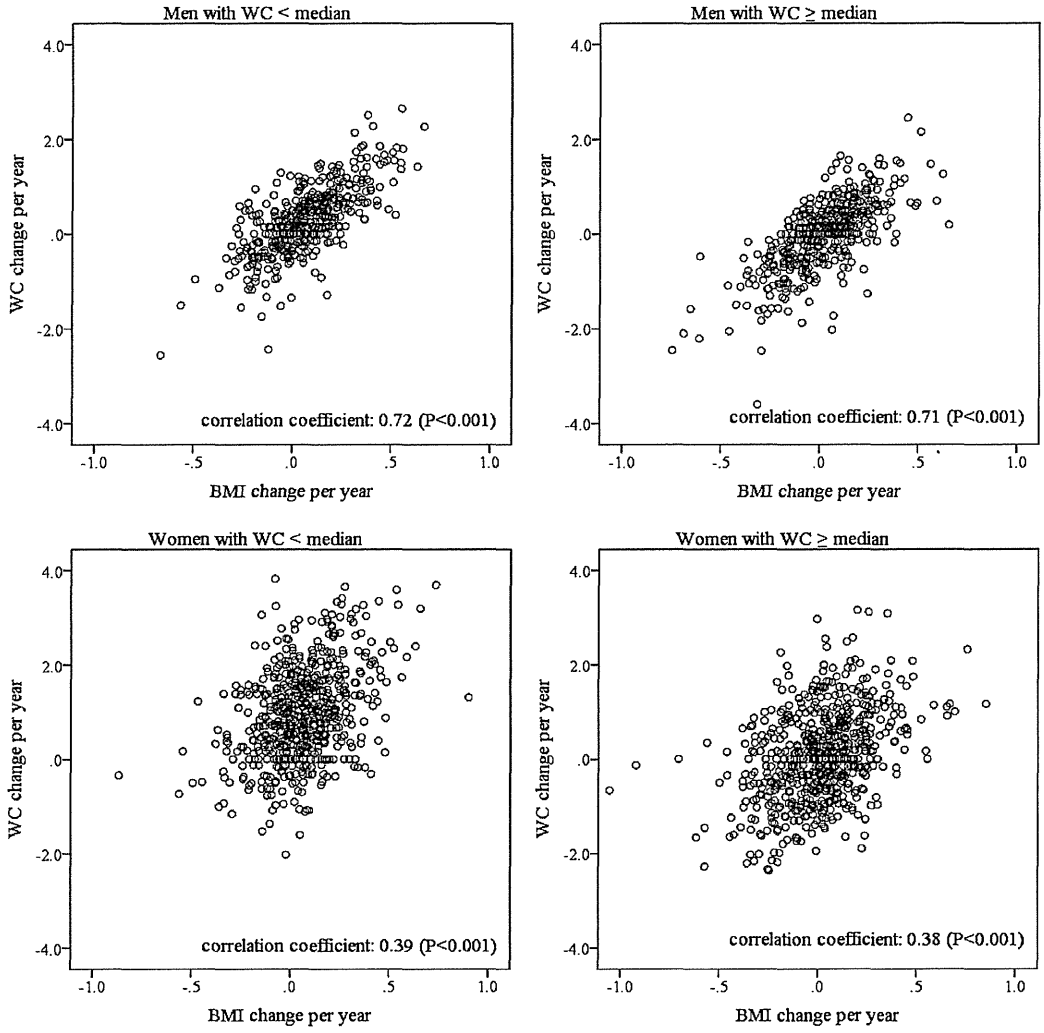

Figure 2. Scatter plots of waist circumference (WC) change and body mass index (BMI) change between examination 1 and examination 2 by sex and WC.

To our knowledge, only two studies have reported the association between WC change and type 2 diabetes. Hadaegh et al reported that WC change during 6 years of follow-up was positively associated with the elevated risk of type 2 diabetes among 4029 community residents in Iran.[14] Odds ratios were 1.6 in men and 1.5 in women per 1 standard deviation increase in WC change (5.2 cm in men and 7.7 cm in women). Koh-Banerjee et al assessed the influence of WC change in 9 years on type 2 diabetes incidences for 4 years after WC change among 22 171 male health professionals in the United States.[7] They demonstrated that men with WC gain ≥14.6 cm (1.6 cm/year) had a higher risk of developing type 2 diabetes than men who had a stable WC (relative risk 2.4; 95% CI, 1.5–3.7). Participants in these studies had higher average WC than those in the present study.[14,22] Because we also observed results similar to previous studies among participants with relatively high WC, the present results would be likely to support the previous ones, although it is difficult to compare the results between the studies because of different observation periods for WC change and ethnicities of participants.

The additional model using the six combined categories of initial WC and subsequent WC change also showed similar results. Compared to individuals with relatively low initial WC levels and subsequent mild WC gain (tertile 2), regardless of sex, WC gain was significantly associated with increased risk of type 2 diabetes only among individuals with relatively high WC levels, while no significant association was observed in other categories. This indirectly suggests that it might be important to combine WC at a certain point and subsequent WC change for estimation of risk of diabetes.

However, an observational study has reported that WC loss was not associated with a decreased risk of type 2 diabetes incidence.[7] In the present study, the effect of WC loss among participants with relatively high WC was not observed, although it is not clear whether WC loss was caused by participants' effort, such as lifestyle changes. Among individuals in the lowest tertile whose WC decreased from Exam 1 to Exam 2 (a 5.4-cm decrease in men with relatively high WC and a 5.9-cm decrease women with relatively high WC), WC increased after Exam 2 (a 2.7-cm increase in men

with a relatively high WC and a 2.5-cm increase in women with relatively high WC) (Table 2). In other words, WC showed a U-shaped change from Exam 1 to the endpoint examination, and it can be inferred that the risk of type 2 diabetes might not decrease merely because of WC gain after Exam 2.

