Original Article

Insulin Resistance and the Development of Cardiovascular Disease in a Japanese Community: the Hisayama Study

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Aims: Although several surrogate measures of insulin resistance have been proposed, their associations with cardiovascular disease (CVD) have not been evaluated sufficiently.
Methods: A total of 2,356 community-dwelling Japanese individuals aged 40 to 79 years who underwent a 75 g oral glucose tolerance test were followed up for 14 years. The status of insulin resistance was estimated by using the Matsuda index or homeostasis model assessment of insulin resistance (HOMA-IR).
Results: During follow-up, 260 subjects developed CVD. The age- and sex-adjusted hazard ratios of CVD significantly decreased with an increasing Matsuda index and rose with increasing HOMA-IR levels (both p for trend <0.05). After adjustment for age, sex, serum total cholesterol, electrocardiogram abnormalities, proteinuria, smoking habits, alcohol intake, and regular exercise, the risk of CVD was significantly lower in the third to fifth quintiles of the Matsuda index and higher in the fifth quintile of HOMA-IR values compared with the first quintile of the corresponding index (Matsuda index Q3: hazard ratio (HR)=0.59 [95% confidence interval 0.40-0.87]; Q4: HR=0.66 [0.45-0.97]; and Q5: HR=0.67 [0.47-0.97]; HOMA-IR Q5: HR=1.55 [1.05-2.29]); however, these associations were attenuated after further adjustment for the metabolic syndrome status. In regard to CVD subtypes, the risks for stroke and coronary heart disease significantly decreased with an increasing Matsuda index, while elevated HOMA-IR levels were a significant risk factor for stroke, but not for coronary heart disease.
Conclusion: Our findings suggest that insulin resistance significantly increases the risk of incident CVD through metabolic syndrome in Japanese.

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Key words; Epidemiology, Cardiovascular disease, Insulin resistance, Cohort study, General populations

Introduction

Insulin resistance and compensatory hyperinsulinemia are closely related to obesity and are considered to be the underlying features of elevated blood pressure[1,2] and metabolic disorder, including impaired glucose tolerance[3,4] and dyslipidemia[5,6], which are collectively identified as metabolic syndrome (MetS)[7]. Prospective population-based studies have shown that subjects with MetS had a significantly higher risk of incident cardiovascular disease (CVD)[8-10], but the association between CVD and insulin resistance itself is less clear. Several surrogate indices have been proposed to evaluate insulin resistance[11-13], because the glucose clamp method, the gold standard for the measurement of insulin resistance, is impractical for use in clinical and epidemiological studies. Homeostasis model assessment of insulin resistance (HOMA-IR), derived from fasting glucose and insulin values, has a strong correlation with insulin sensitivity directly measured by the euglycemic hyperinsulinemic clamp

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method[11, 14] and has been commonly used as a surrogate index of insulin resistance; however, it is uncertain whether insulin resistance estimated by HOMA-IR values is significantly associated with incident CVD[15-22]. Matsuda *et al.* proposed an index of insulin sensitivity calculated by measuring glucose and insulin levels before and after oral glucose loading[12, 13]. Although the Matsuda index also correlates well with directly measured insulin resistance[12, 23], to our knowledge, no prior prospective study has evaluated the association between the Matsuda index and incident CVD.

The purpose of this study was to investigate the associations of the Matsuda index and HOMA-IR levels with the development of CVD in a cohort study of a Japanese population, taking into account various comprehensive risk factors, including the MetS status.

Methods

Study Population

The Hisayama Study is a long-term prospective population-based cohort survey of CVD and its risk factors. It was begun in 1961 in Hisayama, a town of approximately 8,000 people located in a suburb of the Fukuoka metropolitan area on Kyushu Island, Japan[24]. In 1988, a screening survey for the present study was performed in the town. A detailed description of this study has been published previously[25]. In brief, 2,587 residents aged 40 to 79 years (80.2% of the total population of this age range) consented to participate in the examination. After exclusion of 82 subjects who had already had breakfast, 10 who were receiving insulin therapy for diabetes, and 15 who refused a 75-g oral glucose tolerance test (OGTT) due to complaints of nausea or general fatigue during the ingestion of glucose, 2,480 subjects completed the OGTT. Among these, 2 subjects who had died before the start of follow-up, 60 with a past history of stroke or coronary heart disease, 3 for whom either fasting or 2-hour postload insulin levels were not obtained, and 59 who were taking oral hypoglycemic agents were excluded, and the remaining 2,356 subjects (1,006 men and 1,350 women) were included in this study.

Follow-Up Survey

The baseline subjects were followed up prospectively for 14 years from December 1988 through November 2002 by repeated health examinations. The health status was checked yearly by mail or telephone for subjects who did not undergo a regular examination or who had moved out of town. We also established a daily monitoring system among the study team, local physicians, and members of the town's Health and Welfare Office. Using this system, we gathered information on new events of CVD, including suspected cases. When stroke or coronary heart disease occurred or was suspected, physicians in the study team examined the subject and evaluated his/her detailed clinical information. When a subject died, an autopsy was performed in the Department of Pathology of Kyushu University. During the follow-up period, one subject was lost to follow-up and 393 subjects died, of whom 292 subjects (74.3%) underwent autopsy examination.

Definition of Cardiovascular Events

In the present study, incident CVD was defined as the development of stroke or coronary heart disease. Stroke was defined as the sudden onset of nonconvulsive and focal neurological deficit persisting for >24 hours. The diagnosis of stroke was based on the clinical history, neurological examination, all available clinical data, including brain computed tomography and magnetic resonance imaging, and autopsy findings. Coronary heart disease included acute myocardial infarction, silent myocardial infarction, sudden cardiac death within 1 hour after the onset of acute illness, and coronary artery disease treated by coronary artery angioplasty or bypass grafting. Acute myocardial infarction was diagnosed when a subject met at least 2 of the following criteria: 1) typical symptoms, including prolonged severe anterior chest pain; 2) cardiac enzyme levels more than twice the upper limit of the normal range; 3) evolving diagnostic electrocardiographic changes; and 4) morphological changes, including local asynergy of cardiac wall motion on echocardiography, perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars ≥1 cm long accompanied by coronary atherosclerosis at autopsy. Silent myocardial infarction was defined as myocardial scarring without any historical indication of clinical symptoms and/or abnormal cardiac enzyme changes. During the 14-year follow-up, 260 subjects experienced a first-ever CVD event (139 men and 121 women). Of these, 183 had stroke events (83 men and 100 women) and 98 developed coronary heart disease (68 men and 30 women).

Risk Factors

At the baseline examination, after an overnight fast of at least 12 hours, the OGTT was performed with blood samples taken at 0 and 120 min. Plasma glucose levels were determined by the glucose-oxidase method. Serum insulin levels were determined by a commercial double-antibody solid-phase radioimmu-

noassay (Phadeseph Insulin; Pharmacia Diagnostics AB, Uppsala, Sweden). Insulin sensitivity was evaluated by the Matsuda index, calculated as 10,000 per square root of [fasting glucose (mg/dL) × fasting insulin (μU/mL) × postload glucose (mg/dL) × postload insulin (μU/mL)] according to the previously reported method[13]. Insulin resistance was estimated by HOMA-IR values, calculated as [fasting plasma glucose (mg/dL) × fasting serum insulin (μU/mL)] / 405[11]. Diabetes was defined as fasting plasma glucose concentrations of ≥7.0 mmol/L (126 mg/dL), 2-hour postload glucose concentrations of ≥11.1 mmol/L (200mg/dL), and/or the use of antidiabetic medication. Serum total and high-density lipoprotein (HDL) cholesterols and triglyceride concentrations were determined enzymatically. Freshly voided urine samples were collected at the screening, and proteinuria was defined as a value of 1+ or more using a reagent strip.

Waist circumference was measured by a trained staff member at the umbilical level with the subject standing. Blood pressure was measured 3 times using a standard mercury sphygmomanometer in the sitting position after at least 5 minutes of rest. The mean of the 3 measurements was used in the analysis. Hypertension was defined as blood pressure ≥140/90 mmHg and/or current treatment with antihypertensive agents.

Electrocardiogram (ECG) abnormalities were defined as left ventricular hypertrophy (Minnesota Code, 3-1), ST depression (4-1, 2, 3), and/or atrial fibrillation (8-3).

Information on alcohol consumption, smoking habits, and physical activity during leisure time was obtained by the use of a self-administered questionnaire. We also asked whether subjects were taking antihypertensive agents, oral hypoglycemic agents and/or insulin. Alcohol consumption and smoking status were classified as either current use or not. Subjects engaging in sports at least 3 times per week during their leisure time were defined as a regular exercise group.

Subjects were diagnosed as having MetS if 3 or more of the following components were present at baseline: 1) waist circumference ≥90 cm in men and ≥80 cm in women; 2) fasting triglyceride concentrations ≥150 mg/dL (1.7 mmol/L); 3) HDL cholesterol concentrations <40 mg/dL (1.0 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women; 4) blood pressure ≥130/85 mmHg or use of antihypertensive drugs; and 5) fasting plasma glucose ≥100 mg/dL (5.6 mmol/L) or use of antidiabetic medications[26].

