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:

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

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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PAPER

Ten year recurrence after first ever stroke in a Japanese community: the Hisayama study

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Background: Very few population based cohort studies have focused on the long term recurrence of stroke.
Objective: To examine 10 year cumulative recurrence rates for stroke in a Japanese cohort according to pathological type and clinical subtype of brain infarction.
Methods: During a 32 year follow up of 1621 subjects ≥40 years of age, 410 developed first ever stroke. These were followed up prospectively for 10 years after stroke onset.
Results: During follow up, 108 (26%) experienced recurrent stroke. The cumulative recurrence rates were 35.3% at five years and 51.3% at 10 years. The 10 year recurrence rates of subarachnoid haemorrhage (SAH), brain haemorrhage, and brain infarction were 70.0%, 55.6%, and 49.7%, respectively; the difference between SAH and brain infarction was significant (p=0.004). Most recurrent episodes after SAH or brain haemorrhage happened within a year after the index stroke, whereas recurrence of brain infarction increased consistently throughout the observation period. Cardioembolic stroke had a higher recurrence rate (75.2%) than lacunar infarction (46.8%) (p=0.049). The 10 year risk of stroke recurrence increased with age after lacunar or atherothrombotic brain infarction, but not after the other types or subtypes. After atherothrombotic brain infarction, cardioembolic stroke, or SAH, the type and subtype of most recurrent strokes were the same as for the index stroke, but recurrence after lacunar infarction or brain haemorrhage showed divergent patterns.
Conclusions: Japanese people have higher recurrence rates of stroke than other populations. Recurrence rate after a first brain infarct increases consistently through the next 10 years.

Japanese people have high rates of morbidity and mortality from stroke.[1] Among stroke survivors, recurrence is common, resulting in cumulative disability and cognitive dysfunction.[2] Consequently, precise information is needed on the long term rates and determinants of recurrence after first stroke, so that clinical trials can be designed and health care policies for primary and secondary stroke prevention can be established. Most studies on stroke recurrence, reported mainly from Western countries, have been based on stroke registries[3–11] or on series of patients referred to hospitals.[12 13] A truly representative assessment of stroke recurrence in a community would require a prospective cohort of a defined population and an exhaustive follow up system. The Framingham study is the only cohort based examination of both initial and recurrent stroke, but it refers to the recurrence of thrombotic brain infarction only.[14] Stroke is divided into several pathological types. Among them, brain infarction is further classified into several clinical subtypes.[15–17] Very few studies, however, have accurately defined types and subtypes while also evaluating the long term risk of stroke recurrence.[3]

Since 1961, we have been carrying out a prospective cohort study of cardiovascular disease in the town of Hisayama, Japan.[18 19] The most outstanding features of this study are that the causes of death were verified by necropsy and that most of the stroke patients were examined morphologically at necropsy or, before death, by brain imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI). Our aim in this study was to estimate 10 year cumulative recurrence rates after first ever stroke in the community of Hisayama, using data stratified by sex, age, stroke type, and, in cases of brain infarction, the clinical subtype.

METHODS

Subjects and follow up surveys

In 1961, we carried out a screening examination among Hisayama residents and established a cohort consisting of 1621 stroke-free subjects aged ≥40 years (88.1% of the total population in this age range). These subjects were then followed up for 32 years, from 1 November 1961 to 31 October 1993. A detailed description of the study methods has been published previously.[18 19] In brief, we collected information about new cardiovascular events through a daily monitoring system established by the study team, local practitioners, and the town government. When we suspected a patient was having a new neurological symptom or a new deterioration of an already existing symptom, one of the physicians participating in the study would carefully evaluate the subject and try to obtain information by further diagnostic examinations, including lumbar puncture, cerebral angiography, or recent brain CT or MRI. During the 32 year period, all but two subjects were followed up and 1063 subjects died. Of those who died, 861 (81.0%) underwent necropsy.

The study was conducted with the approval of the human ethics review committee of Kyushu University Graduate School of Medical Sciences.

First ever stroke

Stroke, defined as the sudden onset of a non-convulsive and focal neurological deficit persisting for over 24 hours, was classified into four pathological types: brain infarction, brain haemorrhage, subarachnoid haemorrhage, and undetermined. Brain infarction was further divided into four clinical subtypes: lacunar infarction, atherothrombotic brain

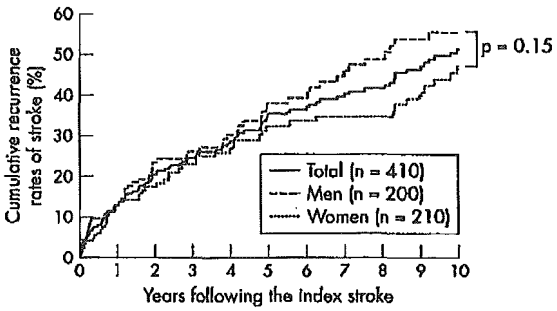

Figure 1 Kaplan–Meier estimates of cumulative recurrence rates of stroke for all subjects and for all subjects divided by sex. Deaths without stroke recurrence were censored.

infarction, cardioembolic stroke, and undetermined. These types and subtypes were defined on the basis of the *Classification of Cerebrovascular Disease III* proposed by the National Institute of Neurological Disorders and Stroke (USA).[15] The subtypes of ischaemic stroke were classified by TOAST (trial of Org 10172 in acute stroke treatment)[16] and by the Cerebral Embolism Task Force.[17] A detailed method of classifying stroke has been published previously.[18] The diagnosis and classification of stroke in our study were based on clinical history, neurological examination, all available clinical information (including brain CT or MRI), and necropsy findings.

During the 32 year follow up, we identified 410 first ever stroke events (200 men and 210 women, mean (SD) age, 73.9 (10.1) years), and divided them into 298 cases of brain infarction, 73 of brain haemorrhage, 35 of subarachnoid haemorrhage, and four undetermined. The cases of brain infarction by subtype consisted of 167 lacunar infarcts, 62 atherothrombotic brain infarcts, 56 cardioembolic strokes, and 13 undetermined.

Recurrent stroke

The definition of recurrent stroke was the same as that of index stroke, but with an additional criterion: there had to be either a new focal neurological deficit or a new deterioration of a previous deficit that was not attributed to brain oedema, haemorrhagic transformation after ischaemia, intercurrent illness, or iatrogenesis. This definition included recurrence in the early stage after the preceding stroke or recurrence in the same vascular territory as the preceding stroke.