Koh-Banerjee et al reported that men with WC gain had a higher risk for type 2 diabetes incidence after adjustment for weight change.[7] Similarly, in the present study, WC change was associated with the incidence of type 2 diabetes almost independently of BMI change among both men and women with relatively high WC levels, although this relationship was more evident in women. On the other hand, BMI change was not associated at all. The present study suggests that WC change should be considered prior to weight change to estimate the risk of type 2 diabetes, especially in Japanese women. In addition, the results of the correlation analyses showed that WC change was much more strongly correlated with BMI change in men than women. This difference in correlation could be involved in the sex difference. Because body fat distribution differs considerably between age groups, sexes, and ethnicities,[23,24] it would be necessary to take these factors into consideration when combining WC and BMI to estimate the risk of type 2 diabetes.

The present study has several limitations. First, 62.0% of participants did not undergo Exam 2 under fasting conditions (≥8 hours), although almost all underwent Exam 1 under fasting conditions. However, there was no significant difference in fasting status among the tertiles of WC change regardless of sex and WC strata, and the time after a meal was ≥5 hours in 87% of participants. Such random misclassifications by measurement error might lead to underestimation of the real relationship (toward the null) between WC changes and the risk of diabetes. Second, the correlation coefficients between change in WC and BMI were high in men (0.71–0.72), so the presence of co-linearity might influence the adjusted HRs in model 3 of Cox proportional hazards regression. However, since the HRs did not change much after adjustment for BMI changes, we think the influence of co-linearity was likely to be limited. Third, single assessment of WC change may lead to underestimation of the relationship between WC change and type 2 diabetes incidences due to regression dilution bias.[25]

In conclusion, WC gain was significantly related to an increased risk of type 2 diabetes in both sexes with a higher WC. In terms of diabetes prevention, it is important to avoid WC gain, especially among men and women with relatively high WC. In addition, assessing WC change may be important than assessing BMI change in estimating the risk of type 2 diabetes, especially in the Japanese women.

ONLINE ONLY MATERIAL

Abstract in Japanese.

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Conflicts of interest: None declared.

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Original Article

Risk of Hypercholesterolemia for Cardiovascular Disease and the Population Attributable Fraction in a 24-year Japanese Cohort Study

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Aims: The population-attributable fraction (PAF) is an indicator of the disease burden. In Western countries, the PAF of hypercholesterolemia in cardiovascular disease (CVD) is the highest among that for traditional risk factors; however, data for Asian populations are limited.
Methods: A 24-year cohort study was conducted among 9,209 randomly selected participants who were not taking statins. We estimated the hazard ratio (HR) after adjusting for covariates and PAF associated with the serum total cholesterol (TC) levels in relation to CVD mortality.
Results: The TC level was found to be positively associated with an increased risk of CVD, coronary heart disease (CHD) and cardiac death (CHD plus heart failure), with an HR of 1.08 (95% confidence interval [CI]: 1.00-1.16), 1.33 (95% CI: 1.14-1.55) and 1.21 (95% CI: 1.08-1.35) for a 1-SD increment in the serum TC level, respectively. Similar positive associations between the TC level and both CHD and cardiac death were observed after classifying the patients by age and sex. Furthermore, the highest serum TC level (≥6.72 mmol/L) was positively associated with CVD death, with an HR of 1.76 (95% CI: 1.25-2.47), as well as both CHD death and cardiac death. In contrast, no significant relationships were observed between the serum TC level and stroke. Meanwhile, the PAF for CVD, CHD, and cardiac deaths due to hypercholesterolemia (serum TC level ≥5.69 mmol/L, defined by the Japan Atherosclerosis Society) was 1.7%, 10.6% and 5.6%, respectively.
Conclusions: The estimated PAF of CVD death due to hypercholesterolemia is moderately high, but lower than that for other risk factors, such as hypertension.

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Key words: Total cholesterol, Cardiovascular disease, Population-attributable fraction, Cohort study, NIPPON DATA80

Introduction

Cardiovascular diseases (CVDs), such as coronary heart disease (CHD), are common causes of death in developed countries, including Japan[1], and a high serum total cholesterol (TC) level is an established risk factor for CVD. The population attributable fraction (PAF) is the proportional reduction in mortality that would occur if the exposure to a risk factor were to be reduced to an alternative ideal level, a parameter that can be used in the management of CVD patients. In studies from Western countries, the PAF of CVD mortality due to hypercholesterolemia is highest among that for traditional risk factors[2-4]; however, evidence of this relationship in Asian countries, including Japan, in which the CHD incidence is low, is scarce[5]. Specifically, the effects of a high serum TC level on the health of the general Japanese population in the context of disease burden is unknown.

Several Japanese studies have estimated the PAF of CVD death based on established CVD risk factors[6, 7], such as smoking and hypertension. However, to the best of our knowledge, no observational studies with a long-term follow-up period of >20 years estimating the PAF for CVD death due to hypercholesterolemia have been conducted in Japan or other Asian countries. We previously reported the relationship between TC and CVD based on the findings of the National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged, 1980 (NIPPON DATA80), trial, with follow-up examinations conducted at 14 and 19 years after study initiation (until 1994 and 1999, respectively)[8, 9]. However, we did not calculate the PAF of CVD caused by hypercholesterolemia.

Therefore, in the current study, we investigated the relationship between the serum TC level and mortality due to CVD in the NIPPON DATA80 cohort with a longer follow-up period than that used in the former study[8, 9] and estimated the PAF of death due to CVD attributable to a high serum TC level.

Methods

Population

The subjects in this cohort were also participants of the National Survey on Circulation Disorders 1980. A total of 10,546 residents ≥30 years of age from 300 randomly selected areas in Japan participated in the follow-up study, the NIPPON DATA80, for a participation rate of 76.6% (10,546/13,771). The details of the NIPPON DATA80 study have been previously reported[9-15]. The subjects were followed up until 2004.