Statistical Analysis

The SAS software package version 9.2 (SAS Institute Inc., Cary, NC) was used to perform all statistical analyses. The Matsuda index, HOMA-IR values, fasting plasma insulin, 2-hour postload insulin, and serum triglyceride levels were transformed into logarithms to improve the skewed distribution. The frequencies of possible risk factors at baseline were adjusted for age and sex by a direct method and compared by logistic regression analysis. The age- and sex-adjusted mean values of risk factors at baseline were estimated and compared by analysis of covariance. To analyze the Matsuda index and HOMA-IR values as categorical variables, these levels were divided into sex-specific quintiles: Matsuda index: men, Q1, 0.88 to 4.03; Q2, 4.04 to 6.21; Q3, 6.22 to 8.77; Q4, 8.78 to 13.73; and Q5, 13.74 to 59.72; women, Q1, 0.47 to 4.06; Q2, 4.07 to 5.74; Q3, 5.75 to 7.82; Q4, 7.83 to 10.99; and Q5, 11.00 to 49.21; HOMA-IR: men, Q1, 0.53 to 0.78; Q2, 0.79 to 1.17; Q3, 1.18 to 1.58; Q4, 1.59 to 2.22; and Q5, 2.23 to 16.79; women, Q1, 0.55 to 0.90; Q2, 0.91 to 1.25; Q3, 1.26 to 1.61; Q4, 1.62 to 2.20; and Q5, 2.21 to 15.24. The incidence rates of CVD were calculated by the person-year method and were adjusted for age and sex by the direct method using 10-year age groupings of the overall study population. The age- and sex-adjusted or multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with the use of the Cox proportional hazards model. The linear trends of HRs across the Matsuda index and HOMA-IR levels were also tested using the Cox proportional hazards model. $P<0.05$ was considered significant in all analyses.

Ethical Considerations

This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Research, and written informed consent was obtained from the participants.

Results

The baseline characteristics of subjects stratified by the presence or absence of incident CVD are shown in **Table 1**. The mean values of age, HOMA-IR, fasting and 2-hour postload glucose, fasting plasma insulin, and systolic and diastolic blood pressures, and the frequencies of men, MetS, diabetes, hypertension, ECG abnormalities, proteinuria, and smoking were higher in subjects who developed CVD than in those who did not. In addition, subjects with incident CVD had lower Matsuda index values and a lower frequency of regular exercise. No differences were observed between subjects with and without

Table 1. Age- and sex-adjusted baseline clinical characteristics of subjects with or without incident cardiovascular disease, 1988

	Incident CVD $n=260$	No incident CVD $n=2,096$	p
Age, years	64 (0.6)	56 (0.2)	<0.001
Men, %	56.3	41.3	<0.001
Fasting plasma glucose, mmol/L	6.0 (0.07)	5.7 (0.03)	<0.001
Two-hour postload glucose, mmol/L	8.1 (0.19)	7.1 (0.07)	<0.001
Fasting plasma insulin, pmol/L	43.6 (41.1-46.3)	40.3 (39.4-41.2)	0.01
Two-hour postload insulin, pmol/L	223.4 (204.1-244.5)	208.9 (202.1-216.0)	0.18
Matsuda index	6.2 (5.7-6.7)	7.0 (6.8-7.3)	0.003
HOMA-IR	1.6 (1.5-1.7)	1.4 (1.38-1.45)	0.002
Diabetes mellitus, %	20.0	9.1	0.001
Waist circumference, cm	82.5 (0.6)	81.3 (0.2)	0.05
Systolic blood pressure, mmHg	141.0 (1.2)	131.9 (0.4)	<0.001
Diastolic blood pressure, mmHg	80.6 (0.7)	77.3 (0.3)	<0.001
Hypertension, %	55.0	36.0	<0.001
Total cholesterol, mmol/L	5.35 (0.07)	5.31 (0.02)	0.57
HDL-cholesterol, mmol/L	1.27 (0.02)	1.30 (0.01)	0.17
Triglycerides, mmol/L	1.25 (1.17-1.33)	1.18 (1.15-1.21)	0.14
Metabolic syndrome, %	49.8	32.6	<0.001
ECG abnormalities, %	23.3	15.5	0.03
Proteinuria, %	8.0	5.2	0.02
Current smoking, %	31.4	24.4	0.02
Current drinking, %	36.9	31.6	0.35
Regular exercise, %	5.3	10.5	0.02

CVD: cardiovascular disease; HOMA-IR: homeostasis model assessment of insulin resistance; HDL: high-density lipoprotein; ECG: electrocardiogram. Values are given as the means (standard error) or as a percentage. Matsuda index, HOMA-IR, fasting plasma insulin, 2-hour postload insulin, and triglycerides are shown as the geometric means and 95% confidence intervals due to the skewed distribution. Hypertension: blood pressures of ≥140/90 mmHg and/or current use of antihypertensive medicine. Diabetes: fasting ≥7.0 mmol/L, 75 g postload or postprandial glucose levels ≥11.1 mmol/L, and/or use of hypoglycemic agents. ECG abnormalities: left ventricular hypertrophy (Minnesota Code 3-1), ST depression (4-1, 2, or 3), and/or atrial fibrillation (8-3).

CVD in the mean values of 2-hour postload insulin, waist circumference, total cholesterol and HDL cholesterols, and triglycerides and the frequency of alcohol intake.

Compared with those within the first quintile of the Matsuda index, the age- and sex-adjusted HR for the development of CVD significantly decreased in subjects in the third to fifth quintiles (model 1 of **Table 2**). As shown in model 2 for the Matsuda index, this association remained unchanged even after adjustment for age, sex, serum total cholesterol, ECG abnormalities, proteinuria, smoking, alcohol intake, and regular exercise (Q3: multivariable-adjusted HR 0.59, 95% CI 0.40 to 0.87, $p=0.008$; Q4: HR 0.66, 95% CI 0.45 to 0.97, $p=0.03$; Q5: HR 0.67, 95% CI 0.47 to 0.97, $p=0.04$). On the other hand, the age- and sex-adjusted HR for CVD was significantly higher in subjects in the fifth quintile of HOMA-IR than in those in the first quintile. This association also remained robust even after adjustment for the aforementioned confounding factors (Q5: HR 1.55, 95% CI 1.05 to 2.29; $p=0.03$). However, these associations between the Matsuda index or HOMA-IR and CVD outcomes were attenuated and became non-significant after further adjustment for the MetS status (model 3). By contrast, MetS was a significant risk factor for CVD events in the model 3 for both indices (for the Matsuda index: HR, 1.53, 95% CI 1.15 to 2.04; $p=0.003$; for HOMA-IR: HR, 1.57, 95% CI 1.19-2.08; $p=0.002$). Similar findings were also observed for a 1 SD increment in the Matsuda index and HOMA-IR values as continuous variables.

In **Table 3**, when CVD was divided into stroke and coronary heart disease, the age- and sex-adjusted incidences and HRs for stroke and coronary heart disease significantly decreased with increasing Matsuda index (p for trend <0.05). By contrast, elevated HOMA-IR levels were a risk factor for stroke, but not

Table 2. Age- and sex-adjusted incidences and adjusted hazard ratios and their 95% confidence intervals of cardiovascular disease according to quintiles of the Matsuda index and HOMA-IR levels, 1988-2002

	Quintile level of insulin resistance					*p* for trend (across categories)	Continuous log scale*	*p* for trend (continuous)
	Q1	Q2	Q3	Q4	Q5			
Matsuda index								
No. of events	73	56	39	43	49			
Population at risk	471	471	473	470	471			
Incidence per 1,000 person-years	13.0	10.6	7.6	8.2	8.9			
Model 1 HR (95% CI)	1.00 (reference)	0.78 (0.55 to 1.10)	0.53 (0.36 to 0.78)	0.60 (0.41 to 0.88)	0.65 (0.45 to 0.93)	0.006	0.75 (0.63 to 0.89)	0.001
Model 2 HR (95% CI)†	1.00 (reference)	0.86 (0.61 to 1.22)	0.59 (0.40 to 0.87)	0.66 (0.45 to 0.97)	0.67 (0.47 to 0.97)	0.01	0.76 (0.64 to 0.91)	0.003
Model 3 HR (95% CI)‡	1.00 (reference)	0.96 (0.67 to 1.37)	0.68 (0.45 to 1.02)	0.82 (0.55 to 1.23)	0.87 (0.58 to 1.31)	0.33	0.86 (0.71 to 1.05)	0.14
HOMA-IR								
No. of events	45	52	48	52	63			
Population at risk	467	479	468	474	468			
Incidence per 1,000 person-years	8.1	9.4	9.6	9.7	11.6			
Model 1 HR (95% CI)	1.00 (reference)	1.14 (0.76 to 1.69)	1.13 (0.76 to 1.70)	1.18 (0.79 to 1.76)	1.63 (1.11 to 2.39)	0.02	1.45 (1.17 to 1.78)	0.02
Model 2 HR (95% CI)†	1.00 (reference)	1.19 (0.80 to 1.78)	1.20 (0.80 to 1.81)	1.28 (0.85 to 1.94)	1.55 (1.05 to 2.29)	0.03	1.41 (1.14 to 1.74)	0.001
Model 3 HR (95% CI)‡	1.00 (reference)	1.15 (0.77 to 1.72)	1.09 (0.72 to 1.65)	1.11 (0.73 to 1.68)	1.19 (0.77 to 1.81)	0.55	1.23 (0.98 to 1.56)	0.08

HR: hazard ratio; CI: confidence interval; HOMA-IR: homeostasis model assessment of insulin resistance.
*HR for 1 standard deviation increase of the log Matsuda index or log HOMA-IR.
Model 1: adjustment was made for age and sex.
Model 2: adjustment was made for age, sex, total cholesterol, electrocardiogram abnormalities, proteinuria, smoking habits, alcohol intake, and regular exercise.
Model 3: adjustment was made for the variables used in Model 2 and metabolic syndrome.

for coronary heart disease.

