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Components of the metabolic syndrome as predictors of cardiovascular disease and type 2 diabetes in middle-aged Japanese men

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Abstract

To determine whether the clustered features of the metabolic syndrome precede the 7 year incidence of cardiovascular disease (CVD) and type 2 diabetes, we examined 6182 Japanese male office workers aged 35–59 years without any history of CVD. The 5588 subjects without type 2 diabetes also constituted the nondiabetic cohort, and were re-examined over seven successive years. Components of the metabolic syndrome included glycemic disorder (type 2 diabetes for the risk of CVD and impaired fasting glucose for the risk of type 2 diabetes), systemic obesity, hypertension, dyslipidemia, proteinuria, and elevated white blood cell (WBC) count. After controlling for age, family history of diabetes, alcohol intake, and cigarette smoking, the multivariate-adjusted relative risk of incidence of CVD compared with absence of components was 3.18, 3.48, 12.55, and 14.15 (P for trend <0.001), for the presence of 1,2,3, and ≥ 4 components, respectively. The corresponding relative risks of incidence of type 2 diabetes were 1.92, 4.36, 6.44, and 15.08 (P for trend <0.001). In both non-smokers and current smokers, the multivariate-adjusted relative risks of incidence of CVD and type 2 diabetes increased as the number of components increased (P for trend <0.001 for all). Our findings indicate that clustered features of the metabolic syndrome are closely associated with development of CVD and type 2 diabetes in middle-aged Japanese.

Keywords: Cardiovascular disease; Type 2 diabetes; Incidence; Metabolic syndrome; Japanese men

1. Introduction

Because of the epidemic of overweight and sedentary lifestyle worldwide [1], the metabolic syndrome, defined by a cluster of risk factors including central obesity, hypertension, and dyslipidemia with or with-

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out glycemic disorder, has been found in many ethnic groups and is becoming increasingly common [2]. The metabolic syndrome is most important because of its association with subsequent development of type 2 diabetes and cardiovascular disease (CVD) [3,4]. Although this syndrome is characterized by insulin resistance and is also known as the insulin resistance syndrome, the World Health Organization (WHO) proposed to call it the metabolic syndrome rather than the insulin resistance syndrome in 1998, because it has not yet been established whether insulin resistance is the cause of all the metabolic disorders or vice versa [5].

The features of the metabolic syndrome have been reported to precede the detection of type 2 diabetes by as much as 10 years, at which time the known increased risk of CVD has been documented [6,7]. Therefore, the importance of the metabolic syndrome from both a clinical and public health perspective may be greatest in its earlier stages, before development of CVD or diabetes. The aim of our longitudinal population study, based on the results of serial annual health examinations at the workplace, was to examine whether by focusing on the components of the metabolic syndrome an increased risk of development of CVD and type 2 diabetes might be detected during the following 7 years in middle-aged Japanese men.

2. Research design and methods

2.1. Study cohort

The study was conducted among employees of Company A, one of the largest building contractors in Japan. Participants were recruited from a network of 10 company offices located in major cities around Japan with baseline assessments made in May and June 1994. Subjects for this study were 6182 Japanese men aged 35–59 years with no prior history of coronary heart disease (CHD) or stroke. All the participants were white-collar workers, most were professionals, and none were acutely ill. Employees are required by the Industrial Safety and Health Law of Japan to participate in annual health examinations, and the employee data, which are anonymous, are available for research with the approval of the employer. We interpreted the return of a self-administered questionnaire signed by the subjects as their consent to participate in the study.

Of the 6182 potential participants, 436 (7.1%) were identified as having type 2 diabetes at the initial examination. The remaining 5746 men constituted the nondiabetic cohort, and were re-examined over seven successive years until 2001. We excluded 158 men who did not participate in all the consecutive annual health examinations. The final study population for analysis of incidence of type 2 diabetes therefore, consisted of 5588 men. Men in whom type 2 diabetes was found during any of the examinations through 2001 were classified as having type 2 diabetes. Altogether, 104 participants who started taking medication for diabetes during the observation period were considered to have type 2 diabetes. Owing to the age range of the study population, all cases of type 2 diabetes were diagnosed when they were older than 35.

