Components of the Metabolic Syndrome and Risk for First-Ever Acute Ischemic Nonembolic Stroke in Elderly Subjects

Haralampos J. Milionis, MD; Evangelos Rizos, MD; John Goudevenos, MD; Konstantinos Seferiadis, PhD; Dimitri P. Mikhailidis, MD, FRCP; Moses S. Elisaf, MD, FRSH

Background and Purpose—Metabolic syndrome (MetSyn) represents a constellation of lipid and nonlipid risk factors for cardiovascular disease and is a recognized target for increased behavioral therapy.

Objective—The association between acute ischemic/nonembolic stroke and the MetSyn in elderly individuals was assessed in a population-based case-control study in the prefecture of Ioannina, Greece.

Study Population—A total of 163 patients aged older than 70 years admitted with first-ever-in-a-lifetime acute ischemic/nonembolic stroke and 166 controls were included.

Results—The prevalence of MetSyn (defined according to NCEP/ATP III criteria) was high in stroke patients (46.0% versus 15.7%, \(P<0.001\)). Compared with controls as a group (with and without MetSyn), stroke patients with the MetSyn showed higher concentrations of triglycerides, lipoprotein(a), uric acid, and fibrinogen, and lower high-density lipoprotein (HDL) cholesterol and apolipoprotein A-I levels. In logistic regression analysis, crude and adjusted odd ratios (ORs) for MetSyn were 5.33 (95% confidence interval [CI], 2.91 to 9.79; \(P<0.0001\)) and 2.59 (95% CI, 1.24 to 5.42; \(P=0.012\)), respectively. The analysis of interaction between MetSyn and its individual components revealed significant associations with abdominal obesity (adjusted OR, 2.74; 95% CI, 1.15 to 6.50; \(P=0.02\)), hypertension (OR, 2.03; 95% CI, 0.91 to 4.49; \(P=0.08\)), high fasting glucose levels (OR, 2.95; 95% CI, 1.19 to 7.35; \(P=0.02\)), high triglyceride (OR, 5.55; 95% CI, 2.71 to 11.37; \(P<0.0001\)), and low HDL cholesterol (OR, 5.42; 95% CI, 2.85 to 10.30; \(P<0.0001\)). Notably, in stroke patients with the MetSyn the inverse relationship between HDL cholesterol levels and ischemic stroke was negated (OR, 1.04; 95% CI, 1.02 to 1.05; \(P<0.0001\)).

Conclusions—MetSyn is associated with an increased risk for acute ischemic/nonembolic stroke in elderly subjects with significant contributions from its individual components. In the presence of MetSyn, HDL cholesterol loses its protective role against ischemic stroke. (Stroke. 2005;36:1372-1376.)

Key Words: elderly ■ lipids ■ ischemic stroke ■ metabolic syndrome

Stroke is a major cause of mortality in the industrialized countries, leading to serious long-term physical and mental disabilities among survivors.\(^1\) Because of its disproportionate impact on the elderly, who comprise the fastest growing proportion of the population, stroke has a major impact on health care systems.\(^2\)

The term “metabolic syndrome” (MetSyn) represents a “constellation” of lipid and nonlipid risk factors for cardiovascular disease and is closely linked to a generalized metabolic disorder referred to as insulin resistance.\(^3\) It has been recognized as a secondary target for increased behavioral therapy in the National Cholesterol Education Program (NCEP)/Adult Treatment Panel (ATP) III.\(^4\) The components of MetSyn identified in these guidelines have been shown to be highly predictive of cardiovascular risk.\(^4\)

In a population-based case-control study, we evaluated potentially modifiable risk factors, including individual components of the MetSyn, for acute ischemic/nonembolic stroke among the elderly.\(^5\) The study was conducted in the prefecture of Ioannina, Epirus (Northwestern Greece), a nonindustrialized part of the country with 170 000 inhabitants, with those older than 70 years representing 18% to 20% of the total population.\(^5\)

Subjects and Methods
A total of 163 elderly patients (88 men, 75 women) who were consecutively hospitalized over a 5-year period for first-ever-in-a-lifetime acute ischemic stroke and 166 volunteers (87 men, 79 women) consecutively evaluated in the primary care setting were included in the study.\(^5\)

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Criteria for inclusion in the study were: (1) subjects aged older than 70 years; (2) residing in the prefecture of Ioannina; (3) known to attend the Public Primary Care Health Centre facilities regularly for the past 5 years before enrollment; and (4) patients reaching the emergency department of the University Hospital of Ioannina (the referral center for patients with cerebrovascular disease older than 65 years in the region) within 12 hours from the onset of symptoms.3 The diagnosis of first-in-a-lifetime acute ischemic/nonembolic stroke was based on history (clinical course, associated symptoms), physical examination (including neurologic and cardiac assessment), and radiologic study (initial noncontrast brain CT scan). Further confirmation involved full cardiac evaluation (history and physical, electrocardiogram, and a transthoracic echocardiogram) and carotid Doppler ultrasound to exclude a cardiac and/or carotid artery source of emboli, and a new brain CT scan when appropriate.

