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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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APPENDIX

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The New Worldwide Definition of Metabolic Syndrome Is Not a Better Diagnostic Predictor of Cardiovascular Disease in Japanese Diabetic Patients Than the Existing Definitions

Additional analysis from the Japan Diabetes Complications Study

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We previously reported (1) the limited clinical significance for Japanese diabetic patients of the widely used World Health Organization (WHO) (2) and National Cholesterol Education Program (NCEP) (3) definitions of metabolic syndrome and suggested that an international definition of metabolic syndrome that was applicable regardless of ethnicity was necessary (1).

Recently, the International Diabetes Federation published a long-awaited new worldwide definition of metabolic syndrome (4) that is intended to be applicable to various ethnic groups. The new definition is similar to the NCEP definition (3) but has several important differences. Notably, most components of the new definition now include subjects who are receiving specific treatments for the abnormalities that comprise metabolic syndrome. Also, central obesity (defined by waist circumference with ethnic modification in its thresholds) has become a mandatory component in the new definition. In this report, we evaluated the predictive power of the new international definition for cardiovascular disease (CVD), as compared with that of previous definitions, in Japanese diabetic patients.

RESEARCH DESIGN AND METHODS — The Japan Diabetes Complications Study (JDCS) has been described in detail elsewhere (1,5). The same dataset was used for evaluation so that the new definition of metabolic syndrome could be directly compared with the WHO and NCEP definitions (1–4). A total of 1,424 Japanese patients (771 men and 653 women, age 58.4 ± 7.4 years [means ± SD]) with previously diagnosed type 2 diabetes but without known CVD were followed for 8 years for coronary heart disease (CHD) and stroke events. Fatal and nonfatal CHD and stroke were defined as previously reported (1). The new International Diabetes Federation definition (4) was used with a recommended ethnic modification for Japanese subjects in relation to waist circumference (men ≥85 cm, women ≥90 cm). Since all of the subjects had diabetes, metabolic syndrome diagnosis was made in patients who met criteria for central obesity plus one or more of the following: increased triglycerides, increased blood pressure, or reduced HDL cholesterol (see Table 1 for detailed thresholds). Incidence rates in the two groups (with and without metabolic syndrome) were estimated under the Poisson assumption using person-year methods. Cox regression analysis was used to calculate the age-adjusted hazard ratio (HR) and 95% CI of metabolic syndrome risk factors with CHD, stroke, or both. The SAS software package (version 8.0; SAS Institute, Cary, NC) was used for all analyses. $P < 0.05$ was considered statistically significant.

RESULTS — At baseline, the prevalence of metabolic syndrome, using the new definition (Table 1), was notably lower, especially in female patients, than the prevalence under the WHO (2) and NCEP (3) definitions, which was ~50% on average (1). Diabetes duration in patients with (9.9 ± 6.9 years) or without (10.7 ± 7.3 years) metabolic syndrome did not differ significantly ($P = 0.07$). The proportion of patients that met the central obesity criterion (an essential component of the new definition) was 36.7% for men and 9.7% for women, such that 87% of men and 95% of women with central obesity had metabolic syndrome.

The incidence (per 1,000 patient-years) of CHD (13.5 [with metabolic syn-

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Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; JDCS, Japan Diabetes Complications Study; NCEP, National Cholesterol Education Program; WHO, World Health Organization.

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

Table 1—*Patient prevalence at baseline, age-adjusted HRs with 95% CIs, and incidence of CHD, stroke, or both in 1,424 Japanese patients with type 2 diabetes (771 men and 653 women) according to individual cardiovascular risk factors comprising the metabolic syndrome as defined by the International Diabetes Federation* (b, c, *and* d *include specific treatment for each abnormality)*

	Prevalence at baseline (%)		HR for CHD		HR for stroke		HR for CHD and/or stroke	
	Men	Women	Men	Women	Men	Women	Men	Women
a) Waist circumference ≥85 cm (men), ≥90 cm (women)	36.7	9.7	1.68 (0.92–3.08)	1.13 (0.26–4.86)	0.91 (0.44–1.86)	1.11 (0.31–4.05)	1.32 (0.83–2.10)	1.13 (0.43–2.97)
b) Triglycerides ≥150 mg/dl	26.5	23.4	2.93 (1.55–5.53)	2.03 (0.81–5.04)	1.10 (0.51–2.36)	0.59 (0.20–1.78)	1.96 (1.21–3.19)	1.13 (0.56–2.26)
c) HDL cholesterol <40 mg/dl (men), <50 mg/dl (women)	19.3	36.3	1.82 (0.94–3.54)	1.48 (0.63–3.49)	0.99 (0.41–2.40)	1.34 (0.61–2.94)	1.53 (0.90–2.61)	1.34 (0.74–2.40)
d) SBP ≥130 mmHg or DBP ≥85 mmHg	64.1	68.8	1.04 (0.53–2.01)	1.05 (0.39–2.84)	2.08 (0.90–4.82)	1.63 (0.60–4.37)	1.29 (0.77–2.17)	1.29 (0.64–2.59)
a plus one or more of *b*, *c*, or *d*	32.0	9.2	1.72 (0.94–3.15)	1.15 (0.27–4.90)	1.14 (0.56–2.34)	1.13 (0.31–4.11)	1.47 (0.91–2.35)	1.14 (0.44–3.01)

DBP, diastolic blood pressure; SBP, systolic blood pressure.

drome] vs. 8.1 [without metabolic syndrome] in men; 5.8 vs. 5.5 in women) or stroke (8.1 vs. 7.5 in men; 8.8 vs. 7.0 in women) did not differ significantly between subjects with or without metabolic syndrome. Age-adjusted HRs were calculated to determine whether the new metabolic syndrome definition or its components could predict cardiovascular events (Table 1). Patients diagnosed as having metabolic syndrome, even when subgrouped by therapeutic contents (oral hypoglycemic agents or insulin use), did not show significantly raised HRs for CHD, stroke, or both compared with subjects without metabolic syndrome. However, male patients with raised triglyceride levels and/or having specific treatment for this condition had a significantly increased risk of CHD (HR 2.93, $P < 0.001$) and combined CHD and stroke (1.96, $P = 0.006$), regardless of whether they had metabolic syndrome (Table 1).

