levels and risk of stroke. Although a positive association was found between elevated hs-CRP levels and risk of total stroke [17] and ischemic stroke [13,20], the further examination for ischemic stroke subtypes as well as hemorrhagic stroke subtypes has not been conducted.

Therefore, we conducted a prospective nested case–control study of men and women in three Japanese communities of the Circulatory Risk in Communities Study (CIRCS) using stored serum samples, to examine the effects of hs-CRP on risks of total stroke and its subtypes.

1. Methods

1.1. Surveyed populations

The present study was an ancillary study to the Circulatory Risk in Communities Study (CIRCS) [21]. The CIRCS is a dynamic cohort of Japanese men and women aged 40 and over in five communities across Japan, conducted by a research team of the Osaka Medical Center for Health Science and Promotion, Osaka University and the University of Tsukuba. Participants in the present study were recruited from all residents who participated in cardiovascular risk surveys in three communities of CIRCS. Where frozen serum samples were available. In the present study, 13,314 men and women 40–85 years of age participated in cardiovascular risk surveys between 1985 and 2000 in a central rural community (Kyowa; the participants and the census population for 40–85, $n = 6829$ and $n = 8557$, respectively) and between 1989 and 1998 in a northeast rural community (Ikawa; $n = 2570$ and $n = 2981$, respectively) and in a southwest rural community (Noichi; $n = 3915$ and $n = 7169$, respectively). The participation rate in cardiovascular risk surveys among men and women 40–85 years of age was 80% in Kyowa, 86% in Ikawa, and 55% in Noichi and 71% for the total population. A 1.0–2.0 ml serum sample obtained from each participant was stored at −80 °C for 1–20 years (median, 10.5 years). Participants with a history of stroke or coronary heart disease ($n = 510$) were excluded from the analyses. The subjects were followed to determine incident strokes occurring by the end of 2005. The Ethics Committee of the University of Tsukuba approved this study.

1.2. Surveillance of stroke and classification of stroke subtypes

All potential cases of stroke were extracted from the national insurance claims, ambulance records, death certificates (as the underlying cause of death: ICD 9 classification, 430–438), reports by local physicians, and reports by public health nurses and health volunteers. To confirm the diagnosis of stroke, we called (approximately 70%), visited (10%) or invited the susceptible subjects to participate in annual cardiovascular risk surveys (20%) to obtained clinical histories. For nonfatal cases, study physicians obtained medical histories and reviewed medical records from local clinics and hospitals. For almost all fatal cases, information was obtained from their families, and medical records were reviewed.

The diagnosis of stroke was made according to the criteria of the National Survey of Stroke [22], which requires a constellation of neurological deficits of sudden or rapid onset lasting ≥24 h or until death. Strokes were classified as intraparenchymal hemorrhage, subarachnoid hemorrhage, or ischemic stroke (embolic infarction thrombotic infarction) by CT or/and MRI using standardized criteria [23]. A diagnosis of embolic infarction was made when evidence of an embolic source was present in the medical records and if imaging studies and a neurology consultation supported the diagnosis. Thrombotic infarctions were further classified as large-artery occlusive infarction, lacunar infarction, or unclassified thrombotic infarction based on the results of CT or/and MRI, according to the criteria of the Perth Community Stroke Study [24]. Strokes with negative findings on imaging studies and unclassified strokes were not included in the present study. In the present study, all of hemorrhagic strokes and more than 90% of ischemic strokes were confirmed by CT while approximately 50% of ischemic strokes were confirmed by both CT and MRI. The imaging studies were usually undertaken within 24 h after the onset. For each new case of stroke, 3 control subjects were selected randomly from the participants with no incident stroke, matched for sex, age (±2 years), community, year of serum storage, and fasting status at serum collection (<8 and ≥8 h).

1.3. Determination of serum high-sensitivity C-reactive protein

Non-fasting venous blood was collected in a 7- to 10-mL plain tube and allowed to stand for <30 min for serum separation. The serum samples were aliquoted immediately and placed on dry ice at survey sites and then stored at −80 °C until analysis.

Serum hs-CRP was measured using an ultra-sensitive latex-enhanced immunoassay with an automatic analyzer (BN Prospec nephrometer; Dade Behring, Tokyo, Japan). In the laboratory, each of the five samples was assayed in quadruplicate on 20 different days along with a single daily measurement of an internal quality control sample. The inter-assay and intra-assay coefficients of variation (CV) were 1.3% and 1.4%, respectively, and the hs-CRP precision was satisfactory based on the AHA/CDC scientific statement that the CV of hs-CRP should be generally <10% in a range of 0.3–10 mg/L [4,15].

1.4. Determination of confounding variables

An interview was conducted to ascertain histories of cigarette smoking (never, ex-, and current smoking), ethanol intake (never, ex, and current; <46 g/day, and 46 g/day or more ethanol), and medication use for hypertension and diabetes. Height in stocking feet and weight in light clothing were measured. Body mass index (BMI) was calculated as weight (kg)/height (m^2).

