Impact of the Metabolic Syndrome on Mortality From Coronary Heart Disease, Cardiovascular Disease, and All Causes in United States Adults

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Background—Mortality resulting from coronary heart disease (CHD), cardiovascular disease (CVD), and all causes in persons with diabetes and pre-existing CVD is high; however, these risks compared with those with metabolic syndrome (MetS) are unclear. We examined the impact of MetS on CHD, CVD, and overall mortality among US adults.

Methods and Results—In a prospective cohort study, 6255 subjects 30 to 75 years of age (54% female) (representative of 64 million adults in the United States) from the Second National Health and Nutrition Examination Survey were followed for a mean ± SD of 13.3 ± 3.8 years. MetS was defined by modified National Cholesterol Education Program criteria. From sample-weighted multivariable Cox proportional-hazards regression, compared with those with neither MetS nor prior CVD, age-, gender-, and risk factor–adjusted hazard ratios (HRs) for CHD mortality were 2.02 (95% CI, 1.42 to 2.89) for those with MetS and 4.19 (95% CI, 3.04 to 5.79) for those with pre-existing CVD. For CVD mortality, HRs were 1.82 (95% CI, 1.40 to 2.37) and 3.14 (95% CI, 2.49 to 3.96), respectively; for overall mortality, HRs were 1.40 (95% CI, 1.19 to 1.66) and 1.87 (95% CI, 1.60 to 2.17), respectively. In persons with MetS but without diabetes, risks of CHD and CVD mortality remained elevated. Diabetes predicted all mortality end points. Those with even 1 to 2 MetS risk factors were at increased risk for mortality from CHD and CVD. Moreover, MetS more strongly predicts CHD, CVD, and total mortality than its individual components.

Conclusions—CHD, CVD, and total mortality are significantly higher in US adults with than in those without MetS. (Circulation. 2004;110:1245-1250.)

Key Words: diabetes mellitus ■ risk factors ■ metabolic syndrome X ■ mortality

Mortality from coronary heart disease (CHD), cardiovascular disease (CVD), and all causes is greater in persons with diabetes and pre-existing CVD.1-4 Metabolic syndrome (MetS) comprises insulin resistance, abdominal fat distribution, dyslipidemia, and hypertension. First characterized by Reaven5 as “syndrome X,” this condition has had evolving definitions. The World Health Organization (WHO)6 and the National Cholesterol Education Program (NCEP) Adult Treatment Panel7 have provided definitions for MetS. The WHO definition includes microalbuminuria and allows the use of plasma insulin or plasma glucose levels to measure insulin resistance.

The prevalence of MetS has been reported to be 24% in the US adult population.8 Most studies have examined how MetS affects mortality in non-US populations.9-11 Using both the WHO and NCEP definitions, Lakka et al12 showed in middle-aged men in Finland approximate greater risks for CHD death, CVD death, and total mortality for those with MetS. Isomaa et al13 used the WHO definition to show higher CVD and overall mortality in adults with MetS in Finland and Sweden.

We examined the impact of MetS in a large sample of adults representative of the US population on CHD, CVD, and overall mortality, as well as how these risks compare to those with diabetes or prior CVD.

Methods

Study Sample and Measurements

We used data on 6255 subjects (weighted to 63.9 million in the United States) 30 to 74 years of age who were participants in the Second National Health and Nutrition Examination Survey (NHANES II) who had mortality information with a mean ± SD follow-up of 13 ± 4 years. NHANES II surveyed 28,000 persons nationwide from 1976 through 1980. The mortality of those with a physical examination (n = 9252) was ascertained by computerized matching to 2 national databases, the National Death Index and the Social Security Administration’s Death Master File for 1976 to 1992.14 CHD mortality was defined by the International Classifica-
CVD mortality was defined by codes 410 through 414. The study was approved by the Institutional Review Board of the University of California, Irvine.

Approximately 23% (n=2145) of the cohort was deceased as of December 31, 1992. Death certificates were available for 98% of the decedents (n=2104) and missing for 41 decedents who were included in the total mortality analysis and censored in the CVD and CHD analyses. Two subjects had incomplete identifying data and were excluded. Because of missing triglycerides, HDL cholesterol (HDL-C), and/or glucose, the absence of MetS could not be confirmed for 2995 participants, leaving 6255 subjects for analysis.

In these subjects, the presence of 3 MetS risk factors, diabetes, prior CVD, or normal levels of 3 MetS risk factors (confirming the absence of MetS) was confirmed to classify individuals. Subjects not included compared with those included in the analysis were younger (48.4 versus 49.7 years of age), were more likely to be male (50.6% versus 45.6%), had lower body mass index (BMI; 25 versus 26 kg/m²), had higher blood pressure (132/84 mm Hg versus 128/81 mm Hg), and were more likely to smoke (38.9% versus 33.9%) (all P<0.0001).