2.2. Study design

Surveillance for CHD and stroke was conducted annually from 1994 through 2001. Endpoints of CVD were ascertained from reported absenteeism owing to sickness, health insurance claims, and a health questionnaire distributed at the annual health examinations. The criteria for CHD were modified from those of the WHO expert committee [8]. Indications of myocardial infarction were typical severe chest pain (lasting at least 30 min and with no definite non-ischemic cause) accompanied by new abnormal and persistent Q or QS waves, consistent changes in cardiac enzyme levels, or both. We also regarded myocardial infarction without typical chest pain as infarction if it was accompanied by the development of new Q waves (Minnesota code: 1-1 or 1-2) [9] on the annual electrocardiogram (ECG), and confirmed on at least three sequential ECGs. Angina pectoris was defined as repeated episodes of chest pain during effort, usually disappearing rapidly after the cessation of effort or upon use of sublingual nitroglycerine. Those who had undergone intervention in the form of coronary artery bypass grafting or percutaneous transluminal coronary angioplasty were regarded as having CHD. Stroke (including both ischemic and hemorrhagic stroke) was defined as a constellation of neurological deficits that were sudden or rapid in onset, and lasted

at least 24 h [10,11]. This information was verified from medical records at the company clinic and local hospitals.

Fasting plasma glucose levels were measured at the annual health examinations from 1994 to 2001. The participants were asked to fast for at least 8 h and to avoid smoking and heavy physical activity for more than 2 h before the examinations. Blood samples were drawn from an antecubital vein, and glucose was measured with the hexokinase-glucose dehydrogenase method [12,13]. Quality control of the laboratory was internal, and the coefficients of variation between and within assays for plasma glucose were no more than 3% from 1994 to 2001. Normal fasting glucose, impaired fasting glucose (IFG), and type 2 diabetes were defined with the criteria of the American Diabetes Association [14]. Normal fasting glucose was defined as a fasting plasma glucose level of <6.1 mmol/l, IFG as a fasting plasma glucose level of 6.1–6.9 mmol/l, and type 2 diabetes as a fasting plasma glucose level of ≥ 7.0 mmol/l or receipt of hypoglycemic medications, because not every subject underwent an oral glucose tolerance test.

Items included in the annual health examinations at study entry were medical history, physical examination, anthropometric measurements, urine test, biochemical measurements, and a questionnaire on health-related behaviors, such as alcohol consumption and smoking. Medical history and history of prescription drug use were assessed by the examining physicians. A family history of diabetes was defined as the presence of a mother, father, sister or brother with diagnosed diabetes. Body mass index (BMI) was used as a measure of overall obesity and calculated as body weight/height^2 (kg/m^2). After a 5 min rest in a quiet room, systolic and diastolic blood pressures were measured in the right arm with a standard mercury sphygmomanometer. Presence of proteinuria was determined with a dipstick in a urine specimen, and the levels of serum triglyceride and high-density lipoprotein (HDL) cholesterol and white blood cell (WBC) count were determined according to standard laboratory procedures [12,13]. The questions about alcohol intake included items about the frequency of alcohol consumption per week, the type of alcoholic beverage, and the average daily amount consumed in units of “go” (a traditional Japanese unit of volume measurement, corresponding to 23 g of ethanol). Weekly alcohol intake was calculated and then converted to daily alcohol consumption. The questionnaire also asked about smoking habits (never, past, or current smoker), and past or current smokers were asked about the number of cigarettes smoked per day and the duration of smoking in years.

Our definitions of the components of the metabolic syndrome were adapted from the criteria recently proposed by the WHO for the classification of diabetes and its complications [5]. The metabolic syndrome was defined (without assumptions of causality) as insulin resistance or the presence of impaired glucose tolerance or type 2 diabetes and the presence of at least two of several items including elevated arterial pressure, elevated triglyceride and/or low HDL cholesterol levels, central obesity or high BMI, and microalbuminuria. Although these core components are mostly suitable for general definitions, the demonstration of associations between WBC count and both insulin resistance and hyperinsulinemia [15–17] argue for including the WBC count in the metabolic syndrome. The components of the metabolic syndrome we included were thus, glycemic disorder, systemic obesity defined by BMI, hypertension, dyslipidemia, proteinuria, and elevated WBC count. The components of the metabolic syndrome were defined as follows: glycemic disorder, IFG and type 2 diabetes for the risk of CVD and IFG for the risk of type 2 diabetes; systemic obesity, BMI ≥ 25; hypertension, systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, or both; dyslipidemia, HDL cholesterol level <1.03 mmol/l; hypertriglyceridemia or triglyceride level ≥ 1.69 mmol/l; proteinuria, protein ≥ 30 mg/dl; and increased WBC count, WBC count $\geq 8.0 \times 10^9$ cells/l.

