Prognostic Impact of Metabolic Syndrome by Different Definitions in a Population with High Prevalence of Obesity and Diabetes: The Strong Heart Study.

Received for publication 18 October 2006 and accepted in revised form 30 March 2007.

Running title: Metabolic syndrome.

Giovanni de Simone, M.D.\textsuperscript{a,b}  
Richard B. Devereux, M.D.\textsuperscript{a}  
Marcello Chinali, M.D.\textsuperscript{b}  
Lyle G. Best, M.D.\textsuperscript{c}  
Elisa T. Lee, Ph.D.\textsuperscript{d}  
James M. Galloway, M.D., M.P.H.\textsuperscript{e}  
Helaine E. Resnick, Ph.D.\textsuperscript{f}  
for the Strong Heart Study Investigators

From: \textsuperscript{a} Weill Medical College of Cornell University, New York, N.Y.; \textsuperscript{b} Federico II University, Naples, Italy; \textsuperscript{c} Missouri Breaks Industries Research, Timber Lake, SD; \textsuperscript{d} Center for American Indian Health Research, University of Oklahoma, Oklahoma City, OK; \textsuperscript{e} Indian Health Service, University of Arizona; \textsuperscript{f} Medstar Research Institute, Washington, D.C.

Corresponding Author: Giovanni de Simone, M.D., Department of Clinical and Experimental Medicine – Federico II University Hospital – v.S.Pansini 5, – 80131 Naples – Italy - E-mail: simogi@unina.it
ABSTRACT

Objective: This study analyzed which definition of the metabolic syndrome (MetS) is more predictive of cardiovascular events in both diabetic and non-diabetic members of a population based sample.

Research Design and Method: Ten-year longitudinal follow-up of the Strong Heart Study cohort has been evaluated. The analysis included 3,945 participants (2,384 women) with complete data (1,700 with diabetes; 1,468 with arterial hypertension) for evaluation of MetS. Those with prevalent cardiovascular disease were excluded (n=287, 127 women). Prevalence of MetS was assessed based on WHO, ATPIII, and IDF definitions. Main outcome was 10-year incidence of combined fatal and non-fatal cardiovascular events (CVe), including stroke, coronary heart disease and congestive heart failure.

Results: Fatal and non-fatal CVe occurred in 1,120 participants. After adjusting for age, sex and diabetes, MetS by all definitions was significantly associated with higher incidence of CVe, (all p<0.0001). In nondiabetic individuals, incident CVe rates were about 30-40% higher in those with MetS, without significant difference among definitions (0.03<p<0.001), and remained significant in WHO and ATPIII definitions even after further adjustment for obesity, hypertension, and low HDL-cholesterol. In the diabetic group, MetS risk for CVe was greatest using the WHO definition (p<0.002 vs other models).

Conclusions: In persons without diabetes, MetS is associated with incident cardiovascular disease, especially with WHO and ATPIII definitions. MetS also predicts higher CV event rates in diabetic participants, a prediction that is greatest using the WHO definition.
The metabolic syndrome represents clusters of cardiovascular risk factors, assuming that cardiovascular risk is amplified more than expected from the effect of single risk factors. Many studies support the utility of this definition, but others have questioned the incremental utility of this approach.

An element of potential confusion concerning the real prognostic utility of defining metabolic syndrome is the availability of several definitions, reflecting different strategies, either identifying a main characteristic as a necessary factor associated with other variable risk factors, or accepting varied combinations of characteristics. 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 cohort.

**RESEARCH DESIGN AND METHODS**

Population: The Strong Heart Study (SHS) is a population-based cohort study of cardiovascular risk factors and disease in 4,549 American Indians from 3 communities in Arizona, 7 in Southwestern Oklahoma and 3 in South and North Dakota, extensively described. Participants seen during the baseline exam, in 1989 to 1992 were representative of the source population.

