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Trends in Sudden Cardiac Death and Its Risk Factors in Japan from 1981 to 2005: time-trend analysis from the Circulatory Risk in Communities Study (CIRCS)

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Article summary

Article focus

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

Key messages

- Age- and sex-adjusted incidence of SCD for four general Japanese populations decreased from 1981-1985 to 1991-1995, and plateaued after 1996, corresponding to the trend for the prevalence of hypertension.
- We suggest that continuous surveillance will be needed to clarify future trends for the incidence of SCD and its risk factors in Japan.

The strength and limitation

- We analyzed trends for SCD using population-based data from a large number of participants in a long-term observational study and conducted annual cardiovascular risk factor surveys ascertained the trends for predisposing risk factors of SCD.
- We only examined the incidence of SCD for the age range of 30-84 years old.
- Clinical features and neuroimaging reports were used to exclude death due to stroke, some cases may have been misclassified, especially in the case of an out-of-hospital death.

Abstract

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

Design and Setting - Population-based longitudinal study. Surveillance of men and women for the SCD incidence and risk factors was conducted from 1981 to 2005.

Subjects - The surveyed population was all residents of men and women aged 30 to 84 years in three rural and an urban communities in Japan.

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

Results - Age- and sex-adjusted incidence of SCD decreased from 1981-1985 to 1991-1995, and plateaued thereafter; the annual incidence per 100,000 person in the 5 time periods was 64.6, 57.8, 33.4, 30.2, and 35.6, respectively. Age- and sex-adjusted prevalence of hypertension decreased from 1981-1985 to 1991-1995, and plateaued thereafter, which corresponded to the SCD trend. The mean levels of body mass index for men and of total cholesterol and the prevalence of diabetes mellitus increased for both sexes from 1981 to 2005.

Conclusions - The incidence of SCD decreased from 1981 to 1995 but unchanged from 1995 to 2005, corresponding to the hypertension trend. Continuous surveillance is necessary to clarify future trends for SCD in Japan, because of increasing trends for other cardiovascular risk factors such as overweight for men and high total cholesterol and diabetes mellitus for both sexes.

In the United States, estimates of the annual number of sudden cardiac death (SCD) 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 per 100,000 person was 410.6 for men and 274.6 for women in 1998 among US residents aged≥35 years [3]. Several population-based studies have reported on the incidence of SCD among Japanese [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 from a sample from Suita City (census population: approximately 340,000) that in persons aged 20-74, the incidence of SCD was 31 (men = 45, women = 20) per 100,000 people. Information on SCD was determined using police records [5]. This suggests that the incidence of SCD in Japan is about one-fifth of that in the United States [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 United States [6,9,10]: this difference might explain the difference in the incidence of SCD between Japan and the United States. However, Kitamura et al. reported a significant increase in the incidence of CHD among middle-aged urban Japanese men from 1980-87 to 1996-2003 [11]. Therefore we expected that 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.

Therefore 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 men and women.

Methods

The CIRCS is a population-based study of cardiovascular risk factors, disease incidence, and their respective trends in Japanese communities. Details of the study design and procedures of CIRCS have been reported elsewhere [11-14]. Briefly, the subjects were Japanese men and women who lived in a north-eastern rural community, Ikawa (1995 census population = 6,206), a south-western rural community, Noichi (1995 census population = 15,828), a central rural community, Kyowa (1995 census population = 17,322), and a south-western urban suburb, the Minami-Takayasu district of Yao (1995 census population = 23,654). All analyses were limited to men and women aged 30 to 84 years because the number of SCD cases aged <30 years was too small (<1%), and for many cases aged ≥85 years their causes of death were difficult to be identified. 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. e total survey populations in Ikawa were 3,997 in 1985, 4,167 in 1995, and 4,172 in 2000, while the corresponding totals were: 13,655, 14,885, and 15,923 in Yao; 8,149, 9,600, and 10,592 in Noichi; and 9,614, 10,801, and 10,948 in Kyowa.

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

We included in our study all SCD events that occurred between January 1, 1981 and December 31, 2005. The morbidity surveillance collected disease data on men and women aged 30-84 in the four communities and used six sources to examine candidate cases: national insurance claims, reports by local physicians, ambulance records, death certificates, reports by public health nurses and health volunteers, and cardiovascular risk surveys (Figure 1) [11-14]. For confirmation of the diagnoses, we also obtained histories from next of kin and reviewed medical records in local hospitals.

The criteria for CHD were modified from those of the World Health Organization Expert Committee [16]. The indication for definite myocardial infarction (MI) was typical, severe chest pain (lasting at least 30 minutes and without definite non-ischemic 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-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 nitroglycerin [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 hour of symptom onset or within 24 hours of having been observed alive and symptom-free. We excluded candidate cases if they survived for over 24 hours 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 with MI, it grouped SCD with MI (SCD_MI), and others were grouped as SCD without MI (SCD_NMI). In addition, SCD cases were divided into two groups stratified by time of symptom onset. If the time of symptom onset was within 1 hour, they were categorized as SCD1, and if it occurred within 24 hours but they were not SCD1, they were categorized as SCD1-24. Finally, SCD cases were divided into two groups based on place of death [3]. If the place of death was in emergency room (ER) or a hospital, the case was categorized as SCD_ER, and if it was outside of a hospital, it was categorized as SCD_NER (Table 1).

Age- and sex-adjusted annual incidence of SCD was calculated from the number of new cases per 100,000 person during the five survey periods, 1981 to 1985, 1986 to 1990, 1991 to 1995, 1996 to

2000, and 2001 to 2005, in the aforementioned four Japanese communities.

Cardiovascular risk factors were ascertained for the population sample during each of the five survey periods. The participants in the risk factors surveys were recruited from all residents aged 30-84 in the four communities. The surveys were conducted for the purpose of promoting primary prevention of cardiovascular disease and stroke.

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

To calculate age- and sex-adjusted incidence, we employed the direct standardization method using the age and sex distributions of the Japanese national model population from 1985. Linear trends in incidence were examined with the chi-square test. Sex-specific age-adjusted means of risk factors were estimated by analysis of covariance, and age-adjusted prevalence by the direct method of standardization.

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-square test for trends. All statistical analyses were performed with the SAS System for Windows (Version 9.1, SAS Institute, Cary, NC).

Results

In the present study, 471 individuals 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 SCD (in parenthesis, SCD_MI) was presented according to the time of symptom onset and the place of death (Supplementary material).

As shown in Table 1, age- and sex-adjusted incidence of SCD decreased from 1981-1985 to 1991-1995, however plateaued after 1996 (p for trend was $p<0.01$ from 1981-1985 to 1991-1995, and $p=0.69$ from 1991-1995 to 2001-2005). The annual incidence of SCD per 100,000 person during the five periods were 64.6, 57.8, 33.4, 30.2 and 35.6, 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 cases. The features of the trends for the age groups 30-64, 65-74 and 75-84 were similar to those of the overall trend.

A similar trend was observed for age- and sex-adjusted incidence of CHD; the annual incidence of CHD per 100,000 person was 84.7, 87.0, 66.3, 48.2 and 55.9, respectively. The corresponding annual incidence of MI per 100,000 person was 47.7, 58.9, 48.8, 33.3 and 44.4 (not shown in Table).

The incidence of SCD was two to three times higher for men than for women, while age- and sex-adjusted annual incidence of SCD per 100,000 person during the five time periods were 93.5, 82.0, 44.5, 45.0 and 54.2 for men and 43.7, 39.5, 23.4, 16.7 and 18.2 for women (Table 1).

We further analyzed 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- and sex-adjusted annual incidence of SCD per 100,000 person was 13.4, 15.5, 11.8, 5.0 and 8.1 for SCD_MI and 51.3, 42.3, 21.7, 25.2 and 27.6 for SCD_NMI. The calculation of the incidence stratified by the time of symptom onset yielded age- and sex-adjusted annual incidence per 100,000 person of 23.4, 19.7, 10.5, 8.8 and 14.5 for SCD1, and 41.3, 38.1, 22.9, 21.5 and 20.4 for SCD1-24. The calculation of the incidence stratified by the place of death yielded the age- and sex-adjusted annual incidence per 100,000 person of 34.9, 25.1, 10.7, 10.9 and 10.2 for SCD_NER, and 29.8, 32.7, 22.8, 19.4 and 25.5 for SCD_ER. These trends showed similar

features to those of the overall trend. We also examined the incidences stratified by community, and found these trends to be similar to the overall trend (data not shown).

Moreover, we estimated the national SCD incidence in 2009 by using the results from this study. For this estimation, we multiplied the age- and sex-specific populations in 2009 by the age- and sex-specific incidences of SCD from 2001 to 2005. For the population aged 85 or over, we used the incidence of SCD for aged 75 to 84. We predicted the number of cases of SCD in Japan to be at least 49,500 cases in 2009.

As shown in Table 2, the overall trends for 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 both 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 both current smoking and heavy drinking decreased constantly from 1981-1985 to 2001-2005 (p for trend 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, respectively) for both sexes. The prevalence of left ventricular hypertrophy dramatically decreased from 1981-1985 to 2001-2005 (p for trend was <0.01, for both sexes). Additionally, we examined the risk factor stratified by community, and found the same trends (not shown in table).

Discussion

In this longitudinal community-based study from 1981 to 2005, we found that the age- and sex-adjusted annual incidence of SCD decreased from 1981 to 1995, and plateaued thereafter. This

trend was similarly observed when SCD was stratified by the presence of MI, in which MI constituted approximately 20 to 35% of all SCD, the time of symptom onset, in which SCD within 1 hour constituted approximately 30% to 45% of all SCD, and the place of death, in which SCD in emergency room or hospital constituted approximately 45% to 70% of all SCD. Although the incidence of SCD was higher for men than for women consistent with previous reports [3,20], trends for the incidence of SCD did not vary according to age or sex. Since Japan is a rapidly aging country, the number of SCD in Japan, although much lower than in the United States [3], may increase in the future due to an increased elderly population.

Several population-based studies have previously reported the incidence of SCD among Japanese. 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 1,110 for men and 1,527 for women, which made it difficult to evaluate trends in the incidence of SCD [7]. Baba et al. reported that the annual SCD incidence was 45 per 100,000persons for men and 20 per 100,000persons for women for subjects aged 20-74 in Suita City in 1992 [5]. Our study showed similar age-adjusted annual incidence of SCD (53 per 100,000 person for men and 18 per 100,000 person for women aged 30-84) 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 the present study, SCD accounts for 10% of all CHD deaths, while CHD accounted for 25% of all SCD cases which was generally consistent with the finding from a previous Japanese population-based study [20]. The lower incidence [11] and mortality [9,10,23] from CHD in Japan than in the United States probably correspond to the lower incidence of SCD in Japanese.

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 for ages 20 years and more in 1988-1998

[24], 45.8 per 100,000 population for ages 35-64 years in 1994-1996 [25], and 49.7 per 100,000 person for ages 20 years and more in 1996-1998 [26]. In the present study, the age-adjusted annual incidence of MI for ages 30-84 years was 33.3 to 58.9 per 100,000 person 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 1990-92 to 1999-2001 in the Takashima AMI Registry [26]. Furthermore, Kitamura et al. reported a significant increase in the of CHD from 1980-87 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 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.

We found in the data presented here 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, elderly age, male sex, smoking, heavy drinking, overweight, diabetes and left ventricular hypertrophy [3]. However, the risk factors for Japanese have not been so thoroughly elucidated. Our study found that mean systolic BP decreased from 1981 to 2005, but mean diastolic BP and the prevalence of hypertension increased from 1995 to 2005. Hypertension may be one of the most important risk factors for SCD among Japanese [20], and we previously showed that hypertension was associated with the incidence of SCD (the multivariable-adjusted OR was 1.51(95%CI, 1.04 to 2.18) [29]) in the CIRCS. Therefore, the trend for hypertension is likely to correspond to the trend for the incidence of SCD. Further, the SCD incidence decreased dramatically from 1981 to 1995, and this may be due to a large reduction in the prevalence of heavy drinking and current smoking. Meanwhile, the plateaued trend for SCD incidence from 1995 or later could be partly explained by potential adverse effects of increased total cholesterol levels for men and women and the increased prevalence of

overweight for in men and of diabetes mellitus for men and women.

The strength of the present study is that we analyzed trends for SCD using population-based data, including both 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 for predisposing risk factors of SCD.

Nonetheless, our study has a few limitations. First, we only examined the incidence of SCD for the age range of 30-84 years old. However the frequency of SCD among persons < 30 years old was less than 1 % even in the United States [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 in the case of an out-of-hospital death. Such misclassification may well have affected the changes in the incidence of SCD occurred out-of-hospital.