Discussion

Using data from a 14-year follow-up study of a general Japanese population, we found that surrogate indices of insulin resistance, the Matsuda index and HOMA-IR levels were clearly involved in the development of CVD after adjustment for confounding factors. In regard to CVD subtypes, the Matsuda index was a risk factor for the development of both stroke and coronary heart disease, while HOMA-IR levels were associated only with stroke incidence; however, these associations were attenuated after further adjustment for MetS status.

The strong associations between insulin resistance and cardiovascular risk factors, including metabolic abnormalities, are well known; however, studies on the influence of directly measured insulin sensitivity on the risk of CVD are limited: only a prospective cohort study in Sweden has revealed a significant inverse association between insulin sensitivity measured by an euglycemic insulin clamp and CVD risk[27, 28]. The methods used to directly measure insulin sensitivity are invasive, complex, and generally too expensive for clinical practice. Thus, some surrogate indices have been developed using insulin and/or glucose levels in the fasted state alone or in combination with insulin and glucose levels on the OGTT. Among these, HOMA-IR levels based on fasting measurements have been most commonly used as a surrogate marker of insulin resistance in epidemiological studies, but findings on the association between HOMA-IR and incident CVD have been inconsistent[15-22]. On the other hand, the Matsuda index derived from OGTT samples has been reported to show the strongest correla-

Table 3. Age- and sex-adjusted incidences and hazard ratios and their 95% confidence intervals of stroke and coronary heart disease according to quintiles of the Matsuda index and HOMA-IR levels, 1988-2002

	Quintile level of insulin resistance					*p* for trend (across categories)	Continuous log scale*	*p* for trend (continuous)
	Q1	Q2	Q3	Q4	Q5			
Stroke								
Matsuda index								
No. of events	55	33	29	31	35			
Incidence per 1,000 person-years	9.8	6.2	5.7	5.7	6.1			
Age- and sex-adjusted HR (95% CI)	1.00 (reference)	0.62 (0.40 to 0.95)	0.53 (0.34 to 0.84)	0.59 (0.38 to 0.91)	0.63 (0.41 to 0.96)	0.03	0.76 (0.61 to 0.94)	0.01
HOMA-IR								
No. of events	33	34	33	36	47			
Incidence per 1,000 person-years	5.9	5.9	6.4	6.6	8.6			
Age- and sex-adjusted HR (95% CI)	1.00 (reference)	1.00 (0.62 to 1.62)	1.05 (0.65 to 1.70)	1.11 (0.69 to 1.79)	1.62 (1.03 to 2.52)	0.03	1.47 (1.14 to 1.88)	0.003
Coronary heart disease								
Matsuda index								
No. of events	25	26	14	17	16			
Incidence per 1,000 person-years	4.0	4.7	2.5	3.3	3.0			
Age- and sex-adjusted HR (95% CI)	1.00 (reference)	1.01 (0.58 to 1.75)	0.52 (0.27 to 1.00)	0.69 (0.37 to 1.28)	0.59 (0.31 to 1.10)	0.04	0.71 (0.53 to 0.94)	0.02
HOMA-IR								
No. of events	18	21	19	17	23			
Incidence per 1,000 person-years	3.1	3.9	3.7	3.1	3.8			
Age- and sex-adjusted HR (95% CI)	1.00 (reference)	1.16 (0.62 to 2.17)	1.16 (0.62 to 2.17)	0.98 (0.50 to 1.89)	1.59 (0.86 to 2.96)	0.28	1.38 (0.98 to 1.95)	0.07

HR: hazard ratio; CI: confidence interval; HOMA-IR: homeostasis model assessment of insulin resistance.
*HR for 1 standard deviation increase of the log Matsuda index or log HOMA-IR.

tions with directly measured insulin sensitivity among surrogate indices[12, 13, 23]; however, it is not known if the Matsuda index is associated with the development of incident CVD. To our knowledge, this is the first population-based prospective study reporting the association of the Matsuda index with incident CVD. Our results showed that the elevated Matsuda index levels were significantly and inversely associated with the risk of stroke and coronary heart disease, while HOMA-IR levels were a risk factor for the development of stroke, but not for coronary heart disease. These findings imply that the measurement of Matsuda index levels might be more valuable for identifying individuals at high risk of CVD than the measurement of HOMA-IR levels.

Although the precise reasons are not clear, one possible explanation for the finding that the Matsuda index was more strongly associated with the risk of coronary heart disease than with HOMA-IR levels is as follows. HOMA-IR values are derived from fasting plasma glucose and insulin concentrations[11]. Since hepatic glucose production is the primary determinant of fasting plasma glucose concentrations[29], and fasting plasma insulin concentrations are the primary regulator of hepatic glucose production[30], the parameters of fasting plasma glucose and serum insulin, such as HOMA-IR, may reflect mainly hepatic insulin resistance. This hypothesis has been confirmed in a study of subjects who received tritiated glucose to measure hepatic glucose production[31]. On the other hand, the Matsuda index calculated from the OGTT is likely to represent insulin resistance of the whole body, which consists mainly of a combination of hepatic and muscle insulin resistance[12]. Thus, a stronger association of

the Matsuda index with coronary heart disease might be observed, since the Matsuda index more accurately reflects insulin resistance than HOMA-IR levels[32].

In our study, both surrogate indices of insulin resistance, the Matsuda index and HOMA-IR levels, were significantly involved in the development of CVD, but these associations were attenuated after further adjustment for MetS status. MetS has also been used as a surrogate measure of the insulin resistance phenotype and as a practical tool for identifying individuals at high risk of CVD. To date, prospective studies in several different communities have examined the associations between MetS and the risk of CVD, but there has been controversy over whether MetS captures all CVD risks associated with insulin resistance. In some epidemiological studies of Western populations, CVD risk significantly increased along with the elevations in surrogate indices of insulin resistance, even after adjusting for MetS and other cardiovascular risk factors[17-22]. On the other hand, in a Chinese population, insulin resistance indices including HOMA-IR levels were also associated with CVD risk, but these associations disappeared after adjustment for MetS[15]. These findings were in accordance with ours. Although the reason for this difference among the studies is unclear, the diversity of insulin resistance levels among races might explain it. Insulin resistance results in a spectrum of metabolic disturbances that includes inflammation[33], endothelial dysfunction[34], and hypercoagulability[35] in addition to the MetS status. For example, Asians have been shown to have much lower levels of systemic inflammation than other ethnic groups[36]. Thus, pathways other than MetS in the insulin resistance state might play more important roles in the development of CVD in Western populations.

The strengths of our study include its longitudinal population-based study design, long duration of follow-up, complete follow-up of subjects, sufficient number of cardiovascular events, and accuracy of the diagnosis of CVD, including stroke and coronary heart disease. However, two limitations of our study should be discussed. The primary limitation is that our findings were based on a single measurement of plasma glucose and insulin concentration, as was the case in other epidemiological studies. During follow-up, risk factor levels could have changed due to modifications of lifestyle or medication, and thus misclassification of insulin resistance was possible. However, this source of variability could not account for the associations observed in the present study, because a random misclassification of this nature would tend to cause an underestimation of study findings and bias the results toward the null hypothesis. Thus, the true association could be stronger than that observed in our study. Another limitation is that the values of the Matsuda index were not derived from 5 times of sampling, as reported in the initial publication of the index, but rather were calculated using samples from only 0 and 120 min; however, DeFronzo *et al.* reported that the Matsuda index calculated using 2-point samples, 0 and 120 min, had a strong correlation with the values determined by the original method[13]. If the calculation using 2-point samples were inferior to that of full-point samples, this would also weaken the association found in this study. Thus, we believe that such a bias does not invalidate the present findings.

In conclusion, the present analysis clearly showed that elevated insulin resistance indices estimated by the Matsuda index and HOMA-IR levels were significant risk factors for the incidence of CVD in a Japanese community. The measurement of these indices may help to identify individuals at high risk of CVD. Further studies are needed to investigate the associations between these indices and CVD.

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Disclosures

The authors report no conflicts of interest.

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Article: Epidemiology

Cut-off values of fasting and post-load plasma glucose and HbA_{1c} for predicting Type 2 diabetes in community-dwelling Japanese subjects: the Hisayama Study

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Abstract

Aims We examined the optimal cut-off values of fasting plasma glucose, 2-h post-load glucose and HbA_{1c} for predicting Type 2 diabetes in community-dwelling Japanese subjects.

