Is the Diagnosis of Metabolic Syndrome Useful for Predicting Cardiovascular Disease in Asian Diabetic Patients?

Analysis from the Japan Diabetes Complications Study

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OBJECTIVE — The metabolic syndrome (MetS) is believed to be associated with an increased risk of cardiovascular disease (CVD). Although its prevalence is extremely high among diabetic patients, its prevalence in those with no history of CVD has not been determined. Moreover, prospective studies published on the association between MetS and cardiovascular events in diabetic populations have used only the World Health Organization (WHO) definition of MetS and included only white European subjects. The aim of this study was to determine the prevalence of MetS, as defined by both the WHO and the National Cholesterol Education Program (NCEP), and its predictive value for CVD in Asian diabetic patients in a long-term, prospective setting.

RESEARCH DESIGN AND METHODS — The baseline characteristics and incidence/hazard ratio of cardiovascular events (coronary heart disease and stroke) were determined in 1,424 Japanese type 2 diabetic patients with and without MetS, as defined by WHO (WHO-MetS) or the NCEP.

RESULTS — A high prevalence (38–53%, depending on sex and definition) of MetS was found among diabetic patients, even those with no history of CVD. During the 8-year study period, only WHO-MetS was a predictor for CVD in female patients. In male patients, although both definitions of MetS were significant predictors for CVD, individual components of MetS, such as hyperlipidemia or hypertension, were equivalent or better predictors.

CONCLUSIONS — We found that MetS is relatively common in diabetic patients with no history of CVD. We suggest that the commonly used definitions of MetS, at least in their present forms, have limited clinical usefulness for Asian diabetic patients and may need some ethnic group–specific modifications for global use.

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The metabolic syndrome (MetS) is an important cluster of metabolic abnormalities linked with insulin resistance and cardiovascular disease (CVD) (1). The diagnostic criteria of MetS proposed by the World Health Organization (WHO-MetS) (2) and the National Cholesterol Education Program (NCEP-MetS) (3) are currently the most widely used. Although the prevalence of MetS in the general population reportedly differs widely among ethnic groups (4–8) and according to the definition of MetS used (7,9–11), the prevalence among patients with known diabetes is consistently high (70–90%) regardless of ethnicity or definition (12–20). Considering the high prevalence of CVD in the diabetic population (21) and the fact that subjects with a history of CVD often have multiple cardiovascular risk factors, it has been speculated that the extremely high prevalence of MetS among diabetic patients (12–20) may be due to the large number of patients who already have a history of CVD. However, the prevalence of MetS in diabetic patients without CVD has not been widely investigated to date. It is rational to examine this because diabetic patients with MetS have a higher incidence of CVD than those without MetS (15,16) and MetS is a stronger risk factor for CVD in patients with type 2 diabetes than in nondiabetic subjects (12).

Most prospective studies have shown that subjects with MetS are at increased risk of incident CVD (22,23) and mortality due to CVD (9,24–27). However,

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Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; ECG, electrocardiogram; HOMA-IR, homeostasis model assessment of insulin resistance; JDCS, Japan Diabetes Complications Study; MetS, metabolic syndrome; NCEP, National Cholesterol Education Program; UKPDS, U.K. Prospective Diabetes Study; WHO, World Health Organization; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

many of these studies excluded diabetic patients from their study populations (9,22–24). Diabetic patients are known to be at greater risk for CVD than nondiabetic subjects (21), and it has been suggested that MetS is responsible for the increased prevalence of coronary heart disease (CHD) seen in diabetic patients (20). Therefore, it is important to evaluate the predictive value of MetS on incident CVD in diabetic patients in long-term, prospective studies. To the best of our knowledge, there have been four cohort studies specifically targeting diabetic patients to determine the relative risk of MetS on the incidence of CVD (12,15,16) and mortality due to CVD (17). Although these studies involved only white European subjects and used only the WHO definition of MetS, most of them (12,15,16) demonstrated, as expected, that the presence of MetS is associated with at least a severalfold increase in the risk of CVD. The above findings notwithstanding, it remains unclear *1*) whether such predictive values of MetS are also applicable to diabetic patients of other ethnicities, *2*) which features of MetS are the best predictors of CVD and should become the critical therapeutic targets for the optimal management of CVD risk in diabetic patients (28), and *3*) whether the commonly used NCEP definition of MetS (3) possesses the same predictive value for CVD as the WHO definition in diabetic patients.