CONCLUSIONS— Our previous analysis (1) showed that HRs for CVD in patients with WHO-defined metabolic syndrome were significantly elevated compared with HRs in subjects without metabolic syndrome (although the HR for CHD in male patients was not elevated). Diagnosis of metabolic syndrome by the NCEP definition was less predictive but still associated with a significantly elevated HR for CHD in male patients. However, metabolic syndrome diagnosis by the new definition was not predictive for CVD in either male or female patients in the same prospective setting. Therefore, the new definition did not improve the prediction of adverse cardiovascular events, and its clinical usefulness in Japanese diabetic patients is rather less than that of the existing definitions or of hypertriglyceridemia alone in male patients.

The indispensability of central obesity to the new definition was a major cause of the decrease in the prevalence of metabolic syndrome observed using the new definition. The fact that most patients with central obesity were classified as having metabolic syndrome revealed that metabolic syndrome diagnosis by the new definition was highly dependent on waist circumference when applied to Japanese diabetic subjects. It also denoted that most patients with central obesity had at least one other cardiovascular risk factor, suggesting a close relationship between central obesity and other cardiovascular risk factors. However, this combination was not necessarily associated with an increased risk of CVD in our patients. This latter observation led us to further evaluate the significance of waist circumference in our patients by modifying the threshold within the 65- and 105-cm range and recalculating the HRs. Interestingly, we could not find any thresholds associated with significantly elevated HRs for cardiovascular events in either male or female subjects (data not shown). Therefore, the new definition's lower prediction power for CVD seemed to be derived from the indispensability of the waist circumference component.

To date, prospective trials examining the significance of metabolic syndrome as a predictor of CVD in diabetic patients (1,6–9) have been inadequate (10,11). Many important issues remain to be resolved. *1*) Is the new definition of metabolic syndrome a good predictor of CVD in diabetic patients of differing ethnicities (12)? *2*) Are there any other combinations of components (or different thresholds) that are better predictors of CVD in Asian diabetic patients (13–15)? *3*) Is the concept of metabolic syndrome truly applicable or relevant to diabetic patients in general? Investigations of these issues would aid the screening of diabetic patients at especially high risk of CVD, as well as inform and direct ethnic group–specific management of diabetes (16–19).

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Statistical Evaluation of the Diagnostic Accuracy of Methods Used to Determine the Progression of Visual Field Defects in Glaucoma

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Objective: To evaluate trend-type analyses to judge the progression of visual field damage (VFD) of glaucoma in terms of ratios of making judgments of progression and specificity, and to report a new method.

Design: Retrospective analysis of visual field (VF) results of actual glaucoma cases and those simulated by computer, and receiver operating characteristic curve analysis of performance of methods to judge the progression of VFD.

Participants: One hundred five eyes of 105 open-angle glaucoma (OAG) patients with progressing VFD and 355 eyes of 355 clinically stable OAG patients for VF simulation from 4 university-based referral practices.

Methods: Methods using regression analysis of total deviation (TD), mean deviation (MD), mean TD of a sectored VF, and original scoring used in the Advanced Glaucoma Intervention Study (AGIS) were compared. A VF test was repeated twice in a short period on the 355 stable OAG eyes, and test–retest fluctuation, including variance at each test point and covariance between 2 test points, was calculated to simulate stable glaucomatous VF series by computer. The sensitivity of each method was calculated with 105 progressing VF series, and specificity was calculated with 10 000 simulated stable glaucomatous VF series.

Main Outcome Measures: Sensitivity (ratios of making judgments of progression), specificity, and diagnostic power.

Results: The methods using the TD slope on one test location showed a sensitivity of 0.848 to 1.000, with a specificity of 0.105 to 0.721, and on 2 adjacent test locations showed a sensitivity of 0.848, with a specificity of 0.722. A significant negative MD slope with $P<0.05$ showed a sensitivity of 0.524, with a specificity of 0.945. The method using a sectored VF showed a sensitivity of 0.695, with a high specificity of 0.946. The AGIS method showed a sensitivity of 0.305 to 0.467, with a very high specificity of 0.999 to 1.000. The method using previously reported mathematically sectored VFs showed a sensitivity of 0.790, with a specificity of 0.900, and higher diagnostic power (1.69) than the others in this study population.

Conclusions: Most of the methods using the TD slope were characterized by high sensitivity, the AGIS method had a very high specificity, and those using VF sectors had reasonable sensitivity and specificity. *Ophthalmology 2004;111:2117–2125*

Automated achromatic static threshold perimetry is the standard method for management of patients with glaucoma. The results of perimetry using such methods as the Humphrey Visual Field Analyzer (HFA; Zeiss Humphrey Systems, Dublin, CA) are suited for quantitative assessment because they are an aggregate of numeric values that are easily analyzed mathematically. Objective assessment of the progression or nonprogression of visual field (VF) dam-

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age is clinically indispensable, not only for the treatment of glaucoma patients but also for the evaluation of therapeutic intervention in glaucoma. However, test results are susceptible to intertest variation, which is often considerable, especially in patients who have glaucomatous VF defects, making it difficult to distinguish true VF deterioration from nonpathological fluctuation.[1–11] Thus, as yet there have been no standard criteria for determining the progression or nonprogression of VF damage measured with automated static threshold perimetry.

Linear regression analysis with various criteria for threshold sensitivity or total deviation (TD) value on each test location,[12–21] mean of the values of clustered test locations,[12,16–18,20,22] mean threshold sensitivity or mean deviation (MD),[12,16–23] corrected pattern standard deviation, or corrected loss variance[12,16,18] have been proposed. These methods are called trend-type analyses and determine progression when the trend of the threshold value is significantly negative. Others have used paired *t* tests,[17,24] confidence intervals,[25] analysis of variance on mean threshold sensitivity,[17,26] pointwise glaucoma change probability analysis,[14,19,21,27–33] or original scoring systems based on results of the C24-2 program of the HFA.[34,35] These methods are called event-type analyses and determine progression when the threshold deteriorates beyond the previously prescribed level.

There were several reports that made comparison among several of the aforementioned methods to determine VF deterioration and discussed their eligibility.[12,15–19,21,26,29,36–43] In daily clinical practice, where physicians must determine the time point to start aggressive intraocular pressure (IOP)–lowering treatment, event-type analysis methods should have an advantage, in that they can determine the time point of significant disease progression from the baseline. On the other hand, when one aims to detect intergroup differences in VF performance during a predetermined study period between different treatment arms, trend-type analysis methods that take all achieved VF data into analysis may be able to detect a subtle continuous deterioration that does not reach the prerequired criteria of the event-type analysis methods, and may be more sensitive than the event-type analysis methods.[19,21,29,36,37,43] In addition, the slope value determined by trend-type analyses may be useful in predicting the future VF performance of the subject.