For the present analysis, individuals with prevalent cardiovascular disease (n=287, 127 women) were excluded. Prevalent and incident cardiovascular events (cardiovascular death, stroke, congestive heart failure, myocardial infarction, coronary heart disease [coronary angiography or combination of typical symptoms with positive treadmill tests or abnormal imaging stress test, or revascularization procedures]) were confirmed by the Strong Heart Study Mortality and Morbidity Committees, using specified criteria for causes of fatal and nonfatal cardiovascular events.

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; 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. Diabetes (≥126 mg/dL or antidiabetic treatment) and impaired fasting glucose (≥110 mg/dL) were diagnosed by 1997 American Diabetes Association recommendations. Obesity was classified based on the 1998 NIH guidelines (BMI≥30 kg/m²). 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.

Table 1 shows the criteria used to define metabolic syndrome by 3 guidelines: WHO, NCEP-ATPIII, and IDF. Insulin-glucose homeostasis for the WHO definition was estimated by the HOMA equation. Based on WHO recommendation, a partition value for HOMA index was arbitrarily determined in the non-diabetic 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 JNC-VII criteria (blood pressure ≥140/90 mmHg or use of antihypertensive treatment).

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

Ten-year relative risk of combined fatal and non-fatal cardiovascular events 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 non-diabetic participants.

To compare the independent prognostic effect of metabolic syndrome by the 3 definitions, likelihood functions were compared. The difference between two -2 log likelihoods has a χ² distribution, which, for this comparison, has 1 degree of freedom. Two-tailed α≤0.01 identified significant differences among the 3 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 ATPIII and IDF showed a substantially higher prevalence in women, with the greatest sex-difference by ATPIII definition (both p<0.0001). The coefficient of concordance (k) among the different definitions in the recognition of metabolic syndrome status was not excellent, being 0.56 and 0.59 for men and women between WHO and ATPIII, 0.58 and 0.77 between ATPIII and IDF, and only 0.49 and 0.50 between WHO and IDF definitions.

Table 2 also shows that, due to differing high blood pressure criteria, the WHO definition was associated with slightly higher blood pressure levels than ATPIII or IDF. Urinary albumin/excretion ratio was highest in participants with metabolic syndrome by WHO definition (including this parameter among criteria for definition), but also higher in the ATPIII 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 to 96% in those with metabolic syndrome). The difference between groups without (66% with central fat) vs with metabolic syndrome (100%) was more accentuated in the IDF, and maximal with the ATPIII definition (50 vs. 91%, respectively). In all definitions, half or more of individuals free of the syndrome exhibited central fat distribution. 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 congestive heart failure and 62 sudden deaths. The incidence of combined fatal and non-fatal cardiovascular events was 2.38-fold greater in participants than in those without metabolic syndrome (95% C.I.=2.04-2.73) by WHO definition, 2.12-fold greater (95% C.I.=1.81-2.47) by ATPIII definition and 1.92-fold greater (95% C.I.=1.62-2.27) by
IDF (all p<0.0001). Table 3 shows that metabolic syndrome was always associated with increased rate of cardiovascular events (all p<0.0001), even independently of age, sex, field center and presence of diabetes. The regression model including metabolic syndrome by 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 of metabolic syndrome remained statistically significant for the definitions by ATPIII (HR=1.28 [1.04-1.56], p<0.02) and WHO (HR=1.35 [1.11-1.64], p<0.002), but not by IDF (HR=1.12 [0.92-1.36] p>0.2).

Cardiovascular risk in diabetic and non-diabetic subjects.

Both in diabetic and non diabetic participants the prognostic effect of metabolic syndrome was confirmed for all three definitions (table 4). The hazard for incident composite fatal and non fatal events was about 30-40% higher in non-diabetic participants with metabolic syndrome, by all definitions, without significant difference among them (figure 1). In contrast, in diabetic participants, the hazard ratio for the metabolic syndrome was not statistically significant using the IDF definition (26% increased risk), higher with ATPIII definition (43% increased risk) and the highest with the WHO definition (near doubled risk), a difference that was statistically significantly (p<0.001).