Of the 10,546 participants, a total of 1,337 were excluded for the following reasons: a history of CHD or stroke (n=280), missing information (n=186) and the absence of a permanent address, which was needed to link the patient to their vital statistical records (n=871). We analyzed the remaining 9,209 participants (4,029 men and 5,180 women). The data collected from these participants were not influenced by the effects of statins, as these drugs were not available at the time of the survey. There were no significant differences in the mean serum TC level between the participants included in this study and those who did not provide their address.

Endpoint Determination

As previously reported[9-15], we confirmed which participants died in each area using computer matching of the area, sex, date of birth and death of the subject with data obtained from the National Vital Statistics database. Information regarding the cause of death, which was coded according to the Ninth International Classification of Death (ICD-9) until the end of 1994 and the Tenth International Classification of Disease (ICD-10) from 1995 onward, was also obtained from the National Vital Statistics database. ICD-coding was carried out by specialists at the Ministry of Health and Welfare who were independent of the NIPPON DATA research group. The details of classification are described elsewhere[9-11]. We defined all deaths due to CVD (ICD-9: 393-459/ICD-10: I00 to I99), CHD (ICD-9: 410-414/ICD-10: I20 to I25), stroke (ICD-9: 430-438/ICD-10: I60 to I69) or cerebral infarction (ICD-9:433, 434 and 437.8a-8b/ICD-10:I63 and I69.3) as the primary endpoint. Furthermore, in the present study, we defined "cardiac death" as death due to CHD or heart failure (HF, ICD-9: 428/ICD-10: I50) and treated HF as a cause of death among CHD survivors because HF is the final outcome of CHD. The use of the National Vital Statistics data was permitted by the Management and Coordination Agency, Japan. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (Nos. 12-18, 2000).

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Table 1. Participant characteristics recorded during the baseline survey in 1980, NIPPON DATA80

	Baseline serum total cholesterol level (mmol/L)							
	<4.14	4.14-4.65	4.66-5.17	5.18-5.68	5.69-6.20	6.21-6.71	6.72-	*p*-values*
Women								
No. of participants	951	1183	1142	925	527	275	177	
Age (years, mean ± SD)	44.7 ± 12.9	47.3 ± 13.0	50.6 ± 12.8	53.1 ± 12.9	54.8 ± 12.0	56.3 ± 11.5	57.0 ± 11.7	<0.001
Albumin (g/dL, mean ± SD)	4.3 ± 0.2	4.3 ± 0.2	4.4 ± 0.3	4.4 ± 0.2	4.4 ± 0.2	4.4 ± 0.3	4.4 ± 0.2	<0.001
BMI (kg/m^2, mean ± SD)	22.1 ± 3.1	22.4 ± 3.2	22.8 ± 3.4	23.3 ± 3.5	23.6 ± 3.4	23.8 ± 3.3	24.3 ± 4.0	<0.001
Hypertension (%)	29.0%	35.2%	41.2%	50.7%	59.2%	60.7%	61.6%	<0.001
Diabetes (%)	1.1%	2.0%	1.8%	4.1%	2.8%	6.5%	5.1%	<0.001
Current smoker (%)	7.9%	7.9%	10.1%	9.2%	11.0%	5.5%	9.0%	0.07
Heavy smoker (%) (>20 cigaretts/day)	0.7%	0.3%	0.8%	0.6%	1.5%	0.7%	0.6%	0.29
Daily drinker (%)	3.2%	2.6%	3.0%	2.7%	3.2%	1.8%	2.8%	0.92
Men								
No.of participants	848	999	936	648	354	167	77	
Age (years, mean ± SD)	51.0 ± 14.0	50.0 ± 13.4	49.3 ± 13.1	48.8 ± 12.6	48.9 ± 11.8	50.2 ± 12.2	49.5 ± 10.9	0.04
Albumin (g/dL, mean ± SD)	4.3 ± 0.3	4.4 ± 0.3	4.4 ± 0.3	4.5 ± 0.3	4.5 ± 0.3	4.6 ± 0.3	4.6 ± 0.3	<0.001
BMI (kg/m^2, mean ± SD)	21.6 ± 2.7	22.0 ± 2.8	22.6 ± 2.8	23.2 ± 2.9	23.5 ± 2.7	23.9 ± 2.8	24.2 ± 2.5	<0.001
Hypertension (%)	47.2%	47.5%	52.6%	53.1%	58.5%	58.7%	87.0%	<0.001
Diabetes (%)	3.7%	3.8%	5.4%	6.2%	7.6%	7.8%	10.4%	<0.01
Current smoker (%)	66.9%	66.4%	63.9%	56.3%	59.3%	57.5%	54.5%	<0.001
Heavy smoker (%) (>20 cigaretts/day)	21.1%	24.6%	25.0%	23.3%	30.5%	29.3%	28.6%	0.02
Daily drinker (%)	46.5%	49.4%	48.9%	49.4%	48.3%	36.5%	50.6%	0.02

SD: standard deviation
*Analysis of variance for continuous variables, chi-square test for categorical variables

Baseline Examinations

The baseline surveys were conducted at public health centers using criteria from a standardized manual. Non-fasting blood samples were drawn and centrifuged within 60 minutes of collection and stored at −70℃ until the analyses. As previously reported, the serum TC and albumin levels were analyzed at a single central laboratory (present name: Osaka Medical Center for Health Science and Promotion) using an auto-analyzer (SMA12/60; Technicon, Tarrytown, USA). Since April 1975, the precision and accuracy of the cholesterol measurements obtained in this laboratory have been certified by the CDC-NHLBI Lipid Standardization Program of the Center for Diseases Control and Prevention[16]. Trained research nurses measured the blood pressure of the seated subject using a standard mercury sphygmomanometer on the right arm after five minutes of rest. Hypertension was defined as a systolic blood pressure of ≥140 mmHg, diastolic blood pressure of ≥90 mmHg, use of antihypertensive drugs, history of hypertension or any combination of these findings. The serum glucose level was measured using the cupric-neocuproine method. Since the serum glucose level is more commonly measured using the hexokinase method, this parameter was adjusted using the following formula: [0.047× (glucose concentration in mg/dL) − 0.541][17]. Diabetes was defined as a non-fasting serum glucose level of ≥11.1 mmol/L, history of diabetes or both. Height in stocking feet and weight in light clothing were measured. Questionnaires responses regarding smoking and drinking habits and medical history were analyzed by public health nurses.

