Association of the Metabolic Syndrome With History of Myocardial Infarction and Stroke in the Third National Health and Nutrition Examination Survey

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Background—The combination of cardiovascular risk factors known as the metabolic syndrome is receiving increased attention from physicians, but data on the syndrome’s association with morbidity are limited.

Methods and Results—Applying National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria, we evaluated 10 357 NHANES III subjects for the 5 component conditions of the metabolic syndrome: insulin resistance, abdominal obesity based on waist circumference, hypertriglyceridemia, low HDL cholesterol (HDL-C), and hypertension, as well as the full syndrome, defined as at least 3 of the 5 conditions. Logistic regression was used to estimate the cross-sectional association of the syndrome and each of its 5 component conditions separately with history of myocardial infarction (MI), stroke, and either MI or stroke (MI/stroke). Models were adjusted for age, sex, race, and cigarette smoking. The metabolic syndrome was significantly related in multivariate analysis to MI (OR, 2.01; 95% CI, 1.53 to 2.64), stroke (OR, 2.16; 95% CI, 1.48 to 3.16), and MI/stroke (OR, 2.05; 95% CI, 1.64 to 2.57). The syndrome was significantly associated with MI/stroke in both women and men. Among the component conditions, insulin resistance (OR, 1.30; 95% CI, 1.03 to 1.66), low HDL-C (OR, 1.35; 95% CI, 1.05 to 1.74), hypertension (OR, 1.44; 95% CI, 1.00 to 2.08), and hypertriglyceridemia (OR, 1.66; 95% CI=1.20 to 2.30) were independently and significantly related to MI/stroke.

Conclusions—These results indicate a strong, consistent relationship of the metabolic syndrome with prevalent MI and stroke. (Circulation. 2004;109:42-46.)

Key Words: syndrome X ▪ risk factors ▪ myocardial infarction ▪ stroke ▪ epidemiology

A set of metabolic and physiological risk factors linked to cardiovascular disease (CVD) has been variously defined as the insulin resistance syndrome, syndrome X, the deadly quartet, the metabolic syndrome, the dysmetabolic syndrome, and the cardiovascular dysmetabolic syndrome. 1–5 Proposed definitions of the metabolic syndrome have differed with respect to components and component cut points. However, recent attempts to define the metabolic syndrome have included 5 conditions: hypertriglyceridemia (HTG), low HDL cholesterol (HDL-C), hypertension (HTN), abdominal obesity, and insulin resistance (IR). The intraindividual correlation of these factors has provided a rationale for grouping them as a syndrome.

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In the present study, we examine the associations of a history of (nonfatal) myocardial infarction (MI) and stroke with the metabolic syndrome and its component conditions.

Our analysis is based on data from the Third National Health and Nutrition Examination Survey (NHANES III). We use the metabolic syndrome definition recently published as part of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) recommendations.

Methods

We applied the condition-specific cut points for the metabolic syndrome from the recent NCEP ATP-III report, with minor modifications as noted.7 The 5 component conditions are IR, HTN, HTG, low HDL-C, and abdominal obesity defined by high waist circumference (WC). IR was defined as fasting glucose ≥110 mg/dL; for purposes of this analysis, IR could also be met by a self-report of current use of insulin or oral hypoglycemics. HTN was defined as systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg; for purposes of this analysis, the HTN definition could also be met by a self-report of current use of anti-HTN medication. HTG was identified based on triglycerides ≥150 mg/dL. Low HDL-C was identified by HDL cholesterol <40 mg/dL in men or <50 mg/dL in women. High WC was defined as a WC ≥102 cm in men or ≥88 cm in women.
The data source for the study was NHANES III. This survey was conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention in 1988 to 1994. NHANES III was designed to provide a variety of detailed information on the health and nutrition status of a representative sample of the civilian noninstitutionalized population of the United States. Out of a sample of 39,695 people selected for the NHANES III, 33,994 were interviewed and 30,818 submitted to an examination by a physician at a mobile examination center, including extensive anthropometric, physiological, and laboratory testing. NHANES III used a complex, multistage sampling design to allow results to be extrapolated to the total United States population as of the early 1990s. The present study was based on a subset of subjects aged 20 to 89 years for whom the relevant data were available, as described below.