DISCUSSION

This study demonstrates that in the Strong Heart Study cohort, metabolic syndrome by all three examined definitions is independently associated with a significantly greater rate of incident composite fatal and non fatal cardiovascular events and a marker of preclinical cardiovascular disease, represented by the increased urinary albumin/creatinine excretion. 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 enhanced impressively the prediction of cardiovascular events, consistent with NHANES-III results, 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%), whereas increasing to 14% in non-diabetic 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. As compared to non-diabetic 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 ATPIII or IDF definitions, with IDF exhibiting the lowest fit. When forcing single cardiovascular risk factors into the proportional hazard model, only WHO and ATPIII definitions maintained an independent prognostic impact, whereas IDF definition did not, possibly due to lower specificity.
associated with the generally lower partition values for single factors.

In non-diabetic 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 both ATPIII and IDF (the hazard ratio of which was not statistically significant). Although the ATPIII 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 Strong Heart Study population and the differences among the different definitions of metabolic syndrome have to be taken into account. The American Indian population of the Strong Heart Study is characterized by higher prevalences of obesity than the overall population in US and in Europe, though this difference is rapidly attenuating. As a consequence, in the Strong Heart Study cohort, the distribution of measures of adiposity is skewed toward higher values, similar to findings in hypertensive populations. 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 non-diabetic SHS participants. That analysis did not report significant independent associations between metabolic syndrome (by ATPIII) and cardiovascular risk, but it included only 4.2 years of follow-up and was limited to some cardiac events. In contrast, the present analysis included also 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 endpoints. In particular, incident congestive heart failure (394 adjudicated events) could be very important, because heart failure is a relevant end point for obesity. Overall, our findings suggest that the metabolic syndrome may take several years to manifest its effects on clinical events (as also figure 1 suggests).

In conclusion, ATPIII 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 prevalence of overweight and obesity, triggering diabetes and other metabolic abnormalities. The identification of the metabolic syndrome can be valuable to focus aggressive intervention strategies, especially when diabetes has not yet occurred.

ACKNOWLEDGMENT

This work has been supported by grants HL41642, HL41652, HL41654, HL65521 and M10RR0047-34 (GCRC) from the National Institutes of Health, Bethesda, MD.

The authors wish to thank the Indian Health Service, the Strong Heart Study
Views expressed in this paper are those of the authors and do not necessarily reflect those of the Indian Health Service.

Participants, the Participating Tribal Communities and the Strong Heart Study Center Coordinators for their help in the realization of this project.
REFERENCES


Table 1: Definition of metabolic syndrome according to WHO (5,9), NCEP-ATPIII (6), and IDF (9). Sine-qua-non factors are highlighted in boldface.

<table>
<thead>
<tr>
<th>Factor</th>
<th>WHO (main criterion + 2 factors)</th>
<th>ATPIII (any combination of 3 factors)</th>
<th>IDF (main criterion + 2 factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td>&gt;30 kg/m² or</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>Waist/Hip&gt;0.9/0.85 (M/W)</td>
<td>&gt;102/88 cm waist (M/W)</td>
<td>&gt;94/80 cm (M/W)†</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/L</td>
<td>≥150 mg/dL</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>&lt;35/39 mg/L (M/W)</td>
<td>&lt;40/50 mg/dL (M/W)</td>
<td>&lt;40/50 mg/dL (M/W)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Hypertension*</td>
<td>≥130/≥85 mmHg</td>
<td>Hypertension* or ≥130/&gt;85 mmHg</td>
</tr>
<tr>
<td>HOMA</td>
<td>&gt;4.3 or</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>present or</td>
<td>---------</td>
<td>present or</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dL</td>
<td>≥110 mg/dL</td>
<td>&gt;100 mg/dL</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>---------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Urinary albumin excretion</td>
<td>≥20 µg/min or ≥30 mg/g crea</td>
<td>---------</td>
<td></td>
</tr>
</tbody>
</table>

* Blood pressure ≥ 140/90 mmHg
† Ethnic group Waist circumference† (as measure of central obesity)

