Table 2
Odds ratios (95% confidence intervals) of stroke and stroke subtypes according to quintiles of serum hs-CRP levels.

	Quintiles of hs-CRP, mg/L						OR for 1SD increment of log hs-CRP
	1 (Low)	2	3	4	5 (High)	*p* for trend	
Serum hs-CRP							
Median (mg/L)	0.176	0.316	0.52	0.927	2.48		
Range (mg/L)	0.030–0.224	0.226–0.406	0.407–0.709	0.710–1.280	1.290–119.00		
Total stroke							
No. of case	45	41	56	46	73		
No. of control	156	157	157	155	158		
Age, sex, and community-matched OR	1.00	0.91(0.57–1.47)	1.24(0.80–1.93)	1.03(0.65–1.65)	1.62(1.04–2.52)*	0.03	1.20(1.05–1.38)†
Multivariable OR[a]	1.00	0.93(0.56–1.54)	1.22(0.77–1.93)	0.91(0.55–1.50)	1.49(0.93–2.41)	0.16	1.17(1.01–1.35)*
Ischemic stroke							
No. of case	26	22	32	33	52		
No. of control	93	97	99	101	105		
Age, sex, and community-matched OR	1.00	0.84(0.45–1.58)	1.19(0.66–2.12)	1.20(0.67–2.17)	1.84(1.05–3.24)*	0.02	1.30(1.10–1.54)†
Multivariable OR[a]	1.00	0.83(0.43–1.62)	1.08(0.58–2.01)	0.99(0.53–1.86)	1.57(0.85–2.91)	0.13	1.27(1.06–1.52)*
Lacunar infarction							
No. of case	20	14	21	24	39		
No. of control	66	76	69	72	71		
Age, sex, and community-matched OR	1.00	0.67(0.34–1.32)	1.00(0.54–1.85)	1.08(0.59–1.95)	1.53(0.89–2.61)	0.04	1.20(1.02–1.41)*
Multivariable OR[a]	1.00	0.58(0.26–1.28)	0.90(0.43–1.89)	0.98(0.47–2.04)	1.46(0.70–3.05)	0.13	1.24(1.00–1.55)
Large-artery occlusive infarction							
No. of case	6	5	7	6	12		
No. of control	21	14	22	21	30		
Age, sex, and community-matched OR	1.00	1.26(0.33–4.81)	1.13(0.34–3.79)	0.98(0.27–3.54)	1.47(0.46–4.70)	0.70	1.29(0.93–1.80)
Multivariable OR[a]	1.00	1.70(0.35–8.15)	1.17(0.28–4.92)	0.75(0.16–3.58)	2.01(0.53–7.59)	0.72	1.38(0.96–1.99)
Hemorrhagic stroke							
No. of case	19	19	24	13	21		
No. of control	63	60	58	54	53		
Age, sex, and community-matched OR	1.00	1.00(0.46–2.13)	1.34(0.67–2.65)	0.80(0.36–1.76)	1.28(0.62–2.64)	0.75	1.06(0.84–1.32)
Multivariable OR[a]	1.00	1.18(0.52–2.69)	1.64(0.78–3.44)	0.893(0.37–2.13)	1.39(0.60–3.19)	0.70	1.06(0.82–1.36)
Intraparenchymal hemorrhage							
No. of case	11	13	21	7	15		
No. of control	44	42	32	45	38		
Age, sex, and community-matched OR	1.00	1.11(0.42–2.91)	2.41(1.02–5.65)	0.63(0.22–1.79)	1.43(0.58–3.52)	0.89	1.08(0.82–1.42)
Multivariable OR[a]	1.00	1.41(0.47–4.22)	4.03(1.50–10.88)	0.74(0.22–2.54)	1.92(0.61–6.07)	0.62	1.15(0.83–1.59)
Subarachnoid hemorrhage							
No. of case	8	6	3	6	6		
No. of control	19	18	26	9	15		
Age, sex, and community-matched OR	1.00	0.99(0.27–3.62)	0.29(0.07–1.19)	1.67(0.44–6.37)	0.98(0.27–3.58)	0.75	1.01(0.68–1.50)
Multivariable OR[a]	1.00	1.65(0.35–7.89)	0.26(0.05–1.47)	2.39(0.41–13.96)	1.62(0.36–7.38)	0.47	1.14(0.70–1.86)

[a] Adjusted for systolic blood pressure, antihypertensive medication use, body mass index, alcohol intake category, cigarette smoking status, serum total cholesterol levels, log-transformed tryglyceride levels, and serum glucose category as well as matching for sex, age, community, year of serum stored, and fasting status.
* $p < 0.05$
† $p < 0.01$

type were estimated according to quintiles of hs-CRP levels and 1-SD increment of log transformed hs-CRP (antilog of SD = 3.0 mg/L) with conditional logistic regression models. Adjustment was made for systolic blood pressure (mmHg), antihypertensive medication use (yes and no), BMI (kg/m^2), ethanol intake (never, former, current: <46 g/day, and 46 g/day or more ethanol), cigarette smoking status (never, ex-, and current smokers), serum total cholesterol levels (mmol/L), log-transformed triglyceride levels (mmol/L), and serum glucose category (normal, impaired glucose tolerance and diabetes) were also conducted. Linear regression was employed to test for linear trends across the hs-CRP categories by using a median variable of hs-CRP for each hs-CRP category. The analyses were repeated, stratified by sex, age (40–64 and 65–85 years), body mass index (<23.1 kg/m^2, and 23.1 or more kg/m^2 split by the median) and smoking status (non-current and current smokers). The significance of the interactions for sex, age, smoking status and body mass index was tested using cross-product terms of sex, age, smoking and body mass index with hs-CRP levels. All probability values of statistical were two- tailed, and values of $p < 0.05$ were regarded as statistically significant. The SAS statistical package version 9.1.3 (Statistical Analysis System Inc., Cary, NC) was used for analyses.

2. Results

During the follow-up period, we identified 261 incident strokes, comprising 165 ischemic strokes (118 lacunar infarctions, 36 large-artery occlusive infarctions and 11 embolic infarctions) and 96 hemorrhagic strokes (67 intraparenchymal hemorrhages and 29 subarachnoid hemorrhages).

Table 1 shows the risk characteristics of total stroke and each stroke subtype compared with control subjects. The average age was 67 years for total stroke, varying from 65 years for subarachnoid hemorrhage to 70 years for large-artery occlusive infarction. The proportion of men was 51% for total stroke, varying from 21% for subarachnoid hemorrhage to 64% for large-artery occlusive infarction. Mean systolic and diastolic blood pressure levels and the prevalence of hypertension were higher in total stroke than in controls; this trend is most evident for ischemic stroke, more specifically lacunar infarction. Mean values of body mass index were higher in total stroke, ischemic stroke and lacunar infarction than in controls. Alcohol intake tended to be higher in total stroke and other stroke types except embolic infarction, but no significant different between cases and control. The prevalence of smoking and impaired glucose tolerance and mean value of serum choles-

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Table 3
Odds ratios (95% confidence intervals) of ischemic stroke according to quintiles of serum hs-CRP levels, stratified by sex, age, body mass index (BMI) and smoking status.

	Quintiles of hs-CRP, mg/L						OR for 1SD increment of log hs-CRP	p for interaction
	1 (Low)	2	3	4	5 (High)	p for trend		
Serum hs-CRP								
Median (mg/L)	0.176	0.316	0.52	0.927	2.48			
Range (mg/L)	0.030–0.224	0.226–0.406	0.407–0.709	0.710–1.280	1.290–119.00			
Men								
No. of case	17	11	20	21	28			
No. of control	52	52	68	56	63			
Multivariable OR[a]	1.00	0.91(0.35–2.33)	0.93(0.41–2.10)	1.02(0.43–2.46)	1.27(0.54–2.99)	0.54	1.25(0.99–1.59)	
Women								
No. of case	9	11	12	12	24			
No. of control	41	45	31	45	42			
Multivariable OR[a]	1.00	0.96(0.35–2.64)	1.30(0.45–3.75)	1.01(0.34–3.05)	2.11(0.78–5.70)	0.20	1.36(0.97–1.90)	0.72
Ages of 40–64								
No. of case	10	7	13	8	12			
No. of control	35	34	29	30	23			
Multivariable OR[a]	1.00	0.79(0.21–2.98)	1.21(0.37–3.95)	1.60(.042–6.06)	2.62(0.60–11.40)	0.12	1.35(0.83–2.17)	
Ages of 65–85								
No. of case	16	15	19	25	40			
No. of control	58	63	70	71	82			
Multivariable OR[a]	1.00	0.99(0.43–2.30)	1.08(0.48–2.42)	1.23(0.55–2.77)	1.76(0.82–3.75)	0.13	1.33(1.08–1.63)[†]	0.61
BMI < 23.1 kg/m²								
No. of case	14	10	17	12	17			
No. of control	62	51	43	42	46			
Multivariable OR[a]	1.00	0.68(0.16–2.95)	2.02(0.61–6.73)	2.96(0.87–10.11)	1.37(0.42–4.50)	0.15	1.30(0.91–1.87)	
BMI ≥ 23.1 kg/m²								
No. of case	12	12	15	21	35			
No. of control	31	46	56	59	59			
Multivariable OR[a]	1.00	0.36(0.10–1.39)	0.76(0.23–2.55)	0.83(0.27–2.54)	1.40(0.45–4.34)	0.25	1.38(0.97–1.98)	0.99
Non-current smokers								
No. of case	18	15	16	24	40			
No. of control	70	72	71	63	69			
Multivariable OR[a]	1.00	0.69(0.29–1.67)	0.75(0.30–1.89)	1.23(0.53–2.86)	2.24(0.99–5.05)	0.03	1.43(1.13–1.83)[†]	
Current smokers								
No. of case	8	7	16	9	12			
No. of control	23	25	28	38	36			
Multivariable OR[a]	1.00	8.96(1.09–73.84)	3.95(0.67–23.19)	1.83(0.31–10.84)	1.44(0.28–7.52)	0.66	1.02(0.64–1.63)	0.12

