Table 2B. Odds ratio for the highest quintile of mean probing pocket depth of each quartile of body fat and results of oral glucose tolerance test in Japanese women

	Mean PD (mm)		Odds ratio (95% CI)		
Variable	< 1.9	≥ 1.9	Univariate	Bivariate	Multivariate
Body fat quartiles (%)					
1 (7.9–24.1)	132	15	1	1	1
2 (24.2–27.9)	116	29	2.2 (1.1–4.3)*	2.2 (1.1–4.4)*	2.6 (1.2–5.3)*
3 (28.0–32.5)	116	30	2.3 (1.2–4.4)*	2.2 (1.1–4.4)*	2.8 (1.3–5.7)†
4 (32.6–52.5)	105	40	3.4 (1.8–6.4)‡	3.1 (1.6–6.0)‡	3.3 (1.6–6.8)†
OGTT					
Normal	360	75	1	1	1
IGT	82	26	1.5 (0.9–2.5)	1.3 (0.8–2.2)	1.0 (0.5–1.8)
Diabetes	27	13	2.3 (1.1–4.7)*	2.1 (1.0–4.4)	1.5 (0.7–3.5)

Bivariate included body fat and OGTT as independent variables.
Multivariate included Body Fat, OGTT, age, plaque index, smoking history, and occupation as independent variables. *$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$.
PD, probing pocket depth; CI, confidence interval; OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance.

Table 2C. Odds ratio for the highest quintile of mean probing pocket depth of each quartile of waist–hip ratio and results of oral glucose tolerance test in Japanese women

	Mean PD (mm)		Odds ratio (95% CI)		
Variable	< 1.9	≥ 1.9	Univariate	Bivariate	Multivariate
WHR quartiles					
1 (0.75–0.89)	124	21	1	1	1
2 (0.89–0.94)	120	26	1.3 (0.7–2.4)	1.2 (0.7–2.3)	1.4 (0.7–2.8)
3 (0.94–0.97)	119	27	1.3 (0.7–2.5)	1.3 (0.7–2.4)	1.2 (0.6–2.4)
4 (0.97–1.12)	106	40	2.2 (1.2–4.0)†	2.0 (1.1–3.6)*	2.1 (1.1–4.1)*
OGTT					
Normal	360	75	1	1	1
IGT	82	26	1.5 (0.9–2.5)	1.4 (0.8–2.3)	1.1 (0.6–1.9)
Diabetes	27	13	2.3 (1.1–4.7)*	2.0 (1.0–4.2)	1.5 (0.7–3.4)

Bivariate included WHR and OGTT as independent variables.
Multivariate included WHR, OGTT, age, plaque index, smoking history, and occupation as independent variables. *$p < 0.05$, †$p < 0.01$.
PD, probing pocket depth; CI, confidence interval; WHR, waist–hip ratio; OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance.

Table 3A. Odds ratio for the highest quintile of mean attachment loss of each quartile of body mass index and results of oral glucose tolerance test in Japanese women

	Mean AL (mm)		Odds ratio (95% CI)		
Variable	< 2.42	≥ 2.42	Univariate	Bivariate	Multivariate
BMI quartiles (kg/m^2)					
1 (15.5–20.8)	124	21	1	1	1
2 (20.8–22.7)	117	29	1.5 (0.8–2.7)	1.5 (0.8–2.8)	1.6 (0.8–3.1)
3 (22.7–24.9)	118	28	1.4 (0.8–2.6)	1.3 (0.7–2.5)	1.3 (0.7–2.6)
4 (25.0–46.7)	108	38	2.1 (1,1–3.8)*	1.8 (1.0–3.3)	1.8 (0.9–3.4)
OGTT					
Normal	360	75	1	1	1
IGT	82	26	1.5 (0.9–2.5)	1.4 (0.8–2.3)	1.1 (0.6–1.9)
Diabetes	25	15	2.9 (1.4–5.7)*	2.7 (1.3–5.5)†	1.5 (0.7–3.2)

Bivariate included BMI and OGTT as independent variables.
Multivariate included BMI, OGTT, age, plaque index, smoking history, and occupation as independent variables. *$p < 0.05$, †$p < 0.01$.
AL, attachment loss; CI, confidence interval; BMI, body mass index; OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance.

indexes (Tables 2A–C). Nevertheless, the significant relationship between diabetes and severe attachment loss remained after adjusting for the obesity indexes in the bivariate models (Tables 3A–C). In the multivariate models, the increased ORs between diabetes and both periodontal parameters did not reach statistical significance, which may be due simply to the small number of subjects, since there were only 40 diabetic subjects in this study. The oral glucose tolerance test results show the subjects' metabolic control status on that day, whereas the duration of their diabetic condition is important when studying the effects of diabetes on complications (12). Given this and the low number of subjects, this study cannot clarify the association between diabetes and periodontal disease. By contrast, impaired glucose tolerance seemed to have no association with either deep pockets or severe attachment loss in any multivariate model, despite the greater number of subjects ($n = 108$), as compared with diabetes ($n = 40$). Impaired glucose tolerance, which is an intermediate glucose condition between diabetes and normal glucose tolerance, may not have any effect on periodontal disease. This concurs with our recent report, in which deep pockets were more closely associated with the development of glucose intolerance from a normal glucose condition than with the past glucose tolerance condition itself, suggesting that deep pockets are a cause of impaired glucose tolerance (16).

In the analyses using attachment loss as a dependent variable, even the highest quartile of obesity indexes had no significant association with severe attachment loss, although the tendency was similar to the analyses using pocket depth. Although both pocket depth and attachment loss are important parameters of periodontal disease, they have slightly different meanings. A deep pocket usually means existing periodontal inflammation, whereas severe attachment loss usually represents a history of periodontal destruction, which does not always mean periodontal inflammation. Of course, the mean pocket depth and mean attachment loss are closely related ($r = 0.79$,

Table 3B. Odds ratio for the highest quintile of mean attachment loss of each quartile of body fat and results of oral glucose tolerance test in Japanese women

Variable	Mean AL (mm)		Odds ratio (95% CI)		
	< 2.42	≥ 2.42	Univariate	Bivariate	Multivariate
Body fat quartiles (%)					
1 (7.9–24.1)	122	25	1	1	1
2 (24.2–27.9)	116	29	1.2 (0.7–2.2)	1.2 (0.7–2.3)	1.3 (0.7–2.5)
3(28.0–32.5)	117	29	1.2 (0.7–2.2)	1.2 (0.6–2.1)	1.3 (0.7–2.5)
4 (32.6–52.5)	112	33	1.4 (0.8–2.6)	1.3 (0.7–2.3)	1.2 (0.6–2.3)
OGTT					
Normal	360	75	1	1	1
IGT	82	26	1.5 (0.9–2.5)	1.5 (0.9–2.5)	1.1 (0.6–2.0)
Diabetes	25	15	2.9 (1.4–5.7)*	2.8 (1.4–5.7)†	1.6 (0.7–3.4)

Bivariate included body fat and OGTT as independent variables.
Multivariate included body fat, OGTT, age, plaque index, smoking history, and occupation as independent variables. *$p < 0.05$, †$p < 0.01$.
AL, attachment loss; CI, confidence interval; OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance.

Table 3C. Odds ratio for the highest quintile of mean attachment loss of each quartile of waist–hip ratio and results of oral glucose tolerance test in Japanese women

Variable	Mean AL (mm)		Odds ratio (95% CI)		
	< 2.42	≥ 2.42	Univariate	Bivariate	Multivariate
WHR quartiles					
1 (0.75–0.89)	121	24	1	1	1
2 (0.89–0.94)	118	28	1.2 (0.7–2.2)	1.1 (0.6–2.1)	1.2 (0.6–2.4)
3 (0.94–0.97)	120	26	1.1 (0.6–2.0)	1.0 (0.6–1.9)	1.0 (0.5–1.9)
4 (0.97–1.12)	108	38	1.8 (1.0–3.1)	1.5 (0.9–2.8)	1.3 (0.7–2.5)
OGTT					
Normal	360	75	1	1	1
IGT	82	26	1.5 (0.9–2.5)	1.4 (0.9–2.4)	1.1 (0.6–2.0)
Diabetes	25	15	2.9 (1.4–5.7)*	2.6 (1.3–5.3)†	1.5 (0.7–3.2)

Bivariate included WHR and OGTT as independent variables.
Multivariate included WHR, OGTT, age, plaque index, smoking history, and occupation as independent variables. *$p < 0.05$, †$p < 0.01$.
AL, attachment loss; CI, confidence interval; WHR, waist–hip ratio; OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance.