Statistical Analysis

The serum TC levels were categorized into the following seven categories: <4.14, 4.14-4.65, 4.66-5.16, 5.17-5.68, 5.69-6.20, 6.21-6.71 and ≥6.72 mmol/L. The participants with a serum TC level of 4.14-4.65 mmol/L formed the reference group. These categories were determined based on the results of our previous study, which provided key evidence for the guidelines for the diagnosis and prevention of atherosclerosis and CVD in the Japanese population issued by the Japan Atherosclerosis Society (JAS)[8]. Cox proportional hazard models were used to estimate the relative risk as the hazard ratio (HR) for death due to CVD according to one standard deviation (SD), i.e., a

Table 2. Number of deaths and multivariable-adjusted HRs for CVD, CHD, cardiac death, stroke and cerebral infarction during the 24-year follow-up period

	1SD increment of serum TC (per 0.87 mmol/L increment)	Category of baseline serum TC level (mmol/L)						
		<4.14	4.14-4.65	4.66-5.17	5.18-5.68	5.69-6.20	6.21-6.71	6.72-
No of Persons	9209	1799	2182	2078	1573	881	442	254
Person-Years	193021.5	37099.5	46260.5	43685.5	33025.5	18612.5	9199	5139
CVD								
No deaths	884	152	189	181	169	101	48	44
HR	1.08	1.04	1.00	1.03	1.15	1.06	1.00	1.76
95%CI	1.00-1.16	0.84-1.30	-	0.84-1.26	0.93-1.43	0.83-1.36	0.73-1.39	1.25-2.47
CHD								
No deaths	172	23	34	28	36	24	11	16
HR	1.33	0.87	1.00	0.89	1.42	1.39	1.25	3.52
95%CI	1.14-1.55	0.51-1.48	-	0.54-1.47	0.87-2.31	0.81-2.39	0.62-2.51	1.89-6.57
Cardiac Death								
No deaths	348	52	69	72	68	42	22	23
HR	1.21	0.99	1.00	1.16	1.35	1.25	1.33	2.68
95%CI	1.08-1.35	0.68-1.42	-	0.83-1.62	0.95-1.91	0.84-1.86	0.81-2.17	1.64-4.38
Stroke								
No deaths	411	72	94	81	82	48	18	16
HR	1.01	0.99	1.00	0.90	1.08	1.00	0.74	1.25
95%CI	0.90-1.12	0.72-1.34	-	0.67-1.22	0.79-1.47	0.70-1.43	0.44-1.24	0.73-2.15
Cerebral infarction								
No deaths	241	40	59	45	48	35	8	6
HR	1.02	0.83	1.00	0.84	1.03	1.20	0.55	0.81
95%CI	0.89-1.18	0.55-1.25	-	0.57-1.25	0.69-1.54	0.77-1.85	0.26-1.16	0.35-1.92

SD: standard deviation, HR: hazard ratio, 95% CI: 95% confidence interval, CVD: cardiovascular disease, CHD: coronary heart disease, HF: heart failure

The HRs were adjusted according to age, sex, the serum albumin level, body mass index, hypertension, diabetes, smoking status and drinking status.

0.87 mmol/L increment in the baseline serum TC level. We evaluated the HRs for total CVD, CHD, cardiac death, stroke and cerebral infarction. In the Cox regression model, age, serum albumin, body mass index (BMI), hypertension, diabetes, smoking status (never-smoker as the reference, ex-smoker, current smoker ≤20 and smoker ≥20 cigarettes/day) and drinking status (never-drinker as the reference, ex-drinker, occasional drinker and daily drinker) were adjusted. We also estimated the HRs according to a Cox model assessing the serum TC level with reference to the seven categories described above. Violation of the proportional hazard assumption was determined using Schoenfeld residuals. Tests for interactions between sex, age (<65 or ≥65 years), hypertension, current smoking and BMI (<25 or ≥25 kg/m^2) were conducted with an interaction term generated by multiplying the continuous serum TC level by the cardiovascular risk factors described above. Tests for interactions were performed for death due to CVD, CHD and cardiac death. In addition, multivariable HRs were calculated following the classification of the subjects into the following groups: age (<65 or ≥65 years), sex, hypertension, current smoking and BMI (<25 or ≥25 kg/m^2).

The PAFs of CVD, CHD and cardiac death were calculated using the formula below[18]:

[Proportion of cases exposed to risk factor × (Adjusted HR-1)/Adjusted HR].

The PAFs for the TC categories ≥5.69 mmol/L (according to the definition of "hypercholesterolemia" provided by the JAS)[19] and ≥6.21 mmol/L (according to the definition provided by the adult treatment panel Ⅲ by the National Cholesterol Education Program, United States: ATP Ⅲ) were estimated as the excess death fractions due to a high TC level. We recalculated the adjusted HR for each hypercholesterolemia case in order to estimate the PAFs.

