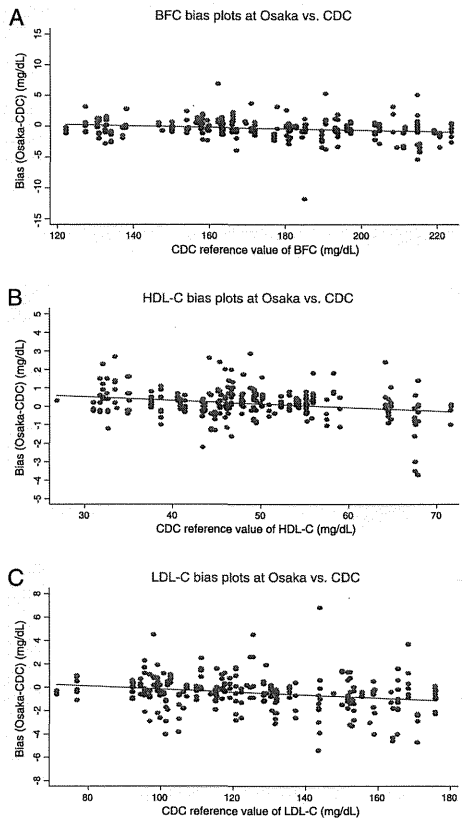

Fig. 1. Scatter plots of bias at Osaka vs. CDC for BFC (A), HDL-C (B) and LDL-C (C). (A) CDC: US Centers for Disease Control and Prevention. BFC: Bottom fraction cholesterol. x-axis indicates CDC reference value of BFC (unit: mg/dL) in the concentration range from 122.3 to 223.7 mg/dL and y-axis indicates the BFC bias between Osaka and CDC (unit: mg/dL). y (bias (Osaka–CDC)) = −0.012 × (CDC reference value) + 1.759 [n: 280, R^2 = 0.042 (p-value: 0.001)]. p-value and 95% CI are 0.001 and (−0.019, −0.005) for slope, respectively. p-value and 95% CI are 0.004 and (0.551, 2.968) for intercept, respectively. (B) CDC: US Centers for Disease Control and Prevention. HDL-C: High-density lipoprotein cholesterol. x-axis indicates CDC reference value of HDL-C (unit: mg/dL) in the concentration range from 27.0 to 72.4 mg/dL and y-axis indicates the HDL-C bias between Osaka and CDC (unit: mg/dL). y (bias (Osaka–CDC)) = −0.020 × (CDC reference value) + 1.112 [n: 280, R^2 = 0.063 (p-value: <0.001)]. p-value and 95% CI are <0.001 and (−0.029, −0.011) for slope, respectively. p-value and 95% CI are <0.001 and (0.671, 1.553) for intercept, respectively. (C) CDC: US Centers for Disease Control and Prevention. LDL-C: Low-density lipoprotein cholesterol. x-axis indicates CDC reference value of LDL-C (unit: mg/dL) in the concentration range from 71.5 to 173.3 mg/dL and y-axis indicates the LDL-C bias between Osaka and CDC (unit: mg/dL). y (bias (Osaka–CDC)) = −0.013 × (CDC reference value) + 1.186 [n: 280, R^2 = 0.059 (p-value: <0.001)]. p-value and 95% CI are <0.001 and (−0.020, −0.007) for slope, respectively. p-value and 95% CI are 0.004 and (0.376, 1.996) for intercept, respectively.

2.5. Statistical analysis

We used protocol EP9-A from the Clinical and Laboratory Standards Institute [20–22] for bias estimation and STATA12 analysis program for all other calculations.

3. Results

The concentration ranges of the 67 lots used in the CRMLN surveys were 122.3–223.7 mg/dL, 27.0–72.4 mg/dL, and 71.5–173.3 mg/dL for BFC, HDL-C, and LDL-C, respectively. For 15 years, the reference laboratory at Osaka meets CRMLN accuracy and precision performance goals for BFC, HDL-C and LDL-C (Table 2).

The mean percent bias between the Osaka laboratory and the CDC reference laboratory was <0.5% for all analytes, with limits of agreement being very narrow. Bias and regression analyses show that the bias, though small, is significant. The observed bias is well-below the allowable bias for CRMLN laboratories. The individual sample biases at low analyte concentrations tend to be positive, and at high concentration the biases are negative for all analytes (Fig. 1A–C).

From the estimation by regression line, the absolute bias between CDC and Osaka in the clinical decision levels was estimated as 0.40 mg/dL for BFC at 180 mg/dL, 0.32 mg/dL for HDL-C at 40 mg/dL and 0.62 mg/dL for LDL-C at 140 mg/dL. The bias was small, but the mean value of absolute bias in upper 10% and lower 10% concentration of reference value was larger than that in middle 80% for BFC (1.45 mg/dL vs. 0.98 mg/dL: p = 0.01). There was no difference of bias related to concentration for HDL-C (0.69 mg/dL vs. 0.54 mg/dL: p = 0.19) and LDL-C (1.04 mg/dL vs. 1.10 mg/dL: p = 0.70) (Table 3).

Assessing measurement bias over time showed no significant trend from May 1997 to October 2012. This is indicated in no significant bias observed with lot bq47, which was analyzed quarterly over 2.5 years. Furthermore, no significant trend in measurement bias was observed for this period (Fig. 2).

Correlation plots between BFC (x-axis, unit: %bias vs. CDC) and LDL-C (y-axis, unit: %bias vs. CDC) of the Osaka laboratory are positively correlated (y = 1.088x − 0.208, n = 280, R^2 = 0.652 (p-value < 0.001), p-value and 95% CI for slope are <0.001 and (0.994, 1.182), respectively, p-value and 95% CI for intercept are <0.001 and (−0.289, −0.128), respectively) (Fig. 3D). In contrast, only weak correlations are observed between the biases from BFC (x-axis, unit: %bias vs. CDC) and HDL-C (y-axis, unit: %bias vs. CDC). (y = 0.480x + 0.513, n = 280, R^2 = 0.057 (p-value < 0.001)) (Fig. 3E). Similarly, only weak correlations existed between the biases from LDL-C (x-axis, unit: %bias vs. CDC) and HDL-C (y-axis, unit: %bias vs. CDC). (y = −0.441x + 0.299, n = 280, R^2 = 0.087 (p-value < 0.001)) (Fig. 3F).

4. Discussion

LDL-C is a key biomarker for cardiovascular disease risk assessment, and it is the primary target for treatment. No RMP currently exists for direct measurement of LDL-C. Therefore, the BQ approach was established to assign LDL-C reference values to serum materials. Like all RMPs, it is not intended for use in patient care because of its technical demands (e.g. overnight UC, manual volumetric sampling, and reconstitution of the bottom fractions) [23,24]. However, the technical limitations of this method such as sample throughput or complexity are similar to those of other RMPs [25]. Because measurement results are traceable to an RMP and the International System of Units, it is important to assure that this method is highly reproducible and accurate over time. Efforts by CDC and its partners to assure the accuracy of LDL-C measurements have been ongoing for over 15 years. The CRMLN assures the accuracy of LDL-C measurements by providing reference measurement service to the clinical laboratory community to establish metrological traceability to the CDC RMP. Only a few studies have examined the performance of BQ RMP [26–28]. This study describes the performance of LDL-C value-assignment performed in one CRMLN laboratory over 15 years.

The actual cholesterol measurements are traceable to pure compound certified reference materials and thus are traceable to SI as outlined in ISO 17511. The isolation of the lipid fractions is traceable to a RMP, which is also outlined in ISO 17511. To our knowledge, ISO 17511 does not define nor require a so called "gold standard". Because

Table 3
Comparison of absolute bias between middle 80% and upper/lower 10% of reference values.

Lipid	Range of middle 80% of reference (CDC) value	Mean of absolute bias in middle 80% of reference (CDC) value	Mean of absolute bias in upper 10% and lower 10%	p-value
BFC	132.80–214.79 mg/dL	0.98 mg/dL	1.45 mg/dL	0.01
HDL-C	33.50–64.50 mg/dL	0.54 mg/dL	0.69 mg/dL	0.19
LDL-C	95.50–165.39 mg/dL	1.10 mg/dL	1.04 mg/dL	0.70

BFC: Bottom fraction cholesterol.

cholesterol measurements are traceable to SI, we prefer to use the term "accuracy" in the manuscript. The CDC BQ RMP is classified as a higher order reference measurement procedure used to assign reference values on frozen reference materials. The CDC LDL-C RMP is the reference point for LDL-C recommended by the NCEP Lipoprotein Measurement Working Group. The accuracy reported in the paper refers to the accuracy compared to the CDC LDL reference values. The CRMLN laboratories achieve traceability to CDC RMP through monitoring.

The BQ method combines the removal of triglyceride (TG)-rich VLDL by UC, isolation of HDL from the UC bottom fraction, and cholesterol analysis of the bottom fraction and HDL supernatant. Therefore, the performance of HDL-C and BFC measurements needs to be considered when assessing factors affecting LDL-C target value assignments.

Over 15 years, the BQ RMP operated at the Osaka laboratory provided highly accurate and precise measurements of HDL-C and LDL-C, as indicated in the high agreement with the CDC reference laboratory. The observed mean bias is well within the allowable bias for CRMLN laboratories. The CRMLN focuses mainly on assuring accuracy of measurements around the clinical decision levels, which would be 40–60 mg/dL for HDL-C and 100–160 mg/dL for LDL-C (Fig. 1B,C); most of the serum pools used in CRMLN cover these ranges. Within these ranges, no significant mean bias and no proportional bias between the 2 methods were observed (Table 3). Considering that the LDL-C value assignments are derived from two separate measurements and that this RMP is technically very demanding, the overall performance and performance over time is remarkable. The data demonstrate that this method can be operated in a highly precise manner over long periods of time.

The CDC BQ method has been accepted as the most reliable RMP for HDL-C and LDL-C measurements, and it was recommended by the NCEP as the RMP method for HDL-C and LDL-C. The BQ method was used to establish the concentrations of the major lipoprotein classes in almost all epidemiological studies and clinical trials on which current guidelines for CVD risk assessment are based. It is used in the assignment of LDL-C reference values to calibrators or standards, patient specimens or bench-level quality control materials, and in the evaluation of direct [29,30] and homogeneous methods [31–33]. In the "Program Recommendations for the Measurement of Low-Density Lipoprotein Cholesterol: Executive Summary" [16], Bachorik et al. encouraged the early development of homogeneous methods and suggested that new methods for measuring LDL-C should be developed that are capable of directly quantifying LDL-C, and which should not be based on calculations of the difference between two or more measured values. The developed homogeneous methods have some advantages, such as the direct measurement of LDL-C by automated analytical instruments and possible use of non-fasting samples. However, they do have limitations [31–33]. Therefore, the BQ method is needed to assure accurate patient data that can be compared to current clinical decision points.

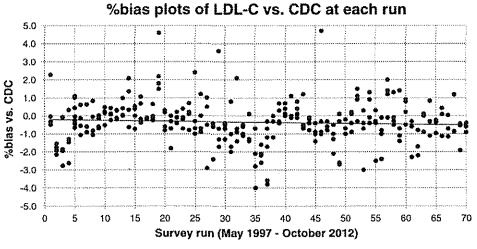

Fig. 2. %Bias plots of LDL-C vs. CDC at each survey run. CDC: US Centers for Disease Control and Prevention. LDL-C: Low-density lipoprotein cholesterol. x-axis indicates survey run number during May 1997 and October 2012 with 70 runs and y-axis indicates %bias of LDL-C vs. CDC. The accuracy criteria of %bias plots of LDL-C is ±2% of CDC reference value. Each survey run consists of 3 to 5 CDC pools for beta quantification analysis.

The reference values obtained with the BQ approach are based on the density of lipoprotein particles and their separation using specific UC conditions. LDL is not a unique molecular species; it consists of a group of similar, mixed, and atherogenic lipoproteins that vary to some degree in their chemical composition and physico-chemical particles [34]. The bottom fraction contains minor, but atherogenic lipoprotein classes such as IDL and Lp(a) [17,35,36]. In normal individuals, both lipoprotein classes can be expected to contribute 2–4 mg/dL, on average, to the total cholesterol measurement; however, their concentrations may be higher in patients with CHD and in patients at risk of developing CHD by virtue of dyslipidemia. The alterations of these lipid classes can affect cardiovascular disease risk, which may not be adequately detected by the BQ approach. Therefore, new approaches, such as measurement of LDL particle numbers, have been suggested to better assess cardiovascular risk in patients with such conditions [37]. The limitation of the BQ approach needs to be considered when using this RMP for reference value assignments.

The strong correlation between the BFC bias and the LDL-C bias, as well as the weak correlation between the LDL-C bias and HDL-C bias, suggests that the accuracy of LDL-C performed is directly affected by the accuracy of the BFC measurement and, to a much lesser extent, by the HDL-C measurement. This is expected because the LDL-C is calculated from the BFC, while HDL-C is an independent measurement. Because of the good agreement between CDC RMP and Osaka RMP, the different UC conditions used by these laboratories do not appear to have a profound effect on the mean bias or individual sample biases.

In conclusion, this study demonstrates that accurate measurement of BFC is critical for LDL-C value assignment. The BQ RMP performed at the Osaka laboratory is accurate and consistent over time. This assures that calibrations of assays used in patient care are accurate, and that measurements performed in patient care meet established performance criteria. Thus, the BQ RMP ensures that current guidelines using LDL-C levels for CVD risk assessments can be applied correctly and consistently.

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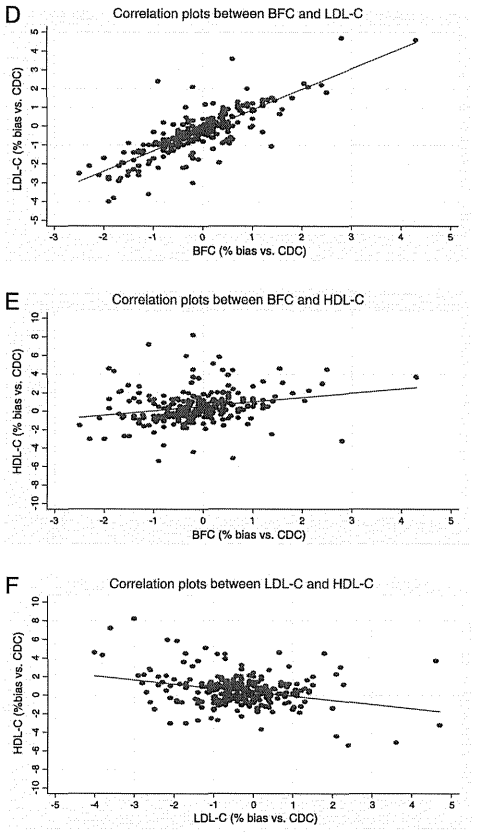

Fig. 3. Scatter plots of correlation and regression at Osaka between BFC and LDL-C (D), BFC and HDL-C (E), and LDL-C and HDL-C (F). (D) CDC: US Centers for Disease Control and Prevention. BFC: Bottom fraction cholesterol. LDL-C: Low-density lipoprotein cholesterol. CI: Confidence interval. x-axis indicates Osaka BFC (unit: %bias vs. CDC) and y-axis indicates Osaka LDL-C (unit: %bias vs. CDC). y (Osaka LDL-C) = 1.088 × (Osaka BFC) − 0.208 [n: 280, R^2 = 0.652 (p-value: <0.001)]. p-value and 95% CI are <0.001 and (0.994, 1.182) for slope, respectively. p-value and 95% CI are <0.001 and (−0.289, −0.128) for intercept, respectively. (E) CDC: US Centers for Disease Control and Prevention. BFC: Bottom fraction cholesterol. HDL-C: High-density lipoprotein cholesterol. CI: Confidence interval. x-axis indicates Osaka BFC (unit: %bias vs. CDC) and y-axis indicates Osaka HDL-C (unit: %bias vs. CDC). y (Osaka HDL-C) = 0.480 × (Osaka BFC) + 0.513 [n: 280, R^2 = 0.057 (p-value: <0.001)]. p-value and 95% CI are <0.001 and (0.250, 0.711) for slope, respectively. p-value and 95% CI are <0.001 and (0.316, 0.710) for intercept, respectively. (F) CDC: US Centers for Disease Control and Prevention. HDL-C: High-density lipoprotein cholesterol. LDL-C: Low-density lipoprotein cholesterol. CI: Confidence interval. x-axis indicates Osaka LDL-C (unit: %bias vs. CDC) and y-axis indicates Osaka HDL-C (unit: %bias vs. CDC). y (Osaka HDL-C) = −0.441 × (Osaka LDL-C) + 0.299 [n: 280, R^2 = 0.087 (p-value: <0.001)]. p-value and 95% CI are <0.001 and (−0.609, −0.273) for slope, respectively. p-value and 95% CI are 0.004 and (0.098, 0.499) for intercept, respectively.

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ORIGINAL ARTICLE
Preventive Medicine

Heavy Alcohol Consumption and Risk of Atrial Fibrillation

– The Circulatory Risk in Communities Study (CIRCS) –

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Background: Evidence regarding the relationship between different levels of alcohol consumption and the risk of atrial fibrillation (AF) is currently limited in Asian populations.

Methods and Results: Between 1991 and 1995, a total of 8,602 Japanese men and women aged 30–80 years took part in the first examination of the Circulatory Risk in Communities Study (CIRCS), a population-based cohort study in Japanese communities. An interviewer obtained detailed information on weekly alcohol intake. During the follow-up period, the incidence of AF was ascertained from annual ECG records, the subject's medical history of AF, and cardiovascular disease surveillance. The hazard ratios (HRs) of incident AF and the 95% confidence intervals (CIs) relative to the never-drinking group were calculated with adjustment for potential confounding factors by using the Cox proportional hazard model. During a median follow-up period of 6.4 years, 296 incidents of AF occurred. A higher incidence of AF was observed among participants with an ethanol intake >69 g/day, compared with never-drinkers. Compared with the never-drinkers, the multivariable-adjusted HRs (CIs) of past, light (<23 g/day), light–moderate (23–46 g/day), moderate (46–69 g/day), and heavy (>69 g/day) drinkers were 1.30 (0.68–2.49), 0.89 (0.60–1.32), 1.19 (0.73–1.95), 1.36 (0.79–2.35), and 2.90 (1.61–5.23), respectively.