In conclusion, age- and sex-adjusted incidence of SCD for a general Japanese population decreased from 1981-1985 to 1991-1995, and plateaued after 1996, corresponding to the trend for the prevalence of hypertension. The prevalence of some risk factors for SCD such as current smoking and heavy alcohol drinking has declined for men, but the prevalence of overweight for men, and of high total cholesterol and diabetes mellitus for men and women has increased. We suggest that continuous surveillance will be needed to clarify future trends for the incidence of SCD and its risk factors in Japan.

Table1. Trends for age- and sex- adjusted incidence of sudden cardiac death per 100,000 person among 30 to 84 year-old men and women in four Japanese general populations from 1981 to 2005, CIRCS

	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	p for trend
Total						
No of cases	114	101	83	76	97	
Age- and sex-adjusted incidence (Incidence/100,000 person)	64.6	57.8	33.4	30.2	35.6	< 0.01
Age- and sex-adjusted incidence (Incidence/100,000 person)						
30-64 y	20.6	19.7	14.9	12.3	16.8	0.367
65-74 y	191.3	100.1	77.5	80.1	100.1	0.004
75-84 y	445.9	526.8	212.3	189.2	177.2	< 0.01
Men						
No of cases	70	61	49	50	67	
Age- and sex-adjusted incidence (Incidence/100,000 person)	93.5	82.0	44.5	45.0	54.2	< 0.01
Age- and sex-adjusted incidence (Incidence/100,000 person)						
30-64 y	33.9	31.6	22.8	21.4	27.4	0.629
65-74 y	174.8	118.8	95.8	133.6	170.6	0.759
75-84 y	795.7	742.3	255.2	206.1	204.7	< 0.01
Women						
No of cases	44	40	34	26	30	
Age- and sex-adjusted incidence (Incidence/100,000 person)	43.7	39.5	23.4	16.7	18.2	< 0.01
Age- and sex-adjusted incidence (Incidence/100,000 person)						
30-64 y	9.3	9.4	7.1	3.3	6.3	0.247
65-74 y	203.0	86.7	62.8	34.6	35.0	< 0.01
75-84 y	214.8	381.1	181.0	176.0	158.3	0.036

Table 2. Trends for age- and sex-adjested cardiovascular risk characteristics among 30 to 84 year-old men and women in four Japanese general populations from 1981 to 2005, CIRCS

	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	*p* for trend
Age-adjusted, mean or percent						
Men						
Number	5350	4992	4836	4432	4900	
Age, year	54	55	58	59	60	
Systolic blood pressure, mmHg	136	134	132	133	132	<0.01
Diastolic blood puressure, mmHg	81	81	81	82	82	<0.01
Antihypertensive medication, %	17.9	16.8	15.6	16.1	18.5	0.427
Hypertention, %	44.3	39.1	35.3	37.8	38.3	<0.01
Body mass index, kg/m^2	22.7	22.9	23.2	23.4	23.8	<0.01
Total cholestrol, mg/dl	187	192	195	202	205	<0.01
%						
Overweight (BMI>=25kg/m^2)	25.1	28.2	30.5	34.8	33.9	<0.01
Total cholestrol>=5.69 mmol/L	16.7	19.9	22.7	28.5	30.9	<0.01
Diabetes mellitus	4.2	6.3	6.6	7.0	8.7	<0.01
Heavy drinking(ethanol intake >=46g/day)	31.0	27.6	26.1	25.0	21.1	<0.01
Current smoking	60.6	56.2	52.6	49.2	45.0	<0.01
ECG findings						
Atrial fibrillation	1.2	1.4	1.3	1.1	1.2	0.549
Ventricular premature contraction	2.8	2.7	3.1	2.5	2.3	0.063
Supraventricular premature contraction	3.1	4.3	4.0	3.3	3.4	0.628
Major ST-T abnormality	4.7	4.1	3.6	3.8	4.0	0.021
Minor ST-T abnormality	13.4	10.9	14.2	12.6	12.4	0.711
PQ prolonged	1.4	1.1	1.5	1.3	1.1	0.492
Complete/incomplete right bundle branch block	5.2	5.1	5.5	5.9	6.6	<0.01
Wide QRS	3.0	3.0	3.3	3.7	4.1	<0.01
Abnomal Q wave	0.5	0.7	0.6	0.6	0.7	0.637
Left ventricular hypertrophy	26.7	25.4	20.6	17.4	15.3	<0.01
Women						
Number	7949	7781	7975	7466	8082	
Age, year	53	54	55	57	57	
Systolic blood pressure, mmHg	134	131	130	129	128	<0.01
Diastolic blood puressure, mmHg	79	78	78	79	77	<0.01
Antihypertensive medication, %	17.9	17.4	16.0	15.4	17.1	0.002
Hypertention, %	39.4	34.8	31.6	31.6	31.5	<0.01
Body mass index, kg/m^2	23.2	23.2	23.1	23.1	23.0	<0.01
Total cholestrol, mg/dl	200	205	206	213	215	<0.01
%						
Overweight (BMI>=25kg/m2)	31.8	31.2	30.6	29.9	25.9	<0.01
Total cholestrol>=5.69 mmol/L	28.1	31.8	33.5	41.3	42.6	<0.01
Diabetes mellitus	2.5	3.6	3.2	3.4	3.8	<0.01
Heavy drinking(ethanol intake >=46g/day)	0.5	0.4	0.4	0.5	0.6	0.417
Current smoking	7.7	7.0	6.9	7.2	8.3	0.273
ECG findings						
Atrial fibrillation	0.6	0.6	0.4	0.3	0.3	<0.01
Ventricular premature contraction	1.9	2.2	1.7	1.9	2.2	0.785
Supraventricular premature contraction	2.4	2.6	3.0	2.8	2.8	0.169
Major ST-T abnormality	6.6	6.1	5.2	4.4	4.9	<0.01
Minor ST-T abnormality	23.5	20.0	22.4	21.1	18.7	<0.01
PQ prolonged	0.6	0.5	0.5	0.5	0.4	0.277
Complete/incomplete right bundle branch block	3.5	3.4	3.2	3.0	3.2	0.063
Wide QRS	1.5	1.6	1.7	1.5	1.6	0.854
Abnomal Q wave	0.1	0.2	0.2	0.2	0.4	0.016
Left ventricular hypertrophy	10.4	9.0	7.3	5.1	4.4	<0.01

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Author's individual contributions

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.

Appendix

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 CIRCS investigators who contributed to this study are as follows: 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, National Cardiovascular Center, Suita; Shinichi Sato, Chiba Prefectural Institute of Public Health, Chiba; Tomoko Sankai,

Kazumasa Yamagishi, Kyoko Kirii, Mitsumasa Umesawa, ChoyLye Chei, Kimiko Yokota and Minako Tabata, University of Tsukuba, Tsukuba; 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.

Data sharing statement

There is no additional data available.

Figure Legends

Figure 1. Determination of sudden cardiac death (SCD)

Figure 2. Trends for age- and sex-adjusted annual incidence of sudden cardiac death, 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 person among men and women aged 30-84 in four general Japanese populations from 1981 to 2005, CIRCS. SCD with MI (SCD_MI) and SCD without MI (SCD_NMI), SCD within 1 hour (SCD1) and SCD between 1 and 24 hours (SCD1-24). SCD in emergency room or a hospital (SCD_ER) and SCD outside of a hospital (SCD_NER).

Figure 1

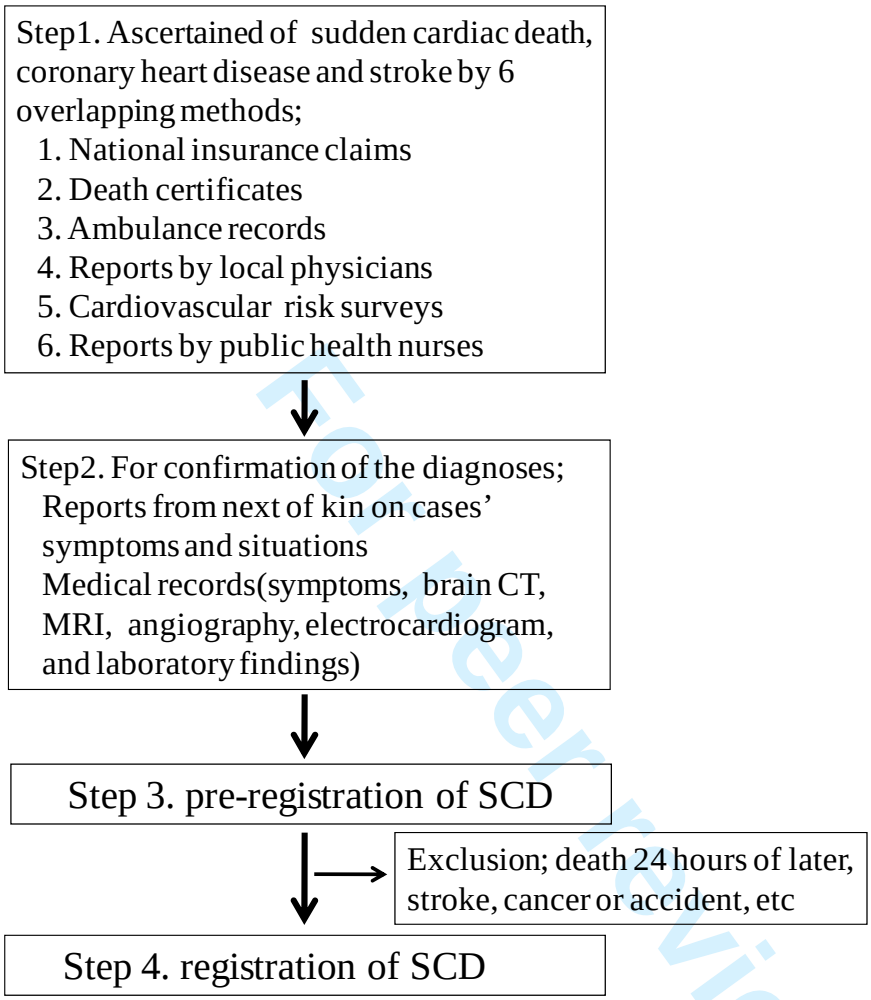
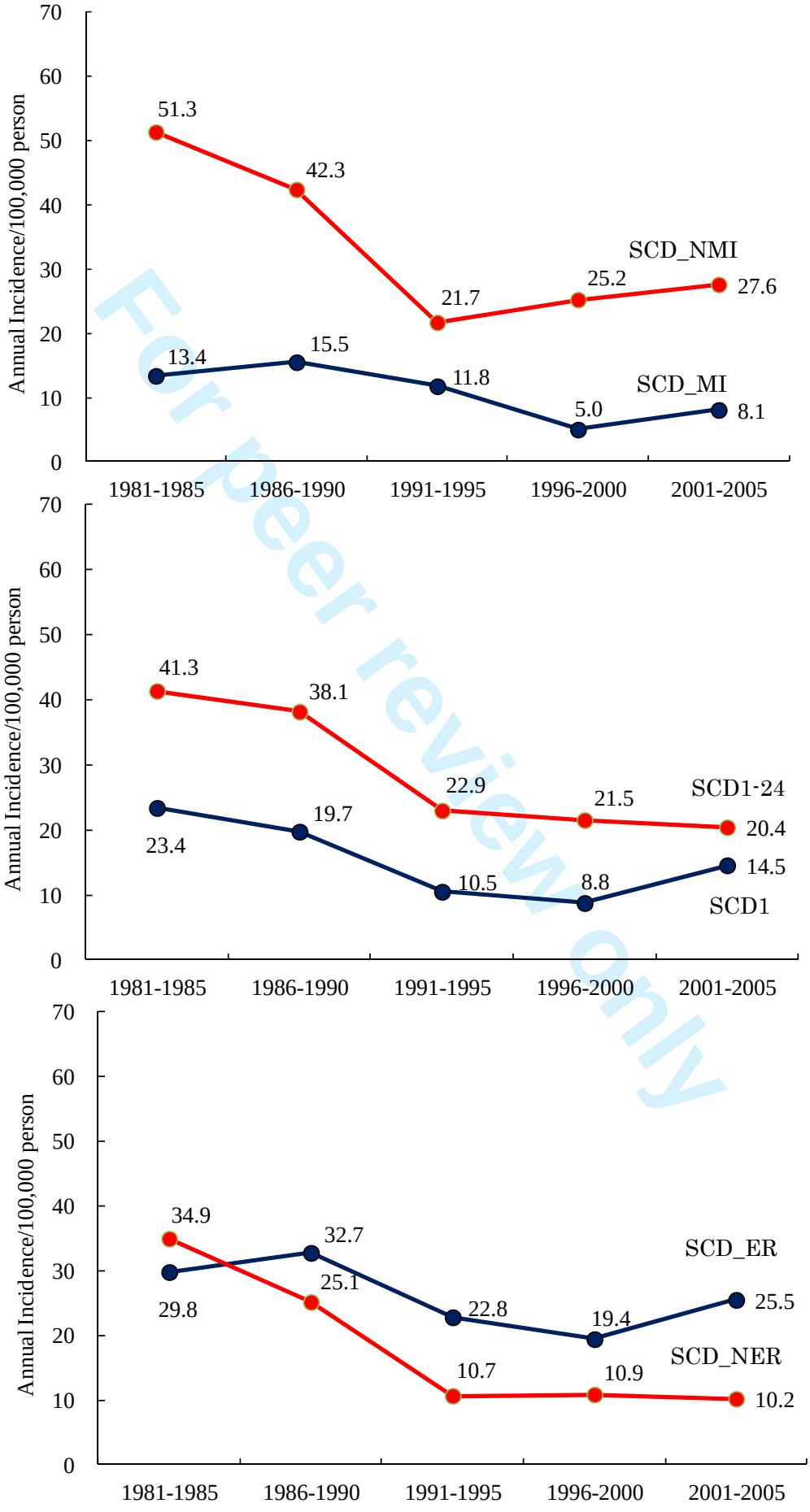


Figure 2



STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	5,6,7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	5,figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	8,table1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9,10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Trends in Sudden Cardiac Death and Its Risk Factors in Japan from 1981 to 2005: time-trend analysis from the Circulatory Risk in Communities Study (CIRCS)

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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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Key words: sudden cardiac death, incidence, general population, Japanese

Word counts:3,362words

Abstract

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

Design and Setting - Population-based longitudinal study. Surveillance of men and women for the SCD incidence and risk factors was conducted from 1981 to 2005.