Methods A total of 1982 subjects without diabetes aged 40–79 years who underwent a 75-g oral glucose tolerance test were followed prospectively for 14 years by annual health examination.

Results During the follow-up, 295 subjects developed Type 2 diabetes. Compared with the first decile, the crude hazard ratio for incident Type 2 diabetes was significantly higher in the fifth fasting plasma glucose decile [5.4–5.4 mmol/l (97–98 mg/dl)] or higher, in the seventh 2-h post-load glucose decile [6.9–7.2 mmol/l (124–131 mg/dl)] or higher, and in the fifth HbA_{1c} decile [34–36 mmol/mol (5.3–5.4%)] or higher. These associations remained substantially unchanged even after adjustment for confounding factors. The receiver operating characteristic curve analysis showed that the optimal cut-off values for predicting Type 2 diabetes were 5.6 mmol/l (101 mg/dl) for fasting plasma glucose, 6.9 mmol/l (124 mg/dl) for 2-h post-load glucose and 37 mmol/mol (5.5%) for HbA_{1c}. In a stratified analysis, the cut-off values were approximately 5.6 mmol/l (101 mg/dl) for fasting plasma glucose and 37 mmol/mol (5.5%) for HbA_{1c}, and these values were unchanged over BMI quartile levels, whereas the 2-h post-load glucose cut-off values declined with decreasing BMI levels.

Conclusions Our findings suggest that the cut-off value for predicting Type 2 diabetes in the Japanese population is 5.6 mmol/l (101 mg/dl) for fasting plasma glucose and 37 mmol/mol (5.5%) for HbA_{1c}, while the 2-h post-load glucose cut-off value is lower than the diagnostic criterion for impaired glucose tolerance.

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Keywords diabetes, epidemiology, HbA_{1c}, impaired fasting glucose, impaired glucose tolerance

Introduction

In 2003, the fasting plasma glucose cut-off value for diagnosing impaired fasting glucose was reduced from 6.1 to 5.6 mmol/l (110 to 100 mg/dl) by the Expert Committee of the American Diabetes Association [1]. Recently, the American Diabetes Association also proposed the use of HbA_{1c} to identify individuals at high risk of developing Type 2 diabetes at a cut-off value of 39 mmol/mol (5.7%) [2]. These cut-off values were based primarily on the findings of several studies in Western populations that investigated the optimal fasting plasma glucose and HbA_{1c} cut-off values for predicting Type 2 diabetes [1–4]. On the one hand, several cohort studies of Asian populations examined the fasting plasma glucose cut-off values to predict Type 2 diabetes. However, in most of these studies, the diagnosis of Type 2 diabetes was based on fasting plasma glucose levels

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alone [5–9] and few cohort studies used a 75-g oral glucose tolerance test for diagnosing Type 2 diabetes [10,11]. Additionally, the HbA_{1c} cut-off values for predicting Type 2 diabetes have not been assessed sufficiently in Asian populations [11–17]. On the other hand, a 2-h post-load glucose of 7.8 mmol/l (140 mg/dl) for defining impaired glucose tolerance was also derived principally from studies in Western populations [18,19]. However, epidemiological studies which investigated the cut-off values of 2-h post-load glucose for predicting future Type 2 diabetes in Asian populations are scarce and it remains uncertain whether a 2-h post-load glucose value of 7.8 mmol/l (140 mg/dl) is adequately diagnostic for impaired glucose tolerance in relatively lean Asians.

The purpose of this study was to determine the cut-off values of fasting plasma glucose, 2-h post-load glucose and HbA_{1c} for predicting the development of Type 2 diabetes, defined by the oral glucose tolerance test, in a prospective study of a community-dwelling Japanese population.

Subjects and methods

Study population and follow-up survey

A population-based prospective study of cardiovascular disease and its risk factors has been underway since 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area on Kyushu Island, Japan. In 1988, a screening survey for the present study was performed in the town. A detailed description of this survey was published previously [20]. Briefly, of the total of 3227 residents aged 40–79 years based on the town registry, 2587 residents (participation rate 80.2%) consented to take part in a comprehensive assessment. After excluding 82 subjects who had already had breakfast, 10 subjects who were on insulin therapy and 15 subjects because of complaints of nausea or general fatigue during the ingestion of glucose, 2480 subjects completed the 75-g oral glucose tolerance test. Among these, 297 subjects with diabetes and two subjects who died before the start of follow-up were excluded; the remaining 2181 subjects (911 men and 1270 women) were enrolled in the baseline examination. The baseline subjects were followed up prospectively from December 1988 to November 2002 by annual health examination. Of the baseline subjects, 1982 subjects (807 men and 1175 women) who underwent re-examinations were finally selected for the present study (follow-up rate 90.9%; mean follow-up period 11.8 years; mean frequency of follow-up examinations, 6.9 times). The study subjects had a similar age distribution and slightly lower frequency of men (40.7 vs. 45.8%) compared with the original population [20].One subject who developed overt Type 1 diabetes clinically during the follow-up period was censored at the time.

Clinical evaluation and laboratory measurements

In the baseline and follow-up examinations, the study subjects underwent the oral glucose tolerance test between 08.00 and 10.30 h after an overnight fast of at least 12 h. Blood for the glucose assay was obtained by venipuncture into tubes containing sodium fluoride at fasting and at 2-h post-load and was separated into plasma and blood cells within 20 min. Plasma glucose concentrations were determined by the glucose–oxidase method. According to the American Diabetes Association criteria in 2003 [1], diabetes was defined as fasting plasma glucose of ≥ 7.0 mmol/l (126 mg/dl) and/or 2-h post-load glucose of ≥ 11.1 mmol/l (200 mg/dl) and/or the use of anti-diabetic medication at one examination.

HbA_{1c} was measured by high-performance liquid chromatography (HLC-723Hb; Tosoh Inc., Tokyo, Japan). Serum insulin levels were measured by double-antibody, solid-phase radioimmunoassay. Insulin secretion was assessed using the homeostasis model assessment of β-cell function (HOMA-β), which was calculated with the formula fasting serum insulin (μU/ml) × 20/[fasting plasma glucose (mmol/l) − 3.5] [21]. HDL cholesterol and triglycerides were determined enzymatically.

The height and weight of each subject, wearing light clothes without shoes, were recorded and BMI (kg/m^2) was calculated. Blood pressure was obtained three times using a mercury sphygmomanometer with the subject in a sitting position after rest for at least 5 min; the average values were used in the analyses. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg, and/or current treatment with anti-hypertensive agents.

Each participant completed a self-administered questionnaire covering medical history, anti-diabetic and anti-hypertensive treatments, alcohol intake, smoking habits and physical activity. Diabetes in first- or second-degree relatives was taken to indicate a family history of diabetes. Alcohol intake and smoking habits were classified as either current use or not. Subjects engaging in sports at least three times per week during their leisure time were defined as the regular exercise group.

Statistical analysis

The SAS software package version 9.2 (SAS Institute, Cary, NC, USA) was used to perform all statistical analyses. To analyse fasting plasma glucose, 2-h post-load glucose and HbA_{1c} levels as categorical variables, these concentrations were divided into 10 groups on the basis of deciles. Fasting insulin, HOMA-β and serum triglycerides values were transformed into logarithms to improve the skewed distribution. The crude and multivariate-adjusted hazard ratios and their 95% confidence intervals were estimated with the use of the Cox proportional hazards model. The following baseline variables that are known or suspected risk factors for Type 2 diabetes in addition to age and sex were used for analysis as confounding factors: family history of diabetes, fasting insulin, BMI, HDL cholesterol, triglycerides, hypertension, alcohol intake, smoking habits and regular exercise. A value of $P < 0.05$ was considered statistically significant in all analyses. The receiver operating characteristic curve analyses were performed to determine the optimal cut-off

values of fasting plasma glucose, 2-h post-load glucose and HbA_{1c} for predicting incident Type 2 diabetes. The optimal cut-off values were obtained from the point on the receiver operating characteristic curve closest to the ideal of 100% sensitivity and 100% specificity.

Ethical considerations

This study was conducted with the approval of the Ethics Committee of the Faculty of Medicine, Kyushu University, and written informed consent was obtained from the participants.

Results

The baseline clinical characteristics of subjects are shown in Table 1. The mean values of fasting plasma glucose, 2-h post-load glucose and HbA_{1c} were 5.5 and 6.6 mmol/l (99 and118 mg/dl) and 36 mmol/mol (5.4%), respectively. The prevalence of impaired fasting glucose was increased from 12.4 to 43.8% by lowering the criterion for impaired fasting glucose from 6.1 to 5.6 mmol/l (110 to 100 mg/dl).