Conclusions: Heavy alcohol consumption is associated with a higher risk of AF. (*Circ J* 2014; **78:** 955–961)

Key Words: Alcohol; Atrial fibrillation; Epidemiology; Risk factors

Atrial fibrillation (AF) is one of the most commonly diagnosed cardiac arrhythmias in clinical practice, affecting 2.3 million people in the United States.[1] Individuals with AF are at substantially increased risk of stroke and have double the mortality rate from cardiovascular disease and overall mortality, compared with those with normal sinus rhythms.[2–4] Epidemiological studies have identified several risk factors for AF, including hypertension, diabetes mellitus, obesity, heavy alcohol drinking, and cardiac dysfunction.[1–12] Although several previous studies have found significant associations between heavy alcohol consumption and increased risk of AF in Western countries,[13–24] few have shown an association between alcohol consumption and AF among Japanese. Furthermore, there is a paucity of data demonstrating the dose-response relationship between alcohol consumption and AF incidence. Alcohol consumption may have significant effects on the incidence of AF among Japanese in comparison with Western populations, as Japanese people do not have sufficient levels of alcohol dehydrogenase.[25]

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To examine the relationship between alcohol consumption and risk of AF, we used data from follow-up of men and women in the Circulatory Risk in Communities Study (CIRCS). Although previous studies conducted in Western countries have detected most AF cases from information derived from discharge records,[17,20,21] the CIRCS is able to detect symptomatic AF and asymptomatic AF not only from AF treatment information but also from annual ECG records, as this survey has been conducted annually since 1963.

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Table 1. Age and Sex-Adjusted Means or Prevalence of Baseline Characteristics of Participants According to Habitual Alcohol Consumption Category (Cross-Sectional Survey) in the Circulatory Risk in Communities Study (CIRCS)

	Alcohol consumption (ethanol g/day)						P for difference
	Never	Past	Light (<23)	Light-moderate (23–46)	Moderate (46–69)	Heavy (>69)	
Men							
n	640	202	758	749	582	227	
Ethanol intake, g/day	0	32.4	11.9	29.4	49.0	75.9	–
Age, years	59.1	64.0	55.9	57.1	55.9	52.7	–
Atrial fibrillation, %	0.9	2.3	0.8	0.8	1.6	1.9	0.28
Current smoking, %	47.1	44.7	42.2	52.3	63.9	70.0	<0.0001
BMI, kg/m^2	23.4	23.4	23.3	23.0	23.1	22.9	0.07
Obesity (BMI ≥30), %	2.5	2.9	2.4	1.5	2.2	2.0	0.74
Systolic BP, mmHg	130.2	129.9	130.7	130.5	130.4	131.4	0.95
Diastolic BP, mmHg	79.1	79.1	79.4	80.0	79.9	79.5	0.63
Antihypertensive medication, %	18.8	18.2	19.4	16.2	18.7	21.8	0.45
Hypertension, %	36.9	33.3	37.0	33.7	35.6	38.9	0.59
Blood glucose, mg/dl	118.5	123.4	118.7	122.7	123.0	122.7	0.13
Hyperglycemia, %	18.7	25.8	22.6	23.5	25.4	28.3	0.02
Total cholesterol, mg/dl	195.6	188.7	192.8	196.2	189.6	188.7	0.0003
Total cholesterol ≥220 mg/dl, %	22.5	21.5	22.6	23.2	19.3	16.7	0.23
Major ST-T abnormality, %	2.6	7.7	3.0	4.0	3.5	3.9	0.03
Previous MI, %	1.5	1.2	1.1	0.8	0.4	1.1	0.53
Heart failure, %	0.3	0	0.4	0.1	0.2	0.1	0.75
Women							
n	4,570	96	669	71	13	5	
Ethanol intake, g/day	0	17.3	6.4	27.8	48.6	102.4	–
Age, years	56.3	53.9	49.9	51.3	50.5	50.2	–
Atrial fibrillation, %	1.0	2.1	0.4	0.2	0.2	0.2	0.46
Current smoking, %	4.0	31.1	11.9	37.6	38.0	19.5	<0.0001
BMI, kg/m^2	23.2	23.1	22.8	23.0	23.9	26.0	0.05
Obesity (BMI ≥30), %	4.0	3.3	3.3	0.4	8.1	20.4	0.18
Systolic BP, mmHg	129.8	132.5	131.4	127.8	128.3	124.7	0.16
Diastolic BP, mmHg	79.0	81.0	79.4	77.9	81.1	80.9	0.35
Antihypertensive medication, %	16.3	11.8	16.4	20.5	1.0	21.0	0.45
Hypertension, %	34.3	37.9	36.6	29.4	24.6	21.6	0.62
Blood glucose, mg/dl	112.2	108.1	111.4	114.0	108.0	116.8	0.74
Hyperglycemia, %	12.7	10.2	11.4	13.1	9.6	26.5	0.80
Total cholesterol, mg/dl	204.6	207.8	203.8	208.9	225.9	190.4	0.14
Total cholesterol ≥220 mg/dl, %	32.3	35.7	31.7	39.9	49.4	23.4	0.48
Major ST-T abnormality, %	4.8	4.5	5.8	6.6	16.5	1.2	0.33
Previous MI, %	0.3	0.1	0.3	0.1	0.1	0.1	0.99
Heart failure, %	0.3	0.1	0.3	0.2	0.2	0.2	0.99

Hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or use of antihypertensive medication. Hyperglycemia was defined as a fasting glucose level ≥110 mg/dl, a non-fasting glucose level ≥140 mg/dl or use of medication for diabetes.
BMI, body mass index; BP, blood pressure; MI, myocardial infarction.

Methods

Study Design and Subjects

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 have been previously reported.[26–28] In brief, participants in this study were Japanese men and women living in the north-eastern rural community of Ikawa (total census population of 6,206 in 1995), the southwestern rural community of Noichi (total census population of 15,828 in 1995), the central rural community of Kyowa (total census population of 17,322 in 1995), and the Minami Takayasu district of Yao, which is a southwestern urban suburb (total census population of 23,654 in 1995). All analyses were limited to men and women aged 30–80 years. Annual cardiovascular risk surveys have been conducted in the district of Yao City, Ikawa, and Noichi since 1963, and in Kyowa since 1981, by a research team from the Osaka Medical Center for Health Science and Promotion, University of Tsukuba, Ehime University, and Osaka University.

For the present study, we analyzed data from 8,602 Japanese men and women aged 30–80 years who participated in the CIRCS between 1991 and 1995. The main aim was to examine the association between cardiovascular risk factors, particularly

Table 2. Age and Sex-Adjusted Means or Prevalence of Baseline Characteristics of Participants With Incident Atrial Fibrillation (AF) and Those Without AF (Longitudinal Survey) in the Circulatory Risk in Communities Study (CIRCS)

	Incident AF	No AF	P value
Men			
n	110	2,465	
Age, years	59.3	57.1	–
Ethanol intake, g/day	32.5	25.7	0.0025
Heavy drinker (ethanol intake ≥69 g/day), %	15.0	6.4	0.0005
Current smoking, %	54.2	50.1	0.40
BMI, kg/m²	23.4	23.2	0.45
Obesity (BMI ≥30), %	3.8	2.1	0.26
Systolic BP, mmHg	131.3	130.6	0.72
Diastolic BP, mmHg	79.7	79.7	0.99
Antihypertensive medication, %	19.5	18.6	0.82
Hypertension, %	36.0	36.3	0.95
Blood glucose, mg/dl	127.9	120.8	0.07
Hyperglycemia, %	32.3	21.9	0.01
Total cholesterol, mg/dl	192.7	192.9	0.94
Total cholesterol ≥220 mg/dl, %	25.7	21.1	0.24
Major ST-T abnormality, %	3.2	3.3	0.95
Previous MI, %	2.6	0.9	0.07
Heart failure, %	0	0.2	–
Women			
n	186	4,445	
Age, years	56.7	55.2	–
Ethanol intake, g/day	1.61	1.49	0.79
Heavy drinker (ethanol intake ≥69 g/day), %	0.54	0.07	0.03
Current smoking, %	3.4	5.4	0.24
BMI, kg/m²	23.7	23.1	0.005
Obesity (BMI ≥30), %	8.0	3.4	0.0009
Systolic BP, mmHg	128.0	129.8	0.17
Diastolic BP, mmHg	77.7	79.0	0.10
Antihypertensive medication, %	15.3	16.3	0.74
Hypertension, %	31.3	34.1	0.43
Blood glucose, mg/dl	118.0	112.3	0.01
Hyperglycemia, %	15.7	12.5	0.20
Total cholesterol, mg/dl	203.2	204.7	0.58
Total cholesterol ≥220 mg/dl, %	28.2	32.4	0.22
Major ST-T abnormality, %	2.9	4.7	0.25
Previous MI, %	0	0.3	–
Heart failure, %	0.5	0.3	0.63

Hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or use of antihypertensive medication. Hyperglycemia was defined as a fasting glucose level ≥110 mg/dl, a non-fasting glucose level ≥140 mg/dl or use of medication for diabetes.
Abbreviations as in Table 1.

alcohol intake and AF incidence, using data from the prospective observational cohort study.

Informed consent was obtained from community representatives to conduct an epidemiological study based on guidelines established by the Council for International Organizations of Medical Science.[29] This study was approved by the Ethics Committee of the Osaka Medical Center for Health Science and Promotion.

Surveillance for AF

Trained interviewers obtained information about past and present history of physician-diagnosed AF from the participants in the annual risk factor surveys. A 12-lead ECG tracing was obtained in the supine position in the risk factor surveys and coded with the Minnesota Code (2nd version)[30] by trained physician-epidemiologists. Information on embolic stroke because of AF was obtained from systematic hospital surveillance of stroke.[26–28]

Of the 8,602 participants, 8,516 who were free of clinical AF were followed up to determine incident AF that occurred by the end of 2000. The majority of participants (7,206, 84.6%) received a follow-up examination at least once during the follow-up period. During this follow-up period, 296 cases of AF were identified; 254 cases (85.8%) diagnosed by ECG during the annual risk factor surveys, 36 cases (12.2%) of physician-diagnosed AF from the risk factor surveys, and 6 cases (2.0%) by hospital surveillance of stroke.

Table 3. Hazard Ratios (HR) and 95% Confidence Intervals (CI) of Atrial Fibrillation (AF) According to Habitual Alcohol Consumption (Longitudinal Survey) in the Circulatory Risk in Communities Study (CIRCS)

	Alcohol consumption (ethanol g/day)					
	Never	Past	Light (<23)	Light-moderate (23–46)	Moderate (46–69)	Heavy (>69)
Men						
n	524	161	614	625	470	174
AF cases	18	9	19	26	22	16
Person-years	3,289	959	3,830	3,884	2,939	1,088
Incidence (/1,000)	5.47	9.38	4.96	6.69	7.49	14.71
Age-adjusted HR	1.00	1.58 (0.71–3.53)	0.95 (0.50–1.82)	1.27 (0.69–2.31)	1.54 (0.82–2.87)	3.31 (1.67–6.55)
Multivariate-adjusted*HR	1.00	1.50 (0.67–3.35)	0.91 (0.48–1.74)	1.22 (0.67–2.23)	1.47 (0.78–2.77)	3.14 (1.58–6.24)
Women						
n	3,949	78	530	53	10	4
AF cases	164	2	17	2	0	1
Person-years	25,633	412	3,332	320	69	35
Incidence (/1,000)	6.40	4.85	5.10	6.25	–	28.57
Age-adjusted HR	1.00	0.77 (0.19–3.10)	0.86 (0.52–1.43)	1.05 (0.26–4.23)	–	4.30 (0.60–30.8)
Multivariate-adjusted*HR	1.00	0.89 (0.22–3.62)	0.90 (0.54–1.50)	1.21 (0.29–4.97)	–	3.56 (0.48–26.4)
Total						
n	4,473	239	1,144	678	480	178
AF cases	182	11	36	28	22	17
Person-years	28,922	1,371	7,162	4,204	3,008	1,123
Incidence (/1,000)	6.29	8.02	5.03	6.66	7.31	15.1
Age and sex-adjusted HR	1.00	1.28 (0.67–2.44)	0.88 (0.60–1.31)	1.16 (0.71–1.89)	1.34 (0.78–2.29)	2.94 (1.64–5.26)
Multivariate-adjusted**HR	1.00	1.30 (0.68–2.49)	0.89 (0.60–1.32)	1.19 (0.73–1.95)	1.36 (0.79–2.35)	2.90 (1.61–5.23)

*HRs were adjusted for age, cigarette smoking status, BMI, hypertension, hyperglycemia, hyperlipidemia, major ST-T abnormality, previous MI and heart failure.
**HRs were adjusted for age, sex, cigarette smoking status, BMI, hypertension, hyperglycemia, hyperlipidemia, major ST-T abnormality, previous MI and heart failure.
Hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or use of antihypertensive medication. Hyperglycemia was defined as a fasting glucose level ≥110 mg/dl, a non-fasting glucose level ≥140 mg/dl or use of medication for diabetes.
Abbreviations as in Table 1.

Baseline Examination

Systolic and 5th-phase diastolic blood pressure (BP) was measured by trained technicians using a standard mercury sphygmomanometer on the right arm of the seated participant after a rest period of at least 5 min. Hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or use of antihypertensive medication. Serum total cholesterol was measured via an enzymatic method at the laboratory of the Osaka Medical Center for Health Science and Promotion, an international member of the US National Cholesterol Reference Method Laboratory Network.[31] Hyperlipidemia was defined as a total cholesterol level ≥ 220 mg/dl (5.69 mmol/L) or use of lipid-lowering medication. Body mass index (BMI) was calculated as the weight (kg)/height (m)². Hyperglycemia was defined as a fasting glucose level ≥110 mg/dl, a non-fasting glucose level ≥140 mg/dl or use of diabetes mellitus medication. An interviewer obtained histories for smoking habit and weekly alcohol intake in units of '*go*' (a traditional Japanese unit of volume corresponding to 23 g of ethanol), which was then converted to grams of ethanol per day.[32,33] One *go* is 180 ml of sake and corresponds to 1 bottle (633 ml) of beer, 2 single shots (75 ml) of whiskey, or 2 glasses (180 ml) of wine. Participants consuming more than 0.3 *go* per week were regarded as current drinkers. Participants smoking at least 1 cigarette per day were classified as current smokers. Previous myocardial infarction or heart failure were defined as a past history of either.

Statistical Analysis

Prevalence of heavy alcohol drinking, current smoking habit, obesity, hyperglycemia, and hyperlipidemia was different between men and women, so we analyzed the data stratified by sex.

The age-adjusted and sex-adjusted incidences of AF were calculated from the number of new cases appearing between 1991 and 2000 in the 4 Japanese communities studied. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazard regression models.

Risk factors were selected based on previous prospective findings for AF,[10–13,17–22] which included excess ethanol intake (ethanol intake ≥69 g/day), smoking status (current or never/former), obesity (BMI ≥30 kg/m², yes or no), hypertension (yes or no), hyperglycemia (yes or no), hyperlipidemia (yes or no), major ST-T abnormality in ECG, previous myocardial infarction (yes or no), and heart failure (yes or no).

SAS version 9.2 (SAS Institute, Cary, NC, USA) was used for analyses. All probability values for statistical tests were 2-tailed and $P<0.05$ was regarded as statistically significant.

Results

Table 1 shows the baseline characteristics of the participants with respect to the categories of alcohol consumption. In men, the prevalence of current smoking, hyperglycemia, major ST-T abnormality, and the mean value of total cholesterol differed among alcohol consumption categories. In contrast, the prevalence of current smoking and mean BMI differed among the

Table 4. Multivariate-Adjusted Hazard Ratios (HR) and 95% Confidence Intervals (CI) of Atrial Fibrillation (AF) for Cardiovascular Risk Factors (Longitudinal Survey) in the Circulatory Risk in Communities Study (CIRCS)

	Men		Women		Total	
	HR	95% CI	HR	95% CI	HR	95% CI
Age	1.03	1.01–1.05	1.02	1.00–1.03	1.02	1.01–1.03
Sex (male)	–		–		0.96	0.72–1.28
Excess ethanol intake (≥69 g/day)	2.68	1.56–4.61	3.62	0.49–26.8	2.61	1.55–4.39
Current smoking	1.22	0.83–1.79	0.63	0.28–1.44	1.01	0.73–1.41
Obesity (BMI ≥30)	1.72	0.63–4.67	2.53	1.48–4.31	2.24	1.41–3.58
Hypertension	1.02	0.69–1.50	0.89	0.66–1.22	0.93	0.73–1.19
Hyperglycemia	1.51	1.01–2.25	1.24	0.84–1.85	1.35	1.02–1.78
Hyperlipidemia	1.46	0.95–2.26	0.79	0.57–1.09	0.96	0.74–1.25
Major ST-T abnormality	1.09	0.40–2.99	0.69	0.30–1.56	0.79	0.42–1.50
Previous MI	2.96	0.92–9.52	–		2.13	0.67–6.74
Heart failure	–		1.85	0.26–13.3	1.22	0.17–8.73

Hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or use of antihypertensive medication. Hyperglycemia was defined as a fasting glucose level ≥110 mg/dl, a non-fasting glucose level ≥140 mg/dl or use of medication for diabetes.
Abbreviations as in Table 1.

alcohol consumption categories for women. There were no significant differences in AF, hypertension, hyperlipidemia, previous myocardial infarction, or heart failure among the alcohol consumption categories for either sex.

Median follow-up period was 6.4 years and the follow-up rate was 84.6%. The mean number of examinations for the participants was 5.2 (2 examinations, 21.3%; 3 examinations, 20.7%; 4 examinations, 11.3%; and >5 examinations, 46.7%). During the follow-up period, 296 cases of incident AF occurred. Table 2 shows the means and prevalence of risk characteristics for previous examinations of the participants with and without AF. For men, the mean values of ethanol intake and the prevalence of heavy alcohol drinking and hyperglycemia were higher among participants with AF than for those without AF. For women, however, the mean BMI and blood glucose values, as well as the prevalence of heavy drinking and obesity, were higher among the participants with AF than for those without AF. There were no significant differences in current smoking status, BP levels, total cholesterol levels, or major ST-T abnormality for either sex.

A higher incidence rate of AF was observed among participants with an ethanol intake >69 g/day compared with never-drinkers, especially among men (Table 3). Relative to the never-drinking group, the multivariable-adjusted HRs (95% CIs) of past, light (<23 g/day), light–moderate (23–46 g/day), moderate (46–69 g/day), and heavy (>69 g/day) drinking groups were 1.30 (95% CI, 0.68–2.49), 0.89 (0.60–1.32), 1.19 (0.73–1.95), 1.36 (0.79–2.35), and 2.90 (1.61–5.23), respectively. Age, excess ethanol intake (≥69 g/day), obesity, and hyperglycemia were associated with risk of AF (Table 4), whereas BP, hyperlipidemia, current smoking, major ST-T abnormality, previous myocardial infarction and heart failure were not. The multivariate-adjusted HRs (95% CIs) were 1.02 (1.01–1.03) for age, 2.61 (1.55–4.39) for excess ethanol intake (≥69 g/day), 2.24 (1.41–3.58) for obesity (BMI ≥30 kg/m^2), and 1.35 (1.02–1.78) for hyperglycemia. When we analyzed the associations stratified by sex, the associations between risk factors and AF were virtually unchanged. Although obesity was significantly associated with AF among women, and hyperglycemia was significantly associated with AF among men, interactions between obesity, hyperglycemia and sex were not statistically significant (P for interaction>0.30).