The most objective and clinically relevant way to discuss the matter is to calculate both the sensitivity and the specificity of each method and compare them to a common standard. Most previous reports, however, mainly focused on the comparison of sensitivity (ratio of making judgment of progression) among the methods, and specificity has rarely been addressed.[41–43]

We previously estimated respective test–retest variability at each test point of the Humphrey central 30-2 full threshold program (C30-2 program) in 355 open-angle glaucoma (OAG) eyes in various stages of the disease.[44] In the present study, we estimated the variance–covariance structure of fluctuation of TD values including covariance among test points on these data, and generated 10 000 time courses of glaucomatous VFs in which test points of the C30-2 program behave randomly and similarly to real data.

The purpose of this study was to compare varying trend-type analysis methods to judge the progression of VF damage in terms of sensitivity, calculated with VF series that were determined to have progressed with prescribed criteria, and specificity, calculated with the above computer-simulated stable glaucomatous VF series. Methods using our mathematically determined sector pattern of test locations of the HFA[44] were also evaluated in an attempt to develop a more optimal application for detecting progression of VF defects.

Materials and Methods

Clinical VF test series of progressive OAG cases of varying severity that had been followed up in departments of ophthalmology at the University of Tokyo Graduate School of Medicine, Gifu University School of Medicine, Niigata University School of Medicine, and Hiroshima University School of Medicine were obtained retrospectively. In each patient, OAG had been clinically diagnosed based on glaucomatous optic nerve head changes[45] with corresponding VF defects, an unoccludable normal open angle, and absence of any other ocular or systemic abnormalities attributable to the optic nerve head change. Progressive cases were searched for by retrospective review of the clinical records of the patients who had been diagnosed as having OAG before January 1, 1995 and had been followed up more than 4 years at the glaucoma clinics in the 4 universities.

Informed consent was obtained from each patient whose VF data were used for analysis, and his or her other personal data were completely masked throughout the study. Because this study was not designed to be analyzed accompanied with any clinical interventions, the results of the judgment of the VFs of each patient in this study had no influence on his or her clinical treatment.

The inclusion criteria were corrected visual acuity (VA) of 20/28 or better, clear ocular media without any clinically significant cataract, absence of any other ocular or intracranial conditions that might affect VF, and absence of any surgical operations such as cataract or glaucoma surgery that might affect the results of a VF test. The inclusion criteria were met throughout the follow-up period, from which VF test results for the present study were obtained. The reliability of the tests was checked with fixation loss of $<20\%$ and false-negative or false-positive responses of $<33\%$. Each patient had to have undergone ≥ 6 visual tests with reliable results from the HFA C30-2 full-threshold program during that period, excluding the first test, those tests that differed by ≥ 3 decibels MD from both preceding and succeeding tests, and those with suspected edge artifacts.

A combination of the modified version of the criteria used in The Glaucoma Laser Trial[46] and a criterion for the rate of deterioration in MD was used as the first step to detect probably progressive cases.

The progression was considered to be probable when (1) the same ≥ 3 adjacent nonedge test locations in the superior or inferior hemifield had pattern deviation values decline ≥ 7 dB from the baseline in 2 consecutive test results and (2) the difference in MD value between the first and last tests from the VF series presently used was ≥ 0.5 dB $\times$ time (years) between the first and last tests. The progression was then confirmed by experienced glaucoma specialists (MA, YS, YK) independently referring to VF results only, and the VF was judged to have progressed only when each of the 3 independently flagged the case as having progressed. Each VF series consisted of 9.2 VF tests, on average. Six tests, including the first and the last during the period, were then selected so that

Table 1. Characteristics of 105 Eyes of 105 Open-Angle Glaucoma Patients Whose Visual Field (VF) Series Were Judged to Be Definitely Progressed

Age at first VF test (yrs)	53.1±12.5 (16–72)
Follow-up period (yrs)	7.5±2.7 (2.67–12.08)
Mean deviation of first VF test (decibels)	−4.2±3.7 (−19.14 to +1.28)
Mean deviation of last VF test (decibels)	−9.6±5.3 (−25.65 to −2.78)

Mean ± standard deviation (range).

Table 2. Characteristics of 355 Eyes of 355 Stable Open-Angle Glaucoma Patients Whose Visual Fields (VFs) Were Tested Twice within 2 Months

Age at first VF test (yrs)	57.2±12.6 (22–89)
Mean deviation of first VF test (decibels)	−9.2±7.2 (−31.35 to +5.70)
Mean deviation of last VF test (decibels)	−9.0±7.1 (−30.84 to +3.56)

Mean ± standard deviation (range).

the 6 time points made approximately the same intervals in every series. In the following analysis, data from the left eyes were converted to mirror images of themselves and analyzed.

One hundred five series of VFs from 105 OAG patients, approximately 10% of the OAG patients whose clinical records were reviewed, were finally judged to have progressed and were used for the data analysis. The characteristics of the subjects are summarized in Table 1, and one VF example is shown in Figure 1.

To obtain fundamental data for the simulation of a stable glaucomatous VF, VF tests were performed twice within 2 months with the HFA C30-2 full-threshold program in 355 eyes of 355 patients with OAG of varying severity, randomly selected from patients in the above 4 medical centers. Their IOPs were judged to be well controlled, and the results of the Humphrey 30-2 program test and optic disc appearance were considered to be stable in terms of data for the last 2 years. They had no media opacities affecting VF testing, their corrected VA was 20/28 or better, they experienced several HFA tests previously, and the reliability of the test results was confirmed as described above. Data from left eyes were converted to mirror images of themselves. The characteristics of the subjects are shown in Table 2. It was assumed that the variation of TD at each test location between 2 tests was ascribed to the long-term fluctuation due to physiological variation and/or measurement variation.[4] We analyzed clinical data and estimated the variance–covariance structure among 74 test locations, except 2 points corresponding to blind spots. Then computer-simulated 6-time-point series of stable VFs for 10 000 eyes were generated according to the estimated variance–covariance structure, in which TD at each test location randomly fluctuated within physiological and/or measurement variation. The variation was assumed to follow a normal distribution.

We estimated the variance–covariance matrix of fluctuation structure V, as shown in the Appendix. Using V, we simulated each visual field $\mathbf{Y}$ (74×1 vector) as $\mathbf{Y} = \mathbf{Y_0} + V^{1/2}\mathbf{u}$, where 74×1 vector $\mathbf{Y_0}$ denoted the mean parameter (baseline values of TD), $V^{1/2}$ denoted the Choleskey decomposition of V, and 74×1 random normal variable vector $\mathbf{u} \sim MVN(\mathbf{0}, I_{74})$. $MVN(\mu,\Sigma)$ denoted the multivariate normal distribution with mean μ and covariance Σ, and I_k denoted the k×k identity matrix. Another $\mathbf{Y}$ corresponding to another time point was simulated similarly using the same baseline $\mathbf{Y_0}$ and an independent vector $\mathbf{u}$.