2.3. Statistical analysis

The χ^2 test and one-way ANOVA were used to analyze the statistical differences among characteristics of the study participants at enrollment categorized according to fasting plasma glucose level. For each participant, person-years of follow-up were calculated from the date of enrollment to the date of the first incidence of CVD and type 2 diabetes or the date of the follow-up where either was diagnosed, whichever came first. The Cox proportional hazards model was

used to evaluate the association of each component and the clustering of components of the metabolic syndrome with development of CVD and type 2 diabetes. Potential confounding factors were treated as categorical variables: age, graded from 1 through 5 (first through fifth quintiles); family history of diabetes (no or yes); alcohol consumption, graded as 1 (none) or as quartile 1 (grade 2) to quartile 4 (grade 5) for drinkers; and cigarette smoking, graded as 1 (never), 2 (past), or tertile 1 (grade 3) to tertile 3 (grade 5) for current smokers.

Data were analyzed by using the SPSS/PC statistical package (SPSS Inc., Chicago, IL, USA). All reported *P*-values are two-tailed, and those less than 0.05 were considered statistically significant.

3. Results

The baseline characteristics of the study sample according to fasting plasma glucose level are shown in Table 1. The mean age, BMI, systolic and diastolic blood pressures, HDL cholesterol level, triglyceride level, and WBC count and the percentages of the subjects with a family history of diabetes, habits of current smoking and current drinking, systemic obesity, dyslipidemia, proteinuria, and elevated WBC count differed significantly among three groups of fasting plasma glucose level. Age, family history of diabetes, current smoking, hypertension, dyslipidemia, proteinuria, and elevated WBC count increased with an increase in fasting plasma glucose level.

Results of stratified analyses for the risk of incidence of CVD and type 2 diabetes according to the presence or absence of each component of the metabolic syndrome are shown in Table 2. During the 7 years of follow-up representing 38,161 person-years, 70 men developed CVD (CHD in 62 and stroke in eight). After adjustment for age, all the components of the metabolic syndrome, except for IFG, were significantly associated with the risk of incidence of CVD. With the additional adjustment for potential risk factors—family history of diabetes, alcohol consumption, cigarette smoking, and all other components of the metabolic syndrome, type 2 diabetes, hypertension, and elevated WBC count remained significant. As for the risk of incidence of type 2 diabetes, 417 men developed type 2 diabetes during the 7 years of follow-up representing 34,492 person-years. After adjustment for age, each component of the metabolic syndrome was significantly associated with the risk of incidence of type 2 diabetes. With the additional adjustment for potential risk factors, all the components of the metabolic syndrome, except for hypertension, remained significant.

Table 1
Baseline characteristics of 6182 Japanese male office workers, according to fasting plasma glucose level

Characteristic	Normal glycemia ($n = 5500$)	Impaired fasting glucose ($n = 246$)	Type 2 diabetes ($n = 436$)	*P*-value
Age (years)	47.1 ± 6.1	49.0 ± 5.8	51.1 ± 5.5	<0.001
Family history of diabetes (%)	7.2	15.9	22.5	<0.001
Current drinkers (%)	83.5	78.5	80.3	0.033
Current smokers (%)	49.4	52.8	58.3	<0.001
Fasting plasma glucose (mmol/l)	4.99 ± 0.37	6.42 ± 0.24	8.07 ± 1.85	<0.001
BMI (kg/m^2)	23.5 ± 2.6	24.6 ± 3.0	24.4 ± 3.2	<0.001
Systemic obesity (%)	26.3	37.8	36.7	<0.001
Systolic blood pressure (mmHg)	127.4 ± 14.5	133.2 ± 16.1	132.8 ± 17.8	<0.001
Diastolic blood pressure (mmHg)	78.3 ± 10.9	80.6 ± 11.1	81.3 ± 11.7	<0.001
Hypertension (%)	23.9	35.4	37.6	<0.001
HDL cholesterol (mmol/l)	1.40 ± 0.34	1.36 ± 0.33	1.35 ± 0.38	<0.001
Triglyceride (mmol/l)	1.48 ± 1.08	1.65 ± 1.17	2.02 ± 1.78	<0.001
Dyslipidemia (%)	31.0	40.2	50.2	<0.001
Proteinuria (%)	3.7	5.3	14.2	<0.001
White blood cell count (10^9 cells/l)	6.42 ± 1.70	6.87 ± 1.63	6.96 ± 1.90	<0.001
Elevated white blood cell count (%)	16.9	24.0	26.4	<0.001