$p < 0.0001$). Therefore, the tendencies in Tables 2A-C and 3A-C were similar and, given sufficient subjects, the relationship might reach statistical significance. Nevertheless, the weak or non-significant association between obesity and attachment loss found in this study suggests that the relationship between obesity and periodontal disease is limited to a relationship between obesity and the primary stage of periodontal disease. Since periodontal destruction, such as alveolar bone loss, is a result of inflammation, with the mechanism of the destruction arising as a consequence of inflammation (10), obesity may be related to the primary stage of periodontal disease and may not be related to the subsequent stage of periodontal destruction.

The NHANES III study found a relationship between obesity and periodontal disease in young adults only, using a combination of deep pockets and attachment loss as criteria of periodontal disease (7). As elderly people lose their teeth as a result of periodontal disease, the relationship between obesity and periodontal disease in the elderly could disappear. Since we limited the subjects of our study to those with ≥ 10 teeth, a relationship between obesity and deep pockets should be more easily detected in our study, as compared to the NHANES III study, which included subjects with fewer than 10 teeth. Although we could not analyze each age group separately, due to the small number of subjects, a relationship between obesity and deep pockets might be detected in the elderly if the subjects were to be limited to those with many teeth. Tobacco smoking is a well-documented risk factor for periodontal disease (9, 10). In this study, however, smoking history was not associated with either deep pockets or severe attachment loss, probably because there was a very low proportion of smokers among our female subjects. The prevalence of obesity is very low among Japanese as compared to the US population, whereas the prevalence of diabetes is about the same (1, 3, 12). As the effect of obesity on health is thought to differ among races, Japanese women may show different relationships between obesity, diabetes, and periodontal disease compared to other races. Since our study and other reports on the relationship between obesity and periodontal disease were cross-sectional studies, a prospective cohort study with different age groups and sexes is required.

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Chronic kidney disease and cardiovascular disease in a general Japanese population: The Hisayama Study

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Chronic kidney disease and cardiovascular disease in a general Japanese population: The Hisayama Study.

Background. Chronic kidney disease has been shown to be an independent risk factor for cardiovascular disease in high-risk populations. However, this relationship is inconclusive in community-based populations.

Methods. To clarify this issue, we followed 2634 community-dwelling individuals without cardiovascular disease, aged 40 years or older, for 12 years and examined the relationship between chronic kidney disease and the incidence of cardiovascular disease.

Results. During the follow-up period, 99 subjects (56 men and 43 women) experienced coronary heart disease, 137 subjects (60 men and 77 women) ischemic stroke, and 60 subjects (26 men and 34 women) hemorrhagic stroke. In men, the age-adjusted incidence of coronary heart disease was significantly higher in subjects with chronic kidney disease than in those without it (6.2 vs. 2.9 per 1000 person-years) ($P < 0.05$), but such a relationship was not observed with ischemic stroke. In contrast, in women, the age-adjusted incidence of ischemic stroke was significantly higher in subjects with chronic kidney disease than in those without it (3.4 vs. 2.5) ($P < 0.05$), while that of coronary heart disease was not. Chronic kidney disease was not found to be associated with the incidence of hemorrhagic stroke. In multivariate analysis, even after adjustments for traditional and nontraditional cardiovascular disease risk factors, chronic kidney disease was found to be an independent risk factor for the occurrence of coronary heart disease in men [hazard ratio (HR), 2.26; 95% CI, 1.06-4.79], and for the occurrence of ischemic stroke in women (HR, 1.91; 95% CI, 1.15-3.15).

Conclusion. Our findings suggest that chronic kidney disease is an independent risk factor for the occurrence of cardiovascular disease in the general Japanese population.

Patients with end-stage renal disease (ESRD) are at a much higher risk of cardiovascular disease than the general population, with the cardiovascular mortality rate in patients with ESRD being 10 to 20 times higher than that in general populations [1]. In 1998, the National Kidney Foundation Task Force on Cardiovascular Disease in Chronic Renal Disease issued a report emphasizing the high risk of cardiovascular disease not only in patients with ESRD, but also in those with chronic kidney disease [2]. The reason for the higher risk of cardiovascular disease in individuals with chronic kidney disease is not entirely clear, but is thought to be related in part to the high prevalence of traditional risk factors for cardiovascular disease in individuals with reduced kidney function [3]. Thus, interest has grown recently in the examination of kidney disease itself as an independent risk factor for cardiovascular disease [4, 5]. Some studies of high-risk populations, such as those who already have cardiovascular disease or who have several coexisting cardiovascular risk factors, have found decreased kidney function to be an independent risk factor for cardiovascular disease [6–20]. In prospective studies of general populations, however, the relationships between the levels of kidney function and cardiovascular disease outcomes have been inconclusive [21–25].

In the present article, we reported the findings of a prospective survey examining the relationships between cardiovascular disease and the incidence of coronary heart disease and stroke in all study subjects of a general Japanese population, taking other traditional and nontraditional risk factors into account.

Key words: chronic kidney disease, cardiovascular disease, prospective study, general populations.

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METHODS

Study population

The Hisayama Study, an epidemiologic study of cerebrovascular and cardiovascular diseases, was established in 1961 in Hisayama, a suburban community adjacent to Fukuoka City, a metropolitan area on Kyushu Island in southern Japan. Hisayama's population of approximately 7000 has been stable for 40 years. Full community surveys of the residents have been repeated since 1961 [26]. In

1988, a screening survey for the present study was performed in Hisayama. A detailed description of this survey was published previously [27]. Briefly, a total of 2736 participants aged 40 years or older (80.7% of the total population of this age group) consented to participate in the examination and underwent a comprehensive assessment. We excluded from the study 99 subjects with a history of myocardial infarction or stroke, as determined by a questionnaire and medical records. In addition, after the exclusion of one subject without a blood sample and two subjects who were on predialysis [glomerular filtration rate (GFR) <15 mL/min/1.73 m^2], the remaining 2634 individuals (1110 men and 1524 women) were enrolled in this study.

Follow-up

The subjects were followed prospectively from December 1988 to November 2000 by repeated health examinations. The health examinations were conducted yearly, and the participation rate was approximately 50% to 80%. Health status was checked yearly by mail or telephone for any subjects who did not undergo a regular examination that year or who had moved out of town. We also established a daily monitoring system among the study team and local physicians or members of the town's Health and Welfare Office. When a subject died, an autopsy was performed at the Department of Pathology of Kyushu University. During the follow-up period, 485 subjects died, of whom 366 (75.5%) underwent autopsy. Only one subject was lost to follow-up.

Definition of chronic kidney disease

GFR was estimated using the simplified prediction equation derived from the Modification of Diet in Renal Disease (MDRD) Study [28] and given by the following equation:

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

GFR <60 mL/min/1.73 m^2 was defined as chronic kidney disease according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines [29].

Definition of cardiovascular events

The criteria for a diagnosis of coronary heart disease included first-ever acute myocardial infarction, silent myocardial infarction, or sudden cardiac death within 1 hour after the onset of acute illness [30]. Acute myocardial infarction was diagnosed when a subject met at least two of the following criteria: (*1*) typical symptoms, including prolonged severe anterior chest pain; (*2*) abnormal cardiac enzymes more than twice the upper limit of the normal range; (*3*) evolving diagnostic electrocardiogram (ECG) changes; or (*4*) morphologic changes, including local asynergy of cardiac wall motion on echocardiography, persistent perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars >1 cm long accompanied by coronary atherosclerosis at autopsy. Silent myocardial infarction was defined as myocardial scarring without any historical indication of clinical symptoms or abnormal cardiac enzyme changes. During the follow-up period, we identified 99 first-ever coronary heart disease events (56 men and 43 women).

Stroke was defined as a sudden onset of nonconvulsive and focal neurologic deficit persisting for >24 hours. The diagnosis of stroke and the determination of its pathologic type were based on the clinical history, neurologic examination, all available clinical data, including brain computed tomography (CT)/magnetic resonance imaging (MRI), and autopsy findings. Stroke was classified as either ischemic or hemorrhagic [30]. Hemorrhagic stroke included cerebral hemorrhage and subarachnoid hemorrhage. During the follow-up period, we identified 197 first-ever stroke events (86 men and 111 women). These were divided into 137 cases of ischemic stroke (60 men and 77 women) and 60 cases of hemorrhagic stroke (26 men and 34 women).