We evaluated the sensitivity (ratio of making judgment of progression) and specificity of several trend-type analysis methods for assessing VF progression, including linear regression analysis of the TD value at each test location according to 4 different criteria,[13–16] linear regression analysis of the MD value,[12,18,21–23] linear regression analysis of the mean TD value of sectored VFs reported by Werner et al,[17] and linear regression analysis of the mean TD value of sectored VFs that we reported previously.[44] An original scoring system used in the Advanced Glaucoma Intervention Study (AGIS)[34] was also tested for comparison as a representative method of event-type analysis.

The 4 criteria of linear regression analysis of TD examined here were that of Noureddin et al (the slope of TD was −0.2 dB per month or less with a significance level of $P<0.05$ for at least one test location),[13] that of Fitzke et al (TD slope was −1.0 dB per year or less for central test locations within 15°, or −2.0 dB per year or less for outer locations, with a significance level of $P<0.10$ for at least one test location),[14] that of Bhandari et al (TD slope was −1.0 dB per year or less with a

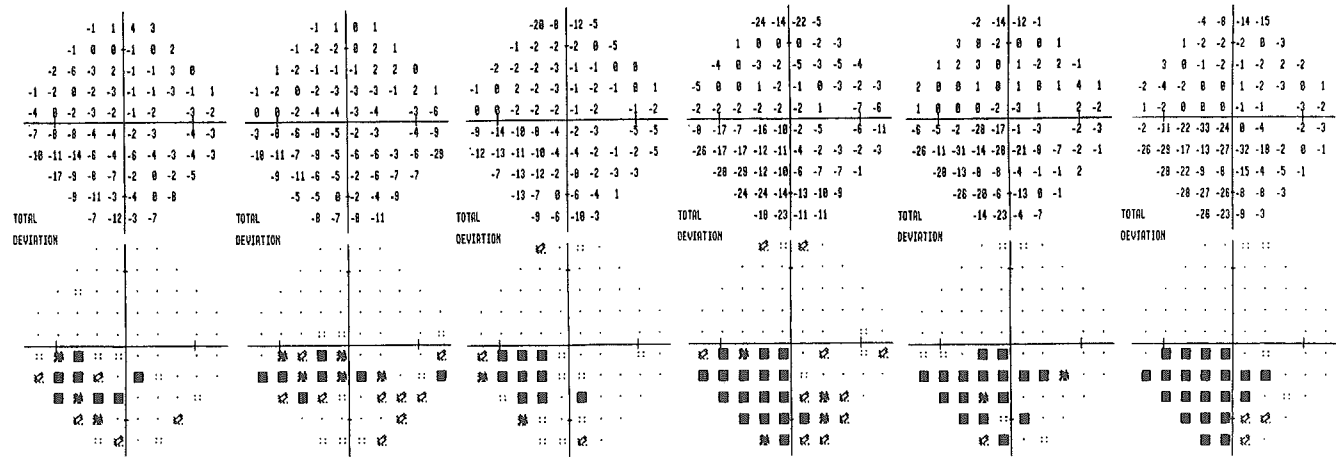

Figure 1. A series of an actual visual field that was judged to have progressed in this study.

significance level of $P<0.01$ for at least one test location),[15] and that of Nouri-Mahdavi et al (TD slope was negative, with a significance level of $P<0.05$ for at least 2 adjacent test locations).[16]

The 3 criteria of linear regression analysis of MD examined here were determination of progression by negative slope with a significance level of $P<0.025$,[18] that of $P<0.05$,[12,21–23] and that of $P<0.1$, for comparison. Because we could not calculate the value of MD in the VFs of simulated stable VF series, which consisted of TD values only, the mean of 74 TD values except 2 points corresponding to blind spots (mean TD), was used instead of the MD value in the analysis below. We confirmed that the mean TD was virtually identical to MD (given by the HFA's STATPAC2) in the total 630 (105×6) actual VF test results from 105 progressing OAG eyes.

Werner et al presented a method of sectoring test locations and dividing them into 10 sectors corresponding to nerve fiber bundle anatomy, and reported the linear regression analysis of the mean threshold value of each sector.[17] We used mean TD values in each of the sectors instead of mean threshold values, and the VF was considered to have progressed when the regression coefficient was significant at a level of $P<0.05$ in at least 2 adjacent sectors or 3 nonadjacent sectors.[17]

Further, linear regression analyses were carried out using the sectored VFs that were mathematically determined by dividing the test locations of the HFA C30-2 program into 15 sectors correlating to the projection of retinal nerve fibers.[44] Linear regression analysis was performed on the mean TD of each sector (sector value), and several different criteria to judge progression were determined with regard to the number of sectors where the sector value showed a significantly negative slope with predetermined P values. The different criteria examined here were the significant negative slope of the sector value at (1) at least 1 sector, (2) at least 2 locally adjacent sectors, (3) at least 2 sectors that had high intersector correlation coefficients of more than 0.5,[44] (4) at least 2 sectors that had high intersector correlation coefficients of more than 0.6,[44] (5) any 2 adjacent or nonadjacent sectors, (6) at least 3 sectors, (7) at least 4 sectors, or (8) at least 5 sectors. The performance of each criterion was examined by continuously changing the P values for the statistical significance of negativeness of the slope fitted to the time change in sector values, and receiver operating characteristic (ROC) curves were drawn by computer (Fig 2). The ratios of making judgments of progression were compared among the aforementioned criteria when specificities were adjusted to 95% and 90%, respectively (Table 3).

In addition, ROC curves of the following 2 methods were drawn together for comparison: (1) a significantly negative TD slope in at least 1 test point and (2) a significantly negative MD slope (Fig 2). The P value for the significance of negativeness of the TD or MD slope was continuously changed as above.

The method used in the AGIS[34] was also tested in this study. Because the AGIS method was designed for data obtained with the HFA C24-2 program, the data of the test locations of the C24-2 program were extracted from the current VF test data performed by the C30-2 program. The AGIS scoring system, with scores ranging from 0 to 20, was based on the TD of each test location. The progression was determined by ≥4 increases in the score in 2 or 3 consecutive tests.