The incidence of CVD in Asian subjects is known to be much less than in white subjects in general (29) and in diabetic populations in particular (30). In addition, the degree of obesity is very different between white and Asian diabetic patients (31,32), and the impact of obesity on CHD risk is known to be entirely different between whites and Asians (33,34). These differences could affect the apparent clinical significance of MetS (35,36), so that it is questionable whether the overall concept of MetS itself and the diagnosis of MetS under the present definitions based on data from mostly European and American patients are applicable to the evaluation of CVD risk in Asian diabetic patients. Therefore, in this long-term, prospective study of Japanese diabetic patients with no history of CVD, we determined the prevalence of MetS and analyzed its individual features and predictive value for incident CVD using the two most widely used definitions of MetS (2,3). Such comparisons are helpful in possibly establishing a global definition of MetS (10,37) and are also warranted to determine if there is heterogeneity in the power of individual MetS components to predict CVD (28).

RESEARCH DESIGN AND METHODS

— The Japan Diabetes Complications Study (JDCS) is a nationwide, multicenter, prospective study of type 2 diabetic patients (38). In 1996, 2,205 patients aged 40–70 years with previously diagnosed type 2 diabetes and HbA_{1c} levels >6.5% were recruited and registered. The eligibility criteria for participating patients has been previously described (38). The duration of the study was 8 years. Of the 2,205 patients, the present study focused on 1,424 patients (771 men and 653 women) who had a complete set of data, including those parameters necessary to satisfy the WHO (2) and NCEP (3) criteria for the definition of MetS at baseline. The JDCS protocol, which is in accordance with the Declaration of Helsinki, received ethical approval from the institutional review boards of all of the participating institutes and was undertaken in accordance with the Ethical Guidelines for Clinical Studies of the Japanese Ministry of Health, Labor, and Welfare. All of the study participants gave written informed consent.

Both the WHO (2) and the NCEP (3) definitions were used to diagnose MetS in this study. However, because the original cut-off for abdominal obesity in the NCEP definition (waist circumference ≥102 cm for men and ≥89 cm for women) has previously been shown to be inappropriate for Asian populations (35,37) and the number of subjects who met these criteria was extremely low, the cut-off limit was adjusted according to the criteria proposed by the Japan Society for the Study of Obesity (≥85 cm for men or ≥90 cm for women), which were based on the risk of obesity-related disorders in a Japanese population (39). The WHO criteria for obesity were adopted because the waist-to-hip ratio (WHR) was used rather than waist circumference. The criteria used for analysis in this study are shown in Table 3. Because all of the study subjects were diabetic, those who fulfilled two or more of criteria 1a, 2a, 5, or 6 were classified as having WHO-MetS and those who fulfilled two or more of criteria 1b, 2b, 3, or 4 were diagnosed as having NCEP-MetS, using a modified NCEP definition (Table 3). For comparisons with other traditional risk factors for CVD, we also evaluated high LDL cholesterol levels, cigarette smoking, and excessive alcohol intake (40). Medication use, including agents for hypertension and hyperlipidemia, were not considered when diagnosing MetS in this study.

Waist and hip circumferences were measured at the umbilicus and trochanter level, respectively. A baseline dietary survey, comprised of food records and a food frequency questionnaire that included alcohol consumption, was undertaken. Information regarding cigarette smoking was collected using a standardized questionnaire. All laboratory tests were undertaken using the standard methods of each of the participating institutes, apart from the HbA_{1c} assays, which used a common standard, with 5.8% as the upper normal limit. Plasma LDL cholesterol was calculated using Friedewald's equation, except for triglyceride levels >400 mg/dl, in which case the LDL cholesterol data were treated as "missing." To estimate insulin resistance, the homeostasis model assessment of insulin resistance (HOMA-IR) was used (41). Plasma insulin levels and the HOMA-IR were not evaluated in patients treated with insulin.