Risk factors

At the baseline examination, each participant completed a self-administered questionnaire covering medical history, antihypertensive treatment, smoking habits, and alcohol intake. The completed questionnaire was checked by trained interviewers at the screening. The latter three variables were classified as either current habitual use or not. Blood pressures were measured three times, after at least 5 minutes of rest, using a standard mercury sphygmomanometer with the subject in the sitting position. The mean of three measurements was used for the analysis. Hypertension was defined as blood pressure ≥140/90 mm Hg and/or current use of antihypertensive agents. 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) and/or ST depression (Minnesota code, 4-1, 2, 3). The study physicians performed a physical examination of each participant and rechecked his or her medical history to improve the precision of the information. Blood samples were collected after an overnight fast for the determination of serum creatinine, urea nitrogen, albumin, hemoglobin A_{1c}, and lipids. These specimens were assayed within 24 hours. A portion of the serum

Table 1. Age-adjusted mean values or frequencies of potential risk factors and laboratory variables according to kidney function by gender

Variables	Men		Women	
	CKD (−) ($N = 1051$)	CKD (+) ($N = 59$)	CKD (−) ($N = 1313$)	CKD (+) ($N = 211$)
Age *years*	58 ± 11	73 ± 11[a]	58 ± 11	71 ± 11[a]
Serum urea nitrogen *mmol/L*	5.5 ± 1.3	7.2 ± 1.4[a]	5.2 ± 1.2	6.4 ± 1.3[a]
Creatinine *μmol/L*	94.7 (75.6-118.6)	127.8 (101.1-161.5)[a]	78.4 (63.2-97.2)	98.9 (78.7-124.2)[a]
Systolic blood pressure *mm Hg*	135 ± 19	140 ± 20	132 ± 20	138 ± 21[a]
Diastolic blood pressure *mm Hg*	80 ± 11	82 ± 12	76 ± 11	77 ± 12
Antihypertensive medication%	11.8	19.8[a]	11.5	18.9[a]
Hypertension%	42.8	60.1[b]	32.8	39.4[a]
ECG abnormalities%	19.0	17.8	12.5	9.3
Albumin *g/L*	43 ± 2	42 ± 2	42 ± 2	42 ± 2
Diabetes mellitus%	14.2	17.6	8.6	6.8
Hemoglobin A_{1c}%	5.6 ± 0.8	5.6 ± 0.8	5.5 ± 0.7	5.6 ± 0.8
Total cholesterol *mmol/L*	5.06 ± 1.06	5.46 ± 1.11[a]	5.51 ± 1.07	5.69 ± 1.14[b]
Triglycerides *mmol/L*	1.31 (0.41-4.16)	1.43 (0.43-4.77)	1.06 (0.42-2.69)	1.12 (0.42-3.00)
HDL cholesterol *mmol/L*	1.25 ± 0.31	1.25 ± 0.32	1.33 ± 0.30	1.33 ± 0.32
Body mass index kg/m^2	22.7 ± 2.9	23.1 ± 3.0	22.9 ± 3.3	23.0 ± 3.5
Total homocysteine *μmol/L*	10.4 ± 5.3	11.4 ± 5.6[a]	8.0 ± 3.7	9.8 ± 4.0[a]
HS-CRP *mg/L*	0.52 (0.02-11.50)	0.48 (0.02-12.05)	0.37 (0.02-7.69)	0.36 (0.01-8.81)
Smoking habits%	51.2	30.0	7.0	7.7
Alcohol intake%	62.0	46.6	9.7	2.9
Menopause%	—	—	64.0	67.8

Abbreviations are: CKD, chronic kidney disease; ECG, electrocardiogram; HDL, high-density lipoprotein; HS-CRP, high-sensitivity C-reactive protein.

Age is not age-adjusted. Hypertension was defined as blood pressure = 140/90 mm Hg and/or current use of antihypertensive agents. Diabetes mellitus was defined according to the criteria recommended by the American Diabetes Association by a 75 g oral glucose tolerance test in 2450 subjects (93.0%), and by a fasting and postprandial glucose concentration in 184 remainders, in addition to a medical history of diabetes. Geometric mean values and 95% confidence intervals of creatinine, triglycerides, and high-sensitivity C-reactive protein are shown due to the skewed distribution. Values are means ± standard deviations or frequencies.

[a] $P < 0.01$; [b] $P < 0.05$ vs. CKD (−).

was stored at −20°C until used in the measurement of total homocysteine and high-sensitivity C-reactive protein (HS-CRP). Serum creatinine concentrations were measured by Jaffé method. Hemoglobin A_{1c} levels were measured by the high-performance liquid chromatography (HPLC) method. The total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were all determined enzymatically. Diabetes mellitus was defined according to the criteria recommended by the American Diabetes Association [31] by a 75 g oral glucose tolerance test in 2450 subjects (93%), and by fasting and postprandial glucose concentrations in 184 remainders, in addition to a medical history of diabetes. Frozen serum samples were thawed and assayed for serum total homocysteine levels by the HPLC method and for HS-CRP by particle-enhanced technology on the Dade Behring BN II nephelometer (Dade Behring, Tokyo, Japan). A high level of HS-CRP was defined as that in the 75th percentile or higher for serum HS-CRP in either gender.

Statistical analysis

The SAS software package was used to perform all statistical analyses. Serum creatinine, triglycerides, and HS-CRP were transformed into logarithms to improve the skewed distribution. The relationships between the kidney-function category and relevant factors were tested with adjustments for age by covariance analysis or the Mantel-Haenszel chi-square test using 10-year age groupings as appropriate. The incidences of cardiovascular disease were calculated by the person-year method and adjusted for the age distribution of the World Health Organization standard population in 1998 by the direct method. Differences in incidence between the kidney function categories were tested by the Cox proportional hazards regression analysis after adjustment for age. The age- or multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were also estimated with the use of the Cox proportional hazards model. In the multivariate analysis, we selected previously reported traditional or nontraditional cardiovascular disease risk factors [3] as confounding factors, and used the stepwise method with $P < 0.2$ required for entering or remaining in the model. We confirmed the assumption of the proportional hazards model, since the log-log survivor functions by the kidney function were found to be parallel. $P < 0.05$ was considered statistically significant in all analyses.

RESULTS

Table 1 shows the baseline clinical and demographic characteristics of the study subjects according to kidney function by gender. In either gender, the subjects with chronic kidney disease were significantly older than those without it. Thus, the mean values or frequencies of other variables were adjusted for age. The mean values of serum urea nitrogen and creatinine were significantly higher in

Table 2. Age-standardized incidence rates of cardiovascular disease according to kidney function by gender

	Men			Women		
	Person-years at risk	No. of events	Age-standardized incidence rate	Person-years at risk	No. of events	Age-standardized incidence rate
Cardiovascular disease						
CKD (−)	10,997	117	8.3	14,624	98	4.8
CKD (+)	441	17	10.7	1991	43	6.7[a]
Coronary heart disease						
CKD (−)	11,284	45	2.9	14,929	28	1.3
CKD (+)	460	11	6.2[a]	2076	15	2.7
Ischemic stroke						
CKD (−)	11,885	56	3.8	15,801	50	2.5
CKD (+)	485	4	3.1	2131	27	3.4[a]
Hemorrhagic stroke						
CKD (−)	11,885	23	1.9	15,801	30	1.4
CKD (+)	485	3	1.2	2131	4	0.8

Abbreviations are: CKD, chronic kidney disease; Incidence rate, per 1000 person-years.
[a] $P < 0.05$ vs. CKD (−).

Table 3. Age- or multivariate-adjusted analysis for occurrence of cardiovascular disease according to kidney function for men

	Hazard ratio (95% confidence interval)		
	Model 1	Model 2	Model 3
Cardiovascular disease			
CKD (−)	1.00	1.00	1.00
CKD (+)	1.45 (0.85–2.50)	1.29 (0.74–2.25)	1.32 (0.76–2.30)
Coronary heart disease			
CKD (−)	1.00	1.00	1.00
CKD (+)	2.45 (1.19–5.03)[a]	2.14 (1.01–4.52)[a]	2.26 (1.06–4.79)[a]
Ischemic stroke			
CKD (−)	1.00	1.00	1.00
CKD (+)	0.62 (0.22–1.77)	0.56 (0.20–1.61)	0.54 (0.19–1.53)
Hemorrhagic stroke			
CKD (−)	1.00	1.00	1.00
CKD (+)	1.40 (0.39–5.01)	1.11 (0.29–4.21)	1.09 (0.29–4.13)

CKD is chronic kidney disease. Model 1 is adjusted for age. Model 2 is adjusted for age, systolic blood pressure, antihypertensive medication, electrocardiogram abnormalities, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, smoking habits, and alcohol intake. Model 3 is adjusted for confounding factors used in the model 2, total homocysteine, and high-sensitivity C-reactive protein.
[a] $P < 0.05$ vs. CKD (−).

both male and female subjects with chronic kidney disease, as determined by the criteria. For both genders, subjects with chronic kidney disease had higher mean values of systolic blood pressure and higher frequencies of antihypertensive medication and hypertension. The mean total cholesterol and total homocysteine levels were also significantly higher in subjects with chronic kidney disease than in those without it in either gender. The mean values or frequencies of other potential risk factors did not differ between the two kidney function groups in either gender.