Systolic and diastolic blood pressures were measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants after a 5-min rest. Hypertension was defined as systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥95 mm Hg and/or taking antihypertensive medication; normotension was defined as systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg and not taking antihypertensive medication [25]. All others were classified as having borderline hypertension.

Serum total cholesterol, triglycerides and glucose were measured by enzymatic method. Serum glucose was measured by the hexokinase method. Impaired glucose tolerance was defined as a fasting glucose of 6.1–6.9 mmol/L and/or a non-fasting glucose level of 7.8–11.0 mmol/L, without medication use for diabetes. Diabetes was defined as a fasting glucose level of ≥7.0 mmol/L and/or a non-fasting glucose level of ≥1.1 mmol/L and/or use of medication for diabetes.

1.5. Statistical analysis

The unpaired Student's t test and Kruskal–Wallis test were used to compare the mean values of baseline cardiovascular risk factors and median variables of hs-CRP and triglycerides levels between incident cases and control subjects. The χ^2 test was used to compare proportions between cases and control subjects. Potential confounding factors according to hs-CRP quartiles were investigated using the analysis of variance for continuous variables and χ^2 test for categorical variables. The conditional odds ratios (OR) and 95% confidence intervals (CI) for total stroke, and stroke sub-

Table 1
Risk characteristics among cases and control subjects by stroke subtype.

	No (%)	Age (Y)	Men (%)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Hypertension (%)	BMI (kg/m^2)	Ethanol intake (g/d)	Current smokers (%)	Serum cholesterol (mmol/L)	Tri-glycerides, (mmol/L)	Impaired glucose tolerance (%)	Diabetes mellitus (%)	hs-CRP (mg/L)
Total stroke														
Cases	261(25)	66.7 ± 9.0	132(51)	140 ± 19‡	82 ± 12‡	142(54)‡	23.8 ± 3.6*	14.3 ± 23.3	73(28)	5.11 ± 0.93	1.30(0.91–1.85)	34(13)	28(11)†	0.63(0.32–1.45)*
Control subjects	783(75)	66.6 ± 9.0	396(51)	135 ± 17	78 ± 11	289(37)	23.2 ± 3.3	12.2 ± 20.1	206(26)	5.13 ± 0.90	1.23(0.89–1.82)	99(13)	45(6)	0.52(0.27–1.09))
Ischemic stroke														
Cases	165 (25)	67.0 ± 8.4	97(59)	141 ± 20‡	82 ± 13‡	93(56)‡	23.9 ± 3.7*	16.0 ± 23.5	52(32)	5.15 ± 0.92	1.39(0.95–2.05)	21(13)	24(15)‡	0.79(0.36–1.68)†
Control subjects	495(75)	66.9 ± 8.3	291(59)	135 ± 17	78 ± 11	182(37)	23.2 ± 3.1	13.6 ± 20.7	150(30)	5.10 ± 0.91	1.22(0.88–1.82)	72(15)	28(6)	0.53(0.29–1.14)
Lacunar infarction														
Cases	118(25)	66.0 ± 8.1	68(58)	140 ± 19‡	82v±v13‡	60(51)‡	24.0 ± 3.8*	16.4 ± 24.3	39(33)	5.19 ± 0.94	1.41(0.96–2.07)	17(15)	16(14)‡	0.80(0.36–1.70)†
Control subjects	354(75)	66.0 ± 7.9	204(58)	134 ± 17	78 ± 11	119(34)	23.1 ± 3.0	12.5 ± 19.7	104(29)	5.12 ± 0.89	1.21(0.91–1.77)	48(14)	15(4)	0.50(028–1.10)
Large-artery occlusive infarction														
Cases	36(25)	70.0 ± 8.9	23(64)	145 ± 26	82 ± 13	27(75)†	23.6 ± 3.5	15.6 ± 21.1	11(31)	4.98 ± 0.88	1.30(0.85–1.74)	3(8)	5(14)	0.73(0.37–2.56)
Control subjects	108(75)	69.9 ± 8.9	69(64)	138 ± 18	78 ± 12	51(47)	23.1 ± 3.0	15.1 ± 21.9	36(33)	4.98 ± 0.94	1.20(0.80–1.81)	21(20)	12(12)	0.68(0.32–1.33)
Embolic infarction														
Cases	11(25)	67.5 ± 8.6	6(55)	141 ± 15	77 ± 12	6(55)	23.8 ± 4.0	12.5 ± 23.8	2(18)	5.29 ± 0.92	1.68(1.31–2.25)	1(10)	3(30)*	0.60(0.30–0.96)
Control subjects	33(75)	67.3 ± 8.5	18(55)	136 ± 13	78 ± 10	12(36)	24.2 ± 3.4	20.7 ± 25.6	10(30)	5.3 ± 1.02	1.47(0.94–2.28)	3(10)	1(3)	0.53(0.32–0.93)
Hemorrhagic stroke														
Cases	96(25)	66.1 ± 10.0	35(35)	138 ± 18	83 ± 13‡	49(51)*	23.5 ± 3.6	11.4 ± 23.0	21(22)	5.05 ± 0.95	1.16(0.89–1.74)	13(14)	4(4)	0.50(0.29–1.13)
Control subjects	288(75)	66.0 ± 10.0	105(35)	134 ± 18	78 ± 10	107(37)	23.2 ± 3.6	9.6 ± 18.7	56(19)	5.18 ± 0.89	1.26(0.90–1.82)	27(10)	17(6)	0.50(0.25–0.94)
Intraparenchymal hemorrhage														
Cases	67(25)	66.4 ± 10.3	29(43)	138 ± 15	83 ± 11‡	35(52)	23.7 ± 3.9	13.8 ± 25.4	16(24)	4.96 ± 0.89	1.00(0.85–1.46)*	10(16)	3(5)	0.53(0.30–1.19)
Control subjects	201(75)	66.4 ± 10.4	87(43)	135 ± 18	79 ± 10	79(39)	23.2 ± 3.5	11.5 ± 20.2	42(21)	5.14 ± 0.92	1.26(0.90–1.81)	19(10)	13(7)	0.52(0.26–0.97)
Subarachnoid hemorrhage														
Cases	29(25)	65.3 ± 9.2	6(21)	138 ± 23	81 ± 15	14(48)	23.0 ± 2.5	5.94 ± 15.2	5(17)	5.26 ± 1.03	1.52(1.03–1.86)	3(10)	1(3)	0.45(0.21–0.96)
Control subjects	87(75)	65.2 ± 9.1	18(21)	133 ± 17	78 ± 11	28(32)	23.3 ± 3.8	5.18 ± 14.0	14(16)	5.26 ± 0.81	1.28(0.88–1.84)	8(9)	4(5)	0.47(0.24–0.73)

