudden deaths. The incidence of combined fatal and nonfatal cardiovascular events was 2.38-fold greater in participants with than in those without metabolic syndrome (95% CI 2.04–2.73) by the WHO definition, 2.12-fold greater (1.81–2.47) by the ATP III definition, and 1.92-fold greater (1.62–2.27) by the IDF definition (all $P < 0.0001$). Table 3 shows that metabolic syndrome was always associated with increased rate of cardiovascular events (all $P < 0.0001$), even independent of age, sex, field center, and presence of diabetes. The regression model including metabolic syndrome by the WHO definition was significantly more predictive than the other models, including the other definitions (both $P < 0.002$).

Alternative Cox regression models adjusted for obesity, low HDL cholesterol, and hypertension, in addition to the covariates used in the previous model. Although reduced, the hazard ratios (HRs) of metabolic syndrome remained statistically significant for the definitions by the NCEP ATP III (HR 1.28 [95% CI 1.04–1.56], $P < 0.02$) and the WHO (1.35 [1.11–1.64], $P < 0.002$) but not by IDF (1.12 [0.92–1.36], $P > 0.2$).

Cardiovascular risk in diabetic and nondiabetic subjects

In both diabetic and nondiabetic participants, the prognostic effect of metabolic syndrome was confirmed for all three definitions (Table 4). The HR for incident composite fatal and nonfatal events was ~30–40% higher in nondiabetic participants with metabolic syndrome, by all definitions, without significant differences among them (Fig. 1). In contrast, in diabetic participants, the HR for the metabolic syndrome was not statistically significant using the IDF definition (26% increased risk), was higher with the NCEP ATP III definition (43% increased risk), and was highest with the WHO definition (near-doubled risk), a difference that was statistically significantly ($P < 0.001$).

CONCLUSIONS — This study demonstrates that in the SHS cohort, metabolic syndrome by all three examined

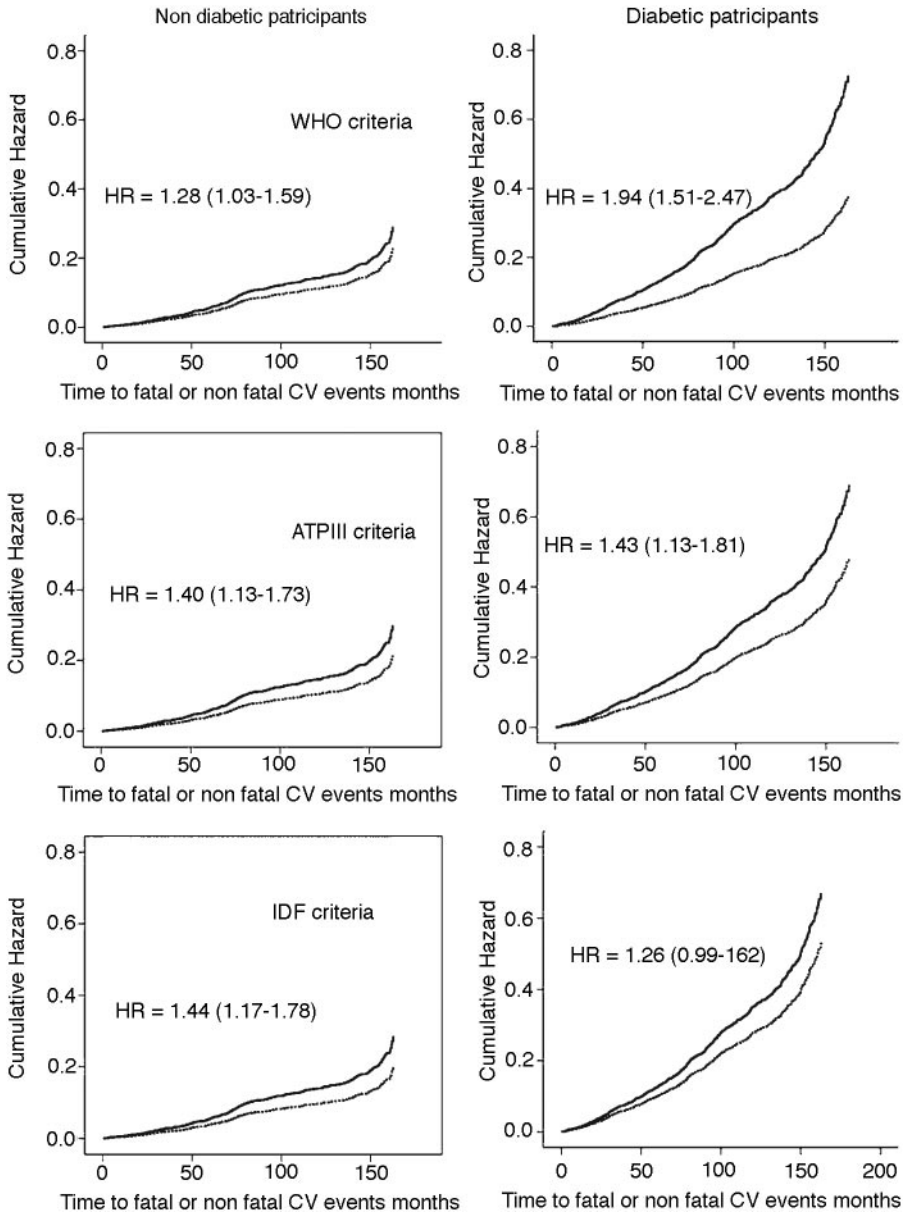

Figure 1—*Adjusted cumulative hazard in participants with (—) or without (----) metabolic syndrome, in nondiabetic or diabetic participants, according to diagnostic criteria issued by the WHO* (top panel)*, ATP III* (middle panel)*, or IDF* (bottom panel).