Using the data from the above 105 progressing OAG eyes, the ratio of making judgments of progression during the follow-up period was calculated with the above-mentioned methods, and the specificity was calculated using 10 000 eyes of simulated stable VFs.

Results

The ratio of making judgments of progression and the specificity of the methods examined in this study population are shown in Table 4. Two methods using the TD slope on 1 test location[13,14] gave very high ratios (0.914–1.000) but rather poor specificities (0.105–0.264). A method with more conservative criteria for the TD slope on 1 test location[15] and a method on 2 adjacent test locations[16] gave a reasonable ratio (0.848), with moderate specificities (0.721–0.722). The method using a significantly negative MD slope ($P<0.025$ or $P<0.05$) gave relatively low ratios (0.457 with $P<0.025$ and 0.524 with $P<0.05$), with high specificities as expected (0.972 with $P<0.025$ and 0.945 with $P<0.05$). The method based on VF sectors of Werner et al[17] gave a ratio of 0.695, with a high specificity, 0.946. The ratios given by the methods using 15 sectors in the central 30° visual field with varying criteria were compared among themselves, adjusting the specificity to 0.90 or 0.95, respectively (Table 3). The method with 4 significantly negative sector value slopes performed better than the others in this study population. The method with a significantly negative slope in at least 4 sectors (the 4-sector method) gave a ratio of 0.714 and a specificity of 0.950, with a P value of 0.078, indicating a significant negative slope of the sector, a ratio of 0.790, and a specificity of 0.90 with $P = 0.105$. The AGIS method gave rather conservative judgments of progression during the follow-up period, with a ratio of 0.305 to 0.467 and a very high specificity of 0.999 to 1.000.

Figure 2 shows the ROC curves of the methods with linear regression while the P value of significance was varied. The methods included a significant negative TD slope in at least 1 test location, MD slope, and the 4-sector method based on 15 sectors.[44] The ratios of making judgments of progression and specificity of the other previously reported methods assessed in the current study were also plotted in the same coordinates. The curve of the MD slope method was located apparently above that of the TD slope method in at least 1 test location. Most of the other methods currently assessed plotted below the curve of the MD slope; whereas methods based on the sectors of Werner and the AGIS plotted above the curve. The curve of the 4-sector method was located above that of the MD slope and all other methods currently assessed, except for the AGIS method.

Discussion

The most confounding problem in assessing the progression of VF defects is the fluctuation of test results. This is due to measurement error and psychophysical factors of patients, and consists of short- and long-term components.[1,4] It has been emphasized that repeated VF tests over a rather long time are needed to determine VF progression.[3,41,42,47]

Computer simulation of VF test results may be a reasonable approach to evaluate the performance of the methods to detect VF progression. Spry et al[42] described a computer model that simulates stable or progressive longitudinal VF test results of glaucoma with simulated short- and long-term fluctuation, and Gardiner and Crabb[41] investigated various criteria of pointwise linear regression analysis using simulated VFs, including fluctuations. Using simulated longitudinal VFs, they concluded that pointwise linear regression analyses tend to overestimate the probability of VF deterioration.[41,42] The simulated fluctuation at each test point depended on the threshold of the same point but was independent of other test points in their studies.[41,42] In glauco-

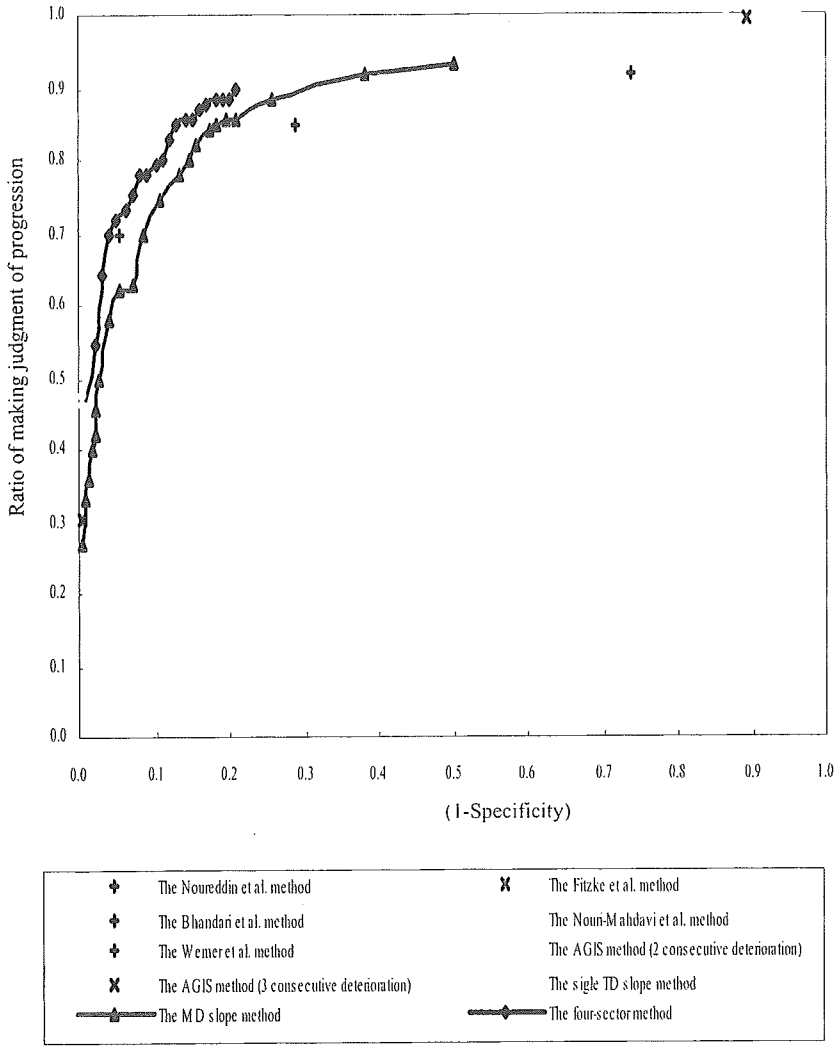

Figure 2. Receiver operating characteristic curve of the methods using a significant negative total deviation (TD) slope in at least 1 test location, that of the mean deviation (MD) slope and that of the 4-sector method, and ratios of making judgment of progression and specificity of other previously reported methods examined in this study (Noureddin et al,[13] Bhandari et al,[15] Werner et al,[17] Fitzke et al,[14] Nouri-Mahdavi et al,[16] Advanced Glaucoma Intervention Study [AGIS][34]).

matous VFs, there are high spatial correlations between not only the measured threshold values[44,48–51] but also fluctuations[51] at each test location, which were not incorporated into these methods of simulation.