Data are shown as mean ± SD, frequency as a number (%).
Triglycerides and hs-CRP are expressed as median (interquartile range).
* $p < 0.05$ for differences from control subjects.
† $p < 0.01$ for differences from control subjects.
‡ $p < 0.001$ for differences from control subjects.

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-

Please cite this article in press as: Chei C-L, et al. C-reactive protein levels and risk of stroke and its subtype in Japanese: The Circulatory Risk in Communities Study (CIRCS). Atherosclerosis (2011), doi:10.1016/j.atherosclerosis.2011.03.001

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 ($p = 0.12$).

Please cite this article in press as: Chei C-L, et al. C-reactive protein levels and risk of stroke and its subtype in Japanese: The Circulatory Risk in Communities Study (CIRCS). Atherosclerosis (2011), doi:10.1016/j.atherosclerosis.2011.03.001

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.

Acknowledgement

CIRCS Investigators

The Circulatory Risk in Communities Study (CIRCS) is a collaborative study managed by the Osaka Medical Center for Health Science and Promotion, University of Tsukuba, Osaka University and Ehime University. The full list of CIRCS investigators was stated in the references #21.

References

[1] Ross R. Atherosclerosis – an inflammatory disease. N Engl J Med 1999;340:115–26.
[2] Libby P, Ridker PM. Inflammation atherothrombosis. J Am Coll Cardiol 2006;48(9 Suppl. A):A33–46.
[3] Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135–43.
[4] Pearson TA, Mensha GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Center for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499–511.
[5] Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation 2003;107:363–9.
[6] Blake GJ, Ridker PM. Inflammatory bio-markers cardiovascular risk prediction. Journal of Internal Medicine 2002;252:283–94.
[7] Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999;340:448–54.
[8] Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973–9.
[9] Folsom AR, Aleksic N, Catellier D, et al. C-reactive protein and incident coronary heart disease in the Atherosclerosis Risk IN Communities (ARIC) study. Am Heart J 2002;144:233–8.
[10] Everett BM, Kurth T, Buring JE, Ridker PM. The relative strength of C-reactive protein and lipid levels as determinants of ischemic stroke compared with coronary heart disease in women. J Am Coll Cardiol 2006;48:2235–42.
[11] Rost NS, Wolf PA, Kase CS, et al. Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: the Framingham study. Stroke 2001;32:2575–9.
[12] Feigin VL, Laws CMM, Bennett DA, Anderson CS. Stroke epidemiology: review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurology 2003;2:43–53.
[13] Makita S, Nakamura M, Satoh K, et al. Serum C-reactive protein levels can be used to predict future ischemic stroke and mortality in Japanese men from the general population. Atherosclerosis 2009;204:234–8.
[14] Ichihara K, Itoh Y, Min WK, et al. Diagnostic and epidemiology implications of regional differences in serum concentrations of proteins observed in six Asian cities. Clin Chem Lab Med 2004;42:800–9.
[15] Saito I, Sato S, Nakamura M, et al. A low level of C-reactive protein in Japanese adults and its association with cardiovascular risk factors: the Japan NCVC-Collaborative Inflammation Cohort (JNIC) Study. Atherosclerosis 2007;194:238–44.
[16] Yamada S, Gotoh T, Nakashima Y, et al. Distribution of serum-C-reactive protein and its association with atherosclerotic risk factors in a Japanese population. Am J Epidemiol 2001;153:1183–90.
[17] Iso H, Cui R, Date C, Kikuchi S, Tamakoshi A, JACC Study group. C-reactive protein levels and risk of mortality from cardiovascular disease in Japanese: the JACC Study. Atherosclerosis 2009;207:291–7.
