TABLE 1. Baseline Characteristics of Study Subjects, the Hisayama Study, 1988

Characteristic	Men (n=1092)	Women (n=1500)
Age, y	58.1±11.4	59.4±11.9
High-sensitivity C-reactive protein, mg/L		
Median	0.54	0.40
Mean	2.07±8.31	1.30±5.45
Systolic blood pressure, mm Hg	134.7±20.1	132.9±22.2
Diastolic blood pressure, mm Hg	80.5±11.4	75.8±10.8
Hypertension, %	45.2%	38.5%
Use of antihypertensive agents, %	14.2%	15.4%
ECG abnormalities, %	20.7%	14.7%
Diabetes mellitus, %	15.1%	9.6%
BMI, kg/m^2	22.8±2.9	22.9±3.3
Total cholesterol, mmol/L	5.09±1.07	5.54±1.07
HDL-cholesterol, mmol/L	1.25±0.31	1.33±0.30
Current smoking, %	49.8%	6.7%
Current drinking, %	60.6%	9.0%
Regular exercise, %	11.8%	9.1%

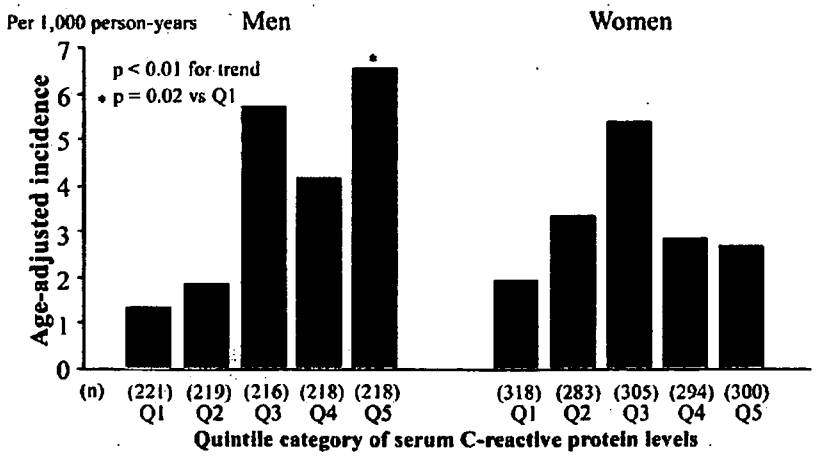
Data are mean±1 SD or percent, unless otherwise specified.

Table 2 shows the multivariate-adjusted RRs and their 95% CIs for the development of ischemic and hemorrhagic stroke according to hsCRP quintile categories. In men, the risk of ischemic stroke significantly increased with rising hsCRP levels even after adjustment for age, systolic blood pressure, ECG abnormalities, diabetes, BMI, total cholesterol, HDL cholesterol, smoking habits, alcohol intake, and physical activity (P=0.02 for trend), and the multivariate-adjusted RR of subjects in the fifth quintile was significantly higher than that of subjects in the first quintile (RR, 3.11; 95%CI, 1.04 to 9.32; P=0.04). However, such associations were not observed for ischemic stroke in women or for hemorrhagic stroke in either sex (Table 2). To examine the combined effects of elevated hsCRP levels and other cardiovascular risk factors on ischemic stroke occurrence, we estimated the age-adjusted RRs of ischemic stroke among 4 groups of male subjects according to the presence or absence of a high-hsCRP level (the fifth quintile, ≥1.57 mg/L) and each risk factor (Table 3). Compared with the reference group having neither high-hsCRP levels nor hypertension, the risk of ischemic stroke for the groups with either high-hsCRP levels or hypertension was not significant, but the risk for the group having both high-hsCRP levels and hypertension was significantly higher (RR, 2.77; 95% CI, 1.31 to 5.83; P<0.01). A similar pattern was observed for the coexistence of high-hsCRP levels and diabetes (RR, 4.30; 95% CI, 1.89 to 9.79; P<0.01), obesity (RR, 4.00; 95% CI, 1.53 to 10.46; P< 0.01), hypercholesterolemia (RR, 3.74; 95% CI, 1.71 to 8.19; P<0.01), or smoking habits (RR, 2.29; 95% CI, 1.78 to 4.87; P=0.03). There were significant interactions between high-hsCRP levels and diabetes (χ^2=5.370; P=0.02), as well as hypercholesterolemia (χ^2=6.052; P=0.01), and a marginally significant interaction (χ^2=3.39; P=0.06) between high-hsCRP levels and hypertension. However, interactions for obesity and smoking were not significant. These associations were substantially unchanged even after adjustment for other risk factors in the multivariate analysis.

Discussion

In a 12-year follow-up examination of a general Japanese population, we demonstrated that elevation of serum hsCRP levels was an independent risk factor for future ischemic stroke in men but not in women, whereas there was no association between serum hsCRP levels and the risk of future hemorrhagic stroke in either sex. Moreover, the coexistence of a high-hsCRP level and another risk factor, such as hypertension, obesity, diabetes, hypercholesterolemia, or smoking, extremely increased the risk of future ischemic stroke in our male subjects.

Recently, the Framingham Study[10] and Cardiovascular Health Study,[11] both which had elderly subjects (mean age,



Quintile range (mg/l)
Men:Q1= ≤ 0.20, Q2=0.21 to 0.40, Q3=0.41 to 0.71, Q4=0.72 to 1.56, Q5=1.57
Women:Q1= ≤ 0.17, Q2=0.18 to 0.30, Q3=0.31 to 0.53, Q4=0.54 to 1.09, Q5=1.10

Figure 1. Age-adjusted incidence rates of first-ever ischemic stroke according to serum high-sensitivity C-reactive protein levels.

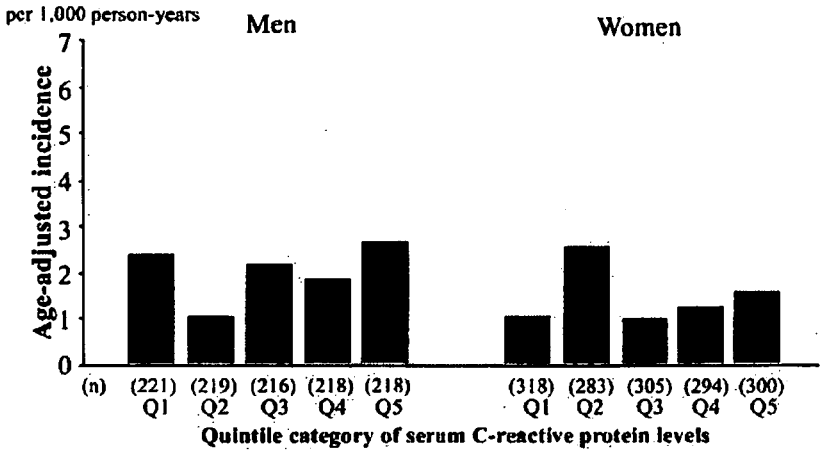


Figure 2. Age-adjusted incidence rates of first-ever hemorrhagic stroke according to serum high-sensitivity C-reactive protein levels.

Quintile range (mg/l)
Men:Q1= ≤ 0.20, Q2=0.21 to 0.40, Q3=0.41 to 0.71, Q4=0.72 to 1.56, Q5=1.57
Women:Q1= ≤ 0.17, Q2=0.18 to 0.30, Q3=0.31 to 0.53, Q4=0.54 to 1.09, Q5=1.10

69.8 and 72.6 years, respectively), and a nested case-control study of Japanese-American men[12] in Hawaii have investigated the association between hsCRP level and the risk of future ischemic stroke. In those studies, the elevation of serum hsCRP was clearly associated with ischemic stroke in men, which support our findings. For women, on the other hand, the effects of high levels of serum hsCRP on ischemic stroke were ambiguous. In the Framingham study women, hsCRP levels were significantly associated with the risk of ischemic stroke,[10] whereas no significant association was observed for the women in the Cardiovascular Health Study,[11] which was in accord with the findings of our study. Recent clinical evidence has shown that endogenous estrogen protects the development of atherosclerosis[17,18] and that estrogen induces the elevation of hsCRP levels.[19] In women, such conflicting effects of sex hormone might weaken the association of hsCRP elevation with ischemic stroke. Another reason for the sex difference in the risk of ischemic stroke might stem from the difference in the atherosclerotic process between men and women. Generally, it is considered that atherosclerosis is more severe in men than in women. Thus, it may be easier to detect the association between hsCRP levels and ischemic stroke in men.

TABLE 2. Multivariate-Adjusted RRs of First-Ever Ischemic and Hemorrhagic Stroke according to Serum High-Sensitivity C-Reactive Protein Levels

Quintiles of Men/Women	RR	95% CI	*P* Value	RR	95% CI	*P* Value
Ischemic stroke						
Q1	1.00	1.00				
Q2	1.08	0.29 to 4.03	0.91	1.27	0.55 to 2.94	0.58
Q3	2.81	0.93 to 8.51	0.07	1.56	0.71 to 3.39	0.27
Q4	2.24	0.73 to 6.92	0.16	1.05	0.46 to 2.42	0.90
Q5	3.11	1.04 to 9.32	0.04	1.34	0.61 to 2.91	0.46
P for trend	0.02	0.65				
Hemorrhagic stroke						
Q1	1.00			1.00		
Q2	0.33	0.07 to 1.65	0.18	2.66	0.82 to 8.61	0.10
Q3	0.58	0.17 to 1.91	0.37	1.00	0.24 to 4.06	0.99
Q4	0.78	0.26 to 2.37	0.67	2.10	0.63 to 7.04	0.23
Q5	0.68	0.21 to 2.26	0.53	1.74	0.51 to 5.85	0.37
P for trend	0.92	0.64				

Men, mg/L: Q1=≤0.20, Q2=0.21 to 0.40, Q3=0.41 to 0.71, Q4=0.72 to 1.56, Q5=≥1.57. Women, mg/L: Q1=≤0.17, Q2=0.18 to 0.30, Q3=0.31 to 0.53, Q4=0.54 to 1.09, Q5=≥1.10. Multivariate adjustment was made for age, systolic blood pressure, ECG abnormalities, diabetes, BMI, total cholesterol, HDL cholesterol, smoking habits, alcohol intake, and physical activity.

