Metabolic Syndrome as a Precursor of Cardiovascular Disease and Type 2 Diabetes Mellitus

Peter W.F. Wilson, MD; Ralph B. D’Agostino, PhD; Helen Parise, ScD; Lisa Sullivan, PhD; James B. Meigs, MD, MPH

Background — The incidence of cardiovascular disease (CVD), coronary heart disease (CHD), and type 2 diabetes mellitus (T2DM) has not been well defined in persons with the metabolic syndrome (at least 3 of the following: abdominal adiposity, low HDL cholesterol, high triglycerides, hypertension, and impaired fasting glucose). The objective was to investigate risk for CVD, CHD, and T2DM according to metabolic syndrome traits.

Methods and Results — The study followed a cohort of 3323 middle-aged adults for the development of new CVD, CHD, and T2DM over an 8-year period. In persons without CVD or T2DM at baseline, the prevalence of the metabolic syndrome (≥3 of 5 traits) was 26.8% in men and 16.6% in women. There were 174 incident cases of CVD, 107 of CHD, and 178 of T2DM. In men, the metabolic syndrome age-adjusted relative risk (RR) and 95% CIs were RR = 2.88 (95% CI 1.99 to 4.16) for CVD, RR = 2.54 (95% CI 1.62 to 3.98) for CHD, and RR = 6.92 (95% CI 4.47 to 10.81) for T2DM. Event rates and RRs were lower in women for CVD (RR = 2.25, 95% CI 1.31 to 3.88) and CHD (RR = 1.54, 95% CI 0.68 to 3.53), but they were similar for T2DM (RR = 6.90, 95% CI 4.34 to 10.94). Population-attributable risk estimates associated with metabolic syndrome for CVD, CHD, and T2DM were 34%, 29%, and 62% in men and 16%, 8%, 47% in women.

Conclusions — Metabolic syndrome is common and is associated with an increased risk for CVD and T2DM in both sexes. The metabolic syndrome accounts for up to one third of CVD in men and approximately half of new T2DM over 8 years of follow-up. (Circulation. 2005;112:3066-3072.)

Key Words: diabetes mellitus ■ coronary disease ■ epidemiology ■ glucose ■ obesity

Editorial p 3030

The incidence of cardiovascular disease (CVD) is greatly increased in the setting of type 2 diabetes mellitus (T2DM). Compared with middle-aged persons without diabetes, the relative risk (RR) for various CVD events in diabetic persons is typically increased 2-fold in men and 3-fold in women. The effects of the metabolic syndrome on the risk of CVD, coronary heart disease (CHD), T2DM, and changing prevalence in a single population sample in the 1990s have not been reported extensively.

The Framingham Heart Study Offspring Study began in the early 1970s but first collected data on all of the features that constitute the metabolic syndrome in the early 1990s. These data provided a baseline examination to investigate the effects of the metabolic syndrome on the risks for T2DM and CVD over 8 years of follow-up in a suburban, largely white population sample.

The NCEP-ATP III criteria for the metabolic syndrome and a publication of prevalence data from the National Health and Nutrition Examination Survey (NHANES) included persons with T2DM. In the present investigation, we elected to exclude persons with T2DM, to use fasting glucose 100 to 125 mg/dL as the impaired fasting glucose (IFG) criterion, as suggested by recent expert committees, and to classify persons taking antihypertensive therapy as hypertensive if they had a blood pressure ≥130/85 mm Hg. This analytic
approach affects the prevalence of the metabolic syndrome and allows analysis for the development of both T2DM and CVD outcomes during follow-up. It also allows assessment of the prevalence of the metabolic syndrome at baseline and 8 years later in a fixed cohort. We also undertook analyses in which a variable number of metabolic syndrome traits were considered.