[a] Adjusted for systolic blood pressure, antihypertensive medication use, body mass index, alcohol intake category, cigarette smoking status, serum total cholesterol levels, log-transformed tryglyceride levels, and serum glucose category as well as matching for sex, age, community, year of serum stored, and fasting status.
[†] $p < 0.01$.

terol were not different between cases and control subjects for total stroke or stroke subtype. Median values of triglycerides were higher in ischemic stroke, but lower in intraparenchymal hemorrhage than controls. The prevalence of diabetes was higher in total stroke and ischemic stroke, but lower in hemorrhagic stroke than in controls. Median values of hs-CRP levels were higher in total stroke and ischemic stroke, more specifically lacunar infarction than controls.

Table 2 shows odds ratios and 95% confidence interval (CIs) for total stroke and stroke subtypes according to quintiles of hs-CRP levels and 1-SD increment in log transformed hs-CRP levels. There was a positive association between hs-CRP and incidence of total stroke, ischemic stroke and lacunar infarction. After adjustment for hypertension, diabetes, serum total cholesterol levels and other cardiovascular risk factors, these positive relationships remained statistically significant for total stroke and ischemic stroke, and marginally significant for lacunar infarction. The multivariable odds ratios associated with 1-SD increment of hs-CRP were 1.17(1.01–1.35), $p = 0.03$ for total strokes, 1.27(1.06–1.52), $p = 0.01$ for ischemic strokes, and 1.24(1.00–1.55), $p = 0.06$ for lacunar infarction. The multivariable odds ratios for the highest vs. lowest quintiles of hs-CRP levels were 1.49(0.93–2.41) for total stroke, 1.57 (0.85–2.91) for ischemic stroke and 1.46(0.70–3.05) for lacunar infarction. The results did not alter when we excluded subjects with hs-CRP levels more than 10 mg/L; the multivariable odds ratios associated with 1-SD increment in log hs-CRP levels were 1.15 (0.98–1.35), $p = 0.09$ for total stroke, 1.25(1.02–1.54), $p = 0.03$ for ischemic strokes, and 1.31(1.03–1.68), $p = 0.03$ for lacunar infarction. Similar results were observed when we excluded subjects with use of lipid-lowering medication (3% of the total subjects); the multivariable odds ratios associated with 1-SD increment in log hs-CRP levels were 1.20(1.03–1.39), $p = 0.02$ for total stroke, 1.30(1.30–1.57), $p = 0.008$ for ischemic strokes, and 1.30(1.02–1.64), $p = 0.03$ for lacunar infarction. The association of hs-CRP with risk of total stroke (p for interaction = 0.48), ischemic stroke (p for interaction = 0.72) and lacunar infarction (p for interaction = 0.78) did not vary by sex. No associations were found between hs-CRP levels and risk of hemorrhagic stroke. The calculation of odds ratio for embolic infarctions are omitted because of the small number of cases ($n = 11$).

Table 3 presents the multivariable odds ratios of ischemic stroke according to quintiles of hs-CRP levels and 1-SD increment in log hs-CRP levels, stratified by sex, age, median BMI and smoking status. The association between hs-CRP levels and incidence of ischemic stroke did not vary significantly between men and women (p for interaction = 0.72), between the 40–64 and 65–85 years of age groups ($p = 0.61$), between persons with BMI <23.1 kg/m² and those with the higher body mass index ($p = 0.99$) or between non-current smokers and current smokers ($p = 0.12$).

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3. Discussion

The present nested case–control study showed a positive association between hs-CRP levels with risks of total, ischemic strokes and more specifically lacunar infraction among Japanese. These associations remained the same after adjustment for known cardiovascular risk factors and the matching variable of age, sex, years of serum storage, and community. There was no significant association between hs-CRP levels and risk of hemorrhagic stroke. The positive association between hs-CRP and risk of ischemic stroke was consistent with the result of a recent Japanese study [13] and we extended the evidence that a positive association with risk of lacunar stroke was found in Japanese men and women.

Our findings were consistent with the hypothesis that systemic inflammation contributes to the development of ischemic stroke, and with previous studies that hs-CRP, a marker of inflammation, predicts the risk of ischemic stroke [8,10,11,20,26]. CRP mediates low density lipoprotein's uptake by macrophages, thus facilitates the formation of foam cells in the process of atherogenesis [27]. CRP also impairs endothelial function by attenuating the production of nitric oxide through the downregulation of endothelial nitric oxide synthase mRNA, and facilitates apoptosis of endothelial cells [28]. Further, CRP activates vascular smooth muscle cells, and stimulates their proliferation and migration [1,29].

We did not find a positive association between hs-CRP and risk of hemorrhagic stroke in the present study, whereas we previously reported that plasma fibrinogen is associated with risk of hemorrhagic stroke, especially intraparenchymal hemorrhage among Japanese [30]. This finding suggested that the role of hs-CRP as a marker of inflammation maybe less important in predicting the risk of hemorrhagic stroke.

The association of hs-CRP levels with risk of ischemic stroke did not vary according to sex, age, BMI or smoking status. We also found that hs-CRP levels may predicts risk of ischemic stroke even among non-current smokers. The Physician's Health Study [8], and a recent meta-analysis study [31] have also observed a similar significant association of hs-CRP levels with vascular risk among non-smokers, the relative risk were 2.8(1.7–4.7) and 1.72(1.55–1.90), respectively.

The strength of the present study is the large number of strokes confirmed by imaging studies, which allowed us to investigate the association between hs-CRP levels and risk of total stroke as well as stroke subtypes.

Our present study has several potential limitations. First, 2% of hs-CRP levels were more than 10 mg/L, where hs-CRP levels greater than 10 mg/L might be due to acute infection or trauma [4]. However, after we excluded the subjects with hs-CRP levels more than 10 mg/L, the results did not change materially. Second, 63% (165 cases) of the stroke cases in the present study were ischemic stroke with majority of lacunar infarction (118 cases). The case number per CRP quintile for other stroke subtypes was small to obtain valid estimates of odd ratios. Thus, further follow-up is necessary to confirm the association of hs-CRP levels with risk of other stroke subtypes. Third, we used frozen serum to estimate hs-CRP levels and we did not examine long-term changes in hs-CRP levels in stored serum samples. However, hs-CRP levels were reported to be stable at −70 °C which stored for 8–11 years [32].

In conclusion, the present study showed that among apparently healthy middle-aged Japanese men and women, hs-CRP predicts the incidence of total and ischemic strokes, independent of sex, age, body mass index and smoking.

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CIRCS Investigators

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Chronic Kidney Disease and Drinking Status in Relation to Risks of Stroke and Its Subtypes : The Circulatory Risk in Communities Study (CIRCS)

Yuji Shimizu, Kenji Maeda, Hironori Imano, Tetsuya Ohira, Akihiko Kitamura, Masahiko Kiyama, Takeo Okada, Yoshinori Ishikawa, Takashi Shimamoto, Kazumasa Yamagishi, Takeshi Tanigawa and Hiroyasu Iso

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Chronic Kidney Disease and Drinking Status in Relation to Risks of Stroke and Its Subtypes

The Circulatory Risk in Communities Study (CIRCS)

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Background and Purpose—Several epidemiological studies have established an association between chronic kidney disease (CKD), based on estimated glomerular filtration rate (GFR), and risk of stroke. However, sex-specific evidence for the relationship between CKD and risk of stroke and its subtypes is still limited.

Methods—We conducted a prospective cohort study of 12 222 Japanese men and women age 40 to 69 years living in 4 communities under systematic surveillance of stroke incidence to determine the relationship between CKD and risk of stroke and its subtypes.

Results—During the 17-year follow-up, there were 566 strokes (327 ischemic and 186 hemorrhagic strokes). GFR was inversely associated with age- and community-adjusted risk of total stroke for both men and women. Compared with the reference group without CKD (GFR ≥60 mL/min per 1.73m^2), the adjusted risks of total stroke for subjects with CKD (GFR <60 mL/min per 1.73m^2) were 1.63 (1.22–2.17) for men and 1.51 (1.13–2.02) for women. Excess risk of stroke associated with CKD was identified primarily for hemorrhagic stroke among men and for ischemic stroke among women. After adjustment for traditional cardiovascular risk factors, associations remained statistically significant. When stratified by drinking status, excess risk of hemorrhagic stroke with CKD was confined to drinkers; adjusted risks were 4.18 (2.31–7.57) for men and 7.00 (1.92–25.56) for women.

