

# Metabolic Syndrome Compared With Type 2 Diabetes Mellitus as a Risk Factor for Stroke

## The Framingham Offspring Study

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**Background:** Metabolic syndrome (MetS) has been recognized as a prediabetic constellation of symptoms and an independent risk factor for cardiovascular disease.

**Methods:** To evaluate the age-adjusted risk of stroke and population-attributable risk associated with MetS and compare with those of overt type 2 diabetes mellitus (hereinafter, "diabetes"), we determined the prevalence of MetS alone, diabetes alone, and both in 2097 subjects in the Framingham Offspring Study, aged 50 to 81 years and free of stroke. Age-adjusted risk ratios, 10-year incidence, and population-attributable risks of stroke were estimated for men and women with MetS alone, diabetes alone, and both.

**Results:** Criteria for MetS were met in 30.3% of men and 24.7% of women. Twenty-four percent of men had MetS alone; 7% had diabetes alone; and 6% had both. Twenty

percent of women had MetS alone; 3% had diabetes alone; and 5% had both. Over 14 years of follow-up, 75 men and 55 women developed a first stroke; all but 4 events were ischemic. Relative risk (RR) of stroke in persons with both diabetes and MetS (RR, 3.28; confidence interval [CI], 1.82-5.92) was higher than that for either condition alone (MetS alone: RR, 2.10; CI, 1.37-3.22; diabetes alone: RR, 2.47; CI, 1.31-4.65). The population-attributable risk, owing to its greater prevalence, was greater for MetS alone than for diabetes alone (19% vs 7%), particularly in women (27% vs 5%).

**Conclusions:** Metabolic syndrome is more prevalent than diabetes and a significant independent risk factor for stroke in people without diabetes. Prevention and control of MetS and its components are likely to reduce stroke incidence.

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**T**YPE 2 DIABETES MELLITUS (hereinafter, "diabetes") is a recognized risk factor for stroke and is now considered equivalent to coronary heart disease (CHD) in the guidelines set forth by the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (NCEP ATP III).<sup>1</sup> However, the atherothrombotic risk imposed by diabetes appears to antedate its overt appearance, lurking in a prediabetic state of insulin resistance lately characterized as *metabolic syndrome* (MetS).<sup>1</sup> Increased risk of coronary disease and stroke has been reported in persons with impaired glucose tolerance, MetS, and/or diabetes.<sup>2-5</sup> It has also been shown that the risk of CHD or stroke associated with diabetes varies depending on the cluster of risk factors that usually accompanies it.<sup>4-6</sup> These accompanying risk factors include those now characterized as MetS.<sup>1</sup>

The cardiovascular risk factors that make up MetS have been shown to be predictors of the occurrence of diabetes.<sup>7-9</sup> Conceptualization of diabetes as a cardiovascular risk factor can now be broadened to include a prediabetic state of insulin resistance promoted by abdominal obesity and the cluster of risk factors that compose MetS. The syndrome as defined by the NCEP ATP III<sup>1</sup> guidelines comprises 3 or more of the following: elevated fasting blood glucose level, increased waist girth, elevated triglyceride level, reduced high-density lipoprotein cholesterol (HDL-C) level, and increased blood pressure. A number of other more novel risk factors also characterize the syndrome and insulin-resistant state, including small and dense low-density lipoprotein cholesterol, endothelial dysfunction, high levels of C-reactive protein, and a prothrombotic tendency with elevated levels of plasminogen activator inhibitor 1, among others.<sup>10</sup>

The present investigation compares, in a general population sample, the prevalence of diabetes and MetS in each sex and

the stroke risk associated with each entity alone and in combination in terms of absolute, relative, and population-attributable risk. The population sample investigated is the Framingham Offspring Study<sup>11</sup> cohort comprising subjects aged 50 to 81 years.