In our subjects, we did not find a clear association between hsCRP levels and hemorrhagic stroke occurrence. Because cerebral hemorrhage develops from the rupture of small vessels, such as cerebral perforating arteries, damaged by hypertension causing lipohyalinosis,[20] or by amyloid angiopathy,[21] it is suggested that elevated hsCRP levels have little or no association with small vessel disease. Although hypertension and smoking may accelerate the development and growth of intracranial aneurysm,[22] which is a main cause of subarachnoid hemorrhage, the association between atherosclerosis and intracranial aneurysm is considered weak.[23] Thus, our finding that there is no association between serum hsCRP levels and hemorrhagic stroke is reasonable.

Our stratified analysis showed an extremely increased risk of ischemic stroke in men who have both a high-hsCRP level and another risk factor. Although the mechanism underlying this phenomenon is not clearly understood, several possible explanations have been proposed. Because inflammation is strongly related to atherosclerosis, elevated hsCRP levels may reflect the existence of advanced atherosclerosis induced by other cardiovascular risk factors. Accordingly, it is conceivable that the coexistence of elevated hsCRP levels and other risk factors is a marker of a group at high risk of atherosclerosis, and, thus, the risk of ischemic stroke is considerably high in that group. Additionally, recent clinical

TABLE 3. Age-Adjusted RRs of First-Ever Ischemic Stroke according to High-Sensitivity C-Reactive Protein Levels and Risk Factors in Men

Risk Factor	CRP Levels	Events/Populations (n)	RR	95% CI	*P* Value
Hypertension					
No	Low	16/472	1.00		
Yes	Low	22/363	1.34	0.69 to 2.56	0.39
No	High	5/105	1.27	0.46 to 3.47	0.65
Yes	High	13/96	2.77	1.31 to 5.83	<0.01
Diabetes mellitus					
No	Low	30/719	1.00		
Yes	Low	8/116	1.65	0.75 to 3.59	0.21
No	High	11/167	1.42	0.71 to 2.84	0.32
Yes	High	7/34	4.30	1.89 to 9.79	<0.01
Obesity					
No	Low	47/635	1.00		
Yes	Low	11/200	1.91	0.93 to 3.93	0.08
No	High	13/162	1.69	0.87 to 3.29	0.12
Yes	High	5/39	4.00	1.53 to 10.46	<0.01
Hypercholesterolemia					
No	Low	31/617	1.00		
Yes	Low	7/218	0.77	0.34 to 1.75	0.54
No	High	10/145	1.15	0.56 to 2.35	0.71
Yes	High	5/56	3.74	1.71 to 8.19	<0.01
Current smoking					
No	Low	21/432	1.00		
Yes	Low	17/403	1.11	0.59 to 2.12	0.74
No	High	8/87	1.48	0.65 to 3.36	0.35
Yes	High	10/114	2.29	1.78 to 4.87	0.03

CRP levels: "high" indicates the fifth quintile; low, the first to fourth quintiles. Hypertension: systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive agents. Diabetes: fasting blood glucose ≥7.0 mmol/L, or postprandial blood glucose level ≥11.1 mmol/L, or current use of hypoglycemic agents. Obesity: BMI ≥25 kg/m^2. Hypercholesterolemia: total cholesterol level ≥5.69 mmol/L.

reviews, as well as experimental and clinical studies, have shown that inflammation is directly associated with the development of atherosclerosis[24] and instability of atheroma.[25,26] It is, therefore, speculated that chronic inflammation directly and extremely enhances the risk of ischemic stroke by such atherogenic effects of inflammation in people whose arterial walls have already been damaged by other risk factors.

Several limitations of our study should be discussed. The primary limitation is that our findings are based on a 1-time measurement of serum hsCRP, which may not accurately reflect the status of the study participants. However, this source of variability could not account for the relationship observed in the present study, because a random misclassification of such nature would tend to underestimate study findings and bias the results toward the null hypothesis. Thus, the true association may be stronger than that observed in our study. A second limitation is that the serum samples were measured after being stored at −20°C for a long period. However, the Reykjavik Study confirmed the stability of CRP concentrations in serum preserved at this temperature for an average of 12 years.[27] The last limitation is that our study lacked information on drug use, which could affect serum CRP levels. It is known that several medications, including statin, angiotensin-converting enzyme inhibitors, fibrates, niacin, thiazolidinedione, and estrogen/progestogen hormone can alter CRP levels.[28] However, these medications were rarely used in our country in 1988, when the serum samples for our study were collected. This suggests that such a bias did not invalidate the present findings.

In conclusion, our study found that, in a general Japanese population, the elevation of serum hsCRP levels was an independent risk factor for future ischemic stroke in men but not for hemorrhagic stroke in either sex. The addition of elevated serum hsCRP levels to the risk factor profile may significantly increase the predictability of ischemic stroke. Moreover, our study revealed that the risk of future ischemic stroke was considerably high in subjects who had both high-hsCRP levels and another risk factor. For such individuals, an elevated serum hsCRP level may provide additional

motivation for both the treating physician and the patient to control these risk factors strictly.

Acknowledgments

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Metabolic Syndrome and CKD in a General Japanese Population: The Hisayama Study

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• ***Background:*** **Metabolic syndrome has been linked with various atherosclerotic diseases, but has not been evaluated sufficiently as a risk factor for the development of chronic kidney disease (CKD) in the general population.** ***Methods:*** **We followed up 1,440 community-dwelling individuals without CKD aged 40 years or older for 5 years and examined the effects of metabolic syndrome, defined by the modified National Cholesterol Education Program Adult Treatment Panel III criteria, on the development of CKD.** ***Results:*** **During follow-up, 88 subjects experienced CKD. The age- and sex-adjusted 5-year cumulative incidence of CKD was significantly greater in subjects with than without metabolic syndrome (10.6% versus 4.8%; $P < 0.01$). In multivariate analysis, even after adjustment for other confounding factors, including insulinemia, metabolic syndrome remained an independent risk factor for the occurrence of CKD (odds ratio, 2.08; 95% confidence interval [CI], 1.23 to 3.52). Compared with subjects with 1 or fewer metabolic syndrome component, multivariate-adjusted odd ratios for CKD in subjects with 2, 3, and 4 or more metabolic syndrome components were 1.13 (95% CI, 0.60 to 2.12), 1.90 (95% CI, 0.98 to 3.69), and 2.79 (95% CI, 1.32 to 5.90), respectively. The rate of change in kidney function during 5 years decreased significantly in subjects with 4 or more metabolic syndrome components compared with those with 1 or fewer component in the age group of 40 to 59 years, whereas it also was significantly low in subjects with 3 metabolic syndrome components in the group aged 60 years or older.** ***Conclusion:*** **Our findings suggest that metabolic syndrome is a significant risk factor for the development of CKD in the general population.** ***Am J Kidney Dis*** **48:383-391.**
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INDEX WORDS: Metabolic syndrome; chronic kidney disease (CKD); prospective study.

CHRONIC KIDNEY DISEASE (CKD) is a worldwide public health problem; CKD is a major risk factor for end-stage renal disease and cardiovascular disease and causes premature death.[1-7] Thus, identifying and treating risk factors for early CKD may be the best approach to prevent and delay advanced outcomes.[2]

Metabolic syndrome, characterized by abdominal obesity, high blood pressure, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol level, and high fasting glucose level, is a common disorder.[8] According to data from the Third National Health and Nutrition Examination Survey, 23.7% of US residents aged 20 years or older have metabolic syndrome.[9] Although metabolic syndrome is less prevalent in Asian than Western populations, with the continuous increase in prevalence of obesity in Japan, metabolic syndrome is expected to be even more common in the near future.[10] Metabolic syndrome has been associated with increased risk for diabetes mellitus and cardiovascular disease, as well as increased mortality from cardiovascular disease and all causes.[11-14] Additionally, several cross-sectional studies identified a strong, positive, and significant relationship between metabolic syndrome and risk for CKD, as well as microalbuminuria.[15-17] However, this problem has not yet been evaluated sufficiently in a prospective cohort study.[18] In the present article, we examine the impact of metabolic syndrome on the development of CKD in a prospective cohort study in a Japanese community.

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METHODS

Study Population

The Hisayama Study, an epidemiological study of cerebrovascular and cardiovascular diseases, was established in 1961 in Hisayama Town, a suburban community adjacent to Fukuoka City, a metropolitan area of Kyushu Island in southern Japan. The population of the town is approximately 7,500, and full community surveys of the residents have been repeated since 1961.[19]

In 1988, a screening survey for the present study was performed in Hisayama Town. A detailed description of this survey was published previously.[20] Briefly, 2,736 residents aged 40 years or older (80.7% of the total population of this age group) consented to participate in the examination and underwent a comprehensive assessment, including estimation of glomerular filtration rate (GFR). After excluding 1 subject for whom no blood sample was obtained; 85 subjects for whom blood samples were postprandial; 50 subjects for whom there was no waist circumference measurement; 57 subjects who had been treated for diabetes, including patients treated with insulin or oral medication; and 324 subjects with moderate or severe CKD (GFR < 60 mL/min/1.73 m^2 [<1.00 mL/s/1.73 m^2]), the remaining 2,219 subjects were enrolled in this study. Of those, 1,440 subjects (591 men, 849 women) who participated in the health examination in 1993 were finally determined to be the cohort for the present study.

