Metabolic Syndrome and the Risk of Stroke in Middle-Aged Men

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Background and Purpose—The metabolic syndrome, a clustering of disturbed glucose and insulin metabolism, obesity and abdominal fat distribution, dyslipidemia, and hypertension, is associated with cardiovascular diseases. The aim of this study was to examine the relationship of metabolic syndrome, as defined by National Cholesterol Education Program (NCEP) and World Health Organization (WHO) criteria, with the risk for stroke.

Methods—Population-based cohort study with an average follow-up of 14.3 years from eastern Finland. A total of 1131 men with no history of cardiovascular disease and diabetes at baseline participated. Sixty-five strokes occurred, of which 47 were ischemic strokes.

Results—Men with the metabolic syndrome as defined by the NCEP criteria had a 2.05-fold (95% CI, 1.03 to 4.11; P=0.042) risk for all strokes and 2.41-fold (95% CI, 1.12 to 5.32; P=0.025) risk for ischemic stroke, after adjusting for socioeconomic status, smoking, alcohol, and family history of coronary heart disease. Additional adjustment for ischemic changes during exercise test, serum low-density lipoprotein cholesterol, plasma fibrinogen, energy intake for saturated fats, energy expenditure of leisure time physical activity, and white blood cell count, the results remained significant. The risk ratios among men with metabolic syndrome as defined by the WHO criteria were 1.82 (95% CI, 1.01 to 3.26; P=0.046) for all strokes and 2.16 (95% CI, 1.11 to 4.19; P=0.022) for ischemic stroke. After further adjustment, the respective risks were 2.08 (95% CI, 1.12 to 3.87; P=0.020) and 2.47 (95% CI, 1.21 to 5.07; P=0.013).

Conclusion—The risk of any stroke is increased in men with metabolic syndrome, in the absence of stroke, diabetes and cardiovascular disease at baseline. Prevention of the metabolic syndrome presents a great challenge for clinicians with respect to stroke. (Stroke. 2006;37:806-811.)

Key Words: diabetes mellitus ■ ischemic stroke ■ metabolic syndrome ■ prospective studies ■ risk factors ■ stroke

The metabolic syndrome, a clustering of disturbed glucose and insulin metabolism, obesity and abdominal fat distribution, dyslipidemia, and hypertension, is associated with cardiovascular disease (CVD) and death together with the subsequent development of type II diabetes mellitus.1 The syndrome is also called insulin resistance syndrome. Insulin resistance syndrome has been widely used because the syndrome is characterized by insulin resistance. The presence of metabolic syndrome has varied widely between studies because of different criteria for the definition of the syndrome. The World Health Organization (WHO) consultation for the classification of diabetes and its complication and National Cholesterol Education Program (NCEP) expert panel have recently published definitions to aid in the research and clinical application of the syndrome.2,5

Whereas sedentary lifestyle contributes to the development of obesity, both have a major impact on the CVD morbidity and mortality worldwide, and the metabolic syndrome is becoming increasingly very common.4 On the basis of NCEP definition, almost one third of middle-aged men and women in the United States have the metabolic syndrome.5 A recent case-control study has shown the risk of ischemic stroke in elderly from metabolic syndrome, whereas another study has shown the relationship between metabolic syndrome and ischemic stroke and transient ischemic attack in patients with atherosclerotic CVD.6,7

However, little is known of the association of the metabolic syndrome with stroke. We assessed the association of the metabolic syndrome based on the definitions of WHO and NCEP with any and ischemic stroke in a population-based cohort of middle-aged men who did not have stroke, diabetes, or CVD at baseline.

Methods

Subjects
Subjects were participants in the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD), which is a population-based, randomly selected sample of 2682 men from eastern Finland2 42, 48, 54, or 60 years of age at baseline who resided in the town of Kuopio or its vicinity. The study was conducted from 1984 to 1989. The KIHD cohort has been updated twice: most recently in 2001. The updated database included information on all recorded hospitalizations and deaths. Subjects with a history of stroke or diabetes at baseline or during follow-up were excluded from the present study. The Ethics Committee of the Kuopio University Hospital approved the study, and informed consent was obtained from all participants.

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surrounding rural communities. For the present study, 1096 men with history of stroke (69), CVD (1016), or diabetes (174) at baseline were excluded. Men with missing data (455) on waist circumference or biochemical values included in the definition of the metabolic syndrome were excluded, leaving 1131 for the analyses.