Figures show mean ± S.D. unless indicated otherwise.

Table 2
Risk of incidence of cardiovascular disease and type 2 diabetes by components of the metabolic syndrome among 6182 Japanese men and 5588 nondiabetic Japanese men during 7 years of follow-up, respectively

Component		Participants, *n*	Cases, *n*	Total person-years	Rate per 1000 person-years	Age-adjusted relative risk (95% CI)	*P*-value	Multivariate-adjusted relative risk[a] (95% CI)	*P*-value
Cardiovascular disease									
Fasting plasma glucose level	Normal glycemia	5500	51	34308	1.5	1.0 (referent)		1.0 (referent)	
	Impaired fasting glucose	246	5	1506	3.3	1.88 (0.75, 4.72)	0.180	1.31 (0.51, 3.34)	0.571
	Type 2 diabetes	436	14	2347	6.0	3.12 (1.71, 5.68)	<0.001	1.97 (1.03, 3.76)	0.039
Systemic obesity	No	4482	42	27859	1.5	1.0 (referent)		1.0 (referent)	
	Yes	1700	28	10302	2.7	1.76 (1.09, 2.84)	0.020	1.40 (0.86, 2.30)	0.180
Hypertension	No	4618	33	28884	1.1	1.0 (referent)		1.0 (referent)	
	Yes	1564	37	9277	4.0	3.04 (1.89, 4.88)	<0.001	2.62 (1.60, 4.28)	<0.001
Dyslipidemia	No	4159	38	25783	1.5	1.0 (referent)		1.0 (referent)	
	Yes	2023	32	12378	2.6	1.70 (1.06, 2.72)	0.027	1.11 (0.67, 1.81)	0.692
Proteinuria	No	5906	60	36495	1.6	1.0 (referent)		1.0 (referent)	
	Yes	276	10	1666	6.0	3.38 (1.73, 6.60)	<0.001	1.93 (0.95, 3.90)	0.070
Elevated white blood cell count	No	5076	40	31356	1.3	1.0 (referent)		1.0 (referent)	
	Yes	1106	30	6805	4.4	3.43 (2.14, 5.51)	<0.001	2.90 (1.71, 4.92)	<0.001
Type 2 diabetes									
Impaired fasting glucose	No	5348	284	33510	8.5	1.0 (referent)		1.0 (referent)	
	Yes	240	133	982	135.5	13.80 (11.18, 17.04)	<0.001	10.98 (8.86, 13.61)	<0.001
Systemic obesity	No	4098	234	25687	9.1	1.0 (referent)		1.0 (referent)	
	Yes	1490	183	8805	20.8	2.25 (1.85, 2.73)	<0.001	1.72 (1.41, 2.10)	<0.001
Hypertension	No	4243	285	26506	10.8	1.0 (referent)		1.0 (referent)	
	Yes	1345	132	7986	16.5	1.44 (1.17, 1.77)	0.001	1.20 (0.97, 1.48)	0.096
Dyslipidemia	No	3833	208	23994	8.7	1.0 (referent)		1.0 (referent)	
	Yes	1755	209	10497	19.9	2.24 (1.84, 2.71)	<0.001	1.71 (1.40, 2.08)	<0.001
Proteinuria	No	5381	384	33264	11.5	1.0 (referent)		1.0 (referent)	
	Yes	207	33	1228	26.9	2.23 (1.57, 3.19)	<0.001	1.65 (1.14, 2.37)	0.008
Elevated white blood cell count	No	4625	307	28657	10.7	1.0 (referent)		1.0 (referent)	
	Yes	963	110	5834	18.9	1.74 (1.40, 2.16)	<0.001	1.35 (1.07, 1.70)	0.013

[a] Controlled for age, family history of diabetes, alcohol consumption, cigarette smoking, and all other components of the metabolic syndrome at study entry.