Risk Factors

At the baseline examination, each participant completed a self-administered questionnaire covering medical history, antihypertensive treatment, smoking habits, and alcohol intake. The questionnaire was checked by trained interviewers at the screening. The latter 3 variables were classified as either current habitual use or not. Blood pressure was measured 3 times by using a standard mercury sphygmomanometer with the subject in the sitting position after a rest of at least 5 minutes. The mean of 3 measurements was used for analysis. Waist circumference was measured at the umbilical level in the standing position by a trained staff member. Study physicians performed physical examinations on all participants and rechecked their medical histories to improve the precision of the information.

Blood samples were collected from an antecubital vein after an overnight fast for determination of serum creatinine, urea nitrogen, albumin, lipid, blood glucose, and serum insulin levels. Serum creatinine levels were measured by means of the Jaffé method using an autoanalyzer (TBA-80S; Toshiba Inc, Tokyo, Japan). Serum urea nitrogen, albumin, total cholesterol, and HDL cholesterol concentrations were determined enzymatically by using the same autoanalyzer. Hemoglobin levels were determined by using sodium lauryl sulfate. Fasting blood glucose levels were measured by means of the glucose oxidase method using a Glucoroder-MK2 (A&T Inc, Tokyo, Japan). Diabetes is defined as fasting blood glucose level of 126 mg/dL or greater (≥7.0 mmol/L). Fasting serum insulin levels were measured using a commercial double-antibody solid-phase radioimmunoassay (Phadeseph Insulin; Pharmacia Diagnostics AB, Uppsala, Sweden). Hyperinsulinemia is defined as a fasting serum insulin level of 10 μU/mL or greater (≥60 pmol/L; 90th percentile of fasting serum insulin levels). Fresh voided urine samples were collected at the examination, and proteinuria is defined as 1^+ or more using a reagent strip.

Definition of Metabolic Syndrome

Metabolic syndrome is defined using criteria recommended in the National Cholesterol Education Program Adult Treatment Panel III (NCEP) guidelines with a modification.[8] Specifically, abdominal obesity is defined as a waist circumference greater than 90 cm in men and greater than 80 cm in women, according to the International Obesity Task Force central obesity criteria for Asians.[21] Elevated blood pressure is defined as average systolic/diastolic blood pressures of 130/85 mm Hg or greater and/or current use of antihypertensive medicine. Hypertriglyceridemia is defined as a serum triglyceride level of 150 mg/dL or greater (≥1.69 mmol/L). Low HDL cholesterol level is defined as less than 40 mg/dL (<1.03 mmol/L) in men and less than 50 mg/dL (<1.29 mmol/L) in women. Elevated blood glucose level is defined as fasting blood glucose level of 110 mg/dL or greater (≥6.10 mmol/L). Metabolic syndrome is defined as the presence of 3 or more of these components.[8]

Definition of CKD and GFR Slope

GFR was estimated by using the following simplified prediction equation derived from the Modification of Diet in Renal Disease Study[22]:

$$\begin{aligned}\text{GFR (mL/min/1.73 m}^2\text{)} &= 170 \times (\text{serum creatinine [mg/dL]})^{-0.999} \\ &\times (\text{age [years]})^{-0.176} \\ &\times (\text{serum urea nitrogen [mg/dL]})^{-0.170} \\ &\times (\text{serum albumin [g/dL]})^{+0.318} \\ &\times (0.762 \text{ if female})\end{aligned}$$

CKD is defined as a GFR less than 60 mL/min/1.73 m^2 (<1.00 mL/s/1.73 m^2) according to the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative guidelines.[2]

The rate of change in GFR was calculated as the GFR slope by using the following equation:

$$\begin{aligned}&\text{GFR slope (mL/min/1.73 m}^2\text{/y)} \\ &= (\text{GFR in 1993 [mL/min/1.73 m}^2\text{]} \\ &\quad - \text{GFR in 1988 pmL/min/1.73 m}^2\text{])/5}\end{aligned}$$

Statistical Analysis

The SAS computer package (SAS Institute, Cary, NC) was used to perform all statistical analyses. Serum creatinine, fasting serum insulin, and serum triglyceride levels were transformed into logarithms to improve the skewed distribution. The statistical significance of differences in mean values of continuous variables and frequencies of

categorical variables was examined by using Student *t*-test and chi-square test, as appropriate. Age- and sex-adjusted cumulative incidences of CKD were calculated by means of the direct method and compared by using logistic regression analysis. Age- and sex-adjusted or multivariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) also were determined by using logistic regression analysis. Relationships between GFR slope and metabolic syndrome status were tested by using multiple regression analysis. Multivariate-adjusted mean values of GFR slope according to numbers of metabolic syndrome components were compared by using covariance analysis and Dunnett *t*-test. *P* less than 0.05 is considered statistically significant in all analyses.

RESULTS

Baseline characteristics of subjects by metabolic syndrome status are listed in Table 1. The prevalence of metabolic syndrome defined by modified NCEP criteria was 24.5% of 1,440 subjects. Mean age was older and the proportion of men was lower in subjects with than without metabolic syndrome. Mean baseline GFR was significantly lower in subjects with than without metabolic syndrome, although there was no difference in mean serum creatinine values. Frequencies of proteinuria, antihypertensive medication use, and diabetes and mean values for serum albumin, systolic and diastolic blood pressures, waist circumference, fasting blood glucose and serum insulin, serum total cholesterol, triglycerides, and hemoglobin were higher in subjects with than without metabolic syndrome, whereas HDL cholesterol levels were lower in subjects with metabolic syndrome. Frequencies of alcohol intake and smoking habits did not differ between groups.

During the 5-year follow-up, 88 subjects experienced CKD. Age- and sex-adjusted cumulative incidences of CKD according to metabolic syndrome status are shown in Fig 1A. Cumulative incidences were 4.8% in subjects without metabolic syndrome and 10.6% in those with metabolic syndrome: the difference was statistically significant (age- and sex-adjusted OR, 2.33; 95% CI, 1.47 to 3.69; $P < 0.01$; model 1 in Table 2). As shown in Fig 1B, the age- and sex-adjusted 5-year cumulative

Table 1. Clinical Characteristics of Study Population in 1988

Variables	No Metabolic Syndrome (n = 1,087)	Metabolic Syndrome (n = 353)
Age (y)	57 ± 10	60 ± 10*
Men (%)	43.7	32.9*
GFR (mL/min/1.73 m^2)	75.9 ± 10.1	73.4 ± 9.3*
Serum creatinine (mg/dL)	1.0 (0.7-1.3)	1.0 (0.7-1.3)
Proteinuria (%)	4.0	7.7*
Serum albumin (g/dL)	4.2 ± 0.2	4.3 ± 0.2*
Systolic blood pressure (mm Hg)	127 ± 19	144 ± 17*
Diastolic blood pressure (mm Hg)	76 ± 11	83 ± 11*
Antihypertensive medication (%)	8.8	24.1*
Waist circumference (cm)	79.4 ± 8.5	88.5 ± 7.5*
Fasting blood glucose (mg/dL)	99.2 ± 14.6	111.0 ± 25.8*
Diabetes (%)	2.7	13.9*
Fasting serum insulin (μU/mL)	5.1 (2.3-11.5)	7.6 (3.1-18.8)*
Serum total cholesterol (mg/dL)	205.9 ± 40.0	217.3 ± 41.7*
Serum triglycerides (mg/dL)	87.3 (37.6-202.7)	166.3 (58.9-470.0)*
Serum HDL cholesterol (mg/dL)	53.0 ± 11.0	43.2 ± 8.7*
Hemoglobin (g/dL)	13.9 ± 1.7	14.3 ± 1.6*
Alcohol intake (%)	31.0	28.3
Smoking habits (%)	23.2	18.7

NOTE. Values expressed as mean ± SD or frequency. Geometric mean values and 95% CIs of serum creatinine, fasting serum insulin, and serum triglyceride levels are shown because of the skewed distribution. To convert GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667; serum creatinine in mg/dL to μmol/L, multiply by 88.4; serum albumin in g/dL to g/L, multiply by 10; fasting blood glucose in mg/dL to mmol/L, multiply by 0.05551; fasting serum insulin in μU/mL to pmol/L, multiply by 7.175; serum total or HDL cholesterol in mg/dL to mmol/L, multiply by 0.02586; serum triglycerides in mg/dL to mmol/L, multiply by 0.01129; hemoglobin in g/dL to g/L, multiply by 10.

*$P < 0.01$ versus no metabolic syndrome.