definitions is independently associated with a significantly greater rate of incident composite fatal and nonfatal cardiovascular events and is a marker of preclinical cardiovascular disease, represented by the increased urinary albumin-to-creatinine ratio. The independent association of metabolic syndrome with cardiovascular events was seen in population strata with or without diabetes.

In participants without diabetes, increased cardiovascular risk is independently associated with metabolic syndrome, suggesting that this diagnosis can help identify high-risk individuals. Similarly, among diabetic individuals, recognition of the metabolic syndrome impressively enhanced the prediction of cardiovascular events, consistent with National Health and Nutrition Examination Survey III results (21), where the age-adjusted prevalence of coronary heart disease in the diabetic population without metabolic syndrome (8%) was similar to that in subjects without diabetes or metabolic syndrome (9%), while increasing to 14% in nondiabetic subjects with metabolic syndrome and to 19% in those with both conditions. However, independent of the presence of full-fledged metabolic syndrome, attention to all cardiovascular risk factors is paramount in the presence of diabetes. Compared with nondiabetic populations, detecting the full presentation of metabolic syndrome might be less important for decision making when diabetes coexists with even one additional risk factor.

This study identifies similarities among the three definitions of metabolic syndrome but also reveals differences. In the whole population, combining participants with or without diabetes, the model using the WHO definition was a better predictor than models using NCEP ATP III or IDF definitions, with IDF exhibiting the lowest fit. When forcing single cardiovascular risk factors into the

proportional hazard model, only the WHO and ATP III definitions maintained an independent prognostic impact, whereas the IDF definition did not, possibly due to lower specificity associated with the generally lower partition values for single factors.

In nondiabetic participants, the risks predicted by the three definitions were not statistically different. In contrast, a substantial difference was evident among diabetic participants, with the WHO definition significantly superior to those of both the NCEP ATP III and IDF (the HR of which was not statistically significant). Although the NCEP ATP III definition was not intended for diabetic individuals, it should be noted that it performed well in participants with or without diabetes, though slightly less well than WHO in those with diabetes.

To evaluate correctly the implications of these findings, both the characteristics of the SHS population and the differences among the different definitions of metabolic syndrome have to be taken into account. The American Indian population of the SHS is characterized by higher prevalence of obesity than the overall population in the U.S. and Europe (12), though this difference is rapidly attenuating (22–25). As a consequence, in the SHS cohort, the distribution of measures of adiposity is skewed toward higher values, similar to findings in hypertensive populations (26). Due to the high prevalence of obesity, the adopted measures of fatness in the WHO definition do not discriminate well between participants with or without the metabolic syndrome. Also with the other definitions, substantial proportions of participants without metabolic syndrome exhibited central fat distribution, maximal with the IDF definition, which uses very low partition values for waist girth. Thus, in the context of a population with very high prevalence of obesity, measures of adiposity or abdominal obesity do not strongly separate individuals with or without metabolic syndrome, since obesity is also highly prevalent among individuals without metabolic syndrome.

The present analysis extends a previous study of metabolic syndrome in nondiabetic SHS participants. That analysis did not report significant independent associations between metabolic syndrome (by the NCEP ATP III definition) and cardiovascular risk (27), but it included only 4.2 years of follow-up and was limited to some cardiac events. In contrast, the present analysis also included diabetic participants, the follow-up was substantially longer, and all clinical manifestations of cardiovascular disease, including cerebrovascular events and congestive heart failure, were considered as end points. In particular, incident congestive heart failure (394 adjudicated events) could be very important, because heart failure is a relevant end point for obesity (28–30). Overall, our findings suggest that the metabolic syndrome may take several years to manifest its effects on clinical events (as Fig. 1 also suggests).

In conclusion, the NCEP ATP III and WHO (but not IDF) definitions of metabolic syndrome predict cardiovascular disease independently of single components of the syndrome; their value may be similar in individuals without diabetes, but in diabetes the WHO definition seems to be more useful. Results of these analyses, obtained in a population with high prevalences of obesity and diabetes, are likely applicable to other populations of different ethnicities in which there is an epidemic rise of prevalences of overweight and obesity (31), triggering diabetes and other metabolic abnormalities (32). The identification of the metabolic syndrome can be valuable to focus aggressive intervention strategies, especially when diabetes has not yet occurred.

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