Discussion

In the present study, a higher incidence of AF was observed among participants with an ethanol intake exceeding 69 g/day compared with never-drinkers in the longitudinal survey. In contrast, however, light to moderate alcohol consumption was not associated with elevated risk of AF. Thus, the association between ethanol intake and AF is suggestive of a threshold pattern effect. Because the prevalence of heavy drinkers was still high among Japanese men (7.2%), to reduce heavy alcohol consumption may not only decrease the risk of AF but also prevent stroke and heart failure related to AF. This must be important from a public health point of view.

On the other hand, there were no significant differences between alcohol intake and the prevalence of AF for both sexes in the cross-sectional survey. In general, people who were diagnosed with AF might receive advice from physicians to reduce their alcohol intake. Therefore, the association between alcohol intake and AF may be underestimated in the cross-sectional survey.

The Framingham study showed that alcohol consumption >36 g/day was associated with 34% increased risk of AF during the follow-up of 50 years and more in a nested case–control study of 1,055 AF cases and covariate-matched controls.[13] From the Copenhagen study of 16,415 women and men aged 25–75 years, more than 35 drinks/week (60 g/day) was associated with a 45% increased risk of AF among men.[21] Furthermore, Frost et al demonstrated that when using the lowest quintile of alcohol consumption (alcohol consumption of 4.1±2.6 g/day) as a reference, the multivariable-adjusted HR (95% CI) in the highest quintile (alcohol consumption of 68.7±22.8 g/day) was 1.46 (1.05–2.04) for men and 1.14 (0.70–1.85) for women.[17] Finally, Kodama reported a dose–response relationship between alcohol consumption and future AF by meta-analysis[22] in a linear regression model, which found that the pooled estimate for increments of 10 g/day of alcohol intake was 1.08 (95% CI: 1.05–1.10).

In the present study, a higher risk of AF was observed among participants whose ethanol intake exceeded 69 g/day. This is in line with previous studies conducted in Western countries. Although Japanese people do not have sufficient levels of alcohol dehydrogenase or aldehyde dehydrogenase, the threshold dose of ethanol intake that induced AF among the Japanese was not lower than the threshold dose for people from Western countries.

Mechanisms by which heavy alcohol consumption increase the incidence of AF are unclear and multifactorial. Alcohol consumption gives rise to a hyperadrenergic state and impairs vagal tone.[34–37] Excess alcohol consumption shortens the effective refractory period of the atrium and promotes the occurrence of atrial premature beats.[38] Furthermore, long-term excess alcohol intake may also cause alcoholic cardiomyopathy and congestive heart failure.[39] The major ethanol metabolite, acetaldehyde, may produce alcoholic cardiomyopathy that manifests as cardiac dysfunction, hypertrophy, and heart failure.[40] Ethanol is metabolized into acetaldehyde by alcohol dehydrogenase, which is then further metabolized into acetate by aldehyde dehydrogenase.[41] Polymorphisms in these 2 enzymes affect the elimination of ethanol and acetaldehyde, and have been reported to change the risk of alcoholic complications.[42] Increased fibrosis of the atrium, indicative of the pathologic changes of alcoholic cardiomyopathy caused by long-term excess alcohol intake, is likely to block electric conduction and create re-entrant circuits in AF.[43] In the present study, there was a significant difference in the prevalence of major ST-T abnormality among the categories of alcohol consumption in men. This may be supported, in part, by the aforementioned mechanisms, because ethanol intake produces major ST-T abnormality through alcoholic cardiomyopathy.[10]

The strength of this study is that we conducted a population-based large cohort study, with a long-term follow-up (mean follow-up period: 6.4 years) and a very high follow-up rate (84.6%). The evaluation of alcohol consumption at baseline was precise and reliable.[33] Furthermore, this study confirmed the association of alcohol intake with risk of AF among Japanese, who do not have sufficient levels of alcohol dehydrogenase.[25]

Study Limitations

Firstly, although AF cases were identified using annual ECG surveys and AF treatment history reports (receiving catheter ablation therapy or medical therapy with anticoagulant and/or antiarrhythmic drugs), the majority of AF cases were detected by annual ECG records (85.8%). Therefore, the number of cases of asymptomatic paroxysmal AF may have been underestimated. Secondly, some participants did not undergo ECG examination every year. In the present study, the mean number of ECG examinations for participants was 5.2 (2 examinations, 21.3%; 3 examinations, 20.7%; 4 examinations, 11.3%; and >5 examinations, 46.7%). There is some possibility of detection bias for AF, although there was no difference in the mean number of ECG examinations between each of the alcohol consumption categories. Finally, our data did not include creatinine levels, therefore we could not analyze the association between chronic kidney disease and AF.

Conclusions

Heavy alcohol consumption may be associated with a higher risk of AF, although there is no association of light to moderate alcohol consumption with risk of AF among Japanese men and women. Although people of Japanese descent do not have sufficient levels of alcohol dehydrogenase and aldehyde dehydrogenase, the threshold ethanol intake that induces AF among Japanese was not lower than that for people from Western countries.

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Disclosures

None.

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Appendix

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I. 概　論

魚・ω−3系多価不飽和脂肪酸摂取と循環器疾患との関連

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Fish and ω−3 polyunsaturated fatty acids in relation to risk of cardiovascular disease

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Abstract

A reason for low rate of heart disease in Japan has been considered due to high consumption of fish/ω−3 polyunsaturated fatty acids among Japanese. Yet, there are growing concerns that Japanese has not consumed much fish compared with 10 years ago, based on the national statistics. Meanwhile, the incidence of myocardial infarction has been increasing among middle−aged men in some urban communities. In this review, we summarized several epidemiological studies which focused on fish/ω−3 fatty acids and risk of cardiovascular diseases including coronary heart disease, sudden cardiac death and heart failure.

Key words: epidemiology, cohort study, observational study, ω−3 fatty acids, myocardial infarction

はじめに

魚に多く含まれるω−3系多価不飽和脂肪酸(ω−3系脂肪酸)は，メチル基から3番目の炭素に最初の二重結合がある脂肪酸の総称である．そのうち炭素数が20以上あるものを'長鎖ω−3系多価不飽和脂肪酸'という．主なものにエイコサペンタエン酸(EPA，C20：5，ω−3)，ω−3系ドコサペンタエン酸(DPA，C22：5，ω−3)，ドコサヘキサエン酸(DHA，C22：6，ω−3)がある．長鎖以外のω−3系脂肪酸では，主なものはα−リノレン酸(ALA，C18：3，ω−3)があり，エゴマやシソなどの油やクルミなどに含まれる．1970年代にDyerbergら[1]が，魚類摂取の多いグリーンランドエスキモー人では飽和脂肪酸の摂取量や血中LDLコレステロール値が低くないにもかかわらず，デンマーク人に比べ虚血性心疾患の発症が少なく出血傾向が大きいことを発表した．そして，魚に多く含まれるω−3系脂肪酸に抗血栓作用があるとする仮説を提唱した．その後，この仮説を検証するため欧米を中心に多くの追跡研究・介入研究が進められた．ω−3系脂肪酸は血小板凝集能の抑制のほかに，血中トリグリセライドの低下作用，抗炎症作用，血管内皮機能改善，抗不整脈作用など，様々な薬理作用を介して，循環器疾患に対し予防的に作用することが明らかにされてきた．

我が国の循環器疾患の疾病構造の特徴は，他の先進国と比べ脳卒中が多く虚血性心疾患が少ないことである．**図1**は，1970年代に世界7カ国で開始されたSeven Countries Studyにおけるコレステロールと虚血性心疾患死の関連を国別にみたものであるが，同じ集団内ではコレステロールが高いほど虚血性心疾患死のリスクが高く，特にコレステロールレベルの高い北欧や米国の集団ではこの関連が強い．当時の我が国はコレステロールレベルが極めて低いことがこの図からも明らかであるが，特筆すべきは，同じコレステロールレベルであっても，我が国や南欧と，北欧・米国とでは虚血性心疾患死の絶対リスクが大きく異なることである．例えば，血清総コレステロールが210 mg/dLでは，我が国や南欧諸国での虚血性心疾患の死亡率が4−5％であったのに対し，北欧では15％であった[2]．このことから，日本で多く使われる魚油(ω−3系脂肪酸)や南欧で使われるオリーブオイル(一価不飽和脂肪酸)に注目が集まった．

しかしながら，日本人と欧米人の魚摂取量の分布は大きく異なる．例えば，秋田と米国ミネソタの血清ω−3系脂肪酸を同じ方法で測定・比較した研究では，秋田の集団の血清ω−3系脂肪酸の割合は8−18％であったのに対し，米国ミネソタの集団では2−4％と，両者の分布は全く重ならなかった[3]．この事実は極めて重要で，欧米の研究成果を，魚摂取の分布が大きく異なる我が国に当てはめることには慎重でなければならず，我が国独自のエビデンスを蓄積・整理することが必要である．

本稿では，魚やω−3系脂肪酸と循環器疾患に関する疫学的知見について，我が国での観察研究の成果を中心に述べる．

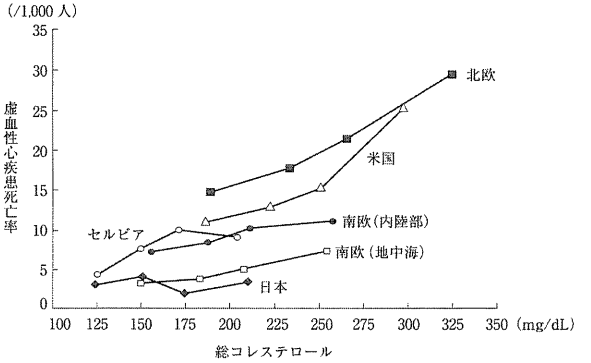

図1　7カ国におけるコレステロール値と虚血性心疾患死亡率の関係
(Seven Countries Study)(文献[2]より引用)

1. 魚・ω−3系脂肪酸摂取と急性心筋梗塞：観察研究

1985年に，7カ国研究の一角を構成するオランダのZutphenの50−69歳男性852人を20年間追跡した成績において，1日30 g以上魚を食べる人は全く食べない人と比べて，虚血性心疾患の死亡が約半分であったことが報告された[4]．その後それまでの欧米での追跡研究のメタアナリシスが行われた．Mozaffarianら[5]は，1日0.25−0.5 gのEPA+DHA摂取により，虚血性心疾患の死亡率は25％以上低下するが，それ以上摂取しても死亡率の低下は顕著でなく，かねて指摘されていたように虚血性心疾患のリスク低下に関しては魚摂取の閾値が存在する可能性を示した(**図2**)．

日本での研究に目を向けると，死亡をエンド

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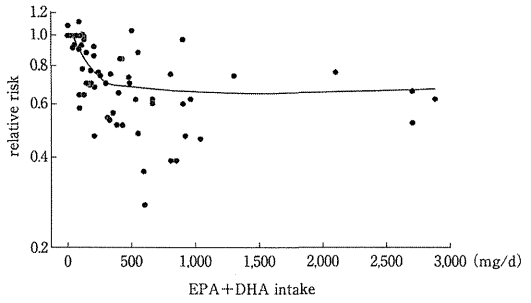

図2 EPA+DHA摂取と虚血性心疾患死亡(文献[5]より引用)

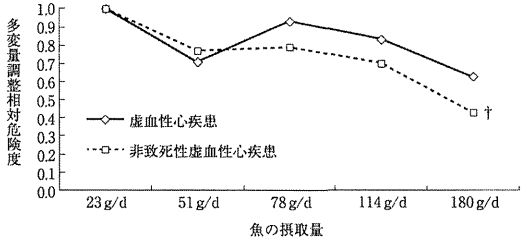

図3 魚の摂取と虚血性心疾患発症(文献[8]より引用)
† $p < 0.01$.

ポイントとしたNIPPON DATA80[6]やJACC研究[7]では，虚血性心疾患死に対して強い予防効果は示されていないが，アジアで唯一，魚・ω-3系脂肪酸摂取と虚血性心疾患の発症との関連を検討した国立がん研究センターなどによるJPHC研究(40-59歳の男女41,578人を12年間追跡)では，急性心筋梗塞の発症リスク比(魚摂取量上位20％対下位20％)は0.47(95％信頼区間0.26-0.85)，虚血性心疾患(急性死を含む)は0.63(0.38-1.04)であった[8]．また虚血性心疾患を致死性・非致死性に分けた場合，非致死性では0.43(0.23-0.81)と有意なリスクの低下がみられたが，致死性では1.08(0.42-2.76)とリスクの低下はみられなかった(**図3**)．これらの結果は，致死性虚血性心疾患で強い予防効果を示す欧米の研究結果とは異なるものであった．

死亡をエンドポイントとした日本人対象の研究で関連が強くなかったことは，多くの日本人は，死に至るような重篤な虚血性心疾患・不整脈を予防するレベルのω-3系脂肪酸の摂取閾値(**図2**)を既に達成しているためと推察される．一方でJPHC研究の結果は，日本人においてこの閾値よりも更に多くの魚を摂取することで，比較的軽度の非致死的な虚血性心疾患をも予防する可能性を示している．

2. 魚・ω-3系脂肪酸摂取と心筋梗塞：介入研究

虚血性心疾患患者を対象に，魚・植物油，ω-3系脂肪酸と虚血性心疾患の再発，循環器疾患死亡，全死亡に関する介入研究がこれまでに報告されてきたが，大規模な研究を2つ紹介する．一つはイタリアのGISSI-Prevenzione Trialであり，3カ月以内に心筋梗塞に罹患した11,234人のイタリア人を，1日1gのω-3系脂肪酸を投与する群，1日300 mgのビタミンEを投与する群，ω-3系脂肪酸とビタミンEの両方を投与する群，対照群の4群に分け3.5年間介入を行った．その結果，ω-3系脂肪酸投与群では対照群に比べ3.5年間の全死亡リスク比が0.79(0.66-0.93)であり，特に急性死は0.55(0.39-0.77)であった[9]．もう一つの重要な介入研究は我が国のJELISである．日本人脂質異常症患者18,645人に対し，スタチンのみの対照群と，スタチンに加えて1日1.8gのEPAを投与する群に分け5年間追跡した結果，EPA投与群では対照群に比べ虚血性心疾患の発症リスク比が0.81(0.69-0.95)であった[10]．このリスクの低下は非致死性では0.81(0.68-0.96)と有意であったが，致死性では0.94(0.57-1.56)と関連はみられなかった．

3. 魚・ω-3系脂肪酸摂取と急性心臓死

急性心臓死は虚血性心疾患に含まれる疾病概念であり，多くは虚血による心室性不整脈が原因であると考えられている．疫学的には，急性症状から1時間以内で死に至る他の要因のない突然死を急性心臓死と定義する．24時間以内に死に至ったものを含める場合もある．欧米の研究では魚・ω-3系脂肪酸と急性心臓死との間には，おおむね強い負の関連が認められている[11]．しかし，我が国で急性心臓死を独立したエンドポイントとしたJPHC研究(症例数37例)[8]，JELIS(35例)[10]，JACC研究(他の不整脈死を含め108例)[7]のいずれも，欧米のような明らかな負の関連がみられていない．これは，上述のように大部分の日本人では致死的心疾患を予防するレベルを超えてω-3系脂肪酸を摂取しているためと考えられる．しかしながら，いずれの研究も急性死の症例が欧米に比べて少ないために(例えばGISSIでの急性心臓死は265例である[9])，有意な関連が検出できなかった可能性もある．

4. 魚・ω-3系脂肪酸摂取と心不全

65歳以上の男女4,738人を12年間追跡した米国のCHS研究において，焼き魚を週に5回以上食べる人では月1回未満の人に比べ，うっ血性心不全の発症リスク比が0.68(0.45-1.03)，EPA+DHA(摂取量上位20％対下位20％)に関してもその発症リスク比が0.73(0.57-0.94)であった[12]．しかし揚げ魚の場合には，週1-2回食べる人では月1回未満の人に比べリスク比が1.35(1.12-1.62)と，むしろ発症リスクの増加が認められた．一方，米国の40-64歳の男女14,153人を17年間追跡したARIC研究では，魚の摂取と心不全の発症との関連は認められなかった[13]．これはARIC研究のFFQでは焼き魚と揚げ魚の区別がなく，対象者が摂取した魚の多くが揚げ魚であったためと推察されている．ARIC研究ではミネソタの集団(n=3,592)にかぎり脂肪酸のバイオマーカーである血漿脂肪酸分画を測定しており，女性でのみ血漿DHAと心不全発症との間に強い負の関連を認めた[14]．このようにω-3系脂肪酸は心不全も抑制すると考えられており，欧米の7つの研究のメタアナリシスによれば，魚摂取が最も多い群では，最も少ない群に比べて15％心不全リスクが低く，血中または食事中のEPAやDHAでもほぼ同様の結果であった[15]．

ただし揚げ魚に関しては注意を要する．多くの米国人にとって揚げ魚とは，ファストフード店などの白身魚のフィッシュ・バーガーのような類のものであり，飽和脂肪酸の多いラードを用いており，日本人の感覚とは相当異なる．日本人はω-3系脂肪酸を多く含む魚類(アジやイワシ，サンマなど)を，竜田揚げやてんぷらなど様々な揚げ方で調理しており，揚げ油にはリノール酸などの多価不飽和脂肪酸の多い植物油を主に使用するため，米国人と日本人で結果が異なる可能性がある．

我が国の心不全についての研究として，先述のJACC研究における心不全死亡リスク比は，ω-3系脂肪酸摂取の多い群では少ない群に比べ0.58(0.36-0.93)，魚類摂取では0.76(0.53-1.09)であり，魚類から揚げ魚を除いても0.78(0.55-1.10)であった[7]．ただしJACC研究は人口動態統計(死亡診断書)の原死因をアウトカム

としているため，その精度には注意を要する．我が国でも心不全の発症を追跡した研究が幾つか始まっているが，現時点で魚やω-3系脂肪酸と心不全の発症との関連をみたコホート研究はない．

おわりに

魚と循環器疾患との関連は，欧米と我が国では異なることが我が国の疫学研究により示されている．我が国は伝統的に魚類の摂取が多く，このことが我が国での虚血性心疾患の発症・死亡を低く抑えてきた大きな要因の一つと考えられる．更に，日本人の中でも魚をより多く摂ることが非致死性心筋梗塞の予防に効果がある可能性が大きい．これまで我が国では増加がみられなかった虚血性心疾患は，都市部の男性では1980年代～2000年代にかけて発症率が約2倍に増加していることが報告されている[16]．更に，国民健康・栄養調査によれば，日本人の魚介類の摂取量は2001年の103 g/日から2011年の79 g/日に減少しており[17]，ここ10年間で魚離れが進んでいる．ここで改めて魚類・ω-3系脂肪酸の生活習慣病予防効果を再認識すべきときにきているといえよう．

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ORIGINAL ARTICLE

Association between dietary behavior and risk of hypertension among Japanese male workers

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Dietary behavior can worsen or prevent hypertension. However, data on the association between dietary behavior and the risk of hypertension in Asians are limited. The aim of this study was to determine these associations in Japanese male workers. We conducted a prospective study of 30–71-year-old Japanese male workers in Osaka, Japan, between 2001 and 2011. The study subjects were 3486 normotensive males who were assessed for an average of 4.6 years using an annual survey. We defined hypertension by a systolic blood pressure of ⩾140 mm Hg, a diastolic blood pressure of ⩾90 mm Hg and/or the use of antihypertensive medications. Dietary behavior questionnaires were included in the annual surveys. For each question on dietary behavior, we calculated the odds ratios (ORs) for the risk of hypertension using logistic regression models. We used subjects who consistently gave affirmative answers in the baseline and end-point surveys as a reference. The number of new cases of hypertension was 846 among 3486 subjects. Compared with subjects who eat meat frequently, subjects who did not eat meat frequently showed a higher risk of hypertension (OR = 1.26, 95% confidence interval (CI): 1.00–1.59). Subjects who did not consume dairy products every day showed a higher risk of hypertension (OR = 1.39, 95% CI: 1.13–1.71) compared with those who did. Meat and dairy product intake was associated with the prevention of hypertension among Japanese male workers.
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INTRODUCTION

Hypertension is one of the most important risk factors for cardiovascular disease in the Japanese, as well as in Western populations.[1–4] Therefore, it is important to determine the risk factors associated with hypertension in order to prevent hypertension and decrease the burden of cardiovascular disease. Although pharmacological treatment of hypertension is widely available, primary prevention of hypertension is desirable.