The WC of NHANES III participants was measured by a trained examiner and determined using a measuring tape positioned at the high point of the iliac crest. The measurement was made at minimal respiration to the nearest 0.1 cm, with the tape snug but not compressing the skin.

Blood pressure was measured by a board-eligible physician at the NHANES Mobile Examination Center. Treatment for hypertension was identified by a positive response to all 3 of the following questions: “Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?”; “Because of your high blood pressure/hypertension, have you ever been told by a doctor or other health professional to take prescribed medicine?”; and “Are you now taking prescribed medicine?”

Triglycerides and HDL-C were measured using a Hitachi 704 Analyzer (Boehringer Mannheim Diagnostics). Fasting plasma glucose was measured using a modified hexokinase enzymatic method (Roche Cobas Mira). History of diabetes was evaluated based on a positive response to either of the questions “Are you now taking insulin?” or “Are you now taking diabetes pills to lower your blood sugar?” These are sometimes called oral agents or oral hypoglycemic agents.

Subject age, race, and cigarette smoking outcome were collected in a structured interview. The data available limited classification of smoking to 3 categories, never, past, or current. History of MI and stroke were elicited based on 2 interview questions, “Has a doctor ever told you that you had a heart attack?” and “Has a doctor ever told you that you had a stroke?”

Evaluating the metabolic syndrome required data from the NHANES III adult questionnaire, examination at the Mobile Examination Center, and laboratory results. A total of 16,926 subjects ages 20 to 89 years had these data available. Data from the subjects who were unable to go to the Mobile Examination Center and were given a limited examination at home (n=457) could not be used, because the home examination did not include plasma glucose and WC measurements. A minimum age cutoff of 20 years is consistent with the NCEP-ATP-III definition of young adult. Subjects older than 89 years of age were excluded because they were arbitrarily assigned a reported age of 90 years to provide confidentiality, precluding accurate statistical adjustment for age in this group. In addition, 332 women who were either pregnant or uncertain of their pregnancy status at the time of the examination were excluded to avoid inaccurate assessment of the metabolic syndrome components.

Of the remaining 16,137 subjects, 14,347 had complete data on all variables used in the analyses. Compared with the 14,347 subjects with complete data, the 1,790 subjects with missing data were on average slightly older (50.4 versus 47.9 years; P<0.0001); however, there did not differ significantly with respect to sex or BMI (where reported). The percentage of subjects having a history of MI or stroke was much higher among the subjects with missing data (11.5% versus 6.4%, P<0.0001).

An additional 657 subjects had sufficient data to demonstrate either a positive or a negative result for at least 3 components. Such subjects could be classified as either positive or negative with respect to the syndrome, increasing the number of potential subjects included in analyses involving the full syndrome to 15,004.

Because fasting may impact HTG and IR, we excluded patients with fasting times less than 7 hours based on analyses indicating no difference in the prevalence of HTG and IR for subjects fasting 7 hours versus those who fasted longer (data not shown).

Of 14,347 patients with complete data, 10,357 reported fasting for 7 or more hours; these subjects were included in the component analyses, and 10,768 were included in the full syndrome analyses.

We fit logistic regression models to determine the association of the component conditions of the metabolic syndrome with prevalent MI and stroke. The component conditions were included as dichotomous variables, based on the NCEP-ATP III–defined cut points. We controlled for age, sex, race, and cigarette smoking as possible confounders. Preliminary analysis showed that total cholesterol was not significant in any model; it was therefore not included in the final set of models. Sex-specific models for combined MI or stroke (MI/stroke) were also examined. In separate models, we looked at association of the full metabolic syndrome with MI, stroke, and MI/stroke.

All analyses were performed using the SUDAAN software, which takes into account the complex sampling techniques used in NHANES III. Where noted, observations were weighted to reflect the general United States population as of the early 1990s, using weights calculated for that purpose by the National Center for Health Statistics. These weights were also designed to adjust for biases attributable to nonresponse.