Subjects with a history of vascular disease (previous stroke, angina, myocardial infarction, revascularizations, peripheral artery disease), active infections, neoplasia, renal or liver disease, thyroid dysfunction, chronic obstructive pulmonary disease, chronic inflammatory bowel disease, and excessive alcohol consumption were excluded. Stroke patients and controls with a known or possible cardiac source of emboli (atrial fibrillation, heart valve disease, patients receiving anticoagulant treatment) were also excluded. None of the participants was receiving specific lipid-lowering treatment (ie, a statin or a fibrate). All subjects gave informed consent and the study protocol was approved by the Institutional Ethics Committee.

Hypertensive patients were recorded according to medical history and relevant drug treatment. Moreover, blood pressure measurements (for patients during the acute episode as well as for controls) were obtained in the sitting position in triplicate on the subject’s nondominant arm and after a 10-minute rest using a validated mercury sphygmomanometer. Diabetes mellitus was coded as present according to the medical records and/or relevant treatment. The diagnosis of MetSyn was made when 3 or more of the following risk factors were present: abdominal obesity (waist circumference [standing position] >102 cm for men; >88 cm for women), triglycerides (TG) ≥150 mg/dL (1.7 mmol/L), low high-density lipoprotein cholesterol (HDL-C) (ie, <40 mg/dL [1.0 mmol/L] for men; <50 mg/dL [1.3 mmol/L] for women), hypertension (history and/or treatment), and fasting glucose ≥110 mg/dL (6.1 mmol/L).4

Laboratory investigation included complete blood count and serum biochemistry (fibrinogen, creatinine, urea, electrolytes, uric acid, albumin, thyroid-stimulating hormone, free thyroxine). Blood glucose and lipid determination were performed after fasting overnight. Patients had a re-evaluation (clinical and laboratory) 6 weeks after the acute episode. All biochemical analyses were performed by commercially available standardized methods within 24 hours after stroke onset using an Olympus AU560 analyser.3

### Statistical Analysis

Values were expressed as mean±SD, except for age, lipoprotein(a), and fibrinogen, which were expressed as median and range. Comparisons of continuous variables were performed by an unpaired 2-tailed Student t test or the Mann–Whitney U test, as appropriate. χ² Tests were used for categorical variables.

The association between MetSyn and its individual diagnostic features and stroke risk was determined by univariate analysis as well as multivariate logistic regression modeling after adjusting for potential confounding factors (Table 1).

To evaluate the contribution of each constituent variable of the MetSyn to the prediction dependent on the MetSyn (ie, the interaction between variables), a new “product” variable was created and added to the logistic regression model. The effect of interaction was tested via the F statistic for the improved fit. In the interaction terms, the presence of the MetSyn, hypertension, high glucose levels, and increased waist circumference were entered as binary variables, whereas HDL-C and TG were expressed both as binary and continuous variables.

Significance was defined as P<0.05 in all cases. SPSS 11.0.1 for Windows (SPSS Inc, 1989 to 2001) was used for the statistical analysis.

### Results

MetSyn was more frequent among patients with a first-ever-in-a-lifetime acute ischemic/nonembolic stroke than in the control group (46.0% versus 15.7%, P<0.001). Stroke patients with the MetSyn exhibited a more atherogenic lipid profile compared with controls as a group (with and without the MetSyn) (Table 2). Specifically, both groups had similar serum total cholesterol, low-density lipoprotein cholesterol, and apolipoprotein (apo) B levels, whereas stroke patients with the MetSyn had higher values of the atherogenic risk ratio (total cholesterol/HDL-C), TG, and lipoprotein(a), but lower concentrations of HDL-C and apoA-I (Table 2). In addition, stroke patients with the MetSyn had increased serum uric acid (5.8±1.8 versus 4.8±1.4 mg/dL; [345±107 versus 285±83 μmol/L], P<0.001) and median plasma fibrinogen levels (402 versus 302 mg/dL, P<0.001) compared with controls in general (Table 2). Stress-induced hypertension and diabetes rates increased during the acute episode of stroke (Table 3). However, only 5 (out of 23) and 4 (out of 12) had hypertension and diabetes diagnosed, respectively, at re-evaluation.