Table 3
Risk of incidence of cardiovascular disease and type 2 diabetes by number of components of the metabolic syndrome, including glycemic disorder[a], systemic obesity, hypertension, and dyslipidemia, among 6182 Japanese men and 5588 nondiabetic Japanese men during 7 years of follow-up, respectively

	Number of components				*P* for trend
	0	1	2	≧3	
Cardiovascular disease					
Participants, *n*	2506	2123	1094	459	
Cases, *n*	7	30	19	14	
Total person-years	15943	13055	6454	2709	
Rate per 1000 person-years	0.4	2.3	2.9	5.2	
Age-adjusted relative risk (95% CI)	1.0 (referent)	4.98 (2.19, 11.33)	5.86 (2.46, 13.98)	9.98 (4.02, 24.80)	<0.001
Multivariate-adjusted relative risk[b] (95% CI)	1.0 (referent)	4.82 (2.11, 11.00)	5.80 (2.43, 13.86)	9.84 (3.95, 24.52)	<0.001
Type 2 diabetes					
Participants, *n*	2378	1928	963	319	
Cases, *n*	66	141	125	85	
Total person-years	15323	11860	5595	1713	
Rate per 1000 person-years	4.3	11.89	22.34	49.62	
Age-adjusted relative risk (95% CI)	1.0 (referent)	2.70 (2.01, 3.61)	4.89 (3.62, 6.59)	10.61 (7.69, 14.65)	<0.001
Multivariate-adjusted relative risk[b] (95% CI)	1.0 (referent)	2.59 (1.93, 3.47)	4.61 (3.41, 6.22)	10.29 (7.45, 14.22)	<0.001

[a] Type 2 diabetes and impaired fasting glucose were included as the component of the metabolic syndtrome for the risk of incidence of cardiovascular disease and type 2 diabetes, respectively.
[b] Controlled for age, family history of diabetes, alcohol consumption, and cigarette smoking at study entry.

Table 3 shows the risk of incidence of CVD and type 2 diabetes according to the number of components of the metabolic syndrome, including glycemic disorder (type 2 diabetes for the risk of CVD and IFG for the risk of type 2 diabetes), systemic obesity, hypertension, and dyslipidemia as the components of the metabolic syndrome. In the analyses of the risk of incidence of CVD, normal glycemia and IFG were combined, because the risk of incidence of CVD did not differ significantly between those with normal glycemia and those with IFG. After adjustment for age, family history of diabetes, alcohol consumption, and cigarette smoking, the relative risk of incidence of CVD compared with the presence of no components was 4.82, 5.80, and 9.84 for the presence of 1, 2, and ≥3 components, respectively (*P* for trend <0.001). The corresponding results for the risk of incidence of type 2 diabetes were 2.59, 4.61, and 10.29 (*P* for trend <0.001).

Table 4 shows the risk of incidence of CVD and type 2 diabetes according to the number of components of the metabolic syndrome, including proteinuria and elevated WBC count as well as glycemic disorder, systemic obesity, hypertension, and dyslipidemia as the components of the metabolic syndrome. After adjustment for potential risk factors, the relative risk of incidence of CVD compared with the presence of no components was 3.18, 3.48, 12.55, and 14.15 for the presence of 1,2,3, and ≥4 components, respectively (*P* for trend <0.001). The corresponding results for the risk of incidence of type 2 diabetes were 1.92, 4.36, 6.44, and 15.08 (*P* for trend <0.001).

To examine whether cigarette smoking affected the association between the clustering of components of the metabolic syndrome and the risk of incidence of CVD and type 2 diabetes, we stratified subjects according to smoking status (Fig. 1). In both non-smokers and current smokers, the multivariate-adjusted relative risk of incidence of CVD and type 2 diabetes increased progressively with an increase in the number of components of the metabolic syndrome (*P* for trend <0.001 for all).