Several studies have reported that lifestyle is significantly associated with blood pressure[5] and the incidence of hypertension.[6] Dietary behavior seems to be an important risk factor because it is directly associated with energy intake, which in turn correlates with body weight control and nutrient intake and is associated with maintenance of the organism.

Several studies have examined dietary behavior in relation to the Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet.[5–10] Both prospective studies[6–9] and intervention studies[5,10] found an inverse association between the Mediterranean diet or the DASH diet and the risk of hypertension or blood pressure levels. The Mediterranean diet involves an abundant intake of plant foods, adequate intake of dairy products and fish, and low intake of meats. The DASH diet involves an abundant or adequate intake of plant foods, fish and low-fat dairy products, with limited intake of sugar-sweetened foods, red meat and added fats.

For the Asian populations, only limited data are available on the association of dietary behavior and the risk of hypertension or blood pressure level. A cross-sectional study of the Chinese population showed an inverse association between fruit and milk intake and the prevalence of hypertension.[11] Another cross-sectional study of the Japanese population showed an inverse association between high fruit and vegetable intake and self-measured blood pressure levels.[12] To our knowledge, however, there are no published prospective studies that have examined the association of dietary behavior and the risk of hypertension or blood pressure levels in an Asian population. Of course, knowledge from Western countries is beneficial to some extent for Asians. The Japanese Society of Hypertension reviewed clinical and epidemiological studies published from around the world and released the Japanese Society of Hypertension Guidelines for the Management of Hypertension in 2009.[13] In these guidelines, desirable dietary behavior was suggested; however, these guidelines were mainly based on the DASH diet. We believe that more data are needed for Asians because an Asian diet is different from that of Western countries.

Our *a priori* hypothesis was that the development of hypertension is associated with dietary behavior in the Japanese population. Dietary behaviors that lead to obesity or involve high sodium intake may increase the risk of hypertension, whereas dietary behaviors that include the consumption of fruits, vegetables and dairy products may reduce the risk of hypertension. To test our hypothesis, we performed the present prospective study in Japanese male workers.

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METHODS

Study subjects

The participants were 30–71-year-old (mean age: 45.0 years) male workers who were employees of six companies in the Osaka area of central Japan and underwent serial government-sponsored annual health checkups. The total number of participants was 6554 at the beginning of the study. We excluded 1743 participants because they were diagnosed with hypertension (⩾140 mm Hg systolic blood pressure and/or ⩾90 mm Hg diastolic blood pressure and/or those who were taking antihypertensive medications) on the baseline cardiovascular disease risk survey. During the follow-up, 1142 participants (mean age: 46.8 years) dropped out of the study following a failure to complete a health checkup. Furthermore, we excluded 183 participants because their serum creatinine concentrations were not measured. Thus, data on 3486 subjects (mean age: 42.9 years) were used for this analysis. We obtained informed consent from all subjects according to the ethical guidelines for epidemiological research by the Ministry of Health, Labor and Welfare. The study was approved by the Ethics Committee of Osaka Medical Center for Health Science and Promotion.

Risk factor survey

The annual Cardiovascular Disease Risk Surveys were performed from 2001 to 2011. The arterial systolic blood pressures and fifth-phase diastolic blood pressures were measured by well-trained observers using a standard mercury sphygmomanometer on the right arm during the survey. The participants were seated quietly for at least 5 min before the measurement. We used the data from the first measurement because the blood pressure was not measured twice in all subjects. Individuals with hypertension included those found to have high blood pressure (⩾140 mm Hg systolic blood pressure and/or ⩾90 mm Hg diastolic blood pressure), as well as those being treated with antihypertensive medications.

With regard to potential confounders, the body mass index was calculated by dividing the weight in kilograms by the height in meters squared. The height was measured with subjects wearing socks, and the weight was measured with subjects wearing light clothing. Every participant was interviewed to determine their usual weekly alcohol consumption in go units, a traditional Japanese unit of volume equivalent to 23 grams of ethanol. We divided weekly ethanol intake by seven to calculate the average daily alcohol intake. The smoking habits and history of the subjects were also determined during the interview, as well as the history of hypertension, stroke, coronary heart disease, renal disease and the use of antihypertensive medications. The estimated glomerular filtration rate was calculated using the following formula established by the working group of the Japanese Chronic Kidney Disease Initiative: estimated glomerular filtration rate (ml min^{-1} 1.73 m^{-2}) = 194 × (serum creatinine)$^{-1.094}$ × (age)$^{-0.287}$.[14] Since 2001, serum creatinine has been measured using the enzymatic method.

Dietary behavior survey

The dietary behavior survey was carried out as part of the annual Cardiovascular Disease Risk Survey from 2001 to 2011 using questionnaires. The questionnaires were based on a health assessment in Japanese.[15] Well-trained public health nurses helped participants who had difficulty in answering the questionnaires. The survey consisted of 19 items related to dietary behavior (Table 1). Subjects answered either 'yes' or 'no.' We examined the reproducibility of the questionnaire by using data from 2251 male subjects who were free from hypertension, hypercholesterolemia and diabetes at baselin and received a dietary behavior survey again the next year. The rang of the concordance rate of each question was from 73.1 (dietary behavio concerned with meat intake) to 89.2% (dietary behavior concerned wit breakfast intake).

Table 1 19 questions of dietary behavior survey

1. Do you have breakfast?
2. Do you have a meal just before bedtime?
3. Do you eat until you are full?
4. Do you eat between meals or before bedtime every day?
5. Do you consume soft drinks every day?
6. Do you have fried food every day?
7. Do you have one or more eggs every day?
8. Do you have meat frequently?
9. Do you have fish or shellfish more than twice a week?
10. Do you season all food salty?
11. Do you have salty soup less than twice a day?
12. Do you have all-noodle soup?
13. Do you have food preserved in salt less than three times a week?
14. Do you use salty sauce before checking the taste?
15. Do you have salty pickles less than twice a day?
16. Do you have vegetables or seaweed at every meal?
17. Do you have fruits every day?
18. Do you have soy products every day?
19. Do you consume dairy products every day?

Statistical analysis

The follow-up period was calculated from the day of the first cardiovascula risk survey (baseline survey) to the day of the end-point survey. For subject who were diagnosed with hypertension, we defined the end-point survey as th survey in which the subject was first diagnosed with hypertension. For subject who were consistently diagnosed as normotensive, we defined the end-poin survey as the last survey.

We prepared 19 dietary behaviors and divided the subjects into four group according to the answers provided in the baseline and end-point question questionnaires. Subjects who answered 'yes' in both the baseline and end-poin questionnaires were assigned to group 1. Subjects who answered 'yes' in th baseline questionnaire and 'no' in the end-point questionnaire were assigned t group 2. Subjects who answered 'no' in the baseline questionnaire and 'yes' i the end-point questionnaire were placed in group 3, and subjects wh answered 'no' in both the baseline and end-point questionnaires were place in group 4 on the questions 1, 3, 4–9, 11, 13 and 15–19. As for questions 2, 1 12 and 14, the subjects were placed in the four groups based on answer opposite to the rules showing above.

Age-adjusted and multivariate-adjusted means and the magnitude o confounding variables were calculated and tested using an analysis o covariance. We calculated the odds ratios (ORs) and 95% confidence interval (CIs) by using the logistic regression model for age-adjusted ORs an multivariate-adjusted ORs for the development of hypertension. We use group 1 as the reference group. We used the baseline age, job, body mass index daily alcohol intake, smoking habits, estimated glomerular filtration rate an systolic blood pressure level at the baseline survey as the confounding variables

Although there were 19 items in the questionnaire, we listed the results o only 5 items in the tables for better presentation. The results of the other 1 items are listed in Supplementary Table 1.

Furthermore, we examined the differences in the baseline characteristics o 3486 subjects who followed up and 1142 subjects who did not follow-up. The results are reported in Supplementary Table 2.

We used the SAS version 9.1.3 software (SAS Institute Inc., Cary, NC, USA for all analyses. *P*-values <0.05 were considered statistically significant (o two-tailed analyses).

RESULTS

During an average 4.6-year follow-up for the 3486 subjects, 846 incident cases (24.3%) of hypertension were documented. Table 2 lists the characteristics of the subjects in the first cardiovascular survey according to the five dietary behaviors that were significantly associated with the risk of hypertension. Subjects who consistently did not have one or more egg every day at both the baseline and end-point surveys (group 4) had a higher diastolic blood pressure compared with subjects who consistently did (group 1, $P = 0.03$). Subjects who did not consistently consume dairy products every day (group 4) had a higher diastolic blood pressure compared with subjects who consistently did (group 1, $P = 0.03$). Subjects who did not consistently eat between meals or before bedtime every day (group 4) had a higher systolic blood pressure compared with subjects who consistently did (group 1, $P = 0.04$).

Table 3 shows the age-adjusted and multivariate-adjusted ORs of the risk of hypertension according to the above five dietary behaviors that showed statistical significance. After adjusting for the confounding variables, the OR values were significantly higher in subjects who consistently did not eat meat frequently (group 4) than subjects who consistently did eat meat frequently (group 1) (OR = 1.32, 95% CI: 1.05–1.65; $P = 0.02$). Regarding dairy products, the OR values were higher in subjects who consistently did not consume dairy products every day (group 4) and who changed their dietary behavior from consuming dairy products every day to not (group 2) than those who consistently did consume dairy products (group 1) (OR = 1.37, 95% CI: 1.11–1.68; $P = 0.003$ and OR = 1.43, 95% CI: 1.08–1.89; $P = 0.01$, respectively). The OR values were higher in subjects who consistently did not eat between meals or before bedtime every day (group 4) than those who consistently did (group 1) (OR = 1.41, 95% CI: 1.00–1.98; $P = 0.05$). The OR values were higher in subjects who changed their dietary behaviors from eating one or more eggs every day to not eating eggs (group 2) than those who did consistently eat one or more eggs every day (group 1) (OR = 1.37, 95% CI: 1.04–1.80; $P = 0.02$). The OR values were higher in subjects who changed their dietary behavior from consuming noodle soup to not consuming noddle soup (group 3) than those who did not consistently consume noodle soup (group 1) (OR = 1.32, 95% CI: 1.03–1.70; $P = 0.03$).

Table 4 shows the multivariate-adjusted ORs and 95% CIs for the risk of hypertension after further adjustment for each dietary behavior listed in Table 2. The associations between dietary behaviors and the risk of hypertension did not change significantly, but the association with eating between meals or before bedtime was no longer statistically significant ($P = 0.09$).

We also calculated the age-adjusted and multivariate-adjusted ORs of the risk of hypertension according to the dietary behaviors that did not show statistical significance. Dietary behaviors characterized by not eating breakfast, eating a meal just before bedtime, not eating fried food, adding salt to meals, using a salty sauce before checking the taste, not having vegetables or seaweed at every meal and not eating fruits led to a higher risk of hypertension, whereas dietary

Table 2 Baseline characteristics of subjects according to the answers given to the questionnaires of the baseline and end-point surveys

	Answers to questionnaires (baseline/end point)				
	Yes/Yes (group 1)	*Yes/No (group 2)*	*No/Yes (group 3)*	*No/No (group 4)*	*Lack of answers*
Subjects who had one or more eggs every day					
Number and percentage of subjects	800 (23%)	539 (15%)	406 (12%)	1740 (50%)	1 (0%)
Age (years)	41.7	42.0	42.1	44.0	55.0
Body mass index (kg m^{-2})[a]	23.6	23.5	23.3	23.1**	27.3
Alcohol intake (g ethanol per day)[a]	25.6	23.7	20.7**	19.4**	40.2
Current smokers (%)[a]	47	49	42	47	0
Systolic blood pressure (mm Hg)[b]	116.7	116.9	116.5	116.5	116.7
Diastolic blood pressure (mm Hg)[b]	73.0	73.4	72.8	73.8*	78.0
Estimated glomerular filtration rate (ml min^{-1} 1.73 m^{-2})[b]	82.5	83.3	82.0	81.4*	87.4
Subjects who had meat frequently					
Number and percentage of subjects	872 (25%)	518 (15%)	485 (14%)	1606 (46%)	5 (0%)
Age (years)	39.5	42.2	41.9	45.3	52.0
Body mass index (kg m^{-2})[a]	23.5	23.5	23.4	23.0**	25.5
Alcohol intake (g ethanol per day)[a]	23.1	23.5	20.8	20.6*	12.2
Current smokers (%)[a]	47	51	42	46	19
Systolic blood pressure (mm Hg)[b]	116.8	116.7	116.7	116.4	108.6
Diastolic blood pressure (mm Hg)[b]	73.5	74.0	73.2	73.4	71.7
Estimated glomerular filtration rate (ml min^{-1} 1.73 m^{-2})[b]	82.0	81.9	81.7	82.3	83.1
Subjects who did not have all-noodle soup					
Number and percentage of subjects	1945 (56%)	235 (7%)	444 (13%)	861 (25%)	1 (0%)
Age (years)	43.2	42.9	42.8	42.4	35.0
Body mass index (kg m^{-2})[a]	23.0	23.0	23.7**	23.7**	27.3
Alcohol intake (g ethanol per day)[a]	19.7	24.0*	23.5**	24.5**	40.4
Current smokers (%)[a]	44	45	47	52**	100
Systolic blood pressure (mm Hg)[b]	116.6	117.0	117.1	116.1	126.8
Diastolic blood pressure (mm Hg)[b]	73.5	73.4	73.6	73.3	80.2
Estimated glomerular filtration rate (ml min^{-1} 1.73 m^{-2})[b]	81.9	83.1	81.6	82.3	89.1
Subjects who consumed dairy products every day					
Number and percentage of subjects	1214 (35%)	443 (13%)	419 (12%)	1408 (40%)	2 (%)
Age (years)	43.6	41.8	44.0	42.4	51.0
Body mass index (kg m^{-2})[a]	23.4	23.2	23.2	23.2*	26.9
Alcohol intake (g ethanol per day)[a]	18.5	20.0	20.9	25.1**	27.3
Current smokers (%)[a]	36	38	48**	58**	49
Systolic blood pressure (mm Hg)[b]	116.4	117.0	116.8	116.6	123.1
Diastolic blood pressure (mm Hg)[b]	73.1	73.6	73.1	73.8*	80.1
Estimated glomerular filtration rate (ml min^{-1} 1.73 m^{-2})[b]	81.5	81.6	80.9	83.0**	83.1
Subjects who ate between meals or before bedtime every day					
Number and percentage of subjects	297 (9%)	237 (7%)	285 (8%)	2663 (76%)	4 (0%)
Age (years)	41.8	40.6	42.6	43.3	48.5
Body mass index (kg m^{-2})[a]	23.4	23.7	22.9*	23.2	25.3
Alcohol intake (g ethanol per day)[a]	12.9	16.9	13.9	23.9**	17.6
Current smokers (%)[a]	34	46**	44*	48**	25
Systolic blood pressure (mm Hg)[b]	115.7	116.5	115.9	116.8	128.6*
Diastolic blood pressure (mm Hg)[b]	72.7	72.9	72.2	73.7*	80.0
Estimated glomerular filtration rate (ml min^{-1} 1.73 m^{-2})[b]	81.4	82.9	83.4	81.9	87.6

*$P<0.05$ and **$P<0.01$.
[a]Adjusted for age (years).
[b]Adjusted for age (years), body mass index (kg m^{-2}), ethanol intake (g per day) and current smoking (yes or no).

Table 3 Age-adjusted and multivariate-adjusted ORs of the development of hypertension according to the answers given to the questionnaires in the baseline and end-point surveys

	Answers to questionnaires (baseline/end point)			
	Yes/Yes (group 1)	*Yes/No (group 2)*	*No/Yes (group 3)*	*No/No (group 4)*
Subjects who had one or more eggs every day				
Number of subjects	6	539	406	1740
Development of hypertension (%)	24	28	22	24
Age-adjusted OR and 95% CI	1.00	1.22 (0.95–1.57)	0.90 (0.68–1.20)	0.91 (0.75–1.11)
Multivariate-adjusted OR and 95% CI	1.00	1.37 (1.04–1.80)	1.08 (0.79–1.48)	1.19 (0.95–1.48)
Subjects who had meat frequently				
Number of subjects	872	518	485	1606
Development of hypertension (%)	21	23	23	27
Age-adjusted OR and 95% CI	1.00	1.02 (0.79–1.33)	1.01 (0.78–1.33)	1.15 (0.94–1.41)
Multivariate-adjusted OR and 95% CI	1.00	1.02 (0.77–1.36)	1.05 (0.78–1.41)	1.32 (1.05–1.65)
Subjects who did not have all-noodle soup				
Number of subjects	1945	235	444	861
Development of hypertension (%)	23	21	32	24
Age-adjusted OR and 95% CI	1.00	0.90 (0.65–1.26)	1.57 (1.25–1.97)	1.05 (0.87–1.27)
Multivariate-adjusted OR and 95% CI	1.00	0.83 (0.58–1.19)	1.32 (1.03–1.70)	0.94 (0.76–1.16)
Subjects who consumed dairy products every day				
Number of subjects	1214	443	419	1408
Development of hypertension (%)	21	26	25	26
Age-adjusted OR and 95% CI	1.00	1.44 (1.12–1.86)	1.24 (0.95–1.61)	1.41 (1.18–1.70)
Multivariate-adjusted OR and 95% CI	1.00	1.42 (1.08–1.88)	1.16 (0.87–1.55)	1.36 (1.11–1.67)
Subjects who ate between meals or before bedtime every day				
Number of subjects	297	237	284	2658
Development of hypertension (%)	18	20	21	26
Age-adjusted OR and 95% CI	1.00	1.24 (0.80–1.92)	1.26 (0.83–1.90)	1.57 (1.15–2.14)
Multivariate-adjusted OR and 95% CI	1.00	1.11 (0.69–1.78)	1.38 (0.88–2.17)	1.41 (1.00–1.98)

Abbreviations: CI, confidence interval; OR, odds ratio.
Adjusted for age (years), job, body mass index (kg m^{-2}), ethanol intake (g per day), current smoking (yes or no), estimated glomerular filtration rate (ml min^{-1} 1.73 m^{-2}) and systolic blood pressure level from baseline survey (mm Hg).