Table 1 Baseline characteristics of subjects, 1988

Variable	n = 1982
Age (years)	57 (10)
Men (%)	40.7
Fasting plasma glucose (mmol/l)	5.5 (0.5)
(mg/dl)	99 (9)
Two-hour post-load glucose (mmol/l)	6.6 (1.6)
(mg/dl)	118 (29)
Haemoglobin A_{1c} (mmol/mol)	36 (5)
(%)	5.4 (0.5)
IFG with 6.1 mmol/l (110 mg/dl) cut-off value (%)*	12.4
IFG with 5.6 mmol/l (100 mg/dl) cut-off value (%)†	43.8
Family history of diabetes (%)	7.5
Fasting insulin (pmol/l)	40.0 (16.5–97.5)
HOMA-β	57.8 (23.4–142.7)
BMI (kg/m^2)	22.9 (3.0)
HDL cholesterol (mmol/l)	1.31 (0.30)
Triglycerides (mmol/l)	1.14 (0.40–3.21)
Systolic blood pressure (mmHg)	131 (19)
Diastolic blood pressure (mmHg)	78 (11)
Hypertension (%)	36.7
Current drinking (%)	30.0
Current smoking (%)	23.0
Regular exercise (%)	10.6

Fasting insulin, HOMA-β and triglycerides are shown by geometric means and 95% confidence intervals because of the skewed distribution. All other values are given as mean (standard deviations) or as a percentage.
*IFG with 6.1 mmol/l (110 mg/dl) cut-off value was defined as fasting plasma glucose levels of 6.1–6.9 mmol/l (110–125 mg/dl).
†IFG with 5.6 mmol/l (100 mg/dl) cut-off value was defined as fasting plasma glucose levels of 5.6–6.9 mmol/l (100–125 mg/dl).
HOMA-β, homeostasis model assessment of β-cell function; IFG, impaired fasting glucose.

During the follow-up, 295 subjects (149 men and 146 women) developed Type 2 diabetes. The crude and multivariate-adjusted hazard ratios for future Type 2 diabetes according to deciles of fasting plasma glucose, 2-h post-load glucose and HbA_{1c} concentrations are shown in Table 2. Compared with the first decile, the crude hazard ratio for Type 2 diabetes was significantly higher in the fifth fasting plasma glucose decile [5.4–5.4 mmol/l (97–98 mg/dl)] or higher, in the seventh 2-h post-load glucose decile [6.9–7.2 mmol/l (124–131 mg/dl)] or higher, and in the fifth HbA_{1c} decile [34–36 mmol/mol (5.3–5.4%)] or higher. These associations remained substantially unchanged even after adjustment for the confounding factors: namely, age, sex, family history of diabetes, fasting insulin, BMI, HDL cholesterol, triglycerides, hypertension, alcohol intake, smoking habits and regular exercise.

To confirm the cut-off values of fasting plasma glucose, 2-h post-load glucose and HbA_{1c} for predicting Type 2 diabetes, we plotted receiver operating characteristic curves and calculated their area under the curve. As shown in Fig. 1, the optimal cut-off value was 5.6 mmol/l (101 mg/dl) for fasting plasma glucose, 6.9 mmol/l (124 mg/dl) for 2-h post-load glucose and 37 mmol/mol (5.5%) for HbA_{1c}. The sensitivity, specificity and area under the curve of these cut-off values were 67.5, 65.6 and 72.2% for fasting plasma glucose, 65.1, 64.2 and 67.8% for 2-h post-load glucose and 66.1, 57.4 and 64.7% for HbA_{1c}, respectively. Furthermore, comparable findings were observed, even if diabetes was defined with high glucose values at two follow-up examinations (data not shown).

To examine the effects of BMI levels on the cut-off values of fasting plasma glucose, 2-h post-load glucose and HbA_{1c}, the cut-off values were estimated using the receiver operating characteristic analyses among the BMI quartiles (Table 3). On the one hand, the cut-off values for future Type 2 diabetes were approximately 5.6 mmol/l (101 mg/dl) for fasting plasma glucose and 37 mmol/mol (5.5%) for HbA_{1c} and these values were unchanged among the BMI quartile groups. On the other hand, the 2-h post-load glucose cut-off values for predicting Type 2 diabetes declined with decreasing BMI levels; the 2-h post-load glucose cut-off value decreased from 7.5 mmol/l (136 mg/dl) in the fourth quartile of BMI, which approximated the diagnostic criterion of 7.8 mmol/l (140 mg/dl), to 6.7 mmol/l (120 mg/dl) in the first quartile.

Finally, the mean values of HOMA-β according to quartiles of BMI by the presence or absence of incident Type 2 diabetes are shown in Fig. 2. The mean values of HOMA-β decreased significantly with declining BMI levels, both in subjects who developed Type 2 diabetes and in those who did not (both P for trend < 0.001), and these values were lower in subjects who developed Type 2 diabetes than in those who did not, especially among subjects with the lowest quartile of BMI (P = 0.001).

Table 2 Crude or multivariate-adjusted hazard ratios and their 95% confidence intervals for the development of Type 2 diabetes according to deciles of fasting plasma glucose, 2-h post-load glucose and HbA_{1c}

	Population at risk, *n*	Number of events, *n*	Crude		Multivariate adjusted*	
			HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
FPG, mmol/l (mg/dl)						
≤ 4.8 (87)	189	9	1 (referent)		1 (referent)	
4.9–5.0 (88–91)	231	17	1.59 (0.71–3.56)	0.26	1.43 (0.63–3.21)	0.39
5.1–5.1 (92–93)	153	11	1.55 (0.64–3.74)	0.33	1.44 (0.59–3.48)	0.42
5.2–5.3 (94–96)	258	16	1.30 (0.58–2.95)	0.53	1.17 (0.52–2.66)	0.70
5.4–5.4 (97–98)	186	23	2.63 (1.22–5.68)	0.01	2.21 (1.02–4.82)	0.045
5.5–5.6 (99–100)	186	20	2.44 (1.11–5.35)	0.03	1.92 (0.87–4.25)	0.11
5.6–5.7 (101–103)	215	38	3.92 (1.90–8.11)	< 0.001	3.10 (1.49–6.46)	0.002
5.8–5.8 (104–106)	189	25	3.03 (1.41–6.48)	0.004	2.35 (1.08–5.07)	0.03
5.9–6.1 (107–111)	189	48	6.26 (3.07–12.76)	< 0.001	4.85 (2.35–10.02)	< 0.001
≥ 6.2 (112)	186	88	15.18 (7.64–30.16)	< 0.001	9.86 (4.85–20.04)	< 0.001
Two-hour PG, mmol/l (mg/dl)						
≤ 4.6 (83)	194	13	1 (referent)		1 (referent)	
4.7–5.2 (84–95)	199	25	1.75 (0.90–3.43)	0.10	1.67 (0.85–3.28)	0.13
5.3–5.7 (96–103)	217	21	1.38 (0.69–2.75)	0.37	1.41 (0.70–2.82)	0.34
5.8–6.0 (104–109)	185	11	0.83 (0.37–1.85)	0.65	0.86 (0.39–1.94)	0.72
6.1–6.4 (110–116)	202	17	1.20 (0.58–2.47)	0.62	1.19 (0.58–2.46)	0.64
6.5–6.8 (117–123)	189	16	1.17 (0.56–2.43)	0.67	1.06 (0.51–2.22)	0.88
6.9–7.2 (124–131)	207	32	2.32 (1.22–4.41)	0.01	1.97 (1.02–3.78)	0.04
7.3–7.8 (132–141)	199	33	2.42 (1.28–4.61)	0.007	2.22 (1.16–4.26)	0.02
7.9–8.7 (142–157)	193	45	3.84 (2.07–7.11)	< 0.001	3.07 (1.64–5.75)	< 0.001
≥ 8.8 (158)	197	82	8.70 (4.85–15.63)	< 0.001	6.64 (3.63–12.16)	< 0.001
HbA_{1c}, mmol/mol (%)						
≤ 28 (4.7)	165	10	1 (referent)		1 (referent)	
29–31 (4.8–5.0)	280	23	1.35 (0.64–2.83)	0.43	1.38 (0.66–2.91)	0.40
32–32 (5.1–5.1)	113	9	1.36 (0.55–3.34)	0.51	1.33 (0.54–3.29)	0.54
33–33 (5.2–5.2)	183	19	1.78 (0.83–3.83)	0.14	1.81 (0.84–3.91)	0.13
34–36 (5.3–5.4)	328	39	2.04 (1.02–4.08)	0.04	2.10 (1.04–4.24)	0.04
37–37 (5.5–5.5)	156	26	3.06 (1.48–6.36)	0.003	2.94 (1.41–6.14)	0.004
38–38 (5.6–5.6)	143	31	3.95 (1.94–8.06)	< 0.001	3.58 (1.74–7.36)	< 0.001
39–40 (5.7–5.8)	245	47	3.31 (1.67–6.55)	< 0.001	3.03 (1.52–6.03)	0.002
41–42 (5.9–6.0)	177	41	4.62 (2.32–9.23)	< 0.001	4.06 (2.02–8.15)	< 0.001
≥ 43 (6.1)	192	50	5.35 (2.72–10.56)	< 0.001	4.09 (2.05–8.15)	< 0.001

*Multivariate adjustment was made for age, sex, family history of diabetes, fasting insulin, BMI, HDL cholesterol, triglycerides, hypertension, alcohol intake, smoking habits and regular exercise.
CI, confidence interval; FPG, fasting plasma glucose; HR, hazard ratio; PG, post-load glucose.