Assessment of Metabolic Syndrome

Blood pressure was measured with a random-zero sphygmomanometer. The mean of 6 measurements (3 while supine, 1 while standing, and 2 while sitting) of systolic and diastolic blood pressure was used. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was calculated as the average of 2 measurements taken after inspiration and expiration at the midpoint between the lowest rib and iliac crest. Waist/hip ratio (WHR) was defined as waist girth/hip circumference measured at the trochanter major.

Participants were asked to fast and to refrain from smoking for 12 hours and to avoid alcohol intake for 3 days before blood sampling. Blood glucose was measured using a glucose dehydrogenase method after precipitation of proteins by trichloracetic acid. Insulin was measured with a radioimmunoassay kit (Novo Nordisk) from the serum samples stored at −80°C. Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) fractions were separated from fresh serum by combined ultracentrifugation and precipitation. Lipoprotein fraction cholesterol and triglycerides were measured enzymatically. Measurement of fibrinogen and white blood cell (WBC) count and socioeconomic status (SES) has been described previously.

Metabolic Syndrome

The metabolic syndrome as defined by the NCEP was the presence of ≥3 of the following: fasting plasma glucose of ≥110 mg/dL (6.1 mmol/L), serum triglycerides of ≥150 mg/dL (1.7 mmol/L), serum HDL cholesterol <40 mg/dL (1.04 mmol/L), blood pressure of ≥130/85 mm Hg, or waist girth of ≥102 cm. Waist girth of ≥94 cm was suggested for men genetically susceptible to insulin resistance. In keeping with the clinically oriented NCEP recommendations, the cutoff for HDL cholesterol was rounded off in SI units (<1.0 mmol/L [39 mg/dL]). The cutoff for elevated blood glucose, 101 mg/dL (5.6 mmol/L), was used.

The metabolic syndrome for men according to the WHO definition was defined as hyperinsulinemia or elevated fasting glyceremia and ≥2 of the following: abdominal obesity, dyslipidemia, or hypertension. Insulin resistance was estimated as hyperinsulinemia based on fasting insulin levels in the upper fourth. Impaired fasting glyceremia was defined as fasting blood glucose of ≥101 to 109 mg/dL (5.6 to 6.0 mmol/L). Diabetes was defined as blood glucose of ≥110 mg/dL (6.1 mmol/L) or a clinical diagnosis of diabetes with dietary, oral, or insulin treatment. Men with diabetes at baseline were excluded.

As suggested by the European Group for the Study of Insulin Resistance, hypertension was defined at a lower level than the original WHO definition for consistency with the WHO International Society of Hypertension and Sixth Joint National Committee recommendations, and microalbuminuria was not included in the definition. The original WHO cutoff for HDL cholesterol was maintained. Abdominal obesity was defined according to the original WHO definition (WHR >0.90 or BMI ≥30) and the European Group for the Study of Insulin Resistance recommendation (waist girth ≥94 cm). These modifications of the WHO and NCEP definitions have been validated recently.

Assessment of Other Covariates

Assessment of smoking, alcohol consumption, SES, fibrinogen, and exercise-induced myocardial ischemia, medical history and medica-
tions, and family history of diseases have been described previously. Leisure time physical activity was assessed using the KIHD 12-Month Leisure-Time Physical Activity Questionnaire. This detailed quantitative questionnaire deals with the most common physical activities of middle-aged Finnish men and enables the assessment of all components of physical activity. Dietary energy intake was assessed using 4-α food recording. Instructions were given, and completed food records were checked by a nutritionist. Intake of nutrients was estimated using the NUTRICoptic software.

Statistical Analysis

The associations of NCEP and WHO definitions of the metabolic syndrome with strokes were analyzed with forced Cox proportional hazards regression models with adjustment for age and examination year (model 1); age, examination year, smoking, alcohol consumption, family history of CHD, and SES (model 2); and age, examination year, LDL cholesterol, smoking, alcohol, family history of CHD, SES, ischemic changes during exercise test, energy intake for saturated fats, energy expenditure of leisure time physical activity, WBC, and fibrinogen concentrations (model 3). Relative hazards, adjusted for risk factors, were estimated as antilogarithms of coefficients from multivariate models. The fit of the proportional hazards models was examined by plotting the hazard functions in different categories of risk factors over time. The results indicated that the application of the models was appropriate. All statistical analyses were performed using the SPSS 11.0 Windows software.