All statistical analyses were performed using the

Table 3. The multivariable-adjusted HRs for CVD, CHD and cardiac death, classified according to age and sex, over the 24-year follow-up period

A. Age

Age <65 years old	No of Persons	Person-years	CVD			CHD			Cardiac Death		
			No deaths	HR	95%CI	No deaths	HR	95%CI	No deaths	HR	95%CI
1SD increment of serum total cholesterol	7713	172219	363	1.09	0.98-1.22	83	1.29	1.04-1.61	132	1.22	1.03-1.46
Category of baseline serum total cholesterol level (mmol/L)											
<4.14	1527	33848	60	1.04	0.75-1.46	12	1.05	0.49-2.23	19	1.04	0.57-1.88
4.14-4.65	1856	41724	79	1.00		16	1.00		26	1.00	
4.66-5.17	1751	39145	65	0.79	0.57-1.10	10	0.60	0.27-1.33	22	0.82	0.46-1.45
5.18-5.68	1302	29144	73	1.20	0.86-1.66	18	1.36	0.68-2.73	26	1.28	0.73-2.25
5.69-6.20	724	16092	48	1.21	0.83-1.75	14	1.54	0.73-3.23	22	1.60	0.89-2.88
6.21-6.71	353	7897	19	0.88	0.52-1.47	5	0.99	0.35-2.79	8	1.06	0.47-2.42
6.72-	200	4369	19	1.63	0.97-2.74	8	3.00	1.23-7.35	9	2.22	1.01-4.89
Age >=65 years old	No of Persons	Person-years	CVD			CHD			Cardiac Death		
			No deaths	HR	95%CI	No deaths	HR	95%CI	No deaths	HR	95%CI
1SD increment of serum total cholesterol	1496	20803	521	1.06	0.96-1.16	89	1.32	1.05-1.65	216	1.17	1.01-1.36
Category of baseline serum total cholesterol level (mmol/L)											
<4.14	272	3252	92	1.13	0.85-1.50	11	0.80	0.37-1.74	33	1.03	0.65-1.65
4.14-4.65	326	4537	110	1.00		18	1.00		43	1.00	
4.66-5.17	327	4541	116	1.25	0.95-1.63	18	1.22	0.63-2.38	50	1.41	0.93-2.14
5.18-5.68	271	3882	96	1.15	0.87-1.54	18	1.46	0.73-2.93	42	1.38	0.88-2.16
5.69-6.20	157	2521	53	0.98	0.70-1.37	10	1.15	0.52-2.55	20	0.98	0.57-1.70
6.21-6.71	89	1302	29	1.16	0.76-1.77	6	1.63	0.63-4.25	14	1.61	0.86-2.99
6.72-	54	770	25	1.92	1.23-3.02	8	3.93	1.62-9.52	14	2.96	1.58-5.57

R version 2.15 software program (R Foundation for Statistical Computing, Vienna, Austria). All confidence intervals (CIs) were estimated at the 95% level, and statistical significance was defined as a p value of <0.05.

Results

The means and prevalence of the baseline characteristics of all subjects in each TC category based on sex are summarized in **Table 1**. The mean serum TC level was 4.88±0.87 mmol/L overall (mean±SD), 4.93±0.88 mmol/L in women and 4.81±0.85 mmol/L in men. The mean age of the subjects in this study was 50.0±13.2 years overall, 50.1±13.3 years in women and 49.7±13.1 years in men. Age, the serum albumin level, BMI and the prevalence of hypertension and diabetes were statistically different in each TC category for both sexes, whereas the proportion of current smokers and drinkers was significantly different among the TC categories only in men.

The total person-years were 193,022 years and the mean follow-up period was 21.0±5.8 years (mean±SD). During the follow-up period, there were 2,566 total deaths (1,365 men and 1,201 women), with 884 deaths due to CVD (34%), including 172 deaths due to CHD (7%), 176 deaths due to heart failure (7%) and 411 deaths due to stroke (16%). The deaths due to stroke also included 241 cerebral infarction-related deaths (9%).

The number of deaths, person-years and multivariable adjusted HRs for the CVD-related deaths according to a 1-SD increment in the serum TC level and the seven TC level categories in all subjects are summarized in **Table 2**. Consequently, a 1-SD increment in the serum TC level was found to be positively associated with an increased risk of CVD death (HR: 1.08, 95% CI: 1.00-1.16). The positive relationships between a 1-SD increment in the serum TC level and an increased risk of CHD death and cardiac death

(Cont Table 3)

B. Sex

Women	No of Persons	Person-years	CVD			CHD			Cardiac Death		
			No deaths	HR	95%CI	No deaths	HR	95%CI	No deaths	HR	95%CI
1SD increment of serum total cholesterol	5180	111018	449	1.06	0.96-1.17	86	1.23	0.99-1.53	187	1.18	1.02-1.37
Category of baseline serum total cholesterol level (mmol/L)											
<4.14	951	20689	56	1.24	0.88-1.75	10	1.05	0.47-2.35	22	1.27	0.73-2.20
4.14-4.65	1183	25878	81	1.00		16	1.00		32	1.00	
4.66-5.17	1142	24431	88	0.94	0.70-1.28	12	0.67	0.32-1.44	35	1.00	0.62-1.62
5.18-5.68	925	19585	100	1.05	0.78-1.41	21	1.19	0.61-2.31	42	1.20	0.75-1.93
5.69-6.20	527	11164	63	1.03	0.74-1.45	12	1.05	0.49-2.25	26	1.20	0.71-2.03
6.21-6.71	275	5752	28	0.92	0.59-1.43	3	0.51	0.15-1.79	12	1.15	0.58-2.27
6.72-	177	3521	33	1.76	1.16-2.67	12	3.48	1.60-7.58	18	2.79	1.54-5.06
Men	No of Persons	Person-years	CVD			CHD			Cardiac Death		
			No deaths	HR	95%CI	No deaths	HR	95%CI	No deaths	HR	95%CI
1SD increment of serum total cholesterol	4029	82004	435	1.08	0.97-1.20	86	1.37	1.11-1.71	161	1.19	1.01-1.40
Category of baseline serum total cholesterol level (mmol/L)											
<4.14	848	16411	96	1.02	0.77-1.35	13	0.91	0.44-1.87	30	0.97	0.59-1.58
4.14-4.65	999	20383	108	1.00		18	1.00		37	1.00	
4.66-5.17	936	19255	93	1.10	0.83-1.46	16	1.07	0.54-2.11	37	1.28	0.81-2.03
5.18-5.68	648	13441	69	1.32	0.97-1.81	15	1.63	0.80-3.32	26	1.52	0.91-2.56
5.69-6.20	354	7449	38	1.09	0.74-1.59	12	1.73	0.81-3.67	16	1.25	0.69-2.29
6.21-6.71	167	3447	20	1.16	0.72-1.89	8	2.41	1.02-5.69	10	1.71	0.84-3.50
6.72-	77	1619	11	1.65	0.88-3.11	4	2.83	0.92-8.71	5	2.14	0.82-5.57