Table 4
Risk of incidence of cardiovascular disease and type 2 diabetes by number of components of the metabolic syndrome, including glycemic disorder[a], systemic obesity, hypertension, dyslipidemia, proteinuria, and elevated white blood cell count, among 6182 Japanese men and 5588 nondiabetic Japanese men during 7 years of follow-up, respectively

	Number of components					*P* for trend
	0	1	2	3	≧4	
Cardiovascular disease						
Participants, *n*	2116	2025	1283	558	200	
Cases, *n*	6	19	14	22	9	
Total person-years	13466	12484	7733	3287	1191	
Rate per 1000 person-years	0.4	1.5	1.8	6.7	7.6	
Age-adjusted relative risk (95% CI)	1.0 (referent)	3.25 (1.30, 8.15)	3.59 (1.38, 9.37)	12.97 (5.24, 32.06)	15.03 (5.34, 42.25)	<0.001
Multivariate-adjusted relative risk[b] (95% CI)	1.0 (referent)	3.18 (1.27, 7.99)	3.48 (1.33, 9.12)	12.55 (5.04, 31.24)	14.15 (4.95, 40.52)	<0.001
Type 2 diabetes						
Participants, *n*	2012	1851	1154	458	113	
Cases, *n*	55	98	140	81	43	
Total person-years	12961	11543	6833	2580	575	
Rate per 1000 person-years	4.2	8.49	20.49	31.40	74.78	
Age-adjusted relative risk (95% CI)	1.0 (referent)	1.96 (1.41, 2.72)	4.56 (3.34, 6.24)	6.85 (4.86, 9.66)	16.43 (11.01, 24.49)	<0.001
Multivariate-adjusted relative risk[b] (95% CI)	1.0 (referent)	1.92 (1.38, 2.67)	4.36 (3.18, 5.98)	6.44 (4.55, 9.11)	15.08 (10.05, 22.61)	<0.001

[a] Type 2 diabetes and impaired fasting glucose were included as the component of the metabolic syndrome for the risk of incidence of cardiovascular disease and type 2 diabetes, respectively.

[b] Controlled for age, family history of diabetes, alcohol consumption, and cigarette smoking at study entry.

