## Ⅳ. 研究成果の刊行物・別刷


1. Maruyama M, Ohira T, Imano H, Kitamura A, Kiyama M, Okada T, Maeda K, Yamagishi K, Noda H, Ishikawa Y, Shimamoto T, Iso H. Trends in sudden cardiac death and its risk factors in Japan from 1981 to 2005: the Circulatory Risk in Communities Study (CIRCS). BMJ Open. 2012 ;22;2(2):e000573.
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BMJ open

# Trends in sudden cardiac death and its risk factors in Japan from 1981 to 2005: the Circulatory Risk in Communities Study (CIRCS)

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**To cite:** Maruyama M, Ohira T, Imano H, *et al*. Trends in sudden cardiac death and its risk factors in Japan from 1981 to 2005: the Circulatory Risk in Communities Study (CIRCS). *BMJ Open* 2012;**2**: e000573. doi:10.1136/bmjopen-2011-000573

► Prepublication history and additional tables for this paper are available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2011-000573).

Received 6 November 2011
Accepted 2 February 2012



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## ABSTRACT

**Objective:** There is little evidence whether sudden cardiac death (SCD) is increasing in Asia, although the incidence of coronary heart disease among urban middle-aged Japanese men has increased recently. We examined trends in the incidence of SCD and its risk factors in the Circulatory Risk in Communities Study.

**Design and setting:** This was a population-based longitudinal study. Surveillance of men and women for SCD incidence and risk factors was conducted from 1981 to 2005.

**Subjects:** The surveyed population was all men and women aged 30–84 years who lived in three rural communities and one urban community in Japan.

**Main outcome measures:** Trends in SCD incidence and its risk factors.

**Results:** Age-adjusted and sex-adjusted incidence of SCD decreased from 1981–1985 to 1991–1995, and plateaued thereafter. The annual incidence per 100 000 person-years was 76.0 in 1981–1985, 57.9 in 1986–1990, 39.3 in 1991–1995, 31.6 in 1996–2000 and 36.8 in 2001–2005. The prevalence of hypertension decreased from 1981–1985 to 1991–1995, and plateaued thereafter for men and women. The age-adjusted prevalence of current smoking for men decreased while that of diabetes mellitus increased for both sexes from 1981–1985 to 2001–2005.

**Conclusions:** The incidence of SCD decreased from 1981 to 1995 but was unchanged from 1996 to 2005. Continuous surveillance is necessary to clarify future trends in SCD in Japan because of an increasing incidence of diabetes mellitus.

## ARTICLE SUMMARY

### Article focus

- The incidence of coronary heart disease among urban middle-aged Japanese men increased from the 1990s to the 2000s, therefore the incidence of sudden cardiac death (SCD) may have increased in recent decades.
- This is the first study to examine recent trends in SCD in Japan.

### Key messages

- The age-adjusted and sex-adjusted incidence of SCD among men and women aged 30–84 years in four Japanese communities decreased from 1981–1985 to 1991–1995 and plateaued after 1996.
- Continuous surveillance is necessary to clarify future trends in SCD in Japan because of an increasing incidence of diabetes mellitus.

### Strengths and limitations of this study

- Trends in SCD were analysed using population-based data from a large number of participants in a long-term observational study and annual cardiovascular risk factor surveys ascertained the trends in predisposing risk factors of SCD.
- The incidence of SCD was only examined for people aged 30–84 years; other age ranges were not included.
- Clinical features and neuroimaging reports were used to exclude death due to stroke; some cases may have been misclassified, especially out-of-hospital deaths.

In the USA, estimates of the annual number of sudden cardiac deaths (SCDs) range from 184 000 to 400 000, accounting for almost half of all coronary heart disease (CHD) deaths.[1–4] The incidence of SCD was 50% higher in men than women, and the age-adjusted annual incidence of SCD among US residents aged ≥35 years in 1998 was 410.6 per 100 000 for men and 274.6 per 100 000 for women.[3] Several population-based studies have reported the incidence of SCD in Japanese adults,[5–8] however these studies are questionable due to methodological problems, such as small sample size,[7] a working population[8] and an inaccurate definition of SCD based on death certificate data only.[6] Baba *et al* reported that in Suita City (census population: approximately 340 000), the

incidence of SCD was 31 (men=45, women=20) per 100 000 people in a sample aged 20–74 years. Information on SCD was determined using police records.[5] These findings suggest that the incidence of SCD in Japan is about one-fifth of that in the USA.[1 3 9]

SCD is generally considered to be caused by CHD. The CHD mortality rate in Japan has been observed to be one-third to one-fifth of that in the USA.[6 9 10] This difference might explain the variation in the incidence of SCD between Japan and the USA. However, Kitamura *et al* reported a significant increase in the incidence of CHD among middle-aged urban Japanese men from 1980–1987 to 1996–2003.[11] Therefore, the incidence of SCD for Japanese individuals may have increased in recent decades. So far, no epidemiological study has been reported which has investigated trends in the incidence of SCD in a large population-based study.

The purpose of this study was to examine trends in the incidence of SCD and its risk factors in the Circulatory Risk in Communities Study (CIRCS), a longitudinal community-based study of Japanese men and women.

## METHODS

The CIRCS is a population-based study of cardiovascular risk factors, disease incidence and their respective trends in Japanese communities (Appendix 1). Details of the study design and procedures have been reported elsewhere.[11–14] Briefly, the subjects were Japanese men and women who lived in a north-eastern rural community, Ikawa, a south-western rural community, Noichi, a central rural community, Kyowa and a south-western urban suburb, the Minami-Takayasu district of Yao. Annual cardiovascular risk surveys have been conducted since 1963 in the district of Yao City and Ikawa, since 1969 in Noichi and since 1981 in Kyowa by a joint research team from the Osaka Medical Center for Health Science and Promotion, the University of Tsukuba, and Osaka University. In Ikawa, the census population for the age range 30–84 years was 3983 in 1985, 4166 in 1995 and 4173 in 2000. The corresponding population figures for the other communities were 12 940, 14 170 and 14 825 in Yao; 81 49, 10 772 and 10 573 in Noichi; and 96 14, 9 590 and 10 948 in Kyowa.

Informed consent was obtained from community representatives to conduct an epidemiological study based on guidelines established by the Council for International Organisations of Medical Science.[15] This study was approved by the Ethics Committee of the Osaka Medical Center for Health Science and Promotion.

The study included all SCD events that occurred among all residents between 1 January 1981 and 31 December 2005. CHD and SCD events were ascertained from national insurance claims, reports by local physicians, ambulance records, death certificates, reports by public health nurses and health volunteers, and annual cardiovascular risk surveys (figure 1).[11–14] Subjects who had moved away from the community or died were treated as censored cases. For confirmation of diagnosis, we also obtained histories from next of kin and reviewed medical records in local hospitals.

CHD criteria were modified from those of the WHO Expert Committee.[16] The indication for definite myocardial infarction (MI) was typical, severe chest pain (lasting at least 30 min and without a definite non-ischaemic cause) accompanied by new, abnormal and persistent Q or QS waves, consistent changes in cardiac enzyme levels or both. If the electrocardiographic and enzyme levels were non-diagnostic or unavailable, but the patient suffered typical chest pain, a diagnosis of possible MI was made. For our study, definite and possible infarctions were combined into a single category, MI. These criteria are essentially the same as those of the WHO Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project.[17] Angina pectoris was defined as repeated episodes of chest pain during effort, usually disappearing rapidly after the cessation of effort or upon use of sublingual nitroglycerine.[12 13] In the present study, CHD included definite or probable MI and angina pectoris.

SCD was defined as sudden unexpected death either within 1 h of symptom onset or within 24 h of having been observed alive and symptom free. We excluded candidate cases if they survived for over 24 h after symptom onset or if there was another apparent cause of death, such as stroke, cancer or accident. The final diagnosis of SCD was made by a panel of three or four trained physician epidemiologists, blinded to the data of cardiovascular risk factors. We further classified the SCD cases into two groups according to the presence or absence of MI.[18] If the SCD case was accompanied by MI, it grouped SCD with MI (SCD_MI), and others were grouped as SCD without MI (SCD_NMI). In addition,

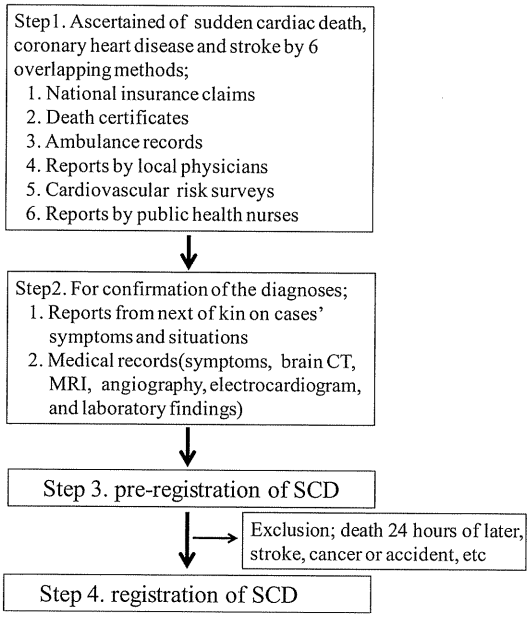


**Figure 1** Determination of sudden cardiac death (SCD).

SCD cases were divided into two groups stratified by time of symptom onset. If the time of symptom onset was within 1 h, they were categorised as SCD1, and if it occurred within 24 h but they were not SCD1, they were categorised as SCD1-24. Finally, SCD cases were divided into two groups based on place of death.[3] If the place of death was in an emergency room (ER) or a hospital, the case was categorised as SCD_ER, and if it was outside of a hospital, it was categorised as SCD_NER (table 1).