**Methods**

Members of the Framingham Offspring Study who attended the fourth examination of the cohort were eligible for the present study. The sample included 1549 men and 1774 women aged 22 to 81 years who were free of CVD at the baseline examination in 1989 to 1993. Data obtained at that examination included determination of waist circumference while standing and measurement of blood pressure while seated. Participants were fasting at the baseline visit, and persons taking oral hypoglycemic agents or insulin were classified as diabetic (n=293) and excluded from the analyses.

Risk factor evaluation at the baseline visit included fasting lipids with determination of total cholesterol, triglycerides, and HDL cholesterol after heparin-manganese precipitation according to previously described methods with the Lipid Research Clinic’s protocol and standardized methods. Features of the metabolic syndrome considered for the present report included an increased waist circumference (>102 cm for men, >88 cm for women), blood pressure elevation (>130/85 mm Hg), low HDL cholesterol (<40 mg/dL [1.0 mmol/L] in men, <50 mg/dL [1.3 mmol/L] in women), high triglycerides (>150 mg/dL [1.7 mmol/L]), and hyperglycemia (fasting glucose ≥100 mg/dL [6.1 mmol/L]). The metabolic syndrome is considered present when at least 3 of the 5 traits are present, and affected individuals typically are insulin resistant. LDL cholesterol was calculated according to the Friedewald formula for persons with triglyceride levels <400 mg/dL. Persons who reported smoking cigarettes regularly during the past year were considered current smokers.

Subjects were followed up for 8 years for the occurrence of new CVD. Surveillance included information from Framingham clinic examinations, personal physician outpatient records, and hospitalizations for the adjudication of vascular disease events during follow-up. The occurrence of myocardial infarction or CHD death was categorized as hard CHD; occurrence of hard CHD or angina pectoris was considered total CHD; and evidence of total CHD, stroke, intermittent claudication, or cardiac failure was considered CVD.

Participants were also followed up for the development of diabetes. During the 8-year interval, the participants were invited to a Framingham clinic examination at follow-up year 4 and year 8. Fasting blood measures were made at each examination, and persons at the return visit who developed CVD in the interim were not excluded from prospective analyses for T2DM. The diagnosis of new T2DM was made for a fasting glucose ≥126 mg/dL (7.0 mmol/L) at the time of a follow-up clinic examination or if hypoglycemic therapy (oral agents or insulin) had been started in the interim.

The prevalence of metabolic syndrome was estimated at baseline by point estimates and 95% CIs. Prevalence estimates of metabolic syndrome 8 years later for persons who attended both examinations were generated by a similar approach, and comparisons were standardized directly to the sex-specific ages at baseline. Risks of adverse sequelae were estimated with the Cox proportional hazards regression model (for CVD events) or logistic regression (for T2DM events) that included metabolic syndrome and age as independent predictor variables. Exponentiation was used for the β-coefficients in the regression models to estimate the RR, and the standard error of the β-coefficients was used to calculate the 95% CIs of the RR estimates by published methods. Population-attributable risk (PAR) calculations were performed, where PAR = proportion of cases exposed to the factor × 100%/(RR - 1)/RR. Subsidiary analyses of outcomes considered alternative definitions of the metabolic syndrome. This approach required that only 2 of 5 metabolic criteria be present to satisfy the definition of the metabolic syndrome.

**Results**

A total of 1937 men and 2082 women in the age range of 22 to 81 years attended the index examination. Participants with diabetes (n=293), missing covariates (n=150), or body mass index <18.5 kg/m² (n=33) were excluded, which left 1549 men and 1774 women in the core analyses. Descriptive statistics for age and risk factors at the baseline examination are shown according to metabolic syndrome status in Table 1. When a level of fasting glucose of 100 to 125 mg/dL was used to satisfy the metabolic syndrome criteria, 11% of the men and 5% of the women did not have metabolic syndrome, and 43% of the men and 41% of the women had this trait. Had we used the fasting glucose criterion of 110 to 125 mg/dL as a metabolic syndrome criterion, the respective frequencies would have been extremely low (2% of men and 1% of women) both for those without metabolic syndrome and for those with metabolic syndrome (14% of men, 13% of women).