Subjects - The surveyed population was all residents of men and women aged 30 to 84 years in three rural and an urban communities in Japan.

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

Results - Age- and sex-adjusted incidence of SCD decreased from 1981-1985 to 1991-1995, and plateaued thereafter; the annual incidence per 100,000 person-year in the 5 time periods was 76.0, 57.9, 39.3, 31.6, and 36.8, respectively. The prevalence of hypertension decreased from 1981-1985 to 1991-1995, and plateaued thereafter for both men and women. The age- adjusted prevalence of current smoking for men decreased, while that of diabetes mellitus for both sexes increased from 1981-1985 to 2001-2005.

Conclusions - The incidence of SCD decreased from 1981 to 1995 but unchanged from 1995 to 2005, which corresponded primarily to the trend for prevalence of hypertension. The continuous surveillance is necessary to clarify future trends for SCD in Japan, because of an increasing trend for diabetes mellitus.

Article Summary

Article focus

□The incidence rate of coronary heart disease among urban middle-aged Japanese men has increased from 1990s to 2000s, therefore the incidence of sudden cardiac death (SCD) for Japanese

individuals may have increased in recent decades.

□This is the first study to examine recent trends in SCD in Japan

Key messages

□Age- and sex-adjusted incidence of SCD among men and women aged 30 to 84 years in four Japanese communities decreased from 1981-1985 to 1991-1995, and plateaued after 1996, which corresponded primarily to the trend for prevalence of hypertension

□Continuous surveillance is necessary to clarify future trends for SCD in Japan, because of an increasing trend for diabetes mellitus.

The strength and limitation

□We analyzed trends for SCD using population-based data from a large number of participants in a long-term observational study and conducted annual cardiovascular risk factor surveys ascertained the trends for predisposing risk factors of SCD.

□We only examined the incidence of SCD for the age range of 30-84 years old, but not other ages.

□Clinical features and neuroimaging reports were used to exclude death due to stroke, some cases may have been misclassified, especially in the case of an out-of-hospital death.

In the United States, estimates of the annual number of sudden cardiac death (SCD) 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 per 100,000 person was 410.6 for men and 274.6 for women in 1998 among US residents aged≥35 years [3]. Several population-based studies have reported on the incidence of SCD among Japanese [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 from a sample from Suita City (census population: approximately 340,000) that in persons aged 20 to74 years, the incidence of SCD was 31 (men = 45, women = 20) per 100,000 people. Information on SCD was determined using police records [5]. This suggests that the incidence of SCD in Japan is about one-fifth of that in the United States [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 United States [6,9,10]: this difference might explain the difference in the incidence of SCD between Japan and the United States. However, Kitamura et al. reported a significant increase in the incidence of CHD among middle-aged urban Japanese men from 1980-87 to 1996-2003 [11]. Therefore we expected that 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.

Therefore 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 men and women.

Methods

The CIRCS is a population-based study of cardiovascular risk factors, disease incidence, and their respective trends in Japanese communities. Details of the study design and procedures of CIRCS 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. The census populations of ages 30 to 84 years in Ikawa were 3,983 in 1985, 4,166 in 1995, and 4,173 in 2000, while the corresponding totals were: 12,940, 14,170, and 14,825 in Yao; 8,149,10,772, and 10,573 in Noichi; and 9,614, 9590, and 10,948 in Kyowa.

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

We included in our study all SCD events that occurred among all residents between January 1, 1981 and December 31, 2005. The events of CHD and SCD 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 out from the community or died were censored case. For confirmation of the diagnosis, we also obtained histories from next of kin and reviewed medical records in local hospitals.

The criteria for CHD were modified from those of the World Health Organization Expert Committee [16]. The indication for definite myocardial infarction (MI) was typical, severe chest pain (lasting at least 30 minutes and without definite non-ischemic 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-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 nitroglycerin [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 hour of symptom onset or within 24 hours of having been observed alive and symptom-free. We excluded candidate cases if they survived for over 24 hours 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 with MI, it grouped SCD with MI (SCD_MI), and others were grouped as SCD without MI (SCD_NMI). In addition, SCD cases were divided into two groups stratified by time of symptom onset. If the time of symptom onset was within 1 hour, they were categorized as SCD1, and if it occurred within 24 hours but they were not SCD1, they were categorized as SCD1-24. Finally, SCD cases were divided into two groups based on place of death [3]. If the place of death was in emergency room (ER) or a hospital, the case was categorized as SCD_ER, and if it was outside of a hospital, it was categorized as SCD_NER (Table 1).

Age- and sex-adjusted annual incidence of SCD was calculated from the number of new cases per 100,000 person-year during the periods, 1981 - 1985, 1986 - 1990, 1991 - 1995, 1996 - 2000, and 2001 - 2005, in the aforementioned four Japanese communities. The rate of moving out from the community 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 to 84 years because the number of SCD cases aged <30 years was

too small (<1%), and for many cases aged ≥85 years their causes of death were difficult to be identified.

Cardiovascular risk factors were ascertained from the participants of residents in risk factor surveys during each of the five survey periods. They were recruited from all residents who were ages 30 to 84 years in four communities, and the surveys were conducted for the purpose of promoting primary prevention of cardiovascular disease (CVD). 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 subjects were restricted to ages 40 to 74 years, the respective participation rate was 57.2%, 48.2%, 44.2%, 40.1% and 35.4%. Farther, the participation rate for ages 40 to 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 the subjects participated in the risk factor survey more than once during each survey period, we used the data from the earliest year.

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

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

: age-adjusted annual incidence of SCD ± 1.96 square root $\left(\frac{\sum \left[\frac{N_i^2 p_i (1 - p_i)}{n_i} \right]}{\left[\sum N_i \right]^2} \right)$

, where N is the standard population for 5-year age category *i*, p is the crude incidence of the population for age category *i*, 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 standardization.

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-square test for trends. All statistical analyses were performed with the SAS System for Windows (Version 9.1, SAS Institute, Cary, NC).

Results

In the present study, 471 individuals 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 SCD (in parenthesis, SCD_MI) was presented according to the time of symptom onset and the place of death (Supplemental Table 1).

As shown in Table 1, age- and sex-adjusted incidence of SCD decreased from 1981-1985 to 1991-1995, however plateaued after 1996 (p for trend was $p<0.01$ 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-year 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 cases. 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- and sex-adjusted incidence of CHD; the annual incidence (95%Cl) of CHD per 100,000 person-year 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. The corresponding annual incidence (95%Cl) of MI per 100,000 person-year was 55.2(28.6 to 81.8), 58.9(33.4 to 84.4), 57.5(34.4 to 80.6), 34.6(17.9 to 51.3) and 45.6(26.9 to 64.3) (not shown in Table).

The incidence of SCD was two to three times higher for men than for women, while age- adjusted annual incidence (95%Cl) of SCD per 100,000 person-year during the five time periods were 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 analyzed 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- and sex-adjusted annual incidence (95%Cl) of SCD per 100,000 person-year 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- and sex-adjusted annual incidence (95%Cl) per 100,000 person-year 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- and sex-adjusted annual incidence (95%Cl) per 100,000 person-year 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), 20.2(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.

Moreover, we estimated the national SCD incidence in 2009 by using the results from this study. For this estimation, we multiplied the age- and sex-specific populations in 2009 by the age- 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 to 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 for 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 both 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 both current smoking and heavy drinking decreased constantly from 1981-1985 to 2001-2005 (p for trend 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, respectively) for both sexes. The prevalence of left ventricular hypertrophy dramatically decreased from 1981-1985 to 2001-2005 (p for trend was <0.01, for both sexes). Additionally, we examined the risk factor trends for ages 40 to 74 years (Supplemental Table 2), and also stratified by community (Ikawa and Kyowa: Supplemental Table 3/ Yao and Noichi: Supplemental Table 4), and found the same trends.

Discussion

In this longitudinal community-based study from 1981 to 2005, we found that the age- and sex-adjusted annual incidence of SCD decreased from 1981 to 1995, and plateaued thereafter. This trend was similarly observed when SCD was stratified by the presence of MI, in which MI constituted

approximately 20 to 35% of all SCD, the time of symptom onset, in which SCD within 1 hour constituted approximately 30% to 45% of all SCD, and the place of death, in which SCD in emergency room or hospital constituted approximately 45% to 70% of all SCD. Although the incidence of SCD was higher for men than for women consistent with previous reports [3,20], trends for the incidence of SCD did not vary according to age or sex. Since Japan is a rapidly aging country, the number of SCD in Japan, although much lower than in the United States [3], may increase in the future due to an increased elderly population.

Several population-based studies have previously reported the incidence of SCD among Japanese. 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 1,110 for men and 1,527 for women, which made it difficult to evaluate trends in the incidence of SCD [7]. Baba et al. reported that the annual SCD incidence was 45 per 100,000persons for men and 20 per 100,000persons for women for subjects aged 20 to 74 years in Suita City in 1992 [5]. Our study showed similar age-adjusted annual incidence of SCD (57.9 per 100,000 person-year for men and 18.2 per 100,000 person-year for women aged 30 to 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 the present study, SCD accounts for 10% of all CHD deaths, while CHD accounted for 25% of all SCD cases which was generally consistent with the finding from a previous Japanese population-based study [20]. The lower incidence [11] and mortality [9,10,23] from CHD in Japan than in the United States probably correspond to the lower incidence of SCD in Japanese.

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 for ages 20 years and more in 1988-1998

[24], 45.8 per 100,000 population for ages 35 to 64 years in 1994-1996 [25], and 49.7 per 100,000 person for ages 20 years and more in 1996-1998 [26]. In the present study, the age-adjusted annual incidence of MI for ages 30 to 84 years was 34.6 to 58.9 per 100,000 person-year 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 1990-92 to 1999-2001 in the Takashima AMI Registry [26]. Furthermore, Kitamura et al. reported a significant increase in the incidence of CHD from 1980-87 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 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.

We found in the data presented here 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, elderly age, male sex, smoking, heavy drinking, overweight, diabetes and left ventricular hypertrophy [3]. Hypertension, current smoking, and diabetes mellitus were found the potential risk factors for SCD among Japanese [20,29]. In the present study, the SCD incidence decreased from 1981 to 1995, which correspond to a reduction in the prevalence of hypertension and current smoking. The plateaued trend for SCD incidence from 1996 to 2005 is explained partly by the unchanged prevalence of hypertension, the decreased prevalence of current smoking and the increased prevalence of diabetes mellitus.

The strength of the present study is that we analyzed trends for SCD using population-based data, including both 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 for predisposing risk factors of SCD.

Nonetheless, our study has a few limitations. First, we only examined the incidence of SCD for the age range of 30 to 84 years old. However the frequency of SCD among persons < 30 years old was less than 1 % even in the United States [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 in the case of an out-of-hospital death. Such misclassification may well have affected the changes in the incidence of SCD occurred out-of-hospital.