We followed up the 410 patients with index stroke from the time of stroke onset until death or 31 August 2003. Under those conditions, all patients completed the follow up period. In the 10 years after the index stroke, 108 patients developed recurrent stroke. Of these, 88 had one recurrent stroke, 13 had two, six had three, and one had four. However, the end point of this study for each subject was the first recurrence.

Morphological evaluation

Brain imaging, including CT or MRI, was carried out in 153 (37%) of the 410 subjects with index stroke and in 43 (40%) of the 108 subjects with recurrent stroke. Necropsy findings were available in 332 (84%) of the 394 deceased stroke patients. As a result, morphological evaluation, including brain imaging or necropsy, was undertaken in 376 (92%) of the index stroke patients and 102 (94%) of the recurrent stroke patients until 31 August 2003.

Because we began collecting data on stroke subjects in 1961, imaging examinations of the brain and heart were non-existent in the early study period. However, we compensated

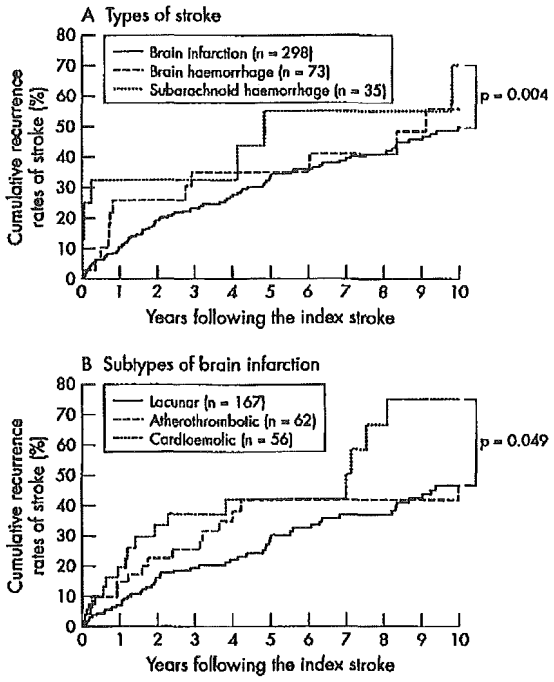

Figure 2 Kaplan–Meier estimates of cumulative recurrence rates of stroke according to stroke type (A) and, in cases of brain infarction, the subtype (B). Deaths without stroke recurrence were censored.

for this disadvantage by carrying out necropsy examinations on the vast majority of deceased patients. We reviewed the brains to evaluate the site, size, and pathological features of the stroke. We also investigated the heart and major vessels in detail—including the aorta, carotids, vertebrobasilar arteries, and the circle of Willis—in order to identify atherothrombotic stenotic lesions and embolic sources. In cases where the necropsy was carried out a long time after stroke onset, it was important to distinguish brain haemorrhage from brain infarction with haemorrhagic transformation. The latter was usually the result of a cardioembolic mechanism. When an infarcted area was surrounded by deposition of haemosiderin—with either no or mild atherosclerosis of the responsible artery, and given the presence of the embolic source—we considered the stroke lesion to be a brain infarct with haemorrhagic transformation. An old lesion that looked like a slit was considered to indicate a brain haemorrhage, especially if found in the basal ganglia or thalamus.

To classify the subtypes of brain infarction, we considered important the size and location of the infarcted area, the presence of stenosis or occlusion of a responsible cerebral artery, and the embolic source, in addition to clinical information including the disease course. Where multiple asymptomatic infarctions were present, we considered an infarct to be the lesion responsible for the stroke when it was most closely in accord with the neurological findings and disease course in the acute period of the stroke. The criteria for diagnosing brain infarction subtypes were given in full detail in our previous report.[19] When sufficient clinical and morphological information was obtained, a diagnosis of subtype was defined as "definite"; on the other hand, when either type of information was insufficient, the diagnostic level was defined as "probable." Among 298 cases of brain infarction, 272 were definite and 26 probable. In this study,

we present the data on the definite and probable cases together, as these combined data were almost identical to the data for definite cases only.

Statistical analysis

SAS software (version 6.12) was used for statistical analysis. The cumulative recurrence rates of stroke and the 95% confidence intervals (CI) were estimated by the Kaplan–Meier product limit method. The Cox proportional hazards model was used to test differences in recurrence rates as well as to estimate relative risks (RR) and 95% CIs of stroke recurrence.

RESULTS

Recurrence rates of stroke

Figure 1 shows the Kaplan–Meier estimates of cumulative recurrence rates of stroke for all subjects and for all subjects divided by sex. The recurrence rates (95% CI) at 1, 5, and 10 years were 12.8% (8.9% to 16.6%), 35.3% (29.0% to 41.5%), and 51.3% (43.8% to 58.9%), respectively, for all subjects. For men, these rates were 12.9% (7.3% to 18.5%), 38.1% (28.9% to 47.2%), and 55.6% (44.9% to 66.4%); for women the rates were 12.5% (7.3% to 17.6%), 32.3% (23.8% to 40.9%), and 47.1% (36.5% to 57.6%). The recurrence rates were slightly higher for men than for women, but the overall difference was not statistically significant ($p = 0.15$).

Figure 2, panel A, shows cumulative recurrence rates of stroke by type of index stroke. The recurrence rates at 1, 5, and 10 years were 10.0% (6.3% to 13.8%), 34.1% (27.3% to 40.9%), and 49.7% (41.4% to 57.9%) after brain infarction; 25.6% (9.0% to 42.2%), 34.9% (16.0% to 53.8%), and 55.6% (32.2% to 79.1%) after brain haemorrhage; and 32.5% (10.3% to 54.6%), 55.0% (25.6% to 84.4%), and 70.0% (39.0% to 100%) after subarachnoid haemorrhage, respectively. The 10 year recurrence rate of subarachnoid haemorrhage was significantly higher than that of brain infarction (RR = 2.89 (95% CI, 1.40 to 5.97); $p = 0.004$). Also, brain haemorrhage recurred at a slightly higher rate than brain infarction, but the difference was not statistically significant ($p = 0.52$). Annual recurrence rates after brain infarction were about 10% per year in the first two years and consistently about 4% per year afterward. On the other hand, 58.3% of recurrent episodes took place within a year after brain haemorrhage, and 66.7% within three months after subarachnoid haemorrhage.