Discussion

Using data from a follow-up study of community-dwelling Japanese subjects, we demonstrated that the risk of incident Type 2 diabetes defined by the oral glucose tolerance test increased significantly in individuals with fasting plasma glucose levels of 5.4 mmol/l (97 mg/dl) or higher, in those with 2-h post-load glucose levels of 6.9 mmol/l (124 mg/dl) or higher, and in those with HbA_{1c} levels of 34 mmol/mol (5.3%) or higher, even after adjustment for comprehensive risk factors. The optimal cut-off values for predicting Type 2 diabetes derived from the receiver operating characteristic analyses were 5.6 mmol/l (101 mg/dl) for fasting plasma glucose, 6.9 mmol/l (124 mg/dl) for 2-h post-load glucose and 37 mmol/mol (5.5%) for HbA_{1c}. Furthermore, in a stratified analysis, BMI levels did not have an influence on the fasting plasma glucose and HbA_{1c} cut-off values from the receiver operating characteristic analyses, whereas the 2-h post-load glucose cut-off values declined with decreasing BMI levels. Our findings suggest that, in the Japanese population, the cut-off value for predicting Type 2 diabetes is 5.6 mmol/l (101 mg/dl) for fasting plasma glucose and 37 mmol/mol (5.5%) for HbA_{1c}, which is comparable with the current American Diabetes Association criterion, while the 2-h post-load glucose cut-off value is lower than the diagnostic criterion of 7.8 mmol/l (140 mg/dl) for impaired glucose tolerance.

The fasting plasma glucose of 5.6 mmol/l (100 mg/dl) for diagnosing impaired fasting glucose in the current American Diabetes Association criteria is derived mainly from studies in Western populations, which have higher BMI levels compared with Asian populations [1]. However, few prospective studies in Asian populations have investigated the fasting plasma glucose

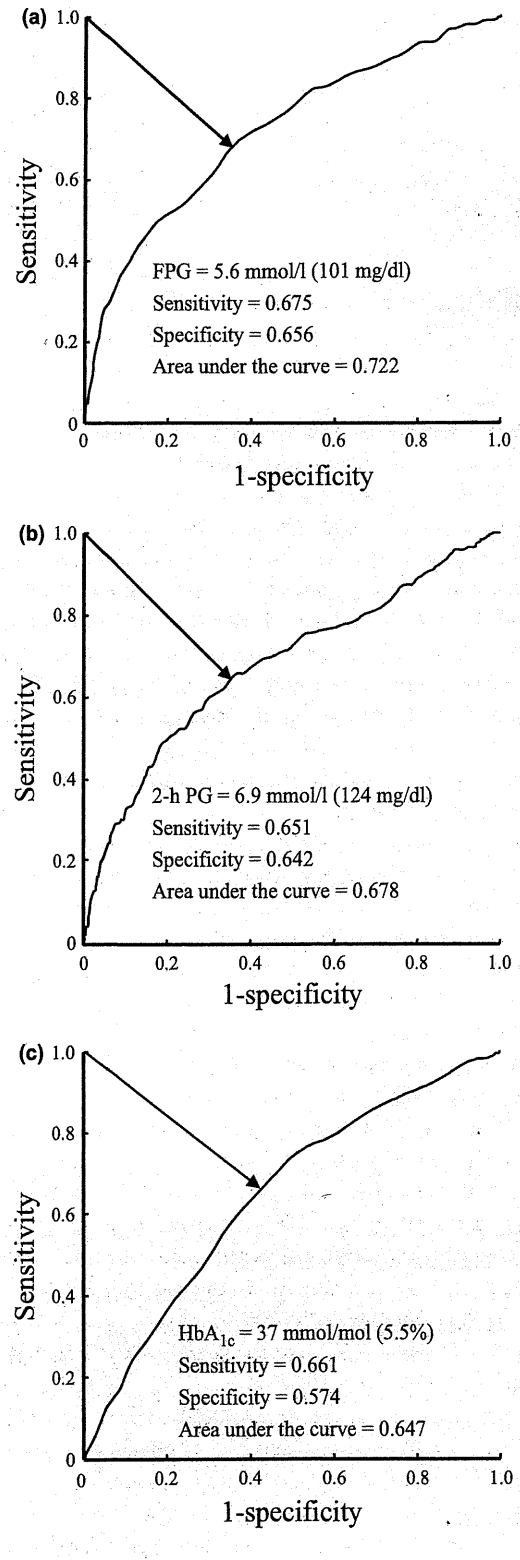

FIGURE 1 Receiver operating characteristic curve analysis for (a) fasting plasma glucose (FPG), (b) 2-h post-load glucose (2-h PG) and (c) HbA_{1c} for predicting incident Type 2 diabetes. The arrows show the optimal cut-off value for predicting incident Type 2 diabetes defined as the closest to the ideal of 100% sensitivity and 100% specificity.

cut-off value for predicting Type 2 diabetes, defined by the oral glucose tolerance test. In the present study, the risk of future Type 2 diabetes, defined by the oral glucose tolerance test, significantly increased at an fasting plasma glucose level above approximately 5.6 mmol/l (100 mg/dl) and the optimal cut-off value of fasting plasma glucose using the receiver operating characteristic analysis was also 5.6 mmol/l (101 mg/dl). The cut-off points were in accordance with those from studies using the oral glucose tolerance test for diagnosing Type 2 diabetes in a Japanese or Singapore population [10,11]. Furthermore, other Asian population studies, which used a measurement of fasting plasma glucose alone for diagnosing Type 2 diabetes, had approximately 5.6 mmol/l (100 mg/dl) as the optimal fasting plasma glucose cut-off value [5–9]. The present analysis confirmed these findings, suggesting that, in Asian populations including Japanese, the optimal fasting plasma glucose cut-off value for predicting future Type 2 diabetes is 5.6 mmol/l (100 mg/dl), just as in Western populations. Moreover, in our stratified analysis, the fasting plasma glucose cut-off values were hardly altered by BMI levels. Taken together, these findings imply that the fasting plasma glucose cut-off value for predicting Type 2 diabetes remains the same, regardless of race or the degree of obesity.

There has been some debate about whether the fasting plasma glucose cut-off value for impaired fasting glucose should or should not be lowered from 6.1 to 5.6 mmol/l (110 to 100 mg/dl) [5–11,19], because lowering this value will lead to a considerable increase in the number of people with impaired fasting glucose. In the present study, lowering the criterion for impaired fasting glucose increased the prevalence 3.5-fold, from 12.4 to 43.8%. Similar findings were observed in another Japanese population study (3.6-fold) [9]. In our study, however, the risk of future Type 2 diabetes significantly increased at fasting plasma glucose levels of approximately 5.6 mmol/l (100 mg/dl). Thus, lowering the cut-off value for impaired fasting glucose may reduce the frequency of missing the subjects at high risk of developing Type 2 diabetes. These findings indicate that fasting plasma glucose of 5.6 mmol/l (100 mg/dl) for diagnosing impaired fasting glucose should be used for predicting future Type 2 diabetes.

There have been very few prospective studies investigating the 2-h post-load glucose cut-off values for predicting Type 2 diabetes in Asian populations and it is unknown whether a 2-h post-load glucose value of 7.8 mmol/l (140 mg/dl), which was based primarily on the findings of studies in Caucasians and Pima Indians [18,19], is appropriate to define impaired glucose tolerance for Asians. In our study, the risk of future Type 2 diabetes significantly increased at 2-h post-load glucose levels of 6.9 mmol/l (124 mg/dl) and the same optimal cut-off value of 2-h post-load glucose was obtained by the receiver operating characteristic analysis. These findings suggest that the 2-h post-load glucose cut-off value in Japanese is lower than the diagnostic cut-off point of 7.8 mmol/l (140 mg/dl) for impaired glucose tolerance. In addition, surprisingly, the 2-h post-load glucose cut-off values for predicting Type 2 diabetes

Table 3 Cut-off values of fasting plasma glucose, 2-h post-load glucose and HbA_{1c} levels for predicting Type 2 diabetes according to quartiles of BMI

BMI level, kg/m^2	Population at risk, *n*	Number of events, *n*	Cut-off value*		
			FPG, mmol/l (mg/dl)	Two-hour PG, mmol/l (mg/dl)	HbA_{1c}, mmol/mol (%)
< 20.8	495	44	5.6 (101)	6.7 (120)	37 (5.5)
20.8–22.7	496	58	5.6 (101)	6.8 (123)	38 (5.6)
22.8–24.8	496	70	5.7 (103)	7.3 (131)	37 (5.5)
≥ 24.9	495	123	5.6 (101)	7.5 (136)	37 (5.5)

*The cut-off values were estimated using the receiver operating characteristic curve analyses.
FPG, fasting plasma glucose; PG: post-load glucose.