The age-standardized incidence rates of cardiovascular disease in each of the kidney function groups are shown by gender in Table 2. The cardiovascular disease incidence was higher in the subjects with chronic kidney disease than in those without it in either gender, but the difference was statistically significant only for women. The incidence of coronary heart disease was twice as high in men with chronic kidney disease as in men without it (6.2 vs. 2.9 per 1000 person-years) ($P < 0.05$), while the incidence of stroke did not differ significantly between men with chronic kidney disease and men without it. In contrast, in women the incidence of ischemic stroke was significantly higher in subjects with chronic kidney disease (3.4 vs. 2.5) ($P < 0.05$), while the incidence of coronary heart disease did not differ significantly between women with chronic kidney disease and women without it. Chronic kidney disease was not associated with hemorrhagic stroke in either gender.

Age- or multivariate-adjusted HRs of chronic kidney disease for the occurrence of cardiovascular disease were estimated for men (Table 3) and women (Table 4). The age-adjusted analysis showed that chronic kidney disease was a significant risk factor for coronary heart disease in men and for ischemic stroke in women (model 1). These relationships remained substantially unchanged even after adjustments for other traditional cardiovascular diseases risk factors, such as systolic blood pressure, antihypertensive medication, ECG abnormalities, diabetes, total cholesterol, HDL cholesterol, triglycerides, body

Table 4. Age- or multivariate-adjusted analysis for occurrence of cardiovascular disease according to kidney function for women

	Hazard ratio (95% confidence interval)		
	Model 1	Model 2	Model 3
Cardiovascular disease			
CKD (−)	1.00	1.00	1.00
CKD (+)	1.55 (1.06–2.28)[a]	1.62 (1.10–2.39)[a]	1.62 (1.10–2.39)[a]
Coronary heart disease			
CKD (−)	1.00	1.00	1.00
CKD (+)	1.58 (0.81–3.08)	1.55 (0.79–3.06)	1.55 (0.79–3.05)
Ischemic stroke			
CKD (−)	1.00	1.00	1.00
CKD (+)	1.84 (1.12–3.04)[a]	1.91 (1.15–3.16)[a]	1.91 (1.15–3.15)[a]
Hemorrhagic stroke			
CKD (−)	1.00	1.00	1.00
CKD (+)	0.56 (0.19–1.67)	0.56 (0.19–1.67)	0.58 (0.19–1.73)

CKD is chronic kidney disease. Model 1 is adjusted for age. Model 2 is adjusted for age, systolic blood pressure, antihypertensive medication, electrocardiogram abnormalities, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, smoking habits, and alcohol intake. Model 3 is adjusted for confounding factors used in the model 2, total homocysteine, and high-sensitivity C-reactive protein.

[a] $P < 0.05$ vs. CKD (−).

Table 5. Age- and gender-adjusted or multivariate-adjusted hazard ratio for occurrence of cardiovascular disease according to kidney function by status of hypertension or high-sensitivity C-reactive protein (HS-CRP) levels in 2634 subjects

	Population at risk	No. of events	Age- and sex-adjusted hazard ratio (95% CI)	Multivariate-adjusted hazard ratio (95% CI)
Hypertension (−)				
CKD (−)	1448	83	1.00	1.00
CKD (+)	91	9	1.03 (0.50-2.13)	1.11 (0.53-2.29)[a]
Hypertension (+)				
CKD (−)	916	132	1.00	1.00
CKD (+)	179	51	1.54 (1.08-2.20)[b]	1.63 (1.14-2.33)[a,c]
Low levels of HS-CRP				
CKD (−)	1806	144	1.00	1.00
CKD (+)	178	39	1.63 (1.10-2.41)[b]	1.59 (1.07-2.36)[b,d]
High levels of HS-CRP				
CKD (−)	558	71	1.00	1.00
CKD (+)	92	21	1.49 (0.88-2.54)	1.46 (0.84-2.52)[d]

Abbreviations are: CKD, chronic kidney disease; CI, confidence interval. Hypertension was defined as blood pressure ≥140/90 mm Hg and/or current use of antihypertensive agents. A high level of high-sensitivity C-reactive protein was defined as that in the 75th percentile or higher for serum high-sensitivity C-reactive protein in either gender.

[a] Adjusted for age, gender, electrocardiogram abnormalities, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, smoking habits, alcohol intake, total homocysteine, and high-sensitivity C-reactive protein.

[b] $P < 0.05$ vs. CKD (−).

[c] $P < 0.01$.

[d] Adjusted for age, gender, systolic blood pressure, antihypertensive medication, electrocardiogram abnormalities, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, smoking habits, alcohol intake, and total homocysteine.

mass index, smoking habits, and alcohol intake (model 2). Furthermore, even after controlling for nontraditional cardiovascular disease risk factors, including total homocysteine and HS-CRP, chronic kidney disease was found to be an independent risk factor for the occurrence of coronary heart disease in men (model 3) (HR 2.26 and 95% CI 1.06-4.79) ($P < 0.05$) and for the occurrence of ischemic stroke in women (HR 1.91 and 95% CI 1.15-3.15) ($P < 0.05$).

We examined the associations between GFR as a continuous variable and cardiovascular disease outcomes. This analysis showed the significant inverse association between GFR levels and the risk of coronary heart disease (CHD) events in men (for a decrease in GFR by 10 mL/min/1.73 m^2) (HR 1.30 and 95% CI 1.01-1.67) ($P < 0.05$), even after adjustments for the traditional and nontraditional cardiovascular disease risk factors named above. A similar tendency was observed for the risk of ischemic stroke in women (HR 1.26 and 95% CI 0.98-1.60) ($P = 0.07$).

There were no significant interactions between kidney function and risk factors, including hypertension, diabetes, smoking habits, ECG abnormalities, total cholesterol, triglycerides, HDL cholesterol, total homocysteine, and HS-CRP in the occurrence of cardiovascular disease.

Because hypertension and inflammation are strong risk factors for cardiovascular disease, we examined the effects of chronic kidney disease on the occurrence of cardiovascular disease stratified by hypertension or levels

of HS-CRP. As shown in Table 5, the age- and gender-adjusted or multivariate-adjusted HR of cardiovascular disease was significantly higher in the subjects with chronic kidney disease than in those without it in the hypertensive group, but not in the normotensive group. On the other hand, chronic kidney disease is a risk factor for cardiovascular disease events regardless of HS-CRP levels, though it is not significant in high levels of HS-CRP, probably because of the small number of subjects in the present study.

DISCUSSION

In a prospective study of a community-dwelling Japanese population, we demonstrated chronic kidney disease to be an independent predictor of coronary heart disease events in men and of the occurrence of cardiovascular disease and ischemic stroke in women. To our knowledge, this is the first population-based prospective study on the association between chronic kidney disease and cardiovascular disease in Japan.

The reduction in kidney function has consistently been found to be an independent risk factor for cardiovascular disease and all-cause mortality in patients after coronary events [6, 7] in those undergoing coronary interventions [8, 9], in patients with heart failure [10–12], in patients with hypertension [13–15] or diabetes [16], and in elderly subjects [17–20]. This relationship has been inconsistent, however, in prospective studies of general populations. In the Atherosclerosis Risk in Communities (ARIC) Study [21] and the Second National Health and Nutrition Examination Survey (NHANES II) [22], reduced kidney function was found to be an independent risk factor for cardiovascular disease events or all-cause mortality. These findings are in accord with those of the present study. These associations were not observed, however, in the Framingham Study [23] and the First National Health and Nutrition Examination Survey (NHANES I) [24]. Differences in the study population are a possible reason for this discrepancy; for example, African Americans were part of the ARIC Study but not of the Framingham Study. Another possible reason is that serum creatinine, which was used as a measure of renal function in both the Framingham Study [23] and the NHANES I [24], is less sensitive than estimated GFR, which was used in our study as well as in the ARIC and NHANES II Studies, in the detection of small differences in the levels of kidney function; thus, an association in low-risk populations may be less detectable when serum creatinine is used. When we examined the associations between serum creatinine and cardiovascular disease events in our population, we found no significant associations between these parameters, indicating that GFR is a better predictor of cardiovascular disease events than serum creatinine.

There are several possible explanations for the independent association of chronic kidney disease with cardiovascular disease outcome [5]. Reduced renal function is associated with a high prevalence of traditional cardiovascular disease risk factors, such as aging, diabetes, smoking habits, elevated blood pressure, and total cholesterol levels, decreased HDL cholesterol levels, and left ventricular hypertrophy by ECG [3]. In addition, a reduced GFR may be associated with increased levels of nontraditional cardiovascular disease risk factors, such as total homocysteine, inflammation, production of nitric oxide, oxidative stress, and thrombogenic factors [3, 32]. These factors could increase the risk of cardiovascular disease in subjects with chronic kidney disease. In our subjects, however, the association between chronic kidney disease and the incidence of cardiovascular disease remained significant even after adjustment for the traditional cardiovascular disease risk factors named above and some of the nontraditional cardiovascular disease risk factors, including total homocysteine and HS-CRP levels. Further investigation is needed into the role of other nontraditional cardiovascular disease risk factors in the occurrence of cardiovascular disease among subjects with chronic kidney disease. Another possible explanation for the chronic kidney disease-cardiovascular disease association is that reduced renal function may be a marker of vascular disease. In our previous autopsy study of deceased Hisayama residents, the development of renal arteriosclerosis and glomerular sclerosis was found to be closely associated with reduced GFR in both genders [33]. It is well recognized that renal arteriosclerosis and glomerular sclerosis are closely related to systemic atherosclerosis [34, 35], suggesting an increased risk of cardiovascular disease in subjects with chronic kidney disease.