Figure 2, panel B, shows the cumulative recurrence rates of stroke by clinical subtype of brain infarction. The recurrence rates at 1, 5, and 10 years were 7.2% (3.1% to 11.2%), 30.4% (22.1% to 38.7%), and 46.8% (36.6% to 56.9%) after lacunar infarction; 14.8% (4.5% to 25.0%), 42.0% (25.5% to 58.5%), and 46.9% (29.2% to 64.5%) after atherothrombotic brain infarction; and 19.6% (6.3% to 32.8%), 42.2% (23.8% to 60.6%), and 75.2% (52.6% to 97.8%) after cardioembolic stroke, respectively. Cardioembolic stroke had a significantly higher risk of 10 year recurrence than lacunar infarction (RR = 1.76 (95% CI, 1.00 to 3.11); $p = 0.049$). The recurrence rate of atherothrombotic brain infarction was slightly higher than that of lacunar infarction, but the difference was not statistically significant ($p = 0.59$).

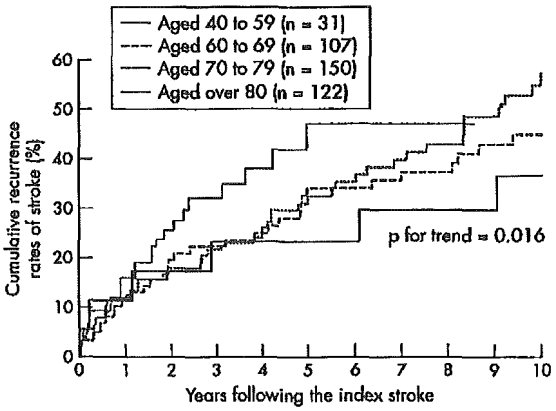

Figure 3 Kaplan–Meier estimates of cumulative recurrence rates of stroke for all subjects divided by age. Deaths without stroke recurrence were censored.

Figure 3 shows the cumulative recurrence rates of stroke by age. The 10 year risk of stroke recurrence was lowest in the youngest age group (40 to 59 years) and increased with age. Table 1 shows the relative risks of stroke recurrence among age groups during 10 years for each type and subtype of index stroke. The 10 year risk of stroke recurrence after brain infarction was lowest in the youngest age group and increased with age. For brain haemorrhage or subarachnoid haemorrhage, on the other hand, there was no significant relation between age and recurrence rates. Among the subtypes of brain infarction, the 10 year risk of recurrence after lacunar and atherothrombotic brain infarction was lowest in the youngest age group and increased with age, whereas for cardioembolic stroke there was no significant relation between age and recurrence rates.

Patterns of stroke recurrence

To evaluate patterns of stroke recurrence, table 2 shows the numbers and frequencies of first recurrent stroke by pathological types and clinical subtypes according to the type of index stroke. Most recurrent strokes after atherothrombotic brain infarction, cardioembolic stroke, or subarachnoid haemorrhage were the same type or subtype as the index stroke. On the other hand, recurrence after lacunar infarction or brain haemorrhage showed divergent patterns. The 51 patients who had recurrent stroke after lacunar infarction were divided as follows: 18 cases (35%) had a second lacunar infarction, 16 (31%) had atherothrombotic brain infarction, nine (18%) had brain haemorrhage, and six (12%) had cardioembolic stroke. Among the 12 recurrent cases of brain haemorrhage, seven (58%) had a second brain haemorrhage, three (25%) had lacunar infarction, and two (17%) had atherothrombotic or cardioembolic infarction.

DISCUSSION

One of the strengths of our study is that we investigated almost all stroke events occurring in a community based prospective cohort. Our study design eliminated the selection bias encountered in stroke registries or in series of hospital inpatients. Another strength is that recurrence rates were estimated up to 10 years after a subject's first ever stroke.

Recurrence rates of stroke

Three previous reports from stroke registries in Australia[3] and Britain[4 5] have reported five year cumulative stroke recurrence rates of 16.6% to 29.5%. In comparison, our study's five year cumulative stroke recurrence rate was 35.3%. There might be several reasons for this difference. First, there was a difference in methodology. The studies of the other three stroke registries all used a single set of criteria, which excluded vascular events occurring in the first 21 days after the index stroke unless such an event was clearly in a different vascular territory.[3–5] On the other hand, our study excluded neither early recurrence (10 cases within 21 days) nor recurrence in the same vascular territory. Second, race might greatly influence stroke recurrence. In our study,

Table 1 Relative risks and 95% confidence intervals of stroke recurrence during 10 years by age in each type or subtype of index stroke

	Age group (years)				
	40 to 59	60 to 69	70 to 79	80 and over	p Value
Index stroke	RR	RR (95% CI)	RR (95% CI)	RR (95% CI)	for trend
All types of stroke	1.0	1.3 (0.5 to 3.0)	1.6 (0.7 to 3.8)	2.2 (0.9 to 5.4)	0.016
Brain infarction	1.0	2.0 (0.6 to 6.5)	2.5 (0.7 to 8.1)	3.9 (1.1 to 13.1)	0.002
Lacunar infarction	1.0	2.2 (0.5 to 9.4)	2.6 (0.6 to 11.1)	4.8 (1.0 to 22.2)	0.022
Atherothrombotic brain infarction	1.0*		1.8 (0.4 to 7.5)	4.7 (1.2 to 18.6)	0.001
Cardioembolic stroke	1.0	0.8 (0.1 to 7.3)	1.4 (0.2 to 12.3)	0.4 (0.0 to 4.1)	0.51
Brain haemorrhage	1.0	0.6 (0.0 to 6.3)	1.2 (0.2 to 10.3)	2.1 (0.2 to 24.3)	0.71
Subarachnoid haemorrhage	1.0	1.0 (0.2 to 6.0)	0.7 (0.1 to 4.4)	0.0	0.60

*Two age groups (40 to 59 and 60 to 69) were combined, as there were no recurrences after atherothrombotic brain infarction in the 40 to 59 age group.
CI, confidence interval; RR, relative risk.

haemorrhagic stroke—including brain haemorrhage and subarachnoid haemorrhage—recurred at higher rates than brain infarction, and the proportion of haemorrhagic stroke (26%) among all types was higher than those found in the three registries in Western countries (14% to 19%).[3–5] In addition, as Asians, including Japanese, have a higher stroke incidence than Europids,[1] they might also have higher rates of stroke recurrence.