- Europids: Men ≥ 94 cm Women ≥ 80 cm
- South Asians: Men ≥ 90 cm Women ≥ 80 cm
- Chinese: Men ≥ 90 cm Women ≥ 80 cm
- Japanese: Male ≥ 85 cm Women ≥ 90 cm
- Ethnic South and Central Americans: Use South Asian recommendations until more specific data are available
- Sub-Saharan Africans: 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
Table 2: Metabolic syndrome by different definitions (see Table 1): concordance and differences in blood pressure and urinary albumin/creatinine ratio. Mean±standard deviation is displayed for blood pressure; median and interquartile range for albumin/creatinine ratio.

<table>
<thead>
<tr>
<th>Prevalence of metabolic syndrome</th>
<th>Systolic Blood pressure (mmHg)</th>
<th>Diastolic Blood pressure (mmHg)</th>
<th>Urinary albumin/creatinine ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>No MetS</td>
</tr>
<tr>
<td>WHO</td>
<td>48%</td>
<td>53%</td>
<td>122±16</td>
</tr>
<tr>
<td>ATPIII</td>
<td>44%</td>
<td>63%</td>
<td>121±17</td>
</tr>
<tr>
<td>IDF</td>
<td>59%</td>
<td>73%</td>
<td>120±16</td>
</tr>
</tbody>
</table>
Table 3: Ten-year hazard for incident fatal/non-fatal cardiovascular associated with metabolic syndrome, according to 3 different definitions, adjusting for age, sex, field center and diabetes. Comparison between likelihood function has been done for 1 degree of freedom.

<table>
<thead>
<tr>
<th></th>
<th>Diabetes</th>
<th>No diabetes</th>
<th>p≤</th>
<th>-2 log likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td>2.29</td>
<td>1.54</td>
<td>0.0001</td>
<td>15033</td>
</tr>
<tr>
<td></td>
<td>(1.97-2.67)</td>
<td>(1.32-1.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATPIII</td>
<td>2.45</td>
<td>1.42</td>
<td>0.0001</td>
<td>15043</td>
</tr>
<tr>
<td></td>
<td>(2.12-2.84)</td>
<td>(1.22-1.66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDF</td>
<td>2.59</td>
<td>1.37</td>
<td>0.0001</td>
<td>15049</td>
</tr>
<tr>
<td></td>
<td>(2.25-2.98)</td>
<td>(1.17-1.61)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4: Ten-year hazard for incident fatal/non-fatal cardiovascular events in separate non diabetic 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. Comparison between likelihood function has been done for 1 degree of freedom.

<table>
<thead>
<tr>
<th></th>
<th>Increase in cardiovascular risk</th>
<th>95% Confidence interval</th>
<th>p≤</th>
<th>-2 log likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non diabetic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO</td>
<td>1.28</td>
<td>1.03-1.59</td>
<td>0.03</td>
<td>5309</td>
</tr>
<tr>
<td>ATPIII</td>
<td>1.40</td>
<td>1.13-1.73</td>
<td>0.002</td>
<td>5305</td>
</tr>
<tr>
<td>IDF</td>
<td>1.44</td>
<td>1.17-1.78</td>
<td>0.001</td>
<td>5302</td>
</tr>
<tr>
<td><strong>Diabetic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO</td>
<td>1.94</td>
<td>1.51-2.47</td>
<td>0.0001</td>
<td>8381</td>
</tr>
<tr>
<td>ATPIII</td>
<td>1.43</td>
<td>1.13-1.81</td>
<td>0.003</td>
<td>8404</td>
</tr>
<tr>
<td>IDF</td>
<td>1.26</td>
<td>0.99-1.62</td>
<td>0.07</td>
<td>8410</td>
</tr>
</tbody>
</table>
Figure 1: Adjusted cumulative hazard in participants with (continuous lines) or without (dotted lines) metabolic syndrome, in non diabetic (left panels) or diabetic participants (right panels), according to diagnostic criteria issued by WHO (top panel), ATPIII (middle panel), or IDF (bottom panel).