In the stratified analysis, we found that chronic kidney disease was a significant predictor of cardiovascular disease in the hypertensive subjects. Previous clinical studies have also found that reduced GFR is a risk factor for cardiovascular disease events in patients with hypertension [17–19]. Because hypertension is a strong risk factor for the progression of systemic atherosclerosis, it is reasonable to consider that subjects with hypertension already have vascular injuries to some extent. Our findings, together with those of the other studies, suggest that chronic kidney disease is a marker of advanced vascular injuries in high-risk populations, or that chronic kidney disease–related metabolic disorders, such as dyslipidemia, oxidative stress, or calcium-phosphate abnormality, accelerate the progression of preexisting vascular injuries [36]. The reason why chronic kidney disease was not a significant risk factor for cardiovascular disease in the normotensive subjects may be that the causes of chronic kidney disease among normotensives, such as primary renal disease, are not directly related

to atherosclerosis. In addition, chronic kidney disease–related metabolic disorders may affect normal or mildly injured vessels to a lesser extent in normotensives than in hypertensives, and therefore, the 12-year follow-up period of our study may be insufficient to allow for the occurrence of cardiovascular disease.

In the present study, chronic kidney disease was found to be an independent risk factor in men for the occurrence of coronary heart disease but not of ischemic stroke. A possible reason for this discrepancy is competition among causes of cardiovascular disease, whereby our men with chronic kidney disease were more likely to suffer from coronary heart disease than from ischemic stroke, thereby causing possible censorship of data due to coronary death. Also, risk factors may have been modified in response to medical advice and treatment after coronary heart disease events, which would probably have weakened the association between chronic kidney disease and ischemic stroke. In contrast, for women with chronic kidney disease, an opposite phenomenon was observed: the risk of ischemic stroke was significantly elevated, while the risk of coronary heart disease was not. This phenomenon is likely due to both inadequate statistical power and to the low risk of coronary heart disease in Japanese women. Some reports indicate a higher risk of stroke in women [37, 38]. Di Tullio et al [38] have shown that smaller aortic plaques are significantly associated with ischemic stroke in women but not in men. This gender difference may be a consequence of the effects of hypercoagulable states [39, 40], lipid abnormalities [41], or gonadal steroids [42–44] in women. Further studies are necessary to elucidate these gender differences in detail.

Several limitations of our study should be discussed. The primary limitation is the small numbers of both subjects and cardiovascular disease events in the study population. Thus, the generalizability of the study results may be somewhat limited. Nonetheless, we believe that the findings of our study represent the actual association between chronic kidney disease and cardiovascular disease outcomes, since we used a highly accurate method of determining all cardiovascular disease cases.

The second limitation is that our results might be biased, because almost 20% of the target population did not participate. At baseline, the mean age of subjects who did not participate was significantly lower than that of subjects who did participate (53 vs. 60 years old), and the proportion of men was significantly higher among nonparticipants (57% vs. 42%). Unfortunately, we could not obtain information on other risk factors among the nonparticipants. However, it is generally agreed that an acceptable participation rate in a population-based study (i.e., a rate that practically eliminates the threat of selection bias attributable to nonparticipants) is above 70% of the target population [45, 46]. Because of the high participation rate in our study (81%), this bias did not seem to have the potential to alter our findings.

The third limitation is that our GFR estimates, which were made using the simplified prediction equation derived from the MDRD Study and that were based on a single blood sample, might not be sufficiently correct, although this prediction equation, among other equations of its type, is considered to be the most precise estimate of GFR [28]. In addition, a recent report has shown that repeated measurements of serum creatinine are necessary to correct within-person measurement variations of serum creatinine [47], suggesting that some nondifferential misclassifications of cases with chronic kidney disease may have occurred in our study. Given that this limitation can reduce the impact of chronic kidney disease, the true association may be stronger than that shown in our findings.

The fourth limitation is that we have no information regarding the severity or duration of hypertension or other cardiovascular disease risk factors. The fifth limitation is that we also could not provide information regarding the type or number of antihypertensive drugs, medication compliance, and blood pressure control. Although ECG abnormalities, which reflect target-organ damage from hypertension or other risk factors, were used as a confounding factor in the multivariate analysis, these limitations may reduce the accuracy of our findings to some extent. Thus, they have the potential to alter our findings, but they are not likely to do so.

The sixth limitation is that our subjects with chronic kidney disease may have undergone more intense medical surveillance than those without it, resulting in a surveillance bias. However, diagnostic procedures such as echocardiography and scintigraphy were usually performed in subjects who presented symptoms or clinical signs of cardiac ischemia, but were not performed in subjects who did not present cardiac symptoms, even if they had chronic kidney disease. Brain CT/MRI was taken in the similar situation. In addition, as described in the **Methods** section, the diagnosis of cardiovascular disease was in principle based on the acute events of heart and brain attack. We performed almost the same follow-up surveys on all study subjects regardless of the presence or absence of chronic kidney disease. The mean number of health investigations was similar for subjects with or without chronic kidney disease in men (4 ± 4 times in subjects with chronic kidney disease vs. 5 ± 4 times in subjects without chronic kidney disease) and in women (5 ± 4 times vs. 6 ± 4 times). Furthermore, health status was checked yearly by mail or telephone for any subjects who did not undergo a regular examination that year or who had moved out of town. Thus, subjects with chronic kidney disease are considered not to have undergone more intense medical surveillance, so the potential for such bias seems to be negligible.

CONCLUSION

Chronic kidney disease was found to be an independent risk factor for the incidence of cardiovascular disease in a general Japanese population. Our findings suggest that subjects with chronic kidney disease should be considered a high-risk population for cardiovascular disease and be recommended for more intensive preventive management of cardiovascular disease, including active detection and strict treatment of cardiovascular risk factors. An additional clinical intervention trial is needed to evaluate preventive measures of cardiovascular disease in subjects with chronic kidney disease.

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Elevated C-Reactive Protein Is a Predictor of the Development of Diabetes in a General Japanese Population

The Hisayama Study

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OBJECTIVE — We examined the association between high-sensitivity C-reactive protein (CRP) levels and the development of diabetes in a general Japanese population.

RESEARCH DESIGN AND METHODS — A total of 1,759 Japanese subjects, aged 40–79 years and without diabetes (according to American Diabetes Association fasting criteria), were stratified into three groups according to CRP tertiles by sex and followed up prospectively for a mean of 9.0 years.

RESULTS — During the follow-up, 131 subjects (67 men and 64 women) developed diabetes. In both sexes, the age-adjusted cumulative incidence of diabetes increased significantly as the tertiles of CRP levels increased. In multivariate analyses, the risk of developing diabetes was significantly higher in the highest CRP tertile than in the lowest after adjustment for a number of confounding factors (odds ratio 2.63 [95% CI 1.23–5.65] for men and 2.25 [1.01–5.01] for women). In stratified analyses, this CRP-diabetes association was stronger in subjects without obesity or other risk factors related to insulin resistance and in nondrinking subjects.

CONCLUSIONS — Our findings suggest that elevated CRP concentration is a significant predictor of diabetes in the general Japanese population, independent of obesity and insulin resistance.

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In some cohort and nested case-control studies in Western countries, an elevated C-reactive protein (CRP) level has been an independent predictor of diabetes (1–10). Recent cross-sectional studies have also demonstrated clear associations of elevated serum CRP levels with obesity and insulin resistance (11–13). These findings suggest that the inflammatory state illustrated by elevated CRP concentrations is associated with hyperglycemia and diabetes through obesity or increased insulin resistance. However, epidemiological findings concerning this issue are still controversial; several studies have reported a significant positive association between elevation in CRP levels and the future risk of diabetes even after adjustment for BMI (1,2,4,7,9,10), whereas in other studies (3,6) this association disappeared after adjustment for BMI.

Japanese are characterized by low BMI levels and low CRP concentrations in blood compared with Westerners (14). Moreover, there have been no reports on the relationship between CRP levels and the development of diabetes among general populations in Japan. The aim of the present study is to examine the effects of serum CRP levels on the development of diabetes in a prospective study of a defined Japanese population, taking into account comprehensive risk factors.