Age-adjusted and sex-adjusted annual incidence of SCD was calculated from the number of new cases per 100 000 person-years during the periods 1981–1985, 1986–1990, 1991–1995, 1996–2000 and 2001–2005 in the four Japanese communities studied. The rate of moving out from the community during these periods was 2.1%, 3.1%, 2.8%, 2.9% and 1.9%, respectively. In this study, all analyses were limited to men and women aged 30–84 years because the number of SCDs in people aged <30 years was too small (<1%) and for many cases aged ≥85 years, causes of death were difficult to identify.

Cardiovascular risk factors were determined from residents of the four communities in risk factor surveys during each of the five study periods. The surveys were conducted to promote primary prevention of cardiovascular disease. The participation rate among the census population in each survey period was 41.9%, 36.8%, 37.1%, 34.8% and 32.0%, respectively. When the age of participants was restricted to 40–74 years, the participation rate was 57.2%, 48.2%, 44.2%, 40.1% and 35.4%, respectively. The participation rate for the age group 40–74 years in Ikawa and Kyowa (with high participation rates) was 73.9%, 62.7%, 61.1%, 57.3%, and 53.6%, respectively, while that in Yao and Noichi (with lower participation rates) was 45.3%, 38.8%, 33.6%, 29.4% and 26.1%, respectively. If people participated in the risk factor survey more than once during each survey period, we used the data from the earliest year.

The items examined in the risk factor surveys included medical history, measurement of total cholesterol, blood pressure, body mass index (BMI), blood glucose, ECG findings, and drinking and smoking habits.[11] Hypertension was defined as systolic blood pressure (BP) ≥140 mm Hg or diastolic BP ≥90 mm Hg, or use of an antihypertensive medication. Diabetes mellitus was defined as a fasting glucose level ≥7.00 mmol/litre, a non-fasting glucose level ≥11.10 mmol/litre or use of an antidiabetic medication. Overweight was defined as a BMI ≥25 kg/m$^2$. ECG data were obtained with the person in the supine position and were coded with the Minnesota Code, second version,[19] by trained physician epidemiologists.

To calculate age-adjusted and sex-adjusted incidence, we employed the direct standardisation method using the age and sex distributions of the Japanese national model population from 1985 as the standard population. Linear trends in incidence were examined with the $\chi^2$ test. We calculated 95% CIs using the following equation:

$$\text{age-adjusted annual incidence of SCD} \pm 1.96 \sqrt{\left[\frac{\sum\left[\frac{N_i^2 p_i (1-p_i)}{n_i}\right]}{\left[\sum N_i\right]^2}\right]}$$

where N is the standard population for the 5-year age category i, p is the crude incidence of the population for age category i, and n is the number of the population for age category i. Sex-specific age-adjusted means of risk factors were estimated by analysis of covariance, and age-adjusted prevalence by the direct method of standardisation.

The significance of risk factor trends was examined for continuous variables by using the regression analysis for repeated measures,[11] with the five periods represented as 1982.5, 1987.5, 1992.5, 1997.5 and 2002.5, and for discrete variables by using the $\chi^2$ test for trends. All statistical analyses were performed with the SAS System for Windows (V.9.1).

## RESULTS

In this study, 471 people with SCD were identified over 25 years, consisting of 117 SCD_MI and 354 SCD_NMI, 163 SCD1 and 308 SCD1-24, 190 SCD_NER, and 281 SCD_ER. The number of SCDs (in parentheses, SCD_MI) was presented according to the time of symptom onset and the place of death (online supplemental table 1).

As shown in table 1, age-adjusted and sex-adjusted incidence of SCD decreased from 1981–1985 to 1991–1995, however the rate plateaued after 1996 (p for trend <0.01 from 1981–1985 to 1991–1995 and p=0.73 from 1991–1995 to 2001–2005). The annual incidence (95% CI) of SCD per 100 000 person-years during the five periods were 76.0 (44.8 to 107.2), 57.9 (32.7 to 83.1), 39.3 (20.3 to 58.3), 31.6 (15.6 to 47.6) and 36.8 (19.8 to 53.8), respectively. A total of 731 individuals with CHD were identified over 25 years: 256 with definite MI, 254 with probable MI and 221 with angina pectoris, and the number of CHD deaths was 178. The features of the SCD trends for the age groups 30–64, 65–74 and also 40–74 were similar to those of the overall trend, while there was a constant decline in the SCD incidence for age group 75–84.

A similar trend was observed for age-adjusted and sex-adjusted incidence of CHD. The annual incidence (95% CI) of CHD per 100 000 person-years was 98.2 (62.7 to 133.7), 87.0 (56.0 to 118.0), 78.0 (50.9 to 105.1), 50.0 (29.8 to 70.2) and 57.5 (36.5 to 78.5), respectively. A slightly different trend was observed for MI. The annual incidence (95% CI) of MI per 100 000 person-years was 55.2 (28.6 to 81.8), 58.9 (33.4 to 84.4), 57.5 (34.4 to

Table 1 Trends in age-adjusted and sex-adjusted incidence of sudden cardiac death per 100 000 person-years (and 95% CIs) among men and women aged 30–84 years in four Japanese communities from 1981 to 2005

| | 1981–1985 | 1986–1990 | 1991–1995 | 1996–2000 | 2001–2005 | p for trend |
|---|---|---|---|---|---|---|
| Total | | | | | | |
| Population | 31 754 | 34 686 | 36 717 | 38 698 | 40 519 | |
| Cases | 114 | 101 | 83 | 76 | 97 | |
| Age-adjusted and sex-adjusted incidence | 76.0 (44.8 to 107.2) | 57.9 (32.7 to 83.1) | 39.3 (20.3 to 58.3) | 31.6 (15.6 to 47.6) | 36.8 (19.8 to 53.8) | <0.01 |
| Age-adjusted and sex-adjusted incidence | | | | | | |
| 30–64 years | 24.1 (4.8 to 43.4) | 19.7 (3.3 to 36.1) | 15.7 (1.8 to 29.6) | 12.4 (0.7 to 24.1) | 17.0 (2.5 to 31.5) | 0.266 |
| 65–74 years | 217.1 (64.9 to 369.3) | 100.2 (1.7 to 198.7) | 99.7 (8.6 to 190.8) | 83.8 (8.9 to 158.7) | 101.8 (24.1 to 179.5) | <0.01 |
| 75–84 years | 541.0 (187.9 to 894.1) | 527.2 (210.6 to 843.8) | 258.5 (67.2 to 449.8) | 204.3 (39.5 to 369.1) | 190.8 (51.1 to 330.5) | <0.01 |
| 40–74 years | 65.0 (29.9 to 100.1) | 40.0 (14.1 to 65.9) | 34.6 (12.2 to 57.0) | 28.8 (10.0 to 47.6) | 33.4 (13.5 to 53.3) | <0.01 |
| Men | | | | | | |
| Population | 15 048 | 16 471 | 17 421 | 18 422 | 19 306 | |
| Cases | 70 | 61 | 49 | 50 | 67 | |
| Age-adjusted incidence | 111.7 (53.1 to 170.3) | 82.1 (36.0 to 128.2) | 54.4 (20.2 to 88.6) | 49.3 (18.6 to 80.0) | 57.9 (26.2 to 89.6) | <0.01 |
| Women | | | | | | |
| Population | 16 706 | 18 215 | 19 296 | 20 276 | 21 213 | |
| Cases | 44 | 40 | 34 | 26 | 30 | |
| Age-adjusted incidence | 50.6 (17.1 to 84.1) | 39.5 (12.0 to 67.0) | 27.1 (6.3 to 47.9) | 16.7 (2.0 to 31.4) | 18.2 (2.5 to 33.9) | <0.01 |

80.6), 34.6 (17.9 to 51.3) and 45.6 (26.9 to 64.3) (data not shown in table 1).