Patients were assessed for CHD and stroke at baseline and yearly thereafter. In all subjects, a 12-lead electrocardiogram (ECG) was recorded at each assessment. Fatal and nonfatal CHD and stroke events identified during follow-up were certified by at least two members of the experts' committee who were masked as to risk factor status and the other member's diagnosis. With regard to CHD, myocardial infarction was defined according to the WHO Monitoring of Trends and Determinants in Cardiovascular Disease criteria (42) and angina pectoris was defined as typical effort-dependent chest pain or oppression relieved at rest or by using nitroglycerine, as validated by exercise-positive ECG and/or angiography. Stroke events were defined as a constellation of focal or global neurological deficits of sudden or rapid onset and for which there was no apparent cause other than a vascular accident, as determined by a detailed history, a neurological examination, and ancillary diagnostic procedures such as computed tomography, magnetic resonance imaging, cerebral angiography, and lumbar puncture. Stroke events were

classified as cerebral infarction (including embolus), intracranial hemorrhage (including subarachnoid hemorrhage), transient ischemic attack, or stroke of undetermined type in accordance with WHO criteria (43). No cases of asymptomatic lesions detected by brain imaging (i.e., silent infarction) were included. Only "first-ever" CHD or stroke events during the study period were counted for the analysis; if a patient had both CHD and stroke events, each event was counted separately.

Data are presented as means ± SD or as a proportion, unless otherwise specified. To compare the distributions of baseline characteristics between groups, Wilcoxon's rank-sum test or Fisher's exact test was used. Incidence rates in the two groups were assessed by a score test under the Poisson assumption. Cox regression analysis was used to calculate the adjusted hazard ratio (HR) and 95% confidence interval (CI) of MetS risk factors with CHD, stroke, or both. Statistical analyses were performed separately by sex. The SAS software package (Version 8.0, Cary, NC) was used for all analyses. $P < 0.05$ was considered to be significant.

RESULTS

Baseline characteristics and prevalence of the metabolic syndrome

The baseline characteristics of the study subjects are shown in Table 1. In all, 51% of male and 53% of female subjects met WHO criteria for MetS, whereas 45% of male and 38% of female subjects met NCEP criteria for MetS. Plasma insulin levels and HOMA-IR were significantly higher in patients with MetS (both definitions) than in those without MetS; however, there were no significant differences in HbA_{1c} or the frequency of oral hypoglycemic agent use. Insulin usage was significantly lower in women with MetS by either definition and in men with NCEP-MetS. Blood pressure and serum triglycerides were significantly higher and HDL cholesterol was significantly lower in MetS patients, despite the fact that the use of medications for both hypertension and hyperlipidemia was much more common than in patients without MetS. Daily energy intake did not differ between patients with and without MetS (data not shown).

Incidence of cardiovascular disease during follow-up

During the 8-year study period, the total number of CVD events was 117, comprised of 62 CHD and 59 stroke events. The combined incidence (per 1,000 patient-years) of CHD and/or stroke was significantly greater in patients with MetS (except in female patients with NCEP-MetS) than in those without MetS (Table 2).

Hazard ratios of the metabolic syndrome and its individual components for coronary heart disease and stroke

HRs were calculated to determine which definition of MetS was the better predictor of CVD and which of the individual MetS components (or other classic risk factors) could most efficiently predict CVD events in our subjects (Table 3). In male patients, WHO-MetS was not significantly associated with an increased risk for either CHD or stroke separately, but was associated with the combination of both (HR = 1.6). Triglyceride, LDL cholesterol (both for CHD), and blood pressure (≥140/90 mmHg) levels (for stroke) showed higher HRs. NCEP-MetS was a significant predictor of CHD in male patients, although its HR (1.9) was lower than that for triglycerides (2.9) or LDL cholesterol (2.1). Thus, neither definition of MetS was a substantially better predictor of CVD than the component parts in male patients. In contrast, in the female patients, WHO-MetS was a significant and strong predictor of CHD (HR = 2.8), stroke (HR = 3.7), and both CHD and stroke (HR = 3.2). In female patients, none of the individual elements nor the other classic risk factors showed significant increases in HRs, with the exception of hypertension (≥140/90 mmHg) for stroke, although its HR (2.4) was still lower than that for WHO-MetS. NCEP-MetS was not a significant risk factor for CHD or stroke in female patients (Table 3).