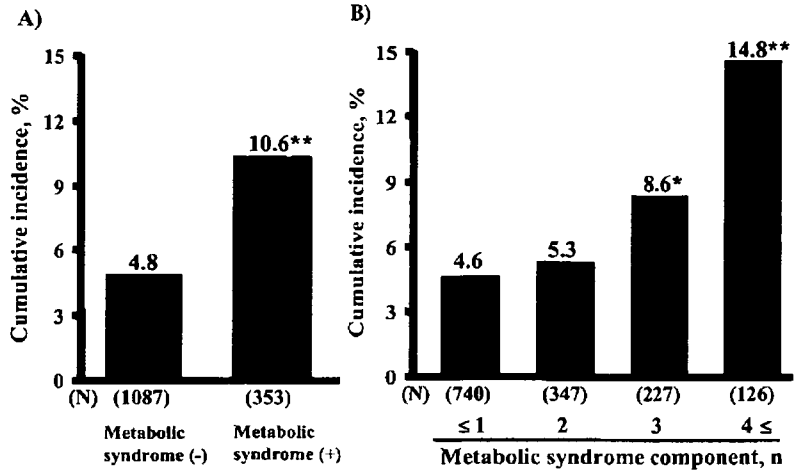

Fig 1. Age- and sex-adjusted 5-year cumulative incidence of CKD according to (A) metabolic syndrome status and (B) number of metabolic syndrome components in 1,440 subjects. *$P <$ 0.05, **$P < 0.01$ versus metabolic syndrome (−) or 1 or fewer component of metabolic syndrome.

incidence of CKD increased linearly with increasing numbers of metabolic syndrome components and was significantly greater in subjects with 4 or more metabolic syndrome components compared with those with 1 or fewer metabolic syndrome component (age- and sex-adjusted OR, 3.43; 95% CI, 1.79 to 6.58; $P < 0.01$; model 1 in Table 3). These associations remained unchanged even after adjustment for other confounding factors, such as baseline GFR, proteinuria, serum albumin level, serum total cholesterol level, hemoglobin level, alcohol intake, and smoking habits (model 2 in Tables 2 and 3). Conversely, a state of insulin resistance has an essential role in the development of metabolic syndrome.[23] Certainly, mean fasting serum insulin levels increased significantly in subjects with compared with without metabolic syndrome (Table 1), and hyperinsulinemia was associated signifi-

Table 2. Multivariate-Adjusted ORs for the Development of CKD According to Metabolic Syndrome Status in 1,440 Subjects During a 5-Year Follow-Up

Variable	Model 1*	Model 2†	Model 3‡
Metabolic syndrome (*v* absence)	2.33 (1.47-3.69)§	2.22 (1.35-3.66)§	2.08 (1.23-3.52)§
Age (/1 y)	1.09 (1.06-1.11)§	1.06 (1.04-1.09)§	1.07 (1.04-1.09)§
Men (*v* women)	1.32 (0.84-2.08)	1.91 (0.97-3.75)‖	1.90 (0.97-3.73)‖
Baseline GFR (/1 mL/min/ 1.73 m^2)	—	0.90 (0.87-0.94)§	0.90 (0.87-0.94)§
Proteinuria (*v* absence)	—	2.61 (1.25-5.46)¶	2.61 (1.25-5.47)¶
Serum albumin (/1 mg/dL)	—	0.27 (0.09-0.86)¶	0.29 (0.09-0.90)¶
Serum total cholesterol (/1 mg/dL)	—	1.00 (0.99-1.01)	1.00 (0.99-1.01)
Hemoglobin (/1 g/dL)	—	1.00 (0.81-1.22)	1.00 (0.81-1.22)
Alcohol intake (*v* absence)	—	0.76 (0.41-1.42)	0.76 (0.41-1.41)
Smoking habits (*v* absence)	—	1.20 (0.66-2.20)	1.20 (0.66-2.21)
Hyperinsulinemia (*v* absence)	—	—	1.29 (0.67-2.48)

NOTE. Values expressed as OR (95% CI). To convert GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667; serum albumin in g/dL to g/L, multiply by 10; serum total cholesterol in mg/dL to mmol/L, multiply by 0.02586; hemoglobin in g/dL to g/L, multiply by 10.

*Adjusted for age and sex.

†Adjusted for age, sex, baseline GFR, proteinuria, serum albumin level, serum total cholesterol level, hemoglobin level, alcohol intake, and smoking habits.

‡Adjusted for confounding factors used in model 2 and hyperinsulinemia.

§$P < 0.01$.

‖$P < 0.1$.

¶$P < 0.05$.

Table 3. Multivariate-Adjusted ORs for the Development of CKD According to Number of Metabolic Syndrome Components in 1,440 Subjects During a 5-Year Follow-Up

Variable	Model 1*	Model 2†	Model 3‡
No. of metabolic syndrome components			
2 (*v* ≤1)	1.13 (0.62-2.07)	1.14 (0.61-2.13)	1.13 (0.60-2.12)
3 (*v* ≤1)	1.97 (1.08-3.58)§	1.98 (1.04-3.79)§	1.90 (0.98-3.69)‖
≤4 (*v* ≤1)	3.43 (1.79-6.58)¶	3.00 (1.49-6.05)¶	2.79 (1.32-5.90)§
Age (/1 y)	1.09 (1.06-1.11)¶	1.06 (1.04-1.09)¶	1.07 (1.04-1.09)¶
Men (*v* women)	1.36 (0.86-2.14)	1.94 (0.99-3.82)‖	1.93 (0.99-3.80)‖
Baseline GFR (/1 mL/min/ 1.73 m^2)	—	0.90 (0.87-0.94)¶	0.90 (0.87-0.94)¶
Proteinuria (*v* absence)	—	2.59 (1.23-5.45)§	2.59 (1.23-5.45)§
Serum albumin (/1 mg/dL)	—	0.28 (0.09-0.90)§	0.29 (0.09-0.93)§
Serum total cholesterol (/1 mg/dL)	—	1.00 (0.99-1.01)	1.00 (0.99-1.01)
Hemoglobin (/1 g/dL)	—	0.99 (0.81-1.21)	0.99 (0.81-1.21)
Alcohol intake (*v* absence)	—	0.76 (0.41-1.41)	0.75 (0.41-1.40)
Smoking habits (*v* absence)	—	1.21 (0.66-2.22)	1.21 (0.66-2.22)
Hyperinsulinemia (*v* absence)	—	—	1.21 (0.62-2.35)

NOTE. Values expressed as OR (95% CI). To convert GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667; serum albumin in g/dL to g/L, multiply by 10; serum total cholesterol in mg/dL to mmol/L, multiply by 0.02586; hemoglobin in g/dL to g/L, multiply by 10.

*Adjusted for age and sex.

†Adjusted for age, sex, baseline GFR, proteinuria, serum albumin level, serum total cholesterol level, hemoglobin level, alcohol intake, and smoking habits.

‡Adjusted for confounding factors used in model 2 and hyperinsulinemia.

§$P < 0.05$.

‖$P < 0.1$.

¶$P < 0.01$.

cantly with the development of CKD after adjustment for age and sex (OR, 2.10; 95% CI, 1.16 to 3.79; $P < 0.05$). When hyperinsulinemia and confounding factors used in model 2 were added to the logistic regression model, metabolic syndrome was still a significant risk factor for the development of CKD, although its OR slightly decreased (OR, 2.08; 95% CI, 1.23 to 3.52; $P < 0.05$; model 3 in Table 2).

Diabetes is a major risk factor for the development and progression of CKD.[24,25] To exclude the influence of diabetes, we examined the impact of metabolic syndrome on the development of CKD in 1,362 subjects without diabetes. Results show that metabolic syndrome also was associated significantly with the development of CKD after adjustment for confounding factors used in model 3 in Table 2 (OR, 1.98; 95% CI, 1.14 to 3.43; $P < 0.05$). In addition, to explore whether risk for CKD in subjects with metabolic syndrome was mediated by blood pressure control during the observation period, we performed additional analyses with a logistic model including systolic blood pressure levels at the end of follow-up in confounding factors. Even after adjustment for systolic blood pressure at the end of the follow-up along with confounding factors used in model 3 in Table 2, the association between metabolic syndrome and development of CKD remained substantially unchanged (OR, 2.09; 95% CI, 1.22 to 3.58; $P < 0.01$). This finding suggests that hypertension management during follow-up did not largely affect the metabolic syndrome–CKD association.

Finally, we performed a slope analysis in which the association between GFR slope and metabolic syndrome was examined by using a multiple regression model after adjustment for the mentioned confounding factors used in model 3. This analysis showed a significantly negative association between GFR slope and metabolic syndrome (for GFR slope by presence of metabolic syndrome: β, −0.41; F, 11.55; $P < 0.01$). Additionally, multivariate-adjusted mean values for GFR slope decreased significantly in subjects with 4 or more metabolic syndrome components compared with those with 1 or fewer metabolic syndrome component (Fig 2A). We further estimated the multivariate-adjusted GFR slope for

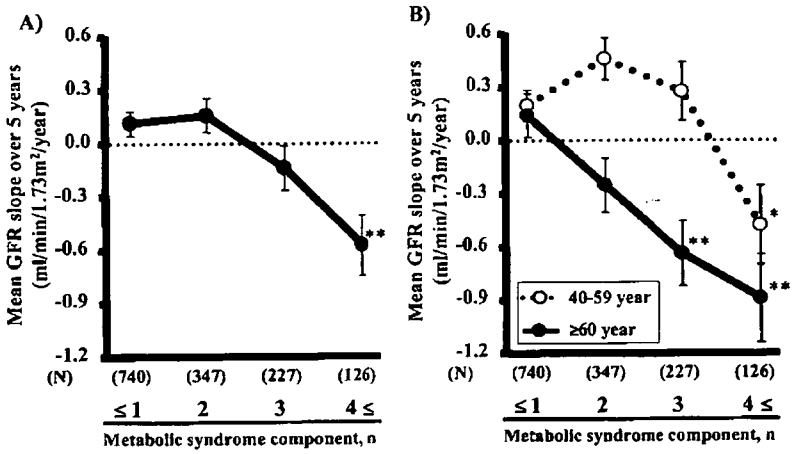

Fig 2. Multivariate-adjusted mean values of the GFR slope during a 5-year follow-up period according to number of metabolic syndrome components in (A) all subjects and (B) by age in 1,440 subjects. Values expressed as mean ± SE. Adjusted for age, sex, baseline GFR, proteinuria, serum albumin level, fasting serum insulin level, serum total cholesterol level, hemoglobin level, alcohol intake, and smoking habits. *$P < 0.05$, **$P < 0.01$ versus 1 or fewer component of metabolic syndrome. To convert GFR in mL/min to mL/s, multiply by 0.01667.

the age groups of 40 to 59 years and 60 years or older (Fig 2B). Multivariate-adjusted mean values for GFR slope decreased significantly in subjects with 4 or more metabolic syndrome components compared with those with 1 or fewer metabolic syndrome component in the age group of 40 to 59 years, whereas the mean of the GFR slope also was significantly low in subjects with 3 metabolic syndrome components in the age group of 60 years or older.