Results

Baseline Characteristics

At the beginning of the follow-up, there were 187 (14.8%) of 1264 men who had metabolic syndrome according to WHO definition and 114 (9.0%) men with metabolic syndrome according to NCEP definition. Baseline characteristics in men with and without metabolic syndrome according to the definition of NCEP are shown in Table 1. Serum insulin and glucose levels, BMI, WHR, and blood pressure were higher and maximal oxygen uptake lower in men with metabolic syndrome. They were more likely to be nonsmokers and consumed more alcohol than men without metabolic syndrome. A total of 65 incident stroke occurred during the
average 14.3-year (range 0.4 to 17.7 years) follow-up, and a total of 47 were because of ischemic reasons.

Metabolic Syndrome (NCEP) and Stroke Risk
Age- and examination year–adjusted relative risk (RR) for stroke in men with metabolic syndrome was 2.0-fold increased risk (Table 2). After adjustment for age, examination year, SES, family history of coronary heart disease, alcohol, and smoking, the risk was even higher (RR, 2.05). When further adjusted for other known risk factors (ischemic changes during exercise test, serum LDL cholesterol, plasma fibrinogen, energy intake for saturated fats, energy expenditure of leisure time physical activity, and WBC), the risk remained 2.39-fold (Table 2).

Age- and examination year–adjusted RR for ischemic stroke in men with metabolic syndrome was 2.31-fold increased risk. After adjustment for age, examination year, SES, family history of coronary heart disease, alcohol, and smoking, the risk was almost the same (RR, 2.41). When further adjusted for other known risk factors (ischemic changes during exercise test, serum LDL cholesterol, plasma fibrinogen, energy intake for saturated fats, energy expenditure of leisure time physical activity, and WBC), the risk for ischemic stroke was 2.78-fold (Table 2).

### TABLE 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Men With No Metabolic Syndrome (n=1017)</th>
<th>Men With Metabolic Syndrome (n=114)</th>
<th>P Value for Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>51.6 (5.8)</td>
<td>51.8 (5.8)</td>
<td>0.767</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.2 (3.0)</td>
<td>30.2 (4.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WHR</td>
<td>0.94 (0.06)</td>
<td>0.99 (0.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>31.5</td>
<td>24.1</td>
<td>0.108</td>
</tr>
<tr>
<td>Cigarette smoking (pack years)</td>
<td>7.75 (15.9)</td>
<td>5.95 (13.3)</td>
<td>0.261</td>
</tr>
<tr>
<td>Alcohol consumption (g/week)</td>
<td>75.1 (119.2)</td>
<td>103.7 (181.4)</td>
<td>0.024</td>
</tr>
<tr>
<td>Fasting serum glucose (μmol/L)</td>
<td>4.54 (0.44)</td>
<td>4.87 (0.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting serum insulin (mU/L)</td>
<td>10.0 (5.0)</td>
<td>16.8 (9.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum total cholesterol (mmol/L)</td>
<td>5.77 (1.0)</td>
<td>6.14 (0.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum LDL cholesterol (mmol/L)</td>
<td>3.92 (0.95)</td>
<td>4.10 (0.94)</td>
<td>0.079</td>
</tr>
<tr>
<td>Serum HDL cholesterol (mmol/L)</td>
<td>1.34 (0.28)</td>
<td>1.00 (0.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum triglycerides (mmol/L)</td>
<td>1.15 (0.57)</td>
<td>2.35 (1.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma fibrinogen (g/L)</td>
<td>2.95 (0.56)</td>
<td>3.02 (0.51)</td>
<td>0.183</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>132.0 (15.8)</td>
<td>139.1 (12.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>87.8 (10.2)</td>
<td>94.8 (8.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dietary energy intake (kJ/day)</td>
<td>10 185 (2713)</td>
<td>9858 (2511)</td>
<td>0.234</td>
</tr>
<tr>
<td>Energy expenditure of CLTPA</td>
<td>137.0 (153.7)</td>
<td>130.1 (170.8)</td>
<td>0.660</td>
</tr>
<tr>
<td>Maximal oxygen uptake (mL/kg per min)</td>
<td>33.6 (7.7)</td>
<td>27.8 (5.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CLTPA denotes conditioning leisure time physical activity on the basis of NCEP definition.