[18] Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 1998;279:1477–82.
[19] Kuo HK, Yen CJ, Chang CH, et al. Relation of C-reactive protein to stroke, cognitive disorders, and depression in the general population: systematic review and meta-analysis. Lancet Neurol 2005;4:371–80.
[20] Wakugawa Y, Kiyohara Y, Tanizaki Y, et al. C-reactive protein and risk of first-ever ischemic and hemorrhagic stroke in a general Japanese population: the Hisayama Study. Stroke 2006;37:27–32.
[21] Ohira T. Psychological distress and cardiovascular disease: the Circulatory Risk in Communities Study (CIRCS). J Epidemiol 2010;20:185–91.
[22] Walker AE, Robins M, Weinfeld FD. The national survey of stroke. Clinical findings. Stroke 1981;12(Suppl. 1):I13–44.
[23] Iso H, Rexrode K, Hennekens CH, Manson JE. Application of computer tomography-oriented criteria for stroke subtype classification in a prospective study. Ann Epidemiol 2000;10:81–7.
[24] Anderson CS, Jamrozik KD, Burvill PW, et al. Determining the incidence of different subtypes of stroke: results from the Perth Community Stroke Study, 1989–1990. Med J Aust 1993;158:85–9.
[25] WHO technical report series, no. 628; 1978 (arterial hypertension: report of a WHO Expert Committee).
[26] Ridler PM. High sensitivity C-protein inflammation, and cardiovascular risk: from concept to clinical practice to clinical benefit. Am Heart J 2004;148:S19–26.
[27] Zwaka TP, Hombach V, Torzewski J. C-reactive protein-mediated low density lipoprotein uptake by macrophages: implications for atherosclerosis. Circulation 2001;103:1194–7.

[28] Verma S, Wang CH, Li SH, et al. A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. Circulation 2002;106:913–9.
[29] Hattori Y, Matsumura M, Kasai K. Vascular smooth muscle cell activation by C-reactive protein. Cardiovasc Res 2003;58:186–95.
[30] Sato S, Iso H, Noda H, et al. Plasma fibrinogen concentrations and risk of stroke and its subtypes among Japanese men and women. Stroke 2006;37:2488–92.
[31] Kaptoge S, Di Angelantonio E, Lowe G, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010;375:132–40.
[32] Nilsson TK, Boman K, Jansson JH, et al. Comparison of soluble thrombomodulin, von Willebrand factor, tPA/PAI-1 complex, and high-sensitivity CRP concentrations in serum, EDTA plasma, citrated plasma, and acidified citrated plasma (stabilyte) stored at −70 °C for 8–11 years. Thromb Res 2005;116:249–54.

Please cite this article in press as: Chei C-L, et al. C-reactive protein levels and risk of stroke and its subtype in Japanese: The Circulatory Risk in Communities Study (CIRCS). Atherosclerosis (2011), doi:10.1016/j.atherosclerosis.2011.03.001

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Stroke Association
A Division of American Heart Association

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

Stroke 2011, 42:2531-2537: originally published online August 18, 2011
doi: 10.1161/STROKEAHA.110.600759
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

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

The Circulatory Risk in Communities Study (CIRCS)

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

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-

Received August 22, 2010; accepted January 26, 2011.

From the School of Public Health, Department of Social and Environmental Medicine (Y.S., H.Im., T.Oh., H.Is.), Osaka University, Graduate School of Medicine, Osaka, Japan; Osaka Medical Center for Health Science and Promotion (Y.S., K.M., T.Oh., A.K., M.K., T.Ok., Y.I., T.S.), Osaka, Japan; Department of Public Health Medicine (K.Y.), Graduate School of Comprehensive Human Sciences and Institute of Community Medicine, University of Tsukuba, Tsukuba, Japan; Department of Public Health, Social Medicine and Medical Informatics (T.T.), Ehime University Graduate School of Medicine, Toon, Japan.