Conclusions—CKD was associated with increased risk of hemorrhagic stroke for men, and of ischemic stroke for women. This sex difference may partly be explained by the difference in prevalence of drinkers between men and women. **(*Stroke*. 2011;42:2531-2537.)**

Key Words: stroke risk ■ follow-up study ■ glomerular filtration rate ■ chronic kidney disease

During the last few decades, clinical and epidemiological studies have indicated that lower glomerular filtration rate (GFR), a marker of chronic kidney disease (CKD), is associated with risk of stroke.[1–6] The Rotterdam study had a 10.2-year follow-up for 4937 men and women age ≥55 years, and it indicated that a reduction in GFR as estimated with the Cockcroft-Gault equation was a strong risk factor for hemorrhagic, but not for ischemic stroke.[2] The Suita study of 5494 men and women age 30 to 79 years showed that CKD was a significant risk for total and ischemic stroke, but this study did not deal with hemorrhagic stroke.[6] However, none of those studies conducted a sex-specific analysis. The Hisayama study, which followed up 2634 men and women age ≥40 years, reported that women with CKD, defined as GFR <60 mL/min per 1.73m^2 with the Modification of Diet in Renal Disease method, were at double the risk of ischemic stroke compared with those without CKD; even so, this association was observed only for women.[3] Therefore, sex-specific evidence for the relationships between CKD and risk of stroke and its subtypes has remained limited.

We therefore examined this relationship among middle-aged men and women in a large, community-based, prospective study.

Methods

Subjects

The Circulatory Risk in Communities Study (CIRCS) is a prospective community-based study that was launched to prevent cardiovas-

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cular disease in Japanese populations.[7–9] The population surveyed included 4822 men and 7400 women age 40 to 69 years. Residents in the northeastern rural community of Ikawa and in the southwestern rural community of Noichi participated in this study between 1985 and 1990; those in the central rural community of Kyowa between 1985 and 1991; and those in the southwestern suburb of Yao between 1985 and 1994. Those whose serum data (89 men; 103 women) and/or alcohol consumption data (10 men; 16 women) were not available, or those with a history of stroke or coronary heart disease (154 men; 70 women), were excluded. The remaining 11 780 persons (4569 men; 7211 women) were followed up until the end of 2004 for Kyowa and Noichi, and until the end of 2007 for Ikawa and Yao, to determine incidence of stroke. The 671 persons (204 men; 467 women) who moved out of their respective communities during follow-up and 1451 persons (845 men; 606 women) who died were censored at the date of moving out or date of death. Median follow-up time was 17.1 years.

Baseline Examination

Details of the risk-factor survey have been described elsewhere.[9] Briefly, height in stocking feet and weight in light clothing were measured, and body mass index was calculated as weight divided by height (in kg/m^2).

GFR was estimated by using the established method with 3 variations recently proposed by a working group of the Japanese Chronic Kidney Disease initiative.[10] According to this adaptation, GFR (ml/min per 1.73m^2)=194×(serum creatinine [enzyme method])$^{-1.094}$×(age)$^{-0.287}$×(0.739 for women). Serum creatinine was assayed with the non-compensated kinetic Jaffe method, which was recently replaced with enzymatic methods. Because creatinine values established with the Jaffe method were approximately 0.2 mg/dL higher those established with the enzymatic method caused by the presence of creatinine chromogens in the sample,[11,12] we calculated our serum data in accordance with the enzymatic method. The serum creatinine (enzymatic method)=serum creatinine (Jaffe method) −0.2 mg/dL. CKD was defined as GFR <60 mL/min per 1.73m^2 in accordance with the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines.[12]

Systolic and fifth-phase diastolic blood pressures in the right arm were measured by trained technicians using a standard mercury sphygmomanometer. The participants were seated and had rested for 5 minutes before the measurements. Trained interviewers obtained information regarding family history of stroke; smoking status; use of antihypertensive agents; medical histories; and usual weekly intake of alcohol in units of gō (a traditional Japanese unit of volume equal to 23 g of ethanol), which was converted to grams of ethanol per day. One gō equals 180 mL of sake rice wine, 1 bottle (633 mL) of beer, 2 single shots (75 mL) of whisky, or 2 glasses (180 mL) of wine. Persons who reported consuming 0.3 gō or more per week were regarded as current drinkers.[9–13]Former drinkers were defined as abstainers for the past 3 months and longer. Former drinkers and current drinkers were classified as drinkers. Persons who smoked ≥1 cigarette per day were defined as current smokers. Diabetes mellitus was defined as a fasting glucose level of ≥7.8mmol/L, a nonfasting glucose level of ≥11.1 mmol/ L, and/or use of medication for diabetes.

End Point Determination

Assessments of medical history, incidence survey, and deaths were conducted once a year during the follow-up-time. Stroke incidence was ascertained by using 6 overlapping sources: national insurance claims, reports by local physicians, ambulance records, death certificates, reports by public health nurses and health volunteers, and cardiovascular risk surveys.[14,15] Cases with stroke as underlying cause of death (International Classification of Disease, Ninth Revision, codes 430–438) were selected from death certificates. To confirm diagnosis of stroke, all living patients were visited or asked to complete risk factor surveys. Physicians participating in this study obtained a medical history and a history of neurological examinations from stroke patients. For deaths, histories were obtained from the families and medical records were reviewed.

Stroke was defined as a focal neurological disorder with rapid onset and persisting for at least 24 hours or until death. Based on this clinical definition, the incidence of stroke was determined by a panel of 3 to 4 physicians participating in the study who were blinded to the data from the risk factor survey. The determination of stroke subtypes (ischemic stroke, intraparenchymal hemorrhage, and subarachnoid hemorrhage) was conducted primarily by means of computed tomography and magnetic resonance imaging using a standard procedure. Films were available for 93.0% of stroke cases. Stroke cases that were diagnosed clinically and yet showed no lesion were classified according to clinical criteria based on those established by Millikan.[16]

Statistical Analysis

Because the prevalence of classical cardiovascular risk factors, such as status of smoking and drinking, were different between men and women, sex-specific analyses were performed in the present study as in previous studies.[17] Differences in age- and community-adjusted mean values or prevalence of potential confounding factors at baseline according to GFR levels and between participants with CKD and without CKD were calculated using ANOVA or logistic regression models. We also analyzed the data after stratification by drinking status. Hazard ratios (HR) and 95% CI of incidence of stroke and its subtypes associated with GFR levels and CKD were calculated using Cox proportional hazard regression models. We tested proportionality by evaluating the interaction between CKD and time for stroke incidence and found no violation in the proportional hazard assumption. In addition, subjects were stratified by drinking status (never drinker, ever drinker) because drinking has a differential effect on risks of hemorrhagic and ischemic stroke.[18] Adjustments for confounding factors were made in 2 ways. First, we adjusted only for age and community. Second, we included other possible confounding factors, such as family history of stroke (yes or no), systolic blood pressure (mm Hg), antihypertensive agent use (yes or no), smoking status (never smoker, former smoker, current smoker), alcohol consumption (never drinker, former drinker, current drinker [<23g/wk, 23–46g/wk, 46–69g/wk, >69g/wk, respectively]), serum total cholesterol (mg/dL), diabetes status (yes or no), body mass index (kg/m^2), and menopausal status for women (pre or post).

All statistical analyses were performed using SAS (version 9.1, SAS Inc). All probability values for statistical tests were 2-tailed, and values of <0.05 were regarded as statistically significant.

Results

Of 4569 men and 7211 women, 566 suffered incident strokes during the 17-year follow-up period: 304 total, 192 ischemic, 78 hemorrhagic, and 34 unclassified strokes for men, and 262 total, 135 ischemic, 108 hemorrhagic, and 19 unclassified for women. The proportions of current-, former-, and never drinkers were, respectively, 72.6%, 5.9%, and 21.5% for men, and 10.4%, 1.3% and 88.3% for women.

Table 1 shows sex-specific baseline characteristics by category of GFR levels (<60, 60–89, and ≥90). Diastolic blood pressure, antihypertensive medication use, body mass index, and total cholesterol were inversely associated with GFR levels for both men and women, whereas prevalence rates of current smokers and current drinkers were positively associated with GFR levels for men. Systolic blood pressure was inversely associated with GFR levels for men, but not for women.