In conclusion, age- and sex-adjusted incidence of SCD for a general Japanese population decreased from 1981-1985 to 1991-1995, and plateaued after 1996, which corresponded primarily to the trend for the prevalence of hypertension. The plateaued trend for SCD incidence from 1996 to 2005 may be in part due to the unchanged prevalence of hypertension, the decreased prevalence of smoking, and the increased prevalence of diabetes mellitus. The continuous surveillance is necessary to clarify future trends for SCD in Japan, because of an increasing trend for diabetes mellitus.

Table 1. Trends for age- and sex- adjusted incidence of sudden cardiac death per 100,000 person-year and 95% CI among men and women aged 30 to 84 years in four Japanese comminuties from 1981 to 2005.

	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	p for trend
Total						
No of populations	31754	34686	36717	38698	40519	
No of cases	114	101	83	76	97	
Age- and sex-adjusted incidence (Incidence/100,000 person-year)	76.0	57.9	39.3	31.6	36.8	< 0.01
95% CI	(44.8 to 107.2)	(32.7 to 83.1)	(20.3 to 58.3)	(15.6 to 47.6)	(19.8 to 53.8)	
Age- and sex-adjusted incidence (Incidence/100,000 person-year)						
30-64 y	24.1	19.7	15.7	12.4	17.0	0.266
95% CI	(4.8 to 43.4)	(3.3 to 36.1)	(1.8 to 29.6)	(0.7 to 24.1)	(2.5 to 31.5)	
65-74 y	217.1	100.2	99.7	83.8	101.8	< 0.01
95% CI	(64.9 to 369.3)	(1.7 to 198.7)	(8.6 to 190.8)	(8.9 to 158.7)	(24.1 to 179.5)	
75-84 y	541.0	527.2	258.5	204.3	190.8	< 0.01
95% CI	(187.9 to 894.1)	(210.6 to 843.8)	(67.2 to 449.8)	(39.5 to 369.1)	(51.1 to 330.5)	
40-74 y	65.0	40.0	34.6	28.8	33.4	< 0.01
95% CI	(29.9 to 100.1)	(14.1 to 65.9)	(12.2 to 57.0)	(10.0 to 47.6)	(13.5 to 53.3)	
Men						
No of populations	15048	16471	17421	18422	19306	
No of cases	70	61	49	50	67	
Age-adjusted incidence (Incidence/100,000 person-year)	111.7	82.1	54.4	49.3	57.9	< 0.01
95% CI	(53.1 to 170.3)	(36.0 to 128.2)	(20.2 to 88.6)	(18.6 to 80.0)	(26.2 to 89.6)	
Women						
No of populations	16706	18215	19296	20276	21213	
No of cases	44	40	34	26	30	
Age-adjusted incidence (Incidence/100,000 person-year)	50.6	39.5	27.1	16.7	18.2	< 0.01
95% CI	(17.1 to 84.1)	(12.0 to 67.0)	(6.3 to 47.9)	(2.0 to 31.4)	(2.5 to 33.9)	

Table 2. Trends for age- and sex-adjested cardiovascular risk characteristics among men and women aged 30 to 84 years in four Japanese communities from 1981 to 2005.

	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	*p* for trend
Age-adjusted, mean or percent						
Men						
Number	5350	4992	5175	5039	4900	
Age, year	55	56	58	59	60	
Systolic blood pressure, mmHg	137	134	133	134	133	<0.01
Diastolic blood puressure, mmHg	81	81	81	82	82	<0.01
Antihypertensive medication, %	19.8	18.6	17.2	18.0	20.1	0.550
Hypertention, %	49.2	44.1	41.3	44.7	44.6	<0.01
Body mass index, kg/m^2	22.7	22.9	23.3	23.5	23.8	<0.01
Overweight (BMI ≥25kg/m^2)	26.2	29.2	29.6	33.5	34.7	<0.01
Total cholestrol, mmol/L	4.75	4.89	4.98	5.13	5.23	<0.01
Total cholestrol ≥5.69 mmol/L, %	14.0	17.7	20.7	26.8	31.4	<0.01
Blood gulcose, mmol/L	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 ≥46g/day)	33.6	29.9	18.6	17.5	22.9	<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
Abnomal 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						
Number	7949	7781	8463	8436	8082	
Age, year	54	55	56	57	58	
Systolic blood pressure, mmHg	134	132	130	130	128	<0.01
Diastolic blood puressure, mmHg	79	78	78	78	77	<0.01
Antihypertensive medication, %	19.2	18.4	16.8	17.0	18.1	<0.01
Hypertention, %	42.0	37.1	34.0	34.9	33.6	<0.01
Body mass index, kg/m^2	23.5	23.4	23.3	23.3	23.2	<0.01
Overweight (BMI ≥25kg/m^2)	34.4	33.4	31.1	30.9	28.0	<0.01
Total cholestrol, mg/dl	5.09	5.24	5.27	5.44	5.49	<0.01
Total cholestrol ≥5.69 mmol/L, %	24.7	29.3	31.1	39.7	44.7	<0.01
Blood gulcose, mmol/L	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 ≥46g/day)	0.5	0.3	0.3	0.3	0.6	0.685
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
Abnomal 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

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Data Sharing

None

Disclosures

None declared.

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Competing Interests

None

Contributorship

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 CIRCS investigators who contributed to this study are as follows: Masamitsu

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Author's individual contributions

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.

Appendix

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 CIRCS investigators who contributed to this study are as follows: 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, National Cardiovascular Center, Suita; Shinichi Sato, Chiba Prefectural Institute of Public Health, Chiba; Tomoko Sankai, Kazumasa Yamagishi, Kyoko Kirii, Mitsumasa Umesawa, ChoyLye Chei, Kimiko Yokota and Minako Tabata, University of Tsukuba, Tsukuba; Hiroyasu Iso, Tetsuya Ohira, Renzhe Cui, Hironori Imano, Ai

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Figure Legends

Figure 1. Determination of sudden cardiac death (SCD)

Figure 2. Trends for age- and sex-adjusted annual incidence of sudden cardiac death, 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 person among men and women aged 30-84 in four Japanese communities from 1981 to 2005, CIRCS. SCD with MI (SCD_MI) and SCD without MI (SCD_NMI), SCD within 1 hour (SCD1) and SCD between 1 and 24 hours (SCD1-24). SCD in emergency room or a hospital (SCD_ER) and SCD outside of a hospital (SCD_NER).

Figure 1

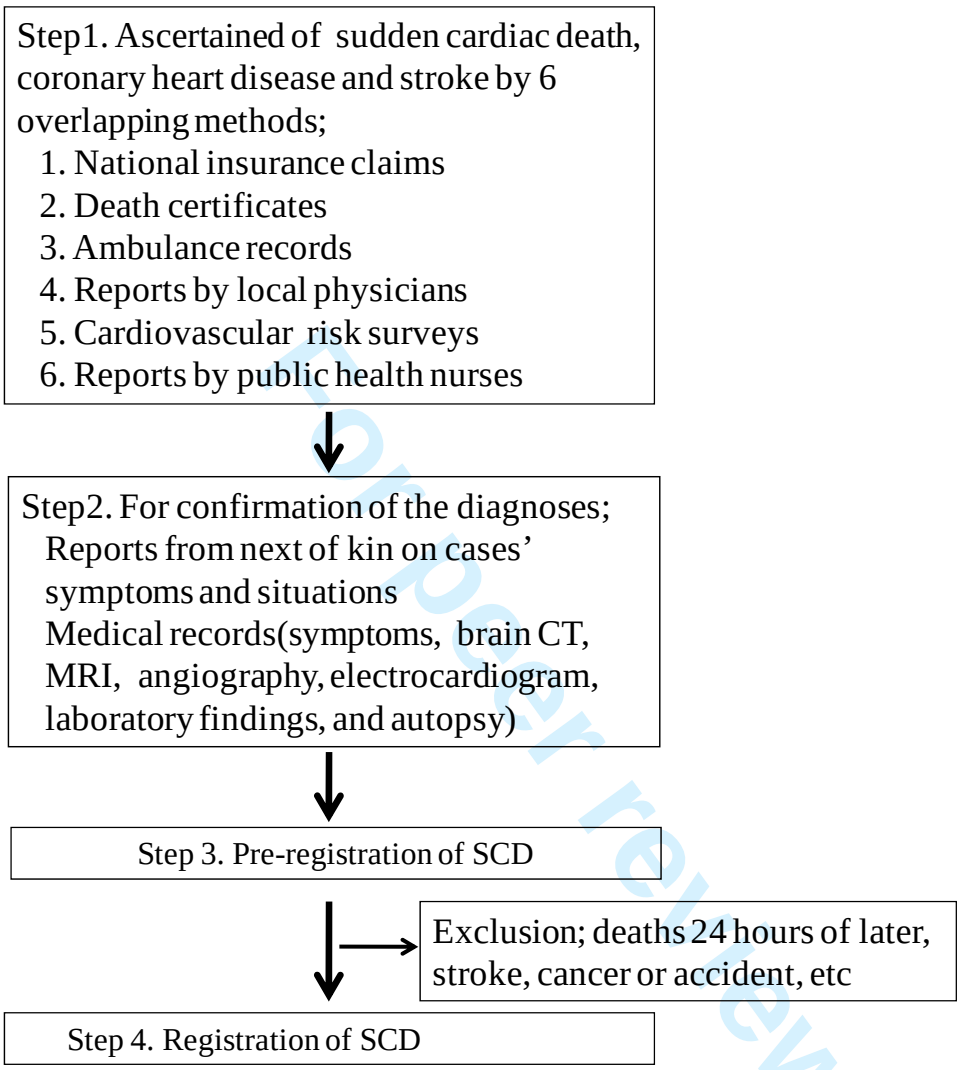
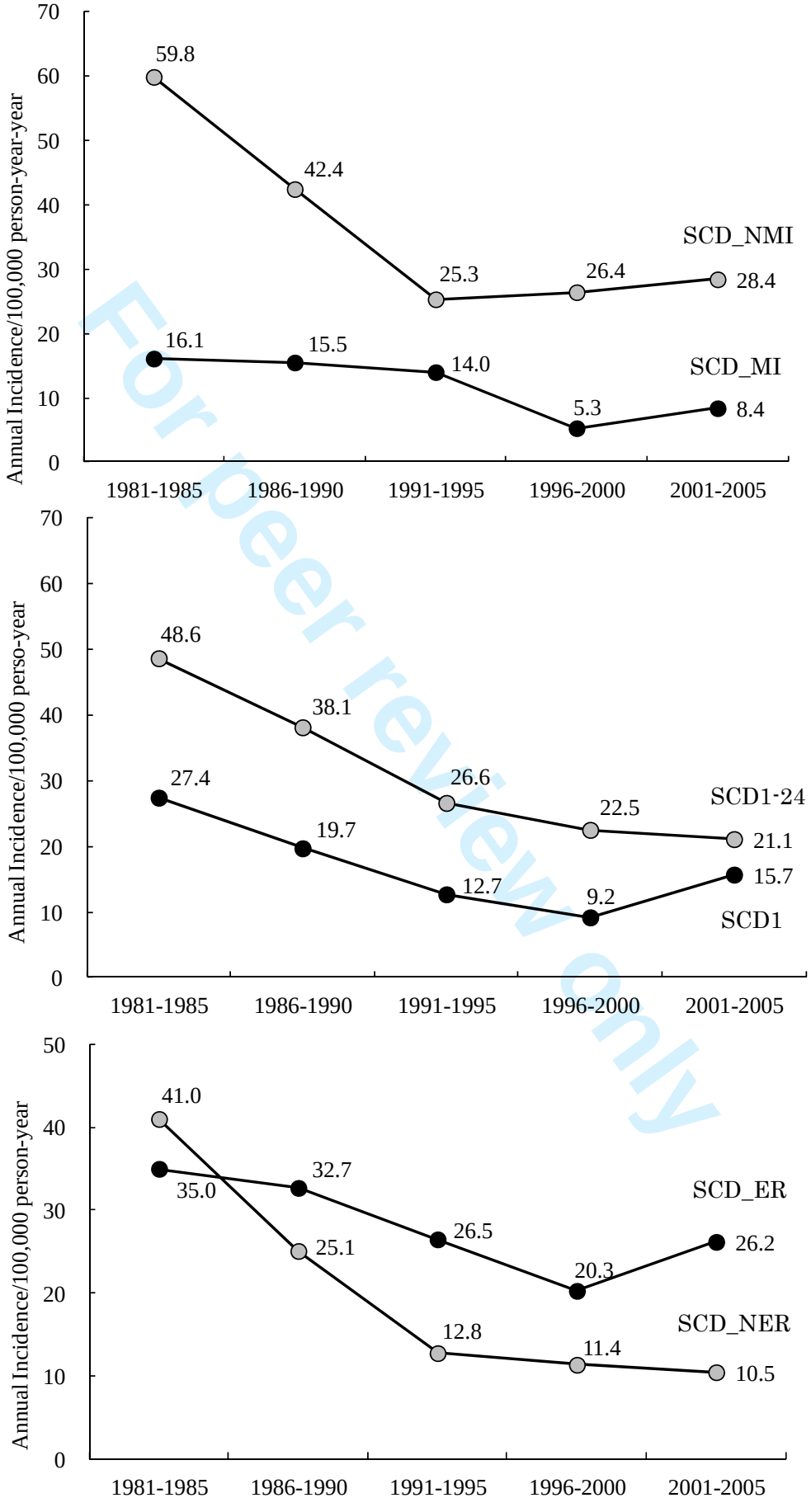


Figure 2



Supplemental Table 1. The Number of Sudden Cardiac Death (SCD) according to the Time of Symptom Onset and the Place of Death.