The prevalence of the individual components of the MetSyn in the study population is shown in Table 3. In logistic regression analysis, crude odds ratio (OR) for the MetSyn was 4.59 and 95% confidence interval (CI) was 2.73 to 7.72 (P<0.0001; Table 1). After adjusting for sex, age, body mass index (BMI), smoking habits, and the presence of hypertension, the association between MetSyn and stroke risk was significant (OR, 5.33; 95% CI, 2.91 to 9.79; P<0.0001), and this was also evident when lipid and nonlipid parameters were included in the model (OR, 2.59; 95% CI, 1.24 to 5.42; P=0.012) (Table 1).

The analysis of the interaction between the MetSyn and its individual components produced intriguing results. In the presence of MetSyn, abdominal obesity, hypertension, or high glucose levels (ie, insulin resistance) were highly associated...
with acute nonembolic ischemic stroke (crude and adjusted ORs are shown in Table 4). However, the association of hypertension did not reach statistical significance; this can be explained by the high prevalence of hypertension in the control group (36.7% versus 73.0%, overall versus subjects with MetSyn, respectively; Table 2). High TG levels and low HDL-C levels proved strong predictors of acute ischemic stroke in elderly individuals with the MetSyn. Remarkably, the protective role of HDL-C in ischemic stroke was attenuated in the presence of the metabolic syndrome (crude and adjusted OR, 1.03; 95% CI, 1.02 to 1.05, and OR, 1.04; 95% CI, 1.02 to 1.05, respectively; *P*<0.0001) (Table 4).

### Discussion

This population-based case-control study showed that MetSyn is a strong independent risk factor for acute ischemic/nonembolic stroke in elderly individuals. This association was not attenuated after adjustment for the presence of established cardiovascular and cerebrovascular risk factors. The prevalence of the MetSyn has been shown to increase with age. In a recent study by the Greek Atherosclerosis Society, the age-standardized prevalence of the MetSyn, both in urban and rural regions, was 23.9%, with a 14.7-fold increase in OR for having the MetSyn in those older than 70 years compared with those aged 19 to 29 years (*P*<0.0001). However, the prevalence of the MetSyn was significantly higher among subjects with than without prevalent vascular disease (48.1% versus 19.6; *P*<0.0001). Our study was

### TABLE 2. Clinical and Laboratory Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Feature</th>
<th>Stroke Patients</th>
<th>Controls</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>56 (34%)</td>
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<td>High triglyceride</td>
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</tr>
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<td>Low HDL-cholesterol</td>
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<td>0.05</td>
</tr>
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<td>Metabolic syndrome</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>46 (28%)</td>
<td>34 (21%)</td>
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<td>Stress-induced hypertension*</td>
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</table>

*Blood pressure >140/90 mm Hg during the acute episode of stroke in nonhypertensive subjects.
†Fasting glucose >126 mg/dL (7.0 mmol) during the acute episode of stroke in nondiabetic subjects.

### TABLE 3. Prevalence of the Diagnostic Features of the Metabolic Syndrome, Diabetes, and Hypertension in the Study Population

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*Blood pressure >140/90 mm Hg during the acute episode of stroke in nonhypertensive subjects.
†Fasting glucose >126 mg/dL (7.0 mmol) during the acute episode of stroke in nondiabetic subjects.
conducted in a nonindustrialized region where at least the elderly lead their lives in a “traditional” way. Eating habits remained unchanged for years (Mediterranean diet, including olive oil and minimal saturated fat consumption), whereas smoking is strictly considered as a “man’s privilege,” in contrast to a more Westernized way of living followed by the urban younger population. These dietary and territorial differences may account for the low prevalence of the MetSyn in the control group.

MetSyn in stroke patients was associated with concurrent metabolic disturbances, such as high levels of lipoprotein(a), fibrinogen, and uric acid, which have been reported to be independently of other risk factors including fasting glucose and lipid levels. In line with recent studies, the individual components of the MetSyn were identified as modifiable risk factors, which might have an additive value to stroke prevention.6,7,11–12

There is evidence that excess body weight is a predictor of stroke (total, ischemic, and hemorrhagic) in men.13 Even though obesity is regarded as a modifiable risk factor for vascular disease, it has been neglected in the overall stroke risk estimation. High values of waist circumference (99 cm or greater) and BMI (28 kg/m² or greater) increase the risk for vascular disease, it has been neglected in the overall stroke risk estimation. However, this association was not statistically significant because of the high rate of hypertension in the control group. This raises the question whether higher blood pressure cut-points than those recommended (ie, >130/85 or even >140/90 mm Hg) would be more appropriate to categorize hypertensive subjects with the MetSyn among the elderly.