In our study, most recurrent episodes occurred within a year after the index haemorrhagic stroke. This may indicate the importance of controlling risk factors and of treating the patient to prevent recurrence without delay in the first days and months after the onset of haemorrhagic stroke. On the other hand, cumulative recurrence rates after brain infarction, especially lacunar infarction, increased steadily during our 10 year study period. The Oxfordshire Community Stroke Project[6] also showed that the recurrence rate after lacunar infarction was low and almost constant throughout the follow up period. Arteriosclerosis, which is thought to progress consistently for a long period, may be related to recurrent thrombotic infarction. Thus careful observation and adequate treatment to prevent recurrence are needed for a long time after brain infarction.

Several studies have focused on the relations between brain infarction subtypes and the risks of recurrent stroke,[1 7–10 12] but their findings are equivocal. Some of those studies have claimed that the subtype of brain infarction is not a predictor of long term recurrence,[3 7 9] while others showed that the highest risk of recurrence is with atherothrombotic brain infarction.[7 10 12] In our study, cardioembolic stroke had the highest risk of recurrence among the three major subtypes of brain infarction. This is probably attributable to our inclusion of early recurrent episodes, which were often observed after cardioembolic stroke.[20 21]

In some studies,[7 11] aging was found to be a predictor of stroke recurrence. In the present study, the risk of recurrence after first ever lacunar or atherothrombotic brain infarction was lowest in the youngest age group and then increased with age. Aging would accelerate atherosclerotic changes in major cerebral arteries and arteriolosclerotic changes in penetrating arteries, thus increasing the risk of recurrent stroke.

Patterns of stroke recurrence

In the present study, the types or subtypes of most recurrent strokes after atherothrombotic brain infarction, cardioembolic stroke, or subarachnoid haemorrhage were the same as those of the index stroke. On the other hand, recurrence after lacunar infarction or brain haemorrhage showed divergent patterns. This finding was also emphasised in some previous reports.[4 12]

Several aetiological mechanisms for lacunar infarction have been proposed[22–24]: lipohyalinosis or microatheroma in a penetrating artery; branch-atheromatous disease, which is located in basilar or middle cerebral arteries and occludes the origins of one or more penetrating arteries; and microembolism from carotid or cardiac disease. These multifactorial aetiologies would support divergence in the type and subtype of recurrent stroke after lacunar infarction. Our findings denote the importance of evaluation to detect any large vessel disease or embolic source, even in patients with lacunar infarction.

Table 2 The numbers and frequencies of first recurrent stroke by pathological types and clinical subtypes according to type of index stroke

	Type or subtype of recurrent stroke								
		Subtype of BI							
Type or subtype of index stroke	All BI	LA	AT	CE	UND-BI	BH	SAH	UND	Total
Brain infarction	74 (85%)	18 (35%)	16 (31%)	6 (12%)	–	10 (13%)	–	3 (3%)	87 (100%)
Lacunar infarction		18 (35%)	16 (31%)	6 (12%)	–	9 (18%)	–	2 (4%)	51 (100%)
Atherothrombotic brain infarction		1 (6%)	14 (82%)	–	1 (6%)	1 (6%)	–	–	17 (100%)
Cardioembolic stroke		–	–	16 (94%)	1 (6%)	–	–	–	17 (100%)
Undetermined subtype of BI (UND-BI)		–	–	–	1 (50%)	–	–	1 (50%)	2 (100%)
Brain haemorrhage	5	3 (25%)	1 (8%)	1 (8%)	–	7 (58%)	–	–	12 (100%)
Subarachnoid haemorrhage	2	1 (11%)	1 (11%)	–	–	1 (11%)	6 (67%)	–	9 (100%)
Undetermined type of stroke	–	–	–	–	–	–	–	–	0 (0%)

Percentages are the proportions of types or subtypes of recurrent stroke calculated using the numbers of total recurrent stroke as the denominators.
AT, atherothrombotic brain infarction; BH, brain haemorrhage; BI, brain infarction; CE, cardioembolic stroke; LA, lacunar infarction; SAH, subarachnoid haemorrhage; UND, undetermined.

Hypertension is a major risk factor for both lacunar infarction and brain haemorrhage, and lesions of all lacunar infarcts and most brain haemorrhages in our patients were located in brain areas that have the common feature of penetrating arteries, such as the basal ganglia, thalamus, and pons. These similarities would support the overlap between lacunar infarction and brain haemorrhage in recurrent stroke types.

Study limitations

There are several potential limitations to the findings in our study. First, we enrolled stroke cases that developed among an inception cohort during 32 years of follow up. The prevalence of cardiovascular risk factors and the risk of stroke recurrence may have changed widely during this long term observation period.[35] Secular trends in stroke recurrence should be examined, and we will do so in another study. Second, the study did not consider the effects of cardiovascular risk factors or those of medical or surgical treatment. Thus our estimates for the risk of stroke recurrence are probably quite conservative. Third, brain imaging was available in only 37% of the index stroke cases. However, we collected available clinical information on both index and recurrent strokes in minute detail and carried out necropsies on 84% of deceased stroke patients. We believe that our exhaustive and careful evaluation of the clinical information, as well as the high rate of necropsy, improved the quality and validity of the diagnosis as well as the stroke classification in our study.

Conclusions

Our findings show higher recurrence rates of stroke in a Japanese community than in Western populations. The divergent patterns of stroke recurrence after index lacunar infarction or brain haemorrhage are of interest and importance for the prevention of recurrent stroke, because the Japanese are characterised by high morbidity of lacunar infarction and brain haemorrhage. The consistent increase in cumulative recurrence rates during the long observation period and the higher recurrence rates after index brain infarction among older patients are both important for medical care. We believe that these findings will contribute to a better understanding of stroke recurrence in the Japanese, who are considered to be at greater risk of stroke than other populations.

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Relationship Between Drinking and Periodontitis: The Hisayama Study

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Background: Although recent studies suggest a relationship between alcohol consumption and periodontal disease, the dose-response relationship between drinking and the severity of periodontitis is unclear.