The incidence of SCD was two to three times higher for men than for women, while age-adjusted annual incidence (95% CI) of SCD per 100 000 person-years during the five time periods was 111.7 (53.1 to 170.3), 82.1 (36.0 to 128.2), 54.4 (20.2 to 88.6), 49.3 (18.6 to 80.0) and 57.9 (26.2 to 89.6) for men and 50.6 (17.1 to 84.1), 39.5 (12.0 to 67.0), 27.1 (6.3 to 47.9), 16.7 (2.0 to 31.4) and 18.2 (2.5 to 33.9) for women (table 1).

We further analysed the incidence of SCD stratified by the presence or absence of MI, the time of symptom onset and the place of death (figure 2). The age-adjusted and sex-adjusted annual incidence (95% CI) of SCD per 100 000 person-years was 16.1 (1.7 to 30.5), 15.5 (2.4 to 28.6), 14.0 (2.7 to 25.3), 5.3 (0 to 11.7) and 8.4 (0.3 to 16.5) for SCD_MI and 59.8 (32.1 to 87.5), 42.4 (20.8 to 64.0), 25.3 (10.0 to 40.6), 26.4 (11.7 to 41.1) and 28.4 (13.4 to 43.4) for SCD_NMI. The calculation of the incidence stratified by the time of symptom onset yielded age-adjusted and sex-adjusted annual incidence (95% CI) per 100 000 person-years of 27.4 (8.6 to 46.2), 19.7 (4.9 to 34.5), 12.7 (1.9 to 23.5), 9.2 (0.3 to 18.1) and 15.7 (4.4 to 27.0) for SCD1, and 48.6 (23.7 to 73.5), 38.1 (17.7 to 58.5), 26.6 (10.9 to 42.3), 22.5 (9.1 to 35.9) and 21.1 (8.4 to 33.8) for SCD1-24. The calculation of the incidence stratified by the place of death yielded the age-adjusted and sex-adjusted annual incidence (95% CI) per 100 000 person-years of 41.0 (18.0 to 64.0), 25.1 (8.5 to 41.7), 12.8 (2.1 to 23.5), 11.4 (1.9 to 20.9) and 10.5 (1.7 to 19.3) for SCD_NER, and 35.0 (13.9 to 56.1), 32.7 (13.7 to 51.7), 26.5 (10.7 to 42.3), 20.3 (7.3 to 33.1) and 26.2 (11.6 to 40.8) for SCD_ER. These trends showed similar features to those of the overall trend.

We estimated the national SCD incidence in 2009 by using the results from this study. For this estimation, we multiplied the age-specific and sex-specific populations in 2009 by the age-specific and sex-specific incidences of SCD from 2001 to 2005. For the population aged 85 years or over, we used the incidence of SCD for ages 75–84 years. We predicted the number of cases of SCD in Japan to be at least 51 700 cases in 2009.

As shown in table 2, the overall trends in risk factors of SCD showed the same features for men and women, except for diastolic BP, BMI, current smoking and heavy drinking. Mean diastolic BP for women decreased from 1981–1985 to 2001–2005 (p for trend was <0.01), whereas that for men was constant from 1981–1985 to 1991–1995, but increased after 1996 (p for trend was <0.01). For men and women, mean systolic BP decreased from 1981–1985 to 2001–2005 (p for trend was <0.01). The prevalence of hypertension decreased from 1981–1985 to 1991–1995, but plateaued after 1996 in both sexes. The mean BMI for women declined from 1981–1985 to 2001–2005 (p for trend was <0.01), whereas BMI for men increased. The prevalence of current smoking and heavy drinking decreased constantly from 1981–1985 to 2001–2005 (p for trend

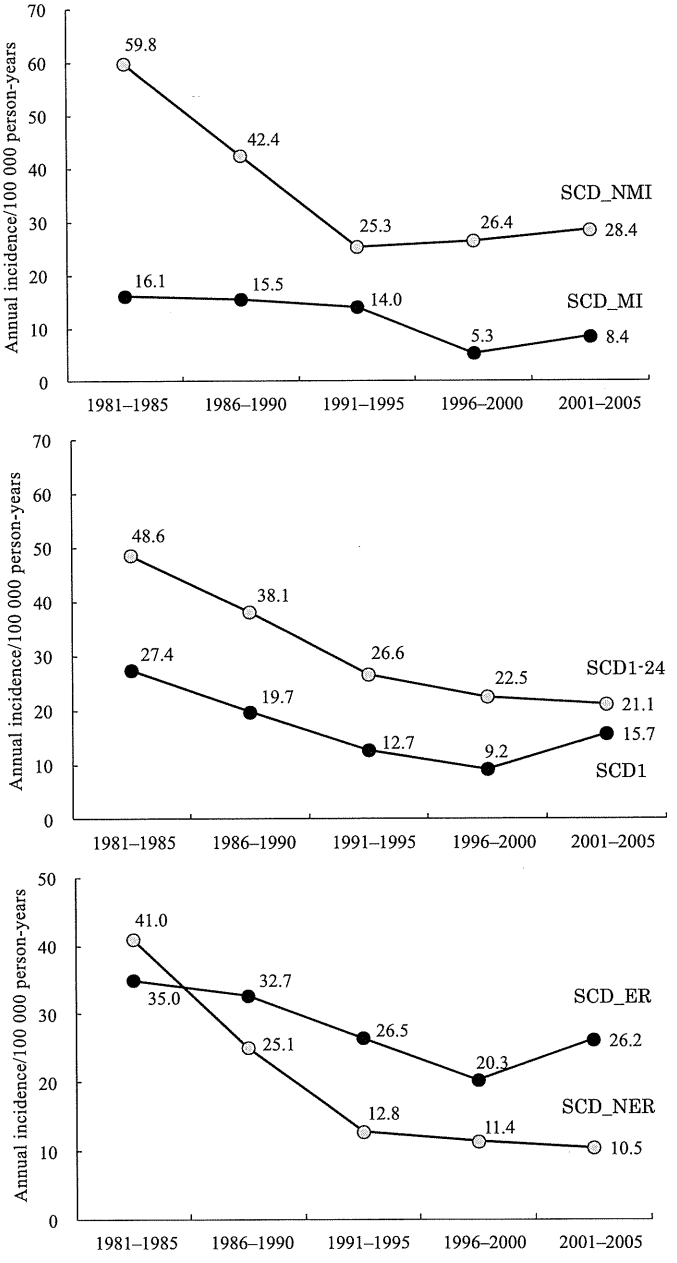


**Figure 2** Trends in age-adjusted and sex-adjusted annual incidence of sudden cardiac death (SCD), stratified by the presence or absence of myocardial infarction (MI), the time of symptom onset and the place of death. Annual incidence per 100 000 among men and women aged 30–84 in four Japanese communities from 1981 to 2005: SCD with MI (SCD_MI) and SCD without MI (SCD_NMI), SCD within 1 h (SCD1) and SCD between 1 and 24 h (SCD1-24), SCD in an emergency room or a hospital (SCD_ER) and SCD outside of a hospital (SCD_NER).

was <0.01, for both) for men but did not change for women. Mean levels of total cholesterol, and the prevalence of diabetes mellitus increased continuously from 1981–1985 to 2001–2005 (p for trend was <0.01, for both sexes). The prevalence of left ventricular hypertrophy dramatically decreased from 1981–1985 to 2001–2005 (p for trend was <0.01, in both sexes). Additionally, we examined the risk factor trends in ages

Table 2 Trends in age-adjusted and sex-adjusted cardiovascular risk factors among men and women aged 30–84 years in four Japanese communities from 1981 to 2005