Table 4 Multivariate-adjusted odds ratios of the development of hypertension after further adjustment for dietary patterns

	Answers to questionnaires (baseline/end point)			
	Yes/Yes (group 1)	*Yes/No (group 2)*	*No/Yes (group 3)*	*No/No (group 4)*
Subjects who had one or more eggs every day				
OR and 95% CI	1.00	1.33 (1.00–1.75)	1.07 (0.78–1.46)	1.11 (0.89–1.40)
Subjects who had meat frequently				
OR and 95% CI	1.00	0.98 (0.73–1.31)	0.99 (0.74–1.34)	1.26 (1.00–1.59)
Subjects who did not have all-noodle soup				
OR and 95% CI	1.00	0.83 (0.58–1.19)	1.32 (1.02–1.71)	0.95 (0.77–1.18)
Subjects who consumed dairy products every day				
OR and 95% CI	1.00	1.43 (1.07–1.89)	1.16 (0.87–1.55)	1.39 (1.13–1.71)
Subjects who ate between meals or before bedtime every day				
OR and 95% CI	1.00	1.07 (0.66–1.72)	1.37 (0.87–2.16)	1.35 (0.96–1.90)

Abbreviations: CI, confidence interval; OR, odds ratio.
Adjusted for age (years), job, body mass index (kg m^{-2}), ethanol intake (g per day), current smoking (yes or no), estimated glomerular filtration rate (ml min^{-1} 1.73 m^{-2}), systolic blood pressure level from baseline survey (mm Hg) and other dietary behaviors.

behaviors characterized by consuming salty soup, eating foods preserved in salt, eating salty pickles and avoiding soy products led to a lower risk of hypertension. Dietary behaviors characterized by eating until full, consuming soft drinks and having fish or shellfish were not significantly associated with hypertension.

DISCUSSION

The main finding of our study of Japanese male workers was that the dietary behavior of eating meat and the daily intake of dairy products were inversely associated with the development of hypertension, even after adjusting for other dietary behaviors. Refraining from eating one or more eggs or having noodle soup was positively associated with the development of hypertension.

To our knowledge, no epidemiological study has reported a significant association between meat intake and the risk of hypertension. The Mediterranean diet and the DASH diet recommend a lower *intake of red meat to prevent hypertension.*[5–10] *However, in the* present study, subjects who did not eat meat frequently demonstrated a 29% higher risk of hypertension compared with subjects who had meat frequently.

As for dairy product intake, several European and US epidemiological studies reported the association between dairy product intake and the risk of hypertension.[16–18] Among middle-aged and elderly females in the United States, the highest and median quintiles of dairy product intake (2.99–22.1 and 1.40–1.92 servings per day, respectively) showed a 14% and 7% lower risk of hypertension, respectively, compared with the lowest quintile (0–0.85 servings per day).[16] Among young overweight US adults, the lowest category of dairy product intake (0–9 times per week) showed a three-fold higher incidence of hypertension compared with the top category of dairy product intake (>35 times per week).[17] Among Dutch males and females aged >55 years, the highest quartile of dairy product intake (median: 691 g per day) showed a 24% lower incidence of hypertension compared with the lowest quartile (164 g per day).[18] In the present study, subjects who did not consume dairy products *every day at the baseline and end-point surveys had a 36% higher risk* of hypertension, and those who stopped consuming dairy products every day between the baseline and end-point surveys had a 44% higher risk of hypertension compared with the subjects who consumed dairy products every day at baseline and end-point surveys. This result implies that the regular intake of dairy products seems to prevent hypertension. Our study is the first to show the association between dairy products and the development of hypertension in an Asian population.

The mechanism of the inverse association of meat and dairy product intake with hypertension merits some discussion. Specific amino acids that are rich in animal products, such as arginine, taurine, tryptophan and tyrosine, are involved in the control of the vascular system. For example, L-arginine is a vasodilator and substrate of nitric oxide. In a human experiment, an infusion of L-arginine produced an immediate reduction in the blood pressure.[19] Taurine seems to affect the central nervous system. In an animal experiment, taurine infusion into the brain ventricles lowered blood pressure,[20] and a human experiment demonstrated *that supplemental intake of taurine at 6 g per day for 7 days lowered* blood pressure levels.[21] Tryptophan and tyrosine also seem to affect the central nervous system by enhancing the synthesis of serotonin, as demonstrated in animal experiments;[22,23] however, there is no evidence for a similar effect in humans. Although eggs and fish also contain these specific amino acids, they are frequently seasoned with salt in Japan. Therefore, dietary behaviors related to egg and fish intake did not show a significant inverse association with the risk of hypertension. As for dairy products, other mechanisms may exist. Milk peptides have antihypertensive activity by inhibiting angiotensin-1-converting enzyme.[24] Calcium and magnesium intake is inversely associated with blood pressure levels.[8,25]

With regard to noodle soup, which has a high sodium content, subjects who changed their dietary behavior from having noodle soup to avoiding noodle soup showed a higher risk of hypertension, although subjects who had an all-noodle soup diet did not consistently show a higher risk of hypertension. We suppose the reason was that subjects who developed high blood pressure levels among *subjects who had an all-noodle soup diet at the baseline survey* were careful to reduce sodium intake and stopped the all-noodle soup diet before the end-point survey.

Subjects who changed their dietary behavior from consuming one *or more eggs every day to avoiding eggs showed a higher risk of* hypertension, although subjects who did not consistently consume one or more eggs every day showed a statistically insignificant higher risk of hypertension. We suppose the reason was that subjects who stopped consuming eggs every day lowered their protein intake, which led to an increase in blood pressure. In a recent randomized trial of protein supplementation, in which egg protein formed 20% of the total protein intake, increased protein intake lowered blood pressure levels.[26]

Based on the results of the present study, Japanese people should consume meat and dairy products frequently to prevent hypertension. The recommendation of high meat intake is different from the DASH diet. However, a previous cross-sectional study of Japanese subjects showed an inverse association between animal protein intake and blood pressure levels,[27] which adds support to the notion that Japanese people should consume meat.

The strength of the present study is that the methodology was superior to that of previous cross-sectional studies of Japanese populations.[12,28] Prospective studies have little *informational bias, and their results are more revealing* than those of cross-sectional studies. The results of prospective studies also reinforce the causal relationships between risk factors and the development of hypertension more clearly than those of cross-sectional studies.

The limitations of the present study warrant discussion. First, we were unable to obtain the precise date of the development of hypertension because our analysis was based on information from annual cardiovascular risk checks. We then used logistic regression analysis to calculate the ORs based on information from the baseline questionnaire. Second, our questionnaire only allowed subjects to choose answers 'yes' or 'no,' which made it difficult to evaluate the dose–response association between each type of dietary behavior and the development of hypertension. Furthermore, we did not determine the validity of the questionnaire fully. Only questions concerning sodium intake were validated.[29,30] However, we previously compared our questionnaire with other validated food frequency questionnaires and found that the subjects who reported eating something frequently had higher intake than the *other subjects,*[31] *which may add some support to the validity* of the questionnaire. Third, we used the first blood pressure measurement in the present study due to the low number of subjects in whom blood pressure levels were measured twice. However, inclusion of the second measurement in the analysis, when available, did not change the results. In addition, we used systolic blood pressure levels measured at baseline in the multiple logistic regression analysis. We confirmed that the results did not change when we used diastolic instead of systolic blood pressure levels. Fourth, because of poor follow-up, we excluded from the analyses 1142 subjects who had a potentially higher risk of hypertension because of age, blood pressure levels and estimated glomerular filtration rate. Fifth, the present study included only males, and the results cannot be applied to females.

In conclusion, our prospective study of Japanese male workers showed that the intake of meat, dairy products and eggs was inversely associated with the risk of hypertension, whereas the intake of noodle soup was positively associated with the risk of hypertension. These results point to a beneficial dietary behavior that can prevent *hypertension in male Japanese workers. Further epidemiological* studies and clinical trials are necessary to establish the best dietary behavior for the prevention of hypertension among Japanese males.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Non-fasting blood glucose and risk of incident coronary heart disease in middle-aged general population: The Circulatory Risk in Communities Study (CIRCS)

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ABSTRACT

Objective. The objective was to determine whether non-fasting glucose concentration is a predictor for incident coronary heart disease.

Methods. We investigated a cohort data of 9,900 40- to 69-year-old residents in four Japanese communities for 1975–1986 baseline surveys of the Circulatory Risk in Communities Study (CIRCS). Non-fasting blood glucose concentrations were available for 7,332 participants. Diabetic type was defined as a glucose level of ≥11.1 mmol/L and/or the use of medication for diabetes mellitus.

Results. A total of 170 coronary heart disease including 113 myocardial infarctions occurred in non-fasting participants within the median 22-year follow-up period. Multivariable hazard ratios (HRs) of incident coronary heart disease for the participants with diabetic type compared with the normal type were 1.98 (0.84–4.68) for men, 3.39 (1.47–7.81) for women, and 2.47 (1.37–4.46) for total subjects. Corresponding HRs for myocardial infarction were 2.14 (0.83–5.55), 5.70 (2.21–14.67) and 3.17 (1.65–6.10), respectively. Multivariable HRs of incident coronary heart disease per one standard deviation of serum glucose levels were 1.17 (1.02–1.36), 1.19 (1.03–1.38), and 1.19 (1.08–1.32), respectively. The corresponding HRs for myocardial infarction were 1.18 (1.00–1.38), 1.27 (1.07–1.49) and 1.23 (1.10–1.37).

Conclusion. Non-fasting glucose concentration, either as diagnosis of diabetic type or as continuous variable, proved to be an independent predictor for incident coronary heart disease in middle-aged general population.

Introduction

A recent meta-analysis of 102 prospective observational studies (Sarwar et al., 2010) found that diabetes mellitus and fasting glucose concentration were associated with increased risk of coronary heart disease and ischemic stroke. Further, a meta-analysis of five prospective randomized controlled trials demonstrated that the intensive glycemic control reduced risk of coronary heart disease (Ray et al., 2009).

On the other hand, previous prospective studies examined the association of the fixed-time postload or postprandial glucose levels with mortality from or incidence of cardiovascular disease. For example, the 1 h or 2 h postload glucose concentration in the oral glucose tolerance test (OGTT) was a good predictor for death or events associated with cardiovascular diseases among subjects of Americans (Lowe et al., 1997), Europeans (DECODE Study Group, 2001), Asians (Nakagami et al., 2004), Japanese ancestry in Hawaii (Donahue et al., 1987) and Japanese (Tominaga et al., 1999). The 1 h or 2 h postprandial glucose concentration was also a stronger predictor for cardiovascular events than fasting glucose concentration among patients with type 2 diabetes (Cavalot et al., 2006; Hanefeld et al., 1996). The importance of the management of postprandial or postload glucose was addressed in the guidelines by the European Society of Cardiology and the European Association for the Study of Diabetes (Rydén et al., 2007) and by the International Diabetes Federation (2007) to prevent cardiovascular disease.

However, the measurement of fix-time postload or postprandial glucose levels is practically difficult to be performed at health screening for general populations, and the data of non-fasting blood glucose are commonly obtained. It is uncertain whether non-fasting glucose concentration is a predictor for incident coronary heart disease. To confirm that non-fasting glucose concentration, either as diagnosis of diabetic type or as continuous variable, is a predictor for incident coronary heart disease, we explored the data of a community-based prospective study of middle aged men and women.

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Methods

Study populations

The present analyses were conducted in the Circulatory Risk in Communities Study (CIRCS) (Imano et al., 2009, 2012; Ohira, 2010), which is a new generic name of the prior and ongoing epidemiological studies, such as Akita–Osaka Study, Ikawa Study and Kyowa Study since 1963. The study populations comprised 10,126 residents (4,092 men and 6,034 women) aged 40–69 years in four communities: Ikawa town (Kitamura et al., 2008; Shimamoto et al., 1989) (a rural community in Akita Prefecture in northwestern Japan), the Minami-Takayasu district (Kitamura et al., 2008) in Yao City (a southwestern suburb in Osaka Prefecture), Noichi town (Okamura, 1994) (a rural community in Kochi Prefecture in southwestern Japan); and Kyowa town (Iso et al., 1996) (a rural community in Ibaraki Prefecture in central Japan). The baseline surveys were conducted in 1975 to 80 in Ikawa town, in 1975 to 84 in the Minami-Takayasu district, in 1975 to 80 in Noichi town, and in 1981 to 86 in Kyowa town. The census population aged 40–69 years old was 2,291 in 1975 for Ikawa town, 5,538 in 1980 for the Minami-Takayasu district, 3,599 in 1975 for Noichi town, and 5,408 in 1980 for Kyowa town. The study participation rate was 60%. After exclusion of 226 participants with a history of coronary heart disease and/or stroke at baseline, the data for 7,332 (2,916 men and 4,416 women) non-fasting subjects were analyzed.

Informed consent was obtained for conducting this study, which was based on the guidelines of the Council for International Organizations of Medical Sciences (1991). This study was approved by the ethics committees of the Osaka Medical Center for Health Science and Promotion and of Osaka University.

Follow-up and ascertainment of cases

Follow-up lasted until the end of 2005 for Noichi and Kyowa, of 2008 for Minami-Takayasu, and of 2009 for Ikawa was terminated at the first incident of coronary heart disease or acute myocardial infarction, exit from the community or death.

The details of endpoint determination have been described in a previous CIRCS report (Kitamura et al., 2008; Shimamoto et al., 1989). To confirm the diagnosis, all living patients were telephoned, visited or invited to take part in risk factor surveys or a medical history was obtained from their families. In addition, medical records in the local clinics and hospitals were reviewed. In case of death, histories were obtained from families and/or attending physicians and medical records were reviewed.

The criteria for coronary heart disease were modified from those established by the World Health Organization Expert Committee (1962) and have been described in a previous CIRCS report (Imano et al., 2011; Kitamura et al., 2008). Definite myocardial infarction was diagnosed as typical severe chest pain (lasting at least 30 minutes) accompanied by the appearance of new abnormal and persistent Q or QS waves, consistent changes in cardiac enzyme levels, or both. Probable myocardial infarction was indicated by typical chest pain, but for which no electrocardiographic findings or findings related to enzyme activity were available. Myocardial infarction was considered present if either definite or probable myocardial infarction was diagnosed. Angina pectoris was defined as repeated episodes of chest pain during effort, especially when walking, usually disappearing rapidly after the cessation of effort or by the use of sublingual nitroglycerin. Sudden cardiac death was defined as death within 1 h of onset, a witnessed cardiac arrest, or abrupt collapse not preceded by not more than 1 h of symptoms. Coronary heart disease was defined as including myocardial infarction, angina pectoris, and sudden cardiac death.

Baseline examination

Blood was drawn into a plain, siliconized glass tube and the serum was separated immediately after centrifugation. The time intervals since the last meal were 0 to <1 h (4.2%), 1 to <2 h (27.3%), 2 to <3 h (54.6%), 3 to <4 h (9.8%), and 4 to <8 h (4.0%). Serum glucose was measured with the cupric-neocuproine method using SMA-6/60 (Technicon, Tarrytown, NY) between 1975 and August 31st in 1986 and with the hexokinase method using SMAC (Technicon) from September 1st in 1986. Glucose values (mmol/L) obtained using the first method were adjusted with the formula: 0.0474 × (glucose concentration in mg/dL) + 0.541. Glucose values were classified into three categories (diabetic type, prediabetic type and normal type). Diabetic type was defined as a glucose level of ≥11.1 mmol/L and/or the use of medication for diabetes mellitus. Normal type was defined as no use of medication for diabetes mellitus and a glucose level of <7.8 mmol/L. Borderline type was defined in those who belong neither to diabetic nor to normal types.

Serum total cholesterol was measured with the Liebermann–Burchard direct method using Autoanalyzer II (Technicon) for the period 1975–1979 and SMA-6/60 from 1979 to 1986. Serum triglycerides were measured with the fluorometric method using Autoanalyzer II from 1975 to 1986. For 60% of total sample ($n = 4{,}385$), high-density lipoprotein (HDL) cholesterol was measured after heparin-manganese precipitation using the Libermann–Burchard method.

All measurements of serum glucose, serum total cholesterol, serum triglycerides and HDL-cholesterol were performed at the laboratory of the Osaka Medical Center for Health Science and Promotion, an international member of the US National Cholesterol Reference Method Laboratory Network. This laboratory has been standardized since 1975 by the Centers for Disease Control-National Heart Lung and Blood Institute (CDC-NHLBI) Lipid Standardized Program provided by the CDC (Atlanta, GA) and successfully met the criteria for both precision and accuracy of serum total cholesterol, triglycerides and HDL-cholesterol measurements (Nakamura et al., 2003).

Blood pressures were measured by trained physicians using standard mercury sphygmomanometers and standardized epidemiological methods (Imano et al., 2009). Height was measured with the subjects in stocking feet and their weight while wearing light clothing. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2).

An interview was conducted to ascertain smoking status, the number of cigarettes smoked per day, usual alcohol intake per week, menopause status, and the use of medication for diabetes mellitus or hypertension.

Statistical analyses

Analysis of covariance was used to test for differences in age-adjusted means and proportions of baseline characteristics according to serum glucose category. HRs and 95% confidence intervals (CIs) for incident myocardial infarction were calculated with the aid of Cox proportional hazards regression models. We tested the assumption of proportional hazards and found no violation of the proportionality principle.

We calculated the sex-specific and sex-adjusted HRs of each diabetic type and borderline type against the normal type as the referent, and the corresponding HRs per one standard deviation increment in serum glucose level (1.9 mmol/L). The initial model was adjusted only for age, while the multivariable adjustment included adjustments for age, sex (for total participants), community, sex-specific quartiles of body mass index (kg/m^2), of serum triglycerides (mmol/L), serum total cholesterol level (mmol/L), systolic blood pressure (mmHg), antihypertensive medication use, cigarette smoking status (never, former and current 1–24 or ≥25 cigarettes per day), alcohol intake (never, former, and current <46, 46–68 or ≥69 g ethanol per day), time category since last meal (0 to <1 h, 1 to <2 h, 2 to <3 h, 3 to <8 h) and for women, menopausal status. Further adjustment for HDL-cholesterol (mmol/L) was conducted among a subsample in which the data on HDL-cholesterol were available.