Correspondence to Professor Hiroyasu Iso, MD, PhD, MPH, School of Public Health, Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, Suita-shi, Osaka 565-0871 Japan. E-mail iso@pbhel.med.osaka-u.ac.jp

***Stroke* is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.110.600759**

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	*P*
	GFR≥90	90>GFR≥60	60>GFR	
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

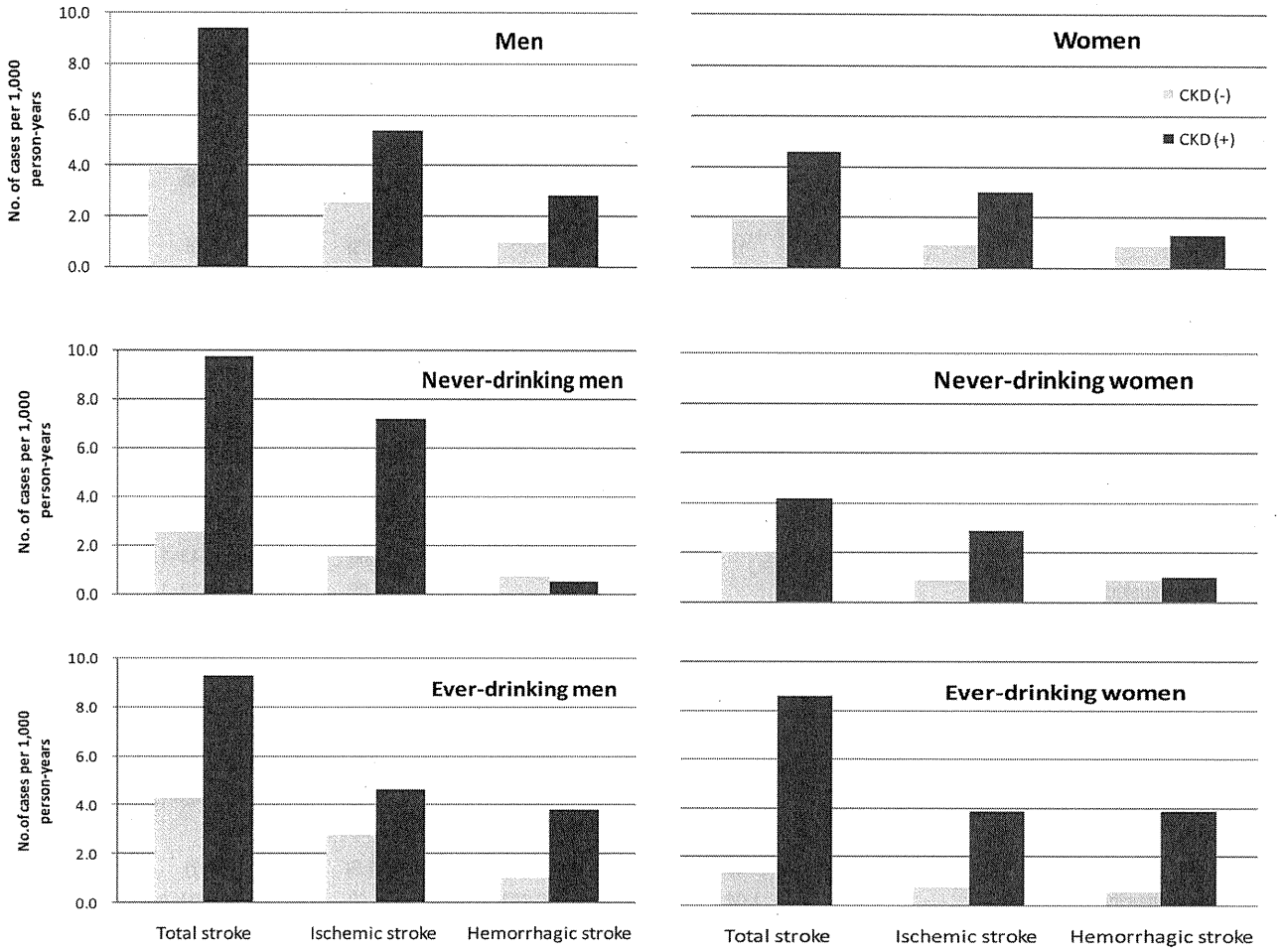


Figure. Incidents of total, ischemic, and hemorrhgic stroke per 1,000 person-years in the presence or absence of CKD. Black-filled bar, CKD-negative; open bar, CKD-positive.

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.

Sources of Funding

This study has been supported by Grants-in-Aids for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan. (No. 14207019 and 19390174).

Disclosures

None.