| | 1981–1985 | 1986–1990 | 1991–1995 | 1996–2000 | 2001–2005 | p for trend |
|---|---|---|---|---|---|---|
| Men | | | | | | |
| N | 5350 | 4992 | 5175 | 5039 | 4900 | |
| Age, years | 55 | 56 | 58 | 59 | 60 | |
| Systolic BP, mm Hg | 137 | 134 | 133 | 134 | 133 | <0.01 |
| Diastolic BP, mm Hg | 81 | 81 | 81 | 82 | 82 | <0.01 |
| Antihypertensive medication, % | 19.8 | 18.6 | 17.2 | 18.0 | 20.1 | 0.550 |
| Hypertension, % | 49.2 | 44.1 | 41.3 | 44.7 | 44.6 | <0.01 |
| BMI, kg/m$^2$ | 22.7 | 22.9 | 23.3 | 23.5 | 23.8 | <0.01 |
| Overweight (BMI ≥25 kg/m$^2$), % | 26.2 | 29.2 | 29.6 | 33.5 | 34.7 | <0.01 |
| Total cholesterol, mmol/litre | 4.75 | 4.89 | 4.98 | 5.13 | 5.23 | <0.01 |
| Total cholesterol ≥5.69 mmol/litre, % | 14.0 | 17.7 | 20.7 | 26.8 | 31.4 | <0.01 |
| Blood glucose, mmol/litre | 63.0 | 69.7 | 67.7 | 63.0 | 61.1 | <0.01 |
| Diabetes mellitus, % | 3.8 | 6.4 | 7.1 | 7.7 | 9.7 | <0.01 |
| Heavy drinking (ethanol intake ≥46 g/day), % | 33.4 | 29.8 | 28.3 | 27.5 | 23.1 | <0.01 |
| Current smoking, % | 60.1 | 55.8 | 52.6 | 49.5 | 44.6 | <0.01 |
| ECG findings, % | | | | | | |
| Atrial fibrillation | 1.4 | 1.6 | 1.4 | 1.5 | 1.4 | 0.731 |
| Ventricular premature contraction | 3.1 | 3.0 | 3.2 | 2.7 | 2.5 | 0.039 |
| Supraventricular premature contraction | 3.3 | 4.4 | 4.1 | 3.6 | 3.5 | 0.547 |
| Major ST-T abnormality | 4.6 | 4.1 | 3.7 | 4.2 | 3.9 | 0.109 |
| Minor ST-T abnormality | 12.5 | 10.1 | 12.7 | 11.9 | 11.7 | 0.871 |
| PQ prolonged | 1.5 | 1.2 | 1.5 | 1.4 | 1.2 | 0.298 |
| Complete/incomplete right bundle | 5.3 | 5.2 | 5.7 | 6.1 | 6.7 | <0.01 |
| Wide QRS | 3.0 | 3.0 | 3.2 | 3.6 | 4.1 | <0.01 |
| Abnormal Q wave | 0.5 | 0.7 | 0.6 | 0.7 | 0.7 | 0.431 |
| Left ventricular hypertrophy | 29.1 | 27.5 | 22.5 | 19.2 | 17.3 | <0.01 |
| Women | | | | | | |
| N | 7949 | 7781 | 8463 | 8436 | 8082 | |
| Age, years | 54 | 55 | 56 | 57 | 58 | |
| Systolic BP, mm Hg | 134 | 132 | 130 | 130 | 128 | <0.01 |
| Diastolic BP, mm Hg | 79 | 78 | 78 | 78 | 77 | <0.01 |
| Antihypertensive medication, % | 19.2 | 18.4 | 16.8 | 17.0 | 18.1 | <0.01 |
| Hypertension, % | 42.0 | 37.1 | 34.0 | 34.9 | 33.6 | <0.01 |
| BMI, kg/m$^2$ | 23.5 | 23.4 | 23.3 | 23.3 | 23.2 | <0.01 |
| Overweight (BMI ≥25 kg/m$^2$), % | 34.4 | 33.4 | 31.1 | 30.9 | 28.0 | <0.01 |
| Total cholesterol, mmol/litre | 5.09 | 5.24 | 5.27 | 5.44 | 5.49 | <0.01 |
| Total cholesterol ≥5.69 mmol/litre, % | 24.7 | 29.3 | 31.1 | 39.7 | 44.7 | <0.01 |
| Blood glucose, mmol/litre | 58.3 | 65.2 | 62.6 | 57.2 | 56.5 | <0.01 |
| Diabetes mellitus, % | 2.1 | 3.5 | 3.3 | 3.9 | 4.4 | <0.01 |
| Heavy drinking (ethanol intake ≥46 g/day), % | 0.5 | 0.3 | 0.5 | 0.6 | 0.6 | 0.109 |
| Current smoking, % | 6.3 | 5.8 | 5.7 | 6.6 | 7.1 | <0.01 |
| ECG findings, % | | | | | | |
| Atrial fibrillation | 0.6 | 0.6 | 0.3 | 0.4 | 0.4 | <0.01 |
| Ventricular premature contraction | 2.0 | 2.3 | 1.8 | 2.0 | 2.3 | 0.825 |
| Supraventricular premature contraction | 2.5 | 2.7 | 3.0 | 2.8 | 2.9 | 0.316 |
| Major ST-T abnormality | 6.5 | 6.0 | 5.0 | 4.5 | 4.8 | <0.01 |
| Minor ST-T abnormality | 21.9 | 18.6 | 19.8 | 19.5 | 17.5 | <0.01 |
| PQ prolonged | 0.6 | 0.5 | 0.5 | 0.5 | 0.4 | 0.212 |
| Complete/incomplete right bundle | 3.5 | 3.4 | 3.2 | 3.3 | 3.2 | 0.099 |
| Wide QRS | 1.5 | 1.6 | 1.7 | 1.6 | 1.6 | 0.751 |
| Abnormal Q wave | 0.2 | 0.2 | 0.2 | 0.2 | 0.4 | 0.015 |
| Left ventricular hypertrophy | 11.1 | 9.6 | 7.8 | 6.0 | 4.9 | <0.01 |

Data are mean values or percentages.
BMI, body mass index; BP, blood pressure.

40–74 years (online supplemental table 2), and also stratified by community (Ikawa and Kyowa: online supplemental table 3/Yao and Noichi: online supplemental table 4), and found the same trends.

## DISCUSSION

In this longitudinal community-based study from 1981 to 2005, we found that the age-adjusted and sex-adjusted annual incidence of SCD decreased from 1981 to 1995 and plateaued thereafter. This trend was similarly observed when SCD was stratified according to the following factors: presence of MI, with MI constituting approximately 20–35% of all SCDs; time of symptom onset, with SCD within 1 h constituting approximately 30–45% of all SCDs; and place of death, with SCD in the emergency room or hospital constituting approximately 4–70% of all SCDs. Although the incidence of SCD was higher for men than for women, which is consistent with previous reports,[3 20] trends in the incidence of SCD did not vary according to age or sex. Since Japan is a rapidly ageing country, the number of SCDs in Japan, although much lower than in the USA,[3] may increase in the future due to an increased older population.

Several population-based studies have previously reported the incidence of SCD among the Japanese population. The Hisayama study reported that the age-adjusted annual incidence rate of SCD between 1988 and 2000 was 76 per 100 000 person-years for men and 19 per 100 000 person-years for women aged 40 and over, and that the incidence rate did not change during the study period. However, the size of this population sample was 1110 for men and 1527 for women, which made it difficult to evaluate trends in the incidence of SCD.[7] Baba *et al* reported that the annual SCD incidence in people aged 20–74 years in Suita City in 1992 was 45 per 100 000 for men and 20 per 100 000 for women.[5] Our study showed a similar age-adjusted annual incidence of SCD (57.9 per 100 000 person-years for men and 18.2 per 100 000 person-years for women aged 30–84 years) in 2001–2005.

In Western countries, SCD accounts for almost half of all CHD deaths,[2 21] while CHD accounted for at least 80% of all SCD cases.[22] In this study, SCD accounts for 10% of all CHD deaths, while CHD accounted for 25% of all SCD cases, which was generally consistent with the findings from a previous Japanese population-based study.[20] The lower incidence[11] and mortality rates[9 10 23] from CHD in Japan than in the USA probably correspond to the lower incidence of SCD in Japan.

Several population-based studies have reported the age-adjusted annual incidence of MI among Japanese men and women[24–26]: 42.3 per 100 000 person-years for age 20 years and over in 1988–1998,[24] 45.8 per 100 000 person-years for the age range 35–64 years in 1994–1996,[25] and 49.7 per 100 000 person-years for age 20 years and over in 1996–1998.[26] In this study, the age-adjusted and sex- adjusted annual incidence of MI for the age range 30–84 years was 34.6–58.9 per 100 000 person-years in 1981–2005. These findings confirm the low incidence of CHD in Japan. However, Rumana *et al* reported that the incidence of acute MI increased from 1990–1992 to 1999–2001 in the Takashima AMI Registry.[26] Furthermore, Kitamura *et al* reported a significant increase in the incidence of CHD from 1980–1987 to 1996–2003 for middle-aged men in an urban community,[11] which was involved in this CIRCS. Because the prevalence of overweight and diabetes mellitus has increased during the last two decades as seen in our study and other Japanese studies,[9 11 27] the incidence of SCD might increase in the future.

The data presented here show that the incidence of SCD_ER decreased from 1981 to 1995, but plateaued after 1996, whereas the incidence of SCD_NER has decreased steadily over time. The plateauing trend of SCD_ER may be due to the doubling of the number of patients transported to emergency rooms by ambulance between 1996 and 2006.[28]

Risk factors for SCD among Americans have been identified as hypertension, hypertensive organic change, older age, male sex, smoking, heavy drinking, overweight, diabetes and left ventricular hypertrophy.[3] Hypertension, current smoking and diabetes mellitus were found to be potential risk factors for SCD among the Japanese population.[20 29] In this study, the SCD incidence decreased from 1981 to 1995 when a reduction in the prevalence of hypertension and current smoking was observed. The SCD incidence remained unchanged from 1996 to 2005 when the prevalence of hypertension was unchanged, the prevalence of current smoking decreased and the prevalence of diabetes mellitus increased.