In this study, we estimated not only the test–retest fluctuation at each test point, but also the intertest point correlation of TD values reflecting the geographical relationship of the test points; therefore, the results of the simulation should provide a more valid and realistic evaluation of proposed statistical methods.

Ten thousand series of stable VF test results was thought to be sufficient for assessment of specificity. The validity of the presently simulated stable VFs was assessed by the calculated specificity. The specificity of the MD slope method with a P value of 0.1 on the simulated stable VF series was 0.892 (α error, 0.108), that with a P value of 0.05 was 0.945 (α error, 0.055), and that with P=0.025 was 0.972 (α error, 0.028). As for the TD value at each test point, an α error of the negative TD slope method with a P value of 0.05 on each simulated VF test point ranged from 0.0451 to 0.0572 (0.0506 ± 0.0026 [average ± standard deviation]), and that with P=0.01 ranged from 0.0077 to 0.0124 (0.0102 ± 0.0010). The close relationship between the predetermined P values and α errors using the simulated VF series supports the following discussion.

Linear regression analysis on a series of TD values, determining progression with a significant negative TD slope in at least 1 test location, gave a very high ratio of the judgment of progression. This result is compatible with the previous result,[42] but may be partly attributed to the fact that the sensitivity in the present study was calculated using progressing VFs in which pointwise TD deterioration (the criterion of the Glaucoma Laser Trial Research Group) was one of the necessary conditions.

In addition, multiple statistical analyses on every test location increase the α error and thus need statistical ad-

Table 3. Comparison of Ratios of Making Judgments of Progression of the Methods Using 15 Sectors in the Central 30° Visual Field with Varying Criteria and the Methods Using the Total Deviation (TD) Slope or the Mean Deviation (MD) Slope, When the Specificities Were Adjusted to 0.90 and 0.95

Method to Determine Progression of Visual Field Defects	Specificity = 0.95	Specificity = 0.90
Significantly negative slope of TD	0.190 (CI, 0.115–0.265) $P = 0.0007$	0.343 (CI, 0.252–0.434) $P = 0.0014$
Significantly negative slope of MD	0.524 (CI, 0.428–0.620) $P = 0.0459$	0.676 (CI, 0.586–0.766) $P = 0.0924$
Significantly negative sector value slopes in at least one sector	0.410 (CI, 0.316–0.504) $P = 0.00324$	0.600 (CI, 0.506–0.694) $P = 0.00714$
Two adjacent sectors	0.657 (CI, 0.566–0.748) $P = 0.0365$	0.743 (CI, 0.659–0.827) $P = 0.0590$
Two sectors (correlation coefficients > 0.5)	0.590 (CI, 0.496–0.684) $P = 0.0390$	0.705 (CI, 0.618–0.792) $P = 0.0624$
Two sectors (correlation coefficients > 0.6)	0.524 (CI, 0.428–0.620) $P = 0.0450$	0.695 (CI, 0.607–0.783) $P = 0.0718$
Any 2 sectors	0.629 (CI, 0.537–0.721) $P = 0.0209$	0.781 (CI, 0.702–0.860) $P = 0.0329$
At least 3 sectors	0.638 (CI, 0.546–0.730) $P = 0.0457$	0.771 (CI, 0.691–0.851) $P = 0.0660$
At least 4 sectors	0.714 (CI, 0.628–0.800) $P = 0.0777$	0.790* (CI, 0.712–0.868) $P = 0.105$
At least 5 sectors	0.676 (CI, 0.586–0.766) $P = 0.113$	0.790* (CI, 0.712–0.868) $P = 0.147$

CI = 95% confidence interval.

Values are ratios of making judgments of progression and *P* values for the statistical significance of negativeness of the slope fitted to the time change of sector values when specificities are adjusted to 0.90 and 0.95, respectively.
*The highest diagnostic power, 0.169.

justment. According to the Bonferroni correction, the significant *P* value should be divided by the number of test locations if there were no correlations between threshold values among all test locations. When the *P* value was set to 0.000676 (0.05/74), the specificity of the negative TD slope method in at least 1 test location increased to 0.958, whereas the sensitivity was 0.170. The low sensitivity after Bonferroni's correction is partly attributed to the presence of correlation between thresholds or TD values between each test location,[44,48–51] and the fact that VF deterioration in

Table 4. Ratios of Making Judgments of Progression and Specificity of the Previously Described Methods Examined in This Study

		Ratio	Specificity	Diagnostic Power
Methods using the TD slope	Noureddin*	0.914 (CI, 0.860–0.968)	0.264 (CI, 0.255–0.273)	1.178
	Fitzke†	1.000 (CI, 1.000–1.000)	0.105 (CI, 0.099–0.111)	1.105
	Bhandari‡	0.848 (CI, 0.779–0.917)	0.721 (CI, 0.712–0.730)	1.568
	Nouri-Mahdavi§	0.848 (CI, 0.779–0.917)	0.722 (CI, 0.713–0.731)	1.569
Methods using the MD slope	MD slope ($P<0.1$)	0.743 (CI, 0.659–0.827)	0.892 (CI, 0.886–0.898)	1.635
	MD slope ($P<0.05$)	0.524 (CI, 0.428–0.620)	0.945 (CI, 0.941–0.949)	1.469
	MD slope ($P<0.025$)	0.457 (CI, 0.362–0.552)	0.972 (CI, 0.969–0.975)	1.429
Methods using visual field sectors	Wemer‖	0.695 (CI, 0.607–0.783)	0.946 (CI, 0.942–0.950)	1.641
Methods using original scoring systems	AGIS¶ score (≥4 increased scores in 2 consecutive tests)	0.467 (CI, 0.372–0.562)	0.999 (CI, 0.998–1.000)	1.466
	AGIS¶ score (≥4 increased scores in 3 consecutive tests)	0.305 (CI, 0.217–0.393)	1.000 (CI, 1.000–1.000)	1.305

CI = 95% confidence interval; MD = mean deviation; TD = total deviation.
*Noureddin BN, Poinoosawmy D, Fietzke [sic] FW, Hitchings RA. Regression analysis of visual field progression in low tension glaucoma. Br J Ophthalmol 1991;75:493–5.
†Fitzke FW, Hitchings RA, Poinoosawmy D, et al. Analysis of visual field progression in glaucoma. Br J Ophthalmol 1996;80:40–8.
‡Bhandari A, Crabb DP, Poinoosawmy D, et al. Effect of surgery on visual field progression in normal-tension glaucoma. Ophthalmology 1997;104:1131–7.
§Nouri-Mahdavi K, Brigatti L, Weitzman M, Caprioli J. Comparison of methods to detect visual field progression in glaucoma. Ophthalmology 1997;104:1228–36.
‖Werner EB, Bishop KI, Koelle J, et al. A comparison of experienced clinical observers and statistical tests in detection of progressive visual field loss in glaucoma using automated perimetry. Arch Ophthalmol 1988;106:619–23.
¶Advanced Glaucoma Intervention Study. 2. Visual field test scoring and reliability. Ophthalmology 1994;101:1445–55.