SD: standard deviation, HR: hazard ratio, 95% CI: 95% confidence interval, CVD: cardiovascular disease, CHD: coronary heart disease, HF: heart failure

The HRs were adjusted based on the following factors:

A. age, sex, the serum albumin level, body mass index, hypertension, diabetes, smoking status and drinking status

B. age, the serum albumin level, body mass index, hypertension, diabetes, smoking status and drinking status

were also noted. The HRs for CHD and cardiac death were 1.33 (95% CI: 1.14-1.55) and 1.21 (95% CI: 1.08-1.35), respectively. Alternatively, deaths due to stroke and cerebral infarction were not associated with a 1-SD increment in the serum TC level. In the analyses of the seven TC level categories, we found a positive association between the highest TC level category and an increased risk of CVD death (HR: 1.76, 95% CI: 1.25-2.47). An increased risk of CHD death and cardiac death was also observed in the highest TC level category. The HR was 3.52 (95% CI: 1.89-6.57) for CHD death and 2.68 (95% CI: 1.64-4.38) for cardiac death. Meanwhile, death due to stroke and/or cerebral infarction was not associated with any TC level category. There were no significant violations of the proportional hazard assumption in these models.

The results obtained after classifying the subjects by age and sex are summarized in **Table 3**. The relationship between a 1-SD increment in the serum TC level and death due to CHD and/or cardiac death was very similar to that observed in the overall analysis. Specifically, we showed that a 1-SD increment in the serum TC level was positively associated with cardiac death in both age categories (<65 or ≥65 years) and sexes (women and men). There were no interactions with age or sex in the associations between the TC level and each endpoint, i.e., CVD, CHD and cardiac death. In **Table 4**, we present the multivariable HRs obtained after stratifying the patients by other risk factors, including hypertension, smoking and BMI. The results of these analyses were similar to those of the over analysis and the analyses performed following classification based on age or sex. There were no interactions with hypertension or BMI in the associations

Table 4. Multivariable-adjusted HRs for CVD, CHD and cardiac death, stratified by hypertension, current smoking and body mass index, during the 24-year follow-up period

A. Hypertension

Hypertension (+)	No of Persons	Person-years	CVD			CHD			Cardiac Death		
			No deaths	HR	95%CI	No deaths	HR	95%CI	No deaths	HR	95%CI
1SD increment of serum total cholesterol	4286	83753	690	1.08	0.99-1.17	127	1.35	1.12-1.62	263	1.19	1.05-1.36
Category of baseline serum total cholesterol level (mmol/L)											
<4.14	676	12281	120	1.16	0.91-1.49	17	0.97	0.51-1.83	41	1.13	0.74-1.72
4.14-4.65	892	17334	136	1.00		23	1.00		49	1.00	
4.66-5.17	962	19079	133	1.02	0.80-1.30	20	0.90	0.49-1.65	50	1.09	0.73-1.62
5.18-5.68	813	16163	135	1.16	0.91-1.49	23	1.23	0.68-2.25	49	1.23	0.81-1.85
5.69-6.20	519	10550	88	1.15	0.87-1.52	22	1.63	0.89-2.99	36	1.30	0.83-2.03
6.21-6.71	265	5311	39	1.00	0.70-1.45	9	1.34	0.60-2.96	18	1.33	0.76-2.33
6.72-	159	3036	39	1.91	1.32-2.76	13	3.69	1.81-7.55	20	2.85	1.66-4.90
Hypertension (−)	No of Persons	Person-years	CVD			CHD			Cardiac Death		
			No deaths	HR	95%CI	No deaths	HR	95%CI	No deaths	HR	95%CI
1SD increment of serum total cholesterol	4923	109269	194	1.06	0.91-1.24	45	1.27	0.94-1.71	85	1.24	0.99-1.55
Category of baseline serum total cholesterol level (mmol/L)											
<4.14	1123	24819	32	0.77	0.49-1.21	6	0.75	0.27-2.11	11	0.70	0.33-1.51
4.14-4.65	1290	28927	53	1.00		11	1.00		20	1.00	
4.66-5.17	1116	24607	48	1.08	0.73-1.60	8	0.96	0.38-2.46	22	1.42	0.76-2.65
5.18-5.68	760	16863	34	1.21	0.77-1.88	13	2.34	0.99-5.50	19	1.99	1.03-3.86
5.69-6.20	362	8063	13	0.75	0.41-1.40	2	0.54	0.12-2.49	6	1.00	0.39-2.56
6.21-6.71	177	3889	9	1.06	0.52-2.19	2	1.04	0.22-4.93	4	1.40	0.47-4.23
6.72-	95	2104	5	1.16	0.46-2.94	3	3.44	0.90-13.16	3	1.98	0.57-6.88

B. Current Smoking

Current Smoking (+)	No of Persons	Person-years	CVD			CHD			Cardiac Death		
			No deaths	HR	95%CI	No deaths	HR	95%CI	No deaths	HR	95%CI
1SD increment of serum total cholesterol	2998	61241	327	1.15	1.02-1.30	69	1.52	1.19-1.93	125	1.28	1.06-1.55
Category of baseline serum total cholesterol level (mmol/L)											
<4.14	642	12648	69	1.00	0.72-1.40	9	0.75	0.32-1.74	24	1.05	0.60-1.84
4.14-4.65	756	15492	77	1.00		14	1.00		26	1.00	
4.66-5.17	713	14788	70	1.08	0.78-1.50	13	1.08	0.50-2.32	29	1.33	0.78-2.27
5.18-5.68	450	9262	51	1.29	0.89-1.86	11	1.47	0.65-3.35	17	1.30	0.69-2.44
5.69-6.20	268	5577	33	1.27	0.83-1.94	12	2.16	0.96-4.88	14	1.50	0.77-2.95
6.21-6.71	111	2286	17	1.48	0.87-2.55	6	2.59	0.95-7.01	10	2.54	1.19-5.43
6.72-	58	1189	10	1.81	0.92-3.56	4	3.29	1.02-10.57	5	2.64	0.98-7.13

between the TC level and each endpoint; however, the interaction term between the serum TC level and current smoking was significant for CHD death (p= 0.02). In addition, the multivariable HR for CHD based on the serum TC level was higher in the current smokers than in the non-smokers (**Table 4**).