All statistical analyses were performed with the Statistical Analysis System (SAS) for Windows (version 9.3; SAS Inc, Cary, NC). All p-values for statistical tests were two-tailed, and values of <0.05 were regarded as statistically significant.

Results

Table 1 compares age-adjusted mean values and prevalences of selected cardiovascular risk factors at baseline according to serum glucose category. The prevalences of diabetic type were 3.7% for men and 2.4% for women, and the corresponding prevalences of borderline type were 20.6% and 11.5%. Glucose abnormality was positively associated with many other cardiovascular risk factors for both sexes.

During follow-up, we documented 170 incident coronary heart disease (98 men and 72 women), 113 incident myocardial infarctions (71

Table 1
Age-adjusted mean values or prevalences of risk factors at baseline according to serum glucose category in non-fasting subjects.

	Men				Women			
	Normal type	Borderline type	Diabetic type	*p* Value for difference	Normal type	Borderline type	Diabetic type	*p* Value for difference
No. at risk	2209	600	107		3802	509	105	
Age, year	52.3 (0.2)	52.5 (0.4)	56.2 (0.8)	<0.001	51.9 (0.1)	53.9 (0.4)	55.9 (0.8)	<0.001
Serum glucose, mmol/L	6.3 (0.0)	8.8 (0.0)	13.8 (0.1)	<0.001	6.2 (0.0)	8.7 (0.0)	14.6 (0.1)	<0.001
Body mass index, kg/m^2	22.7 (0.1)	23.0 (0.1)	23.2 (0.3)	0.008	23.2 (0.1)	23.8 (0.1)	24.7 (0.3)	<0.001
Systolic blood pressure, mmHg	135 (0.4)	142 (0.8)	139 (2.0)	<0.001	132 (0.3)	139 (0.9)	143 (1.9)	<0.001
Diastolic blood pressure, mmHg	82 (0.3)	84 (0.5)	83 (1.2)	0.002	79 (0.2)	80 (0.5)	81 (1.1)	0.010
Antihypertensive medication, %	10.6	15.3	16.9	0.001	10.9	16.4	20.8	<0.001
Hypertension, %	42.4	52.6	55.1	<0.001	35.6	48.7	59.4	<0.001
Serum total cholesterol, mmol/L	4.73 (0.02)	4.80 (0.04)	4.85 (0.08)	0.129	5.01 (0.01)	5.18 (0.04)	5.28 (0.09)	<0.001
Serum triglycerides, mmol/L	1.68 (0.03)	1.80 (0.05)	2.23 (0.13)	<0.001	1.48 (0.01)	1.59 (0.04)	2.07 (0.09)	<0.001
Serum HDL-cholesterol, mmol/L	1.44 (0.01)	1.49 (0.02)	1.45 (0.05)	0.111	1.50 (0.01)	1.50 (0.02)	1.41 (0.05)	0.183
Current smokers, %	64.3	68.7	76.1	0.009	7.3	7.4	10.8	0.402
Ex-smokers, %	16.5	15.3	4.8	0.005	1.1	0.5	2.6	0.128
Ethanol intake, g/day	27.1 (0.6)	31.9 (1.1)	29.9 (2.7)	<0.001	1.4 (0.1)	1.5 (0.4)	0.4 (0.8)	0.440
Postmenopausal, %	–	–	–		57.0	57.8	57.3	0.862

In parentheses; standard errors. HDL-cholesterol; high-density lipoprotein cholesterol.

men and 42 women), 624 censored out of the community (193 men and 431 women) and 2,260 deaths (1,174 men and 1,086 women).

For reference, the corresponding results among fasting subjects or among fasting and non-fasting ones were shown in Supplemental Table 1.

Table 2 shows the relationship between serum glucose category and risks of coronary heart disease and myocardial infarction. Multivariable HRs of coronary heart disease for diabetic type were approximately 2 to 3 and were statistically significant for women and for total subjects. The HRs of myocardial infarction for diabetic type tended to be higher than those of coronary heart disease and were statistically significant except for men. The HRs of coronary heart disease associated with one standard deviation increment of serum glucose were statistically significant for men, for women and for total subjects. The results were much the same in myocardial infarction.

For reference, the corresponding results among fasting subjects or among fasting and non-fasting ones were showed in Supplemental Table 2.

When we excluded the subjects who took medication for diabetes mellitus ($n=26$, 12% of diabetic type), the results did not change substantially, that is, the multivariable HRs (95% CI) for risk of coronary heart disease for diabetic type were 2.40 (1.02–5.67) for men, 3.64 (1.58–8.42) for women and 2.86 (1.58–5.15) for total subjects. The corresponding HRs (95% CI) of myocardial infarction were 2.53 (0.98–6.57), 6.00 (2.32–15.50) and 3.55 (1.85–6.84). When we restricted the subjects to <3 h postprandial status ($n=6,321$, 86.2% of total non-fasting subjects), the results did not change substantially. The multivariable HRs for risk of coronary heart disease for diabetic type were 1.81 (0.71–4.64) for men, 3.53 (1.51–8.26) for women and 2.46 (1.33–4.56) for total subjects. The corresponding HRs of myocardial infarction were 1.79 (0.62–5.14), 6.14 (2.34–16.08) and 3.07 (1.54–6.10). When we adjusted further for HDL-cholesterol levels among a subsample in which the data on HDL-cholesterol were available ($n=4,385$, 59.8% of total non-fasting subjects), the multivariable HRs for risk of coronary heart disease for diabetic type were 2.61 (0.76–8.94) for men, 2.73 (0.33–22.95) for women and 2.20 (0.78–6.22) for total subjects. The corresponding HRs of myocardial infarction were 3.43 (0.97–12.19), 4.08 (0.38–44.21) and 3.11 (1.06–9.12).

Discussion

The community-based observational study presented here shows that non-fasting glucose concentration, either as diagnosis of diabetic type or as continuous variable, is an independent significant predictor for incident coronary heart disease and myocardial infarction in middle-aged general population. A prospective study of Japanese representative sample (Kadowaki et al., 2008) ($n=9,444$, mean follow-up period 17.3 years) investigated the association between casual (combined fasting and non-fasting) blood glucose and mortality from coronary heart disease for men and women combined. In that study, the multivariable HRs (95% CI) of coronary heart disease mortality were 2.43 (1.29–4.58) for borderline high casual blood glucose (7.77 to <11.10 mmol/L) and 2.62 (1.46–4.67) for high casual blood glucose (≥11.10 mmol/L) compared with lower blood glucose levels (<5.22 mmol/L). Another Japanese study (Saito et al. 2011) ($n=31,192$, median follow-up period 12.9 years) showed a similar result on the excess risk of coronary heart disease associated with borderline and diabetes mellitus, but it showed no significant association between non-fasting glucose concentration, neither as diagnosis of diabetic type nor as continuous variable, and the risk of coronary heart disease. Our results were inconsistent with that previous study. However, in the present study, the follow-up period was longer (22 years vs. 12.9 years) and the percentage of non-fasting blood samples in whole subjects was higher (74.1% vs. 57.5%) than the previous study. Therefore this study may have been able to detect the association.

The HRs of coronary heart disease and of myocardial infarction for subjects with diabetic type were greater for women than for men. Our finding extended the evidence from an Italian prospective study of type 2 diabetic patients, which showed that blood glucose 2 h after lunch, but not fasting blood glucose was a significant predictor for cardiovascular events, particularly in women (Cavalot et al. 2006). Although women seem to be more susceptibility to hyperglycemia for the risk of coronary heart disease, additional research is needed to clarify the sex difference mechanism.

The multivariable HRs (95% CI) of coronary heart disease for subjects with borderline type were 1.49 [1.03–2.15]. It is consistent with the result of a previous meta-analysis of 38 prospective observational studies dealing with postload glucose, casual glucose, fasting glucose or hemoglobin A1c (Levitan et al., 2004). It identified nondiabetic hyperglycemia as a risk marker for cardiovascular disease (HR 1.19, [95% CI, 1.07–1.32]). Further follow up is necessary to examine the effect of borderline type on risk of myocardial infarction.

The mechanisms for the progression of atherosclerosis by non-fasting hyperglycemia were suggested by several animal studies. The repetitive postprandial fluctuations in glucose concentrations of diabetic rats induced by being fed twice daily were found to generate the monocyte adhesion to endothelial cells of the thoracic aorta even at lower hemoglobinA1c levels (mean values were less than 4.0%) (Azuma et al., 2006). Further, the repetitive postprandial glucose spikes in apolipoprotein E-deficient mice induced by being fed maltose, accelerated the macrophage adhesion to endothelial cells and the formation of fibrotic arteriosclerotic lesions (Mita et al., 2007). Diabetic rats produced by inducing insulin-mediated rapid "glycemic swings" (exaggeratedly changing blood glucose levels), regardless of their effect on average blood glucose levels, have impaired endothelium-dependent relaxation, in part via enhanced activation of the poly(ADP-ribose) polymerase pathway (Horváth et al., 2009). In another study, oxidative stress, estimated from 24 h urinary excretions rates of unbound 8-iso-prostaglandin F2α, was correlated with acute glucose fluctuations but not with hemoglobinA1c or fasting glucose concentration (Monnier et al., 2006).

The strength of the current study was population-based cohort study based on the standardized epidemiological methods, so that our findings may be more appropriate to generalize. Second, we used incident coronary heart disease or myocardial infarction as the target endpoint because it reflects more directly the relationship with risk factors than does mortality from coronary heart disease or myocardial infarction.

Table 2
Multivariable hazard ratios (HRs, 95% CI) of coronary heart disease and myocardial infarction according to serum glucose category and glucose concentration in non-fasting subjects.

	Person years	Coronary heart disease			Person years	Myocardial infarction		
		No of events	Age adjusted HR (95% CI)§	Multivariable HR (95% CI)		No of events	Age adjusted HR (95% CI)§	Multivariable HR (95% CI)
Men								
Normal type	45,987	64	Ref.	Ref.	46,176	47	Ref.	Ref.
Borderline type	12,233	28	1.65 (1.06–2.57)*	1.41 (0.89–2.25)	12,304	19	1.52 (0.90–2.60)	1.24 (0.71–2.16)
Diabetic type	1674	6	2.44 (1.05–5.65)*	1.98 (0.84–4.68)	1674	5	2.86 (1.13–7.22)*	2.14 (0.83–5.55)
HR per 1SD increment of glucose	59,894	98	1.24 (1.09–1.41)†	1.17 (1.02–1.36)*	60,154	71	1.27 (1.10–1.46)†	1.18 (1.00–1.38)
Women								
Normal type	85,565	51	Ref.	Ref.	85,946	28	Ref.	Ref.
Borderline type	11,628	14	1.89 (1.04–3.41)*	1.49 (0.80–2.75)	11,712	8	1.91 (0.87–4.21)	1.40 (0.61–3.18)
Diabetic type	2105	7	4.90 (2.21–10.87)‡	3.39 (1.47–7.81)†	2129	6	7.76 (3.18–18.92)‡	5.70 (2.21–14.67)‡
HR per 1SD increment of glucose	99,298	72	1.30 (1.14–1.48)‡	1.19 (1.03–1.38)*	99,787	42	1.39 (1.20–1.61)‡	1.27 (1.07–1.50)†
Total								
Normal type	131,552	115	Ref.	Ref.	132,122	75	Ref.	Ref.
Borderline type	23,860	42	1.74 (1.22–2.49)†	1.49 (1.03–2.15)*	24,016	27	1.66 (1.07–2.58)*	1.35 (0.85–2.13)
Diabetic type	3779	13	3.34 (1.88–5.96)‡	2.47 (1.37–4.46)†	3803	11	4.44 (2.35–8.40)‡	3.17 (1.65–6.10)‡
HR per 1SD increment of glucose	159,191	170	1.26 (1.15–1.38)‡	1.19 (1.08–1.32)‡	159,941	113	1.32 (1.19–1.46)‡	1.22 (1.09–1.37)‡

Test for significance: *$P<0.05$, †$P<0.01$, ‡$P<0.001$. §: Age and sex adjusted HR for total subjects.
Multivariable hazard ratio adjusted for age, sex, community, sex-specific quartiles of body mass index, of serum triglycerides, serum total cholesterol, hypertensive status, antihypertensive medication use, cigarette smoking status, alcohol intake category, time since last meal and for women, menopausal status.

Conclusion

Our population-based cohort study of Japanese showed that non-fasting glucose concentration, either as diagnosis of diabetic type or as continuous variable, proved to be an independent predictor for incident coronary heart disease and myocardial infarction.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Cost-effectiveness and budget impact analyses of a long-term hypertension detection and control program for stroke prevention

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See editorial comment on page 1706

Objectives: The nation-wide, community-based intensive hypertension detection and control program, as well as universal health insurance coverage, may well be contributing factors for helping Japan rank near the top among countries with the longest life expectancy. We sought to examine the cost-effectiveness of such a community-based intervention program, as no evidence has been available for this issue.

Methods: The hypertension detection and control program was initiated in 1963 in full intervention and minimal intervention communities in Akita, Japan. We performed comparative cost-effectiveness and budget-impact analyses for the period 1964–1987 of the costs of public health services and treatment of patients with hypertension and stroke on the one hand, and incidence of stroke on the other in the full intervention and minimal intervention communities.

Results: The program provided in the full intervention community was found to be cost saving 13 years after the beginning of program in addition to the fact of effectiveness that; the prevalence and incidence of stroke were consistently lower in the full intervention community than in the minimal intervention community throughout the same period. The incremental cost was *minus* 28 358 yen per capita over 24 years.

Conclusion: The community-based intensive hypertension detection and control program was found to be both effective and cost saving. The national government's policy to support this program may have contributed in part to the substantial decline in stroke incidence and mortality, which was largely responsible for the increase in Japanese life expectancy.

Keywords: health check-ups, health policy, prevention, public health, screening

INTRODUCTION

Japan has had high incidence of stroke and mortality from stroke among developed countries [1]. The high incidence of stroke has produced a burden for the national insurance system [2] as well as a reduction in the quality-of-life for patients and their families. Stroke prevention programs have therefore been conducted in several communities in Japan, since the 1960s [3,4]. We previously reported the effects of a long-term hypertension detection and control program on stroke incidence and prevalence, in which we compared two northeastern Japanese communities, one with full and the other with minimal intervention [5], which showed an approximately 20% greater decline in stroke incidence in the full intervention community. However, as far as we know, no evidence has been available for the cost-effectiveness of such a community-based intervention program for cardiovascular disease prevention. Such information of cost-effectiveness and budget impact could be useful for the planning and implementation of health policy, in not only developed, but developing countries because lifestyle-related disease including stroke have emerged as global burden for health [6].

We therefore conducted a cost-effectiveness analysis of a long-term hypertension control program for a comparison of the two communities. The aim of this study was to compare the costs of public health services and of treatment of patients with hypertension and stroke in the full intervention and minimal intervention communities. Our *a priori* hypothesis was that the full intervention community would incur higher costs for the prevention of strokes but achieve superior results (i.e. a steeper reduction in stroke incidence).

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METHODS

Survey population

The surveyed communities were Ikawa (full intervention; census population ≥30 years was 3219 in 1965, and 4115 in 1985) and a district of city H (minimal intervention; 1468 in 1965, and 1589 in 1985) in Akita Prefecture, northeastern Japan [5].

Hypertension detection and control program: full intervention community

Strategies for hypertension control included free-of-charge systematic cardiovascular screening, referral of high-risk individuals to local clinics for antihypertensive medication, health education for hypertensives at blood pressure (BP) screening sites and group education, and during public health nurse home visits, training of about 150 'healthy-diet' volunteers for health education, and community-wide media-disseminated education to encourage participation in BP screening and reducing salt intake. These components of the program have been previously described in detail [5]. Treatment of hypertension was performed by local physicians of each community using primarily thiazide diuretics and secondarily β-adrenergic blocking agents. Calcium channel antagonists and angiotensin-converting enzyme inhibitors were rarely used before the mid-1980s. The program started in 1963 and has been implemented every year since then.

Hypertension detection and control program: minimal intervention community

A similar organization was established in 1963 in the minimal intervention community. Strategies of the program were similar to those of the full intervention community, but did not include group education or community-wide media education. The municipal publicity system was used only for recruiting participants for BP screenings. The initial BP screening performed from 1964 to 1968 was free-of-charge, but the local government started to charge the participants for BP screening beginning in 1969. Between 1964 and 1972, an enthusiastic nurse visited about 200 hypertensives each year, and a similar intensity of the program may have been achieved because of the smaller population size compared with the full intervention community. At the beginning of the intervention, the participation rate of health checkups among residents aged 40–69 was 87% in the full intervention community and 86% in the minimal intervention community [5]. BPs levels, prevalence of hypertensives and proportion of treatment among hypertensives were similar between the communities at the beginning of the intervention [5]. After her retirement in 1973, however, the systematic visits ended and the intensity of the program was reduced.

Cost of public health services

We reviewed all the annual balance sheets from 1964 to 1987 from the two municipal governments, published by each municipal government. The costs of public health services were calculated as the sum of expenses for overall public health, including general administration for public health, personnel, and health promotion and health check-up projects. We also included the expenses for other public health services, such as maternity health, but excluded those for environmental health such as garbage or sewage disposal. Therefore, the cost of public health services was derived from the actual cost that each municipal government spent.

Cost of hypertension and stroke treatment

As the direct and community-specific costs of hypertension and stroke treatment were not available, we estimated these costs as follows. The estimated medical costs for treatment of hypertension were calculated as the number of treated hypertensives aged 30 or more, multiplied by hypertension treatment cost for outpatient clinics per treated person. The numbers of treated hypertensives were derived from the actual number of hypertensives, who reported antihypertensive medication use at the cardiovascular risk screenings. Treated hypertensives, who did not attend the screenings were not included because their treatments were not likely to be affected by the program. The cost for outpatient clinics per treated person was derived from the annual report of National Health Insurance [7]. This report is an annual sampling survey performed in May based on the claims of National Health Insurance, which self-employees and farmers are required to be covered. The estimated costs of stroke treatment were calculated as the number of strokes multiplied by stroke treatment cost per capita. The number of stroke was derived from community stroke register system, which had registered all stroke events in the community, so we used actual number of strokes. Stroke treatment cost per capita was also derived from the annual report of National Health Insurance [7], and we assumed that stroke treatment involved 1 month of hospital treatment and 35 months of outpatient treatment, based on the national statistics showing the median duration of hospitalization for stroke was approximately 30–40 days throughout the study period [8], and the findings of previous study by us indicated that the average survival term of poststroke patients was approximately 3 years (unpublished). All per capita costs were calculated by dividing total cost by the number of members of the population aged at least 30 years. Table 1 shows the source of data.

We did not perform the cost-effective analysis for coronary heart disease, as the primary target of the hypertension detection and control program was stroke and the incidence of coronary heart disease was very rare (approximately one-twelfth of stroke for men and one-fortieth for women) in the Northeastern Japanese communities [9].