Table 2 shows sex-specific age- and community-adjusted and multivariate-adjusted HRs of total stroke and stroke subtypes for men and women. There were inverse associations between GFR and risks of total and stroke subtypes for men and women in both age- and community-adjusted and

Table 1. Sex-Specific Age- and Community-Adjusted Mean Values and Proportions by GFR Category and CKD

Characteristic	CKD-Negative GFR≥90	CKD-Negative 90>GFR≥60	CKD-Positive 60>GFR	P
Men				
At risk, n	1366	2721	482	
Age, y	50.7	55.0	60.4	
Family history of stroke, n	25	25	27	0.688
Sytolic blood pressure, mm Hg	133	133	135	0.035
Diastolic blood pressure, mm Hg	81	82	84	<0.001
Antihypertensive medication, %	9	13	25	<0.001
Body mass index, kg/m^2	22.5	23.4	24.0	<0.001
Diabetus melitus, %	7	5	5	0.169
Current smoker, %	62	57	49	<0.001
Ex-smoker, %	22	25	32	<0.001
Current drinker, %	78	72	62	<0.001
Ex-drinker, %	4	6	10	<0.001
Total cholesterol, mg/dL	188	191	197	<0.001
Serum creatinine (Jaffe method, mg/dl)	0.82	1.04	1.34	<0.001
Estimated glomerular filtration rate (ml/min per 1.73 mm^2)	105.3	76.1	54.6	<0.001
Women				
At risk, n	2765	3619	827	
Age, y	51.8	53.5	59.5	
Family history of stroke, n	25	28	31	0.002
Sytolic blood pressure, mm Hg	130	130	131	0.158
Diastolic blood pressure, mm Hg	78	79	80	0.017
Antihypertensive medication, %	9	14	23	<0.001
Body mass index, kg/m^2	23.3	23.5	23.8	<0.001
Diabetus melitus, %	3	2	3	0.201
Current smoker, %	6	7	6	0.438
Ex-smoker, %	2	1	2	0.517
Current drinker, %	11	10	9	0.087
Ex-drinker, %	10	13	22	0.028
Total cholesterol, mg/dL	200	205	208	<0.001
Serum creatinine (Jaffe method, mg/dl)	0.67	0.85	1.06	<0.001
Estimated glomerular filtration rate (ml/min per 1.73 mm^2)	108.1	74.8	56.4	<0.001
Postmenopausal, %	62	63	64	0.259

Chronic kidney disease was defined as GFR<60 mL/min 1.73 mm^2. Family history of stroke referred to stroke history of parents.

GFR indicates glomerular filtration rate; CKD, chronic kidney disease.

multivariate-adjusted models. Compared with the non-CKD reference group, participants with CKD showed higher risk of total and hemorrhagic stroke for men and of ischemic stroke for women.

Figure shows the number of cases per 1000-person-years for incidence of total, ischemic, and hemorrhagic strokes for participants with and without CKD, stratified by sex and drinking status. Compared with participants without CKD, those with CKD had higher incidence of ischemic and hemorrhagic strokes, independent of sex and drinking status, except for hemorrhagic stroke among never drinkers.

In the overall fully-adjusted model including sex except for drinking status, HRs for sex of men were 2.80 (95% CI, 1.43–5.49) for ischemic stroke and 1.44 (95% CI, 0.75–2.76) for hemorrhagic stroke. In that model, HRs for CKD were 1.51 (95% CI, 1.16–1.98) for ischemic stroke and 1.54 (95% CI, 1.06–2.26) for hemorrhagic stroke. After additional adjustment for drinking status, HRs for men were weakened, but remained statistically significant for ischemic stroke: 2.39 (95% CI, 1.19–4.80). In that model, HRs for CKD were 1.54 (95% CI, 1.17–2.01) for ischemic stroke and 1.58 (95% CI, 1.08–2.31) for hemorrhagic stroke. When we examined HRs

Table 2. Sex-Specific Hazard Ratios and 95% CI for Stroke by GFR Category and CKD

Characteristic	CKD-Negative		CKD-Positive	
	GFR≥90	90>GFR≥60	60>GFR	*P*
Men				
At risk, n	1366	2721	482	
Total stroke				
Case, n (%)	59 (4.3)	182 (6.7)	63 (13.1)	
Age- and community-adjusted HR	1.00	1.18 (0.87–1.60)	1.86 (1.27–2.74)	0.002
		1.00	1.63 (1.22–2.17)	0.001
Multivariate-adjusted HR	1.00	1.22 (0.89–1.66)	1.90 (1.28–2.82)	0.002
		1.00	1.61 (1.20–2.17)	0.002
Ischemic stroke				
Case, n (%)	39 (2.9)	117 (4.3)	36 (7.5)	
Age- and community-adjusted HR	1.00	1.05 (0.72–1.53)	1.36 (0.84–2.22)	0.213
		1.00	1.31 (0.90–1.90)	0.166
Multivariate-adjusted HR	1.00	1.07 (0.73–1.58)	1.34 (0.81–2.21)	0.256
		1.00	1.26 (0.86–1.85)	0.239
Hemorrhagic stroke				
Case, n (%)	18 (1.3)	41 (1.5)	19 (3.9)	
Age- and community-adjusted HR	1.00	1.17 (0.66–2.08)	3.36 (1.65–6.84)	<0.001
		1.00	2.97 (1.71–5.18)	<0.001
Multivariate-adjusted HR	1.00	1.33 (0.74–2.38)	4.09 (1.96–8.54)	<0.001
		1.00	3.27 (1.85–5.76)	<0.001
Women				
At risk, n	2765	3619	827	
Total stroke				
Case, n (%)	67 (2.4)	132 (3.6)	63 (7.6)	
Age- and community-adjusted HR	1.00	1.23 (0.91–1.65)	1.73 (1.21–2.47)	0.003
		1.00	1.51 (1.13–2.02)	0.006
Multivariate-adjusted HR	1.00	1.21 (0.90–1.63)	1.58 (1.10–2.28)	0.013
		1.00	1.39 (1.03–1.87)	0.030
Ischemic stroke				
Case, n (%)	28 (1.0)	66 (1.8)	41 (5.0)	
Age- and community-adjusted HR	1.00	1.42 (0.91–2.22)	2.47 (1.50–4.07)	<0.001
		1.00	1.94 (1.33–2.83)	0.001
Multivariate-adjusted HR	1.00	1.41 (0.90–2.20)	2.30 (1.39–3.81)	0.002
		1.00	1.82 (1.24–2.67)	0.002
Hemorrhagic stroke				
Case, n (%)	31 (1.1)	59 (1.6)	18 (2.2)	
Age- and community-adjusted HR	1.00	1.23 (0.79–1.90)	1.20 (0.66–2.19)	0.552
		1.00	1.05 (0.62–1.76)	0.862
Multivariate-adjusted HR	1.00	1.23 (0.79–1.92)	1.10 (0.60–2.03)	0.755
		1.00	0.96 (0.56–1.62)	0.866

Multivariate-adjusted HR was further adjusted for family history of stroke, body mass index, systolic blood pressure, antihypertensive medication use, smoking, alcohol consumption, serum total cholesterol, diabetes mellitus, and for women, menopausal status.

HR indicates hazard ratio; GFR, glomerular filtration rate; CKD, chronic kidney disease.

by drinking status, HRs for men were not significant for ischemic stroke among either never drinkers or ever drinkers: 1.14 (95% CI, 0.72–1.82) and 2.16 (95% CI, 0.64–7.27), respectively.

For never-drinking men and women, CKD showed a positive association primarily with risk of ischemic stroke, but not with hemorrhagic stroke; however, a positive association was observed with hemorrhagic stroke for ever-drinking