Methods: Alcohol consumption was evaluated using the frequency of drinking and the daily alcohol intake for 961 individuals aged 40 to 79 years. Periodontal status was evaluated using probing depth (PD) and clinical attachment loss (CAL).

Results: Alcohol consumption was linearly associated with the extent of PD and CAL in univariate analyses ($P<0.001$). In multivariate logistic regression analyses, the subjects drinking 15 to 29.9 g alcohol per day (odds ratio [OR] = 2.7; 95% confidence interval [CI] = 1.1 to 6.6) or more than 30 g per day (OR = 2.5; 95% CI = 1.1 to 5.7) had a significantly higher risk of having more than 35% of their teeth with PD ≥4 mm than non-drinkers, independent of other confounding variables. No significant relationship between drinking and CAL was observed in the multivariate analysis.

Conclusion: These results suggest that the effect of drinking on periodontal condition is limited to subjects with deep periodontal pockets associated with more than one-third of their teeth. *J Periodontol 2005;76:1534-1541.*

KEY WORDS

Alcoholic beverages/adverse effects; periodontitis/epidemiology; risk factors.

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Both smoking and drinking are lifestyle factors that cause health problems. Numerous studies have shown a relationship between smoking and periodontitis,[1-3] while there is very limited information about the relationship between drinking and periodontitis.[4-7] Previous studies examined the relationship between drinking and probing depth (PD)[4] or clinical attachment loss (CAL).[5] Pitiphat et al. reported a longitudinal relationship between drinking and self-reported periodontitis.[6] Recently, Nishida et al. reported that alcohol consumption is a risk indicator in subjects with the aldehyde dehydrogenase-2 ($ALDH_2$) *1/*2 genotype, but not in subjects with $ALDH_2$ *1/*1 genotype.[7] However, these studies did not find a dose-response relationship between drinking and the severity of periodontitis or conclude whether drinking has a greater effect on PD or CAL.

Drinking also affects several systemic diseases in adults, and many studies have reported J- or U-shaped associations, in which light or moderate alcohol consumption lowers the risk of hypertension,[8,9] coronary heart disease,[10,11] systemic markers of inflammation,[12] and mortality.[13] However, there are no reports on the effect of a low alcohol intake on periodontal disease. In this study, we examined the dose-response relationship between drinking and various stages of periodontal condition and examined how alcohol intake is related to periodontal condition using the results of a health examination conducted in Hisayama.

MATERIALS AND METHODS

Study Population

The Hisayama Study began in 1961 and is an ongoing population based prospective cohort study of cardiovascular diseases. The town population, based on data from national census, was shown to be representative of Japan as a whole.[14] As a part of the study, from July to September 1998, 982 Hisayama residents aged 40 to 79 years (21.6% of the total population in that age group) underwent a comprehensive health examination, including a dental examination. We excluded 21 subjects who had less than 10 teeth or lacked data for the variables studied; consequently we analyzed 961 subjects (378 male, 583 female) in this study. The Ethics Committee of Kyushu University Faculty of Dental Science and the Department of General Affairs and Health and Welfare of Hisayama approved the study design, data collection methods, and procedure for obtaining informed consent.

Oral Examination

The periodontal examination followed the method of the Third National Health and Nutrition Examination Survey (NHANES III).[15] As periodontal parameters, PD and CAL were measured at mesio-buccal and mid-buccal sites for all of the teeth present in two randomly selected quadrants: one maxillary and one mandibular. We divided the subjects into four categories according to the proportion of teeth with PD ≥4 mm. None: no teeth with PD ≥4 mm; low: 0.1% to 19.9% teeth with PD ≥4 mm; mid: 20% to 34.9% teeth with PD ≥4 mm (the second highest 10th percentile); and high: ≥35% teeth with PD ≥4 mm (the highest 10th percentile). Similarly, the proportion of teeth with CAL ≥5 mm was categorized into four categories. None: no teeth with CAL ≥5 mm; low: 0.1% to 9.9% teeth with CAL ≥5 mm; mid: 10% to 21.9% teeth with CAL ≥5 mm (the second highest 10th percentile); and high: ≥22% teeth with CAL ≥5 mm (the highest 10th percentile). Oral hygiene status was evaluated using the plaque index[16] and we used the mean score of each subject in the analyses.

General Examination

A self-administered questionnaire was completed in advance and checked by trained nurses. Participants answered items concerning their frequency of alcohol intake over the previous year and the kinds and amounts of alcoholic beverages habitually consumed. The alcohol intake per drink was converted into the weight of 100% ethanol in grams. The estimated alcohol content was 21.5 g for a cup of Japanese sake (180 ml), 22.6 g for a bottle of beer (633 ml), 35.7 g for a cup of distilled spirits (180 ml), and 31.8 g for a glass of whiskey (100 ml). The daily amount of drinking was estimated by multiplying the frequency of consuming each drink per week by the weight of ethanol in each drink and dividing the sum by seven (g/day). The daily amount of drinking was divided into four categories: non-drinker (0 g/day), light drinker (0.1 to 14.9 g/day), moderate drinker (15 to 29.9 g/day), and heavy drinker (≥30 g/day). As the number of former drinkers was very low (N = 27, 2.8%), we included past drinkers with non-drinkers. The amount of smoking, including past smoking, was given as the number of cigarettes smoked per day multiplied by the total years of smoking. The amount of smoking was divided into four categories: never smoked, light smoker (1 to 399), moderate smoker (400 to 799), and heavy smoker (≥800). Blood samples were collected from an antecubital vein after an overnight fast. Laboratory analyses of the blood samples followed previously described methods.[17] A 75 g oral glucose tolerance test was performed between 8:00 a.m. and 10:30 a.m. Before and 120 minutes after ingesting the 75 g glucose solution, blood samples were obtained for laboratory measurements. The glucose tolerance was categorized into three groups: normal (fasting and 2-hour post-challenge plasma glucose levels <110 and <140 mg/dl, respectively), diabetes (levels ≥126 or ≥200 mg/dl, respectively), and impaired (other than normal or diabetes).