References

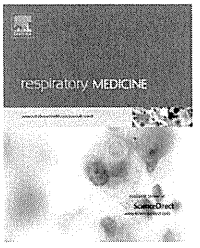
1. Yahalom G, Schwartz R, Schwammenthal Y, Merzeliak O, Orion D, Sela BA, et al. Chronic kidney disease and clinical outcomes in patients with acute stroke. *Stroke*. 2009;40:1296–1303.
2. Michiel JB, Peter JK, Albert H, Monique MB. Decreased glomerular filtration rate is a risk factor for hemorrhagic stroke. The Rotterdam Study. *Stroke*. 2007;38:3127–3132.
3. Ninomiya T, Kiyohara Y, Kubo M, Tanizaki Y, Doi Y, Okubo K, et al. Chronic kidney disease and cardiovascular disease in a general Japanese population: The Hisayama Study. *Kidney Inter*. 2005;68:228–236.
4. Ovbiagele B. Impairment in glomerular filtration rate or glomerular filtration barrier and occurrence of stroke. *Arch Neurol*. 2008;65: 934–938.
5. Korean-Morag N, Goldbourt U, Tanne D. Renal dysfunction and risk of ischemic stroke or TIA in patients with cardiovascular disease. *Neurology*. 2006;67:224–228.
6. Kokubo Y, Nakamura S, Okamura T, Yoshimasa Y, Makino H, Watanabe M, et al. Relationship between blood pressure category and incidence of stroke and myocardial infarction in an urban Japanese population with and without chronic kidney disease. The Suita Study. *Stroke*. 2009;40: 2674–2679.
7. Iso H, Sato S, Kitamura A, Imano H, Kiyama M, Yamagishi K, et al. Metabolic syndrome and the risk of ischemic heart disease and stroke among Japanese men and women. *Stroke*. 2007;38:1744–1751.
8. Imano H, Kitamura A, Sato S, Kiyama M, Ohira T, Yamagishi K, et al. Trends for blood pressure and its contribution to stroke incidence in the middle-aged Japanese population: the Circulatory Risk in Communities study (CIRCS). *Stroke*. 2009;40:1571–1577.
9. Simamoto T, Komachi Y, Inada H, Doi M, Iso H, Sato S, et al. Trends for coronary heart disease and stroke and their risk factors in Japan. *Circulation* 1989;79:503–515.
10. Imai E. Equation for estimating GFR from creatinine in Japan. *Nippon Rinsho*. 2008;66:1725–1729.
11. Coresh J, Astor BC, McQuillan G, Kusek J, Greene T, Van Lente F, et al. Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *Am J Kidney Dis*. 2002;39:920–929.
12. Imai E, Horio M, Watanabe T, Iseki K, Yamagata K, Hara S, et al. Prevalence of chronic kidney disease in the Japanese general population. *Clin Exp Nephrol*. 2009;13:621–630.
13. Iso H, Kitamura A, Shimamoto T, Sankai T, Naito Y, Sato S, et al. Alcohol Intake and risk of cardiovascular disease in middle-aged Japanese men. *Stroke*. 1995;26:767–773.
14. Iso H, Sato S, Umemura U, Kudo M, Koike K, Kitamura A, et al. Linoleic acid, other fatty acids, and the risk of stroke. *Stroke*. 2002;33:2086–2093.
15. Shimamoto T, Iida H, Doi M, Komachi Y. Recent morbidity trends in myocardial infarction in Japan: investigation of death certificates and the survival rates at coronary care units. *Jpn Circ J*. 1987;51:314–318.
16. Millikan C. A Report by an ad hoc committee established by the advisory council for the National Insitute of Neurological Disease and Blindness, Public health service: a Classification and outline of cerebrovascular diseases. *Neurology*. 1958;8:393–433.
17. Shimizu Y, Imano H, Ohira T, Kitamura A, Kiyama M, Okada T, et al. γ-Glutamyltranspeptidase and incident stroke among Japanese men and women. *Stroke*. 2010;41:385–388.
18. Iso H, Baba S, Mannami T, Sasaki S, Okada K, Konishi M, et al. Alcohol consumption and risk of stroke among middle-aged men: The JPHC study cohrt I. *Stroke*. 2004;35:1124–1129.
19. Endemann DH, Schiffrin EL. Endothelial dysfunction. *J Am Soc Nephrol*. 2004;15:1983–1992.
20. Fujihara CK, De Nucci G, Zatz R. Chronic nitric oxide synthase inhibition aggravates glomerular injury in rat with subtotal nephrectomy. *J Am Soc Nephrol*. 1995;5:1498–1507.
21. O' Rourke MF, Safer ME. Relationship between aortic stiffing and microvascular disease in brain and kidney: Cause and logic of therapy. *Hypertension*. 2005;46:200–204.
22. Konishi M, Iso H, Komachi Y, Iida M, Shimamoto T, Jacobs DR Jr, et al. Associations of serum total cholesterol different types of stroke, and stenosis distribution of cerebral arteries. The Akita pathology study. *Stroke*. 1993;24:954–964.
23. Moncada S, Randomski NW. The problem and the promise of prostaglangin influences in atherosclerosis. *Ann NY Acad Sci*. 1985;454: 121–130.
24. Murray RP, Connett JE, Tyas SL, Bond R, Ekuma O, Silversides CK, et al. Alcohol volume, drinking pattern, and cardiovascular disease morbidity and mortality: is there a U-shaped function? *Am J Epidemiol*. 2002;155:242–248.
25. Laug WE. Ethyl alcohol enhances plasminogen activator secretion by endothelial cells. *JAMA*. 1983;250:772–776.
26. Strokes GS. Hypertension and alcohol: is there a link? *J Chronic Dis*. 1982;35:759–762.
27. Ohira T, Tanigawa T, Tabata M, Imano H, Kitamura A, Kiyama M, et al. Effect of habitual alcohol intake on ambulatory blood pressure, heart rate, and its variability among Japanese men. *Hypertension*. 2009;53:13–19.
28. Metoki H, Ohkubo T, Kikuya M, Asayama K, Obara T, Hashimoto J, et al. Prognostic significance for stroke of a morning pressure surge and a nocturnal blood pressure decline: The Ohasama Study. *Hypertension*. 2006;47:149–154.
29. Tamakoshi K, Toyoshima H, Yatsuya H, Matsushita K, Okamura T, Hayakawa T, et al. White blood cell count and risk of all-causes and cardiovascular mortality in nationwide sample of Japanese. Results from the NIPPON DATA 90. *Circulation*. 2007;71:479–485.