Serum total cholesterol and triglycerides were measured with a Technicon Auto-Analyzer II, which uses a Lieberman-Burchard reagent for cholesterol and a fluorometric measurement of triglycerides. HDL-C was determined by the β quantification method, which uses ultracentrifugation and heparin-nanoparticulate precipitation. The mean of 2 sitting blood pressure readings was used. Physical activity was assessed by self-reported recreation exercise and dichotomized into much or moderate exercise versus little or no exercise.

MetS was defined by modified NCEP criteria if ≥3 of the following were present: (1) BMI ≥30 kg/m², (2) HDL-C <1.04 mmol/L (40 mg/dL) if male or <1.29 mmol/L (50 mg/dL) if female, (3) triglycerides ≥1.69 mmol/L (150 mg/dL) if fasting or ≥2.42 mmol/L (400 mg/dL) if not fasting, (4) blood pressure ≥130/85 mm Hg or use of antihypertension medication, and (5) glucose ≥6.1 mmol/L (110 mg/dL) if fasting or 2-hour postload glucose ≥7.77 mmol/L (140 mg/dL). Of the 6255 included subjects, 73 did not have fasting triglycerides, so a value of ≥4.52 mmol/L (400 mg/dL) was accepted as abnormal. Diabetes was defined by a physician informing the subject of having diabetes, a fasting glucose ≥7.77 mmol/L (140 mg/dL), 2-hour postload glucose ≥11.1 mmol/L (200 mg/dL), or use of dietary treatment. Diabetes was included within those defined with MetS and as a separate category in which we examined mortality risk in those with MetS who did not have diabetes. Also, we examined those with 1 and 2 combined and 3 to 5 combined MetS risk factors (defining MetS), with and without diabetes, as separate groups using an “optimal” risk reference group consisting of no MetS risk factors. Pre-existing CVD was defined if participants self-reported that a physician had diagnosed them with CHD, heart failure, other cardiac disease, or stroke. We also examined the relation of individual MetS risk factors compared with MetS as a syndrome to mortality.

Statistical Analyses

The χ² test of proportions or ANOVA was used to compare the prevalence or mean levels of the individual MetS components and other baseline characteristics across clinical conditions. Multivariable Cox proportional-hazards regression, adjusted for age, gender, total cholesterol, physical activity, and cigarette smoking (risk factors not comprising the definition for MetS), examined the risk for CHD, CVD, and overall mortality in those with MetS or CVD compared with those free of these conditions (reference group). To examine for gender differences, interaction terms of the disease group and gender were used, as were analyses stratified by gender. Age- and gender-adjusted rates for each mortality end point were also determined for each clinical condition.

We also examined risks in those defined with MetS (but without diabetes) and diabetes in a separate Cox regression model to determine whether the observed findings with MetS were dependent on diabetes being included in the definition. Also, we evaluated risks compared with an optimal risk group (no MetS risk factors) for those with 1 to 2 combined and 3 to 5 combined MetS risk factors, in addition to those groups defined above.

To compare the impact of MetS (including those with diabetes) on each mortality end point compared with the impact of individual MetS risk factors, we also conducted multivariable Cox regression with each mortality outcome in 2 separate models: MetS or its individual components. Those with pre-existing CVD were excluded to prevent confounding with the individual component risk factors.

Statistical procedures were done with SAS version 8.1 (SAS Institute), and procedures using sample weights for projection to the US population distribution used SUDAAN version 8.02 (Research Triangle Institute).

Results

Overall, 26.0% of subjects (weighted to a population of 16.6 million) were defined as having MetS, and 19.8% had pre-existing CVD (12.6 million). When those with diabetes were considered separately, further subdividing the MetS category, 19.2% (12.3 million) were defined as having MetS only, 6.8% (4.3 million) as having diabetes, 16.9% (10.7 million) with pre-existing CVD, and 2.9% (1.9 million) with diabetes and pre-existing CVD. Table 1 shows the prevalence of individual MetS risk factors by clinical condition and in our overall study sample. Table 2 shows how age, gender, other risk factors, and follow-up times vary between clinical conditions. The Figure shows age- and gender-adjusted CHD, CVD, and total mortality rates per 1000 person-years by disease group.

After adjustment for age, gender, smoking status, physical activity, and total serum cholesterol levels and weighting to the US population by use of the NHANES II sample weights, MetS was associated with a hazard ratio (HR) of CHD mortality of 2.02 (95% CI, 1.42 to 2.89). Individuals with baseline CVD had a higher risk (HR, 4.19; 95% CI, 3.04 to 5.79). When CVD mortality was the outcome, HRs were increased in a similar pattern as for CHD mortality. MetS was also associated with an increase in overall mortality (HR, 1.40; 95% CI, 1.19 to 1.66). Pre-existing CVD led to an even higher risk (HR, 1.87; 95% CI, 1.60 to 2.17) (Table 3).