Many researchers believe that insulin resistance is the pathophysiological process underlying the clustering of vascular risk factors in the MetSyn.16 Indices of insulin resistance predict atherosclerosis and vascular events independently of other risk factors including fasting glucose and lipid levels. Current NCEP/ATP III guidelines use impaired fasting glucose (>110 mg/dL; 6.1 mmol/L) as one criterion for identifying subjects with the MetSyn.4 Measurement of fasting glucose during the acute episode of stroke may represent a limitation of the study. However, many subjects with normal fasting glucose levels have insulin resistance. In addition to the role of glucose status (normal, impaired glucose tolerance, or diabetic), there are other aspects of glucose metabolism that may play a role as a risk factor for ischemic stroke, specifically hyperinsulinemia and increased insulin resistance.18 In non-Hispanic white and Hispanic subjects, increased insulin resistance is associated with increased atherosclerosis of the carotid arteries independent of glucose status, insulin levels, and other major vascular risk factors.19

Dyslipidemia is a hallmark of the MetSyn. It is characterized by elevated TG and low HDL-C levels.20,21 In our analysis, dyslipidemia had the strongest and more consistent relationship with ischemic stroke among all the MetSyn components. There is a controversy regarding the association between serum TG levels and stroke.22 It has been shown that postprandial hypertriglyceridemia is associated with carotid artery atherosclerosis.23 Nonetheless, in the Copenhagen City Heart Study, a log-linear association between serum TG levels and nonhemorrhagic stroke was found, which was independent of age and sex.24 In general, in the majority of studies, an inverse association between HDL-C and stroke

### TABLE 4. Univariate and Multivariate Logistic Regression Analyses of the Association Between MetSyn and Its Components and Acute Ischemic Nonembolic Stroke

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>MetSyn+OB</td>
<td>3.466 (1.863–6.448)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MetSyn+HTN</td>
<td>3.940 (2.211–7.021)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MetSyn+HGL</td>
<td>3.301 (1.711–6.366)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MetSyn+high TG</td>
<td>5.086 (2.685–9.635)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MetSyn+TG</td>
<td>1.010 (1.006–1.013)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MetSyn+low HDL-C</td>
<td>4.967 (2.831–8.816)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MetSyn+HDL-C</td>
<td>1.032 (1.019–1.046)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**OB**, presence of abdominal obesity (waist circumference >102 cm in men, >88 cm in women); **HTN**, presence of hypertension; **HGL**, presence of high fasting glucose (>110 mg/dL); **TG** and **HDL-C**, triglyceride and HDL cholesterol levels in mg/dL (continuous variables). **High TG**, presence of hypertriglyceridemia (>150 mg/dL) (binary variable). **Low HDL-C**, presence of low HDL-C levels (<40 mg/dL in men and <50 mg/dL in women) (binary variable).

*Adjusted for age, sex, smoking, body mass index, and lipid and nonlipid metabolic parameters.
risk has been documented.\textsuperscript{5,22} In the Northern Manhattan Stroke Study, increased levels of HDL-C were associated with a reduced risk of ischemic stroke in the elderly and among different racial or ethnic groups.\textsuperscript{22} In our cohort, HDL-C levels were inversely related to the risk of acute ischemic stroke in elderly subjects. In support of this finding, low levels of HDL-C added to the predictive value of the established diagnosis of MetSyn. However, in the face of MetSyn the protective role of HDL-C was attenuated.

Considering the remarkable increase in the proportion of the elderly population throughout the industrialized world, it is becoming increasingly important for societies to reduce the burden of illness in their ageing populations.\textsuperscript{2,26} Most authorities suggest that clinical problems and/or metabolic disturbances in the elderly patient should be considered as the result of a disease process rather than the result of “just getting old.”\textsuperscript{26} Because the MetSyn represents a condition associated with substantially high risk, pharmacological therapy to reduce cardiovascular risk would seem appropriate in most patients.\textsuperscript{27} Data from statin trials, such as PROSPER and the Heart Protection Study, showed that statin therapy is also beneficial to the elderly.\textsuperscript{28,29} However, low-density lipoprotein cholesterol levels are not elevated in most patients with the MetSyn, and there is no consensus on the appropriate low-density lipoprotein cholesterol target in the MetSyn. It appears logical that targeted management should involve pharmacological treatment together with “therapeutic lifestyle changes” to reduce obesity, control hypertension and glycemia, and improve dyslipidemia.\textsuperscript{30}

References

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