DISCUSSION

In a prospective cohort study of a general population, we show a positive and significant association between metabolic syndrome and risk for the development of CKD. Risk for CKD increased progressively with a higher number of components of metabolic syndrome. This association remained substantially unchanged even after adjustment for hyperinsulinemia, as well as other confounding factors. Additionally, the impact of metabolic syndrome on progression of GFR decline was stronger in elderly than middle-aged subjects.

Several epidemiological studies examined the association between metabolic syndrome and risk for CKD.[15-18] In a cross-sectional survey of nondiabetic native Americans, subjects with 3 or more of the 5 components of insulin resistance syndrome, ie, hypertension, impaired fasting glucose level, hyperinsulinemia, hypertriglyceridemia, and hypo-HDL-cholesterolemia, had a 2-fold greater prevalence of microalbuminuria than those with no components.[15] For participants in the Third National Health and Nutrition Examination Survey, metabolic syndrome as defined by NCEP criteria was associated with a 2.6-fold increased prevalence of CKD (and microalbuminuria).[16] According to results of health checks in Okinawa, a southern island in Japan, the prevalence of CKD was 1.5-fold greater in subjects with metabolic syndrome as defined by modified NCEP criteria than in those without metabolic syndrome.[17] To our knowledge, the 9-year follow-up survey of the Atherosclerosis Risk in Communities Study[18] is the only prospective cohort study to examine the impact of metabolic syndrome on the development of CKD. This study showed that subjects with metabolic syndrome as defined by NCEP criteria had a 1.4-fold greater risk for CKD compared with those without metabolic syndrome. Our findings, which showed a 2-fold greater risk for CKD in subjects with metabolic syndrome, are in accord with those of previous studies and indicate that metabolic syndrome is an independent risk factor for CKD in the general population.

Several possible explanations were proposed for the mechanism underlying the association between metabolic syndrome and risk for CKD. Insulin resistance and compensatory hyperinsulinemia, considered fundamental pathogenetic factors of metabolic syndrome, may directly contribute to the development of renal injury by worsening renal hemodynamics through multiple mechanisms, including sodium retention,[26] activation of the sympathetic nervous system,[27] decreased Na^+, K^+-ATPase activity,[28] and eleva-

tion of glomerular filtration fraction.[29,30] However, in the present study, metabolic syndrome was still an independent risk factor for the development of CKD, even after adjustment for hyperinsulinemia, although its OR was slightly decreased. This suggests the existence of another mechanism in addition to direct effects of insulin resistance or hyperinsulinemia.

Another possible explanation for the relationship between metabolic syndrome and incident CKD is that metabolic syndrome components directly damage the kidneys through systemic atherosclerosis. Previous epidemiological surveys showed that individual components of metabolic syndrome, including glucose intolerance, hypertension, and dyslipidemia, could act directly as risk factors for renal damages through renal or systemic atherosclerosis.[24,25,31-35] In our previous autopsy-based survey, hypertension, glucose intolerance, and total cholesterol level also were significant risk factors for renal arteriosclerosis.[36] However, in the present study, we found that clusters of these risk factors had a stronger impact on the development of CKD than individual risk factors. Furthermore, the accumulation of 3 or more of the metabolic disorders defined by NCEP criteria promoted the development of CKD or progression of GFR decline. These findings support the hypothesis that clusters of atherogenic metabolic disorders induce renal vessel injury, resulting in deterioration of renal function.

In our subjects, accumulation of metabolic syndrome components was associated clearly with progression of GFR decline during the 5-year follow-up, even after adjustment for baseline GFR and other confounding factors. This denies the possibility that subjects with a lower GFR at baseline develop CKD more quickly. Conversely, our findings show that greater accumulation of metabolic syndrome components was needed for progression of GFR decline in middle-aged compared with elderly subjects. The reason for this finding may be that middle-aged subjects have milder atherosclerotic renal vessels than elderly subjects, and the 5-year follow-up period of our study was insufficient to allow a GFR decline for middle-aged subjects with fewer components of metabolic syndrome.

Several limitations of our study should be discussed. The primary limitation is that our results are biased by the exclusion of subjects who did not return to the follow-up examination. Of 779 subjects without a follow-up examination (419 men, 360 women), 88 subjects died during the follow-up period: 41 patients, cancer; 14 subjects, cardiovascular disease; and the remaining subjects, other diseases. At baseline, mean serum creatinine values and frequencies of men, hypertension, diabetes, smoking habits, and hyperinsulinemia were significantly greater in nonparticipants than participants, although the frequency of metabolic syndrome was not significantly different in both groups. We speculate that the high-risk population for the development of CKD was excluded in this study. Thus, this bias has the potential to alter our findings, but is not likely to do so.

The second limitation is that our GFR values, estimated by using the simplified prediction equation derived from the Modification of Diet in Renal Disease Study, might not be sufficiently accurate, although this prediction equation is considered to afford the most precise estimate of GFR of equations of its type.[21] Therefore, some nondifferential misclassifications of cases with CKD may have occurred in our study. Given that this limitation can reduce the impact of CKD, our findings may be conservative.

The final limitation is that we have no information about the kind of underlying renal disease. Such information could be obtained by detailed clinical examination, including renal biopsy and ultrasonography, but these diagnostic procedures are not considered feasible for a cohort study recruited from a general population such as ours. Certainly, because renal function of patients with diabetic nephropathy may deteriorate quickly, the possibility remains that the impact of metabolic syndrome on the development of CKD is overestimated. However, in our study, the magnitude of the association between metabolic syndrome and risk for CKD was unchanged in the analysis of selected nondiabetic participants. Thus, the influence of diabetic nephropathy would seem to have been negligible.

In conclusion, findings of this study suggest that metabolic syndrome is an independent risk factor for the development of CKD in the general population, and there is a graded relationship between number of metabolic syndrome components and risk for CKD. A clinical trial is needed

to clarify whether the effect of preventing and treating metabolic syndrome will result in improved renal prognosis.

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RESEARCH REPORTS
Clinical

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ABSTRACT

Recent studies have suggested that several systemic conditions—such as obesity, hypertension, hyperlipidemia, and diabetes—are related to periodontitis. The objective of this study was to examine the relationship between periodontitis and 5 components of metabolic syndrome—abdominal obesity, triglyceride level, high-density lipoprotein cholesterol level, blood pressure, and fasting blood sugar level—in 584 Japanese women. In multivariate analyses, persons exhibiting more components of metabolic syndrome had significantly higher odds ratios for a greater pocket depth and clinical attachment loss than did those with no components; the odds ratios for a greater pocket depth and clinical attachment loss of the persons exhibiting 4 or 5 components were 6.6 (95% confidence interval = 2.6-16.4) and 4.2 (95% confidence interval = 1.2-14.8), respectively. These results indicate that metabolic syndrome increases risk of periodontitis, and suggest that people exhibiting several components of metabolic syndrome should be encouraged to undergo a periodontal examination.

KEY WORDS: metabolic syndrome, periodontal disease, risk factor, epidemiology, Japanese women.

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Relationship of Metabolic Syndrome to Periodontal Disease in Japanese Women: The Hisayama Study

INTRODUCTION

Obesity, hypertension, impaired glucose tolerance, and abnormal lipid metabolism have received a great deal of attention as risk factors for arteriosclerotic diseases, including coronary artery disease. The term 'metabolic syndrome' is commonly used to refer to a condition in which several such components are present in an individual (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). The prevalence of metabolic syndrome is increasing worldwide (Cameron *et al.*, 2004). Although each component of metabolic syndrome independently increases the risk for cardiovascular disease (McGill *et al.*, 2002; The DECODE Study Group, 2003; Eberly *et al.*, 2003; Masley *et al.*, 2006), many studies have reported that an accumulation of these components significantly enhances the risk of death from all causes and cardiovascular disease (Isomaa *et al.*, 2001; Lakka *et al.*, 2002).

Obesity has emerged as a risk indicator of periodontal disease (Saito *et al.*, 2001, 2005), and some studies have reported that individuals with peridontitis had higher blood pressure than individuals without periodontitis (Joss *et al.*, 1994). Furthermore, many studies have reported that periodontitis is more prevalent in persons with diabetes (Page *et al.*, 1997; Soskolne and Klinger, 2001), and that individuals with periodontitis have abnormal lipid metabolism (Losche *et al.*, 2000; Noack *et al.*, 2000; Katz *et al.*, 2002; Moeintaghavi *et al.*, 2005). However, it is unclear whether the accumulation of the components of metabolic syndrome increases the risk of periodontal disease. In this study, we examined the relationship between periodontal disease and the components of metabolic syndrome, singly and in combination, through a community-based health examination held in the town of Hisayama, Fukuoka, Japan.