Statistical Analysis

The differences in percentages were evaluated using Pearson's chi square test and its linearity was evaluated using the Mantel-Haenszel chi square test. The differences in the mean values were evaluated using Student *t* test. To protect against spurious significance with multiple inference, we used Bonferroni's correction to interpret the significance of *P* value. We performed univariate and multivariate logistic regression analyses to determine the effect of alcohol consumption on periodontal parameters, and calculated the odds ratio (OR) and 95% confidence interval (CI). As both PD and CAL were classified into four categories, we performed three logistic regression models using none versus each of the other three categories (low, mid, and high) as the dependent variable. Multivariate models were adjusted for amount of smoking, glucose tolerance, age, sex, number of teeth, and mean plaque index. The statistical analysis was performed using a software program.‡

RESULTS

Tables 1 and 2 show the characteristics of the subjects according to the proportion of teeth with PD ≥4 mm and with CAL ≥5 mm, respectively. The more alcohol the subjects consumed, the greater the proportion of their teeth with PD ≥4 mm and CAL ≥5 mm,

‡ Version 11.0, SPSS Japan, Tokyo, Japan.

Table 1.

Study Population Variables According to Periodontal Status (PD)

Variable	Teeth With PD ≥4 mm: None 549 (57.1%)	Low 220 (22.9%)	Mid 102 (10.6%)	High 90 (9.4%)	*P* Value
	N (%)				
Alcohol consumption					
None (0 g/day)	355 (60.1)	126 (21.3)	67 (11.3)	43 (7.3)	<0.001*
Light (0.1-14.9 g/day	91 (59.1)	41 (26.6)	14 (9.1)	8 (5.2)	<0.001†
Moderate (15-29.9 g/day)	46 (50.0)	24 (26.1)	7 (7.6)	15 (16.3)	
Heavy (≥30 g/day)	57 (46.0)	29 (23.4)	14 (11.3)	24 (19.4)	
Smoking					
Never (0)	400 (62.3)	137 (21.3)	59 (9.2)	46 (7.2)	<0.001*
Light (1-399)	47 (52.8)	27 (30.3)	8 (9.0)	7 (7.9)	<0.001†
Moderate (400-799)	63 (51.6)	31 (25.4)	12 (9.8)	16 (13.1)	
Heavy (≥800)	39 (36.1)	25 (23.1)	23 (21.3)	21 (19.4)	
Glucose tolerance					
Normal	404 (60.3)	145 (21.6)	67 (10.0)	54 (8.1)	0.065*
Impaired	97 (50.8)	51 (26.7)	20 (10.5)	23 (12.0)	0.002†
Diabetes	48 (48.0)	24 (24.0)	15 (15.0)	13 (13.0)	
Gender					
Male	189 (50.0)	94 (24.9)	46 (12.2)	49 (13.0)	0.001*
Female	360 (61.7)	126 (21.6)	56 (9.6)	41 (7.0)	<0.001†
	Mean ± SD				
Age	55.6 ± 8.7	57.3 ± 8.5	59.0 ± 8.5§	55.6 ± 8.7	
Number teeth	25.6 ± 3.7	25.0 ± 3.5	23.7 ± 4.9§	23.7 ± 4.6§	
Mean plaque index	1.0 ± 0.5	1.1 ± 0.6‡	1.4 ± 0.7§‖	1.6 ± 0.7§‖	

* Non-linear component calculated using Pearson's chi square test.
† Linear component calculated using Mantel-Haenszel chi square test.
‡ $P<0.05$ compared with none; Student *t* test applied with Bonferroni's correction of *P* value for type 1 errors in multiple comparisons.
§ $P<0.01$ compared with none; Student *t* test applied with Bonferroni's correction of *P* value for type 1 errors in multiple comparisons.
‖ $P<0.01$ compared with low; Student *t* test applied with Bonferroni's correction of *P* value for type 1 errors in multiple comparisons.

which was the same as when the subjects consumed more cigarettes. The subjects with poor diabetic conditions had more teeth with PD ≥4 mm and CAL ≥5 mm. The variables age, gender, number of teeth, and mean plaque index were each significantly associated with the proportion of teeth with PD ≥4 mm and CAL ≥5 mm in the univariate analyses (Tables 1 and 2).

Table 3 shows the univariate and multivariate logistic regression analyses for each of the three different PD conditions. Alcohol consumption did not show any significant influence for having the low or mid PD condition. However, moderate and heavy drinkers had a significantly high OR for having a high proportion of teeth with PD ≥4 mm in the univariate and multivariate analysis adjusting for confounding variables. In the analysis, heavy smoking and a higher plaque index also had a significantly increased OR for having the high PD condition. Table 4 (pages 1540 and 1541) shows the univariate and multivariate ORs for each of the three CAL conditions. Although moderate and heavy drinking had a significantly increased OR for having a high proportion of CAL ≥5 mm in the univariate analysis, the relationship disappeared after multivariate adjustment. Moderate and heavy smoking were associated with significantly increased OR for high CAL, and heavy smoking had a significantly increased OR for low CAL.

DISCUSSION

This study showed that subjects who drank more than 15 g alcohol per day had a significantly increased risk for widespread periodontal disease; i.e., more than one third of teeth with PD ≥4 mm, as compared to non-drinkers. Conversely, drinking did not indicate an increased risk for having less than 35% of the teeth with PD ≥4 mm. It was reported that the subjects with $ALDH_2$ *1/*2 genotype who consumed ≥33 g alcohol per day had a significantly greater percentage of PD ≥3.5 mm than those whose daily consumption was lower, while there was no significant difference in periodontal status associated with alcohol consumption in $ALDH_2$ *1/*1 subjects.[7] The subjects with $ALDH_2$ genotypes *1/*2 or *2/*2 lack $ALDH_2$ activity and become flushed after alcohol intake owing to the marked elevation in the blood acetaldehyde concentration.[18] Therefore, it is thought that drinking raises the risk of periodontitis when drinking causes an accumulation of acetaldehyde. As about half of all Japanese lack $ALDH_2$ activity,[19,20] many subjects with $ALDH_2$ *1/*2 genotype might have been included in the subjects with many teeth with PD ≥4 mm in our study.

Periodontitis is a chronic inflammatory disease of the soft and hard periodontal tissues and recent studies have suggested a relationship between periodontitis and circulatory diseases.[21-23] Inflammation plays an important role in both the initiation and pro-

Table 2.