glaucoma eyes does not localize pointwise.[45,52] Modification of the negative TD slope method by Noureddin et al[13] and Fitzke et al[14] succeeded in obtaining high sensitivity, but specificity was thought to be unsatisfactory. Among the methods using TD slope presently examined, one with a more conservative significance level of $P<0.01$ in at least 1 test location[15] and one considering 2 adjacent test locations[16] showed reasonable ratios of making judgments of progression with moderate specificity. Those methods should have an advantage over other methods in detecting localized deterioration in VFs.

The MD slope method displayed a moderate ratio of making judgments of progression when the significance level was appropriately set. The specificity calculated using simulated VF test results was close to the expected value. The MD value is thought to be one of the most commonly used indexes in clinical practice to estimate the extent of VF damage, and the current results may favor the clinical usefulness of MD. It must be noted, however, that the sensitivity in the present study was calculated with presumably progressing VFs that were judged with predetermined criteria, including MD deterioration. This likely favored the sensitivity of the methods using MD.

In glaucoma, progression of VF damage takes place locally rather than over the entire VF.[45,52] The methods using sectors in the VF may have an advantage over the MD method in detecting localized damage and over TD methods in being less affected by variation at each test point.[12,16] In fact, the methods using sectored VFs performed better than the MD slope method (Fig 2), and the diagnostic power (a numerical sum of sensitivity and specificity of the method) of the method of Werner et al[17] was higher than that of any other previous method presently tested (Table 4).

The sensitivity of the AGIS method was thought to be low, as compatible with former reports.[38,39,43] However, it is possible that the value obtained here was an underestimation of the true performance of the AGIS method for the following reasons: the present actual VF series consisted of 6 VFs, and the AGIS score must increase by ≥4 by the forth or fifth VF to be considered as having progressed. In clinical practice, however, repeated VF tests at shorter intervals for confirmation were available. The AGIS method was designed to use the results of the HFA C24-2 program, but we used data extracted from the results of the C30-2 program in this study. It must be noted that the true performance of this method may be different from that obtained here. On the other hand, the AGIS method showed excellent specificity (0.999–1.000), although this may be an overestimation, for the same reason as discussed above. It is suggested that this method is suited for clinical cases or trials where rather aggressive intervention is planned and strict specificity is required in judging progression.

Among several approaches described to reduce the variation in VF test results, including a filtering process[53,54] or alternative VF test system,[32,55,56] sectoring VFs (clustering of several test points) into multiple sectors is a simpler procedure. The sum or average of the clustered threshold values is less affected by variation at each test point[51] and more sensitive than MD or other global indices to localized VF change. The clinical performance of this approach, such as the glaucoma hemifield tests,[57] has been well established.

We attempted to improve the performance of the sectoring method using mathematical sectored patterns previously presented by Suzuki et al[44] with varying criteria. Assuming a situation in which VF change is assessed to determine the necessity of additional more aggressive treatment or to compare the effectiveness of different treatment methods, specificity should be considered first. The 4-sector method gave a ratio of making judgments of progression of almost 0.8, at a specificity of 0.90, and a ratio of 0.71, at a specificity of 0.95, slightly higher than that given by the method of Werner et al[17] (Table 3).

The most optimal criteria for judging progression may vary with the type of glaucoma; disease stage; other eye conditions, including those of the other eye; or the manner of planned intervention itself. The performance of the criteria or methods shown in this study may not be directly applicable to other patient populations or conditions. For example, because the VFs of this study were in an earlier stage of the disease (Tables 1, 2), the present results may not be directly extrapolated to populations with a more advanced stage of the disease. Further, the sensitivity of each method would be somewhat different from the one presently calculated, if progressive glaucoma VFs were chosen under different criteria from the present one.

Despite these limitations, the results of this study and the specificity of each method should be useful in choosing a more suitable method of trend-type analysis in judging progression or nonprogression of VF damage of glaucoma. Methods using the TD slope with a relatively high sensitivity and a low specificity may be suited for studies with exploratory purposes. A method with very high specificity, such as the AGIS method, would be useful in studies requiring aggressive interventions. A method using linear regression analysis on VF sectors may have an advantage in clinical situations, giving information on local deterioration during follow-up as well as reasonable sensitivity–specificity by using all VF test results available during the follow-up.

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Appendix

We estimated the variance–covariance structure V (74×74 matrix) among 74 test locations from the clinical VF data of 355 stable glaucoma patients, except 2 points corresponding to blind spots. A part of the actual components of V is shown below.

$$V = \begin{pmatrix} 35.91 & 18.30 & 15.42 & 15.13 & \dots & 6.17 & 5.72 & 0.54 & 4.72 \\ 18.30 & 38.26 & 18.51 & 15.73 & \dots & 9.73 & 7.26 & 0.98 & 4.28 \\ \cdot & & & & & & & & \\ \cdot & & & & & & & & \\ \cdot & & & & & & & & \\ 0.54 & 0.98 & 5.30 & 1.96 & \dots & 15.43 & 15.13 & 31.69 & 20.35 \\ 4.72 & 4.28 & 6.63 & 2.86 & \dots & 17.14 & 17.00 & 20.35 & 35.13 \end{pmatrix}$$

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Alcohol consumption and other risk factors for self-reported diabetes among middle-aged Japanese: a population-based prospective study in the JPHC study cohort I

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Abstract

Aims Few prospective studies have examined the relationship between lifestyle characteristics and the incidence of diabetes mellitus in an Asian general population. This study was undertaken to evaluate the risk factors for Type 2 diabetes in a population-based prospective study of middle-aged Japanese.

Methods We investigated 12 913 men and 15 980 women, aged 40–59 years at baseline (year 0), who participated in the Japan Public Health Center-based prospective study on cancer and cardiovascular diseases (JPHC Study) Cohort I. The participants were followed for up to 10 years. Incident cases of diabetes were identified by self-reporting of a physician's diagnosis on two questionnaires sent to each participant, one at year 5 and the second at year 10.