Place of death	Time of symptom onset		
	< 1 hour SCD1	1-24 hours SCD1-24	Total
Outside of hospital SCD_NER	58(4)	132(19)	190(23)
Emergency room or hospital SCD_ER	105(14)	176(80)	281(94)
Total	163(18)	308(99)	471(117)

In parentheses, the number of SCD with myocardial infarction (SCD_MI)

Supplemental Table 2. Trends for age- and sex-adjested cardiovascular risk characteristics among men and women aged 40 to 74 years in four Japanese communities from 1981 to 2005.

	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	*p* for trend
Age-adjusted, mean or percent						
Men						
Number	4678	4315	4408	4281	4038	
Age, year	55	56	57	59	60	
Systolic blood pressure, mmHg	137	134	133	135	133	<0.01
Diastolic blood puressure, mmHg	82	82	81	83	83	<0.01
Antihypertensive medication, %	19.7	18.6	17.1	18.0	19.2	0.322
Hypertention, %	50.2	41.6	41.6	45.3	45.1	<0.01
Body mass index, kg/m^2	22.8	23.0	23.3	23.6	24.0	<0.01
Overweight (BMI ≥25kg/m^2)	26.5	29.4	30.3	34.1	35.8	<0.01
Total cholestrol, mmol/L	4.76	4.90	4.99	5.15	5.27	<0.01
Total cholestrol ≥5.69 mmol/L, %	14.1	17.9	21.2	27.5	32.7	<0.01
Blood gulcose, mmol/L	61.9	69.6	68.0	63.8	62.3	<0.01
Diabetes mellitus, %	4.8	7.1	7.3	7.7	9.8	<0.01
Heavy drinking(ethanol intake ≥46g/day)	33.7	30.3	19.2	18.7	24.9	<0.01
Current smoking, %	61.0	56.3	52.4	49.9	44.6	<0.01
ECG findings						
Atrial fibrillation	1.3	1.5	1.1	1.3	1.3	0.639
Ventricular premature contraction	3.0	2.8	2.9	2.5	2.1	0.013
Supraventricular premature contraction	2.8	3.7	3.6	3.0	2.8	0.535
Major ST-T abnormality	4.5	4.0	3.7	4.0	3.9	<0.01
Minor ST-T abnormality	12.5	9.9	12.5	11.8	11.6	<0.01
PQ prolonged	1.4	1.1	1.3	1.4	1.0	0.465
Complete/incomplete right bundle branch block	5.3	5.0	5.1	5.6	6.1	0.449
Wide QRS	2.9	2.8	2.8	3.2	3.5	0.075
Abnomal Q wave	0.4	0.6	0.5	0.6	0.7	0.307
Left ventricular hypertrophy	29.3	27.6	23.3	19.5	17.5	<0.01
Women						
Number	6954	6766	7131	7041	6524	
Age, year	55	56	56	57	58	
Systolic blood pressure, mmHg	135	132	130	131	129	<0.01
Diastolic blood puressure, mmHg	79	78	78	79	78	<0.01
Antihypertensive medication, %	19.3	18.4	16.5	16.6	17.4	<0.01
Hypertention, %	43.4	38.1	34.7	35.8	34.1	<0.01
Body mass index, kg/m^2	23.6	23.5	23.5	23.5	23.3	<0.01
Overweight (BMI ≥25kg/m^2)	35.8	35.0	32.6	32.8	29.2	<0.01
Total cholestrol, mg/dl	5.12	5.28	5.33	5.53	5.59	<0.01
Total cholestrol ≥5.69 mmol/L, %	25.5	30.7	33.3	43.1	48.7	<0.01
Blood gulcose, mmol/L	58.2	65.7	63.2	57.6	56.6	<0.01
Diabetes mellitus, %	2.8	3.9	3.5	3.9	4.1	<0.01
Heavy drinking(ethanol intake ≥46g/day)	0.5	0.3	0.3	0.3	0.6	0.549
Current smoking, %	6.4	5.7	5.6	6.0	6.1	0.659
ECG findings						
Atrial fibrillation	0.6	0.5	0.3	0.3	0.3	<0.01
Ventricular premature contraction	2.0	2.2	1.7	1.8	1.9	0.269
Supraventricular premature contraction	2.3	2.5	2.9	2.4	2.5	0.653
Major ST-T abnormality	6.5	5.8	4.9	4.4	4.6	0.970
Minor ST-T abnormality	22.5	19.0	19.9	20.0	17.4	0.283
PQ prolonged	0.5	0.5	0.4	0.5	0.4	0.063
Complete/incomplete right bundle branch block	3.1	3.4	3.1	3.2	3.0	<0.01
Wide QRS	1.4	1.6	1.5	1.6	1.5	0.598
Abnomal Q wave	0.1	0.2	0.2	0.2	0.3	0.010
Left ventricular hypertrophy	10.8	9.6	7.7	5.7	4.5	<0.01

Supplemental Table 3. Trends for age- and sex-adjested cardiovascular risk characteristics among men and women aged 40 to 74 years in Ikawa and Kyowa with high participation rates from 1981 to 2005.

	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	*p* for trend
Age-adjusted, mean or percent						
Men						
Number	2698	2384	2533	2506	2381	
Age, year	55	55	57	59	59	
Systolic blood pressure, mmHg	139	136	134	135	133	<0.01
Diastolic blood puressure, mmHg	82	83	81	82	82	0.913
Antihypertensive medication, %	21.7	21.7	19.3	20.6	21.6	0.425
Hypertention, %	55.0	50.3	44.1	47.4	46.7	<0.01
Body mass index, kg/m^2	22.9	23.2	23.4	23.7	23.9	<0.01
Overweight (BMI ≥25kg/m^2)	27.3	32.1	29.0	32.7	36.0	<0.01
Total cholestrol, mmol/L	4.69	4.82	4.92	5.07	5.21	<0.01
Total cholestrol ≥5.69 mmol/L, %	13.4	15.5	18.5	24.0	30.5	<0.01
Blood gulcose, mmol/L	59.0	72.7	70.3	64.1	61.3	<0.01
Diabetes mellitus, %	4.2	9.1	8.1	8.1	10.3	<0.01
Heavy drinking(ethanol intake ≥46g/day)	39.2	37.4	16.2	16.2	27.5	<0.01
Current smoking, %	65.1	61.0	56.1	53.2	47.2	<0.01
ECG findings, %						
Atrial fibrillation	1.5	1.9	1.4	1.7	1.4	0.588
Ventricular premature contraction	3.4	2.9	3.6	2.6	2.2	0.011
Supraventricular premature contraction	3.2	3.4	3.5	3.2	3.1	0.520
Major ST-T abnormality	5.0	4.7	3.5	4.0	3.4	<0.01
Minor ST-T abnormality	11.2	9.3	11.3	10.8	9.9	0.507
PQ prolonged	1.4	1.1	0.9	1.2	1.0	0.375
Complete/incomplete right bundle branch block	5.1	4.9	4.8	4.8	5.6	0.628
Wide QRS	2.9	2.6	2.8	2.8	3.1	0.634
Abnomal Q wave	0.6	0.7	0.5	0.7	0.7	0.869
Left ventricular hypertrophy	31.1	29.8	29.1	21.6	21.5	<0.01
Women						
Number	3543	3299	3618	3686	3473	
Age, year	55	56	57	57	58	
Systolic blood pressure, mmHg	136	134	131	132	130	<0.01
Diastolic blood puressure, mmHg	80	80	78	78	78	<0.01
Antihypertensive medication, %	22.2	21.7	19.2	20.1	19.7	<0.01
Hypertention, %	47.3	42.6	36.9	37.8	35.7	<0.01
Body mass index, kg/m^2	24.0	24.1	23.9	23.9	23.8	<0.01
Overweight (BMI ≥25kg/m^2)	41.3	41.7	36.4	36.4	33.6	<0.01
Total cholestrol, mmol/L	5.06	5.23	5.26	5.42	5.51	<0.01
Total cholestrol ≥5.69 mmol/L, %	23.3	28.8	30.8	38.9	45.7	<0.01
Blood gulcose, mmol/L	54.8	67.7	65.3	58.3	56.4	<0.01
Diabetes mellitus, %	2.7	5.4	4.2	4.5	4.6	0.204
Heavy drinking(ethanol intake ≥46g/day)	0.4	0.4	0.1	0.1	0.5	0.525
Current smoking, %	5.3	4.2	4.3	4.7	4.8	0.600
ECG findings, %						
Atrial fibrillation	0.6	0.7	0.4	0.5	0.4	0.133
Ventricular premature contraction	2.4	2.7	1.8	2.0	2.2	0.119
Supraventricular premature contraction	2.7	2.7	2.7	2.5	3.1	0.653
Major ST-T abnormality	7.5	6.2	4.2	4.5	3.6	<0.01
Minor ST-T abnormality	20.8	18.2	18.2	17.9	12.9	<0.01
PQ prolonged	0.4	0.4	0.4	0.6	0.5	0.120
Complete/incomplete right bundle branch block	2.4	3.1	2.9	3.3	3.3	0.049
Wide QRS	1.1	1.5	1.3	1.5	1.6	0.107
Abnomal Q wave	0.1	0.2	0.1	0.1	0.3	0.254
Left ventricular hypertrophy	11.5	10.9	10.1	7.4	5.7	<0.01

Supplemental Table 4. Trends for age- and sex-adjested cardiovascular risk characteristics among men and women aged 40 to 74 years in Yao and Noichi with lower participation rates from 1981 to 2005.

	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	*p* for trend
Age-adjusted, mean or percent						
Men						
Number	1980	1931	1875	1775	1657	
Age, year	56	57	58	60	61	
Systolic blood pressure, mmHg	135	132	132	134	133	0.401
Diastolic blood puressure, mmHg	81	80	82	83	83	<0.01
Antihypertensive medication, %	17.0	14.9	14.1	14.2	15.8	0.251
Hypertention, %	43.7	37.5	38.3	42.2	42.6	0.598
Body mass index, kg/m^2	22.6	22.8	23.2	23.5	24.0	<0.01
Overweight (BMI ≥25kg/m^2)	25.3	26.1	32.0	36.2	35.6	<0.01
Total cholestrol, mmol/L	4.88	5.00	5.09	5.27	5.36	<0.01
Total cholestrol ≥5.69 mmol/L, %	15.3	20.9	24.7	32.6	35.9	<0.01
Blood gulcose, mmol/L	67.3	67.0	65.3	62.2	62.0	<0.01
Diabetes mellitus, %	5.4	4.9	6.3	7.0	9.0	<0.01
Heavy drinking(ethanol intake ≥46g/day)	26.7	21.6	23.1	22.2	21.1	<0.01
Current smoking, %	55.8	50.5	47.5	45.1	40.8	<0.01
ECG findings, %						
Atrial fibrillation	1.1	1.0	0.8	0.8	1.1	0.767
Ventricular premature contraction	2.5	2.7	2.0	2.4	2.1	0.362
Supraventricular premature contraction	2.1	4.1	3.8	2.7	2.5	0.781
Major ST-T abnormality	3.7	3.1	3.9	4.1	4.7	0.037
Minor ST-T abnormality	14.3	10.7	14.2	13.2	14.1	0.396
PQ prolonged	1.5	1.1	1.8	1.5	0.9	0.567
Complete/incomplete right bundle branch block	5.5	5.2	5.4	6.6	6.8	0.023
Wide QRS	3.0	3.1	2.8	3.8	4.1	0.035
Abnomal Q wave	0.2	0.6	0.5	0.5	0.5	0.159
Left ventricular hypertrophy	27.0	25.0	15.4	16.4	11.5	<0.01
Women						
Number	3411	3467	3513	3355	3051	
Age, year	55	55	56	58	59	
Systolic blood pressure, mmHg	133	131	130	130	129	<0.01
Diastolic blood puressure, mmHg	79	77	79	80	79	0.025
Antihypertensive medication, %	16.4	15.3	13.5	12.8	14.8	0.014
Hypertention, %	39.3	33.7	32.4	33.6	32.4	<0.01
Body mass index, kg/m^2	23.1	23.0	23.0	23.0	22.8	<0.01
Overweight (BMI ≥25kg/m^2)	30.3	28.6	28.7	29.0	24.2	<0.01
Total cholestrol, mmol/L	5.20	5.33	5.40	5.64	5.67	<0.01
Total cholestrol ≥5.69 mmol/L, %	28.4	32.5	35.9	47.7	52.0	<0.01
Blood gulcose, mmol/L	61.6	63.9	61.3	56.8	56.9	<0.01
Diabetes mellitus, %	2.8	2.6	2.8	3.4	3.5	0.020
Heavy drinking(ethanol intake ≥46g/day)	0.5	0.3	0.5	0.5	0.7	0.151
Current smoking, %	7.5	7.1	6.9	7.4	7.5	0.774
ECG findings, %						
Atrial fibrillation	0.6	0.3	0.2	0.1	0.2	<0.01
Ventricular premature contraction	1.5	1.8	1.7	1.6	1.6	0.974
Supraventricular premature contraction	2.0	2.3	3.1	2.2	2.0	0.900
Major ST-T abnormality	5.4	5.4	5.6	4.3	5.6	0.613
Minor ST-T abnormality	24.2	19.8	21.6	22.3	22.5	0.721
PQ prolonged	0.6	0.6	0.4	0.3	0.3	0.008
Complete/incomplete right bundle branch block	3.9	3.6	3.3	3.0	2.6	0.005
Wide QRS	1.7	1.6	1.8	1.6	1.4	0.505
Abnomal Q wave	0.1	0.2	0.3	0.2	0.4	0.015
Left ventricular hypertrophy	10.1	8.4	5.1	4.0	3.1	<0.01