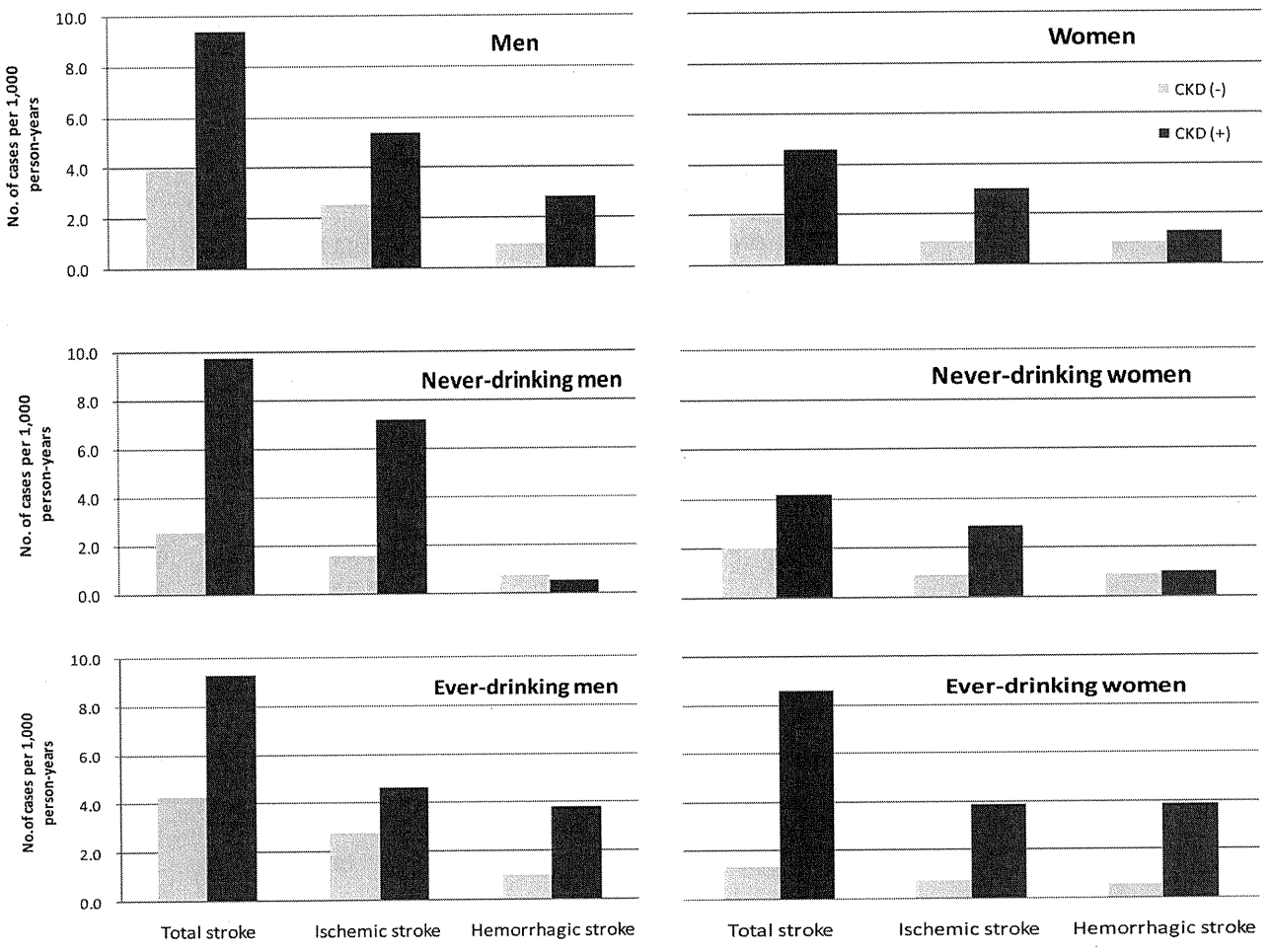

Figure. Incidents of total, ischemic, and hemorrhgic stroke per 1,000 person-years in the presence or absence of CKD. Black-filled bar, CKD-negative; open bar, CKD-positive.

men and women (Table 3). Multivariate-adjusted HRs of ischemic stroke for CKD among never drinkers were 2.81 (95% CI, 1.28–6.17) for men and 1.68 (95% CI, 1.12–2.53) for women, whereas corresponding HRs of hemorrhagic stroke among ever drinkers were 4.18 (95% CI, 2.31–7.57) for men and 7.00 (95% CI, 1.92–25.56) for women. For former drinkers, the number of stroke cases limited the statistical power of analysis. Although the number of former drinkers among men were limited (270 at risk and 17 cases), the associations between CKD and stroke subtypes for former drinkers were essentially same as for current drinkers. For women, we could not analyze the association for former drinkers, because the number of cases was only 2. Among former-drinking men, multivariate HRs of ischemic and hemorrhagic strokes were 0.38 (95% CI, 0.05–3.20) and 7.92 (95% CI, 0.40–158.0), respectively.

When we excluded participants with arterial fibrillation (36 men; 21 women) from the analysis, the results did not change materially; the multivariate-adjusted HRs of ischemic stroke for never drinkers were 2.81 (95% CI, 1.28–6.18) for men and 1.68 (95% CI, 1.10–2.56) for women, whereas adjusted HRs of hemorrhagic stroke for drinkers were 4.19 (95% CI, 2.31–7.58) for men and for 7.27 (95% CI, 1.97–26.80) for women.

Discussion

Major findings of the present study were that CKD appeared to be associated with risk of total stroke, especially of hemorrhagic stroke for men and of ischemic stroke for women, after adjustment for cardiovascular risk factors, and after exclusion of persons with arterial fibrillation.

In the study presented here, the prevalence of ever drinkers was high among men (78.5%) and low among women (11.7%). Also, the association between CKD and hemorrhagic stroke was more evident for ever drinkers, whereas the association between CKD and ischemic stroke was more evident for never- drinkers. The sex difference in the prevalence of ever drinkers may explain the sex difference in the associations between CKD and stroke subtypes, in that CKD was associated with risk of hemorrhagic stroke for men and of ischemic stroke for women. However, the sex difference does not solely explain these relationships, which maintains the significant association between CKD and ischemic stroke after adjustment for drinking status.

The mechanisms underlying the associations between CKD and stroke subtypes have not been clearly elucidated. Endothelial dysfunction has been recognized as 1 of the initial mechanisms, and leads to glomerular injury[19] and atherosclerosis, which demonstrates an important link be-

Table 3. Sex-Specific Hazard Ratios and 95% CI for Stroke by CKD by Drinking Status

	Men			Women		
	CKD-Negative	CKD-Positive	*P*	CKD-Negative	CKD-Positive	*P*
Never drinker						
At risk, n	841	142		5622	745	
Total stroke						
Case, n (%)	32 (3.8)	19 (13.4)		183 (3.3)	52 (7.0)	
Age- and community-adjusted HR	1.00	2.38 (1.29–4.38)	0.006	1.00	1.32 (0.96–1.81)	0.091
Multivariate-adjusted HR	1.00	2.28 (1.20–4.34)	0.012	1.00	1.19 (0.86–1.64)	0.290
Ischemic stroke						
Case, n (%)	20 (2.4)	14 (9.9)		85 (1.5)	36 (4.8)	
Age- and community-adjusted HR	1.00	2.67 (1.28–5.58)	0.009	1.00	1.84 (1.23–2.76)	0.003
Multivariate-adjusted HR	1.00	2.81 (1.28–6.17)	0.010	1.00	1.68 (1.12–2.53)	0.013
Hemorrhagic stroke						
Case, n (%)	9 (1.1)	1 (0.7)		83 (1.5)	13 (1.7)	
Age- and community-adjusted HR	1.00	. . .	. . .	1.00	0.79 (0.43–1.43)	0.428
Multivariate-adjusted HR	1.00	. . .	. . .	1.00	0.71 (0.39–1.31)	0.275
Ever drinker						
At risk, n	3246	340		762	82	
Total stroke						
Case, n (%)	209 (6.4)	44 (12.9)		16 (2.1)	11 (13.4)	
Age- and community-adjusted HR	1.00	1.49 (1.06–2.09)	0.020	1.00	4.40 (1.94–9.97)	<0.001
Multivariate-adjusted HR	1.00	1.45 (1.03–2.03)	0.035	1.00	5.61 (2.43–12.98)	<0.001
Ischemic stroke						
Case, n (%)	136 (4.2)	22 (6.5)		9 (1.2)	5 (6.1)	
Age- and community-adjusted HR	1.00	1.04 (0.66–1.65)	0.863	1.00	2.95 (0.94–9.25)	0.063
Multivariate-adjusted HR	1.00	0.97 (0.61–1.55)	0.902	1.00	3.97 (1.22–12.88)	0.022
Hemorrhagic stroke						
Case, n (%)	50 (0.6)	18 (5.3)		7 (0.9)	5 (6.1)	
Age- and community-adjusted HR	1.00	3.73 (2.10–6.65)	<0.001	1.00	5.57 (1.61–19.30)	0.007
Multivariate-adjusted HR	1.00	4.18 (2.31–7.57)	<0.001	1.00	7.00 (1.92–25.56)	0.003

Multivariate-adjusted HR was adjusted further for family history of stroke, body mass index, systolic blood pressure, antihypertensive medication use, smoking, alcohol consumption, serum total cholesterol, diabetes mellitus, and for women, menopausal status.

HR indicates hazard ratio; CI, confidence interval; CKD, chronic kidney disease.

tween CKD and elevated risk of cardiovascular events.[20] In addition, CKD correlates with arteriosclerosis in kidney and brain.[21]

Atherosclerosis is a basic pathological factor for atherothrombotic brain infarction, whereas arteriosclerosis is for intraparenchymal hemorrhage.[22] Furthermore, light-to-moderate alcohol consumption is associated with reduced risk of ischemic stroke, but heavy alcohol consumption was associated with increased risk of hemorrhagic stroke.[18] These associations can be explained by alcohol-induced reduction of platelet aggregation[23] and plasma fibrinogen levels,[24] as well as enhancement of fibrinolysis,[25] which is counterbalanced by high blood pressure.[26] Those mechanisms may explain why CKD is a risk factor for ischemic stroke among never drinkers.

In contrast, heavy alcohol drinking increases not only blood pressure levels, but also blood pressure variability including the morning surge,[27] which increases risk of hemorrhagic stroke.[28] Therefore, the association between CKD and hemorrhagic stroke may be stronger among drinkers.