Respiratory Medicine (2011) 105, 796–800

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed



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

Renzhe Cui [a,b,*], Takeshi Tanigawa [c], Susumu Sakurai [c], Kazumasa Yamagishi [d], Isao Muraki [a,b], Hironori Imano [a,b], Tetsuya Ohira [a,b], Masahiko Kiyama [b], Akihiko Kitamura [b], Yoshinori Ishikawa [b], Hiroyasu Iso [a], CIRCS Investigators

[a] *Public Health, Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka Suita-City, Osaka 565-0871, Japan*
[b] *Osaka Medical Center for Health Science and Promotion, Osaka, Japan*
[c] *Department of Public Health, Doctoral Program in Social Medicine, Ehime University Graduate School of Medicine, Ehime, Japan*
[d] *Department of Public Health Medicine, Graduate School of Comprehensive Human Sciences and Institute of Community Medicine, University of Tsukuba, Ibaraki, Japan*

Received 4 November 2010; accepted 6 January 2011
Available online 28 January 2011

KEYWORDS
Alcohol consumption;
Women;
Sleep-disordered breathing;
Epidemiology

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.

* Corresponding author. Public Health, Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka Suita-City, Osaka 565-0871, Japan. Tel.: +81 6 6879 3911; fax: +81 6 6879 3919.
E-mail address: cui@pbhel.med.osaka-u.ac.jp (R. Cui).

0954-6111/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2011.01.003

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.

Acknowledgments

The authors are grateful to Ms. Yukiko Ichikawa, Ms. Miyuki Notsute, Ms. Minako Tabata, Ms. Ai Ikeda, Dr Hiroyuki Noda, and Dr. Mitsumasa Umesawa for the excellent technical assistance and help in data collection. This study was supported in part by a Grant-in-Aid for Scientific Research B (No. 18390194 in 2006–2008) and for Exploratory Research (No. 18659179 in 2006–2007) from the Japanese Society for the Promotion of Science, and by a Sports Research Grant

(No. 17659184 in 2005–2006) from the Ministry of Health, Education, Culture, Sports, Science and Technology, Japan.

Conflict of interest

None.