In analyses restricted to 1163 men and 1386 women who attended the baseline and follow-up examinations and who did not have CVD or T2DM at either visit, the prevalence of the metabolic syndrome (≥3 of 5 traits) in men with a mean age of 50 years at baseline was 21.4% (95% CI 19.3% to 24.0%) at the outset, and at the end of the 8-year interval, it was 38.8% (95% CI 36.0% to 41.6) and 33.9% (95% CI 31.2% to 36.7%) after direct adjustment to the baseline age, demonstrating an adjusted increase of 56% over the baseline rate. Correspondingly, for women with a mean age of 51 years at the outset, the prevalence was 12.5% (95% CI 10.7% to 14.2%) at the outset, and 8 years later, it was 30.6% (95% CI 28.2% to 33.0%) unadjusted and 23.6% (95% CI 21.3% to 25.8%) adjusted, which represents an increase of 47%.

RRs and PAR percent estimates for the development of CVD, total CHD, hard CHD, and T2DM during 8 years of surveillance are shown in Table 2 for men and women. During follow-up, there were 107 cases of total CHD (78 men, 29 women), 174 cases of CVD (116 men, 58 women), and 178 cases of T2DM (99 men, 79 women). In men, the age-adjusted RR was increased for CVD (RR=2.88), total CHD (RR=2.54), and hard CHD (RR=2.58). The age-adjusted PAR was ≈30% for both CVD and CHD, which indicates the fraction of vascular events that could be attributed to presence of the metabolic syndrome at the baseline evaluation. The age-adjusted RR for T2DM was markedly increased (RR=6.92), and the PAR was 62%.

In women, the age-adjusted RRs for CVD (RR=2.25, 95% CI 1.31 to 3.88), total CHD (RR=1.54, 95% CI 0.68 to 3.53), and hard CHD (RR=2.50, 95% CI 0.80 to 7.79) were modestly increased, and the age-adjusted PAR results were 16% for CVD and 8% for total CHD, much lower than the attributable risks for men. The age-adjusted RR for T2DM was also greatly increased in women (RR=6.90, 95% CI 4.35 to 10.94), with an estimated age-adjusted PAR of 47% (Table 2).

Analyses were undertaken that considered the potential effects of competing risks for adverse events in men and women with at least 3 of 5 metabolic syndrome traits, as shown in Table...
3. For example, in an analysis for persons at risk for CVD, those individuals who developed T2DM during the follow-up interval were excluded. Correspondingly, when we performed analyses for risk of T2DM, those individuals who developed CVD were excluded. The competing risk analyses did not appreciably alter the estimates of the RRs, statistical probability of the findings, or the overall results and are not shown.

The relation between the number of metabolic syndrome traits and RR for incident CVD and T2DM was investigated in greater detail in an analysis shown in Table 3. The