## METHODS

### PATIENTS

We evaluated the prevalence of diabetes and MetS in 4019 men and women attending the fourth examination cycle (1988-1990) of the Framingham Offspring Study.<sup>11</sup> We excluded individuals younger than 50 years or who had a history of stroke, leaving a population at risk for initial stroke events in relation to their diabetes or MetS status. Since cardiovascular disease is a prominent risk factor for the development of stroke, subjects with CHD, heart failure, and/or peripheral artery disease were not excluded.

### MEASUREMENTS

The baseline evaluation included a cardiovascular history, physical examination, and fasting blood tests. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Blood pressure was measured in the left arm of seated subjects using a mercury sphygmomanometer and, when required, a large cuff. Levels of total cholesterol, HDL-C, and triglycerides were determined after a 12-hour fast using Lipid Research Clinics methods.<sup>12</sup> Patients with diabetes were defined as those having a blood glucose level of at least 126 mg/dL (7.00 mmol/L) or receiving treatment for diabetes. *Metabolic syndrome* was diagnosed when 3 or more of the following were present: blood glucose level elevation (110-125 mg/dL [6.10-6.99 mmol/L]), elevated blood pressure ( $\geq 130/\geq 85$  mm Hg or treatment with antihypertensive medication), increased triglyceride level ( $\geq 150$  mg/dL [1.7 mmol/L]), reduced HDL-C level ( $< 40$  mg/dL [1.03 mmol/L] for men and  $< 50$  mg/dL [1.29 mmol/L] for women), or abdominal obesity (waist girth,  $> 88$  cm in women and  $> 102$  cm in men).

Onset of stroke morbidity and mortality were monitored by routine periodic clinic examinations and hospital surveillance. Occurrence of initial suspected stroke events, categorized according to stroke subtypes, were reviewed by a panel of 3 experienced neurologist investigators who had to agree that the event met established criteria.<sup>13</sup>

### STATISTICAL ANALYSIS

We first generated descriptive statistics on each study variable including means and standard deviations (SDs) for continuous variables and relative frequencies for discrete variables. We then estimated, in age decades, the proportions of men and women who met criteria for diabetes alone, MetS alone, and both. The effect of diabetes alone, MetS alone, and both on the risk of stroke was estimated after adjusting for age and standard clinical risk factors using Cox proportional hazards regression models. The model was sex pooled to increase precision. The interactions between sex and diabetes and sex and MetS status were examined and determined to be nonsignificant based on a change in log likelihood test findings. Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported. Population-attributable risks were computed as prevalence  $\times$  (relative risk [RR] - 1) / (1 + prevalence  $\times$  [RR - 1]). All analyses were conducted with SAS software, version 8.2 (SAS Institute Inc, Cary, NC).

**Table 1. Characteristics of Study Subjects\***

Characteristic	Men (n = 1059)	Women (n = 1038)	All
Age, y	59.1 (6.2)	59.1 (6.0)	59.1 (6.1)
Systolic blood pressure, mm Hg	134.7 (18.5)	133.1 (20.3)	133.9 (19.4)
Treated for hypertension	30.6	24.2	27.4
Total cholesterol, mg/dL	207.2 (37.5)	220.6 (39.9)	213.8 (39.3)
HDL-C, mg/dL	42.9 (12.2)	55.4 (15.7)	49.1 (15.4)
Triglycerides, mg/dL	148.3 (100.2)	131.1 (121.1)	139.8 (111.4)
BMI	27.8 (3.8)	26.7 (5.2)	27.2 (4.6)
Glucose, mg/dL	102.7 (32.9)	96.9 (27.6)	99.8 (30.6)
Smokers	20.4	23.7	22.0
Left ventricular hypertrophy	5.5	1.8	3.7
Cardiovascular disease	16.0	7.6	11.8
Prior atrial fibrillation	2.7	1.2	2.0

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); HDL-C, high-density lipoprotein cholesterol.

SI conversion factors: To convert HDL-C and total cholesterol measurements to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; glucose to millimoles per liter, multiply by 0.0555.