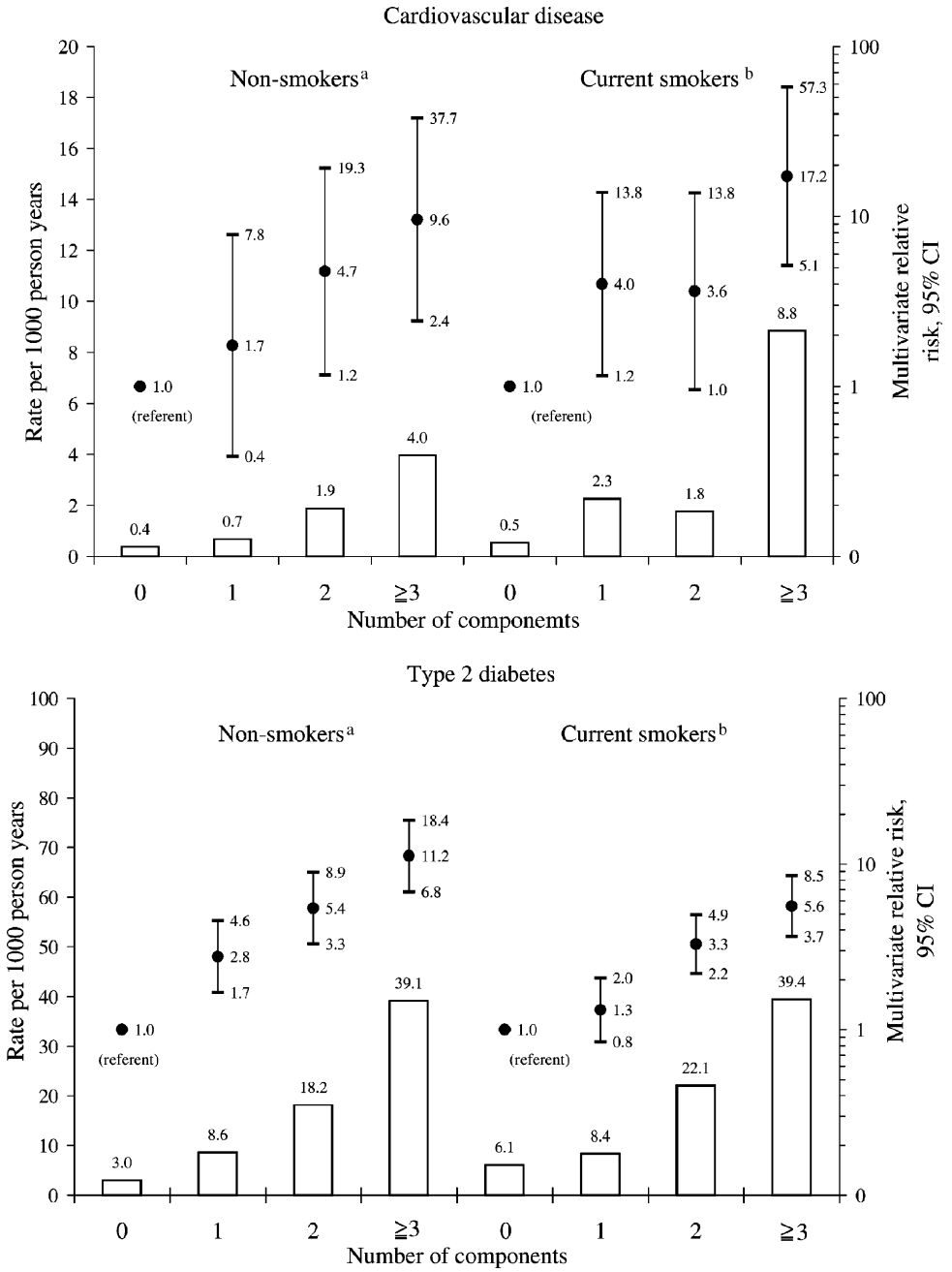

Fig. 1. Risk of incidence of cardiovascular disease and type 2 diabetes by smoking status and number of components of the metabolic syndrome among 6182 Japanese men and 5588 nondiabetic Japanese men during 7 years of follow-up, respectively. Glycemic disorder, systemic obesity, hypertension, dyslipidemia, proteinuria, and elevated white blood cell count were included as the component of the metabolic syndrome. Type 2 diabetes and impaired fasting glucose were included as the component of the metabolic syndrome for the risk of incidence of cardiovascular disease and type 2 diabetes, respectively. ([a]) Relative risks were controlled for age, family history of diabetes, alcohol consumption, and smoking history (never and past) at study entry. ([b]) Relative risks were controlled for age, family history of diabetes, alcohol consumption, and cigarettes smoked per day at study entry.

4. Discussion

We found that the presence of each component of the metabolic syndrome, defined by us, posed an increased risk of incidence of CVD and type 2 diabetes during the 7-year period. While individual components of the metabolic syndrome may not contribute equally to such risk, they became much more powerful when occurring in combination and the increased risk related to clustered features of the metabolic syndrome was more pronounced when proteinuria and elevated WBC count were included. Risk analyses according to smoking status also revealed that in both non-smokers and current smokers the risk for development of CVD and type 2 diabetes increased in proportion to the increase in the number of components. These results indicate that the clustering of the components of the metabolic syndrome increases the risk for development of CVD and type 2 diabetes independently of cigarette smoking.

The metabolic syndrome, originally described in 1923 by Kylin [18], is reported to precede the risk of incidence of CVD and type 2 diabetes by as much as 10 years [6,7]. Our results for middle-aged Japanese men support this hypothesis that the features of the metabolic syndrome actually precede the incidence of CVD and type 2 diabetes. In this population, except for the relationships of an elevated WBC count with systemic obesity and hypertension, all the pairwise relationships of components of the metabolic syndrome (type 2 diabetes, systemic obesity, hypertension, dyslipidemia, proteinuria, and elevated WBC count) showed significant correlations ($P < 0.001$). Since the components of the metabolic syndrome are closely interrelated, intervention with one of a pair of components may also affect the other. In addition, studies such as the United Kingdom Prospective Diabetes study and the Scandinavian Simvastatin Survival study have clearly shown that factors other than glycemic control play vital roles in macrovascular disease [19,20]. The recent Diabetes Prevention Trial [21] attests to the efficacy of lifestyle intervention in order to alter risk factors for the prevention of diabetes. The management of individuals with hyperglycemia and other features of the metabolic syndrome should focus not only on blood glucose control but also include strategies for reduction of the other CVD risk factors [22].