This study has the following strengths. We analysed trends in SCD using population-based data, including urban and rural areas, from a large number of participants in a long-term observational study. The cause of death from death certificates was validated by medical records and/or information from next of kin. In addition, annual cardiovascular risk factor surveys ascertained the trends in predisposing risk factors of SCD.

Nonetheless, our study has a few limitations. First, we only examined the incidence of SCD for the age range 30–84 years. However the frequency of SCD among people <30 years old was found to be <1% even in the USA,[3] so this age window is unlikely to substantially affect the results. Second, although clinical features and neuroimaging reports were used to exclude death due to stroke, some cases may have been misclassified, especially out-of-hospital deaths. Such misclassifications may well have affected the changes in the incidence of SCD that occurred out of hospital. Third, since we did not include cases of resuscitated SCDs for over 24 h after symptom onset, the true incidence of SCD might be underestimated. However, the magnitude of underestimation should be small because the annual number of resuscitated cardiac arrest cases in our surveyed

population was only around 0.7 based on the 2003 statistics of the Fire and Disaster Management Agency.[30]

In conclusion, age-adjusted and sex-adjusted incidence of SCD for a general Japanese population decreased from 1981–1985 to 1991–1995 and plateaued after 1996, when a reduction in the prevalence of hypertension and current smoking was observed. Continuous surveillance is necessary to clarify future trends in SCD in Japan because of an increasing trend for diabetes mellitus.

**Acknowledgements** The authors thank the other investigators, staff and the participants of the CIRCS for their valuable contributions. We acknowledge Drs Hiromichi Kimura, Sachiko Masuda and Toshihiko Yamada, University of Tokyo, and Dr Koji Tachikawa, University of Nagoya for their valuable comments on the manuscript.

**Contributors** Minako Maruyama analysed and interpreted the data, drafted the manuscript, and provided statistical expertise. Akihiko Kitamura, Masahiko Kiyama, Takeo Okada, Kenji Maeda, Yoshinori Ishikawa and Takashi Shimamoto acquired the data and critically revised the manuscript. Tetsuya Ohira, Hironori Imano, Hiroyuki Noda, Kazumasa Yamagishi and Hiroyasu Iso conceived and designed the study, acquired and interpreted the data, and critically revised the manuscript.

**Funding** This work was supported in part by a grant from the Japanese Ministry of Education, Culture, Sports, Science and Technology (grant-in-aid for research C: 21590731).

**Competing interests** None.

**Ethics approval** Osaka Medical Center for Health Science and Promotion.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** There are no additional data.

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## APPENDIX 1

### CIRCS study collaborators

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 following CIRCS investigators contributed to this study: Masamitsu Konishi, Yoshinori Ishikawa, Akihiko Kitamura, Masahiko Kiyama, Takeo Okada, Kenji Maeda, Masakazu Nakamura MD, Masatoshi Ido, Masakazu Nakamura PhD, Takashi Shimamoto, Minoru Iida and Yoshio Komachi, Osaka Medical Center for Health Science and Promotion, Osaka; Yoshihiko Naito, Mukogawa Women's University, Nishinomiya; Tomonori Okamura, Keio University, Tokyo; Shinichi Sato, Chiba Prefectural Institute of Public Health, Chiba; Tomoko Sankai, Kazumasa Yamagishi, Kyoko Kirii, ChoyLye Chei, Kimiko Yokota and Minako Tabata, University of Tsukuba, Tsukuba; Mitsumasa Umesawa, Ibaraki Prefectural University of Health Sciences, Inashiki; Hiroyasu Iso, Tetsuya Ohira, Renzhe Cui, Hironori Imano, Ai Ikeda , Satoyo Ikehara, Isao Muraki and Minako Maruyama, Osaka University, Suita; Takeshi Tanigawa, Isao Saito, Katsutoshi Okada and Susumu Sakurai, Ehime University, Toon; Masayuki Yao, Ranryoen Hospital, Ibaraki; and Hiroyuki Noda, Osaka University Hospital, Suita, Ai Ikeda, National Cancer Center, Tokyo.

# Trends in sudden cardiac death and its risk factors in Japan from 1981 to 2005: the Circulatory Risk in Communities Study (CIRCS)

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*BMJ Open* 2012 2:
doi: 10.1136/bmjopen-2011-000573

Advance Publication by J-STAGE

J Epidemiol 2012
doi:10.2188/jea.JE20110109

Original Article

# Self-Reported Snoring Frequency and Incidence of Cardiovascular Disease: The Circulatory Risk in Communities Study (CIRCS)

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Received September 22, 2011; accepted December 15, 2011; released online March 10, 2012

## ABSTRACT

**Background:** Although associations between snoring and cardiovascular disease have been reported in several prospective studies, there is limited evidence from Asian populations. The objective of this study was to determine if there is an association between self-reported snoring frequency and the incidence of cardiovascular disease in Japanese.

**Methods:** The subjects were 2350 men and 4163 women aged 40 to 69 years who lived in 3 communities in Japan. All subjects were participants in the Circulatory Risk in Communities Study (CIRCS) and were followed for 6 years. Incidence of cardiovascular disease during the follow-up period comprised events of myocardial infarction, angina pectoris, sudden cardiac death and stroke.

**Results:** During the 6-year follow-up period, 97 participants (56 men and 41 women) had cardiovascular events. After adjustment for potential confounding factors, self-reported snoring frequency was associated with an increased risk of cardiovascular events among women but not men. The hazard ratios (95% CI) for cardiovascular events were 0.9 (0.4–2.0) for sometimes snoring and 2.5 (1.0–6.1) for everyday snoring in women and 0.7 (0.3–1.3) and 1.0 (0.5–2.1), respectively, in men. Further adjustment for body mass index attenuated the association in women; the respective hazard ratios for cardiovascular events were 0.9 (0.4–1.9) and 2.1 (0.9–5.4).

**Conclusions:** Self-reported habitual snoring was associated with increased risk of cardiovascular events among Japanese women. Overweight may partly mediate this association.

***Key words:*** cardiovascular events; obstructive sleep apnea; population-based study; prospective cohort study

## INTRODUCTION

Sleep-disordered breathing (SDB) is characterized by repeated episodes of apnea and hypopnea events during sleep.[1] Recently, SDB was identified as a risk factor for various disorders and diseases such as hypertension,[2–5] insulin and glucose abnormalities,[6] and cardiovascular disease.[7] Evidence has shown that self-reported snoring is a surrogate marker for SDB.[8] Associations of snoring and SDB with cardiovascular disease were examined cross-sectionally[9,10] in clinical and large-scale epidemiologic studies, most of which clearly showed an independent positive association between the 2 conditions, even after adjustment for potential confounding factors such as age, sex, and body mass index (BMI).[11]

This causal relationship has also been observed in studies of Western populations. As compared with non-snorers, the relative risk of developing cardiovascular disease among habitual snoring American women was 30% higher in the Nurses' Health Study,[12] and the risk among habitual and frequent snoring Finish men was 2.1-fold higher.[13] However, evidence from Asian populations is still very limited, and these results from Western studies cannot simply be extrapolated to Asian populations, because substantial differences exist between Asian and white populations, such

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as disparities in physique and prevalence of cardiovascular disease subtypes.[14]

In our previous large cross-sectional study,[15] we reported that the prevalence of snorers among Japanese men was about 70%, despite the low prevalence of obesity. The study revealed that alcohol consumption and cigarette smoking increased snoring risk among Japanese, especially among those who were not overweight. We also reported differences in the distribution of cardiovascular disease subtypes among Japanese versus whites, eg, among Japanese, the proportion of stroke was 2 times higher,[16] and the proportion of ischemic heart disease was one quarter, compared to the respective values reported in the United Kingdom and United States.[17] It is thus important to assess the risks of habitual snoring in Asians, because snoring is affected not only by obesity but also other factors, and Asian populations have different distributions of cardiovascular disease subtypes. We therefore examined the risk of cardiovascular events among habitual snorers compared with non-snorers in a large community-based prospective study of Japanese adults.

## METHODS

### Study subjects

Subjects were recruited from participants in the Circulatory Risk in Communities Study (CIRCS, see Appendix), a prospective community-based study of cardiovascular disease in 5 communities across Japan that was launched in 1963.[18] The subjects of the present sleep study comprised Japanese men and women aged 40 to 69, and none had previously received a diagnosis of SDB. Baseline data on snoring frequency and cardiovascular risk factors were obtained during annual surveys between 2001 and 2005 in the district of Yao City (midwestern suburban community, $n = 1994$), Ikawa (northeastern rural community, $n = 1446$), and between 2000 and 2004 in Kyowa (mideastern rural community, $n = 3209$). We excluded participants with incomplete data on sleep questionnaires ($n = 82$), those with missing data for BMI or other parameters ($n = 10$), and those with a history of ischemic heart disease ($n = 17$) or stroke ($n = 19$). A total of 2350 men and 4163 women were enrolled in the present study. All subjects had the protocol explained in detail and gave their informed consent for participation. The study protocol was approved by the Medical Ethics Committees of the University of Tsukuba.