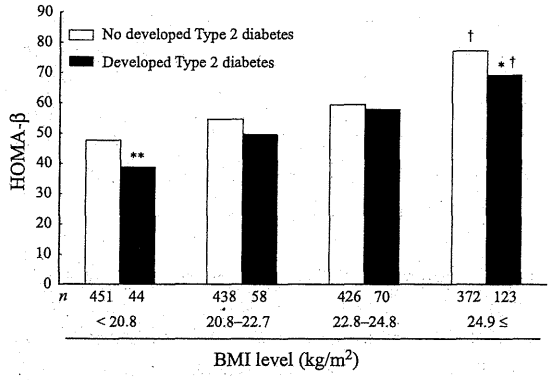

FIGURE 2 The mean values of homeostasis model assessment of β-cell function (HOMA-β) according to quartiles of BMI by the presence or absence of incident Type 2 diabetes. Homeostasis model assessment of β-cell function is shown by geometric means because of the skewed distribution. *$P < 0.05$, **$P < 0.01$ vs. no developed Type 2 diabetes. †P for trend < 0.001.

declined with decreasing BMI levels in our subjects. To the best of our knowledge, the present study is the first report to indicate that adiposity affects the cut-off value of 2-h post-load glucose for predicting Type 2 diabetes. Although the precise reason why the 2-h post-load glucose cut-off value is lower in lean subjects is unknown, a difference in the capacity for insulin secretion in response to glucose load may be a cause of this phenomenon. In some epidemiological studies, diminished insulin response was more strongly associated with higher 2-h post-load glucose levels than fasting plasma glucose levels [22–25]. Furthermore, reduced insulin secretion has been shown to play a major role in the development of Type 2 diabetes among lean subjects [26,27]. In our subjects, insulin secretion was markedly reduced in individuals who developed Type 2 diabetes compared with those who did not, especially among those with BMI levels < 20.8 kg/m^2, which supports the findings of the previous studies [26,27]. Thus, it is speculated that, among individuals at risk of developing Type 2 diabetes, lean persons have a much greater reduction in insulin secretion and develop Type 2 diabetes at lower levels of 2-h post-load glucose compared with obese persons. This may explain our finding that lower BMI levels were accompanied by lower cut-off values of 2-h post-load glucose for predicting Type 2 diabetes. Additionally, insulin response to glucose load is known to be lower in Asians than in Western populations [28]. Thus, reduced insulin secretion may lead to much lower 2-h post-load glucose cut-off values for predicting Type 2 diabetes in relatively lean Asian populations, including Japanese, than in Western populations. This might be a reason why the 2-h post-load glucose cut-off value in our subjects was lower than the diagnostic criterion of 7.8 mmol/l (140 mg/dl) for impaired glucose tolerance. Further epidemiological studies are needed to confirm our findings.

There are limited cohort studies that have investigated the HbA_{1c} cut-off values for predicting Type 2 diabetes in Asian populations. The present study indicated that individuals with HbA_{1c} levels above 35 mmol/mol (5.3%) are at high risk of developing Type 2 diabetes and that an HbA_{1c} of 37 mmol/mol (5.5%) was the optimal cut-off value in the receiver operating characteristic analysis. Similarly, in several studies of Japanese populations, a significantly increased risk of Type 2 diabetes was observed in subjects with HbA_{1c} levels above 37 mmol/mol (5.5%) [14–16]. A Chinese population study also found in a receiver operating characteristic analysis that the optimal HbA_{1c} cut-off value was 40 mmol/mol (5.8%) [17]. These findings suggest that the optimal HbA_{1c} cut-off value for predicting Type 2 diabetes is likely to be in the range of 37–40 mmol/mol (5.5–5.8%) in Asian populations, and that the HbA_{1c} cut-off value of 39 mmol/mol (5.7%), which was proposed by the American Diabetes Association, is considered acceptable in Asians.

In our study, the sensitivity, specificity and area under the curve of fasting plasma glucose, 2-h post-load glucose and HbA_{1c} were lower than those in other epidemiological studies [3–9,16,17]. The reason for this is not clear, but a relatively longer follow-up period in our cohort may be responsible for this difference. During a long follow-up period, a potential change in the glucose tolerance of participants may occur, which would weaken the relationships of baseline glucose and HbA_{1c} levels with the future risk of developing Type 2 diabetes. Thus, the discriminative abilities of fasting plasma glucose, 2-h

post-load glucose and HbA_{1c} in our study would be lower than in other studies.

The strengths of our study include a longitudinal population-based design, a sufficient number of Type 2 diabetes events, high participation and follow-up rates. In addition, the diagnosis of Type 2 diabetes based on the oral glucose tolerance test may provide us an opportunity to precisely examine the cut-off values of fasting plasma glucose and 2-h post-load glucose to predict Type 2 diabetes. One limitation of our study is that the glucose and HbA_{1c} categories at baseline were based on a single measurement, as was the case in most other epidemiological studies. During the follow-up, risk factor levels were changed because of modifications in lifestyle or medication and misclassification of glucose and HbA_{1c} categories was possible. However, we believe that such misclassification would occur equally among all glucose and HbA_{1c} categories and therefore would not have substantially altered our findings.

In conclusion, the present analysis has shown that, in a Japanese population, the cut-off value for predicting future Type 2 diabetes is 5.6 mmol/l (101 mg/dl) for fasting plasma glucose and 37 mmol/mol (5.5%) for HbA_{1c}, which are comparable with the current American Diabetes Association criteria, while the cut-off value of 2-h post-load glucose is lower than the diagnostic criterion for impaired glucose tolerance. Furthermore, the fasting plasma glucose and HbA_{1c} cut-off values remained unchanged, irrespective of BMI levels, but a decrease in the 2-h post-load glucose cut-off values accompanied a downward trend in BMI. These findings suggest that the cut-off values for fasting plasma glucose and HbA_{1c} may be more robust than that for the 2-h post-load glucose for predicting Type 2 diabetes. Further studies are needed to verify these findings in other populations.

Competing interests

Nothing to declare.

Acknowledgments

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Original Article

Impact of lower range of prehypertension on cardiovascular events in a general population: the Hisayama Study

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Objectives: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) defined blood pressure (BP) levels of 120–139/80–89 mmHg as prehypertension. The objective of the present analysis was to examine the impact of prehypertension and its population-attributable fraction for development of cardiovascular events in a general Japanese population.

Methods: Two thousand, six hundred and thirty-four residents of the town of Hisayama aged at least 40 years without cardiovascular disease were followed up for 19 years. BP categories were defined using JNC7, and prehypertension was divided into the lower (120–129/80–84 mmHg) and higher ranges (130–139/85–89 mmHg). During the follow-up period, 449 participants developed cardiovascular disease (305 strokes and 187 coronary heart diseases).

Results: The frequencies of normal BP, prehypertension, and stages 1 and 2 hypertension were 24.9, 37.7, 23.8, and 13.6%, respectively. The age and sex-adjusted incidence of cardiovascular disease rose progressively with elevation of BP levels ($P < 0.001$ for trend). The risks of cardiovascular disease in lower and higher ranges of prehypertension were 58% [95% confidence interval (CI) 11–126%] and 70% (95% CI 18–144%) higher than normal BP even after controlling for other cardiovascular risk factors. The population-attributable fraction of prehypertension was 13.2%, which was similar to those of stages 1 and 2 hypertension.

Conclusions: The risks of cardiovascular disease increased significantly from the lower range of prehypertension in a general Japanese population. Approximately one-third of excess cardiovascular events attributable to elevated BP levels were estimated to occur among individuals with prehypertension.

Keywords: blood pressure, cardiovascular disease, population-attributable fraction, prehypertension, prevention, prospective cohort studies, stroke

Abbreviations: BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; JNC7, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; PAF, population-attributable fraction

INTRODUCTION

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) defined the blood pressure (BP) levels of 120–139/80–89 mmHg as prehypertension based on the evidence of a modest increase in cardiovascular risk among individuals with such BP levels [1]. However, current evidence of increased risks of cardiovascular disease (CVD) associated with prehypertension has mainly been reported for its higher range (130–139/85–89 mmHg) [2,3], and it is still unclear about the cardiovascular risks among individuals with the lower range of prehypertension (120–129/80–84 mmHg), particularly in the Japanese. Because the prevalence of prehypertension has been reported to be as high as 31–43% [4–6], a large portion of the burden of CVD is likely attributable to prehypertension. Although a number of large-scale observational studies have shown population-attributable fractions (PAFs) of this BP category for premature deaths or deaths due to cardiovascular causes [7,8], uncertainty remains surrounding the frequency of 'fatal and nonfatal' cardiovascular events attributable to prehypertension.

The Hisayama Study has demonstrated that the incidence rates of stroke significantly increased from BP levels of 140/90 mmHg among participants recruited in 1961 [5].

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However, the effects of BP on the risks of stroke and coronary heart disease might have changed since then because of the substantial changes in lifestyle and the improved awareness, treatment, and control of hypertension [9]. The objective of the present new analysis from the Hisayama Study is to investigate the influence of BP on cardiovascular events among participants recruited in 1988 and to estimate population-attributable risks of prehypertension (lower and higher ranges) and hypertension for incident CVD in a general Japanese population.

METHODS

Study population

The Hisayama Study is a population-based prospective cohort study of CVD established in 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area in Kyushu Island of Japan. Based on data from the national census, the age and occupational distributions in Hisayama have been almost identical to those in Japan since the 1960s [10]. In 1988, a total of 2742 residents aged at least 40 years consented to participate in the screening examination (participation rate 80.9%). After the exclusion of 106 residents with a history of stroke or coronary heart disease and two residents who died before the start of follow-up, the remaining 2634 residents (1107 men and 1527 women) were enrolled in this study. The study design and characteristics of this cohort population have been described in detail elsewhere [11–13].