To examine the clustering effects of the individual components of MetS, the association between CVD risk and the number of MetS components fulfilled (other than diabetes) was analyzed (Table 3). Increasing the cut-off component number for the diagnosis of NCEP-MetS from ≥2 to ≥3 in male subjects did not dramatically improve the HR but did greatly reduce the number of patients diagnosed as having MetS, from 45 to 14.5% (Table 3). In female patients, changing the diagnostic cut-off component numbers was not particularly beneficial in improving the prognostic value of WHO-MetS (Table 3).

CONCLUSIONS — The prevalence of MetS in our diabetic patients who were free from CVD was not as high as that reported in previous studies that included patients with previous CVD (12–20) but was nevertheless relatively high (38–53%). Although we did not have age-matched nondiabetic control subjects, the prevalence of MetS was much higher than that reported in Japanese general population workers, namely 19.5% in men and 7.9% in women (33). Hypertension and dyslipidemia are much more common in diabetic patients than in nondiabetic subjects (21), and it has been speculated that the features of MetS more easily aggregate, even in the absence of current or previous CVD, leading to the observed increase in the prevalence of MetS. On the other hand, the prevalence of NCEP-MetS in the U.S. general population age 50 years and older is 44% (20), which is relatively close to that in our Japanese diabetic patients. However, even in the U.S. (excluding Asian Americans), the prevalence of MetS in those who have a BMI range equivalent to that of Japanese subjects is not >10% (44). This implies that in the U.S., obesity has a potent impact on the prevalence of MetS, as has also been shown in a recent study (45). This is in contrast to findings in Japan, where diabetes rather than obesity may have the greater influence on the prevalence of MetS, as Japanese diabetic patients are not obese by comparison with white diabetic patients or nondiabetic Japanese subjects (31,32).

The clinical importance of MetS is related to its putative impact on CVD morbidity and mortality. Among Italian patients with type 2 diabetes, the risk for CVD was 4.9 (CI 1.2–20.7) times higher in patients with WHO-MetS than in those without it (16), which was a higher rate than that seen in our male (1.6 [CI 1.0–2.6] times) and female (3.2 [CI 1.6–6.5] times) patients. These results suggest that the clinical impact of MetS on diabetic patients varies by ethnic group. Comparing cardiovascular risk factors in our Japanese patients to those in patients in the U.K. Prospective Diabetes Study (UKPDS) (46,47), hypertension is a common

Table 1—*Baseline characteristics of study subjects, grouped by metabolic syndrome status*