### Results

Among 15,922 subjects for whom self-reported disease history was available, there were 752 subjects with a history of MI, 464 with a history of stroke, and 1,098 with a history of MI/stroke, for unadjusted prevalences of 4.7%, 2.9%, and 6.9%, respectively. Weighted to the general United States population, the prevalences of MI, stroke, and MI/stroke were 3.7%, 2.0%, and 5.2%, respectively. Men had a higher weighted, age-adjusted prevalence of MI/stroke than women (6.8% versus 3.8%, P<0.0001), driven mostly by greater history of MI (5.2% versus 2.4%, P<0.0001). Compared with non-Hispanic white subjects, non-Hispanic black subjects had significantly higher MI/stroke (6.0% versus 5.0%, P<0.05) attributable almost entirely to stroke (3.0% versus 1.8%, P<0.01). None of the other differences between non-Hispanic white subjects and other races were statistically significant at P<0.05.

Table 1 shows the prevalence of the component conditions and the full metabolic syndrome among subjects with and without prevalent disease. The prevalence of the metabolic syndrome was significantly higher in all 3 disease groups (40.8% to 43.5%) compared with the subjects with no history of disease (22.8%), as was the prevalence of each of the individual components, although not all comparisons reached statistical significance.

Table 2 shows the association of MI and stroke with the full metabolic syndrome and its component conditions, adjusted for age, sex, race, and smoking status by logistic regression. For each disease definition, 2 models are presented: 1 for the full metabolic syndrome and another for the 5 component conditions. Table 3 shows sex-specific results limited (for power reasons) to MI/stroke.

The metabolic syndrome was significantly associated with MI/stroke (OR, 2.05; 95% CI, 1.64 to 2.57), MI (OR, 2.01; 95% CI, 1.53 to 2.64), and stroke (OR, 2.16; 95% CI, 1.48 to 3.16) (Table 2). The metabolic syndrome was significantly associated with MI/stroke in both men (OR, 1.93; 95% CI, 1.53 to 2.43) and women (OR, 2.05; 95% CI, 1.64 to 2.57).
1.34 to 2.78) and women (OR, 2.20; 95% CI, 1.56 to 3.11) (Table 3). Interaction models indicated that this modest sex difference was not statistically significant.

HTG was significantly associated with MI, stroke, and MI/stroke and had the largest OR of any of the component conditions in each of the 3 models. In the sex-specific analysis, HTG was significantly associated with MI/stroke in women but had a weaker, borderline-significant association in men. Low HDL-C was significantly associated with MI and MI/stroke but not with stroke alone. Low HDL-C was significantly associated with MI/stroke in men but not in women. Among the component conditions, only abdominal obesity (high WC) was not independently related to prevalent disease.

The association of HTN with MI/stroke was of borderline significance (OR, 1.44; 95% CI, 1.00 to 2.08). OR estimates for MI and stroke separately were similar in magnitude and also of borderline significance (P<0.10). MI/stroke was not significantly related to HTN in men but was significantly related in women (OR, 2.19; 95% CI, 1.15 to 4.14). IR was significantly associated with MI/stroke (OR, 1.30; 95% CI, 1.03 to 1.66) but not with MI or stroke separately.

Syndrome and component condition models all included adjustment for age, sex, race, and smoking history. Age was highly significantly related to prevalent disease in all models, with ORs of 1.08 to 1.09 per additional year of age. There was no significant interaction between age and the metabolic syndrome in models for the combined disease history, MI, or stroke; ie, the predictive strength of the metabolic syndrome was similar at younger and older ages. Female sex was significantly protective for combined MI/stroke and MI but not for stroke.

After adjustment for other factors, non-Hispanic black subjects had significantly higher odds of MI/stroke compared with non-Hispanic white subjects (OR, 1.36; 95% CI, 1.06 to 1.76). In sex-specific models, this seems to be attributable to a strong association in women (OR, 1.87; 95% CI, 1.31 to 2.67) but not men (OR, 1.05; 95% CI, 0.73 to 1.51). The increased odds of disease for non-Hispanic black subjects was significant for stroke (OR, 1.49; 95% CI, 1.03 to 2.17) but not for MI. This was the only statistically significant ethnic difference.