Follow-up survey

The participants were followed up prospectively for 19 years, from December 1988 to November 2007, by annual health examinations. The health status of any individual who did not undergo a regular examination or who moved out of town was checked yearly by mail or telephone. We also established a daily monitoring system among the study team, local physicians, and members of the town's Health and Welfare Office. Using this system, we gathered information on new events of CVD, including suspected cases. When stroke or coronary heart disease occurred or was suspected, physicians in the study team examined the individual and evaluated his/her detailed clinical information. The clinical diagnosis of stroke or coronary heart disease was based on the patient's history, physical and neurological examinations, and ancillary laboratory examinations. Furthermore, when a patient died, an autopsy was performed at the Departments of Pathology of Kyushu University. During the follow-up period, there was no true loss to follow-up, and 842 patients died, of whom 605 (71.9%) underwent autopsy.

Blood pressure measurements and classification

At the baseline examination, BP was measured three times using a standard mercury sphygmomanometer in the sitting position after rest for at least 5 min. Appropriately-sized cuffs were used for BP assessment. Korotkoff phase 5 was taken as the diastolic BP unless the sound persisted at 0, in which case Korotkoff phase 4 was recorded. The mean of the three measurements was used for the analysis. BP levels were classified into four categories according to JNC7: normal BP (<120/80 mmHg), prehypertension (120–139/80–89 mmHg), stage 1 hypertension (140–159/90–99 mmHg), and stage 2 hypertension (≥160/100 mmHg) [1]. Prehypertension was divided into two subcategories: lower (120–129/80–84 mmHg) and higher (130–139/85–89 mmHg) BP ranges. If systolic and diastolic BP readings for a participant were in different categories, that participant was categorized into the higher of the two BP categories. Antihypertensive drug users were classified according to BP levels at baseline.

Other risk factor measurement

At baseline, each participant completed a self-administered questionnaire covering medical history, treatment for hypertension and diabetes, smoking habits, alcohol intake, and exercise. Smoking habits and alcohol intake were classified into currently habitual or not. The participants engaging in sports or other forms of exertion at least three times a week during their leisure time made up a regular exercise group. Body height and weight were measured in light clothing without shoes, and the body mass index (kg/m^2) was calculated. Electrocardiogram (ECG) abnormalities were defined as left-ventricular hypertrophy (Minnesota code 3–1), ST depression (4–1, 2, 3), or atrial fibrillation (8–3).

Serum total and high-density lipoprotein (HDL) cholesterol levels were determined enzymatically. Hypercholesterolemia was defined as total cholesterol at least 5.7 mmol/l. Blood glucose levels were measured by the glucose oxidase method. Diabetes was determined by medical history, plasma glucose levels (fasting glucose level ≥7.0 mmol/l or postprandial glucose level ≥11.1 mmol/l), or a 75-g oral glucose tolerance test using the 1998 World Health Organization criteria [14]. Serum creatinine was measured by the noncompensated Jaffé method. The Jaffé method value was converted to an enzymatic method value by using the following equation [15]:

$$\begin{aligned}&\text{Serum creatinine (enzymatic method [mg/dl])}\\&\quad = 0.9754\\&\qquad \times \text{serum creatinine (Jaffé method [mg/dl])}\\&\qquad - 0.2802.\end{aligned}$$

Estimated glomerular filtration rate (eGFR) was calculated using the isotope dilution mass spectrometry-traceable 4-variable Modification of Diet in Renal Disease (IDMS-MDRD) Study equation modified with the Japanese correction [16]:

$$\begin{aligned}&\text{eGFR (ml/min per 1.73 m}^2\text{)}\\&\quad = 194\\&\qquad \times \text{serum creatinine (enzymatic method)}^{-1.094}\\&\qquad \times \text{age}^{-0.287} \times 0.742 \text{ (if women).}\end{aligned}$$

Chronic kidney disease was defined as proteinuria (+ or more using the test paper method) or eGFR below 60 ml/min per 1.73 m^2 according to the National Kidney

Foundation Kidney Disease Outcomes Quality Initiative guidelines [17].

Endpoint definition

Cardiovascular disease was defined as first-ever development of stroke or coronary heart disease. In principle, stroke was defined as an acute onset of nonconvulsive and focal neurological deficit lasting more than 24 h. The clinical diagnosis of stroke was determined on the basis of a detailed history, neurological examination, and ancillary laboratory examinations, including computed tomography and magnetic resonance image. Stroke was classified as either ischaemic or haemorrhagic (intracerebral or subarachnoid haemorrhage).

The criteria for a diagnosis of coronary heart disease included acute myocardial infarction, silent myocardial infarction, sudden cardiac death within 1 h after the onset of acute illness, and coronary artery disease followed by coronary intervention or bypass surgery. Acute myocardial infarction was diagnosed when a participant met at least two of the following criteria: typical symptoms, including prolonged severe anterior chest pain; abnormal cardiac enzymes more than twice the upper limit of the normal range; evolving diagnostic ECG changes; and morphological changes, including local asynergy of cardiac wall motion on echocardiography, persistent perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars greater than 1 cm long accompanied by coronary atherosclerosis at autopsy. Silent myocardial infarction was defined as myocardial scarring without any historical indication of clinical symptoms or abnormal cardiac enzyme changes. Clinical diagnoses were corrected by autopsy findings when necessary.

Statistical analysis

The age and sex-adjusted mean values of risk factors were calculated and tested by the analysis of covariance. Frequencies of risk factors were adjusted for age and sex by the direct method and were compared using the logistic regression analysis. The age and sex-adjusted cumulative incidence of CVD was estimated, and the differences among BP categories were tested using the Cox proportional hazards model. The incidence rate was calculated by the person-year method and adjusted for age and sex by the direct method. Differences in age and sex-adjusted incidences among BP levels were tested by the Cox proportional hazards model. The adjusted hazard ratio and its 95% confidence interval (CI) were also calculated using the Cox proportional hazards model. The heterogeneity in the relationship between subgroups was estimated by adding an interaction term to the Cox model. The PAF of each BP category was calculated using the following equation with the observed multivariate-adjusted hazard ratio of each category and its frequency in event cases (Pe) [18].

$$PAF = Pe(HR - 1)/HR$$

The CI of the PAF was estimated by the method proposed by Greenland [19]. All statistical analyses were performed with the SAS program package version 9.2 (SAS Institute Inc., Cary, North Carolina, USA). P values of less than 0.05 were considered statistically significant.

Ethical considerations

The study protocol was approved by Kyushu University Institutional Review Board for Clinical Research, and the procedures followed were in accordance with national guidelines. The participants provided written informed consent.

RESULTS

The frequencies of normal BP, prehypertension, stage 1 hypertension, and stage 2 hypertension were 24.9, 37.7, 23.8, and 13.6%, respectively. The age and sex-adjusted mean values or frequencies of cardiovascular risk factors are listed according to BP categories in Table 1. Individuals with higher BP levels were older and more likely to be men. The mean values of body mass index and total cholesterol, and frequencies of diabetes, chronic kidney disease, ECG abnormalities, and alcohol intake increased with elevating BP levels, whereas the mean value of HDL cholesterol and frequency of smoking habits decreased. Such trends were not observed for regular exercise.

During the 19-year follow-up, 449 individuals developed CVD events (229 men and 220 women). These CVD cases had 305 first-ever stroke (213 ischaemic and 92 haemorrhagic strokes), and 187 first-ever coronary events. Figure 1 shows the age and sex-adjusted cumulative incidence curves of CVD according to BP categories. The incidence of CVD significantly increased with elevating BP categories; compared with normal BP, the incidence of CVD became significantly higher from the 6th year in lower range of prehypertension, the 6th year in higher range of prehypertension, the 4th year in stage 1 hypertension, and the 5th year in stage 2 hypertension. Table 2 shows the age and sex-adjusted incidence of CVD and its subtypes according to BP categories. The age and sex-adjusted incidence of CVD rose progressively with elevation of BP levels: normal BP 7.5 per 1000 person-years, lower range of prehypertension 12.6, higher range of prehypertension 12.1, stage 1 hypertension 13.7, and stage 2 hypertension 24.6. The incidence rates were significantly higher from the lower range of prehypertension compared to normal BP. Similar associations were observed in both sexes ($P = 0.62$ for heterogeneity). The age and sex-adjusted incidence of stroke increased continuously with elevating BP levels, and the difference in the incidence between normal BP and lower range of prehypertension was significant. A similar tendency was observed for both ischaemic and haemorrhagic strokes. The association between BP levels and the incidence of coronary heart disease was somewhat weak, and the incidence was significantly elevated only in stage 2 hypertension. The associations of BP categories with the risks of CVD, stroke, and coronary heart disease were substantially unchanged even after adjusting for potential confounding factors such as age, sex, body mass index, total and HDL cholesterol, diabetes, chronic kidney disease, ECG abnormalities, smoking, drinking, and regular exercise (Table 3). There was a continuous relationship of BP levels with total CVD, and a significant increase was observed from the