Statistical analyses

Cost-effectiveness analysis

Theoretically, the cost-effective analysis evaluates a given health intervention through the use of cost-effectiveness

TABLE 1. Sources of data to determine costs and effectiveness of hypertension detection and control program

	Data	Source	Data category	Study
Population	Number of persons aged 30 years or more	National census, 1965–1985	Measured/monitored	Ref [5]
Cost of public health services	Cost of general administrations for public health, personnel, and health promotion and health checkups projects	Reports of annual balance sheets of municipal governments, 1964–1987	Measured/monitored	Balance sheet review
Number of treated hypertensives	Number of treated hypertensives detected by annual checkups	Reports of annual health checkups by municipal governments, 1964–1987	Measured/monitored	This study
Cost of hypertension treatment per treated patient	Cost for hypertension outpatient treatment at clinic per 1 person-month, multiplied by 12 months	Annual surveillance of medical benefits from National Health Insurance, 1964–1987	Estimated	Ref [7]
Number of incident strokes	Number of incident first-ever stroke	Stroke registration system by municipal governments, 1964–1987	Measured/monitored	Ref [5]
Cost of stroke treatment per treated patient	Cost of in-hospital stroke inpatient treatment per 1 person-month + cost of in-hospital stroke outpatient treatment per 1 person-month, multiplied by 35 months	Annual surveillance for medical benefits from National Health Insurance, 1964–1987	Estimated	Ref [7]
Cost of hypertension/stroke treatment per capita	Cost of hypertension/stroke treatment per treated patient multiplied by treated hypertension/stroke patients, and then devided by number of population	Calculated by derived data	Calculated	This study

ratio [10]. However in our case, the program was found 'cost saving' (i.e., the lower the stroke incidence rate with the lower the cost), and thus the cost-effectiveness ratio was not calculated. Instead, we presented the cumulative total cost differences between the full and the minimal intervention communities according to time frame (see Fig. 1 legend). We totaled the above-mentioned costs of public health services and of hypertension and stroke treatment every year for each community. All the costs were then adjusted for changes in the consumer price index [11], and were further discounted at an annual rate of 4% per year during the study period. A threshold analysis was performed to ensure the uncertainty of the cost of treatment in the communities, as the costs of hypertension and stroke treatments were estimated based on the national statistics.

Budget impact analysis

To assess long-term trends in costs, we compared the aforementioned costs for 6-year periods (i.e., 1964–1969, 1970–1975, 1976–1981, 1982–1987). The costs were adjusted for change in the consumer price index, but not discounted in order to be able to compare the impact of the

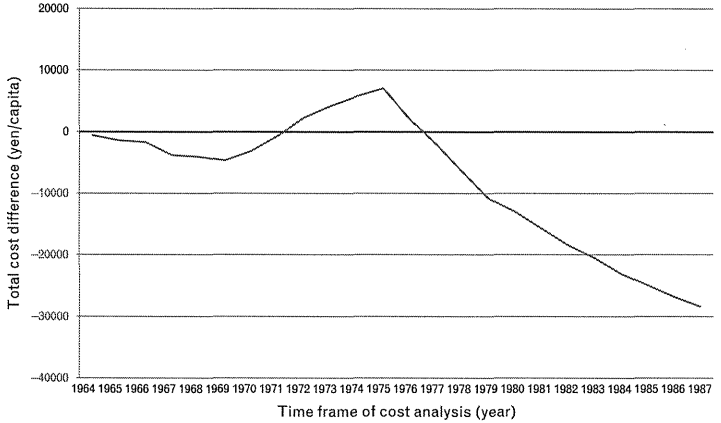

FIGURE 1 Cost analyses of the hypertension detection and control program, 1964–1987. X-axis: time frame of cost analysis (t). Y-axis: total cost difference by year defined as follows: Total cost difference $= \sum_{\text{year}=1964}^{t}\{C_A(1-0.04)^{\text{year}-1964} - C_B(1-0.04)^{\text{year}-1964}\}$, $t = 1964 - 1987$ where, C_A stands for total cost (after adjustment for consumer price index) in the full intervention community and C_B stands for that in the minimal intervention community. Discount rate was 4% per year.

TABLE 2. Budget impact of hypertension detection and control programs on two Japanese communities between 1964 and 1987

	Full intervention community				Minimal intervention community				Budget impact			
	1964–1969	1970–1975	1976–1981	1982–1987	1964–1969	1970–1975	1976–1981	1982–1987	1964–1969	1970–1975	1976–1981	1982–1987
Number of population	3219	3481	3789	4115	1468	1479	1556	1589				
Proportion of men, %	47	47	47	47	46	45	46	46				
Proportion of individuals with age >70, %	7	10	12	15	6	9	13	16				
Health checkup participation rate with age 40–69[b], %	87	86	77	82	86	59	58	65				
Cost of public health services per capita[a], yen/year	2099	5577	9707	11 799	1990	3412	6414	7058	109	2165	3293	4741
Number of treated hypertensives[b]	125	543	627	607	70	211	329	301				
Proportion of treated hypertensives among hypertensives, %	17	60	79	72	24	66	92	91				
Cost of hypertension treatment per capita[a], yen/year	4241	23715	28462	25 075	5208	21 689	36 368	32 201	−967	2026	−7905	−7126
Number of incident stroke per year	21	16	15	12	10	9	9	8				
Cost of stroke treatment per capita[a], yen/year	4502	4182	4591	3333	4745	5561	6310	5833	−244	−1379	−1719	−2500
Total cost[a] per capita, yen/year	10 842	33 474	42 760	40 207	11 943	30 663	49 091	45, 091	−1102	2812	−6331	−4884

[a]Adjusted for consumer price index.
[b]Health checkup participation rates and numbers of treated hypertensives were based on slightly different terms from other variables due to unavailability of data: the terms should be read as 1963–1966, 1972–1975, 1979–1982 and 1984–1987 for the full intervention community, and 1964–1968, 1970–1971, 1979–1980, and 1985–1986 for the minimal intervention community.

hypertension detection and control program on healthcare financing overtime. The budget impact was defined as the costs of the program in the full intervention community minus those in the minimal intervention community.

Ethical issue

This study was approved by the Committee for Medical Ethics of University of Tsukuba.

RESULTS

Overall, the program provided in the full intervention community was cost saving (i.e., less cost with a lower stroke incidence) throughout the study period, in addition to the fact of effectiveness that the prevalence and incidence of stroke were consistently lower in the full intervention than in the minimal intervention community throughout the same period; age-adjusted stroke incidence rates per 1000 person-years were 38 in 1964–1969, 23 in 1970–1975, 19 in 1976–1981, and 12 in 1982–1997, whereas those in the minimal intervention community was 41, 33, 26 and 22, respectively [5]. The incremental cost was −28 358 yen per capita for 24 years (Fig. 1). The cost savings started to appear 13 years after the start of the program. The threshold analysis showed that the cost savings disappeared if the costs for hypertension and stroke treatment in the communities were lower by 43% or more than reported by the national statistics.

To assess long-term trends in costs, we performed a budget impact analysis every 6 years (Table 2). For the first 6 years (1964–1969), there was no major difference in the total cost between the two communities. During 1970–1975, the cost was 2812 yen per capita per year higher for the full intervention than for the minimal intervention community. This difference was mainly accounted for by the cost of hypertension treatment as well as that of public health services. For the minimal intervention community, the free-of-charge BP screening program was terminated in 1968, after which the participation rate for health checkups dropped from 86 to 59%. After 1975, the total cost of the program became lower for the full intervention than for the minimal intervention community. The long-term cost of public health services was consistently higher for the full intervention than for the minimal intervention community, whereas the cost of treatments for hypertension and stroke was higher for the minimal intervention community in 1976–1981 and 1982–1987.

DISCUSSION

This is the first study to use actual costs and actual effects for a cost-effectiveness analysis of a community-based hypertension detection and control program. Against our *a priori* hypothesis, the program proved to be both effective and cost saving, that is, the full intervention community had the lower overall cost of implementing the hypertension detection and control program with a greater benefit for stroke prevention (i.e., lower incidence). These findings were in line with previous studies based on the simulation model studies that showed the community intervention programs to reduce sodium intake were generally cost-effective [12].

We assumed that the intensity of the programs in the two communities were similar for the first several years, because the participation rate of health checkups, one of indicators for the intensity of intervention, was similar between the two communities. The minimal intervention community was initially provided with a hypertension detection and control program and free-of-charge BP screening service as it was for the full intervention community, so there was no major difference in the results of the budget analysis for 1964–1969. After the free BP screening service for the minimal intervention community was terminated, the cost of the program for that community became less than that for the full intervention community between 1970 and 1975 (Table 2), mostly due to the lower cost of hypertension treatment as well as public health services. This cost difference for hypertension treatment was the result of the reduction in the number of persons detected with hypertension due to the lower participation rate in screening for aged 40–69 years in the minimal intervention community (from 86% in 1964–1968 to 59% in 1970–1971 compared with 87% in 1963–1966 to 86% in 1972–75 for the full intervention community [5]). After 1975, however, the cost of the program for the two communities became reversed due to the vastly higher hypertension and stroke treatment costs for the minimal intervention community. The budget impacts involved 12–15% of the total cost for the program after 1975.

The program for the full intervention community was seen as a pilot program for the establishment of a nationwide hypertension screening and control program. In 1982, the Japanese government enacted the Health Service for the Elderly Act, which ensured cardiovascular screening and health education for residents aged 40 years and over, as well as care for the elderly [13]. The health service was provided by the municipal governments and financed with the help of prefectural and national governments, and has been functioning in conjunction with medical services under the universal health insurance coverage established in 1961, which allowed residents in Japan to see physicians under a reduced charge. We showed that the community-based intensive hypertension detection and control program was both effective and cost saving. The national government policy to support the program may have contributed in part to the substantial decline in stroke incidence [9] and mortality [1], regardless of socioeconomic status [14], which was one of the major contributing factors for the increase in life expectancy among Japanese since the late 1960s.

A limitation of this study is that the program ended in the minimal intervention community in 1987 when the incidence of stroke was still high. The difference in stroke incidence between the two communities observed here could be smaller in the current era, since mortality rate in Japan has declined during the past two decades (by 62% among men and by 71% among women from 1985 to 2009). The present results are unlikely to be extrapolated to other societies with low incidence of stroke and with different insurance and health service systems. Similarly, the results of our 'historical' cost-effectiveness analysis cannot be directly transmitted to the 21st century, as the prevalence of hypertension, stroke incidence, medical and public health expenditures and lifestyles are different from those 25–50 years ago [2]. Nevertheless, we believe our experience would be able to be of use for many countries, especially developing countries, with high incidence of and mortality from stroke to accomplish the steep reduction of stroke and prolongation of life expectancy, as Japan has experienced.

In conclusion, the long-term community-based intensive hypertension detection and control program was found to be both effective and cost saving. However, it takes more than 10 years to attain this cost savings, because the early detection of hypertension increased the cost of treated hypertensive patients in the full intervention community in the first decade.

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Conflicts of interest

There are no conflicts of interest.

Appendix

The CIRCS Investigators

The Circulatory Risk in Communities Study (CIRCS) is a collaborative study managed by the Osaka Center for Cancer and Cardiovascular Disease Prevention, University of Tsukuba, Osaka University, and Ehime University. The CIRCS investigators who contributed to this study are as follows: Yoshinori Ishikawa, Akihiko Kitamura, Masahiko Kiyama, Masakazu Nakamura MD, Takeo Okada, Kenji Maeda, Masatoshi Ido, Masakazu Nakamura PhD, Masamitsu Konishi, Takashi Shimamoto, Hideki Ozawa, Minoru Iida, and Yoshio Komachi, Osaka Center for Cancer and Cardiovascular Disease Prevention, Osaka; Yoshihiko Naito, Mukogawa Women's University, Nishinomiya; Shinichi Sato, Chiba Prefectural Institute of Public Health, Chiba; Tomoko Sankai, Kazumasa Yamagishi, Mitsumasa Umesawa, ChoyLye Chei and Minako Tabata, University of Tsukuba, Tsukuba; Hiroyasu Iso, Tetsuya Ohira, Hironori Imano, Renzhe Cui, Ai Ikeda, Hiroyuki Noda, Satoyo Ikehara, Yuji Shimizu, Isao Muraki and Masanori Nagao, Osaka University, Suita; Takeshi Tanigawa, Isao Saito, Susumu Sakurai, Shinichi Hitsumoto, Kotatsu Maruyama, Eri Eguchi and Minako Maruyama, Ehime University, Tōon.

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Original Article

Risk factors for sudden cardiac death among Japanese: the Circulatory Risk in Communities Study

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Objective: There is little evidence concerning risk factors for sudden cardiac death (SCD) among Asians.

Patients and methods: A prospective, nested, case–control study of Japanese patients aged between 30 and 84 years was undertaken using data collected from 26 870 participants in cardiovascular risk surveys conducted in four communities between 1975 and 2005. The incidence of SCD was ascertained by systematic surveillance, with 239 cases of SCD identified over this period. For each case of SCD, three control patients were selected, matched by age, sex, examination year, follow-up time, and community.

Results: Hypertension, diabetes mellitus, smoking, major ST-T abnormalities, left high amplitude R waves, and increased heart rate (≥77 beat/min) were all independently associated with a 1.5–3.2-fold increase in SCD risk, whereas no associations were observed for body mass index and hypercholesterolemia. The population-attributable fraction [95% confidence interval (CI)] was 23.0% (2.9–39.0) for hypertension, 15.3% (3.8–25.5) for current smoking, 14.5% (8.0–20.5) for major ST-T abnormalities, and 8.1% (2.2–13.7) for diabetes mellitus. The number of SCD risk factors (hypertension, diabetes, smoking, and ECG abnormalities) was positively associated with increased SCD risk. The odds ratio for increased SCD risk with three or more risk factors versus zero risk factors was 5.76 (95% CI 3.20–10.39).

Conclusions: Among the Japanese population, hypertension, smoking, major ST-T abnormalities, left high amplitude R waves, and diabetes mellitus were associated with an increased incidence of SCD, whereas there were no associations of body mass index or hypercholesterolemia with SCD incidence.

Keywords: cardiac death, nested case–control study, population-based, prospective study, risk factors

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; CIRCS, Circulatory Risk in Communities Study; ECG, electrocardiogram; LHAR, left high amplitude R waves; OR, odds ratio; PAF, population-attributable fraction; SCD, sudden cardiac death; ST-T, ST-segment and T-wave; SVPC, supraventricular premature contraction; VPC, ventricular premature contraction

Sudden cardiac death (SCD) is an important cause of mortality in Western countries, and raises significant clinical and public health concerns, with 250 000–400 000 reported cases in the US every year [1,2]. Epidemiological studies have identified several risk factors for SCD, which include hypertension, smoking, heavy drinking, obesity, diabetes mellitus, renal dysfunction, electrocardiogram (ECG) abnormalities, and hypercholesterolemia [3–11].

Racial differences in SCD rates have also been reported [2,12]. In the US, the African American population has the highest age-adjusted rate of SCD, followed by Caucasians, American Indians and Alaskan Natives. Asians and Pacific Islanders generally have the lowest rates of SCD, at rates approximately half that of African Americans [2]. A population-based study in Osaka, Japan, showed that the incidence rate of SCD was 0.31 per 1000 people for those aged 20–74 years [13], which is equivalent to approximately one-fifth of that seen in the US. Such a difference in SCD incidence between Japan and the US can possibly be attributed to differences in SCD risk factor prevalence and less atherosclerotic and hypertensive heart disease. Few studies, however, have investigated risk factors for SCD among the Japanese population.

A prospective study of 7591 middle-aged Hawaiian-Japanese men showed that blood pressure (BP), serum cholesterol, serum glucose, current smoking, history of parental heart attack, and left-ventricular hypertrophy were positively associated with an increased risk of SCD, whereas alcohol intake and the number of years spent in Japan were inversely associated with SCD risk [5]. There has been no prospective study in the literature of a similar nature which has looked at SCD risk factors among Japanese individuals residing in Japan. We therefore examined the relationship of cardiovascular risk factors with the incidence of SCD in men and women using prospective data obtained from the Circulatory Risk in Communities Study (CIRCS).

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PATIENTS AND METHODS

Population

Circulatory Risk in Communities Study is a population-based study of cardiovascular risk factors, cardiovascular disease incidence, and their trends in Japanese communities. Details of study design and study procedures have been published elsewhere [14–16]. In brief, participants in this study were Japanese men and women living in the north-eastern rural community, Ikawa (with a total census population of 6206 in 1995), the south-western rural community, Noichi (with a total census population of 15 828 in 1995), a central rural community, Kyowa (with a total census population of 17 322 in 1995), and a south-western urban suburb, the Minami Takayasu district of Yao (with a total census population of 23 654 in 1995). All analyses were limited to men and women aged 30–84 years because of the small number of younger cases of SCD. Annual cardiovascular risk surveys have been conducted since 1963 in the district of Yao City, Ikawa, and Noichi, and since 1981 in Kyowa, by a research team from the Osaka Medical Center for Health Science and Promotion, the University of Tsukuba, and Osaka University.

The study used data from 1975 to 2005 for Yao, Ikawa, and Noichi, and from 1981 to 2005 for Kyowa; this yielded data for 26 870 participants (10 965 men and 15 905 women). As an ancillary study to CIRCS, the main aim of this study was to examine the association between cardiovascular risk factors and SCD incidence using data from a prospective, observational, nested, case–control study. Informed consent was obtained from the community representatives to conduct an epidemiological study based on guidelines of the Council for International Organizations of Medical Science [17]. This study was approved by the Ethics Committee of the Osaka Medical Center for Health Science and Promotion.

Surveillance for sudden cardiac death

The participants were followed up to determine incident SCD occurring by the end of 2005. The CIRCS morbidity surveillance system collected disease data on men and women aged 30–84 years in the four communities and used six sources to identify and validate 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 [14–16]. To confirm the diagnosis, we also obtained histories from next of kin and reviewed medical records in local hospitals. For definition of SCD, World Health Organization criteria were employed, and SCD was defined as a sudden unexpected death, either within 1 h of symptom onset (for witnessed events), or within 24 h of having been observed alive and symptom-free. Cases were excluded if death occurred later than 24 h following the onset of symptoms, or if the apparent cause of death was found to be something other than SCD, such as cerebrovascular disease, cancer or accidental death.

Cases of SCD were categorized into two groups according to the presence or absence of coronary heart disease (CHD), denoted as SCD-CHD and SCD-NCHD, respectively. The indication of definite myocardial infarction (MI) was typical severe chest pain (lasting at least 30 min, with definite nonischemic causes excluded), accompanied by new, abnormal and persistent Q or QS waves, or consistent changes in cardiac enzyme levels [15]. Patients who reported typical chest pain, but for whom electrocardiographs and enzyme levels were nondiagnostic or unattainable, were diagnosed as having possible MI. In this study, definite and possible MIs were both included under the category of CHD. In addition, SCD cases were divided into two groups based on stratification by place of death. If the place of death was in a hospital or an emergency room, the case was categorized as in-hospital SCD, and if was outside of a hospital, it was categorized as out-of-hospital SCD.