		WHO-defined metabolic syndrome			NCEP-defined metabolic syndrome		
	Total	Without	With	*P*	Without	With	*P*
n							
Men	771	376 (48.8)	395 (51.2)	—	424 (55.0)	347 (45.0)	—
Women	653	310 (47.4)	343 (52.6)	—	405 (62.0)	248 (38.0)	—
Age (years)							
Men	58.2 ± 7.4	57.4 ± 7.6	58.9 ± 7.2	0.01	58.0 ± 7.6	58.4 ± 7.2	0.50
Women	58.7 ± 7.4	57.9 ± 7.7	59.5 ± 7.0	0.01	58.4 ± 7.4	59.4 ± 7.2	0.11
Diabetes duration (years)							
Men	10.9 ± 7.6	11.0 ± 7.6	10.9 ± 7.6	0.66	11.5 ± 7.8	10.2 ± 7.4	0.01
Women	10.1 ± 6.7	10.7 ± 7.3	9.5 ± 6.0	0.10	10.6 ± 7.0	9.4 ± 6.0	0.07
BMI (kg/m^2)							
Men	22.9 ± 2.6	22.0 ± 2.4	23.7 ± 2.6	<0.01	21.8 ± 2.3	24.2 ± 2.4	<0.01
Women	23.4 ± 3.3	22.3 ± 3.0	24.3 ± 3.3	<0.01	22.6 ± 3.1	24.6 ± 3.3	<0.01
Waist circumference (cm)							
Men	82.3 ± 7.7	79.0 ± 7.1	85.3 ± 7.0	<0.01	78.4 ± 6.4	87.0 ± 6.5	<0.01
Women	76.5 ± 9.8	72.4 ± 8.3	80.1 ± 9.7	<0.01	74.1 ± 8.6	80.4 ± 10.4	<0.01
Waist-to-hip ratio							
Men	0.89 ± 0.07	0.86 ± 0.05	0.92 ± 0.06	<0.01	0.87 ± 0.06	0.92 ± 0.06	<0.01
Women	0.83 ± 0.08	0.80 ± 0.06	0.86 ± 0.07	<0.01	0.82 ± 0.07	0.86 ± 0.08	<0.01
Blood pressure (mmHg)							
Men	132 ± 16/78 ± 10	124 ± 13/74 ± 9	139 ± 15/81 ± 10	<0.01	127 ± 16/75 ± 9	137 ± 15/81 ± 9	<0.01
Women	132 ± 17/76 ± 10	124 ± 13/73 ± 9	139 ± 16/79 ± 11	<0.01	128 ± 17/74 ± 10	138 ± 14/80 ± 10	<0.01
HbA_{1c} (%)							
Men	7.61 ± 1.36	7.53 ± 1.42	7.67 ± 1.30	0.05	7.54 ± 1.36	7.68 ± 1.36	0.18
Women	8.05 ± 1.45	8.07 ± 1.51	8.04 ± 1.40	0.79	8.09 ± 1.47	7.99 ± 1.42	0.41
Fasting plasma glucose (mmol/l)*							
Men	8.3 (7.2–10.0)	8.2 (7.0–9.7)	8.6 (7.4–10.4)	<0.01	8.2 (7.1–9.8)	8.6 (7.4–10.3)	0.02
Women	8.6 (7.3–10.2)	8.6 (7.2–10.2)	8.6 (7.3–10.2)	0.74	8.6 (7.2–10.3)	8.5 (7.4–9.9)	0.77
Fasting plasma insulin (pmol/l)†‡							
Men	6.2 (0.5–1.9)	5.4 (0.5–1.9)	7.2 (0.5–1.9)	<0.01	5.2 (0.5–1.9)	7.7 (0.5–1.9)	<0.01
Women	7.1 (0.5–1.9)	5.9 (0.5–1.9)	8.3 (0.6–1.8)	<0.01	6.2 (0.5–1.9)	8.7 (0.5–1.9)	<0.01
HOMA-IR‡							
Men	3.1 ± 3.1	2.6 ± 2.6	3.6 ± 3.4	<0.01	2.4 ± 2.1	3.9 ± 3.8	<0.01
Women	3.3 ± 2.6	2.8 ± 2.2	3.8 ± 2.8	<0.01	2.9 ± 2.1	4.1 ± 3.1	<0.01
Serum total cholesterol (mmol/l)							
Men	5.01 ± 0.90	4.93 ± 0.84	5.09 ± 0.94	0.01	4.97 ± 0.82	5.07 ± 0.98	0.16
Women	5.44 ± 0.85	5.38 ± 0.84	5.50 ± 0.86	0.05	5.41 ± 0.83	5.50 ± 0.89	0.28
Serum HDL cholesterol (mmol/l)							
Men	1.34 ± 0.39	1.42 ± 0.39	1.27 ± 0.38	<0.01	1.48 ± 0.38	1.18 ± 0.34	<0.01
Women	1.47 ± 0.44	1.57 ± 0.45	1.37 ± 0.41	<0.01	1.65 ± 0.43	1.17 ± 0.26	<0.01
Serum triglycerides (mmol/l)†							
Men	1.2 (0.6–1.6)	1.0 (0.7–1.5)	1.5 (0.6–1.6)	<0.01	1.0 (0.7–1.5)	1.6 (0.6–1.6)	<0.01
Women	1.1 (0.6–1.7)	0.9 (0.6–1.6)	1.4 (0.6–1.6)	<0.01	9 (0.7–1.5)	1.6 (0.6–1.6)	<0.01