References

1. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000;**342**:1378–84.
2. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea–hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005;**365**:1046–53.
3. Marshall NS, Wong KK, Liu PY, Cullen SR, Knuiman MW, Grunstein RR. Sleep apnea as an independent risk factor for all-cause mortality: the Busselton health study. *Sleep* 2008;**31**: 1079–85.
4. Ohira T, Tanigawa T, Tabata M, et al. Effects of habitual alcohol intake on ambulatory blood pressure, heart rate, and its variability among Japanese men. *Hypertension* 2009;**53**: 13–9.
5. Ikehara S, Iso H, Toyoshima H, et al. Alcohol consumption and mortality from stroke and coronary heart disease among Japanese men and women: the Japan collaborative cohort study. *Stroke* 2008;**39**:2936–42.
6. Scanlan MF, Roebuck T, Little PJ, Redman JR, Naughton MT. Effect of moderate alcohol upon obstructive sleep apnoea. *Eur Respir J* 2000;**16**:909–13.
7. Taasan VC, Block AJ, Boysen PG, Wynne JW. Alcohol increases sleep apnea and oxygen desaturation in asymptomatic men. *Am J Med* 1981;**71**:240–5.
8. Tsutsumi W, Miyazaki S, Itasaka Y, Togawa K. Influence of alcohol on respiratory disturbance during sleep. *Psychiatry Clin Neurosci* 2000;**54**:332–3.
9. Mitler MM, Dawson A, Henriksen SJ, Sobers M, Bloom FE. Bedtime ethanol increases resistance of upper airways and produces sleep apneas in asymptomatic snorers. *Alcohol Clin Exp Res* 1998;**12**:801–5.
10. Enright PL, Newman AB, Wahl PW, Manolio TA, Haponik EF, Boyle PJ. Prevalence and correlates of snoring and observed apneas in 5,201 older adults. *Sleep* 1996;**19**:531–8.
11. Jennum PJ, Hein HO, Suadicani P, Gyntelberg F. Cardiovascular risk factors in snorers: a cross-sectional study of 3,323 men aged 54 to 74 years. The copenhagen male study. *Chest* 1992; **102**:1371–6.
12. Jennum P, Sjol A. Snoring, sleep apnoea and cardiovascular risk factors: the MONICA II study. *Int J Epidemiol* 1993;**22**:439–44.
13. Stradling JR, Crosby JH. Predictors and prevalence of obstructive sleep apnoea and snoring in 1001 middle aged men. *Thorax* 1991;**46**:85–90.
14. Tanigawa T, Tachibana N, Yamagishi K, Muraki I, Umesawa M, Shimamoto T, et al. Usual alcohol consumption and arterial oxygen desaturation during sleep. *JAMA* 2004;**292**:923–5.
15. Peppard PE, Austin D, Brown RL. Association of alcohol consumption and sleep disordered breathing in men and women. *J Clin Sleep Med* 2007;**3**:265–70.
16. Olson LG, King MT, Hensley MJ, Saunders NA. A community study of snoring and sleep-disordered breathing: prevalence. *Am J Respir Crit Care Med* 1995;**152**:711–6.
17. Schmidt-Nowara WW, Coultas DB, Wiggins C, Skipper BE, Samet JM. Snoring in a Hispanic-American population. Risk factors and association with hypertension and other morbidity. *Arch Intern Med* 1990;**150**:597–601.
18. Imano H, Kitamura A, Sato S, et al. Trends for blood pressure and its contribution to stroke incidence in the middle-aged Japanese population: the circulatory risk in communities study (CIRCS). *Stroke* 2009;**40**:1571–7.
19. International guidelines for ethical review of epidemiological studies. *Law Med Health Care* 1991;**19**:247–58.
20. Clark JS, Votteri B, Ariagno RL, et al. Noninvasive assessment of blood gases. *Am Rev Respir Dis* 1992;**145**:220–32.
21. Cui R, Tanigawa T, Sakurai S, et al. Associations of sleep-disordered breathing with excessive daytime sleepiness and blood pressure in Japanese women. *Hypertens Res* 2008;**31**:501–6.
22. Nakamata M, Kubota Y, Sakai K, et al. The limitation of screening test for patients with sleep apnea syndrome using pulse oximetry. *J Jpn Soc Respir Care* 2003;**12**:401–6 [in Japanese].
23. Robinson RW, White DP, Zwillich CW. Moderate alcohol ingestion increases upper airway resistance in normal subjects. *Am Rev Respir Dis* 1985;**132**:1238–41.
24. St John WM, Bartlett Jr D, Knuth KV, Knuth SL, Daubenspeck JA. Differential depression of hypoglossal nerve activity by alcohol. Protection by pretreatment with medroxyprogesterone acetate. *Am Rev Respir Dis* 1986;**133**:46–8.
25. Villaneuva AT, Buchanan PR, Yee BJ, Grunstein RR. Ethnicity and obstructive sleep apnoea. *Sleep Med Rev* 2005;**9**:419–36.
26. Oksenberg A, Silverberg DS, Arons E, Radwan H. Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data. *Chest* 1997;**112**:629–39.
27. Shimamoto T, Komachi Y, Inada H, et al. Trends for coronary heart disease and stroke and their risk factors in Japan. *Circulation* 1989;**79**:503–15.
28. Shimamoto T, Iso H, Tanigawa T, et al. Stroke, ischemic heart disease and their risk factors in Kyowa town, Ibaraki, Japan. *Cardioangiology* 2000;**48**:127–33 [in Japanese].
29. Kitamura A, Sato S, Naito Y, et al. Trends in the incidence of cardiovascular diseases and risk factors among urban and rural Japanese males. *Nippon Koshu Eisei Zasshi* 2001;**48**:378–94 [in Japanese].

Original Article

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

Kazuyo Hirasada[1], Hideshi Niimura[1], Takuro Kubozono[2], Akihiko Nakamura[1], Masaya Tatebo[1], Shin Ogawa[1], Noriko Tsunematsu[1], Shirabe Chiba[1], Toshifumi Matsushita[3], Ken Kusano[4], Masaaki Miyata[2] and Toshiro Takezaki[1]

[1]Department of International Island and Community Medicine, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan
[2]Department of Cardiovascular, Respiratory and Metabolic Medicine, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan
[3]Kagoshima Branch Clinic, Japan Health Promotion Club Corp., Kagoshima, Japan
[4]JA Kagoshima Kouseiren Medical Health Care Center, Kagoshima, Japan

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.

J Atheroscler Thromb, 2012; 19:69-80.

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-

Address for correspondence: Toshiro Takezaki, Department of International Island and Community Medicine, Graduate School of Medical and Dental Sciences, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima 890-8544, Japan
E-mail: takezaki@m.kufm.kaghoshima-u.ac.jp
Received: July 31, 2010
Accepted for publication: August 9, 2011