Study Population According to Periodontal Status (CAL)

Variable	Teeth With CAL ≥5 mm: None 624 (64.9%)	Low 146 (15.2%)	Mid 95 (9.9%)	High 96 (10.0%)	*P* Value
	N (%)				
Alcohol consumption					
None (0 g/day)	394 (66.7)	85 (14.4)	65 (11.0)	47 (8.0)	0.002*
Light (0.1-14.9 g/day)	106 (68.8)	26 (16.9)	12 (7.8)	10 (6.5)	<0.001†
Moderate (15-29.9 g/day)	57 (62.0)	12 (13.0)	8 (8.7)	15 (16.3)	
Heavy (≥30 g/day)	67 (54.0)	23 (18.5)	10 (8.1)	24 (19.4)	
Smoking					
Never (0)	458 (71.3)	84 (13.1)	62 (9.7)	38 (5.9)	<0.001*
Light (1-399)	53 (59.6)	18 (20.2)	10 (11.2)	8 (9.0)	<0.001†
Moderate (400-799)	70 (57.4)	20 (16.4)	14 (11.5)	18 (14.8)	
Heavy (≥800)	43 (39.8)	24 (22.2)	9 (8.3)	32 (29.6)	
Glucose tolerance					
Normal	461 (68.8)	90 (13.4)	59 (8.8)	60 (9.0)	<0.001*
Impaired	114 (59.7)	36 (18.8)	27 (14.1)	14 (7.3)	<0.001†
Diabetes	49 (49.0)	20 (20.0)	9 (9.0)	22 (22.0)	
Gender					
Male	206 (54.5)	69 (18.3)	42 (11.1)	61 (16.1)	<0.001*
Female	418 (71.7)	77 (13.2)	53 (9.1)	35 (6.0)	<0.001†
	Mean ± SD				
Age	55.0 ± 8.6	57.7 ± 8.3‡	59.7 ± 8.2‡	59.9 ± 9.1‡	
Number of teeth	25.7 ± 3.8	25.9 ± 2.7	23.5 ± 4.4‡§	22.0 ± 4.7‡§	
Mean plaque index	1.0 ± 0.6	1.1 ± 0.6	1.2 ± 0.6‡	1.6 ± 0.6‡§‖	

* Non-linear component calculated using Pearson's chi square test.
† Linear component calculated using Mantel-Haenszel chi square test.
‡ $P<0.01$ compared with none; Student *t* test applied with Bonferroni's correction of *P* value for type 1 errors in multiple comparisons.
§ $P<0.01$ compared with low; Student *t* test applied with Bonferroni's correction of *P* value for type 1 errors in multiple comparisons.
‖ $P<0.01$ compared with mid; Student *t* test applied with Bonferroni's correction of *P* value for type 1 errors in multiple comparisons.

gression of atherosclerosis,[24] and the systemic inflammatory marker such as C-reactive protein (CRP) is a predictor of cardiovascular events.[25] The subjects with periodontitis had a higher CRP level than the subjects with healthy periodontal tissue.[26,27] Periodontal disease was significantly associated with a higher CRP level in a longitudinal study[28] and recent studies reported that control of periodontal health decreased the serum CRP level.[29,30] Although CRP level is unknown in this study, as our results showed that moderate to heavy drinking was associated with a significant risk of having many teeth with deep PD, increased periodontal inflammation with alcohol consumption may increase the risk of coronary heart disease, in addition to the direct effect of alcohol on the circulatory system.

Tezal et al. reported a significant relationship between the frequency of drinking and CAL.[5] We did not find a significant relationship between drinking and CAL. It may be owing to small sample size, especially the low number of drinkers in this study. Alcohol is considered an important risk factor for various bone-related disorders, such as reduced bone mass and fractures, and chronic alcohol abuse is a major risk factor for osteoporosis.[31,32] A 2001 study found a relationship between osteoporosis and periodontitis in menopausal women.[33] If drinking exacerbates alveolar bone resorption, the observed effect of drinking on increasing periodontal pocket depth may lead to extensive periodontal destruction.

Some studies have reported J- or U-shaped relationship in which light drinkers had a lower risk of hypertension, coronary heart disease, systemic markers of inflammation, and mortality of all causes than did non-drinkers or heavy drinkers.[8-13] Previous studies of the relationship between drinking and periodontitis failed to find a significant association between light drinking and periodintitis, although two studies showed that light drinkers tended to have better periodontal health than non-drinkers.[5,7] In our study, although light drinkers had a relatively low risk for having many teeth with deep PD, the relationship was not significant statistically. It is thought that a large number of study subjects is needed to clarify the effect of light drinking on periodontitis.

Smoking is an important lifestyle-related risk factor for periodontitis, and this study suggests that heavy drinking is also a risk factor for periodontitis. Smoking cessation should be strongly recommended for patients with periodontitis. As our results were based on a cross-sectional investigation, we could not clarify causal relationship between drinking and periodontitis. Therefore, at this stage, we may advise heavy drinkers with periodontitis to reduce the amount they drink to improve both their systemic and oral health. In order to establish the

Table 3.

Risk for Low, Mid, and High Proportion of Teeth With PD ≥4 mm According to Alcohol Consumption and Other Variables