Current smoker (%; men/women)	43.9/8.7	46.6/8.1	41.3/9.2	0.08/0.38	44.7/7.1	42.9/11.3	0.33/0.049
Excessive alcohol intake (%; men/women)§	12.4/0.2	8.2/0.0	16.4/0.3	<0.01/0.51	7.7/0.3	18.4/0.0	<0.01/0.62
OHA use (without insulin) (%; men/women)	72/77	72/76	73/78	0.38/0.33	72/75	72/79	0.50/0.20
Insulin use (with or without OHA) (%; men/women)	16/20	18/24	15/16	0.16/0.01	20/22	11/15	<0.01/0.02
Medication for hypertension (%; men/women)	22/29	12/17	32/40	<0.01/<0.01	16/23	30/40	<0.01/<0.01
Medication for hyperlipidemia (%; men/women)	15/35	11/30	19/39	<0.01/<0.01	10/32	21/40	<0.01/0.02

Data are *n* (%), means ± SD, *median (interquartile range), or †geometric means (1 SD). ‡Patients with insulin therapy were excluded. §Excessive alcohol intake was defined as more than three drinks (38 g ethanol) per day. OHA, oral hypoglycemic agent.

and potent risk factor for stroke (Table 3) (46). By contrast, HDL cholesterol levels, hypertension, and smoking, all of which were identified as significant risk factors for CHD in UKPDS patients (47), were not associated with a significant elevation of HRs in our Japanese patients (Table 3). Instead, triglyceride levels, which were not significant in UKPDS patients (47), were a strong predictor for CHD in male Japanese patients. These findings imply that the critical therapeutic targets among the components of MetS for preventing cardiovascular complications (28) may need to be modified according to a patient's ethnic group.

Most of the previous studies evaluating the predictive power of MetS for CVD calculated the HRs by including sex as one of the independent variables for statistical adjustment, and very few studies have analyzed CVD risk separately by sex (24). Sex is reportedly an independent predictor for CVD, with an odds ratio of 2.6, which is larger than that of age, HbA_{1c}, and even of MetS itself in type 2 diabetic patients (16). Our results revealed drastic differences in the HRs between sexes. In our female patients, WHO-MetS presented an increased risk for CVD events to a greater degree than could be predicted by the sum of the individual components (Table 3), whereas, in contrast, in our male patients, WHO-MetS was not even a significant risk factor for CVD. At baseline, obvious sex differences were observable in the proportion of subjects who smoked or consumed excessive alcohol, both of which were much higher in male patients. Of particular interest, the proportion of male subjects with excessive alcohol intake was at least twice as high in male patients with MetS than in those without MetS, whereas the proportion of current smokers did not differ in patients with and without MetS (Table 1). It can be speculated that excessive alcohol intake could be closely associated with MetS in male Japanese diabetic patients. Moreover, moderate alcohol intake, which has been shown to be beneficial for preventing CHD in U.S. and European diabetic patients, is not beneficial for Japanese patients (40).

Few studies have applied both the WHO and NCEP definitions of MetS to the same subjects to compare the prevalence of MetS or its predictive value for CVD. It has been reported that the prevalence of WHO-MetS is generally higher than that of NCEP-MetS in both sexes (7,12). This was confirmed in our Japanese diabetic subjects, although the difference in prevalence was not great. Regarding the predictive value of MetS, in subjects without diabetes or other cardiovascular risks, Hunt et al. (27) reported that the NCEP-MetS tended to be more predictive for cardiovascular mortality than the WHO-MetS, whereas Lakka et al. (9) reported a contrary result. In our diabetic patients, the NCEP guidelines, even modified for optimal use by Japanese subjects, were not more predictive than the WHO guidelines in female patients nor did they show excellent clinical usefulness in male patients. One possible explanation for this difference in our patients could be the hypertension cut-off used, with 140/90 mmHg in the WHO defini-

Table 2—*Incidence of coronary heart disease and/or stroke (per 1,000 patient-years) among study subjects grouped by metabolic syndrome status*