### TABLE 1. Age-/Sex-Adjusted, Weighted Proportion of Subjects With Metabolic Syndrome Component Conditions or Metabolic Syndrome

<table>
<thead>
<tr>
<th>No Event</th>
<th>MI or Stroke</th>
<th>MI</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>N*</td>
<td>14 824</td>
<td>1098</td>
<td>752</td>
</tr>
<tr>
<td>Average age*</td>
<td>46.7</td>
<td>68.5</td>
<td>68.2</td>
</tr>
<tr>
<td>Metabolic syndrome, %</td>
<td>22.8</td>
<td>40.8†</td>
<td>41.5†</td>
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<tr>
<td>Component conditions, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>37.1</td>
<td>58.2†</td>
<td>51.8†</td>
</tr>
<tr>
<td>High triglycerides§</td>
<td>28.6</td>
<td>54.1†</td>
<td>43.2</td>
</tr>
<tr>
<td>Low HDL-C, %</td>
<td>36.2</td>
<td>50.4‡</td>
<td>45.0%</td>
</tr>
<tr>
<td>Hypertension, %§</td>
<td>35.5</td>
<td>55.1†</td>
<td>48.2</td>
</tr>
<tr>
<td>Insulin resistance, %§</td>
<td>11.0</td>
<td>22.1†</td>
<td>25.6†</td>
</tr>
</tbody>
</table>

*Based on 15,922 subjects reporting MI and stroke history, unweighted.
†P<0.0001 vs no event.
‡P=0.001 vs no event.
§Only subjects fasting ≥7 hours included.
‖P<0.05 vs no event.
¶P<0.01 vs no event.