In total, 239 cases of SCD were identified during the follow-up period. Seventy-two cases were found to have CHD and 167 cases were found to be without documented CHD, 131 cases were witnessed and 108 were unwitnessed death, and 150 cases were in-hospital and 89 cases were out-of-hospital.

Baseline measurements

Systolic and fifth-phase diastolic BPs were measured by trained technicians using a standard mercury sphygmomanometer on the right arm of seated participants after at least a 5-min rest. Hypertension was defined as a systolic BP at least 140 mmHg, a diastolic BP at least 90 mmHg, or use of antihypertensive medication. Serum total cholesterol was measured with the Liebermann-Burchard direct method between 1975 and 1986, and with an enzymatic method from 1986 onwards. All measurements were performed at the laboratory of the Osaka Medical Center for Health Science and Promotion, an international member of the US National Cholesterol Reference Method Laboratory Network [18]. Hyperlipidemia was defined as a total cholesterol level of 220 mg/dl (5.69 mmol/l) or more, or use of a lipid-lowering medication. Body mass index (BMI) was calculated as weight (kg)/height (m)^2. Diabetes mellitus was defined as a fasting glucose level of at least 126 mg/dl (7.0 mmol/l), a nonfasting glucose level of at least 200 mg/dl (11.1 mmol/l), and/or use of medication for diabetes.

An interviewer obtained histories for smoking and weekly alcohol intake in units of '*go*' (a Japanese traditional unit of volume corresponding to 23 g of ethanol), which was afterwards converted to grams of ethanol per day. One *go* is 180 ml of sake, and corresponds to one bottle (633 ml) of beer, two single shots (75 ml) of whiskey, or two glasses (180 ml) of wine. Those consuming more than 0.3 *go* per week were regarded as current drinkers. Participants who smoked at least one cigarette per day were classified as being current smokers.

A 12-lead ECG tracing was obtained in the supine position, and coded with the Minnesota Code, second version, by trained physician-epidemiologists [19]. The presence of at least one of the following criteria was used to classify minor ST-segment and T-wave (ST-T) abnormalities: Minnesota Code 4–3 to 4–4; ST-J depression not greater than 0.5 mm, but a downward or horizontally sloping ST segment, and a segment or T-wave nadir at least 0.25 mm below P-R baseline in any of leads I, II, augmented vector left (aVL), or V2 to V6 (modified Minnesota Code 4–5); Minnesota Code 5–3 to 5–4; or T-wave amplitude positive and a T to R-wave ratio of less than 1 : 10 when R-wave amplitude in the corresponding leads was at least 10.0 mm (modified Minnesota Code 5–5). Major ST-T abnormalities were classified as Minnesota Code 4–1 to 4–2 or 5–1 to 5–2 [19,20]. Left high amplitude R waves (LHAR) were defined as Minnesota Code 3–1: R amplitude greater than 26 mm in either lead V5 or V6; R amplitude greater than 20 mm in any of leads I, II, III, or aVF; R amplitude greater than 12 mm in lead aVL [19].

Nested case–control design

A nested case–control design was employed to study prospective associations between SCD incidence and cardiovascular risk factors as measured in annual risk factor surveys. For the identified SCD cases, the latest data from the risk factor surveys were used for analysis, with a median follow-up duration of 3.5 years. Controls were selected at random from participants in the annual risk factor surveys, and represented participants who were still alive and residing within the community at the time of the SCD case. Three controls were selected per case, individually matched by age (±3 years), sex, examination year (±1 year), follow-up time (case's event date within 1 year of controls' assigned date), and study area (Ikawa, Kyowa, Yao, and Noichi). Selection yielded 717 controls for the 239 cases.

Statistical analysis

Means or prevalences for baseline variables of interest were compared between SCD cases and controls using Student *t*-tests or chi-squared tests. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using conditional logistic regression models. We selected risk factors based on previous prospective findings for SCD [3–8], which included BP (mmHg), BMI (kg/m^2), diabetes status (yes or no), serum cholesterol (mg/dl), excess ethanol intake (ethanol intake ≥46 g/day), smoking status (current or never/former), heart rate (beat/min), atrial fibrillation (yes or no), supraventricular premature contraction (SVPC)/ventricular premature contraction (VPC) on 12-lead ECG (yes or no), and other ECG abnormalities, such as major ST-T abnormality (yes or no), minor ST-T abnormality (yes or no), LHAR (yes or no), and wide QRS (>0.12 s).

Population-attributable fraction (PAF), the percentage of SCD risk in the population associated with having risk factors, was calculated using the formula p(OR-1)/[1-p(OR-1)], where p is the prevalence of risk factors among cases. Greenland's formula was used to calculate 95% CIs [21].

We used SAS version 9.1 (SAS Institute, Cary, North Carolina, USA) for the analyses. All probability values for statistical tests were two-tailed, and values of P less than 0.05 were regarded as statistically significant.

RESULTS

Table 1 shows means or prevalence of risk characteristics at previous examination for SCD cases and controls. Mean values of systolic BP and heart rate, and the prevalences of hypertension, diabetes mellitus, current smoking, atrial fibrillation, major and minor ST-T abnormalities, and LHAR on ECG were significantly higher among cases than among controls. There were no significant differences in BMI, total cholesterol levels, or excess ethanol intake between cases and controls.

TABLE 1. Means (SD) or prevalence of baseline characteristics of participants who did or did not develop sudden cardiac death, CIRCS

Baseline characteristics	SCD cases (n = 239)	Controls (n = 717)	P value
Age (years)*	66.1 (10.3)	66.0 (10.1)	
Sex (% women)*	41.8	41.8	
Body mass index (kg/m^2)	22.9 (3.5)	23.2 (3.4)	0.303
Systolic blood pressure (mmHg)	142 (22)	137 (18)	0.003
Diastolic blood pressure (mmHg)	81 (13)	79 (11)	0.141
Hypertension (%)	67	57	0.004
Antihypertensive medication use (%)	41	33	0.038
Diabetes Mellitus (%)	10.9	4.6	<0.001
Serum total cholesterol (mg/dl)	200	196	0.247
Hyperlipidemia (%)	30.5	27.5	0.401
Lipid-lowering medication use (%)	2.5	2.4	0.903
Excess ethanol intake, >=46 g/day (%)	13.2	15.7	0.358
Current smoking (%)	37.7	30.6	0.043
Electrocardiogram findings			
Heart rate (beats/min)	73 (15)	69 (12)	0.004
Atrial fibrillation (%)	5.4	2.1	0.008
SVPC/VPC (%)	10.9	9.3	0.488
Major ST-T abnormalities, (%)	21.3	7.4	<0.0001
Minor ST-T abnormalities, (%)	28.0	20.9	0.023
Prolonged PQ duration, >0.22 s (%)	1.7	1.5	0.881
Wide QRS, >0.12 s (%)	5.0	3.2	0.196
Left high amplitude R wave (%)	32.2	23.2	0.005
Abnormal Q wave (%)	2.9	1.1	0.051

SVPC, supraventricular premature contraction; VPC, ventricular premature contraction. P value: *t*-test or chi-squared test.
*Matching factor. SCD: sudden cardiac death.

Table 2 presents ORs and 95% CIs of SCD for each potential risk characteristic. Compared with patients who did not have individual risk factors, the OR (95% CI) of SCD was 1.69 (1.21–2.36) for hypertension, 2.54 (1.46–4.42) for diabetes, 1.55 (1.08–2.24) for current smoking, 2.68 (1.26–5.72) for atrial fibrillation, 3.48 (2.26–5.72) for major ST-T abnormalities, 1.47 (1.05–2.05) for minor ST-T abnormalities, 1.58 (1.14–2.19) for LHAR, and 2.79 (0.97–8.02) for Q-wave abnormalities. The highest quartile for heart rate (≥77 beats/min) was associated with a 2.13-fold higher OR (95% CI 1.32–3.43) of SCD, when compared with the lowest quartile (<62 beats/min). Hypercholesterolemia, BMI, excess ethanol intake, SVPC/VPC, PQ prolongation, and wide QRS were not associated increased SCD incidence.

Multivariate analyses demonstrated that hypertension, diabetes mellitus, current smoking, increased heart rate, major ST-T abnormalities, and LHAR were independent risk factors for SCD (Table 3), with multivariate ORs (95% CI) of SCD of 1.52 (1.05–2.19) for hypertension, 2.24 (1.23–4.07) for diabetes mellitus, 1.70 (1.13–2.57) for current smoking, 1.85 (1.10–3.12) for increased heart rate, 3.12 (1.89–5.15) for major ST-T abnormalities, and 1.48 (1.02–2.15) for LHAR. There were borderline associations of atrial fibrillation and wide QRS with SCD incidence (P = 0.05 and 0.06, respectively). At 23% (95% CI 2.9–39.0), the PAF for hypertension was higher than those for other risk factors. The PAFs (95% CI) for current smoking, major ST-T abnormalities, LHAR, and diabetes were 15.3% (3.8–25.5), 14.5% (8.0–20.5), 10.5% (0.4–19.5), and 8.1% (2.2–13.7), respectively. When we analyzed the association between risk factors and SCD after excluding cases of out-of-hospital death, similar associations were observed (data not shown). When we further analyzed the associations between risk factors and SCD after excluding cases of unwitnessed death, the associations were virtually unchanged except for diabetes mellitus and LHAR. The multivariate ORs (95% CI) of SCD were 2.04 (1.21–3.45) for hypertension, 1.13 (0.48–2.67) for diabetes mellitus, 1.71 (0.97–3.00) for current smoking, 1.46 (0.72–2.97) for increased heart rate, 4.11 (2.06–8.21) for major ST-T abnormalities, and 1.06 (0.64–1.76) for LHAR.

Sudden cardiac death risk was positively associated with a number of risk factors, including hypertension, current smoking, diabetes mellitus, and ECG abnormalities

TABLE 2. Odds ratios (ORs) and 95% confidence intervals (CIs) of sudden cardiac death for cardiovascular risk factors, CIRCS

Variable		Cases	Controls	OR	95% CI
Hypertension	No	80	313	1.00	Reference
	Yes	159	404	1.69	1.21–2.36
Diabetes mellitus	No	213	684	1.00	Reference
	Yes	26	33	2.54	1.46–4.42
Hyperlipidemia	No	148	466	1.00	Reference
	Yes	65	177	1.17	0.82–1.66
Excess ethanol intake, >=46 g/day	No	191	573	1.00	Reference
	Yes	29	107	0.81	0.50–1.31
Current smoking	No	147	492	1.00	Reference
	Yes	89	217	1.55	1.08–2.24
Body mass index (kg/m^2)	<18.5	23	54	1.36	0.80–2.32
	18.5–24.9	135	428	1.00	Reference
	25.0–29.9	62	198	0.99	0.70–1.40
	>=30.0	12	25	1.52	0.75–3.06
Electrocardiogram findings					
Heart rate (beats/min)	<61	35	147	1.00	Reference
	61–66	43	143	1.29	0.78–2.15
	67–75	42	128	1.44	0.86–2.40
	>=76	77	160	2.13	1.32–3.43
Atrial fibrillation	No	226	702	1.00	Reference
	Yes	13	15	2.68	1.26–5.72
SVPC/VPC	No	213	650	1.00	Reference
	Yes	26	67	1.20	0.73–1.97
Major ST-T abnormalities	No	188	664	1.00	Reference
	Yes	51	53	3.48	2.26–5.36
Minor ST-T abnormalities	No	172	567	1.00	Reference
	Yes	67	150	1.47	1.05–2.05
Prolonged PQ duration, >0.22 s	No	235	706	1.00	Reference
	Yes	4	11	1.10	0.34–3.54
Wide QRS, >0.12 s	No	227	694	1.00	Reference
	Yes	12	23	1.57	0.78–3.15
Left high amplitude R wave	No	162	551	1.00	Reference
	Yes	77	166	1.58	1.14–2.19
Abnormal Q wave	No	232	709	1.00	Reference
	Yes	7	8	2.79	0.97–8.02

SVPC, supraventricular premature contraction; VPC, ventricular premature contraction.

TABLE 3. Multivariate-adjusted* odds ratios (OR), PAFs, and 95% confidence intervals (CI) of sudden cardiac death for cardiovascular factors, CIRCS

Variable	OR	95% CI	PAF	95% CI
Hypertension	1.52	1.05–2.19	23.0	2.9–39.0
Diabetes mellitus	2.24	1.23–4.07	8.1	2.2–13.7
Current smoking	1.70	1.13–2.57	15.3	3.8–25.5
Electrocardiogram findings				
Heart rate, >=76 versus <61 beats/min	1.85	1.10–3.12	14.8	3.4–24.9
Atrial fibrillation	2.30	0.98–5.36	3.1	−0.3–6.3
SVPC/VPC	1.06	0.62–1.80	0.6	−5.2–6.1
Major ST-T abnormalities	3.12	1.89–5.15	14.5	8.0–20.5
Minor ST-T abnormalities	0.99	0.67–1.48	−0.2	−12.1–10.4
Wide QRS, >0.12 s	2.18	0.97–4.89	2.7	−0.5–5.8
Left high amplitude R wave	1.48	1.02–2.15	10.5	0.4–19.5
Abnormal Q wave	1.50	0.44–5.09	1.0	−2.0–3.8

PAF, population-attributable risk fraction; SVPC, supraventricular premature contraction; VPC, ventricular premature contraction.
*ORs were adjusted for body mass index, excess ethanol intake, and aforementioned variables.

(major ST-T abnormality, increased heart rate, atrial fibrillation, wide QRS, or LHAR). Multivariate ORs of SCD (95% CI) for one, two, and three or more risk factors versus no risk factors were 1.37 (0.77–2.42), 2.62 (1.49–4.61), and 5.76 (3.20–10.39), respectively.

DISCUSSION

The findings of this study demonstrate that, whereas the incidence rate of SCD among the Japanese population is less than a quarter of the incidence among whites and African Americans [12], most traditional risk factors such as hypertension, smoking, and diabetes mellitus were associated with SCD risk among Japanese. This is consistent with previous studies conducted in Western populations [3–10]. In our study, hypertension was found to be the largest contributor to SCD risk as demonstrated by PAF. The age and sex-adjusted incidence of SCD in CIRCS populations decreased from 1981–1985 to 1991–1995, and reached a plateau after 1996, which corresponded primarily to the trend for the prevalence of hypertension [22]. Since the prevalence of hypertension in Japan remains higher than in Western counties [23], there is a need to continue intensive prevention programs for hypertension to prevent future SCDs as well as other cardiovascular events.

Obesity and hypercholesterolemia were not seen to be predictors of SCD in the present study, although these factors have been previously reported as risk factors for SCD in studies in the US and Europe [1,6,8,10]. Although obesity and hypercholesterolemia are also important risk factors for CHD in the Japanese population, CHD-related mortality in Japan is only a quarter of that seen in the US, because the prevalences of obesity and hypercholesterolemia in Japan are lower than those in the US [24]. Furthermore, only a quarter of SCD cases in the present study had CHD, compared to almost half in the US [25]. The low proportion of SCD due to CHD in the Japanese population may therefore partially explain the lack of association between obesity and hypercholesterolemia and SCD risk, and may also explain the lower SCD incidence in Japan compared to the US.

In addition to traditional risk factors, ECG findings of increased heart rate, major ST-T abnormalities, atrial fibrillation, and LHAR were predictive of SCD, whereas other ECG abnormalities such as SVPC and/or VPC and prolonged PQ duration were not. The existing literature consistently shows that major ST-T abnormalities and left-ventricular hypertrophy detected by ECG are associated with increased risk of SCD [1,4–6,10]. Since ST-T abnormalities and left-ventricular hypertrophy reflect the end-organ effects of longstanding hypertension, the associated increase in SCD risk might possibly be attributed to the development of ventricular tachycardia, low left-ventricular ejection fraction, and prolonged QT interval in these conditions [26–28].

Increased resting heart rate has been thought to be an important predictive marker for SCD in men, but not in women [6–8]. In the present study, our analysis of heart rate and SCD risk revealed that the ORs were higher for men than for women, with adjusted ORs of 2.29 (95% CI 1.17–4.48) for men and 1.26 (95% CI 0.50–3.16) for women. These results are concordant with findings of previous studies [6–8]. An increased heart rate can reflect shifts in autonomic balance, for example from increased sympathetic output and reduced parasympathetic tone, which was affected by physical conditioning and chronic psychological stress [29]. Increase in heart rate precedes episodes of ventricular tachycardia and ventricular fibrillation [30]. Therefore, increased heart rate may lead to an increased risk of SCD, in part through the development of ventricular tachycardia or ventricular fibrillation. Further, Jouven *et al.* [31] reported that a resting heart rate and heart rate profile during exercise (difference between maximum heart rate and resting heart rate) and recovery (difference between maximum heart rate and rate at one minute after cessation of exercise) were strong predictors of SCD from MI, but not nonsudden death form MI. This suggests that altered heart rate responses during exercise and recovery may reflect the susceptibility to cardiac arrhythmia but not the development of atherosclerosis [31].

In the present study, atrial fibrillation was associated with increased risk of SCD, but there have been inconsistent results regarding the association between atrial fibrillation and SCD incidence in the literature. A recent prospective study reported that atrial fibrillation was associated with future coronary events [32]; thus, atrial fibrillation may be associated with SCD caused by coronary embolism from atrial thrombi.

A strength of the present study was the use of population-based data in our analysis of SCD risk in both men and women, with relatively large numbers of SCD cases in a prospective study. Potential limitations of this study warrant consideration. Although neuroimaging reports and clinical features were used to exclude deaths due to cerebrovascular disease, some cases may have been misclassified, especially in the case of out-of-hospital death or unwitnessed death. In the present study, 37% of SCD cases occurred as out-of-hospital deaths and 45% occurred as unwitnessed deaths. Although a post mortem examination is necessary to confirm the cause of death in unwitnessed death, we could not obtain the post mortem data in most SCD cases, leading to the misclassification. However, when we further analyzed the data after excluding cases of out-of-hospital death or unwitnessed death, the findings on risk factors were virtually unchanged. Another limitation of the study was the potential for misclassification of SCD subtypes despite the use of ECG findings, serum cardiac enzyme levels, and clinical features. This may have led to an over or underestimation of the impact of various risk factors by SCD subtype. Additionally, we did not examine the association of SCD with other residual ECG findings like QT prolongation or Brugada-type ECG findings, which are known risk factors for SCD but rare [33,34].

In conclusion, although we cannot verify that all risk factor associations observed were causal, most conventional risk factors, especially hypertension, major ST-T abnormalities, smoking and diabetes, were associated with increased SCD incidence in Japanese, whereas BMI and hypercholesterolemia were not. Further research on other risk factors and genetic determinants may lead to a better understanding of SCD and its prevention in Japan, especially SCD not associated with CHD.

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Conflicts of interest

There are no conflicts of interest.

APPENDIX

CIRCS Collaborators

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