### Determination of endpoint

Follow-up lasted until the end of 2009 for Ikawa, until the end of 2008 for Yao, and until the end of 2006 for Kyowa. The criteria for ischemic heart disease were modified from those established by the World Health Organization (WHO) Expert Committee.[19] Definite myocardial infarction was defined as characteristic severe chest pain (lasting for ≥30 min) together with the appearance of new abnormal and persistent Q or QS waves and/or consistent changes in cardiac enzyme activity. Probable myocardial infarction was defined as characteristic chest pain in the absence of electrocardiographic findings or findings related to enzyme activity. Angina pectoris was defined as repeated episodes of chest pain during effort, especially when walking, that usually rapidly disappeared after cessation of effort or use of sublingual nitroglycerin. Sudden cardiac death was defined as death within 1 hour of symptom onset, a witnessed cardiac arrest, or abrupt collapse not preceded by symptoms persisting 1 hour or longer. Stroke was defined as a focal neurological disorder of rapid onset that persisted at least 24 hours or until death. Determination of incident strokes was conducted based on clinical criteria.[20] A panel of 3 or 4 physician-epidemiologists who were blinded to data from the risk factor surveys made the final diagnoses for these suspected cases of ischemic heart disease and stroke. Cardiovascular disease included events related to ischemic heart disease (definite and probable myocardial infarction, angina pectoris, and sudden cardiac death) and stroke during the follow-up period.

For case ascertainment, histories of cardiovascular events were obtained from annual cardiovascular risk surveys, national insurance claims, ambulance records, reports of local physicians, and public health nurses. To confirm the diagnosis, all living patients were telephoned or visited to obtain a medical history, and their medical records were reviewed. For deaths, we obtained histories from families and reviewed medical records. The protocol has been described in detail elsewhere.[20,21]

### Risk factor measurements

At the annual cardiovascular surveys, each participant was asked about their snoring frequency. Answer options for the question "Did you snore during the past 3 months?" were almost every day, sometimes, never, and unknown. Information on smoking and drinking habits, menopausal status (for women), and measurements of blood pressure, serum glucose concentration, and physique were obtained according to the CIRCS protocol.[22] Hypertension was defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or antihypertensive treatment; diabetes mellitus was defined as fasting blood glucose of 126 mg/dl or higher, non-fasting blood glucose of 200 mg/dl or higher, or antihyperglycemic treatment; and hypercholesterolemia was defined as serum total cholesterol of 220 mg/dl or higher or treatment with lipid-lowering medication.

### Statistical analyses

Person-years for cardiovascular events were calculated as the sum of individual follow-up time until cardiovascular event, emigration, or the end of the follow-up period. Age- and community-adjusted and multivariable-adjusted hazard ratios (HRs) and 95% CIs for cardiovascular events were calculated according to baseline snoring frequency by using the Cox

proportional hazards model. The interaction of snoring with sex in relation to cardiovascular events was tested using their cross-product terms.

Confounding variables included age (continuous), BMI (continuous), alcohol consumption (never, ex-, <23 g and ≥23 g ethanol per day), cigarette smoking (never, ex-, <20 and ≥20 cigarettes per day), community (categorical), and menopausal status (for women; yes, no). To confirm the hypothesis that snoring induces cardiovascular events by increasing the risk of hypertension and metabolic disorders, we further adjusted for systolic blood pressure (continuous), use of antihypertensive medication (dichotomous), diabetes mellitus (dichotomous), and hypercholesterolemia (dichotomous). All statistical analyses were performed using SAS version 9.1 software (SAS Institute Inc., Cary, NC, USA). All statistical tests were 2-tailed, and $P$ values less than 0.05 were regarded as statistically significant.

## RESULTS

### Demographic characteristics at baseline

The mean (± SD) age of participants was 56.3 ± 8.3 years, mean BMI was 23.5 ± 3.2 kg/m$^2$, mean systolic blood pressure was 132.3 ± 18.6 mm Hg, and mean diastolic blood pressure was 80.4 ± 11.1 mm Hg.

Analysis revealed that 42.5% of participants had hypertension, 17.5% were using antihypertensive medication, 5.9% had diabetes mellitus, 44.7% had hypercholesterolemia, 37.6% were current drinkers, 21.1% were current smokers, and 69.1% of women were post-menopausal. Baseline demographic characteristics, by sex, are shown in Table 1.

**Table 1. Sex-specific mean values (SD) and prevalence of selected cardiovascular risk characteristics among 2350 men and 4163 women aged 40–69 years**

| | Men $n$ = 2350 | Women $n$ = 4163 | $P$ value |
|---|---|---|---|
| Age (years) | 57.5 (8.2) | 55.6 (8.3) | <0.001 |
| Body mass index (kg/m$^2$) | 23.9 (3.0) | 23.3 (3.3) | <0.001 |
| Systolic blood pressure (mm Hg) | 135.1 (17.6) | 130.7 (18.9) | <0.001 |
| Diastolic blood pressure (mm Hg) | 83.3 (10.9) | 78.7 (10.8) | <0.001 |
| Antihypertensive use (%) | 19.2 | 16.5 | 0.005 |
| Hypertension (%)[a] | 51.1 | 37.6 | <0.001 |
| Diabetes mellitus (%)[b] | 9.1 | 4.1 | <0.001 |
| Hypercholesterolemia (%)[c] | 34.5 | 50.5 | 0.28 |
| Alcohol consumption (%) | | | |
| never | 19.6 | 78.5 | <0.001 |
| ex-drinker | 7.3 | 4.0 | |
| <23 g ethanol per day | 22.6 | 15.1 | |
| ≥23 g ethanol per day | 50.6 | 2.4 | |
| Cigarette smoking (%) | | | |
| never | 17.0 | 90.5 | <0.001 |
| ex-smoker | 35.4 | 3.3 | |
| <20 cigarettes per day | 13.2 | 4.4 | |
| ≥20 cigarettes per day | 34.3 | 1.8 | |
| Menopause (%) | — | 69.1 | — |

[a]Hypertension was defined as blood pressure ≥140/90 mm Hg or current treatment.
[b]Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dl, non-fasting blood glucose ≥200 mg/dl, or current treatment.
[c]Hypercholesterolemia was defined as total cholesterol ≥220 mg/dl or current treatment.

### Prevalence of snoring and its correlates

The distribution of snoring frequency was as follows: 14.0% (23.9% in men and 8.5% in women) reported snoring almost every day, 46.7% (48.7% in men and 45.6% in women) reported snoring sometimes, 28.9% (20.7% in men and 33.6% in women) reported never snoring, and 10.3% (6.8% in men and 12.3% in women) reported that their snoring frequency as unknown. Sex-specific, age-adjusted characteristics classified according to snoring frequency are shown in Table 2. The mean values and proportions of baseline risk characteristics tended to be higher with increasing snoring frequency, except for mean age in men and women and prevalence of diabetes mellitus in men. As compared with women who reported a snoring frequency, those who answered "unknown" were 2.6 years older ($P$ < 0.001), 0.5 points lower in mean BMI ($P$ = 0.001), and 4.3% higher in the mean proportion of current smokers ($P$ < 0.001) in women. There was no significant difference among men.

### Incidence of cardiovascular events

During the 6-year median follow-up duration, 97 participants (56 men and 41 women) experienced cardiovascular events, including 30 (22 in men and 8 in women) incident cases of ischemic heart disease and 67 (34 in men and 33 in women) strokes. The numbers of ischemic heart disease and stroke events, according to snoring frequency and sex, are shown in Table 3.