Those with MetS but without diabetes had an HR of CHD mortality of 1.65 (95% CI, 1.10 to 2.47), those with diabetes had an HR of 2.87 (95% CI, 1.84 to 4.47), those with baseline CVD but no diabetes had an HR of 3.89 (95% CI, 2.79 to 5.43), and those with combined diabetes and CVD had the highest risk (HR, 6.45; 95% CI, 4.24 to 9.79) (Table 3, indented categories). Similar trends for increased risks of CVD mortality also were seen. For total mortality, increased risks were seen for those with diabetes and in those with pre-existing CVD, with the highest risk among those with both diabetes and CVD (Table 3).

When those with no MetS risk factors were used as the reference group, HRs for CHD mortality were 2.10 (95% CI, 1.05 to 4.19) for those with 1 to 2 MetS risk factors and 3.51 (95% CI, 1.81 to 6.81) for those with MetS (including those with diabetes) (Table 4). Among those with MetS but without diabetes (3 to 5 MetS risk factors), the HR was 2.87 (95% CI, 1.44 to 5.73), and for those with diabetes, the HR was 5.02 (95% CI, 2.47 to 10.23) (Table 4, indented categories). Risks were greatest for those with pre-existing CVD alone and for those with combined diabetes and CVD. For CVD mortality, similar increases in risk across disease and risk factor
categories were noted (all \( P < 0.0001 \) to \( P = 0.01 \)). Although those with 1 to 2 risk factors did not have an increased risk of total mortality, those with MetS (including diabetes) did (HR, 1.47; 95% CI, 1.15 to 1.87). Those with MetS but without diabetes had no statistically significant risk of overall mortality, whereas those with diabetes and/or CVD had significant 2- to 3-fold increases in risk (Table 4).

We found no significant differences in mortality prediction between men and women (\( P = 0.56, 0.35, \) and 0.83 for interactions of MetS with gender for CHD, CVD, and total mortality, respectively). In analyses stratified by gender, women and men had similar HRs for CHD, CVD, and total mortality. MetS carried a 2-fold risk of CHD mortality in women (HR, 2.17; 95% CI, 1.23 to 3.81), whereas men had only a slightly lower risk (HR, 1.92; 95% CI, 1.22 to 3.05). Women with MetS had a similar risk of CVD death (HR, 2.02; 95% CI, 1.36 to 2.99), whereas men with MetS had a slightly lower risk (HR, 1.71; 95% CI, 1.21 to 2.43). Overall mortality associated with MetS was similar between men (HR, 1.41; 95% CI, 1.13 to 1.76) and women (HR, 1.41; 95% CI, 1.09 to 1.81).

In multivariable models examining MetS risk factors in predicting mortality, only single components predicted risk: low HDL-C resulted in a greater risk only for CHD mortality (HR, 1.92; 95% CI, 1.31 to 2.82); hypertension resulted in an increased risk (HR, 1.70; 95% CI, 1.20 to 2.43) only for CVD mortality; and impaired fasting or impaired 2-hour glucose resulted in a higher risk only for overall mortality (HR, 1.31; 95% CI, 1.06 to 1.62). These risks can be compared with slightly greater risks seen for MetS (including diabetes) for
CHD, CVD, and total mortality (HR, 1.98, 1.87, and 1.44, respectively; all \( P \leq 0.0001 \)).

**Discussion**

MetS is associated with an increased risk of death from CHD, CVD, or all causes in US adults. Although diabetes is defined as a CHD risk equivalent,\(^1\)\(^7\) persons with MetS but without diabetes have a wide spectrum of risk.\(^1\)\(^6\) Persons with MetS who do not have diabetes, increased risks of CVD and CHD mortality remain. CHD, CVD, and total mortality risks are as high or nearly as high as risks in those with diabetes compared with those with pre-existing CVD, providing support to previous studies\(^1\)\(-\)\(^4\) and guidelines.\(^7\) Those with diabetes and CVD are at highest risk. Even those with 1 or 2 MetS risk factors are at a 2-fold-greater risk of CHD and CVD mortality, suggesting that risk is not “optimal” unless all MetS risk factors are absent. Finally, MetS predicts CHD, CVD, and total mortality more strongly than individual MetS risk factors, consistent with previous reports.\(^1\)\(^3\)

Our findings suggest the need for intensified treatment recommendations in persons with MetS and even in those with only 1 or 2 MetS risk factors. Intensive treatment of diabetes involving control of blood pressure, blood sugar, and blood lipids can result in reducing macrovascular and microvascular complications by \( \approx 50\% \).\(^1\)\(^7\) In persons with MetS, up to 80% of CHD events may be preventable from optimal control of LDL-C, HDL-C, and blood pressure.\(^1\)\(^6\)