### TABLE 2. Risk of Stroke According to WHO Definition of Metabolic Syndrome

<table>
<thead>
<tr>
<th>Metabolic Syndrome</th>
<th>Risk for Any Stroke (65 cases)</th>
<th>Risk for Ischemic Stroke (47 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>No (n=1017)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Yes (n=114)</td>
<td>2.00 (1.01–3.95)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

*On the basis of NCEP definition.*

Model 1, adjusted for age, examination year; model 2, adjusted for age, examination year, family history of coronary heart disease, smoking, alcohol, and SES; model 3, adjusted for age, examination year, family history of coronary heart disease, smoking, alcohol, SES, ischemic changes during exercise test, serum LDL cholesterol, plasma fibrinogen, energy intake for saturated fats, energy expenditure of leisure time physical activity, and WBC.
stroke in men with metabolic syndrome. After adjustment for age, examination year, family history of coronary heart disease, alcohol consumption, SES, and smoking, the risk was RR, 1.82 (95% CI, 1.01 to 3.26; \( P = 0.046 \)). When further adjusted for other known risk factors (ischemic changes during exercise test, serum LDL cholesterol, plasma fibrinogen, energy intake for saturated fats, energy expenditure of leisure time physical activity, and WBC), the risk for ischemic stroke was 2.08 (95% CI, 1.12 to 3.87; \( P = 0.020 \); Table 3).

The metabolic syndrome as defined by WHO was associated with 2.16 times (95% CI, 1.10 to 4.19; \( P = 0.022 \)) higher risk for ischemic stroke, after adjustment for age, examination year, family history of coronary heart disease, alcohol, SES, and smoking. Further adjustment for ischemic changes during exercise test, serum LDL cholesterol, energy intake for saturated fats, energy expenditure of leisure time physical activity, WBC count, and plasma fibrinogen, the risk was 2.47 times (95% CI, 1.21 to 5.07; \( P = 0.013 \)) higher risk for ischemic stroke compared with men with no metabolic syndrome.

### Discussion

This prospective population-based cohort shows the association of the metabolic syndrome using recently proposed definitions with the risk of any and ischemic stroke in middle-aged men who were free of stroke diabetes and CVD at baseline. This is the first prospective population-based cohort study reporting the association of the metabolic syndrome using recently proposed definitions with the risk of stroke. The increased risk of any and ischemic strokes observed in this study was independent of other known risk factors such as alcohol consumption, LDL cholesterol, and smoking among men with metabolic syndrome.

In this cohort, the prevalence of metabolic syndrome at baseline varied from 9% to 14% depending on the definition used. A recent study had shown that the prevalence of metabolic syndrome is 43% in stroke patients.

These figures are lower than the alarming nearly 30% prevalence of the metabolic syndrome (NCEP with waist >102 cm) reported for 40- to 59-year-old men in the National Health and Nutrition Examination Survey III. The same disturbing trends of increasing overall and abdominal obesity that are occurring globally are also occurring in Finland. It is likely that as the prevalence of the metabolic syndrome increases, so will the disease burden imposed by its consequences, such as type 2 diabetes and CVD.

A previous study has shown that metabolic syndrome is associated with self-reported history of stroke and myocardial infarction and stroke together. This study did not show the results according to different types of strokes separately. In our study, the risk of stroke was quite similar whether we used the definition based on WHO or NCEP criteria (Figures 1 and 2). The differences observed in risk between the WHO definitions based on WHR and waist circumference were more subtle and overlapped widely. Second, we found previously that the WHO definition of the metabolic syndrome with adiposity based on WHR detected more cases (67%) of diabetes during follow-up, whereas NCEP definitions missed most cases of diabetes, especially that with waist >102 cm.

The metabolic syndrome is a risk factor for stroke that seemingly has an underlying metabolic causation. Central obesity is the centerpiece of the metabolic alterations. Accordingly, increased abdominal adiposity contributes to dyslipidemia, hyperglycemia, and hypertension. In \( \approx \) 20% of the

### Table 3. Risk of Stroke According to Metabolic Syndrome* in Men With No Previous CVD or Diabetes Mellitus

<table>
<thead>
<tr>
<th>Metabolic Syndrome</th>
<th>Risk for Any Stroke (65 cases)</th>
<th>Risk for Ischemic Stroke (47 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1 RR (95% CI)</td>
<td>( P ) Value</td>
</tr>
<tr>
<td>No (n=956)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes (n=175)</td>
<td>1.85 (1.04–3.30)</td>
<td>0.037</td>
</tr>
</tbody>
</table>

*On the basis of WHO definition.