Insulin resistance, including impaired glucose tolerance (IGT) or type 2 diabetes, high blood pressure, dyslipidemia, and central obesity are established components of the metabolic syndrome [5,23,24]. The typical lipoprotein profile in this condition includes low HDL cholesterol and high triglyceride levels. Although microalbuminuria or proteinuria is reported to be a strong predictor of type 2 diabetes and CVD [25–27], the inclusion of microalbuminuria as part of the metabolic syndrome has been questioned [28] because of its rarity and lack of association with insulin resistance in some studies [29,30]. However, whether insulin resistance is involved in the pathogenesis of proteinuria may be less important than the fact that proteinuria is closely associated with an increased risk of CVD and type 2 diabetes. Furthermore, concentrations of inflammatory markers and mediators of inflammation—cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6—are higher in patients with type 2 diabetes, particularly in those with features of insulin resistance [31–33]. WBC, a major component of the inflammatory process, and C-reactive protein (CRP), an exquisitely sensitive acute-phase reactant, are increased by cytokines, especially IL-6 [34–36]. The lipid pattern of high triglycerides and low HDL cholesterol is a feature of inflammation and, more specifically, of TNF-α action [35]. Elevated WBC count and CRP have been shown to be positively associated with both insulin resistance and hyperinsulinemia [15–17,37–39] and to predict the occurrence of type 2 diabetes [12,40,41]. Because some features of low-graded inflammation such as glucose intolerance and dyslipidemia are identical to the components of the metabolic syndrome [3], an increase in WBC count could represent an insulin-resistant state or involvement in the metabolic syndrome.

Our study has several limitations. Although both IFG and IGT are similarly associated with an increased risk of diabetes, IGT is more strongly associated with CVD outcomes and an independent relationship with fasting plasma glucose is only found above 7.0 mmol/l [42]. Consistent with the findings of earlier studies, a fasting plasma glucose level of $\geq$7.0 mmol/l was significantly associated with development of CVD but IFG was not in this

study. Because IFG and IGT differ in their prevalence, population distribution, phenotype, and risk of CVD, research is needed to clarify the significance of isolated IFG, isolated IGT, and combined IFG and IGT for development of CVD. Among 62 men who developed CHD, 18 were diagnosed as having myocardial infarction. Among the remaining 44 men, 30 had undergone intervention in the form of coronary artery bypass or percutaneous transluminal coronary angioplasty without typically repeated episodes of chest pain during the effort. The inclusion of these cases might have underestimated the association between the components of the metabolic syndrome and development of CVD. The presence of protein in the urine $\geq$30 mg/dl ($\geq$1 + reading of the dipstick) was considered potential abnormal. The routine urinalysis dipstick is insensitive to albuminuria, being positive only when urinary albumin concentration reaches 30 mg/dl or greater [43]. As microalbuminuria is a strong predictor of CVD and type 2 diabetes [25–27], it is critical to determine the presence and amount of albumin in the urine. Furthermore, several components of the metabolic syndrome, such as visceral adiposity (waist-to-hip ratio) and fasting insulin level could not be included in this study. The central pattern of distribution, with its increased waist-to-hip ratio, is associated with more insulin resistance than is the peripheral pattern of distribution [44,45], and individuals with the central pattern are more likely to have glucose intolerance and hyperinsulinemia resulting from insulin resistance [46,47]. Therefore, visceral adiposity (waist-to-hip ratio) and fasting insulin level should be included in future studies. Although our study is not highly relevant for evaluating the impact of components of the metabolic syndrome proposed by the WHO [5] or National Cholesterol Education Program [24] on the risk of incidence of CVD and type 2 diabetes, we believe that our findings complement such studies.

In conclusion, the presence of components of the metabolic syndrome, both singly and in combination, actually precede the development of CVD and type 2 diabetes over a 7-year period among middle-aged Japanese men. This heightens the importance of determining ways to intervene on some or all of the components of the components and implementing such interventions promptly.

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