MATERIALS & METHODS

Study Population

From July to September, 1998, a total of 982 Hisayama residents aged 40-79 yrs (21.6% of the total population in that age group) underwent a comprehensive health examination that included a periodontal examination (Saito *et al.*, 2004). In this study, we analyzed 584 women with at least 10 teeth (Saito *et al.*, 2005). The Ethics Committee of the Kyushu University Faculty of Dental Science and the Department of General Affairs and Health and Welfare of Hisayama approved the study design, data collection methods, and procedure for obtaining informed consent.

Oral Examination

Following the method of the Third National Health and Nutrition Examination Survey (Brown *et al.*, 1996), a periodontal examination was performed on randomly selected quadrants, one maxillary and one mandibular. The periodontal examination was carried out by one of four dentists trained to perform a clinical examination of oral health status. The examiner reliability of

Table 1. Characteristics of the Participants According to Periodontal Status

Characteristics	Total Participants (n = 584) Mean ± SD	Mean PD[a] < 2.0 mm (n = 484) Mean ± SD	Mean PD[a] ≥ 2.0 mm (n = 100) Mean ± SD	Mean CAL < 3.0 mm (n = 547) Mean ± SD	Mean CAL ≥ 3.0 mm (n = 37) Mean ± SD
Age (yrs)	55.7 ± 8.8	55.5 ± 8.8	56.9 ± 8.4	55.5 ± 8.7	59.3 ± 8.6*
Mean PD (mm)	1.5 ± 0.5	1.4 ± 0.3	2.4 ± 0.4**	1.5 ± 0.4	2.5 ± 0.6**
Mean CAL (mm)	1.9 ± 0.7	1.7 ± 0.6	2.8 ± 0.6**	1.8 ± 0.6	3.4 ± 0.4**
Waist (cm)	83.3 ± 10.0	82.7 ± 10.1	85.8 ± 8.9***	83.2 ± 10.0	84.6 ± 9.8
Systolic blood pressure (mm Hg)	127.4 ± 20.8	127.0 ± 20.8	129.4 ± 20.5	127.2 ± 20.6	131.1 ± 22.8
Diastolic blood pressure (mm Hg)	76.4 ± 10.4	76.2 ± 10.5	77.4 ± 10.0	76.4 ± 10.4	76.1 ± 10.4
Total cholesterol (mg/dL)	213.4 ± 35.3	213.7 ± 35.3	211.7 ± 35.1	213.8 ± 35.2	206.6 ± 36.3
HDL cholesterol (mg/dL)	61.2 ± 13.7	62.0 ± 13.8	57.7 ± 12.8***	61.4 ± 13.5	59.3 ± 16.3
LDL cholesterol (mg/dL)	129.4 ± 31.8	129.3 ± 31.6	129.5 ± 32.6	129.8 ± 31.5	122.8 ± 36.0
Triglyceride (mg/dL)	115.0 ± 79.7	113.4 ± 82.1	122.5 ± 66.6	114.5 ± 80.5	122.6 ± 66.9
Fasting plasma glucose (mg/dL)	98.2 ± 14.4	97.2 ± 12.8	102.5 ± 20.1*	97.6 ± 13.1	105.7 ± 26.4
	n (%)	n (%)	n (%)	n (%)	n (%)
Smoker (current or post)	39 (6.7)	31 (6.4)	8 (8.0)	36 (6.6)	3 (8.1)
Medical history of hypertension	146 (25.0)	110 (22.7)	36 (36.0)***	133 (24.3)	13 (35.1)
Use of antihypertensive medication	85 (14.5)	62 (12.8)	23 (23.0)***	77 (14.1)	8 (21.6)
Medical history of diabetes	34 (5.8)	25 (5.2)	9 (9.0)	29 (5.3)	5 (13.5)*
Use of antidiabetic agent	7 (1.2)	6 (1.2)	1 (1.0)	7 (1.3)	0 (0)
Insulin therapy	4 (0.7)	2 (0.4)	2 (2.0)	3 (0.5)	1 (2.7)
Lipid-lowering medication	54 (9.2)	45 (9.3)	9 (9.0)	52 (9.5)	2 (5.4)

* $P < 0.05$.
** $P < 0.001$.
*** $P < 0.01$.
[a] Abbreviations: pocket depth (PD), clinical attachment loss (CAL).

the periodontal examination was verified by an inter-examiner calibration of outpatients visiting Kyushu University Dental hospital; the kappa value for the periodontal examination exceeded 0.8, suggesting very good inter-examiner agreement (Shimazaki *et al.*, 2004). The pocket depth and clinical attachment loss were measured as periodontal parameters at mesio-buccal and mid-buccal sites for all of the teeth in 2 quadrants. We divided the participants into two groups, based on mean pocket depth: < 2.0 mm (n = 484, 82.9% of all participants) and ≥ 2.0 mm (n = 100, 17.1%). Similarly, we divided the participants into two groups based on mean clinical attachment loss: < 3.0 mm (n = 547, 93.7%) and ≥ 3.0 mm (n = 37, 6.3%).

General Examination

Blood pressure was measured 3 consecutive times, after participants rested for at least 5 min, by means of a standard mercury sphygmomanometer, with the participants in the sitting position, and the average value was used for the analysis. A blood sample was collected from the antecubital vein the morning after an overnight fast and analyzed for serum cholesterol, triglycerides, and fasting plasma glucose, according to previously described methods (Kubo *et al.*, 1999). Trained nurses measured the participants' waist circumference at the level of the umbilicus. The measurement was taken after the participants exhaled. Each participant completed a self-administered questionnaire in advance that included a medical history of diabetes, hypertension, smoking, and medication use; the questionnaire was checked by trained nurses.

The National Cholesterol Education Program (NCEP) definition of metabolic syndrome requires the presence of 3 or more of 5 components: abdominal obesity (waist circumference > 88 cm), triglycerides ≥ 150 mg/dL, decreased serum high-density lipoprotein (HDL) cholesterol (< 50 mg/dL), systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg, and fasting plasma glucose ≥ 110 mg/dL (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). The participants receiving antihypertensive medication were counted as positive for hypertension, and those receiving antidiabetic medication or insulin therapy were counted as positive for glucose intolerance.

Statistical Analysis

Differences in mean values and proportions were evaluated by Student's *t* test and Pearson's chi-square test, respectively. We performed logistic regression analyses to determine the effect of the number of positive components of metabolic syndrome on pocket depth and clinical attachment loss, calculating the odds ratio and 95% confidence interval. The statistical analysis was performed with SPSS (version 12.0; SPSS Japan, Tokyo, Japan).

RESULTS

The overall mean pocket depth and clinical attachment loss values were 1.5 and 1.9, respectively (Table 1). The mean pocket depth was similar between the participants with a mean pocket depth ≥ 2.0 mm and those with a mean clinical attachment loss ≥ 3.0. The mean clinical attachment loss in

Table 2. Risk for PD[a] and CAL According to Each Component of Metabolic Syndrome

Components of Metabolic Syndrome		Mean PD		Crude OR (95% CI)	Adjusted OR[b] (95% CI)	Mean CAL		Crude OR (95% CI)	Adjusted OR[b] (95% CI)
		< 2.0 mm	≥ 2.0 mm			< 3.0 mm	≥ 3.0 mm		
		No. of Participants (%)				No. of Participants (%)			
Waist (cm)	≤ 88	346 (71.5)	57 (57.0)	1	1	378 (69.1)	25 (67.6)	1	1
	> 88	138 (28.5)	43 (43.0)	1.9 (1.2-2.9)*	1.8 (1.2-2.8)**	169 (30.9)	12 (32.4)	1.1 (0.5-2.2)	0.9 (0.4-1.9)
Blood pressure (mm Hg)									
systolic < 135 and diastolic	< 85	281 (58.1)	47 (47.0)	1	1	312 (57.0)	16 (43.2)	1	1
systolic ≥ 135 or diastolic	≥ 85	203 (41.9)	53 (53.0)	1.6 (1.0-2.4)**	1.5 (0.9-2.3)	235 (43.0)	21 (56.8)	1.7 (0.9-3.4)	1.3 (0.6-2.7)
HDL cholesterol (mg/dL)	≥ 50	397 (82.0)	67 (67.0)	1	1	442 (80.8)	22 (59.5)	1	1
	< 50	87 (18.0)	33 (33.0)	2.2 (1.4-3.6)*	2.2 (1.4-3.6)*	105 (19.2)	15 (40.5)	2.9 (1.4-5.7)*	2.8 (1.4-5.6)*
Triglyceride (mg/dL)	< 150	396 (81.8)	74 (74.0)	1	1	445 (81.4)	25 (67.6)	1	1
	≥ 150	88 (18.2)	26 (26.0)	1.6 (1.0-2.6)	1.5 (0.9-2.6)	102 (18.6)	12 (32.4)	2.1 (1.0-4.3)**	2.0 (1.0-4.2)
Fasting plasma glucose (mg/dL)	< 110	432 (89.3)	78 (78.0)	1	1	481 (87.9)	29 (78.4)	1	1
	≥ 110	52 (10.7)	22 (22.0)	2.3 (1.3-4.1)*	2.2 (1.3-3.9)*	66 (12.1)	8 (21.6)	2.0 (0.9-4.6)	1.7 (0.7-4.0)

* $P < 0.01$.
** $P < 0.05$.
[a] Abbreviations: pocket depth (PD), clinical attachment loss (CAL), odds ratio (OR), confidence interval (CI).
[b] Adjusted for age and smoking status.

participants with a mean pocket depth ≥ 2.0 mm was 2.8, and the mean clinical attachment loss in those with a mean clinical attachment loss ≥ 3.0 mm was 3.4 (Table 1). Participants with a mean pocket depth ≥ 2.0 mm had a larger waist circumference, lower HDL cholesterol, and higher fasting plasma glucose than those with a mean pocket depth < 2.0 mm (Table 1). The proportion of participants who had a history of hypertension and were taking antihypertensive medication was higher in the group with a mean pocket depth ≥ 2.0 mm (Table 1). The participants with a mean clinical attachment loss ≥ 3.0 mm were older and more likely to have a history of diabetes than those with a mean clinical attachment loss < 3.0 mm (Table 1).