\*Data are reported as percentage of subjects or mean (SD) values.

## RESULTS

There were 4019 Framingham Offspring Study<sup>11</sup> subjects who attended the fourth examination cycle. Of these, 1791 were younger than 50 years and so carried a very low risk of stroke; therefore, they were eliminated from the population at risk. Also excluded were 46 subjects with a documented history of a stroke and 85 with missing risk factor values. This left 2097 individuals in the population at risk under consideration and free of stroke. The characteristics of all subjects free of stroke in the 50- to 81-year-old range who attended the fourth examination are summarized in **Table 1**. Sixty-seven (6%) of the men had both diabetes and MetS; 70 (7%) had diabetes alone; and 254 (24%) had MetS alone. In women, 50 (5%) had both; 29 (3%) had diabetes alone; and 206 (20%) had MetS alone. Estimates of the prevalence of diabetes alone, MetS alone, and both are listed in **Table 2**. Prevalence of the components of MetS are indicated for the Framingham Offspring Study cohort in **Table 3** and for nondiabetic participants with MetS in **Table 4**.

During the 14 years of follow-up, there were 75 men (7.1%) and 55 women (5.3%) who developed first strokes of all types: 4 of these were hemorrhagic; the remainder were ischemic events. As summarized in **Table 5**, the adjusted RR for persons with both diabetes and MetS developing a stroke was 3.28 (95% CI, 1.82-5.92). The stroke RR for MetS alone was 2.10 (95% CI, 1.37-3.22), and for diabetes alone, 2.47 (95% CI, 1.31-4.65). These effects were not significantly different ( $P = .64$ ). There were no sex by diabetes or MetS status interactions ( $P = .73$  based on the change in log likelihood). The sex-specific estimates are reported for comparison purposes but must be interpreted with caution owing to the small numbers of events, particularly in women. Table 4 summarizes the data adjusted

**Table 2. Prevalence of Diabetes and Metabolic Syndrome\***

Characteristic	Neither	Diabetes Alone	Metabolic Syndrome Alone	Both
<b>All Subjects (N = 2097)</b>	1421 (68)	99 (5)	460 (22)	117 (5)
Age, y				
50-59 (n = 1154)	825 (71)	42 (4)	240 (21)	47 (4)
60-69 (n = 838)	527 (63)	46 (5)	202 (24)	63 (8)
70-81 (n = 105)	69 (66)	11 (10)	18 (17)	7 (7)
Men only (n = 1059)	668 (63)	70 (7)	254 (24)	67 (6)
Age, y				
50-59 (n = 577)	373 (65)	30 (5)	151 (26)	23 (4)
60-69 (n = 426)	263 (62)	31 (7)	93 (22)	39 (9)
70-81 (n = 56)	32 (57)	9 (16)	10 (18)	5 (9)
Women only (n = 1038)	753 (72)	29 (3)	206 (20)	50 (5)
Age, y				
50-59 (n = 577)	452 (78)	12 (2)	89 (15)	24 (4)
60-69 (n = 412)	264 (64)	15 (4)	109 (26)	24 (6)
70-81 (n = 49)	37 (76)	2 (4)	8 (16)	2 (4)

\*Data are reported as number (percentage) of subjects.

**Table 3. Population Prevalence of Metabolic Syndrome Features In Subjects With and Without Type 2 Diabetes Mellitus\***

Feature	Men (n = 1059)	Women (n = 1038)	All Subjects (N = 2097)
Waist girth $\geq 102$ cm in men or $\geq 88$ cm in women	31.3	30.3	30.8
Triglycerides $\geq 150$ mg/dL	36.9	25.7	31.4
HDL-C $< 40$ mg/dL in men or $< 50$ mg/dL in women	43.5	41.2	42.4
Blood pressure $\geq 130/\geq 85$ mm Hg (or treatment)	70.9	63.2	67.1
Fasting glucose $\geq 110$ mg/dL	7.8	5.3	6.6
Metabolic syndrome, 3 or more components	30.3	24.7	27.5
Stroke events, No. (%)	75 (7.1%)	55 (5.3%)	130 (6.2%)

Abbreviation: HDL-C, high-density lipoprotein cholesterol.