RESEARCH DESIGN AND METHODS

Study population and follow-up survey

In 1988, a screening survey for the present study was performed in the Town of Hisayama in Japan. A total of 2,587 residents aged 40–79 years (80.2% of the total population of this age-group) participated in the baseline survey. The diabetes classification was based on the fasting criteria of the American Diabetes Association (15), i.e., subjects with fasting plasma glucose levels ≥7.0 mmol/l or those who were taking diabetes medications were considered diabetic.

After the exclusion of 80 subjects who had already eaten breakfast before the examination, 233 subjects with diabetes, and 67 subjects whose CRP concentrations could not be measured due to insufficient quantities of stored sera, the remaining 2,207 subjects (926 men and 1,281 women) were enrolled in the baseline examination. Among those, 1,759 subjects (694 men and 1,065 women) underwent follow-up examinations in 1993–1998 (follow-up rate 79.7%). We considered a subject to have developed diabetes when he/she met the above-mentioned baseline criteria. During this period, 131 subjects (67 men and 64 women) developed diabetes.

Laboratory measurements

Plasma glucose levels were determined by a glucose-oxidase method, and serum insulin was measured by radioimmunoassay. HbA_{1c} levels were measured by high-pressure liquid chromatography. Total cholesterol, HDL cholesterol, and triglycerides were all determined enzymatically. Serum specimens collected at the time of CRP measurement were stored at −20°C until used in 2002. High-sensitivity CRP

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Abbreviations: CRP, C-reactive protein.

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

concentrations were determined using a modification of the Behring latex-enhanced CRP assay. Sitting blood pressure was obtained three times and the average values used in the analyses. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or current treatment with antihypertensive agents. BMI (kilograms per meters squared) was used as an indicator of obesity.

Diabetes in first- or second-degree relatives indicated a family history of diabetes. Those subjects engaging in sports at least three times a week during their leisure time comprised a regular exercise group. Information on smoking habits and alcohol intake was used to classify subjects as having current habits or not.

Statistical analysis

Because the distributions of CRP, fasting insulin, and triglycerides were skewed, these variables were natural log transformed for statistical analyses. To analyze CRP levels as categorical variables, these levels were divided into tertiles by sex (0.05–0.28, 0.29–0.77, and 0.78–13.5 mg/l for men and 0.05–0.24, 0.25–0.57, and 0.58–5.78 mg/l for women). The age-adjusted cumulative incidence of diabetes was calculated by the direct method and compared by the Mantel-Haenszel χ^2 test using 10-year age-groupings. Age- and multivariate-adjusted odds ratios (ORs) and 95% CIs were calculated by logistic regression analysis. $P < 0.05$ was considered statistically significant in all analyses.

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

Table 1—*Characteristics of subjects by sex*

	Men	Women
n	694	1,065
Age (years)	58 ± 10	57 ± 10
High-sensitivity CRP (mg/l)	0.49 (0.07–7.14)	0.36 (0.06–3.22)
Fasting plasma glucose (mmol/l)	5.6 ± 0.5	5.5 ± 0.5
HbA_{1c} (%)	5.5 ± 0.5	5.4 ± 0.5
Family history of diabetes (%)	9.3	7.3
Fasting insulin (pmol/l)	30.0 (18.0–72.0)	36.0 (18.0–72.0)
BMI (kg/m^2)	22.9 ± 2.9	23.0 ± 3.1
Total cholesterol (mmol/l)	5.10 ± 1.04	5.57 ± 1.05
HDL cholesterol (mmol/l)	1.26 ± 0.30	1.35 ± 0.29
Triglycerides (mmol/l)	1.25 (0.58–3.49)	1.02 (0.49–2.33)
Systolic blood pressure (mmHg)	131 ± 19	130 ± 20
Diastolic blood pressure (mmHg)	80 ± 11	75 ± 11
Hypertension (%)	41.5	32.7
Current drinking (%)	61.0	8.5
Current smoking (%)	47.6	5.4
Regular exercise (%)	16.1	4.9

Data are means ± SD or medians (95% CI) unless otherwise indicated.

RESULTS — The clinical characteristics of the subjects by sex are shown in Table 1. The mean age was 58 years for men and 57 years for women.

In both sexes, the age-adjusted cumulative incidence of diabetes increased significantly with elevating tertiles of baseline serum CRP concentrations. The incidences in the 3rd tertile for both sexes and in the 2nd tertile for men were significantly higher than in the 1st tertile (Fig. 1). As shown in Table 2, the risk of future diabetes in either sex was more than threefold higher in the 3rd tertile than in the 1st tertile after adjustment for age. These associations remained substantially unchanged even after adjustment for the other confounding factors, including age, family history of diabetes, fasting insulin, BMI, total cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, current drinking, current smoking, and physical activity (adjusted OR 2.63 [95% CI 1.23–5.65], $P = 0.014$, for men and 2.25 [1.01–5.01], $P = 0.049$, for women).

We next estimated the age- and sex-adjusted ORs and 95% CIs for the development of diabetes by an increment of 1 log CRP in men and women together according to the other risk factor levels (Table 3). Analyses were performed by dividing the subjects into three groups according to tertiles of BMI, triglycerides, and HDL cholesterol levels or into two

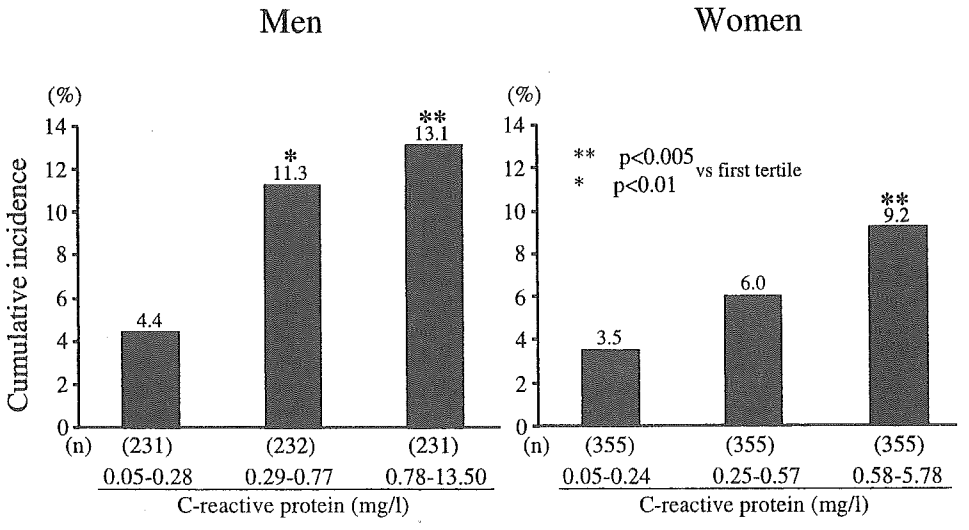

Figure 1—*Age-adjusted cumulative incidence of diabetes according to tertiles of serum high-sensitivity CRP levels by sex.*

Table 2—*Age- or multivariate-adjusted ORs and 95% CIs for occurrence of diabetes according to tertiles of serum high-sensitivity CRP levels by sex*

	High-sensitivity CRP level (mg/l)							
	Men				Women			
	0.05–0.28	0.29–0.77	0.78–13.50	*P* for trend	0.05–0.24	0.25–0.57	0.58–5.78	*P* for trend
Population at risk (*n*)	231	232	231		355	355	355	
Cases of diabetes (*n*)	11	26	30		10	21	33	
Age-adjusted OR (95% CI)	1 (referent)	2.67 (1.28–5.56)	3.23 (1.57–6.70)	0.002	1 (referent)	2.12 (0.98–4.58)	3.35 (1.60–7.03)	0.001
Multivariate-adjusted OR (95% CI)	1 (referent)	1.96 (0.92–4.19)	2.63 (1.23–5.65)	0.014	1 (referent)	1.76 (0.80–3.87)	2.25 (1.01–5.01)	0.049

Multivariate adjustment was made for age, family history of diabetes, fasting insulin, BMI, total cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, current drinking, current smoking, and physical activity.

groups by hypertension status, current drinking, and current smoking. Significant positive associations between CRP levels and incident diabetes were observed among subjects in the 1st tertile of BMI, among subjects in the 1st and 2nd tertiles of triglycerides, among subjects of the 2nd and 3rd tertiles of HDL cholesterol, and among subjects without hypertension or current drinking. Significant associations were also observed in both smokers and nonsmokers. However, clear CRP-diabetes associations were not seen in the other categories of any risk factors.

CONCLUSIONS — We demonstrated in a prospective study of a general Japanese population that elevated CRP level is an independent predictor of diabetes for both sexes even after adjustment for comprehensive risk factors. In stratified analyses, the CRP-diabetes association was stronger in subjects without risk factors related to insulin resistance, such as obesity, dyslipidemia, and hypertension, and among nondrinkers, whereas the presence of a current smoking habit did not affect this association.