### Association of snoring with cardiovascular events

As compared with never snorers, the age- and community-adjusted HR of ischemic heart disease and stroke combined was higher among female but not male everyday snorers; the HRs (95% CI) for cardiovascular events were 0.9 (0.5–2.0) for sometimes snoring and 2.6 (1.1–6.3) for everyday snoring in women and 0.7 (0.4–1.4) and 1.1 (0.5–2.2), respectively, in men (Table 3). These associations in men did not vary by age group (40–59 and 60–69 years), smoking status (current and non-current), or drinking status (current and non-current) (data not shown in table). After adjustment for age, community, and other confounding variables, the association between self-reported snoring frequency and cardiovascular events was unchanged in women: the HRs (95% CI) for cardiovascular events were 0.9 (0.4–2.0) for sometimes snoring and 2.5 (1.0–6.1) for everyday snoring in women (Table 3, Model 1). Further adjustment for BMI attenuated the association in women: the respective HRs for cardiovascular events were 0.9 (0.4–1.9) and 2.1 (0.9–5.4; Table 3, Model 2). To confirm

**Table 2. Sex-specific, age-adjusted, mean values (standard error) and prevalence of selected cardiovascular risk characteristics according to snoring frequency among 2350 men and 4163 women aged 40–69 years**

| Snoring frequency | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | Never *n* = 486 | Sometimes *n* = 1144 | Daily *n* = 561 | Unknown *n* = 159 | Never *n* = 1399 | Sometimes *n* = 1900 | Daily *n* = 352 | Unknown *n* = 512 |
| Age (years)[a] | 59.0 (0.4) | 57.1 (0.2) | 56.8 (0.3) | 57.9 (0.6) | 55.1 (0.2) | 55.2 (0.2) | 55.9 (0.4) | 57.9 (0.4) |
| Body mass index (kg/m$^2$) | 23.1 (0.1) | 23.8 (0.1) | 24.9 (0.1) | 23.6 (0.2) | 22.6 (0.1) | 23.6 (0.1) | 24.9 (0.2) | 22.8 (0.1) |
| Systolic blood pressure (mm Hg) | 133.4 (0.8) | 135.1 (0.5) | 136.5 (0.7) | 135.0 (1.3) | 128.3 (0.5) | 132.4 (0.4) | 133.5 (0.9) | 129.0 (0.8) |
| Diastolic blood pressure (mm Hg) | 81.9 (0.5) | 83.0 (0.3) | 85.3 (0.5) | 83.2 (0.9) | 77.0 (0.3) | 79.6 (0.2) | 80.8 (0.6) | 78.6 (0.5) |
| Antihypertensive use (%) | 18.6 | 17.6 | 22.1 | 22.8 | 13.3 | 18.1 | 22.3 | 15.0 |
| Hypertension (%)[b] | 48.3 | 49.3 | 56.8 | 52.2 | 31.5 | 41.4 | 46.0 | 34.8 |
| Diabetes mellitus (%)[c] | 9.2 | 9.2 | 8.8 | 9.3 | 3.4 | 4.3 | 6.2 | 3.8 |
| Hypercholesterolemia (%)[d] | 30.2 | 35.6 | 37.4 | 28.9 | 46.7 | 51.8 | 55.4 | 52.7 |
| Cigarette smoking (%) | | | | | | | | |
| never | 22.4 | 15.6 | 15.0 | 18.2 | 92.5 | 91.1 | 87.4 | 84.8 |
| ex-smoker | 34.5 | 35.8 | 36.1 | 33.7 | 2.6 | 3.2 | 4.3 | 5.2 |
| <20 cigarettes per day | 13.6 | 14.1 | 10.9 | 13.7 | 3.9 | 4.2 | 4.6 | 6.2 |
| ≥20 cigarettes per day | 29.5 | 34.6 | 38.1 | 34.3 | 1.0 | 1.6 | 3.7 | 3.8 |
| Alcohol consumption (%) | | | | | | | | |
| never | 23.2 | 19.0 | 17.4 | 20.2 | 82.5 | 77.8 | 72.5 | 74.8 |
| ex-drinker | 10.5 | 6.2 | 6.1 | 9.9 | 3.1 | 3.8 | 6.6 | 5.1 |
| <23 g ethanol per day | 21.9 | 24.2 | 21.0 | 18.4 | 13.2 | 16.1 | 16.1 | 16.1 |
| ≥23 g ethanol per day | 44.4 | 50.6 | 55.6 | 51.5 | 1.2 | 2.3 | 4.9 | 4.0 |
| Menopause (%) | — | — | — | — | 67.1 | 70.0 | 71.5 | 69.2 |

[a]Age was not included in the adjustment variables.
[b]Hypertension was defined as blood pressure ≥140/90 mm Hg or current treatment.
[c]Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dl, non-fasting blood glucose ≥200 mg/dl, or current treatment.
[d]Hypercholesterolemia was defined as total cholesterol ≥220 mg/dl or current treatment.

**Table 3. Sex-specific age- and community-adjusted and multivariable-adjusted hazard ratios (95% CI) for incidence of cardiovascular events according to snoring frequency**

| Snoring frequency | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | Never | Sometimes | Daily | Unknown | Never | Sometimes | Daily | Unknown |
| Person-years | 2792 | 7014 | 3427 | 951 | 8462 | 11 715 | 2119 | 3268 |
| Subjects (*n*) | 486 | 1144 | 561 | 159 | 1399 | 1900 | 352 | 512 |
| Incident cardiovascular event (*n*) | 15 | 22 | 16 | 3 | 13 | 16 | 8 | 4 |
| Incident ischemic heart disease (*n*) | 7 | 10 | 7 | 2 | 1 | 4 | 2 | 1 |
| Incident stroke (*n*) | 8 | 12 | 9 | 1 | 12 | 12 | 6 | 3 |
| Age- and community-adjusted HR (95% CI) | (Reference) | 0.7 (0.4–1.4) | 1.1 (0.5–2.2) | 0.7 (0.2–2.3) | (Reference) | 0.9 (0.5–2.0) | 2.6 (1.1–6.3) | 0.8 (0.2–2.4) |
| Model 1 HR (95% CI)[a] | (Reference) | 0.7 (0.3–1.3) | 1.0 (0.5–2.1) | 0.7 (0.2–2.3) | (Reference) | 0.9 (0.4–2.0) | 2.5 (1.0–6.1) | 0.8 (0.2–2.4) |
| Model 2 HR (95% CI)[b] | (Reference) | 0.6 (0.3–1.3) | 1.0 (0.5–2.0) | 0.6 (0.2–2.3) | (Reference) | 0.9 (0.4–1.9) | 2.1 (0.9–5.4) | 0.8 (0.2–2.4) |
| Model 3 HR (95% CI)[c] | (Reference) | 0.6 (0.3–1.2) | 0.9 (0.4–1.9) | 0.6 (0.2–2.1) | (Reference) | 0.8 (0.4–1.7) | 1.9 (0.8–4.9) | 0.7 (0.2–2.2) |

HR: hazard ratio; CI: confidence interval.
[a]Model 1 was adjusted for age, alcohol consumption, cigarette smoking, community, and, for women, menopausal status at baseline.
[b]Model 2 was adjusted for factors in Model 1 plus body mass index.
[c]Model 3 was adjusted for factors in Model 2 plus systolic blood pressure, antihypertensive medication use, diabetes mellitus, and hypercholesterolemia.

the hypothesis that snoring induces cardiovascular events by increasing the risk of hypertension and metabolic disorders, we further adjusted for systolic blood pressure, antihypertensive medication use, diabetes mellitus and hypercholesterolemia. The respective HRs (95% CI) for cardiovascular events were 0.8 (0.4–1.7) and 1.9 (0.8–4.9; Table 3, Model 3). The association between everyday snoring and risk of cardiovascular events was not significantly modified by sex ($P$ for interaction = 0.12). The risk of cardiovascular events associated with unknown snoring was not increased and was similar to the risk associated with sometimes snoring in both men and women.

## DISCUSSION

In the present prospective study, snoring frequency was associated with an increased incidence of cardiovascular events among community-dwelling middle-aged Japanese

women. This association was independent of age and other confounding factors. As compared with never snorers, 'everyday snoring' women had a 2.5-fold higher risk of cardiovascular events during 6 years of follow-up. The association of everyday snoring with cardiovascular events was attenuated after adjustment for BMI and after further adjustment for systolic blood pressure, antihypertensive medication use, diabetes mellitus, and hypercholesterolemia. This suggested that overweight partly mediated the association and that hypertension and metabolic abnormalities partly caused by snoring contribute to the risk of cardiovascular events in women who snore every day. This is the first study to show a relationship between habitual snoring and risk of cardiovascular events among a population in Asia, which has a low prevalence of obesity.

The biological mechanisms that link habitual snoring to the development of cardiovascular disease remain to be fully elucidated, but a number of mechanisms have been proposed. Habitual snoring is often accompanied by sleep apnea or hypopnea. Repetitive episodes of intermittent complete and partial airway collapse during sleep result in hypoxemia, hypercapnia, changes in intrathoracic pressure, and repeated arousal from sleep. Episodes of snoring and apneic events can cause acute hemodynamic changes[11] (such as increased cardiac output, enhanced cardiac arrhythmia, patent foramen ovale appearance,[23] increased intracranial pressure, and decreased cerebral blood flow),[24] increased platelet aggregation[25] and fibrinogen concentrations,[26] and decreased fibrinolysis, which directly affect the cardiovascular system. Abnormal metabolic conditions such as hypertension, diabetes mellitus, and hypercholesterolemia may also increase the risk of cardiovascular disease via elevation of sympathetic activation,[27,28] oxidative stress,[29] activation of the hypothalamic-pituitary-adrenal axis due to sleep fragmentation,[30,31] and endothelial dysfunction.[32]

In the present study, habitual snorers were more likely to be overweight, hypertensive, and diabetic than non-snorers, and the association between snoring frequency and the risk of cardiovascular events was attenuated when we further adjusted for these factors. This suggests that overweight partly mediates the association and that habitual snoring increases the risk of cardiovascular events partly through increasing the risk of hypertension and metabolic disorders.