Of the 5 components of metabolic syndrome, large waist circumference, low HDL cholesterol level, and high fasting plasma glucose level were associated with significantly higher odds ratios for greater pocket depth values; the adjusted odds ratios for these components were 1.8 (95% confidence interval, 1.2-2.8), 2.2 (95% confidence interval, 1.4-3.6), and 2.2 (95% confidence interval, 1.3-3.9), respectively (Table 2). The participants with low HDL cholesterol had a higher odds ratio (odds ratio, 2.8; 95% confidence interval, 1.4-5.6) for a greater clinical attachment loss value after adjustment for age and smoking status (Table 2).

The crude and adjusted odds ratios for greater pocket depth and clinical attachment loss values in individuals exhibiting multiple components of metabolic syndrome, in comparison with those having no components, are presented in Table 3. In those with 3 or more components, the adjusted odds ratios for greater pocket depth and clinical attachment loss values were 4.7 (95% confidence interval, 2.4-9.7) and 3.3 (95% confidence interval, 1.2-8.8), respectively (Table 3). In individuals with 4 or 5 components, the odds ratios for greater pocket depth and clinical attachment loss values were 6.6 (95% confidence interval, 2.6-16.4) and 4.2 (1.2-14.8), respectively, after adjustment for age, smoking status, lipid-lowering medication, and total cholesterol (Table 3).

DISCUSSION

In this study, we analyzed the relationship between the components of metabolic syndrome and periodontal disease in Japanese middle-aged and older women. We did not include oral health parameters such as plaque level in the analyses, because the purpose of this study was to predict the risk of periodontal disease from the results of the general health examination. When we analyzed each component separately, waist, HDL cholesterol, and fasting plasma glucose had significant relationships with periodontal disease. If the participants had more of the components of metabolic syndrome, the risk of periodontal disease tended to increase according to the number of the components.

A large waist circumference (> 88 cm), suggesting an accumulation of visceral fat, showed an independent, significant association with a greater pocket depth, but not with clinical attachment loss value. The present results agreed with those of our previous study, in which body mass index, body fat, and waist-hip ratio were used as obesity indexes (Saito *et al.*, 2005), although the obesity index was not as closely related to periodontitis in the present study. The difference may be the result of differences in the obesity indices and cut-off points used in the two studies. In the present study, blood pressure did not have a significant relationship to periodontitis in an independent analysis. Given that many of the participants with greater pocket depth values were taking antihypertensive medication, a strong relationship between blood pressure and periodontitis would not have been expected.

Table 3. Risk for PD[a] and CAL by Accumulation of Positive Components of Metabolic Syndrome

		Mean PD		Crude OR (95% CI)	Adjusted OR[b] (95% CI)	Mean CAL		Crude OR (95% CI)	Adjusted OR[b] (95% CI)
		< 2.0 mm	≥ 2.0 mm			< 3.0 mm	≥ 3.0 mm		
		No. of Participants (%)				No. of Participants (%)			
No. of positive components of metabolic syndrome	0	166 (34.3)	17 (17.0)	1	1	175 (32.0)	8 (21.6)	1	1
	1 or 2	250 (51.7)	53 (53.0)	2.1 (1.2-3.7)*	2.1 (1.2-3.8)*	287 (52.5)	16 (43.2)	1.2 (0.5-2.9)	1.1 (0.4-2.6)
	≥ 3	68 (14.0)	30 (30.0)	4.3 (2.2-8.3)**	4.7 (2.4-9.7)**	85 (15.5)	13 (35.1)	3.3 (1.3-8.4)*	3.3 (1.2-8.8)*
No. of positive components of metabolic syndrome	0	166 (34.3)	17 (17.0)	1	1	175 (32.0)	8 (21.6)	1	1
	1	161 (33.3)	33 (33.0)	2.0 (1.1-3.8)*	2.0 (1.1-3.8)*	184 (33.6)	10 (27.0)	1.2 (0.5-3.1)	1.0 (0.4-2.7)
	2	89 (18.4)	20 (20.0)	2.2 (1.1-4.4)*	2.3 (1.1-4.6)*	103 (18.8)	6 (16.2)	1.3 (0.4-3.8)	1.2 (0.4-3.5)
	3	48 (9.9)	18 (18.0)	3.7 (1.8-7.6)***	4.1 (1.9-8.9)**	58 (10.6)	8 (21.6)	3.0 (1.1-8.4)*	2.9 (1.0-8.6)
	4 or 5	20 (4.1)	12 (12.0)	5.9 (2.4-14.0)**	6.6 (2.6-16.4)**	27 (4.9)	5 (13.5)	4.1 (1.2-13.3)*	4.2 (1.2-14.8)*

* $P < 0.05$.
** $P < 0.001$.
*** $P < 0.01$.
[a] Abbreviations: pocket depth (PD), clinical attachment loss (CAL), odds ratio (OR), confidence interval (CI).
[b] Adjusted for age, smoking status, lipid-lowering medication, and total cholesterol.

In this study, the participants with low HDL cholesterol levels had a higher risk for periodontitis; of the 5 components, HDL cholesterol had the highest odds ratio for a greater pocket depth and clinical attachment loss. Several studies have reported a significant relationship between abnormal lipid metabolism and periodontitis, but the significant indices for lipid metabolism differed from study to study (Losche *et al.*, 2000; Noack *et al.*, 2000; Katz *et al.*, 2002; Moeintaghavi *et al.*, 2005). If the study populations were different, the relationship between periodontal condition and lipid metabolism would differ because of the differences in genetic background, diet, population age and sex structure, and body habitus. Also, fasting plasma glucose was significantly associated with periodontitis. The significant relationship between diabetes and periodontitis is well-known, and some studies have suggested that impaired glucose tolerance is associated with periodontal disease (Saito *et al.*, 2004, 2006), and that periodontal treatment in diabetics has a beneficial effect on the control of blood-sugar level (Grossi *et al.*, 1997; Stewart *et al.*, 2001). From these studies, periodontitis would have a close relationship with abnormal lipid metabolism and impaired glucose tolerance.

In this study, female participants exhibiting several components of metabolic syndrome had higher risk for periodontal disease. Although periodontitis is a chronic inflammatory disease caused by Gram-negative anaerobic bacteria, such as *Porphyromonas gingivalis* and *Tannerella forsythia*, periodontal conditions are significantly associated with the frequency of toothbrushing, regular dental visits, and smoking and drinking habits (Sakki *et al.*, 1995; Albandar *et al.*, 2000; Shimazaki *et al.*, 2005; Krustrup and Petersen, 2006). Thus, negative lifestyle habits may aggravate periodontal disease as well as health conditions such as obesity, hypertension, impaired glucose tolerance, and abnormal lipid metabolism. We propose that there is a bidirectional association between the components of metabolic syndrome and periodontal disease. However, we could not confirm a causal link between metabolic syndrome and periodontal disease, because this was a cross-sectional study; longitudinal cohort studies are required for confirmation.

Although an annual general health examination is common in Japan, a yearly dental examination is not. Without a dental check-up, many would be unaware of the presence of periodontal disease, because the subjective symptoms are weak. The results of this study suggest that people with several components of metabolic syndrome may be at higher risk for periodontal disease. We recommend that anyone exhibiting several components of metabolic syndrome receive a dental and periodontal check-up, along with a general health examination.

This study had a few limitations. Although some components of metabolic syndrome did not have a significant, independent relationship with periodontal disease, our results cannot assert an insignificant bilateral relationship between periodontal disease and these components, because the sample size was not large enough to verify the insignificance. This study showed the relationship between components of metabolic syndrome and periodontal condition only in female participants; we do not know the relationship in males. Our periodontal examination at the mesio-buccal and mid-buccal sites of each tooth in 2 quadrants may have led to bias, because we did not examine the periodontal condition at 6 sites *per* tooth in all of the teeth present. Further investigations are required to clarify the relationship between metabolic syndrome and periodontal disease in men, and to determine whether oral health care in individuals exhibiting metabolic syndrome has the potential to reduce the incidence of various systemic diseases.

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Impact of Metabolic Syndrome on the Development of Cardiovascular Disease in a General Japanese Population

The Hisayama Study

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Background and Purpose—The metabolic syndrome (MetS) is associated with an increased risk of cardiovascular disease (CVD) events in general populations. However, well-designed prospective studies in Asian populations are very limited.

Methods—We prospectively evaluated a total of 2452 community-dwelling Japanese individuals aged 40 years or older from 1988 to 2002 and examined the effects of MetS defined by the modified National Cholesterol Education Program Adult Treatment Panel III criteria on incident CVD.