SI conversion factors: To convert HDL-C and total cholesterol measurements to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; and glucose to millimoles per liter, multiply by 0.0555.

\*Unless otherwise indicated, data are reported as percentage of subjects.

**Table 4. Prevalence of Metabolic Syndrome Features Subjects Without Diabetes\***

Feature	Men (n = 254)	Women (n = 206)	All Subjects (N = 460)
Elevated systolic blood pressure or treatment	95	93	94
HDL-C $< 40$ mg/dL in men or $< 50$ mg/dL in women	88	90	89
Triglycerides $\geq 150$ mg/dL	79	74	77
Waist girth $\geq 102$ cm in men or $\geq 88$ cm in women	65	73	69
Fasting glucose 110-125 mg/dL	16	17	17

Abbreviation: HDL-C, high-density lipoprotein cholesterol.

SI conversion factors: To convert HDL-C and cholesterol measurements to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; and glucose to millimoles per liter, multiply by 0.0555.

\*All data are reported as percentage of subjects.

## COMMENT

for systolic blood pressure and treatment of hypertension. This adjustment was made to determine if the MetS-stroke relationship was driven chiefly by elevated blood pressure, which does not appear to be the case. Total cholesterol level was not adjusted for, since it was no different in persons with and without MetS and does not influence stroke risk. Adjustment for the associated cardiovascular disease was made. The impact of MetS alone, diabetes alone, or both on stroke incidence was also analyzed in subjects free of cardiovascular diseases at baseline with minimal effect on the risk ratios (data not shown).

In comparing diabetes with MetS in terms of prevalence and RR, we found that MetS has a larger population-attributable risk, particularly in women. It thus appears that MetS alone accounts for more of the strokes in the population than diabetes alone (12% vs 6% in men and 27% vs 5% in women).

The relation of MetS to stroke occurrence is not well documented. However, adiposity that predisposes to diabetes and MetS has been extensively examined as a stroke risk factor. The relation of BMI to stroke occurrence<sup>14-19</sup> is reported less consistently than its association with waist girth,<sup>15-22</sup> thereby implicating insulin resistance and its co-existing variables shared by MetS with increased stroke risk. Diabetes, a condition conferring insulin resistance, has been shown to increase stroke risk between 1.5- and 3-fold.<sup>14</sup>

Hyperinsulinemia and insulin resistance are accepted as prominent features of diabetes.<sup>9,10</sup> Many of the features of MetS, as defined by NCEP ATP III,<sup>1</sup> have been shown to be predictors of diabetes, suggesting that, like impaired glucose tolerance and impaired fasting glucose levels, MetS may signal a prediabetic state.<sup>1,23</sup> However, there have been few prospective studies relating hyperinsulinemia to the occurrence of stroke.<sup>24,25</sup> In the ARIC investigation,<sup>26</sup> the influence of diabetes on stroke incidence was not entirely explained by a set of risk factors

with which it is known to be associated. In a recent report of the relation of BMI to risk of stroke in the Physicians Health Study,<sup>27</sup> a significant increase was found in the RR of both ischemic and hemorrhagic stroke, independent of associated effects of hypertension, diabetes, and cholesterol. In the present study of the Framingham Offspring Study<sup>11</sup> cohort, the influence of MetS on stroke incidence also persists after adjustment for its component risk factors. This suggests that a number of other features of MetS such as systemic inflammation and abnormal endothelial and vascular function may be operative. In the ARIC study,<sup>26</sup> the population-attributable risk for diabetes, taking into account its prevalence (blood glucose level, >140 mg/dL [7.77 mmol/L]), was 21%. Abdominal adiposity was a strong risk factor in univariate analysis, but the risk it imposed tended to be explained by the risk factors that obesity promotes. Fasting insulin level, a marker for insulin resistance in persons without diabetes, is also not consistently and independently related to the rate of occurrence of stroke.<sup>25,26,28</sup> However, taken together, the data on adiposity, insulin resistance, and diabetes in relation to stroke occurrence suggest an important role for insulin resistance and MetS.