Potential limitations of this study warrant mentioning. For analysis of the association between GFR and stroke incidence, we used a single assessment of serum creatinine at baseline, which is prone to misclassification as usual serum creatinine, depending on the individual. However, other previous cohort studies also used a single measurement of creatinine and showed significant associations between CKD and risk of stroke.[1–6] Although a significant association between CKD and hemorrhagic stroke was observed among female ever drinkers, the estimate of HR showed a wide confidence interval because of the small number of incident cases. Additional investigation of a cohort with a larger number of drinking women is necessary to validate our findings. In this study, rates of participation in CIRCS were higher for women than men because men tend to receive health check-ups under industrial health plans. However, the sex distribution of our study (61.2%) was not so different from that of other community-based studies such as the Rotterdam study (61.3%)[2]; the Hisayama study (57.9%)[3]; and the Nippon Data, a national sample study (59.0%).[29]

In conclusion, CKD was found to be associated with an increased risk of stroke, especially hemorrhagic stroke for men and ischemic stroke for women, in general Japanese populations. Sex difference in the relationship between CKD and stroke subtypes was confounded by drinking status.

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Disclosures

None.

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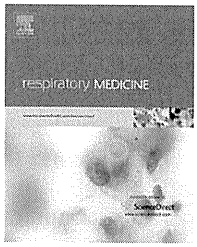

Associations between alcohol consumption and sleep-disordered breathing among Japanese women

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Alcohol consumption;
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Summary
Background: The associations between alcohol consumption and sleep-disordered breathing in women are uncertain.
Methods: We conducted a cross-sectional study of 3113 women aged 30–69 years. The 3% oxygen desaturation index (3%ODI), based on overnight pulse oximetry findings, was selected as an indicator of sleep-disordered breathing.
Results: 3%ODI frequencies of ≥5 were higher for drinking women with ethanol intakes of ≥23.0 g/d than for never drinkers: the respective multivariable odds ratios and 95% confidence intervals was 1.8(1.0–3.4). The corresponding odds ratio was 3.0(1.6–5.8) for habitual snoring. The associations of ethanol intakes of ≥23.0 g/d with 3%ODI ≥ 5 was more evident among women with BMI <23.0 kg/m^2 (median) than those with higher BMI but did not vary by habitual snoring. The multivariable odds ratios of 3%ODI ≥ 5 for women with ethanol intakes of ≥23.0 g/d versus never drinkers were 2.7(1.0–6.7) for lower BMI and 1.5(0.6–3.3) for higher BMI and the corresponding odds ratio were 2.8(1.6–7.2) and 3.2(1.3–7.9) for habitual snoring, respectively.
Conclusion: Alcohol consumption was associated with higher prevalence of sleep-disordered breathing among Japanese women.

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Introduction

Sleep-disordered breathing (SDB) is associated with risk of hypertension[1] and cardiovascular disease[2] as well as with all causes of mortality.[2,3] Alcohol consumption is associated with elevated morning blood pressure levels[4] and risk of mortality from cardiovascular disease.[5] Previous clinical studies reported that alcohol consumption prior to bedtime was associated with an increase in the number and duration of hypopnea and apnea occurrences in snorers or sleep-disordered breathing patients,[6–8] and required higher levels of continuous positive airway pressure (CPAP) to prevent apnea and hypopnea.[9] However, it is not yet clear to what extent alcohol consumption by women is associated with risk of SDB. Several previous epidemiological studies found that alcohol consumption was associated with snoring for men[10,11] and for men and women combined.[12] However, such an association with SDB was observed only in men,[13–15] but not in women[15] or in men and women combined.[16,17] Further, a previous study of Japanese men showed that this association was more evident in men with low BMI than in those with high BMI.[14]

To examine the associations between alcohol consumption and sleep-disordered breathing specifically among Japanese women, we conducted a large community-based study.

Methods

Study population

The Circulatory Risk in Communities Study (CIRCS) is a dynamic community cohort study of Japanese covering five communities in Japan.[18] The CIRCS underwent sleep investigation in three communities: Yao City, Osaka Prefecture; Ikawa town, Akita Prefecture; and Kyowa town, Ibaraki Prefecture from 2001 to 2005. The participants of 981 women from the district of Yao (recruitment rate among the cardiovascular survey participants = 78% for women), 608 women from Ikawa (85%), and 1559 women from Kyowa (78%) were available for the present sleep study with satisfactory recording by a pulse-oximeter. Also, women with self-reported history of stroke or coronary heart disease (n = 35) were excluded because they were likely to change their lifestyles. The data for 3113 women aged 30–69 years were used for the analysis. The study protocol was approved by the Medical Ethics Committees of the University of Tsukuba, Osaka University and the Osaka Medical Center for Health Science and Promotion. Informed consent was obtained from the community representatives to conduct an epidemiological study based on guidelines of the Council for International Organizations of Medical Science.[19]

Measurement of cardiovascular risk factors

Height in stocking feet and weight in light clothing were also measured, and body mass index (BMI) was calculated as weight (kg)/height (m^2). Interviews were conducted to ascertain the frequency of snoring (often, sometimes, never, unknown), number of cigarettes smoked per day, ethanol intake per day, and past histories of sleep apnea, stroke and coronary heart disease.

Persons who replied "often" for snoring over the previous three months were labeled as suffering from habitual snoring. Persons who smoked one or more cigarettes per day were defined as current smokers and those who had not smoked for 3 months or more were defined as former smokers, while both never smokers and occasional smokers were regarded as non-smokers because the latter are very rare in Japan. The usual weekly alcohol intake was assessed in units of "*go*", a Japanese unit of volume corresponding to 23 g ethanol, which was then converted to grams of ethanol per day.[4,14] One "*go*" is equivalent to 180 ml of sake and corresponds to one bottle (633 ml) of beer, two single shots (75 ml) of whiskey, or two glasses (180 ml) of wine. Subjects who drank >8 g of ethanol per week were considered to be current drinkers and those who had not drunk for 3 months or more were defined as former drinkers.

Assessment of sleep-disordered breathing

Arterial oxygen saturation during one night of sleep at home was measured with a pulse-oximeter (PULSOX-3Si; Minolta Co., Osaka, Japan). The device stores values of peripheral blood oxygen saturation by performing a moving average for the last 5 s, updated every second. This sampling time was short enough to avoid the underestimation of oxygen desaturation.[20] The stored data were downloaded to a personal computer via an interface (PULSOX IF-3; Minolta) and analyzed using proprietary software supplied with the equipment (DS-3 version. 2.0a; Minolta) and the records reviewed by trained physicians. The oxygen desaturation index (ODI) was calculated based on frequency of ≥3% reductions in arterial oxygen saturation during sleep. The 3% ODI as an indicator of sleep-disordered breathing described in previous studies[14,21] was also used for this study. It represents the number of events per hour of adjusted measurement time in which blood oxygen decreases by ≥3%. The individuals filled out a sleep diary in order to exclude waking time from the analysis to minimize the potential overestimation of sleep duration. All data were reviewed by trained physicians and total recording time less than 4 h or the artifact likely due to frequent body movement or inadequate fitting of the probe were excluded. Overall 3%ODI was established as the mean value of 3%ODIs over at least a 4-h period of sleep as measured by pulse oximetry. The sleep-disordered breathing was defined in terms of 3%ODI level as ≥5 events per hour and the 3%ODI <5 was used as the reference category. A previous validity study reported that sensitivity was 80% and specificity 95% for 3%ODI ≥5 to detect an apnea-hypopnea index (AHI) of ≥5 by full polysomnography.[22]

Statistical analysis

Age-adjusted population characteristics according to categories of drinking status (never, former, and ethanol intakes of <23.0 and ≥23.0 g/day) were calculated by using analysis of covariance and the chi-square test. Logistic regression analysis was used to estimate the odds ratio of the

prevalence of 3%ODI $\geq$ 5 and habitual snoring according to categories of ethanol intake. The potentially confounding variables were age (year), BMI (kg/m^2), smoking status (never, ex- and current smoking), and communities (Yao, Ikawa, and Kyowa). The associations of alcohol consumption with 3%ODI $\geq$ 5 and habitual snoring were examined and stratified by using the median BMI (<23.0 and $\geq$23.0 kg/m^2). The significance for interactions by body mass index was tested by using the cross-product terms of ethanol intake and body mass index categories in multivariable models.

All statistical analyses were performed with SAS version 9.1.3 software (SAS Institute Inc., Cary, NC). All probability values for statistical tests were two-tailed, and values of $p < 0.05$ were regarded as statistically significant.

Results

The proportion of sleep-disordered breathing equivalent to 3%ODI $\geq$ 5 were 17.4% for total subjects aged 30–69 years, 17.5% for never drinkers, and 23.9% for women with ethanol intake of $\geq$23.0 g/d. The respective proportion of habitual snoring was 10.5%, 10.1% and 23.5%. Compared with never-drinking women, women with ethanol intake of $\geq$23.0 g/d were younger, showed higher mean values of 3%ODI and were more likely to smoke. Mean body mass index did not differ between women with ethanol intake of $\geq$23.0 g/d and never-drinking women (Table 1).

The proportions of sleep-disordered breathing and habitual snoring were higher for women with ethanol intake of $\geq$23.0 g/d compared with never drinkers (Table 2). The multivariable odds ratios of these outcomes were 1.8 (1.0–3.4) and 3.0(1.5–5.8), respectively.