### TABLE 2. Cross-Sectional Association of MI and Stroke With the Metabolic Syndrome and Component Conditions

<table>
<thead>
<tr>
<th>Syndrome model</th>
<th>MI or Stroke</th>
<th>MI</th>
<th>Stroke</th>
<th>P Value</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome</td>
<td>2.05</td>
<td>1.64–2.57</td>
<td>&lt;0.0001</td>
<td>2.01</td>
<td>1.53–2.64</td>
<td>&lt;0.0001</td>
<td>2.16</td>
<td>1.48–3.16</td>
<td>0.0002</td>
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<tr>
<td>Race (vs non-Hispanic white)</td>
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<tr>
<td>Non-Hispanic black</td>
<td>1.36</td>
<td>1.06–1.76</td>
<td>0.0177</td>
<td>1.18</td>
<td>0.84–1.67</td>
<td>0.3316</td>
<td>1.49</td>
<td>1.03–2.17</td>
<td>0.0358</td>
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<tr>
<td>Mexican-American</td>
<td>0.81</td>
<td>0.56–1.18</td>
<td>0.2681</td>
<td>0.82</td>
<td>0.54–1.24</td>
<td>0.3484</td>
<td>0.91</td>
<td>0.58–1.42</td>
<td>0.6746</td>
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<tr>
<td>Other</td>
<td>1.44</td>
<td>0.71–2.92</td>
<td>0.2996</td>
<td>1.00</td>
<td>0.38–2.64</td>
<td>1.0000</td>
<td>2.11</td>
<td>0.94–4.74</td>
<td>0.0704</td>
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<tr>
<td>Smoking (never=reference)</td>
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<tr>
<td>Current</td>
<td>2.17</td>
<td>1.49–3.14</td>
<td>0.0001</td>
<td>2.49</td>
<td>1.58–3.92</td>
<td>0.0002</td>
<td>2.13</td>
<td>1.36–3.32</td>
<td>0.0013</td>
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<tr>
<td>Past</td>
<td>1.60</td>
<td>1.24–2.07</td>
<td>0.0006</td>
<td>1.98</td>
<td>1.46–2.70</td>
<td>0.0001</td>
<td>1.35</td>
<td>0.90–2.04</td>
<td>0.1428</td>
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<tr>
<td>Age (1-year difference)</td>
<td>1.08</td>
<td>1.07–1.09</td>
<td>&lt;0.0001</td>
<td>1.08</td>
<td>1.07–1.09</td>
<td>&lt;0.0001</td>
<td>1.08</td>
<td>1.06–1.09</td>
<td>&lt;0.0001</td>
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<tr>
<td>Sex (female vs male reference)</td>
<td>0.48</td>
<td>0.38–0.61</td>
<td>&lt;0.0001</td>
<td>0.40</td>
<td>0.29–0.54</td>
<td>&lt;0.0001</td>
<td>0.94</td>
<td>0.65–1.38</td>
<td>0.7667</td>
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<td>Components model</td>
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<tr>
<td>Syndrome components</td>
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<tr>
<td>Abdominal obesity</td>
<td>1.11</td>
<td>0.88–1.42</td>
<td>0.3719</td>
<td>1.15</td>
<td>0.86–1.54</td>
<td>0.3475</td>
<td>0.97</td>
<td>0.58–1.64</td>
<td>0.9154</td>
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<tr>
<td>High triglycerides§</td>
<td>1.66</td>
<td>1.20–2.30</td>
<td>0.0030</td>
<td>1.51</td>
<td>1.04–2.20</td>
<td>0.0311</td>
<td>1.87</td>
<td>1.22–2.87</td>
<td>0.0052</td>
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<tr>
<td>Low HDL-C</td>
<td>1.35</td>
<td>1.05–1.74</td>
<td>0.0199</td>
<td>1.41</td>
<td>1.03–1.95</td>
<td>0.0353</td>
<td>1.18</td>
<td>0.73–1.90</td>
<td>0.5012</td>
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<tr>
<td>Hypertension</td>
<td>1.44</td>
<td>1.00–2.08</td>
<td>0.0510</td>
<td>1.42</td>
<td>0.94–2.15</td>
<td>0.0947</td>
<td>1.56</td>
<td>0.94–2.59</td>
<td>0.0827</td>
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<tr>
<td>Insulin resistance</td>
<td>1.30</td>
<td>1.03–1.66</td>
<td>0.0298</td>
<td>1.25</td>
<td>0.92–1.71</td>
<td>0.1461</td>
<td>1.36</td>
<td>0.93–1.98</td>
<td>0.1119</td>
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</table>
With respect to smoking, both current and past smoking were associated with significantly elevated odds of combined MI/stroke and MI; only current smoking was significantly associated with stroke.

For age, sex, race, and smoking, the ORs and CIs cited above are those from the full syndrome model. ORs and CIs for these covariates from models including the individual component conditions were very similar in direction and magnitude (not shown).

To determine the potential effect of the inclusion of diabetic subjects in the analysis, logistic regression models were run separately for nondiabetic and diabetic subjects. Based on self-reported use of insulin or oral hypoglycemics or fasting plasma glucose ≥126 mg/dL, there were 9923 subjects without diabetes and 845 subjects with diabetes. Among nondiabetic subjects, the metabolic syndrome ORs for combined disease history, MI, and stroke were 1.90, 1.89, and 2.02, respectively (*P*<0.05 for all models), compared with relative risks of 2.05, 2.01, and 2.16 when all subjects were analyzed. Finally, models including all subjects irrespective of fasting status showed similar results to the models above, but the ORs, particularly for IR, were somewhat higher (data not shown).

**Discussion**

In the present study, we found that the metabolic syndrome was significantly associated with self-reported MI, stroke, and MI/stroke. It was also significantly associated with MI/stroke in separate sex-specific models. These findings suggest that the metabolic syndrome has clinical utility in identifying patients at increased risk of MI and stroke.

The strength and significance of the associations of the individual component conditions with the 3 disease definitions were consistent with those reported for the full syndrome. It is possible that the strength and significance of these associations would be enhanced if the components were modeled as continuous variables.