		WHO-defined metabolic syndrome			NCEP-defined metabolic syndrome		
	Total (%)	Without (%)	With (%)	*P*	Without (%)	With (%)	*P*
Incidence among Men							
CHD	9.8	8.4	11.3	0.34	7.0	13.5	0.04
Stroke	7.7	5.1	10.3	0.05	6.6	9.1	0.35
CHD and/or stroke	17.1	12.7	21.6	0.03	13.0	22.6	0.02
Incidence among Women							
CHD	5.5	2.9	8.0	0.04	4.4	7.3	0.27
Stroke	7.2	2.8	11.2	<0.01	6.2	8.8	0.38
CHD and/or stroke	12.6	5.7	19.0	<0.01	10.7	15.6	0.22

Table 3—*Patient prevalence at baseline and hazard ratios for coronary heart disease, stroke, or both in Japanese study subjects grouped by metabolic syndrome status*

	Prevalence at baseline		Hazard ratios for CHD		Hazard ratios for stroke		Hazard ratios for CHD and/or stroke	
	Men	Women	Men	Women	Men	Women	Men	Women
Criteria of individual components								
1a. BMI >30 or WHR >0.90 (men) or >0.85 (women)	39.4	37.5	1.3 (0.7–2.5)	1.2 (0.5–3.0)	1.3 (0.7–2.6)	1.1 (0.5–2.3)	1.4 (0.8–2.2)	1.2 (0.6–2.1)
1b. Waist circumference ≥85cm (men) or ≥90 cm (women)	36.7	9.6	1.7 (0.9–3.0)	1.0 (0.2–4.4)	0.90 (0.4–1.9)	1.1 (0.3–3.7)	1.3 (0.8–2.1)	1.1 (0.4–2.8)
2a. SBP ≥140 or DBP ≥90 mmHg	38.9	38.9	0.8 (0.4–1.6)	1.0 (0.4–2.6)	2.1 (1.1–4.3)	2.4 (1.1–5.5)	1.3 (0.8–2.1)	1.8 (1.0–3.2)
2b. SBP ≥130 or DBP ≥85 mmHg	60.7	62.2	0.9 (0.5–1.6)	0.9 (0.4–2.2)	1.4 (0.7–2.9)	1.8 (0.7–4.5)	1.1 (0.6–1.7)	1.2 (0.7–2.4)
3. Triglycerides ≥150 mg/dl	24.8	21.0	2.9 (1.6–5.3)	1.7 (0.6–4.4)	1.1 (0.5–2.4)	0.7 (0.2–1.9)	2.0 (1.2–3.2)	1.1 (0.5–2.2)
4. HDL cholesterol ≤40 mg/dl	19.3	36.3	1.8 (0.9–3.5)	1.5 (0.6–3.6)	1.0 (0.4–2.5)	1.3 (0.6–2.9)	1.6 (0.9–2.6)	1.3 (0.7–2.4)
5. Triglycerides ≥150 mg/dl or HDL cholesterol <35 mg/dl	28.5	27.0	2.8 (1.6–5.2)	1.8 (0.7–4.5)	0.9 (0.4–1.9)	1.6 (0.7–3.5)	1.8 (1.1–2.9)	1.6 (0.9–2.9)
6. Urinary albumin excretion >30 μg/g creatinine	51.2	57.7	1.2 (0.6–2.3)	2.9 (0.9–8.7)	1.8 (0.9–3.8)	1.1 (0.5–2.4)	1.4 (0.9–2.3)	1.6 (0.8–3.0)
7. LDL cholesterol ≥120 mg/dl	45.1	65.2	2.1 (1.1–3.9)	1.2 (0.5–3.2)	0.9 (0.5–1.8)	0.6 (0.3–1.3)	1.4 (0.9–2.3)	0.8 (0.4–1.4)
8. Current smoker	43.9	8.7	1.4 (0.7–2.5)	0.6 (0.1–4.3)	0.9 (0.4–1.8)	2.5 (0.8–7.3)	1.2 (0.7–1.9)	1.6 (0.6–4.1)
9. Alcohol intake >3 drinks/day*	12.4	0.2	0.7 (0.3–2.1)	0.0 (0.0–0.0)	1.0 (0.4–2.8)	0.0 (0.0–0.0)	0.9 (0.4–1.8)	0.0 (0.0–0.0)
Number of components comprising WHO-MetS other than diabetes (i.e., among 1a, 2a, 5, and 6)								
0	18.6	16.4	1.00	1.00	1.00	1.00	1.00	1.00
≥1 (vs. <1)	81.5	83.6	1.7 (0.7–4.5)	3.9 (0.5–28.4)	1.0 (0.4–2.5)	2.3 (0.5–9.7)	1.2 (0.7–2.4)	2.8 (0.9–9.0)
≥2 (vs. <2; i.e., WHO-MetS)	51.2	52.5	1.3 (0.7–2.4)	2.8 (1.0–7.9)	2.0 (0.9–4.1)	3.7 (1.4–9.9)	1.6 (1.0–2.6)	3.2 (1.6–6.5)
≥3 (vs. <3)	21.8	20.7	1.8 (0.9–3.5)	1.3 (0.5–3.7)	2.1 (1.0–4.4)	1.1 (0.4–2.7)	1.9 (1.2–3.2)	1.2 (0.6–2.4)
Number of components comprising NCEP-MetS other than diabetes (i.e. among 1b, 2b, 3, and 4)								
0	20.1	21.6	1.00	1.00	1.00	1.00	1.00	1.00
≥1 (vs. <1)	79.9	78.4	1.9 (0.7–4.9)	1.6 (0.4–5.6)	1.0 (0.4–2.2)	6.4 (0.9–46.7)	1.3 (0.7–2.4)	2.7 (0.9–7.7)
≥2 (vs. <2; i.e., NCEP-MetS)	45.0	38.0	1.9 (1.0–3.6)	1.7 (0.7–4.0)	1.4 (0.7–2.8)	1.3 (0.6–2.8)	1.8 (1.1–2.8)	1.4 (0.8–2.5)
≥3 (vs. <3)	14.5	11.5	2.5 (1.3–4.9)	0.9 (0.2–3.7)	0.9 (0.3–2.4)	0.3 (0.0–2.2)	1.8 (1.0–3.2)	0.5 (0.2–1.7)