<table>
<thead>
<tr>
<th>Event</th>
<th>No. of Events/Nonevents, Metabolic Syndrome Absent</th>
<th>No. of Events/Nonevents, Metabolic Syndrome Present</th>
<th>RR (95% CI)</th>
<th>Age-Adjusted Statistical Significance</th>
<th>PAR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>53/1081</td>
<td>63/352</td>
<td>2.88 (1.99–4.16)</td>
<td>&lt;0.0001</td>
<td>33.7</td>
</tr>
<tr>
<td>Hard CHD (MI or CHD death only)</td>
<td>23/1111</td>
<td>25/390</td>
<td>2.58 (1.46–4.57)</td>
<td>0.0011</td>
<td>29.9</td>
</tr>
<tr>
<td>Total CHD</td>
<td>38/1096</td>
<td>40/375</td>
<td>2.54 (1.62–3.98)</td>
<td>&lt;0.0001</td>
<td>29.4</td>
</tr>
<tr>
<td>T2DM</td>
<td>28/1106</td>
<td>71/344</td>
<td>6.92 (4.47–10.81)</td>
<td>&lt;0.0001</td>
<td>61.5</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>37/1442</td>
<td>21/274</td>
<td>2.25 (1.31–3.88)</td>
<td>0.0034</td>
<td>15.8</td>
</tr>
<tr>
<td>Hard CHD (MI or CHD death only)</td>
<td>8/1471</td>
<td>5/290</td>
<td>2.50 (0.80–7.79)</td>
<td>0.1151</td>
<td>18.4</td>
</tr>
<tr>
<td>Total CHD</td>
<td>21/1458</td>
<td>8/287</td>
<td>1.54 (0.68–3.53)</td>
<td>0.3038</td>
<td>7.5</td>
</tr>
<tr>
<td>T2DM</td>
<td>33/1446</td>
<td>46/249</td>
<td>6.90 (4.35–10.94)</td>
<td>&lt;0.0001</td>
<td>46.9</td>
</tr>
</tbody>
</table>

*Defined as the presence of >3 of the 5 metabolic risk factors. All analyses are age-adjusted.
TABLE 3. Metabolic Syndrome and Age-Adjusted Risk for Outcomes for Framingham Offspring at 8-Year Follow-Up

<table>
<thead>
<tr>
<th>Event</th>
<th>No. of Metabolic Syndrome Risk Factors</th>
<th>Men, RR (95% CI)</th>
<th>Women, RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD</td>
<td>0 Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>1 or 2</td>
<td>1.48 (0.69–3.16)</td>
<td>3.39 (1.31–8.81)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>3.99 (1.89–8.41)</td>
<td>5.95 (2.20–16.11)</td>
<td></td>
</tr>
<tr>
<td>Hard CHD</td>
<td>0 Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>1 or 2</td>
<td>0.98 (0.36–2.67)</td>
<td>3.77 (0.45–31.28)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>2.55 (0.96–6.79)</td>
<td>7.21 (0.81–64.37)</td>
<td></td>
</tr>
<tr>
<td>Total CHD</td>
<td>0 Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>1 or 2</td>
<td>1.24 (0.54–2.83)</td>
<td>3.29 (0.95–11.34)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>3.01 (1.33–6.83)</td>
<td>3.96 (1.02–15.38)</td>
<td></td>
</tr>
<tr>
<td>T2DM</td>
<td>0 Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>1 or 2</td>
<td>4.16 (0.98–17.64)</td>
<td>6.10 (1.85–20.10)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>23.83 (5.80–98.01)</td>
<td>29.69 (9.10–96.85)</td>
<td></td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction.

age-adjusted RRs for CVD and T2DM are increased in persons with 1 or 2, or ≥3 of the metabolic syndrome traits are shown, and there were ∼22% of men and 37% of women without any metabolic syndrome traits who served as the referent groups. In this comparison, the RRs for CVD and T2DM rose in proportion to the number of metabolic syndrome traits present, and the gradient was much steeper for the outcome of T2DM.

The potential effects of various combinations of metabolic syndrome traits on the outcomes studied was investigated according to presence of single traits and their occurrence in pairs or triplets, as shown in Table 4. Risk for outcomes associated with specific trait combinations was estimated with the group without that specific combination used as the comparator. This analysis demonstrated the heterogeneity in distribution of the various trait combinations that make up the aggregate metabolic syndrome and the associated heterogeneity in risk for outcomes. The entries in the top of the table show the age- and sex-adjusted RRs for single risk factors. For example, the metabolic syndrome blood pressure criterion (model 1.4) was present in 48.8% of the participants and imparted an RR of 2.0 for CVD events, using a comparison group of persons without the metabolic syndrome blood pressure criterion. The metabolic syndrome traits that contributed most to CVD outcomes were blood pressure and HDL cholesterol, with PAR estimates of 33% (model 1.4 in Table 4) and 25% (model 1.5 in Table 4), respectively.