The lack of association between abdominal obesity (high WC) and prevalent disease differs from some previous studies that have shown linear relationships between coronary heart disease and either BMI or waist-to-hip ratio independent of BMI after adjustment for other risk factors. The absence of an independent association of high WC with prevalent disease in these data may reflect an indirect effect of high WC through other components of the syndrome, a hypothesis supported by the finding that in a model excluding the other component conditions, high WC was significantly related to MI/stroke (OR, 1.43; 95% CI, 1.15 to 1.78; not shown).

In our analysis, HTG had the strongest and most consistent relationship with disease among all of the metabolic syndrome components. Some but not all studies have shown a significant association between triglycerides and coronary heart disease. A 1996 meta-analysis of 17 prospective studies suggested a significant relationship among both men and women, even after multivariable adjustment for other risk factors; however the pooled relative risk estimate (1.14 in men, 1.37 in women) was somewhat lower than that seen in the present study. The larger point estimate of the HTG OR observed in women versus men in the present study is consistent with the gender differences observed in other studies.

The similar ORs for the metabolic syndrome whether or not diabetic subjects were included in the analysis indicates that the metabolic syndrome is strongly predictive, even in the absence of overt diabetes. The somewhat higher OR for
IR in the analyses including all subjects irrespective of fasting may reflect the inclusion of insulin users, a high-risk group who were generally nonfasting by instruction and thus excluded from the fasting analyses.

MI and stroke history in the present analysis are based on self-report of physician-diagnosed disease and are therefore subject to potential errors and biases related to recall. To our knowledge, no validation of self-reported disease history information has been attempted in NHANES III. As a test of the reasonability of the self-reported MI data, we looked at the ECG data available for NHANES III, which is limited to subjects age 40 years and older. We found that, among 8440 subjects with a probable or possible history of MI based on ECG, 47.6% reported a history of MI. Conversely, only 22.9% of subjects reporting a history of MI had a probable or possible history of MI based on ECG. In an analysis of self-report and ECG diagnosis of coronary disease in NHANES III, Ford et al. suggested discrepancies might be related to non-Q-wave MI and to aborted infarctions attributable to timely interventions. Unfortunately, NHANES III did not include data on coronary interventions. In other groups studied, 60% to 75% of self-reported MI and 54% to 55% of self-reported stroke have been validated using medical records.

Based on its cross-sectional design, the present analysis is inherently limited in its ability to elucidate causal relationships between risk factors and outcomes. In addition, fatal events were not considered. Secondary prevention interventions after initial MI or stroke may be successful in reducing risk factors, thus attenuating the observed association of risk factors with disease.

Results from only 1 prospective study have been published. Lakka et al. reported the association of the metabolic syndrome using recently proposed definitions (NCEP and WHO with modification) with CVD and overall mortality. Subjects were 1209 Finnish men free of CVD, diabetes, and cancer at baseline. Using the NCEP ATP III metabolic syndrome definition, they reported a lower prevalence of the metabolic syndrome than in this study (8.8% versus 24.0%) and a hazard ratio of 4.16 (95% CI, 1.60 to 10.8) for coronary mortality versus the OR of 2.01 (95% CI, 1.53 to 2.64) for nonfatal MI reported in the present study.

In an unpublished analysis, McNeill and colleagues have reported a hazard ratio of 2.58 for women and 1.74 for men for incident coronary disease in a general population sample, based on the NCEP ATP III definition of the syndrome, prospective results also quite similar to our cross-sectional estimates. McNeill et al. used the definition currently used in the Atherosclerosis Risk in Populations cohort, AHA Scientific Sessions, November 2002).

In conclusion, we have found that the metabolic syndrome is significantly associated with self-reported history of MI, stroke, and MI/stroke. In addition, with the exception of high

WC, all of the component conditions of the metabolic syndrome were significantly associated with MI/stroke. These findings reaffirm the clinical importance of the metabolic syndrome as a significant risk factor for cardiovascular disease and the need to develop strategies for controlling this syndrome and its component conditions.

Acknowledgments

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References

6. Deleted in proof.
Association of the Metabolic Syndrome With History of Myocardial Infarction and Stroke in the Third National Health and Nutrition Examination Survey
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