Data are percent or hazard ratios (95% CIs) and are grouped according to individual and combined cardiovascular risk factors mostly comprising the metabolic syndrome as defined by the World Health Organization or the National Cholesterol Education Program. *Equivalent to 38 g ethanol/day. DBP, diastolic blood pressure; SBP, systolic blood pressure; WHR, waist-to-hip ratio.

tion being a significant predictor for stroke, whereas 130/85 mmHg in the NCEP definition is not.

The strengths of our study were that *1*) it is the first prospective study to determine the predictive value of MetS on CVD in Asian subjects, *2*) the two most widely used definitions of MetS were applied to the same cohort for the evaluation of their clinical usefulness, and *3*) the follow-up was mainly carried out in university or large general hospitals, which facilitated the reliable assessment of follow-up data and event diagnosis/records. Nevertheless, we acknowledge that the study had certain limitations: *1*) Our study subjects were hospital-based patients with diabetes of a relatively long duration; therefore, we cannot make inferences beyond a similar group. *2*) We analyzed both intervention (lifestyle modification through diabetes self-management care) and control (continuance of conventional care) groups of the JDCS together, although mild intervention produced only limited differences in glycemic control (0.1–0.2% in HbA_{1c}) as well as a lack of significant differences in known classical cardiovascular risk factors, as previously reported (38). *3*) We did not consider medication use in the diagnosis of MetS in this study. *4*) Mortality was not analyzed because we did not have sufficient occurrences at this stage of the study.

In conclusion, we found a high prevalence of MetS among diabetic patients with no history of CVD. For Japanese female patients with type 2 diabetes, WHO-MetS but not NCEP-MetS was predictive for CVD. In male patients, although both WHO-MetS and NCEP-MetS were somewhat predictive for CVD, hyperlipidemia or hypertension had equivalent or higher HRs for CVD and seemed to be sufficient for the prediction of CVD. We suggest that the commonly used definitions of MetS, at least in their present forms, have limited clinical usefulness for Asian diabetic patients and may need some ethnic group−specific modifications for global use.

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APPENDIX

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