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	5,6,7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	5,figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	8,table1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9,10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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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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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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Word counts:3,416words

Abstract

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

Design and Setting - Population-based longitudinal study. Surveillance of men and women for the SCD incidence and risk factors was conducted from 1981 to 2005.

Subjects - The surveyed population was all residents of men and women aged 30 to 84 years in three rural and an urban communities in Japan.

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

Results - Age- and sex-adjusted incidence of SCD decreased from 1981-1985 to 1991-1995, and plateaued thereafter; the annual incidence per 100,000 person-year in the 5 time periods was 76.0, 57.9, 39.3, 31.6, and 36.8, respectively. The prevalence of hypertension decreased from 1981-1985 to 1991-1995, and plateaued thereafter for both men and women. The age- adjusted prevalence of current smoking for men decreased, while that of diabetes mellitus for both sexes increased from 1981-1985 to 2001-2005.

Conclusions - The incidence of SCD decreased from 1981 to 1995 but unchanged from 1995 to 2005. The continuous surveillance is necessary to clarify future trends for SCD in Japan, because of an increasing trend for diabetes mellitus.

In the United States, estimates of the annual number of sudden cardiac death (SCD) 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 per 100,000 person was 410.6 for men and 274.6 for women in 1998 among US residents aged≥35 years [3]. Several population-based studies have reported on the incidence of SCD among Japanese [5-8], however these studies are questionable due to methodological problems, such as small sample size [7], and a working population [8], and an inaccurate definition of SCD based on death certificate data only [6]. Baba et al. reported from a sample from Suita City (census population: approximately 340,000) that in persons aged 20 to74 years, the incidence of SCD was 31 (men = 45, women = 20) per 100,000 people. Information on SCD was determined using police records [5]. This suggests that the incidence of SCD in Japan is about one-fifth of that in the United States [1, 3, and 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 United States [6, 9, and 10]: this difference might explain the difference in the incidence of SCD between Japan and the United States. However, Kitamura et al. reported a significant increase in the incidence of CHD among middle-aged urban Japanese men from 1980-87 to 1996-2003 [11]. Therefore we expected that 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.

Therefore 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 men and women.

Methods

The CIRCS is a population-based study of cardiovascular risk factors, disease incidence, and their respective trends in Japanese communities. Details of the study design and procedures of CIRCS 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. The census populations of ages 30 to 84 years in Ikawa were 3,983 in 1985, 4,166 in 1995, and 4,173 in 2000, while the corresponding totals were: 12,940, 14,170, and 14,825 in Yao; 8,149,10,772, and 10,573 in Noichi; and 9,614, 9590, and 10,948 in Kyowa.

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

We included in our study all SCD events that occurred among all residents between January 1, 1981 and December 31, 2005. The events of CHD and SCD 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 out from the community or died were censored case. For confirmation of the diagnosis, we also obtained histories from next of kin and reviewed medical records in local hospitals.

The criteria for CHD were modified from those of the World Health Organization Expert Committee [16]. The indication for definite myocardial infarction (MI) was typical, severe chest pain (lasting at least 30 minutes and without definite non-ischemic 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-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 nitro-glycerine [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 hour of symptom onset or within 24 hours of having been observed alive and symptom-free. We excluded candidate cases if they survived for over 24 hours 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 with MI, it grouped SCD with MI (SCD_MI), and others were grouped as SCD without MI (SCD_NMI). In addition, SCD cases were divided into two groups stratified by time of symptom onset. If the time of symptom onset was within 1 hour, they were categorized as SCD1, and if it occurred within 24 hours but they were not SCD1, they were categorized as SCD1-24. Finally, SCD cases were divided into two groups based on place of death [3]. If the place of death was in emergency room (ER) or a hospital, the case was categorized as SCD_ER, and if it was outside of a hospital, it was categorized as SCD_NER (Table 1).

Age- and sex-adjusted annual incidence of SCD was calculated from the number of new cases per 100,000 person-year during the periods, 1981 - 1985, 1986 - 1990, 1991 - 1995, 1996 - 2000, and 2001 - 2005, in the aforementioned four Japanese communities. The rate of moving out from the community 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 to 84 years because the number of SCD cases aged <30 years was too small (<1%), and for many cases aged ≥85 years their causes of death were difficult to be identified.

Cardiovascular risk factors were ascertained from the participants of residents in risk factor surveys during each of the five survey periods. They were recruited from all residents who were ages 30 to 84 years in four communities, and the surveys were conducted for the purpose of promoting primary prevention of cardiovascular disease (CVD). 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 subjects were restricted to ages 40 to 74 years, the respective participation rate was 57.2%, 48.2%, 44.2%, 40.1% and 35.4%. Further, the participation rate for ages 40 to 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 the subjects participated in the risk factor survey more than once during each survey period, we used the data from the earliest year.

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

To calculate age- and sex-adjusted incidence, we employed the direct standardization method using the age and sex distributions of the Japanese national model population from 1985 as standard population. Linear trends in incidence were examined with the chi-square test. We calculated 95% CI

as following equation,

: age-adjusted annual incidence of SCD ± 1.96 square root $\left(\frac{\sum \left[\frac{N_i^2 p_i (1 - p_i)}{n_i} \right]}{\left[\sum N_i \right]^2} \right)$

, where N is the standard population for 5-year age category *i*, p is the crude incidence of the population for age category *i*, 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 standardization.

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-square test for trends. All statistical analyses were performed with the SAS System for Windows (Version 9.1, SAS Institute, Cary, NC).

Results

In the present study, 471 individuals 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 SCD (in parenthesis, SCD_MI) was presented according to the time of symptom onset and the place of death (Supplemental Table 1).

As shown in Table 1, age- and sex-adjusted incidence of SCD decreased from 1981-1985 to 1991-1995, however plateaued after 1996 (p for trend was $p<0.01$ from 1981-1985 to 1991-1995, and $p=0.73$ from 1991-1995 to 2001-2005). The annual incidence (95%Cl) of SCD per 100,000 person-year 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 cases. 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- and sex-adjusted incidence of CHD; the annual incidence (95%Cl) of CHD per 100,000 person-year 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, while a slightly different trend was observed for MI; the annual incidence (95%Cl) of MI per 100,000 person-year was 55.2(28.6 to 81.8), 58.9(33.4 to 84.4), 57.5(34.4 to 80.6), 34.6(17.9 to 51.3) and 45.6(26.9 to 64.3) (not shown in Table).

The incidence of SCD was two to three times higher for men than for women, while age- adjusted annual incidence (95%Cl) of SCD per 100,000 person-year during the five time periods were 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 analyzed 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- and sex-adjusted annual incidence (95%Cl) of SCD per 100,000 person-year 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- and sex-adjusted annual incidence (95%Cl) per 100,000 person-year 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- and sex-adjusted annual incidence (95%Cl) per 100,000 person-year 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), 20.2(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.

Moreover, we estimated the national SCD incidence in 2009 by using the results from this study. For this estimation, we multiplied the age- and sex-specific populations in 2009 by the age- 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 to 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 for 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 both 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 both current smoking and heavy drinking decreased constantly from 1981-1985 to 2001-2005 (p for trend 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, respectively) for both sexes. The prevalence of left ventricular hypertrophy dramatically decreased from 1981-1985 to 2001-2005 (p for trend was <0.01, for both sexes). Additionally, we examined the risk factor trends for ages 40 to 74 years (Supplemental Table 2), and also stratified by community (Ikawa and Kyowa: Supplemental Table 3/ Yao and Noichi: Supplemental Table 4), and found the same trends.

Discussion

In this longitudinal community-based study from 1981 to 2005, we found that the age- and sex-adjusted annual incidence of SCD decreased from 1981 to 1995, and plateaued thereafter. This

trend was similarly observed when SCD was stratified by the presence of MI, in which MI constituted approximately 20 to 35% of all SCD, the time of symptom onset, in which SCD within 1 hour constituted approximately 30% to 45% of all SCD, and the place of death, in which SCD in emergency room or hospital constituted approximately 45% to 70% of all SCD. Although the incidence of SCD was higher for men than for women consistent with previous reports [3, 20], trends for the incidence of SCD did not vary according to age or sex. Since Japan is a rapidly aging country, the number of SCD in Japan, although much lower than in the United States [3], may increase in the future due to an increased elderly population.

Several population-based studies have previously reported the incidence of SCD among Japanese. 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 1,110 for men and 1,527 for women, which made it difficult to evaluate trends in the incidence of SCD [7]. Baba et al. reported that the annual SCD incidence was 45 per 100,000persons for men and 20 per 100,000persons for women for subjects aged 20 to 74 years in Suita City in 1992 [5]. Our study showed similar age-adjusted annual incidence of SCD (57.9 per 100,000 person-year for men and 18.2 per 100,000 person-year for women aged 30 to 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 the present study, SCD accounts for 10% of all CHD deaths, while CHD accounted for 25% of all SCD cases which was generally consistent with the finding from a previous Japanese population-based study [20]. The lower incidence [11] and mortality [9, 10, and 23] from CHD in Japan than in the United States probably correspond to the lower incidence of SCD in Japanese.

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 for ages 20 years and more in 1988-1998 [24], 45.8 per 100,000 population for ages 35 to 64 years in 1994-1996 [25], and 49.7 per 100,000 person for ages 20 years and more in 1996-1998 [26]. In the present study, the age-adjusted annual incidence of MI for ages 30 to 84 years was 34.6 to 58.9 per 100,000 person-year 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 1990-92 to 1999-2001 in the Takashima AMI Registry [26]. Furthermore, Kitamura et al. reported a significant increase in the incidence of CHD from 1980-87 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 increased during the last two decades as seen in our study and other Japanese studies [9, 11, and 27], the incidence of SCD might increase in the future.

We found in the data presented here 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, elderly age, male sex, smoking, heavy drinking, overweight, diabetes and left ventricular hypertrophy [3]. Hypertension, current smoking, and diabetes mellitus were found the potential risk factors for SCD among Japanese [20,29]. In the present 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 there were the unchanged prevalence of hypertension, the decreased prevalence of current smoking and the increased prevalence of diabetes mellitus.

The strength of the present study is that we analyzed trends for SCD using population-based data, including both 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 for predisposing risk factors of SCD.

Nonetheless, our study has a few limitations. First, we only examined the incidence of SCD for the age range of 30 to 84 years old. However the frequency of SCD among persons < 30 years old was less than 1 % even in the United States [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 in the case of an out-of-hospital death. Such misclassification may well have affected the changes in the incidence of SCD occurred out-of-hospital. Third, since we did not include the resuscitated SCD for over 24 hours 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 estimated only around 0.7, based on the 2005 statistics of Fire and Disaster Management Agency [30].

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

Table 1. Trends for age- and sex- adjusted incidence of sudden cardiac death per 100,000 person-year and 95% CI among men and women aged 30 to 84 years in four Japanese comminuties from 1981 to 2005.