We also calculated the population-attributable risk fractions for CVD, CHD and cardiac death, although the HRs for CVD were not significant (**Table 5**). The number of estimated excess deaths due

(Cont Table 4)

B. Current Smoking

Current Smoking (−)	No of Persons	Person-years	CVD			CHD			Cardiac Death		
			No deaths	HR	95%CI	No deaths	HR	95%CI	No deaths	HR	95%CI
1SD increment of serum total cholesterol	6211	131781	557	1.03	0.94-1.12	103	1.20	0.98-1.46	223	1.16	1.01-1.33
Category of baseline serum total cholesterol level (mmol/L)											
<4.14	1157	24452	83	1.19	0.89-1.58	14	1.08	0.54-2.15	28	1.05	0.65-1.70
4.14-4.65	1426	30769	112	1.00		20	1.00		43	1.00	
4.66-5.17	1365	28898	111	0.99	0.76-1.29	15	0.73	0.37-1.44	43	1.05	0.68-1.61
5.18-5.68	1123	23764	118	1.10	0.84-1.43	25	1.29	0.70-2.35	51	1.32	0.87-2.01
5.69-6.20	613	13036	68	1.01	0.74-1.37	12	1.04	0.50-2.15	28	1.16	0.71-1.89
6.21-6.71	331	6913	31	0.85	0.56-1.27	5	0.72	0.27-1.96	12	0.93	0.48-1.79
6.72-	196	3950	34	1.76	1.19-2.62	12	3.49	1.66-7.33	18	2.68	1.52-4.74

C. Body Mass Index

Body Mass Index <25	No of Persons	Person-years	CVD			CHD			Cardiac Death		
			No deaths	HR	95%CI	No deaths	HR	95%CI	No deaths	HR	95%CI
1SD increment of serum total cholesterol	7258	151366	700	1.11	1.03-1.21	135	1.33	1.12-1.59	278	1.22	1.08-1.39
Category of baseline serum total cholesterol level (mmol/L)											
<4.14	1559	31987	127	1.00	0.79-1.27	20	0.80	0.45-1.42	45	1.00	0.67-1.50
4.14-4.65	1825	38630	156	1.00		30	1.00		55	1.00	
4.66-5.17	1640	34307	147	1.07	0.85-1.35	24	0.90	0.53-1.56	64	1.39	0.96-2.00
5.18-5.68	1160	24216	126	1.22	0.96-1.56	22	1.13	0.64-2.00	51	1.50	1.01-2.23
5.69-6.20	615	12899	77	1.19	0.90-1.57	19	1.49	0.82-2.70	32	1.47	0.94-2.30
6.21-6.71	293	6036	35	1.08	0.74-1.58	9	1.46	0.68-3.16	16	1.51	0.85-2.68
6.72-	166	3293	32	1.97	1.33-2.92	11	3.40	1.64-7.06	15	2.84	1.57-5.13
Body Mass Index >=25	No of Persons	Person-years	CVD			CHD			Cardiac Death		
			No deaths	HR	95%CI	No deaths	HR	95%CI	No deaths	HR	95%CI
1SD increment of serum total cholesterol	1951	41656	184	0.95	0.81-1.11	37	1.32	0.95-1.84	70	1.17	0.92-1.51
Category of baseline serum total cholesterol level (mmol/L)											
<4.14	240	5113	25	1.42	0.84-2.39	3	1.30	0.29-5.87	7	0.88	0.35-2.20
4.14-4.65	357	7631	33	1.00		4	1.00		14	1.00	
4.66-5.17	438	9379	34	0.88	0.54-1.43	4	0.86	0.21-3.49	8	0.47	0.20-1.14
5.18-5.68	413	8810	43	0.95	0.59-1.51	14	2.79	0.88-8.83	17	0.86	0.41-1.79
5.69-6.20	266	5714	24	0.78	0.46-1.34	5	1.17	0.30-4.57	10	0.70	0.30-1.63
6.21-6.71	149	3164	13	0.77	0.40-1.50	2	0.85	0.15-4.87	6	0.81	0.30-2.21
6.72-	88	1846	12	1.23	0.62-2.44	5	4.47	1.13-17.77	8	1.89	0.76-4.70

SD: standard deviation, HR: hazard ratio; 95% CI: 95% confidence interval, CVD: cardiovascular disease, CHD: coronary heart disease, HF: heart failure

The HRs were adjusted based on the following factors:

A. age, sex, the serum albumin level, body mass index, diabetes, smoking status and drinking status

B. age, sex, the serum albumin level, body mass index, hypertension, diabetes and drinking status

C. age, sex, the serum albumin level, body mass index, hypertension, diabetes, smoking status and drinking status

Table 5. PAF and excess deaths due to hypercholesterolemia for CVD, CHD and cardiac death

	CVD death	CHD death	Cardiac Death
JAS definition (TC >=5.69 mmol/L)			
HR (95%CI)	1.08 (0.92-1.28)	1.55 (1.10-2.19)	1.29 (1.00-1.66)
PAF	1.7%	10.6%	5.6%
Excess Death	14.6	18.2	19.5
ATPIII definition (TC >=6.21 mmol/L)			
HR (95%CI)	1.19 (0.95-1.48)	1.79 (1.16-2.74)	1.53 (1.11-2.12)
PAF	1.7%	6.9%	4.6%
Excess Death	14.6	11.9	15.6

HR: hazard ratio, 95%CI: 95% confidence interval, JAS: Japan Atherosclerosis Society, TC: total cholesterol, CVD: cardiovascular disease, CHD: coronary heart disease, PAF: population attributable fraction

to hypercholesterolemia was 14.6, 18.2 and 19.5 for CVD, CHD and cardiac death, respectively. The PAF of hypercholesterolemia determined based on the JAS definition (TC level ≥5.69 mmol/L) was 1.7%, 10.6% and 5.6% for CVD, CHD and cardiac death, respectively. Using the ATP Ⅲ definition (a TC level of ≥6.21 mmol/L), the PAFs for CVD, CHD and cardiac death were 1.7%, 6.9% and 4.6%, respectively. The number of excess deaths was also estimated to be 14.6 for CVD, 11.9 for CHD and 15.6 for cardiac death.