Independent Variable	Model 1				Model 2			
	Teeth With PD ≥4 mm		Univariate	Multivariate	Teeth With PD ≥4 mm		Univariate	Multivariate
	None	Low	OR (95% CI)	OR (95% CI)	None	Mid	OR (95% CI)	OR (95% CI)
Alcohol consumption								
None (0 g/day)	355	126	1	1	355	67	1	1
Light (0.1-14.9 g/day)	91	41	1.3 (0.8-1.9)	1.3 (0.8-2.0)	91	14	0.8 (0.4-1.5)	0.7 (0.4-1.5)
Moderate (15-29.9 g/day)	46	24	1.5 (0.9-2.5)	1.3 (0.7-2.4)	46	7	0.8 (0.3-1.9)	0.8 (0.3-2.0)
Heavy (≥30 g/day)	57	29	1.4 (0.9-2.4)	1.1 (0.6-2.0)	57	14	1.3 (0.7-2.5)	0.7 (0.3-1.7)
Smoking								
Never (0)	400	137	1	1	400	59	1	1
Light (1-399)	47	27	1.7 (1.0-2.8)*	1.7 (0.9-3.1)	47	8	1.2 (0.5-2.6)	1.4 (0.6-3.7)
Moderate (400-799)	63	31	1.4 (0.9-2.3)	1.4 (0.7-2.5)	63	12	1.3 (0.7-2.5)	1.4 (0.6-3.5)
Heavy (≥800)	39	25	1.9 (1.1-3.2)*	1.6 (0.8-3.2)	39	23	4.0 (2.2-7.2)‡	3.5 (1.4-8.7)†
Glucose tolerance								
Normal	404	145	1	1	404	67	1	1
Impaired	97	51	1.5 (1.0-2.2)	1.4 (0.9-2.0)	97	20	1.2 (0.7-2.1)	1.0 (0.6-1.8)
Diabetes	48	24	1.4 (0.8-2.4)	1.1 (0.7-2.0)	48	15	1.9 (1.0-3.6)	1.5 (0.7-3.0)
Gender								
Male	189	94	1	1	189	46	1	1
Female	360	126	0.7 (0.5-1.0)*	1.1 (0.6-1.8)	360	56	0.6 (0.4-1.0)*	1.2 (0.6-2.7)
Age (years)			1.0 (1.0-1.0)*	1.0 (1.0-1.0)			1.0 (1.0-1.1)‡	1.0 (1.0-1.0)
Number of teeth			1.0 (0.9-1.0)*	1.0 (0.9-1.0)			0.9 (0.9-0.9)‡	1.0 (0.9-1.0)
Mean plaque index			1.5 (1.1-2.0)†	1.3 (1.0-1.7)			3.6 (2.5-5.2)‡	3.0 (2.0-4.4)‡

* $P<0.05$.
† $P<0.01$.
‡ $P<0.001$.

effect of drinking as a risk factor for periodontitis, larger-scale epidemiological and interventional studies, for example examining the effect of temperance and abstinence from drinking in heavy drinkers with periodontitis, are needed to confirm the causal relationship between drinking and periodontitis, as well as supportive experimental studies to clarify the mechanisms for the relationship between drinking and periodontitis.

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Table 3. (continued)

Risk for Low, Mid, and High Proportion of Teeth With PD ≥4 mm According to Alcohol Consumption and Other Variables

Model 3			
Teeth With PD ≥4 mm		Univariate	Multivariate
None	High	OR (95% CI)	OR (95% CI)
355	43	1	1
91	8	0.7 (0.3-1.6)	0.6 (0.3-1.6)
46	15	2.7 (1.4-5.2)†	2.7 (1.1-6.6)*
57	24	3.5 (2.0-6.2)‡	2.5 (1.1-5.7)*
400	46	1	1
47	7	1.3 (0.6-3.0)	1.2 (0.4-3.2)
63	16	2.2 (1.2-4.1)*	1.7 (0.7-4.2)
39	21	4.7 (2.5-8.6)‡	2.8 (1.1-7.3)*
404	54	1	1
97	23	1.8 (1.0-3.0)*	1.2 (0.7-2.3)
48	13	2.0 (1.0-4.0)*	1.3 (0.6-3.0)
189	49	1	1
360	41	0.4 (0.3-0.7)‡	1.7 (0.7-3.9)
		1.0 (1.0-1.0)	1.0 (0.9-1.0)
		0.9 (0.9-0.9)‡	0.9 (0.9-1.0)
		5.4 (3.6-8.0)‡	4.6 (3.0-7.0)‡

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Table 4.

Risk for Low, Mid, and High Proportion of Teeth With CAL ≥5 mm According to Alcohol Consumption and Other Variables

Independent Variable	Model 1				Model 2			
	Teeth With CAL ≥5 mm		Univariate OR (95% CI)	Multivariate OR (95% CI)	Teeth With CAL ≥5 mm		Univariate OR (95% CI)	Multivariate OR (95% CI)
	None	Low			None	Mid		
Alcohol consumption								
None (0 g/day)	394	85	1	1	394	65	1	1
Light (0.1-14.9 g/day)	106	26	1.1 (0.7-1.9)	1.0 (0.6-1.7)	106	12	0.7 (0.4-1.3)	0.6 (0.3-1.3)
Moderate (15-29.9 g/day)	57	12	1.0 (0.5-1.9)	0.7 (0.3-1.5)	57	8	0.9 (0.4-1.9)	0.6 (0.2-1.4)
Heavy (≥30 g/day)	67	23	1.6 (0.9-2.7)	0.9 (0.5-1.8)	67	10	0.9 (0.4-1.8)	0.5 (0.2-1.1)
Smoking								
Never (0)	458	84	1	1	458	62	1	1
Light (1-399)	53	18	1.9 (1.0-3.3)*	2.0 (1.0-3.9)	53	10	1.4 (0.7-2.9)	1.5 (0.6-3.5)
Moderate (400-799)	70	20	1.6 (0.9-2.7)	1.5 (0.8-3.1)	70	14	1.5 (0.8-2.8)	1.1 (0.5-2.6)
Heavy (≥800)	43	24	3.0 (1.8-5.3)‡	2.6 (1.3-5.4)*	43	9	1.5 (0.7-3.3)	0.9 (0.3-2.3)
Glucose tolerance								
Normal	461	90	1	1	461	59	1	1
Impaired	114	36	1.6 (1.0-2.5)*	1.5 (0.9-2.3)	114	27	1.9 (1.1-3.0)*	1.7 (1.0-2.9)*
Diabetes	49	20	2.1 (1.2-3.7)*	1.7 (0.9-3.1)	49	9	1.4 (0.7-3.1)	0.9 (0.4-2.0)
Gender								
Male	206	69	1	1	206	42	1	1
Female	418	77	0.6 (0.4-0.8)†	1.0 (0.5-1.7)	418	53	0.6 (0.4-1.0)†	0.5 (0.2-0.9)*
Age (years)			1.0 (1.0-1.1)†	1.0 (1.0-1.1)†			1.1 (1.0-1.1)‡	1.0 (1.0-1.1)†
Number teeth			1.0 (1.0-1.1)	1.1 (1.0-1.1)*			0.9 (0.8-0.9)‡	0.9 (0.9-1.0)†
Mean plaque index			1.4 (1.0-1.9)*	1.3 (0.9-1.7)			1.8 (1.3-2.6)‡	1.3 (0.8-1.8)

* $P<0.05$.
† $P<0.01$.
‡ $P<0.001$.

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