We also examined the association of drinking status with sleep-disordered breathing and habitual snoring, stratified by median BMI (BMI <23.0 versus $\geq$23.0 kg/m^2) (Table 3). The association between ethanol intake and sleep-disordered breathing were more evident among women with lower BMI than those with higher BMI although the interaction by BMI did not reach the levels of statistical significance ($p = 0.23$).

The multivariable odds ratios of 3%ODI $\geq$ 5 for ethanol intakes of $\geq$23.0 g/d versus never drinking were 2.7 (1.0–6.7) for lower BMI and 1.5(0.6–3.3) for higher BMI. The association between ethanol intake and sleep-disordered breathing did not vary by habitual snoring.

Discussion

In our study of a general population of 3113 Japanese women, we found that ethanol intakes of $\geq$23.0 g/d were associated with approximately 2.0-fold higher prevalence of sleep-disordered breathing equivalent to 3%ODI $\geq$ 5.

To the best of our knowledge, this is the first study to show an association between alcohol consumption and higher prevalence of sleep-disordered breathing among a general population of Japanese women. Our findings are in agreement with the results of clinical experimental studies, which demonstrated an increase in mean AHI,[6] increased frequency of arterial oxygen desaturation[7,8] and the need for higher continuous positive airway pressure to eliminate snoring[9] after the ingestion of alcohol prior to bedtime. The adverse effects of alcohol on SDB are narrowing of the pharyngeal airways and an increase in nasal resistance,[23] selective reduction in hypoglossal motor nerve activities,[24] and diminished arousal response.[7]

Our study showed that the association of alcohol consumption with sleep-disordered breathing equivalent to 3%ODI $\geq$ 5 was more evident among women with lower BMI (<23.0 kg/m^2) than those with higher BMI. The Wisconsin Sleep Cohort Study found no association between alcohol consumption and SDB among 645 women.[15] In that study, however, they did not conduct a stratified analysis by BMI, whose mean BMI was much higher (31 kg/m^2) than that in our present population (23.0 kg/m^2). This suggests that the strong effect of excess weight on sleep-disordered breathing may mask a moderate effect of alcohol consumption. Further, compared with whites, Asians tend to have a lower position of the hyoid bone and shorter dimension of the posterior airway space,[25] Japanese may have a higher risk of sleep-disordered breathing than whites when they drink habitually. Moreover, the positional sleep apnea occurs more commonly in the less obese subjects.[26] In addition, we previously reported a positive association between alcohol consumption and sleep-disordered breathing among Japanese men: the multivariable OR of 3%ODI $\geq$ 5 was 1.95 (1.15–3.31) for ethanol intake $\geq$1.0 g/d per kg for men aged 40–69 years.[14]

Table 1 Age-adjusted mean and prevalence of selected cardiovascular risk factors among 3113 Japanese women aged 30–69 years.

	Total subjects	Never drinkers	Ex-drinkers	Ethanol intake, g/day	
				<23.0	≥23.0
No.	3113	2368	174	492	79
Age, years	55.5	56.1	54.3†	53.0‡	52.7‡
3%ODI, episodes/h	3.0	3.0	2.8	2.9	3.9*
Subjects with 3%ODI ≥ 5, %	17.4	17.5	17.7	16.0	23.9
Habitual snoring, %	10.5	10.1	10.4	10.7	23.5‡
Body mass index, kg/m^2	23.3	23.4	23.3	22.8†	23.1
Current smokers, %	5.8	3.5	19.2‡	7.6‡	34.6‡

*$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$, are compared with never drinkers. Habitual snoring: snoring "often" over the last three months.

Table 2 Multivariable odds ratios and 95% confidence intervals of sleep-disordered breathing and habitual snoring according to alcohol consumption.

	Never drinkers	Ex-drinkers	Ethanol intake, g/day	
			<23.0	≥23.0
Total number	2368	174	492	79
3%ODI ≥ 5, No.	428	29	68	17
Age-adjusted OR	1.0	1.0 (0.7–1.5)	0.9 (0.7–1.2)	1.6 (0.9–2.8)
Multivariable OR	1.0	1.0 (0.6–1.6)	1.0 (0.8–1.4)	1.8 (1.0–3.4)*
Habitual snoring, No.	205	15	46	15
Age-adjusted OR	1.0	1.0 (0.6–1.8)	1.1 (0.8–1.5)	2.7 (1.5–5.0)†
Multivariable OR	1.0	1.0 (0.5–1.7)	1.1 (0.8–1.6)	3.0 (1.6–5.8)*

*$p < 0.05$, †$p < 0.01$ compared with never drinkers.
Multivariable adjustment: age (year), body mass index (kg/m^2), smoking status (never, ex- and current smoking), and community.

Table 3 Multivariable odds ratios and 95% confidence intervals of 3%ODI ≥5 according to alcohol consumption by median BMI subgroups.

	Never drinkers	Ex-drinkers	Ethanol intake, g/day	
			<23.0	≥23.0
Total number	2368	174	492	79
BMI < 23.0 kg/m^2	1150	84	285	40
3%ODI ≥ 5, No.	118	7	18	7
Multivariable OR	1.0	0.9 (0.4–2.1)	0.7 (0.4–1.2)	2.7 (1.0–6.7)*
Habitual snoring, No.	62	5	15	7
Multivariable OR	1.0	1.0 (0.4–2.7)	0.9 (0.5–1.6)	2.8 (1.1–7.2)†
BMI ≥ 23.0 kg/m^2	1218	90	207	39
3%ODI ≥ 5, No.	310	22	50	10
Multivariable OR	1.0	1.0 (0.6–1.7)	1.2 (0.8–1.9)	1.5 (0.6–3.3)
Habitual snoring, No.	143	10	31	8
Multivariable OR	1.0	0.9 (0.5–1.9)	1.4 (0.9–2.1)	3.2 (1.3–7.9)†

*$p < 0.05$, †$p < 0.01$ compared with never drinkers.
Multivariable adjustment variables are similar as shown in Table 2.

A major strength of our study is the use of a large general population sample, which has the advantage of providing a more realistic estimation for the association between alcohol consumption and sleep-disordered breathing than can be attained with hospital or laboratory studies, because the subjects can maintain regular daily habits such as sleeping or alcohol consumption. Also, SDB[14] and cardiovascular risk factors[27–29] were measured with standardized methods with proven satisfactory reliability and precision.

The limitation of our study is that since we used pulse oximetry to evaluate sleep-disordered breathing, we could not accurately ascertain the severity of SDB, sleep architecture changes, relationships with REM sleep, sleep fragmentation and positional nature of hypoxia, while the sensitivity was 80% and specificity 95% for 3%ODI ≥ 5 to detect an AHI ≥ 5 by full PSG.[22] Second, pulse oximetry inherently underestimates respiratory disturbance events during sleep compared with measurements obtained with full PSG, particularly for non-obese subjects such as those studied here (mean BMI = 23.6 kg/m^2). In fact, one study found that, for the 3%ODI of ≥5 to screen for AHI ≥5/h by PSG, the sensitivity was 68% for subjects with BMI ≤ 27.0 kg/m^{2}and 94% for those with BMI > 27.0 kg/m^2.[22] Third, we conducted the multivariable analysis to examine relationships between alcohol consumption and sleep-disordered breathing, but we have no data on potential confounding factors such as income, pulmonary disease, psychiatric disease, allergies, and use of benzodiazepines, narcotics, antidepressants and illicit drugs. Fourth, the number of drinkers was still small due to the low prevalence in drinkers among Japanese women.[5] A larger study is of value to confirm our findings.

In conclusion, habitual alcohol consumption was found to be associated with higher prevalence of sleep-disordered breathing among Japanese women.

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Conflict of interest

None.

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Original Article

Values of Cardio-Ankle Vascular Index (CAVI) between Amami Islands and Kagoshima Mainland Among Health Checkup Examinees

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Aim: To investigate the prevalence and geographical variation of high arterial stiffness in groups from the Amami islands (Amami) and Kagoshima mainland (mainland), Japan, using the cardio-ankle vascular index (CAVI) as a surrogate marker of arterial stiffness.
Methods: We recruited 4,523 health checkup examinees from Amami and 440 examinees from the mainland, with an age range of 40-69 years. The frequency of high arterial stiffness (CAVI ≥9.0) was geographically compared between the regions, and both mean CAVI values were compared with those of the healthy Japanese population with less risk factors for coronary artery disease. Clinical, lifestyle, and regional factors for increased CAVI values were estimated by the multiple linear regression model.
Results: The frequency of high arterial stiffness on Amami was significantly lower than on the mainland. Mean CAVI values on Amami were similar in males and lower in females than in the healthy Japanese population, but those on the mainland were higher for both sexes. Age, systolic blood pressure, triglycerides, fasting blood glucose, and a history of hypertension and diabetes mellitus were positively related to increased CAVI values on Amami. The regional factor of Amami, compared with the mainland, was negatively related to increased CAVI values in both sexes after adjusting for traditional cardiovascular risk factors.
Conclusion: CAVI values in Amami residents were significantly lower than in mainland residents, suggesting that environmental or genetic factors might have improved arterial stiffness in the Amami population.