Results—The prevalence of the MetS was 21% in men and 30% in women at baseline. During the follow up, 307 CVD events occurred. Compared with those without MetS, the age-adjusted incidence of CVD (per 1000 person-years) was significantly higher in subjects with the MetS in both men (21.8 versus 11.6, $P<0.01$) and women (12.9 versus 6.5, $P<0.01$). The risk of CVD events was significantly higher even after adjusting for the following confounding factors: age, proteinuria, electrocardiographic abnormalities, serum total cholesterol, smoking habits, alcohol intake, and regular exercise (hazard ratio, 1.86; 95% CI, 1.32 to 2.62 in men and hazard ratio, 1.70; 95% CI, 1.22 to 2.36 in women). The risk of incident CVD was found to increase with the number of components of MetS and became significantly predictive when the number of components reached 3. Similar associations were also observed when CVD was divided into coronary heart disease and stroke.

Conclusions—Our findings suggest that MetS is a significant risk factor for the development of CVD in the Japanese middle-aged population. (***Stroke*. 2007;38:2063-2069.)**

Key Words: cardiovascular disease ■ epidemiology ■ metabolic syndrome ■ myocardial infarction ■ stroke

Metabolic syndrome (MetS), also known as syndrome X,[1] the insulin resistance syndrome,[2] and deadly quartet,[3] is a constellation of dyslipidemia, central obesity, elevated blood pressure, and impaired glucose tolerance. It is associated with high risk for the development of type 2 diabetes mellitus and cardiovascular disease (CVD).[4–7] In the past several years, a great deal of attention has been directed to it attributable to increases in its prevalence worldwide[6] and its association with CVD morbidity and mortality. Although each of the components of MetS has been shown to increase CVD risk,[8–12] the presence of MetS has been reported to identify additional risk.[7] Different prospective studies[7,13–25] based on the definitions from the National Cholesterol Education Program's (NCEP) Third Adult Treatment Panel Report III[5] and World Health Organization[26] showed that subjects with MetS are at increased risk of incident CVD, CVD mortality, and all-cause mortality in the general population with or without diabetes mellitus. However, most of these studies were based on Western populations, and well-designed prospective studies in Asian populations are very limited.[27–29] Thus, there is a dearth of literature regarding the relationship of MetS with incident CVD based on general population cohorts with a reasonable length of follow-up time in ethnic groups other than whites. In this study, we examined the impact of MetS on CVD events in a general Japanese population cohort based on 14-year prospective follow-up data.

Materials and Methods

Study Population

The Hisayama Study, an epidemiological study of cerebro- and cardiovascular diseases, was established in 1961 in Hisayama Town, a suburban community adjacent to Fukuoka City, a metropolitan area of Kyushu Island in southern Japan. The population of the town is

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approximately 7500, and full community surveys of the residents have been repeated since 1961.[30] In 1988, a screening survey for the present study was performed in the town. A detailed description of this survey was published previously.[31] Briefly, a total of 2736 residents aged 40 years or over (80.7% of the total population of this age group) consented to participate in the examination and underwent a comprehensive assessment. After excluding 102 subjects with a history of coronary heart disease or stroke, as determined by a questionnaire and medical records, one subject for whom no blood sample was obtained, 120 subjects with postprandial blood sample, and 61 subjects without the measurements of their waist circumferences, the remaining 2452 subjects (1050 men and 1402 women) were enrolled in this study.

Follow-Up Survey

The subjects were followed prospectively from December 1988 to November 2002 by repeated health examinations. Health status was checked yearly by mail or telephone for any subjects who did not undergo a regular examination or who had moved out of town. We also established a daily monitoring system among the study team and local physicians or members of the town's health and welfare office. When a subject died, an autopsy was performed at the Department of Pathology of Kyushu University. During the follow-up period, only one subject was lost to follow up and 479 subjects died, of whom 362 (75.6%) underwent autopsy.

Definition of Cardiovascular Events

CVD was defined as first-ever development of coronary heart disease (CHD) or stroke. The criteria for a diagnosis of CHD included first-ever acute myocardial infarction, silent myocardial infarction, sudden cardiac death within 1 hour after the onset of acute illness, or coronary artery disease followed by coronary artery bypass surgery or angioplasty.[32] Acute myocardial infarction was diagnosed when a subject met at least 2 of the following criteria: (1) typical symptoms, including prolonged severe anterior chest pain; (2) abnormal cardiac enzymes more than twice the upper limit of the normal range; (3) evolving diagnostic electrocardiographic changes; and (4) morphological changes, including local asynergy of cardiac wall motion on electrocardiography, persistent perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars >1 cm long accompanied by coronary atherosclerosis at autopsy. Silent myocardial infarction was defined as myocardial scarring without any historical indication of clinical symptoms or abnormal cardiac enzyme changes. Stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit persisting for >24 hours. The diagnosis of stroke and the determination of its pathological type were based on the clinical history, neurological examination, and all available clinical data, including brain CT/MRI and autopsy findings. Stroke was classified as either ischemic or hemorrhagic.[32]

Risk Factor Measurement

At the baseline examination, each participant completed a self-administered questionnaire covering medical history, exercise, treatment for hypertension or diabetes, smoking habits, and alcohol intake. The questionnaire was checked by trained interviewers at the screening. The subjects engaging in sports or other forms of exertion ≥3 times a week during their leisure time made up a regular exercise group. Smoking habits and alcohol intake were classified into currently habitual or not.

Blood pressure was measured 3 times using a standard mercury sphygmomanometer in the sitting position after rest for at least 5 minutes. The mean of the 3 measurements was used for the analysis. Hypertension was defined as blood pressure ≥140/90 mm Hg and/or current use of antihypertensive agents. The waist circumference was measured at the umbilical level in a standing position by a trained staff member. Body height and weight were measured in light clothing without shoes and the body mass index (kg/m^2) was calculated. Electrocardiographic abnormalities were defined as left ventricular hypertrophy (Minnesota code, 3 to 1) and/or ST depression (Minnesota code, 4 to 1, 2, or 3).

Blood samples were collected from an antecubital vein after an overnight fast for the determination of lipids and blood glucose levels. Serum total cholesterol, triglycerides, and high-density lipoprotein cholesterol concentrations were determined enzymatically. Fasting blood glucose levels were measured by the glucose oxidase method. Diabetes was defined as fasting blood glucose ≥126 mg/dL (7.0 mmol/L) and/or current use of insulin or oral medication for diabetes. Fresh voided urine samples were collected at the examination and proteinuria was defined as 1+ or more using a reagent strip.

Definition of Metabolic Syndrome

MetS was defined by using criteria recommended in the NCEP Adult Treatment Panel III guideline[5] with a modification. Specifically, abdominal obesity was defined as a waist circumference >90 cm in men and >80 cm in women according to International Obesity Task Force central obesity criteria for Asia.[33] Elevated blood pressure was defined as average systolic/diastolic blood pressures of ≥130/85 mm Hg and/or current use of antihypertensive medicine. Hypertriglyceridemia was defined as serum triglycerides of ≥1.69 mmol/L. Low high-density lipoprotein cholesterol was defined as serum high-density lipoprotein cholesterol levels of <1.03 mmol/L in men and of <1.29 mmol/L in women. Elevated blood glucose level was defined as fasting blood glucose of ≥6.10 mmol/L and/or current use of insulin or oral medication for diabetes. MetS was defined as the presence of 3 or more of these components.[5]

Statistical Analysis

The SAS software package (SAS Institute, Inc, Cary, NC) was used to perform all statistical analyses. Serum triglycerides were transformed into logarithms to improve the skewed distribution. The statistical significance of differences in mean values of continuous variables and frequencies of categorical variables was examined using the Student t test and χ^2 test as appropriate. The incidences were calculated by the person-year method. Differences in incidences between MetS status were tested by the Cox proportional hazards regression analysis after adjustment for age. The age- or multivariate-adjusted hazard ratios (HRs) and 95% CIs were also estimated with the use of the Cox proportional hazards model. $P<0.05$ was considered statistically significant in all analyses.

Results

The overall prevalence of MetS at baseline was 25.9%. The baseline characteristics on the basis of sex and MetS are shown in Table 1. Men with MetS had significantly higher mean values of blood pressures, waist circumference, body mass index, fasting blood glucose, and serum triglycerides and lower mean values of serum high-density lipoprotein cholesterol compared with those without MetS. Moreover, the frequencies of antihypertensive medication, hypertension, proteinuria, diabetes, and alcohol intake were higher in men with MetS than in those without MetS. A similar distribution was observed in women with MetS in terms of the previously mentioned variables except for alcohol intake. In addition, women with Mets were significantly older and had higher serum total cholesterol compared with those without MetS.

During the 14-year follow up, 307 first-ever CVD events (158 men and 149 women) occurred. Of these, there were 125 CHD (78 men and 47 women) and 209 stroke events (94 men and 115 women). The age-adjusted incidences of CVD were significantly higher in subjects with MetS compared with those without MetS for both sexes (men: 21.8 versus 11.6 per 1000 person-years, $P<0.01$; women: 12.9 versus 6.5, $P<0.01$) (Table 2). The same was true for CHD incidence in both sexes (men: 9.2 versus 5.7, $P<0.01$; women: 5.1 versus 1.5, $P<0.01$) and for stroke in men (14.1 versus 6.4, $P<0.01$). When we divided strokes into ischemic and hemorrhagic type, the age-adjusted incidences of ischemic stroke were

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