	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	p for trend
Total						
No of populations	31754	34686	36717	38698	40519	
No of cases	114	101	83	76	97	
Age- and sex-adjusted incidence (Incidence/100,000 person-year)	76.0	57.9	39.3	31.6	36.8	< 0.01
95% CI	(44.8 to 107.2)	(32.7 to 83.1)	(20.3 to 58.3)	(15.6 to 47.6)	(19.8 to 53.8)	
Age- and sex-adjusted incidence (Incidence/100,000 person-year)						
30-64 y	24.1	19.7	15.7	12.4	17.0	0.266
95% CI	(4.8 to 43.4)	(3.3 to 36.1)	(1.8 to 29.6)	(0.7 to 24.1)	(2.5 to 31.5)	
65-74 y	217.1	100.2	99.7	83.8	101.8	< 0.01
95% CI	(64.9 to 369.3)	(1.7 to 198.7)	(8.6 to 190.8)	(8.9 to 158.7)	(24.1 to 179.5)	
75-84 y	541.0	527.2	258.5	204.3	190.8	< 0.01
95% CI	(187.9 to 894.1)	(210.6 to 843.8)	(67.2 to 449.8)	(39.5 to 369.1)	(51.1 to 330.5)	
40-74 y	65.0	40.0	34.6	28.8	33.4	< 0.01
95% CI	(29.9 to 100.1)	(14.1 to 65.9)	(12.2 to 57.0)	(10.0 to 47.6)	(13.5 to 53.3)	
Men						
No of populations	15048	16471	17421	18422	19306	
No of cases	70	61	49	50	67	
Age-adjusted incidence (Incidence/100,000 person-year)	111.7	82.1	54.4	49.3	57.9	< 0.01
95% CI	(53.1 to 170.3)	(36.0 to 128.2)	(20.2 to 88.6)	(18.6 to 80.0)	(26.2 to 89.6)	
Women						
No of populations	16706	18215	19296	20276	21213	
No of cases	44	40	34	26	30	
Age-adjusted incidence (Incidence/100,000 person-year)	50.6	39.5	27.1	16.7	18.2	< 0.01
95% CI	(17.1 to 84.1)	(12.0 to 67.0)	(6.3 to 47.9)	(2.0 to 31.4)	(2.5 to 33.9)	

Table 2. Trends for age- and sex-adjested cardiovascular risk characteristics among men and women aged 30 to 84 years in four Japanese communities from 1981 to 2005.

	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	*p* for trend
Age-adjusted, mean or percent						
Men						
Number	5350	4992	5175	5039	4900	
Age, year	55	56	58	59	60	
Systolic blood pressure, mmHg	137	134	133	134	133	<0.01
Diastolic blood puressure, mmHg	81	81	81	82	82	<0.01
Antihypertensive medication, %	19.8	18.6	17.2	18.0	20.1	0.550
Hypertention, %	49.2	44.1	41.3	44.7	44.6	<0.01
Body mass index, kg/m^2	22.7	22.9	23.3	23.5	23.8	<0.01
Overweight (BMI ≥25kg/m^2)	26.2	29.2	29.6	33.5	34.7	<0.01
Total cholestrol, mmol/L	4.75	4.89	4.98	5.13	5.23	<0.01
Total cholestrol ≥5.69 mmol/L, %	14.0	17.7	20.7	26.8	31.4	<0.01
Blood gulcose, mmol/L	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 ≥46g/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
Abnomal 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						
Number	7949	7781	8463	8436	8082	
Age, year	54	55	56	57	58	
Systolic blood pressure, mmHg	134	132	130	130	128	<0.01
Diastolic blood puressure, mmHg	79	78	78	78	77	<0.01
Antihypertensive medication, %	19.2	18.4	16.8	17.0	18.1	<0.01
Hypertention, %	42.0	37.1	34.0	34.9	33.6	<0.01
Body mass index, kg/m^2	23.5	23.4	23.3	23.3	23.2	<0.01
Overweight (BMI ≥25kg/m^2)	34.4	33.4	31.1	30.9	28.0	<0.01
Total cholestrol, mg/dl	5.09	5.24	5.27	5.44	5.49	<0.01
Total cholestrol ≥5.69 mmol/L, %	24.7	29.3	31.1	39.7	44.7	<0.01
Blood gulcose, mmol/L	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 ≥46g/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
Abnomal 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

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Author's individual contributions

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.

Appendix

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 CIRCS investigators who contributed to this study are as follows: 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

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Figure Legends

Figure 1. Determination of sudden cardiac death (SCD)

Figure 2. Trends for age- and sex-adjusted annual incidence of sudden cardiac death, 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 person among men and women aged 30-84 in four Japanese communities from 1981 to 2005, CIRCS. SCD with MI (SCD_MI) and SCD without MI (SCD_NMI), SCD within 1 hour (SCD1) and SCD between 1 and 24 hours (SCD1-24). SCD in emergency room or a hospital (SCD_ER) and SCD outside of a hospital (SCD_NER).

Figure 1

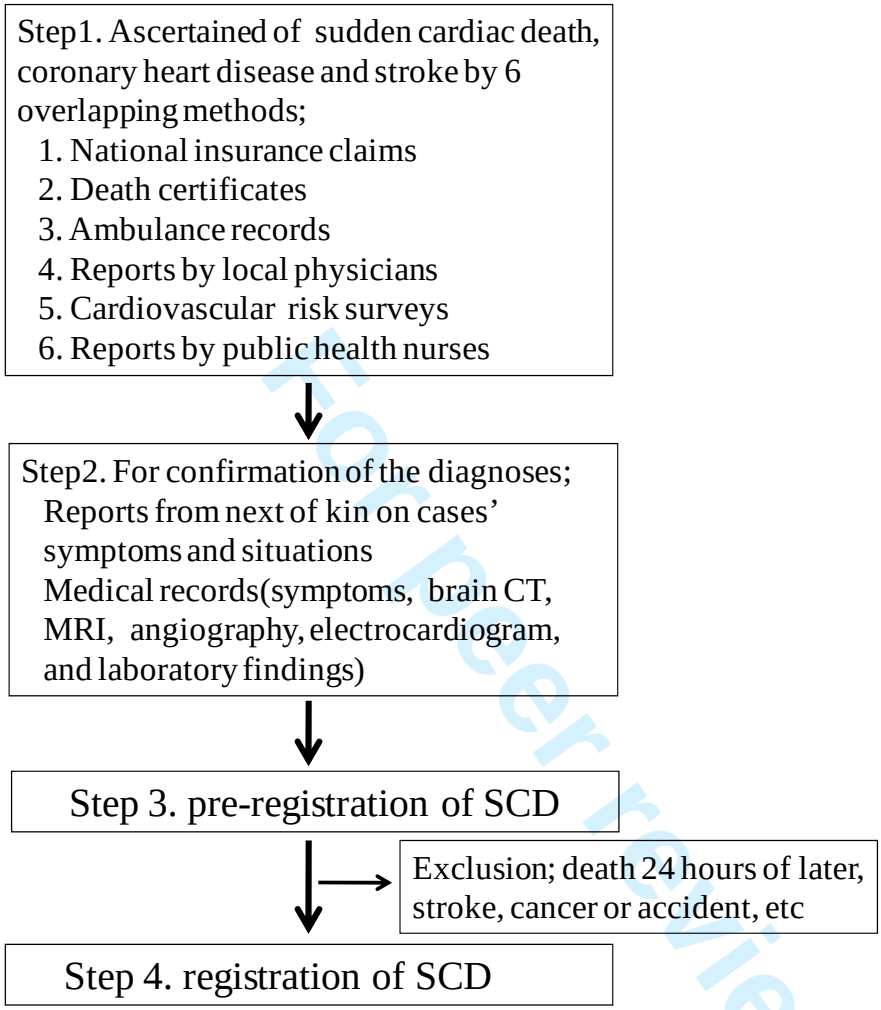
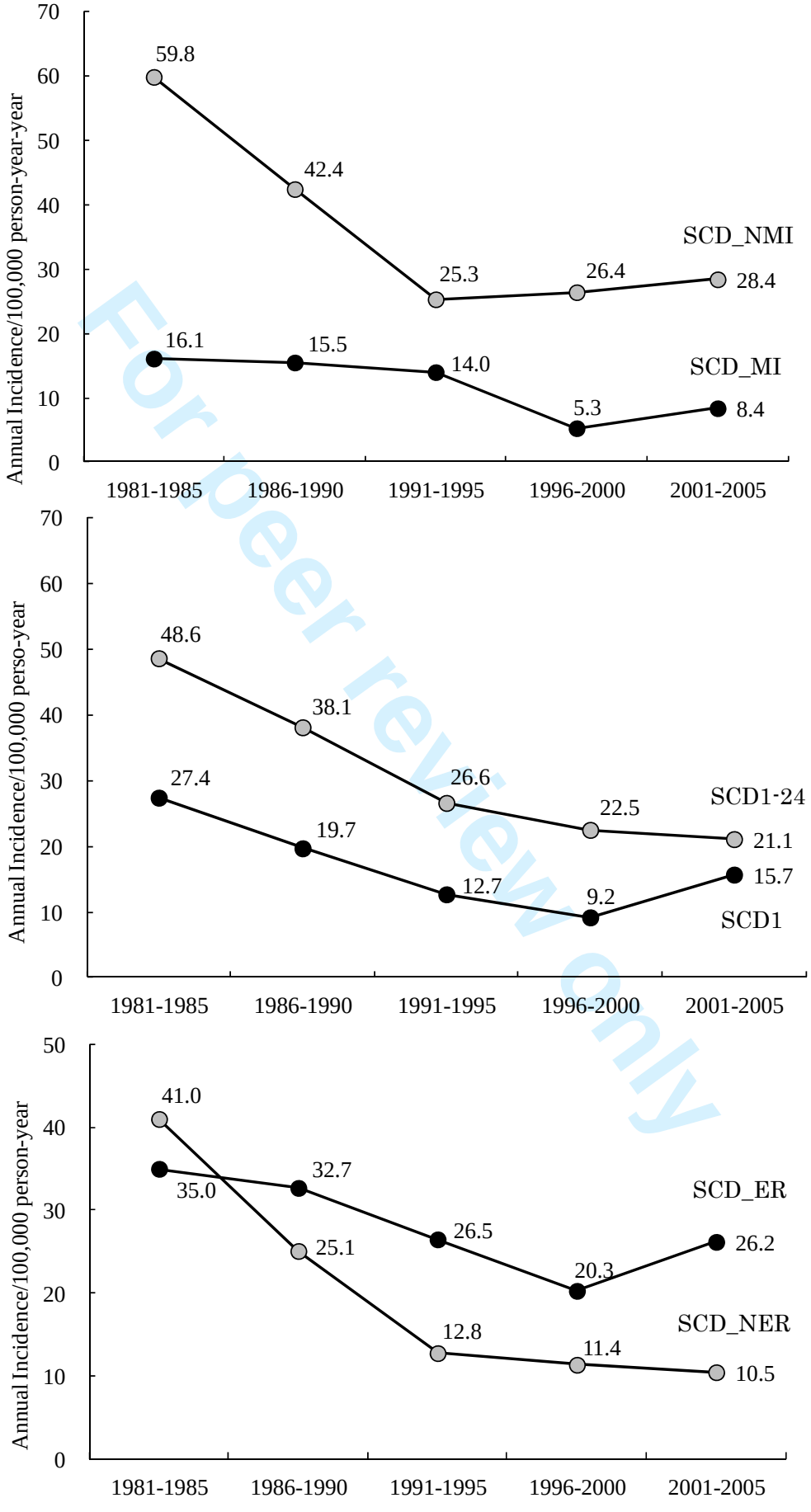


Figure 2



Supplemental Table 1. The Number of Sudden Cardiac Death (SCD) according to the Time of Symptom Onset and the Place of Death.

Place of death	Time of symptom onset		
	< 1 hour SCD1	1-24 hours SCD1-24	Total
Outside of hospital SCD_NER	58(4)	132(19)	190(23)
Emergency room or hospital SCD_ER	105(14)	176(80)	281(94)
Total	163(18)	308(99)	471(117)

In parentheses, the number of SCD with myocardial infarction (SCD_MI)

Supplemental Table 2. Trends for age- and sex-adjested cardiovascular risk characteristics among men and women aged 40 to 74 years in four Japanese communities from 1981 to 2005.