To our knowledge, this is the first report to indicate that the low-grade inflammatory state illustrated by increased CRP is an independent risk factor for developing diabetes in a general Japanese population. Similar findings were observed in a Japanese-American population (13) as well as in some other Western populations (5–12,14). Since Japanese Americans have a Western lifestyle, their findings cannot be generalized to Japanese living in Japan. Our subjects were thinner than those in previous reports (1–10). Our findings suggest that the subclinical inflammatory process has an important role in the development of diabetes in relatively lean Asian populations, as it does in Western populations.

Recent cross-sectional epidemiological data have demonstrated that elevated serum CRP levels are associated with obesity, insulin resistance, and glucose intolerance (11–13). These findings suggest that the inflammatory state affects glucose levels in blood and increases the risk of diabetes via obesity or insulin resistance. However, our study showed that the association between CRP levels and the development of diabetes is independent of serum insulin levels as well as BMI. These findings are in accord with those of several other cohort studies (1,9). Additionally, our stratified analyses showed that the CRP-diabetes association was stronger particularly in individuals with low levels of risk factors related to insulin resistance. Therefore, a low-grade inflammatory state can be considered a risk factor for diabetes independent of obesity and insulin resistance, and unknown mediators are also thought to be involved in the development of diabetes.

In our subjects, the influence of CRP on the incidence of diabetes was stronger in nondrinkers than in drinkers. Some studies have shown that moderate alcohol

Table 3—*Age- and sex-adjusted ORs and 95% CIs for occurrence of diabetes by an increment of 1 log high-sensitivity CRP in all subjects according to risk-factor levels*

Risk factor	Population at risk (*n*)	Cases of diabetes (*n*)	Age- and sex-adjusted OR (95% CI)	*P*
BMI (kg/m^2)				
≤21.5	586	29	1.36 (1.05–1.75)	0.017
21.6–24.2	587	35	1.20 (0.92–1.57)	NS
≥24.3	586	67	1.25 (0.99–1.59)	NS
Triglycerides (mmol/l)				
≤0.88	587	30	1.30 (1.01–1.67)	0.042
0.89–1.34	582	29	1.50 (1.12–2.01)	0.007
≥1.35	590	72	1.16 (0.94–1.43)	NS
HDL cholesterol (mmol/l)				
≤1.14	572	49	1.04 (0.82–1.31)	NS
1.15–1.40	583	44	1.43 (1.13–1.81)	0.003
≥1.41	604	38	1.57 (1.20–2.07)	0.001
Hypertension				
Without	1,123	54	1.45 (1.18–1.77)	0.0003
With	636	77	1.16 (0.95–1.41)	NS
Current drinking				
Without	1,246	77	1.43 (1.20–1.71)	0.0001
With	513	54	1.14 (0.92–1.42)	NS
Current smoking				
Without	1,372	95	1.29 (1.09–1.53)	0.003
With	387	36	1.34 (1.04–1.72)	0.022

consumption is associated with lower CRP concentrations (16,17). Additionally, recent cohort studies have revealed that moderate alcohol consumption reduced the risk of future type 2 diabetes (18,19). Therefore, the intake of alcohol may attenuate the influence of CRP on the development of diabetes.

A recent cohort study has reported a significant association between inflammation and future diabetes among nonsmokers but not among smokers (8). In our subjects, however, an association between elevated CRP levels and incident diabetes was observed in both nonsmokers and smokers. This suggests that the CRP-diabetes association is independent of current smoking.

Several limitations of our study should be discussed. The primary limitation is that a diagnosis of diabetes was not based on a 75-g oral glucose tolerance test, but on a single reading of fasting glucose level, as was the case in other epidemiological studies (2,8,9). Subjects with diabetes having normal fasting glucose levels were misdiagnosed in our study. Additionally, some of the participants who were classified as having worsening fasting glucose status may not have been so categorized after repeated testing. These misclassifications should weaken the association found in this study. Therefore, the true association may be stronger than that shown in our findings. A secondary limitation is that CRP concentrations were measured in serum conserved for a long period at −20°C. However, the stability of CRP concentrations in serum preserved at this temperature for an average of 12 years was confirmed in the Reykjavik Study (20). The last limitation is that our study lacked information on drug use, which could affect serum CRP levels. It is known that several medications can alter CRP levels, including statins, ACE inhibitors, fibrates, niacin, thiazolidinedione, and estrogen/progestogen hormone (21). However, these medications were rarely used in our country in 1988. This suggests that such a bias does not invalidate the present findings.

In conclusion, we showed that subclinical elevation in CRP concentrations is an independent predictor of diabetes in a general Japanese population. CRP was an effective predictor of diabetes in individuals with the lowest BMI as well as in individuals without other risk factors related to insulin resistance. These findings add to the notion that low-grade inflammation is an important factor in the pathogenesis of type 2 diabetes. Further study is necessary to clarify the role of inflammation in the cascade to the development of diabetes.

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6 メタボリックシンドロームにおける高血圧の臨床的意義を教えて下さい

島本和明

メタボリックシンドローム(Met S)を構成する因子のなかで、高血圧は40歳以上の服薬していない一般住民で男性56%、女性45%とともに最も頻度の高い因子です。Met Sと診断された方で、わが国のガイドラインの危険因子をみると、高血圧は84%を占め、腹部肥満83%とともに最も頻度の高い危険因子です。さらに、NCEP-ATP Ⅲ[1]で高血圧を必須として他の2つ以上危険因子をもつものは、他の危険因子を必須とする場合に比べて、心血管疾患発症リスクは最も強くなります。Met Sの成因として重要なインスリン抵抗性も高血圧では約半数に認められます。このように、Met S各危険因子のなかで、高血圧は特にわが国においては重要な因子といえます。

高血圧はメタボリックシンドローム構成因子のなかで最も高頻度である

一般住民において、男女ともに高血圧はMet S構成因子のなかで最も高頻度を示す。一方、**表1**に示すようにMet Sと診断された対象における各危険因子の頻度は、やはり高血圧が最も高く、特にわが国におけるMet Sにおける高血圧の貢献は大きいと思われる。NCEP-ATP Ⅲ[1]のわが国の基準に置き換えた成績では、5つの危険因子のうち血圧高値を必須とした場合の心疾患発症リスクは2.27倍と有意に大きく、5つのうち3つ以上とする場合(2.23倍)よりむしろ増大した。一方、高血圧以外の3つ以上のリスクを有するものでは発症リスクは2倍前後とリスクが低下し、有意な差も消失した。このようにMet Sでは、少なくともわが国では、高血圧のもつ臨床的意義は大きいものがある。Met Sにおける昇圧機序は、主として肥満-腹部肥満より派生するイン

NCEP-ATP Ⅲ

インスリン抵抗性

血圧高値	168/198 (84.8%)
腹部肥満	167/198 (84.3%)
高TG血症	164/198 (82.8%)
低HDL血症	90/198 (45.5%)
高FPG血症	74/198 (37.4%)

表1　メタボリックシンドローム群での各危険因子保有の頻度(MS群に占める割合)

	男性			女性	
	n=133	r	p	n=263	r	p
Leptin & SBP		0.139	0.057	Leptin & SBP	0.120	0.027
Leptin & DBP		0.149	0.045	Leptin & DBP	0.109	0.039
Leptin & FIRI		0.147	0.047	Leptin & FIRI	0.457	<0.001
Leptin & HOMA		0.120	0.087	Leptin & HOMA	0.438	<0.001

表2　レプチンと高血圧、インスリン抵抗性との関連
regression analysis adjusted for age and BMI

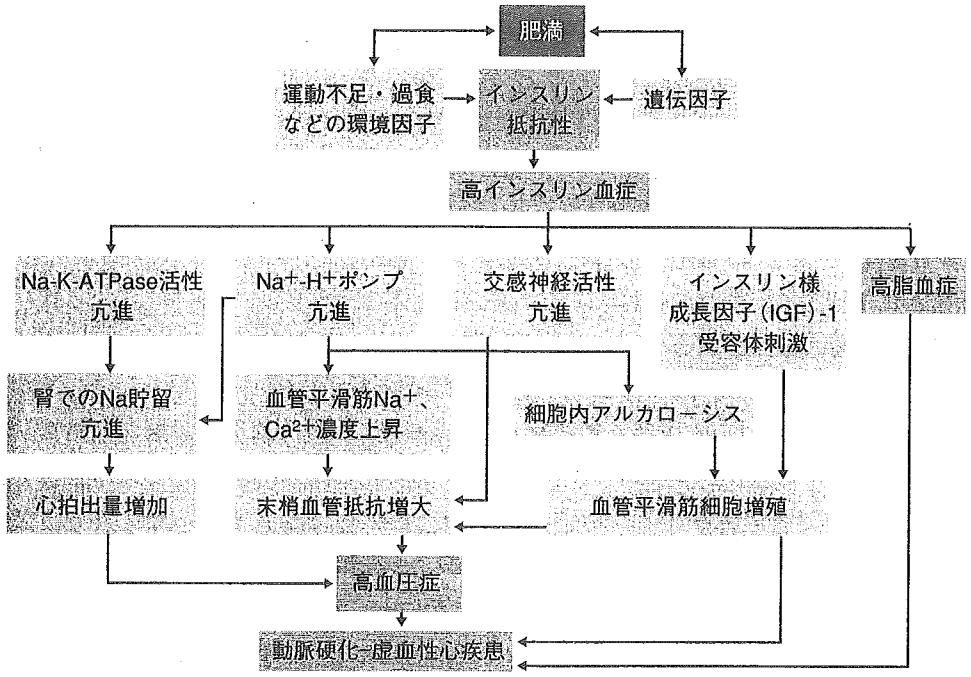

図1　高インスリン血症による血圧上昇機転

スリン抵抗性が主な機序を成している。最近はアディポサイトカインであるレプチンも高血圧、インスリン抵抗性と密接な関連を有し(**表2**)、交感神経活性亢進を介して昇圧に関与することが判明している[2]。一方、アディポネクチンはインスリン抵抗性を介して昇圧に関与し、直接作用は少ないものと思われる。**図1**にMet Sにおける昇圧機序を示す。