Prediction of T2DM shown in models 1.1 through 1.5 with each of the metabolic syndrome traits taken individually showed similar effects, with PAR estimates of 30% to 43%, except for IFG, which was associated with a very large 12-fold increased risk for incident T2DM and a PAR of 62%. Different combinations of 2 and 3 metabolic syndrome traits, shown at the bottom of Table 4, provided estimates for the outcomes, but the prevalence of some combinations was small. Analyses based on a larger number of persons at risk or that combined groups were more informative. For example, models 3.1 through 3.6 (Table 4), which included IFG were all highly related to the development of T2DM and had RRs for vascular disease outcomes that were much lower. The composite model 3a (Table 4) synthesized information for all groups that included IFG and 2 additional metabolic syndrome traits. This trait grouping was present in 8.9% of individuals and was associated with a very high RR for T2DM during follow-up (RR = 11.0) and less impressive RRs (2.1 to 2.5) for vascular disease events. Model 3b synthesized information for all groups, including a large waist circumference but not including IFG. This trait grouping was present in 13.2% of individuals and was associated with an elevated RR for T2DM (5.0), and risk for incident CVD was also increased ∼2-fold.

Discussion

This article presents the prevalence and change in prevalence during the 1990s of the metabolic syndrome using NCEP ATP III criteria that were modified to exclude diabetes. We provide evidence of an age-adjusted increase in prevalence of the metabolic syndrome of ∼50% over the 8-year follow-up interval. The greater frequency at the follow-up examination is undoubtedly linked to overweight and obesity and the propensity for risk factors to cluster with excess adiposity. The present metabolic syndrome trend analysis was restricted to persons who attended both examinations, and a portion of the greater prevalence is attributed to aging itself. A recent publication based on NHANES survey data reported an age-adjusted prevalence of the metabolic syndrome of 24.1% in NHANES III and 27.0% in NHANES 1999 to 2000; sex-specific analyses showed an age-adjusted increase in the metabolic syndrome of 23.5% in women and 2.2% in men. The changes in the NHANES reports are much smaller, and estimates are derived from 2 separate cross-sectional surveys, whereas the Framingham analysis is based on a single cohort that was assessed on 2 occasions.

Risks for CHD, hard CHD, and CVD were increased in male participants with the metabolic syndrome at baseline. Several studies have evaluated risk of initial CVD events in persons with prior evidence of the metabolic syndrome and found similar vascular risk elevations as in the present report, but it is difficult to generalize from the experience of a population sample that was at high risk for CHD, such as the West of Scotland Coronary Prevention Study (WOSCOPS) cohort. In addition, no increased CVD risk was seen in American Indians in the Strong Heart Study, and CVD mortality risk was relatively modest in the NHANES III follow-up study for persons with the metabolic syndrome. The RR for CVD outcomes was typically doubled for men in the present study, and only modest vascular disease effects were observed in women, which is probably attributable to the fact that many of the women were premenopausal or perimenopausal and at relatively lower risk for CVD events.

It has been suggested that hyperinsulinemia may provide especially valuable information to identify persons with the metabolic syndrome who are at greater risk for CVD. We did not have fasting insulin measures at the baseline examination, but we observed a doubling of risk for vascular disease outcomes in men with metabolic syndrome (Tables 2 and 4). A greater number of metabolic syndrome traits led to...
a greater risk for events (Table 3). Previous research suggests that CVD risk factors have an additive effect on risk for CVD, and the same statement is generally true for metabolic syndrome traits and risk for CVD and T2DM.22 As shown in Table 4, the finding that clusters of 3 traits do not substantially increase risk for outcomes over risk associated with clusters of 2 traits is consistent with the hypothesis that even a modest degree of risk factor clustering reflects a global underlying insulin-resistant pathophysiology,23 and individual risk factors may contribute marginally to risk associated with the insulin-resistant phenotype.