	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	*p* for trend
Age-adjusted, mean or percent						
Men						
Number	4678	4315	4408	4281	4038	
Age, year	55	56	57	59	60	
Systolic blood pressure, mmHg	137	134	133	135	133	<0.01
Diastolic blood puressure, mmHg	82	82	81	83	83	<0.01
Antihypertensive medication, %	19.7	18.6	17.1	18.0	19.2	0.322
Hypertention, %	50.2	41.6	41.6	45.3	45.1	<0.01
Body mass index, kg/m^2	22.8	23.0	23.3	23.6	24.0	<0.01
Overweight (BMI ≥25kg/m^2)	26.5	29.4	30.3	34.1	35.8	<0.01
Total cholestrol, mmol/L	4.76	4.90	4.99	5.15	5.27	<0.01
Total cholestrol ≥5.69 mmol/L, %	14.1	17.9	21.2	27.5	32.7	<0.01
Blood gulcose, mmol/L	61.9	69.6	68.0	63.8	62.3	<0.01
Diabetes mellitus, %	4.8	7.1	7.3	7.7	9.8	<0.01
Heavy drinking(ethanol intake ≥46g/day)	33.5	30.2	29.6	29.6	25.1	<0.01
Current smoking, %	61.0	56.3	52.4	49.9	44.6	<0.01
ECG findings						
Atrial fibrillation	1.3	1.5	1.1	1.3	1.3	0.639
Ventricular premature contraction	3.0	2.8	2.9	2.5	2.1	0.013
Supraventricular premature contraction	2.8	3.7	3.6	3.0	2.8	0.535
Major ST-T abnormality	4.5	4.0	3.7	4.0	3.9	<0.01
Minor ST-T abnormality	12.5	9.9	12.5	11.8	11.6	<0.01
PQ prolonged	1.4	1.1	1.3	1.4	1.0	0.465
Complete/incomplete right bundle branch block	5.3	5.0	5.1	5.6	6.1	0.449
Wide QRS	2.9	2.8	2.8	3.2	3.5	0.075
Abnomal Q wave	0.4	0.6	0.5	0.6	0.7	0.307
Left ventricular hypertrophy	29.3	27.6	23.3	19.5	17.5	<0.01
Women						
Number	6954	6766	7131	7041	6524	
Age, year	55	56	56	57	58	
Systolic blood pressure, mmHg	135	132	130	131	129	<0.01
Diastolic blood puressure, mmHg	79	78	78	79	78	<0.01
Antihypertensive medication, %	19.3	18.4	16.5	16.6	17.4	<0.01
Hypertention, %	43.4	38.1	34.7	35.8	34.1	<0.01
Body mass index, kg/m^2	23.6	23.5	23.5	23.5	23.3	<0.01
Overweight (BMI ≥25kg/m^2)	35.8	35.0	32.6	32.8	29.2	<0.01
Total cholestrol, mg/dl	5.12	5.28	5.33	5.53	5.59	<0.01
Total cholestrol ≥5.69 mmol/L, %	25.5	30.7	33.3	43.1	48.7	<0.01
Blood gulcose, mmol/L	58.2	65.7	63.2	57.6	56.6	<0.01
Diabetes mellitus, %	2.8	3.9	3.5	3.9	4.1	<0.01
Heavy drinking(ethanol intake ≥46g/day)	0.5	0.4	0.5	0.6	0.5	0.041
Current smoking, %	6.4	5.7	5.6	6.0	6.1	0.659
ECG findings						
Atrial fibrillation	0.6	0.5	0.3	0.3	0.3	<0.01
Ventricular premature contraction	2.0	2.2	1.7	1.8	1.9	0.269
Supraventricular premature contraction	2.3	2.5	2.9	2.4	2.5	0.653
Major ST-T abnormality	6.5	5.8	4.9	4.4	4.6	0.970
Minor ST-T abnormality	22.5	19.0	19.9	20.0	17.4	0.283
PQ prolonged	0.5	0.5	0.4	0.5	0.4	0.063
Complete/incomplete right bundle branch block	3.1	3.4	3.1	3.2	3.0	<0.01
Wide QRS	1.4	1.6	1.5	1.6	1.5	0.598
Abnomal Q wave	0.1	0.2	0.2	0.2	0.3	0.010
Left ventricular hypertrophy	10.8	9.6	7.7	5.7	4.5	<0.01

Supplemental Table 3. Trends for age- and sex-adjested cardiovascular risk characteristics among men and women aged 40 to 74 years in Ikawa and Kyowa with high participation rates from 1981 to 2005.

	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	*p* for trend
Age-adjusted, mean or percent						
Men						
Number	2698	2384	2533	2506	2381	
Age, year	55	55	57	59	59	
Systolic blood pressure, mmHg	139	136	134	135	133	<0.01
Diastolic blood puressure, mmHg	82	83	81	82	82	0.913
Antihypertensive medication, %	21.7	21.7	19.3	20.6	21.6	0.425
Hypertention, %	55.0	50.3	44.1	47.4	46.7	<0.01
Body mass index, kg/m^2	22.9	23.2	23.4	23.7	23.9	<0.01
Overweight (BMI ≥25kg/m^2)	27.3	32.1	29.0	32.7	36.0	<0.01
Total cholestrol, mmol/L	4.69	4.82	4.92	5.07	5.21	<0.01
Total cholestrol ≥5.69 mmol/L, %	13.4	15.5	18.5	24.0	30.5	<0.01
Blood gulcose, mmol/L	59.0	72.7	70.3	64.1	61.3	<0.01
Diabetes mellitus, %	4.2	9.1	8.1	8.1	10.3	<0.01
Heavy drinking(ethanol intake ≥46g/day)	39.0	37.3	34.3	34.7	27.7	<0.01
Current smoking, %	65.1	61.0	56.1	53.2	47.2	<0.01
ECG findings, %						
Atrial fibrillation	1.5	1.9	1.4	1.7	1.4	0.588
Ventricular premature contraction	3.4	2.9	3.6	2.6	2.2	0.011
Supraventricular premature contraction	3.2	3.4	3.5	3.2	3.1	0.520
Major ST-T abnormality	5.0	4.7	3.5	4.0	3.4	<0.01
Minor ST-T abnormality	11.2	9.3	11.3	10.8	9.9	0.507
PQ prolonged	1.4	1.1	0.9	1.2	1.0	0.375
Complete/incomplete right bundle branch block	5.1	4.9	4.8	4.8	5.6	0.628
Wide QRS	2.9	2.6	2.8	2.8	3.1	0.634
Abnomal Q wave	0.6	0.7	0.5	0.7	0.7	0.869
Left ventricular hypertrophy	31.1	29.8	29.1	21.6	21.5	<0.01
Women						
Number	3543	3299	3618	3686	3473	
Age, year	55	56	57	57	58	
Systolic blood pressure, mmHg	136	134	131	132	130	<0.01
Diastolic blood puressure, mmHg	80	80	78	78	78	<0.01
Antihypertensive medication, %	22.2	21.7	19.2	20.1	19.7	<0.01
Hypertention, %	47.3	42.6	36.9	37.8	35.7	<0.01
Body mass index, kg/m^2	24.0	24.1	23.9	23.9	23.8	<0.01
Overweight (BMI ≥25kg/m^2)	41.3	41.7	36.4	36.4	33.6	<0.01
Total cholestrol, mmol/L	5.06	5.23	5.26	5.42	5.51	<0.01
Total cholestrol ≥5.69 mmol/L, %	23.3	28.8	30.8	38.9	45.7	<0.01
Blood gulcose, mmol/L	54.8	67.7	65.3	58.3	56.4	<0.01
Diabetes mellitus, %	2.7	5.4	4.2	4.5	4.6	0.204
Heavy drinking(ethanol intake ≥46g/day)	0.4	0.3	0.5	0.7	0.5	0.140
Current smoking, %	5.3	4.2	4.3	4.7	4.8	0.600
ECG findings, %						
Atrial fibrillation	0.6	0.7	0.4	0.5	0.4	0.133
Ventricular premature contraction	2.4	2.7	1.8	2.0	2.2	0.119
Supraventricular premature contraction	2.7	2.7	2.7	2.5	3.1	0.653
Major ST-T abnormality	7.5	6.2	4.2	4.5	3.6	<0.01
Minor ST-T abnormality	20.8	18.2	18.2	17.9	12.9	<0.01
PQ prolonged	0.4	0.4	0.4	0.6	0.5	0.120
Complete/incomplete right bundle branch block	2.4	3.1	2.9	3.3	3.3	0.049
Wide QRS	1.1	1.5	1.3	1.5	1.6	0.107
Abnomal Q wave	0.1	0.2	0.1	0.1	0.3	0.254
Left ventricular hypertrophy	11.5	10.9	10.1	7.4	5.7	<0.01

Supplemental Table 4. Trends for age- and sex-adjested cardiovascular risk characteristics among men and women aged 40 to 74 years in Yao and Noichi with lower participation rates from 1981 to 2005.

	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	*p* for trend
Age-adjusted, mean or percent						
Men						
Number	1980	1931	1875	1775	1657	
Age, year	56	57	58	60	61	
Systolic blood pressure, mmHg	135	132	132	134	133	0.401
Diastolic blood puressure, mmHg	81	80	82	83	83	<0.01
Antihypertensive medication, %	17.0	14.9	14.1	14.2	15.8	0.251
Hypertention, %	43.7	37.5	38.3	42.2	42.6	0.598
Body mass index, kg/m^2	22.6	22.8	23.2	23.5	24.0	<0.01
Overweight (BMI ≥25kg/m^2)	25.3	26.1	32.0	36.2	35.6	<0.01
Total cholestrol, mmol/L	4.88	5.00	5.09	5.27	5.36	<0.01
Total cholestrol ≥5.69 mmol/L, %	15.3	20.9	24.7	32.6	35.9	<0.01
Blood gulcose, mmol/L	67.3	67.0	65.3	62.2	62.0	<0.01
Diabetes mellitus, %	5.4	4.9	6.3	7.0	9.0	<0.01
Heavy drinking(ethanol intake ≥46g/day)	26.7	21.6	23.1	22.2	21.1	<0.01
Current smoking, %	55.8	50.5	47.5	45.1	40.8	<0.01
ECG findings, %						
Atrial fibrillation	1.1	1.0	0.8	0.8	1.1	0.767
Ventricular premature contraction	2.5	2.7	2.0	2.4	2.1	0.362
Supraventricular premature contraction	2.1	4.1	3.8	2.7	2.5	0.781
Major ST-T abnormality	3.7	3.1	3.9	4.1	4.7	0.037
Minor ST-T abnormality	14.3	10.7	14.2	13.2	14.1	0.396
PQ prolonged	1.5	1.1	1.8	1.5	0.9	0.567
Complete/incomplete right bundle branch block	5.5	5.2	5.4	6.6	6.8	0.023
Wide QRS	3.0	3.1	2.8	3.8	4.1	0.035
Abnomal Q wave	0.2	0.6	0.5	0.5	0.5	0.159
Left ventricular hypertrophy	27.0	25.0	15.4	16.4	11.5	<0.01
Women						
Number	3411	3467	3513	3355	3051	
Age, year	55	55	56	58	59	
Systolic blood pressure, mmHg	133	131	130	130	129	<0.01
Diastolic blood puressure, mmHg	79	77	79	80	79	0.025
Antihypertensive medication, %	16.4	15.3	13.5	12.8	14.8	0.014
Hypertention, %	39.3	33.7	32.4	33.6	32.4	<0.01
Body mass index, kg/m^2	23.1	23.0	23.0	23.0	22.8	<0.01
Overweight (BMI ≥25kg/m^2)	30.3	28.6	28.7	29.0	24.2	<0.01
Total cholestrol, mmol/L	5.20	5.33	5.40	5.64	5.67	<0.01
Total cholestrol ≥5.69 mmol/L, %	28.4	32.5	35.9	47.7	52.0	<0.01
Blood gulcose, mmol/L	61.6	63.9	61.3	56.8	56.9	<0.01
Diabetes mellitus, %	2.8	2.6	2.8	3.4	3.5	0.020
Heavy drinking(ethanol intake ≥46g/day)	0.5	0.3	0.5	0.5	0.7	0.151
Current smoking, %	7.5	7.1	6.9	7.4	7.5	0.774
ECG findings, %						
Atrial fibrillation	0.6	0.3	0.2	0.1	0.2	<0.01
Ventricular premature contraction	1.5	1.8	1.7	1.6	1.6	0.974
Supraventricular premature contraction	2.0	2.3	3.1	2.2	2.0	0.900
Major ST-T abnormality	5.4	5.4	5.6	4.3	5.6	0.613
Minor ST-T abnormality	24.2	19.8	21.6	22.3	22.5	0.721
PQ prolonged	0.6	0.6	0.4	0.3	0.3	0.008
Complete/incomplete right bundle branch block	3.9	3.6	3.3	3.0	2.6	0.005
Wide QRS	1.7	1.6	1.8	1.6	1.4	0.505
Abnomal Q wave	0.1	0.2	0.3	0.2	0.4	0.015
Left ventricular hypertrophy	10.1	8.4	5.1	4.0	3.1	<0.01

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	5,6,7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	5,figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	8,table1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9,10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.