**Model 1**, adjusted for age, examination year; **model 2**, adjusted for age, examination year, family history of coronary heart disease, smoking, alcohol, and SES; **model 3**, adjusted for age, examination year, family history of coronary heart disease, smoking, alcohol, SES, ischemic changes during exercise test, LDL cholesterol, energy intake for saturated fats, energy expenditure of leisure time physical activity, blood leukocyte count, and plasma fibrinogen.
cases with metabolic syndrome, there is also \( \beta \)-cell dysfunction that leads to the clinical manifestation of diabetes mellitus. Recent evidence suggests that increased obesity is also associated with inflammation. Furthermore, hypertension accelerates the atherosclerotic process in carotid and vertebral arteries\(^{20}\) that usually starts in the larger extracerebral arteries, particularly in the carotid bifurcation. This process with time spreads distally to the smaller intracerebral arteries, leading to increased vascular resistance and hypertension during exercise and hence the increased risk of cardiovascular events.\(^{21}\)

The elevations of inflammatory markers are associated with metabolic risk factors and with accelerated atherosclerotic diseases. Obesity, insulin resistance, and the risk factors of the metabolic syndrome are related to high levels of inflammatory markers that may provide a causal pathway to atherosclerotic cerebrovascular diseases. Insulin resistance has been linked with a proinflammatory state and the elevations of inflammatory markers.\(^{22}\) In a recent finding from our study population, low-grade inflammation may increase the risk of metabolic syndrome, although some of the risk is mediated through obesity and factors related to insulin resistance.\(^{23}\) On the other hand, atherogenesis of cerebral arteries may represent a low-grade chronic inflammation. When atherogenesis is accelerated by multiple risk factors, it is possible that the inflammatory response within the arterial wall is sufficiently severe to elicit increased levels of acute phase reactants, such as C-reactive protein and fibrinogen. In previous studies,\(^{24}\) C-reactive protein is a marker of systemic inflammation that had been associated with an increased risk of incident stroke.\(^{25}\) It is suggested that C-reactive protein levels are related to future development of hypertension, suggesting that hypertension is in part in inflammatory disorder.\(^{26}\) Second, C-reactive protein levels have been found to have a prognostic value in the occurrence of persistent atrial fibrillation, which may increase the risk of stroke.\(^{25,26}\)

Previous evidence shows that relatively modest lifestyle interventions can have an impact on decreasing the risk for diabetes in glucose-intolerant individuals.\(^{27,28}\) Physical activity,\(^{29}\) weight loss,\(^{4}\) and diet\(^{30}\) have been shown to favorably affect components of the metabolic syndrome, at least in the relatively short term. It is known that good cardiorespiratory fitness and physical activity are related to the risk of stroke.\(^{31}\) No studies exist showing that lifestyle interventions can prevent the metabolic syndrome itself.

The strengths of this study include its prospective population-based design, with reliable data on various causes of diseases including assessment of causes of stroke, detailed assessment of metabolic risk factors, and exclusion of stroke, diabetes, and CVD at baseline. The different types of strokes were prospectively ascertained by Finnish National Discharge Registry using personal identification codes. Our study emphasizes the importance of metabolic syndrome in a relatively homogenous middle-aged male population from eastern Finland. A limitation is the absence of women and elderly from the cohort. Furthermore, the study design does not allow generalization to other races. Our population is exclusively white and homogenous, which may limit the generalizability to other ethnic groups. The small number of strokes requires caution while interpreting results of our study. Some residual confounding may not explain the statistically significant findings in this study, despite the careful adjusting for many well-known risk factors.

Middle-aged men with the metabolic syndrome as defined by the NCEP and WHO have an increased risk for stroke in the absence of stroke, diabetes, and CVD at baseline. Because of additional evidence from our study showing an association between metabolic syndrome and stroke, the threat to public health will continue to increase as the metabolic syndrome becomes more common. Early identification, treatment, and ultimately prevention of the metabolic syndrome present a major challenge for health care professionals and public health policy-makers facing an epidemic of overweight and sedentary lifestyle.

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