レプチン

アディポネクチン

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11 なぜ正常高値高血圧(130/85mmHg以上)がメタボリックシンドロームの診断基準になるのですか？

島本和明

メタボリックシンドローム(Met S)は生活習慣の欧米化による肥満、特に腹部肥満がインスリン抵抗性の上流に位置して、各種危険因子を派生する結果、心血管系疾患の強い危険因子になる疾患概念です。血圧と心血管疾患の関係をみると、心血管疾患は血圧上昇とともに連続的に増加し、120/80mmHg以上の正常血圧、130/85mmHg以上の正常高値血圧、140/80mmHg以上の高血圧、そして160/100mmHg以上の中等症高血圧、180/110mmHg以上の重症高血圧の順に増加します。そのため、至適血圧(120/80mmHg未満)に比べると正常血圧、正常高値血圧も心血管疾患のリスクになっております。140/90mmHg以上の高血圧は薬物療法で治療する対象として決められています。Met Sのように他の危険因子が合併し、心血管疾患のより発症しやすい状況では、130/85mmHgとさらに低い降圧目標が必要となり、診断基準も低くなります。

動脈硬化危険因子が併発すると、より低い血圧群で心血管疾患の頻度が増す

図1に端野・壮瞥町研究[1]と久山町研究[2]の結果を示す。端野・壮瞥町研究では正常血圧、正常高値血圧、軽症高血圧、中等症以上の高血圧と、血圧が高い順に、20年の追跡において心血管疾患死が有意に増加しいる。そして一般住民では140/90mmHg以上で有意な死亡率増加を示している。久山町研究では、脳梗塞の頻度をみるが、やはり血圧上昇とともに脳梗塞発症は増加している。

端野・壮瞥町研究

久山町研究

一方、**図2**に示すように、耐糖能異常、あるいは糖尿病を有する対象では、130/80mmHg以上で心血管疾患死亡が有意に増加し、耐糖能異常や糖尿病を有する群では、130/80mmHg以上が高血圧として治療の対象となってくる[3]。このように、動脈硬化危険因子が併発すると当然ながら、より低い血圧群で心血管疾患の頻度が増すことになる。わが国のMet Sの診断基準[4]を用いて心血管疾患発症のリスクをみた場合、血圧130/85mmHg以上を採択した場合の心血管疾患発症率は、非Met S群に比べて1.8倍高値となり、140/90mmHg以上を基準にした場合は2.1倍で、同等の危険率を示している。これらのことより、心血管疾患の一次予防の意味で血圧値は140/90mmHgよりはもっと低い130/85mmHg以上を血圧高値の基準として採用している。

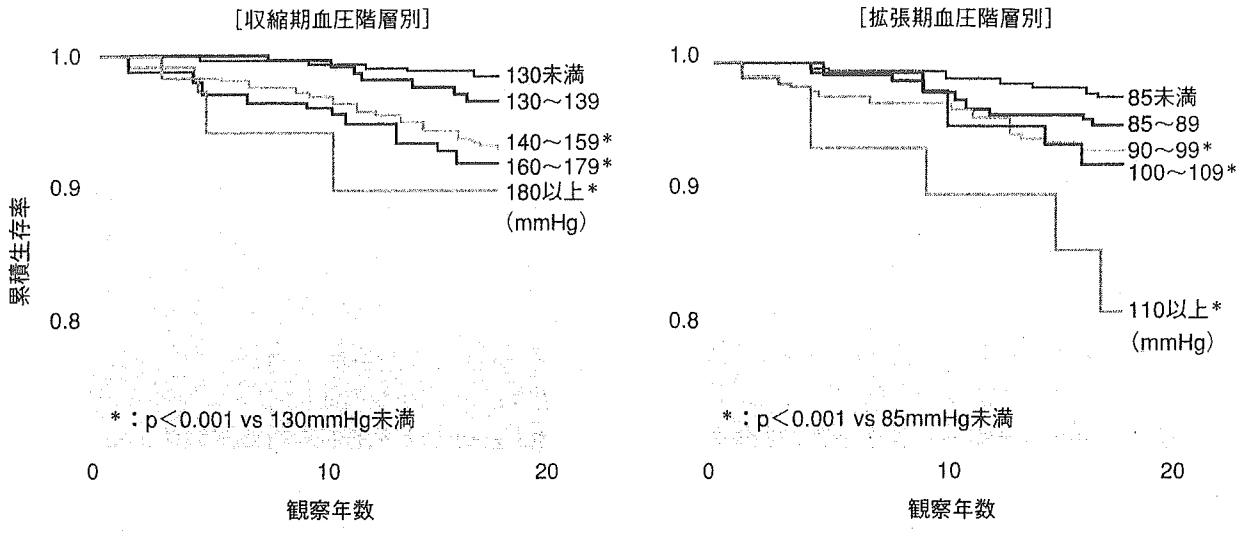

図1　血圧階層別の累積生存率：心・血管死亡（端野・壮瞥町研究）

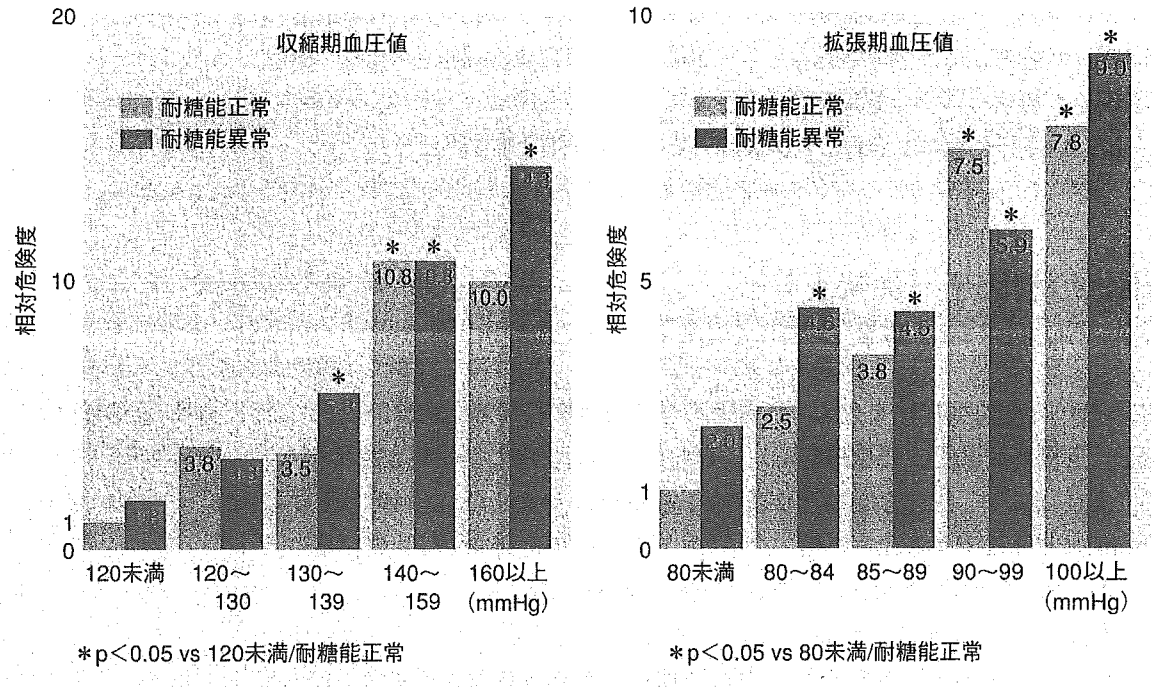

図2　耐糖能異常と正常耐糖能における血圧レベル別にみた血管死亡の相対危険（文献3より引用）

文献

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