In the present study, the RR of incident T2DM was greatly increased in persons with metabolic syndrome at baseline. The overall RRs exceeded 4 in both sexes. Other studies have shown that metabolic syndrome confers an increased risk for the development of T2DM, with a variety of RR estimates.
including an RR of 3.5 in WOSCOPS, \textsuperscript{19} \(\approx 2\) in the Strong Heart Study, \textsuperscript{9} 5.9 with 3 metabolic syndrome traits and 17.9 with \(\geq 4\) metabolic syndrome traits in the Beaver Dam Study, \textsuperscript{18} \(\leq 1.5\) in the Pima Indian Study, \textsuperscript{30} and 6.3 in the San Antonio Heart Study. \textsuperscript{31} Other investigators have noted that the IFG trait in particular identifies metabolic syndrome subjects at high risk of developing T2DM. \textsuperscript{18, 31, 32} The present data corroborate that finding and use the most recent definition of IFG (fasting glucose 100 to 125 mg/dL). \textsuperscript{8, 7, 33} as seen in Table 4 for models that include the glucose criterion. Ancillary data from a glucose tolerance test or C-reactive protein levels may further identify persons at greater risk for T2DM. \textsuperscript{31} The present data show that IFG without the knowledge of other factors or IFG accompanied by 1 or more metabolic syndrome traits deserves special attention because it portends poor glycemic control and subsequent development of T2DM. However, trait combinations that did not include IFG also imparted an increased risk for incident T2DM, which is consistent with the concept that metabolic syndrome trait combinations reflect an underlying insulin-resistant pathophysiology. A subgroup analysis similar to what we show in Table 4 was undertaken by scientists in the Atherosclerosis Risk In Communities study in an analysis of associations between metabolic syndrome traits and carotid intima-media thickness. They identified increased risk for thicker intima-media thickness in persons with hypertension and elevated triglycerides \textsuperscript{34}; the present results did not show that specific clusters of 3 or more metabolic factors were associated with greater risk for CVD outcomes (Table 4, models 3.1 to 3.10).

The PAR for the development of T2DM in the present study was \(\approx 60\%\) in men and 45\% in women, which indicates that a large fraction of persons who developed T2DM had the metabolic syndrome during the past 8 years. Greater risk for T2DM than for CVD may reflect the fact that insulin resistance is a powerful risk factor for diabetes and is situated in a critical step on the causal pathway, \textsuperscript{35} but insulin resistance may be less important in the development of CVD, especially after dyslipidemia, hypertension, and the age of the cohort are taken into consideration. \textsuperscript{36} The large PAR of the metabolic syndrome for T2DM has important implications for prevention. Amelioration of metabolic syndrome traits through lifestyle interventions or medications in persons with impaired glucose tolerance has been shown to effectively prevent or retard the development of T2DM. \textsuperscript{37}

These Framingham results reflect the experience of a suburban population sample of white individuals. A single baseline evaluation was used for these analyses, and the metabolic syndrome traits are subject to misclassification, but we believe that our analyses provide conservative estimates of outcome risks. Different results might be obtained with other racial and ethnic groups or in other locales, \textsuperscript{38} but the experiences in Finland and Scotland are consistent with what we report. \textsuperscript{17, 19}

In conclusion, we have shown a rise in the prevalence of the metabolic syndrome over 8 years in a population-based sample that was examined twice. The metabolic syndrome increased the RR for CVD in men and for T2DM in both sexes in middle-aged adults. Our findings suggest that there may be value in diagnosing the metabolic syndrome, not just for specific treatment of insulin resistance but to identify persons (even with only modestly elevated risk factors) with an extremely adverse metabolic state that warrants aggressive intervention for specific traits.

**Acknowledgments**

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**Disclosure**

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**References**


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