Results During the 10-year follow-up, 703 men and 482 women reported newly diagnosed diabetes. Age, body mass index (BMI), family history of diabetes and cigarette smoking were independent risk factors in both genders by multivariate analysis. Among men with a BMI ≤ 22 kg/m^2, a significant positive association was observed between the diabetes incidence and moderate (23.0 < 46.0 g/day) to high (> 46.0 g/day) alcohol consumption, odds ratio 1.91 (95% CI, 1.05–3.46) and 2.89 (1.63–5.11), respectively. Among men with a BMI > 22 kg/m^2, a small non-significant increase in odds ratio was observed with alcohol consumption.

Conclusions Established risk factors for diabetes in western populations were also identified as predictors of the disease among Japanese. Moderate to high alcohol consumption was positively associated with the incidence of diabetes in Japanese lean (BMI ≤ 22 kg/m^2) men.

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Keywords diabetes mellitus, prospective study, risk factor

Abbreviations BMI, body mass index; CI, confidence interval; JPHC, Japan Public Health Center-based prospective study on cancer and cardiovascular diseases; OR, odds ratio; PHC, public health centre

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Introduction

Type 2 diabetes is associated with a genetic predisposition [1], but is also strongly influenced by lifestyle-related factors, such as eating habits and/or physical activity [2,3]. Japanese immigrants residing in the United States and Brazil, with a westernised lifestyle but a genetic background such as siblings in their homeland, have a higher prevalence of diabetes than Japanese people living in the Far East [4–7].

However, the situation may now have changed. The prevalence of diabetes has increased dramatically in many Asian nations over the past decades [8], including Japan, possibly because of changes from a traditional to a westernised lifestyle. Prevention of diabetes through suitable lifestyle modifications is an urgent health issue in this area of the world. Thus, it is important to evaluate the risk factors for diabetes in Asian general populations to determine whether the risk factors established in western populations [2,3] also apply to Asian ethnic groups. This will help to determine whether the strategies that have proven effective in Western countries can be applied to Asians. Few published studies have attempted to answer this question by a direct comparison of the influence of lifestyles on the future development of diabetes. Some have been cross-sectional [9,10] or, despite being longitudinal, were conducted in subjects who did not represent the general population [11–16]; others were too short to be reliable [17].

To quantify the risk factors for diabetes in a general Japanese population, we conducted a community-based, prospective cohort study on a relatively large number of middle-aged adults with an adequate follow-up period.

Patients and methods

The Japan Public Health Center-based prospective study on cancer and cardiovascular diseases (JPHC Study) is an ongoing, longitudinal cohort study, investigating cancer, cardiovascular diseases and other lifestyle-related diseases. The total cohort has been divided into two, Cohort I and Cohort II [18], and the current study was conducted within the population-based part of Cohort I (the other smaller part consists of health check-up examinees), namely those residents who registered their address in one of 14 administrative districts supervised by four public health centres: the city of Ninohe and the town of Karumai in the Ninohe Public Health Center (PHC) area of Iwate Prefecture, the city of Yokote and the town of Omonogawa in the Yokote PHC area of Akita Prefecture, eight districts in Minami-Saku County in the Saku PHC area of Nagano Prefecture, and the city of Gushikawa and village of Onna in the Ishikawa PHC area of Okinawa Prefecture. The criteria for selecting the areas, subjects, and the methods of data collection have been reported previously [18,19]. This study was approved by the institutional review board of the National Cancer Center of Japan.

Participants

Briefly, 43 149 individuals (20 665 men and 22 484 women), aged 40–59 years at baseline, completed the baseline questionnaire upon enrolment in 1990 (year 0; response rates: 76% for men and 82% for women). Follow-up questionnaires were sent to each individual at years 5 and 10, and a total of 32 126 individuals (14 551 men and 17 575 women) returned both follow-up questionnaires (total follow-up rate: 74.5%; 70.4% for men and 78.2% for women). To construct the cohort for the current analysis, we excluded individuals who had any of the following conditions at baseline: diabetes (n = 1120; 742 men and 378 women), cardiovascular disease (n = 470; 257 men and 213 women), chronic liver disease (n = 311; 215 men and 96 women), kidney disease (n = 546; 214 men and 332 women) or cancer (n = 689; 205 men and 484 women). Individuals who had missing baseline data for any of the exposure parameters described below were also excluded (n = 298; 121 men and 177 women). After these exclusions, the remaining cohort consisted of 28 893 participants (12 913 men and 15 980 women) with data on incident diabetes.

Data collection

Each participant completed a self-administered questionnaire that included questions regarding weight and height, usual pattern of physical activity, smoking habits, alcohol intake, previously diagnosed medical conditions (including diabetes and hypertension), family history of diabetes, use of drugs, and other lifestyle factors. Subjects were classified according to smoking habit as 'never smoked', 'former smokers', and 'current smokers'; the last group was subdivided into two groups according to the number of cigarettes smoked daily: 1–19 or ≥ 20 cigarettes/day. Questions on alcohol intake included items about the types of alcoholic beverages consumed, the frequency of alcohol consumption (per week), and the usual amount of alcohol consumed daily. Total daily alcohol intake was calculated by multiplying the frequency of consumption by the alcohol content of the beverage: 23 g ethanol per 180 ml of Japanese sake (rice wine), 36 g ethanol per 180 ml of shochu or awamori (both Japanese distilled liquors), 10 g ethanol per 30 ml of whisky or brandy, 6 g ethanol per 60 ml of wine and 23 g ethanol per 633 ml of beer. According to their current drinking behaviour, the subjects were classified into two groups: 'non-drinkers and infrequent occasional drinkers (who consume alcohol on three or fewer days per month)' and 'drinkers'. The 'drinkers' category was further subdivided by the tertiles of daily ethanol consumption. We previously reported that this questionnaire was found to measure average alcohol consumption with a high degree of validity [19]. Physical activity was assessed using the replies to questions regarding the number of times per week or month that the subject engaged in sports activities during leisure time. Subjects were considered physically active if they participated in sports at least once a week; all other subjects were considered inactive. A history of hypertension was considered to exist if the subject had been informed of a diagnosis of hypertension by a doctor and/or was receiving a prescription for anti-hypertensive drug(s). The prevalence of hypertension as documented using the self-administered questionnaire was verified in a subpopulation of the cohort for whom health check-up data were available. In this subpopulation, documented hypertension was confirmed in 90.2% (1989/2204) of the subjects, i.e. those 1989 subjects fulfilled at least one of the following criteria: (i) systolic blood pressure ≥ 140