Diabetes is a condition conferring insulin resistance presumed to be preceded by MetS. Many MetS components are associated with an excess risk of developing diabetes.<sup>1,2,4,8-10,29</sup> Obesity, hypertension, dyslipidemia, elevated triglyceride levels, reduced HDL-C levels, and high-normal blood glucose levels all confer increased risk of diabetes. Diabetes appears to be a greater hazard for atherosclerotic cardiovascular disease and stroke in particular than MetS. However, because MetS is almost 3 times as prevalent as diabetes, the population impact of the syndrome is greater, accounting for more of the strokes than overt diabetes.

Reported national estimates of the prevalence of MetS suggest that 47 million US residents, or 22% of men and 24% of women aged 20 years or older, have the condition, including those with diabetes.<sup>30</sup> These estimates are similar to those determined in the Framingham Offspring Study,<sup>11</sup> in which, including those with diabetes, the prevalence was found to be 26.6% for men and 18.7% for women in patients between ages 30 and 74 years. It has been estimated that those with MetS have a 3-fold increased risk of developing CHD or stroke and a 5-fold excess risk of cardiovascular mortality.<sup>3</sup> The present study's estimate of the hazard for initial stroke is somewhat smaller: 1.57-fold increase in men, 2.81-fold increase in women, and 2.10-fold increase overall, when subjects with diabetes are excluded.

### LIMITATIONS

The Framingham Offspring Study<sup>31</sup> is composed primarily of a population-based white cohort who are descendants of those enrolled in the original Framingham Heart Study<sup>31</sup> cohort. Since the prevalence of MetS and stroke risk has been shown to vary in different ethnic populations, our results may not be applicable to other racial groups and may likely underestimate the prevalence of MetS and associated risks for adverse vascular outcomes. Additionally, the American Diabetes Associa-

**Table 5. Risk Ratio and Population-Attributable Risk for Occurrence of Stroke in Subjects with Type 2 Diabetes Mellitus vs MetS**

Study Group*	Prevalence, %	Risk Ratio (95% CI)†	Population-Attributable Risk, %
All subjects			
MetS alone	22	2.10 (1.37-3.22)	19
Diabetes alone	5	2.47 (1.31-4.65)	7
Both	5	3.28 (1.82-5.92)	10
Men only			
MetS alone	24	1.57 (0.88-2.79)	12
Diabetes alone	7	1.93 (0.86-4.33)	6
Both	6	2.51 (1.20-5.25)	8
Women only			
MetS alone	20	2.81 (1.48-5.33)	27
Diabetes alone	3	2.70 (0.80-9.16)	5
Both	5	4.51 (1.75-11.61)	15

Abbreviations: CI, confidence interval; MetS, metabolic syndrome.

\*The effects of type 2 diabetes mellitus alone vs MetS alone were not significantly different in the total sample ( $P = .64$ ), among men ( $P = .64$ ), or among women ( $P = .95$ ).

†Risk ratios are adjusted for age, systolic blood pressure, treatment for hypertension, history of cardiovascular disease, atrial fibrillation, and/or left ventricular hypertrophy, and smoking status.

tion defines at-risk prediabetic subjects as those having a fasting glucose level of 100 mg/dL (5.6 mmol/L) or higher.<sup>23</sup> It is plausible that such mild glucose level elevation may predispose individuals to macrovascular complications similar to those seen at higher levels, but lack of supporting data and our adherence to NCEP ATP III guidelines precluded our study of this.