The present results are consistent with those from studies of Western women[12] but not men[13]; however, this study is the first to note an independent association in a population with a different distribution of cardiovascular disease subtypes and a low prevalence of obesity. Among Japanese, 70% of cardiovascular events are strokes—whereas in Western countries ischemic heart disease is the largest cause of such events—and the risk factors for cardiovascular events among populations with low obesity are hypertension and metabolic abnormalities rather than overweight.[33]

In contrast to the significant association of habitual snoring with cardiovascular events in women, no such association was observed in men. Large population-based prospective studies of middle-aged men,[13] women,[12] and a population of men and women aged 20 years or older[34] have reported positive associations between habitual snoring and cardiovascular events. However, no study has reported a sex difference in the association. Recent reports from the Sleep Heart Health Study (a large population-based study of American residents aged 40 or older) have noted sex differences in the association between SDB, as defined by the apnea-hypopnea index (AHI), and the risk of coronary heart disease, heart failure, and stroke.[35,36] The multivariable HRs associated with a 10-unit increase in AHI were 1.1 (1.0–1.3) for incident heart failure in men and 1.1 (1.0–1.2) for incident coronary heart disease in men aged 70 years or younger, whereas no such associations were observed in women.[35] Similarly, the multivariable HR for ischemic stroke incidence was 2.9 (1.1–7.4) in men and 1.2 (0.7–2.2) in women for the highest (>19) as compared with the lowest (≤4) AHI quartiles.[36] The reasons for the present lack of association between habitual snoring and risk of cardiovascular events in men are unknown. We found no association in men when the analysis was stratified by age, smoking, or drinking status. Further research is necessary to elucidate this sex difference.

The strengths of the present study include the use of systematic surveillance of cardiovascular events and complete data collection on incident stroke and ischemic heart disease, including sudden cardiac death. Our large population-based prospective cohort study enabled us to examine sex-specific associations between snoring frequency and risk of cardiovascular events and provides the first evidence of a positive association between these conditions in an Asian population.

The limitations of the present study are as follows: first, our data on snoring frequency were obtained from a self-reported questionnaire, so lack of awareness of snoring or the absence of a sleep partner may have resulted in misclassification. However, in our simultaneous subsample study (1564 men and 2806 women aged 40–69 years) using a 3% oxygen desaturation index (ODI) measured by pulse oxymetry (PULSOX-3Si; Minolta, Osaka, Japan) during 1 night of sleep at a participants' homes, we found that the proportion of SDB (ODI ≥5 events/hours) was 22% in never snorers, 36% in sometime snorers, and 50% in everyday snorers among men. The respective proportions for women were 9%, 19%, and 34%. Thus, self-reported snoring seemed to be reliable. Second, data on sleep duration were not obtained in this study. According to a recent meta-analysis, both short (≤5–6 hours per night in most studies) and long sleep duration (≥8–9 hours per night in most studies) were associated with increased risks of coronary heart disease and stroke.[37] Further studies of the effects of sleep quality and quantity on the risk of cardiovascular disease will be necessary to confirm an effect of habitual snoring.

In summary, the present large cohort study showed that habitual snoring was associated with an increased risk of cardiovascular events among community-dwelling middle-aged Japanese women and that overweight, snoring-related hypertension, and metabolic disorders may partly mediate the association. The present study provides epidemiologic evidence for physicians and other health professionals that habitual snoring should be considered in the prevention of cardiovascular disease among middle-aged Japanese.

## ACKNOWLEDGMENTS

This was not an industry-funded study. This study was supported in part by grants from the Japanese Ministry of Education, Culture, Sports, Science and Technology (Grant-in-Aid for Research B, 14370132); a Health and Labor Sciences Research Grant (Clinical Research for Evidence Based Medicine, J060701211), Ministry of Health, Welfare and Labor; and a University Research Project Research Grant (B), University of Tsukuba.

Conflicts of interest: None declared.

## APPENDIX

### CIRCS investigators

The Circulatory Risk in Communities Study (CIRCS) is a collaborative study managed by the Osaka Medical Center for Health Science and Promotion, Osaka University, University of Tsukuba, and Ehime University. CIRCS investigators who contributed to this study are as follows: Hiroyasu Iso, Tetsuya Ohira, Hironori Imano, Renzhe Cui, Ai Ikeda, Hiroyuki Noda, Satoyo Ikehara, Isao Muraki, and Kotatsu Maruyama, Osaka University, Suita; Tomoko Sankai and Kazumasa Yamagishi, Mitsumasa Umesawa, Choy-Lye Chei, Kimiko Yokota, and Minako Tabata, University of Tsukuba, Tsukuba; Masamitsu Konishi, Yoshinori Ishikawa, Masakazu Nakamura, Akihiko Kitamura, Masahiko Kiyama, Takeo Okada, Kenji Maeda, Masatoshi Ido, Masakazu Nakamura, Takashi Shimamoto, Minoru Iida, and Yoshio Komachi, Osaka Medical Center for Health Science and Promotion, Osaka; Shinichi Sato, Chiba Prefectural Institute of Public Health, Chiba; Takeshi Tanigawa, Isao Saito, Susumu Sakurai, and Shinichi Hitsumoto Ehime University, Toon; Masayuki Yao, Ranryoen Hospital, Ibaraki.

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Atherosclerosis xxx (2011) xxx–xxx

Contents lists available at ScienceDirect

Atherosclerosis

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

# C-reactive protein levels and risk of stroke and its subtype in Japanese: The Circulatory Risk in Communities Study (CIRCS)

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ARTICLE INFO

*Article history:*
Received 12 July 2010
Received in revised form 24 February 2011
Accepted 1 March 2011
Available online xxx

*Key words:*
hs-CRP
Stroke
Nested case–control study
Japanese

ABSTRACT

*Background:* Epidemiological studies have shown high-sensitive C-reactive protein (hs-CRP) to predict cardiovascular disease. However, there are only limited studies on the effects of hs-CRP levels on risk of stroke especially stroke subtypes. We examined associations of hs-CRP levels with risks of total stroke and its subtypes.

*Methods:* A prospective nested case–control study of Japanese 40–85 years of age was conducted using frozen serum samples collected from 13,521 men and women who participated in cardiovascular risk surveys from 1984 to 2001 for one community and 1989 to 1998 for the other two communities under the Circulatory Risk in Communities Study (CIRCS). Three control subjects per case were matched by sex, age, community, year of serum storage, and fasting status.

*Results:* By the end of 2005, we identified 261 incident strokes (165 ischemic strokes and 96 hemorrhagic strokes). There was a positive association between hs-CRP and incidence of incidence of total stroke, ischemic stroke and lacunar infarction. After further adjustment for known cardiovascular risk factors, these relationships remained statistically significant. The multivariable conditional odds ratios associated with 1-SD increment of log-transformed hs-CRP were 1.17(1.01–1.35) for total stroke, 1.27(1.06–1.52) for ischemic stroke, and 1.24(1.00–1.55) for lacunar infarction. The association between hs-CRP levels and incidence of ischemic stroke did not vary by sex, age, body mass index and smoking. No associations were found between hs-CRP levels and risk of hemorrhagic stroke.

*Conclusions:* hs-CRP predicts the incidence of total and ischemic strokes among middle-aged Japanese men and women.



Inflammatory processes contribute to the initiation of atherosclerotic lesions, as well as the development of acute ischemic syndrome [1–3]. C-reactive protein, an acute-phase reactant and a marker of systemic inflammation has been associated with an increased risk of cardiovascular disease [4–7]. Previous prospective studies also reported that high sensitive C-reactive protein (hs-CRP) predicts coronary heart disease [8,9] and ischemic stroke [8,10,11].

Japanese populations have a higher incidence of stroke [12] and a lower concentration of CRP than western populations [13–16]. The JACC study [17] reported that median CRP levels in the top quartile of Japanese (1.5–1.8 mg/L) were close to those in the bottom tertile of Caucasians, Blacks and Hispanics (approximately 1.0 mg/L) [18,19]. Whether the association between elevated hs-CRP levels and risk of stroke in a low hs-CRP population is of research interest. However, only a few prospective studies in Japan have examined the association between elevated hs-CRP

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doi:10.1016/j.atherosclerosis.2011.03.001

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 $\chi^2$ 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 $\chi^2$ test for categorical variables. The conditional odds ratios (OR) and 95% confidence intervals (CI) for total stroke, and stroke sub-

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 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.

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