Previous studies have not examined mortality risks in persons with MetS after separating out those with diabetes or those with known CVD.\(^1\)\(^2\)\(^,\)\(^1\)\(^3\)\(^,\)\(^1\)\(^8\) In those with MetS, >40% are at intermediate risk (10% to 20% 10-year risk) of CHD; \( \approx 20\% \) of men are at higher risk.\(^1\)\(^6\) Moreover, \( \approx 40\% \) of persons with MetS either are at high risk or have significant coronary calcium (\( \geq 75\% \)th percentile for age and sex); in these individuals, more aggressive risk factor management may be warranted.\(^1\)\(^9\)

Strengths of our study include its prospective design, reliable assessment of causes of death, generalizability from the use of a sample representative of the US population, and assessment of the impact of MetS alone relative to diabetes and pre-existing CVD on mortality end points. Our study excluded 2995 participants because of missing risk factor information on glucose and lipids. From a sensitivity analyses including these subjects, our main effects remained significant and in the same direction, despite some reduction in our HRs, probably as a result of some misclassification in the no-disease category. We classified all included subjects in our main analyses by confirming that those included in the

**TABLE 3. Multivariable Cox Proportional-Hazards Regression Relating Each Disease/Condition Compared With Neither Condition to CHD, CVD, and Overall Mortality in US Adults**

<table>
<thead>
<tr>
<th>Condition</th>
<th>CHD Mortality</th>
<th>CVD Mortality</th>
<th>Overall Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>No MetS, diabetes, or CVD</td>
<td>2878</td>
<td>1.0</td>
<td>…</td>
</tr>
<tr>
<td>MetS (all)</td>
<td>1698</td>
<td>2.02</td>
<td>1.42–2.89</td>
</tr>
<tr>
<td>MetS (no diabetes)*</td>
<td>1178</td>
<td>1.65</td>
<td>1.10–2.47</td>
</tr>
<tr>
<td>Diabetes*</td>
<td>520</td>
<td>2.87</td>
<td>1.84–4.47</td>
</tr>
<tr>
<td>Pre-existing CVD (all)</td>
<td>1679</td>
<td>4.19</td>
<td>3.04–5.79</td>
</tr>
<tr>
<td>Pre-existing CVD (no diabetes)*</td>
<td>1398</td>
<td>3.89</td>
<td>2.79–5.43</td>
</tr>
<tr>
<td>Diabetes and CVD*</td>
<td>281</td>
<td>6.45</td>
<td>4.24–9.79</td>
</tr>
</tbody>
</table>

\( n \) indicates unweighted sample sizes. HRs and 95% CIs are weighted to US population and adjusted for gender, age, smoking, physical activity, and total cholesterol.

*Categories represented in lieu of MetS (all) and pre-existing CVD (all) in a separate regression model.
TABLE 4. Multivariable Cox Proportional-Hazards Regression Examining Relation of Each MetS Risk Factor and Disease Category Compared With Those With No MetS Risk Factors to CHD, CVD, and Overall Mortality in US Adults

<table>
<thead>
<tr>
<th>Condition</th>
<th>CHD Mortality</th>
<th>CVD Mortality</th>
<th>Overall Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>No MetS RF</td>
<td>1228</td>
<td>1.0</td>
<td>…</td>
</tr>
<tr>
<td>1–2 MetS RF</td>
<td>1650</td>
<td>2.10</td>
<td>1.05–4.19</td>
</tr>
<tr>
<td>MetS (all)</td>
<td>1698</td>
<td>3.51</td>
<td>1.81–6.81</td>
</tr>
<tr>
<td>MetS (no diabetes)*</td>
<td>1178</td>
<td>2.87</td>
<td>1.44–5.73</td>
</tr>
<tr>
<td>Diabetes*</td>
<td>520</td>
<td>5.02</td>
<td>2.47–10.23</td>
</tr>
<tr>
<td>CVD (all)</td>
<td>1679</td>
<td>7.30</td>
<td>3.83–13.89</td>
</tr>
<tr>
<td>Pre-existing CVD*</td>
<td>1398</td>
<td>6.81</td>
<td>3.55–13.06</td>
</tr>
<tr>
<td>Diabetes and CVD*</td>
<td>281</td>
<td>11.30</td>
<td>5.66–22.56</td>
</tr>
</tbody>
</table>

RF indicates risk factors; n, unweighted sample sizes. HRs and 95% CIs are weighted to US population and adjusted for gender, age, smoking, physical activity, and total cholesterol.

*Categories represented in lieu of MetS (all) and pre-existing CVD (all) in a separate regression model.

References