The connection between MetS and insulin resistance has not been established. The biochemical diagnosis of insulin resistance requires the euglycemic clamp technique, which is useful for basic research but impractical for clinical or epidemiologic investigation. Fasting insulin levels correlate reasonably well with the degree of insulin resistance, but this was measured too recently in the Framingham Offspring Study<sup>11</sup> to provide sufficient follow-up to link it to the occurrence of stroke. Also, fasting insulin level measurement is not widespread; standard methods for performing the test have yet to be adopted; and criteria for normal and degrees of abnormality need to be established. Investigation in the Framingham Study and elsewhere<sup>31-34</sup> demonstrates that there is a lack of sensitivity of MetS, as defined by the NCEP ATP III, as a surrogate for insulin resistance and vice versa. Of subjects reported not to have MetS by NCEP ATP III criteria, 15% had insulin resistance as defined by the World Health Organization guidelines (homeostasis model assessment values in the upper quartile).<sup>33</sup> Of subjects with such elevated values, 45% were classified as not having NCEP ATP III MetS. However, in the Framingham Heart Study cohort, those with MetS had a 5-fold increased risk of developing diabetes (unpublished data, 2005). Owing to the limited number of stroke events in the present study, it was not possible to examine the relationship of MetS to stroke subtypes, specifically ischemic stroke. It is likely that MetS is most closely

linked to the incidence of brain infarction resulting from atherothrombosis. The inclusion of all strokes may well have provided an underestimate of the strength of relationship.

## CLINICAL IMPLICATIONS

Based on the clinical trial evidence demonstrating the benefit of improving risk factors such as blood lipid levels and blood pressure in general, and among subjects with diabetes in particular, it appears that there is great potential for substantial reduction of stroke risk in people with MetS by treatment of its components.<sup>1,35</sup> Use of agents that improve insulin sensitivity appears promising for reversing the spectrum of atherogenic components of MetS. For example, thiazolidinediones improve insulin-mediated glucose uptake and favorably affect cardiovascular risk factors and markers of insulin resistance.<sup>36-39</sup>

Type 2 diabetes mellitus, characterized by insulin resistance and inadequate beta cell secretion of insulin, affects more than 90% of people with diabetes and atherosclerosis. There is an emerging epidemic of macrovascular sequelae of diabetes that confronts primary care physicians, who appear not to have adopted sufficiently aggressive management strategies. Too many physicians cling to the traditional approach to treatment that emphasizes glycemic control. This approach appears effective for microvascular disease, but it has not been shown to benefit macrovascular disease.<sup>40</sup> Evidence supports antiatherosclerotic management for diabetes and MetS. Blood pressure control, lipid-correcting therapy, angiotensin-converting enzyme inhibition, and antiplatelet drugs significantly reduce the risk of cardiovascular events and stroke in patients with diabetes. Diabetes is considered by NCEP ATP III to be a CHD equivalent.<sup>1</sup> Data suggest that MetS should also be considered in that category, despite its somewhat lower estimated hazard ratio, because it is so much more prevalent in the population, conferring a large population-attributable risk. More of the population burden of atherosclerotic cardiovascular disease and stroke in particular is attributable to MetS than to diabetes. Also, because MetS probably signals a prediabetic state, its identification and treatment likely will prevent occurrence of overt diabetes. Health professionals are well advised to institute vigorous preventive measures in prediabetic persons with evidence of MetS before the advent of overt diabetes.

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### Announcement

#### Clinical Trial Registration

In concert with the International Committee of Medical Journal Editors (ICMJE), *Archives of Internal Medicine* will require, as a condition of consideration for publication, registration of clinical trials in a public trials registry (such as <http://ClinicalTrials.gov> or <http://controlled-trials.com>). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after March 1, 2006. For trials that began enrollment before this date, registration will be required by June 1, 2006. The trial registration number should be supplied at the time of submission.

For details about this new policy see the editorials by DeAngelis et al in the September 8, 2004 (2004;292:1363-1364) and June 15, 2005 (2005;293:2927-2929) issues of *JAMA*.