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Key words; Arterial stiffness, Cardio-ankle vascular index, Geographical variation

Introduction

Ischemic heart disease and stroke are major causes of death in Japan[1)] and Western countries[2)]. High arterial stiffness is reported to be a risk factor for the development of these diseases[3-6)], as well as peripheral arterial disease[7)] and disorders of the kidney and retinopathy[8, 9)]; therefore, evaluation of high arterial stiffness could be an effective control tool for these diseases.

High arterial stiffness is caused by thickening of the intimal layer due to cholesterol deposition, smooth muscle cell proliferation, and the proliferation of con-

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nective tissue; calcification of the arterial lumen due to cholesterol deposits and macrophage infiltration; and loss of arterial wall flexibility due to thickness, calcification, and narrowing. Risk factors are dyslipidemia[10], hypertension[11], diabetes mellitus[8, 9], smoking habits[12], family history[13, 14], male gender, and advanced age[15-17].

Arterial stiffness can be evaluated by various methods: stiffness parameter-β, pulse wave velocity (PWV)[18], carotid-femoral pulse wave velocity (cfPWV)[19], heart-femoral pulse wave velocity (hfPWV)[20], and brachial-ankle pulse wave velocity (baPWV)[21, 22] are used as common noninvasive clinical indices, but these methods are limited because PWV is dependent on blood pressure at the measurement time. Cardio-ankle vascular index (CAVI) is a recently developed method that uses PWV in the aorta, femoral artery, and tibial artery, and it is less dependent on blood pressure than other PWV methods[23-25]. Indeed, a recent study has demonstrated that CAVI is independent of blood pressure at the time of measurement, while the previous PWV was an influence[26]. Furthermore, CAVI is more easily conducted for a large number of subjects in the epidemiological field. The validity and reproducibility of CAVI have already been successfully evaluated[23, 27, 28]. CAVI values are correlated with carotid intima-media thickness[24, 25, 29, 30]. Several studies have revealed a significant relationship between CAVI and the presence and severity of patients with coronary artery disease[31], hemodialysis[32, 33], and chronic kidney disease[34]. Changes in arterial stiffness following cessation of smoking and application of CAVI have been reported recently[35]; however, there is little information on the prevalence and geographical variation of high arterial stiffness evaluated by CAVI among the general population.

We have been conducting a genome-cohort study in a remote region of Amami of Kagoshima Prefecture, Japan, as a member of the Japan Multi-Institutional Collaborative Cohort Study (J-MICC Study) since 2005[36, 37]. The Amami islands are located in the southern part of Kagoshima and Japan, and neighbor Okinawa. We conducted a cross-sectional study using the baseline data obtained in this genome-cohort study and compared it with that obtained on the mainland of Kagoshima.

Aim

The aim of the present study was to investigate the prevalence and geographical variation of high arterial stiffness in groups from the Amami islands (Amami) and the Kagoshima mainland (mainland) in Kagoshima, Japan, using CAVI as a surrogate marker of arterial stiffness.

Methods

Study Subjects

We conducted a baseline survey in 1 city and 9 towns located on 5 islands in the Amami region from 2005 to 2008. After obtaining written informed consent (response rate: 65.4%), we recruited 5,154 subjects aged 40-69 years from the general population, who had routine health checkups conducted by the local government or private companies. The baseline survey consisted of a questionnaire survey, blood collection using serum, plasma, buffy coat, urine collection, and examination of arterial stiffness using CAVI. Results of the routine health checkups were also obtained after informed consent. We excluded subjects who withdrew their participation before February 2010 (n=15); whose questionnaire (n=98), health checkup (n=350), or CAVI (n=54) data were not available; and whose CAVI data quality were insufficient due to arrhythmia, such as atrial fibrillation or undetectable pulse wave (n=49). We also excluded subjects who had a low ankle-brachial index (ABI $<$0.9) (n=65) because such cases had inaccurate CAVI values due to decreased blood flow[23]. Ultimately, 4,523 subjects (1,853 males and 2,670 females) were eligible for analysis.

We also used the stored data of examinees who had health checkups, questionnaires, and CAVI assessments completed at JA Kagoshima Kouseiren Medical Health Care Center located on the mainland from 2004 to 2007, after deleting personal information. We were able to obtain data for 1,033 subjects aged 18-82 years. Excluded subjects were under 40 years or over 69 years old (n=330), who lived on Amami or at an unknown residence (n=231), who had no health checkup data (n=29), and who had low ABI values (n=3). The eligible number of subjects aged 40-69 years in the mainland group was 440 (240 males and 200 females).

The present study was approved by the ethics committee on Life Sciences and Genetic Analysis, Kagoshima University Graduate School of Medical and Dental Sciences.

Questionnaire

We collected information about the lifestyle and medical history of subjects on Amami using a structured questionnaire standardized by the J-MICC Study[36]. Information about subjects on the mainland

was collected by another structured questionnaire. Both self-administrative questionnaires were checked by trained health professionals after the subjects had been interviewed. We used information that was common to both questionnaires.

Health Checkup

We obtained health checkup data from JA Kagoshima Kouseiren Medical Health Care Center and Oshima Medical Association, with which local governments on Amami had contracts for health checkups. Health checkups on the mainland were also conducted by JA Kagoshima Kouseiren Medical Health Care Center.

Blood samples were obtained after fasting. The health checkups included assessments of total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), fasting blood sugar (FBS), blood urea nitrogen (BUN), creatinine (Cr), and uric acid (UA).

Since LDL-C was not examined at JA Kagoshima Kouseiren Medical Health Care Center, the LDL-C values were estimated using the Friedewald formula[38].

Measurement of CAVI

CAVI was measured by the standardized method using a Vasera VS-1000 or VS-1500 (Fukuda Denshi Co., Ltd, Tokyo, Japan) for the Amami and mainland groups, as described previously[27, 31, 32]. In brief, a cuff was placed on the right and left ankles and the brachium; electrodes for electrocardiography were attached to both upper arms, and a microphone was placed on the sternal angle for phonocardiography. CAVI was measured in the supine position. PWV was calculated by dividing the distance from the aortic valve to the artery of the ankle by the sum of the time between the closing sound of the aortic valve and the notch of brachial pulse wave and the time between the rise of the brachial pulse wave and the ankle pulse wave. To minimize cuff inflation effects on blood flow dynamics, pulse waves were measured with the cuff inflated to lower than diastolic blood pressure (DBP: 50 mmHg). Blood pressure (BP) was measured with an oscillometer. Systolic blood pressure (SBP), DBP, and pulse pressure (PP) were measured by the BP of the right brachial artery. CAVI was calculated by the following equation:

$$CAVI = a\ [\{2\rho \times 1/(SBP - DBP)\} \times \{\ln(SBP/DBP) \times PWV^2\}] + b$$

where a and b are constant and ρ is blood density. The right CAVI value was used for analysis.

Healthy Japanese Population with Less Risk Factors for Coronary Artery Disease

Suzuki *et al.* showed the mean and standard deviation (SD) of CAVI by sex in every 5-year and 10-year age group using data on 5,969 healthy subjects (2,239 males and 3,730 females) of 32,627 Japanese subjects aged 20-74 years after excluding subjects with established risk factors of high arterial stiffness, such as hypertension, dyslipidemia, hyperglycemia, and renal dysfunction[28]. They also excluded subjects with abnormal WBC, electrocardiography, or fundus examination results or a history of hypertension, dyslipidemia, heart diseases, stroke, diabetes mellitus, renal diseases, or gout. These subjects were recruited from the participants and their family members in 42 prefectures of Japan, who had received the standard health checkup for workers in Japan from 2005 to 2007. They were asked to add a CAVI examination for use in this survey after oral explanation with documents. We used these data for the healthy Japanese population with less risk factors for coronary artery disease.

Definition

We defined the group with high arterial stiffness as having CAVI ≥9.0. The definition of related factors other than clinical characteristics are as follows: smoking: never smokers vs. ex-smokers and current smokers; drinking: nondrinkers and ex-drinkers vs. current drinkers of <20 g alcohol/day vs. 20-40 g alcohol/day vs. >40 g alcohol/day; exercise: <1 time/month vs. ≥1 time/month and <3 times/week vs. ≥3 times/week; and a history of hypertension, coronary artery disease, diabetes mellitus, or dyslipidemia. Information with respect to their diagnosis or medication for these diseases was obtained from the questionnaire. TC was not included in this model because HDL-C and LDL-C were used.

Statistical Analysis

We compared the clinical characteristics of subjects in the Amami and mainland groups using the mean and SD of the examination values. Differences between the 2 groups were examined using an unpaired *t*-test. The prevalence of high arterial stiffness was compared between regions by sex and age groups using the chi-square test and Fisher's exact test. We also used multiple linear regression analysis to examine the relationship between CAVI and clinical characteristics, lifestyles, and a history of clinical status, and regional factors. Differences in the mean CAVI values between the Amami subjects and the mainland subjects, and the healthy Japanese popula-