Discussion

In this 24-year Japanese cohort study, we found a 1-SD increment in the serum TC level to be positively associated with an increased risk of CVD, CHD and cardiac death. Similar results were also observed after classifying the participants by age (<65 or ≥65 years) and sex. Moreover, in the analyses of the seven TC level categories, the highest TC level (≥6.72 mmol/L) was found to be significantly associated with an increased risk of death due to CVD, especially CHD and cardiac death, and the PAFs of these diseases were moderately high. Furthermore, the relationship between the serum TC level and cardiovascular outcome was similar to that observed after classifying the subjects based on other risk factors, such as the prevalence of hypertension and current smoking. To the best of our knowledge, this is the first study to estimate the PAF for CVD death due to a high serum TC level in a Japanese population with a long follow-up period. Our results were based on data collected in 1980 and were not influenced by statins, as these drugs were not available in the market at the time of the survey.

In previous studies conducted in Western countries, the estimated PAF of CVD death due to hypercholesterolemia was found to be the highest among that for other risk factors[2-4]. However, the estimated PAFs in our study were lower than those for other risk factors, such as smoking (29%) and hypertension (8%), reported in previous studies assessing Japanese populations[6, 7]. Generally, the serum TC levels are lower in Asia countries, including Japan, than in Western countries[20, 21]. This observation may reflect the different impact of PAF of CVD death due to hypercholesterolemia. Furthermore, the reason for this difference appears to be due to differences in the prevalence of CHD and stroke in the Japanese population. Compared to that observed in Western countries, the prevalence of CHD is lower than that of stroke in Japan[20]. Moreover, as demonstrated in this study, hypercholesterolemia is not related to stroke mortality, although hypertension, smoking and diabetes are positively associated with stroke as well as CHD. Consequently, these factors resulted in lower PAFs due to hypercholesterolemia than those due to other risk factors in the present study.

As described above, neither a 1-SD increment nor high serum TC level were found to be associated with death due to stroke. This observation is consistent with the findings of other studies conducted in Japan[22-24]. In Japan, hypertension is the strongest risk factor for stroke; therefore, the influence of hypercholesterolemia is thought to be relatively weak[25]. Moreover, one subtype of stroke, atherothrombotic infarction, is positively associated with hypercholesterolemia, although its incidence among stroke cases is relatively low in Japan[26, 27]. This may be why hypercholesterolemia is not positively associated with stroke in Japan. The absence of a positive association between the cholesterol levels and stroke mortality has also been noted in studies in Western countries, especially

among elderly populations or patients with high blood pressure[28]. This is why the HRs and PAFs for total CVD death due to hypercholesterolemia were lower than those for CHD and/or cardiac death in the present study.

Moreover, we found a significant interaction between the serum TC level and smoking for CHD death, and the HR for smoking was higher than that for non-smoking in the subgroup analysis. These results are consistent with those reported by the Asia Pacific Cohort Studies Collaboration[29] and NIPPON DATA80[30] studies, although such findings have not been observed consistently[31]. Further research is therefore needed to confirm our findings.

As demonstrated in previous studies[8, 9], hypercholesterolemia is an important risk factor for CHD in Japan. However, the rate of fatalities from CHD among the Japanese population is lower than that observed in Western countries[32-34]. Heart failure is representative of end-stage CHD; therefore, HF may be registered as the cause of death in patients with CHD who survive a heart attack. Shiba *et al.* showed that the frequency of HF with an ischemic etiology is increasing in Japan[35]. Hence, we evaluated the endpoint "cardiac death," defined as death due to CHD or HF, and observed a similar result as that obtained for CHD only. Notably, the estimated PAF of CHD was higher than that of cardiac death, although this trend reversed when considering the estimated number of excess deaths.

As mentioned above, although the PAFs for smoking and hypertension estimated in other studies[6] are very high (29%), the rate of smoking is currently decreasing in Japan, and the prevalence of hypertension has not changed, even after adjusting for age[36, 37]. In contrast, the incidence of hypercholesterolemia is increasing[37]. As a result, the PAF of hypercholesterolemia may be higher in the future than that estimated in this study. Moreover, because the generation with hypercholesterolemia is reaching an age at which the risk for CVD increases, treating hypercholesterolemia is becoming increasingly important.

This study is associated with several limitations. First, we assessed risk factors, including the serum TC level, at baseline only; therefore, the relationship between the serum TC level and mortality may have been underestimated due to random errors in measuring the serum TC levels, known as the regression dilution effect[38]. Moreover, we did not have any information regarding changes in lifestyle or medications among the study subjects. For these reasons, it is necessary to apply the PAFs determined in this study to the present Japanese population with caution. Second, we were unable to obtain detailed information regarding the subtypes of stroke and heart failure because we could not view the subjects' death certificates. In Japan, the single underling cause of death is determined according to the ICD-9 code (until 1994) or ICD-10 code (from 1995 onwards) by a government officer based on a review of the death certificate. However, we believe this process may minimize the potential for information bias because the endpoints of NIPPON DATA were not defined by the researchers themselves. Third, we did not have access to data for other lipid parameters, such as high-density lipoprotein cholesterol, because the lipid profiles, with the exception of the TC level, were not generally evaluated in Japan during the baseline survey period.

Conclusion

In conclusion, in this long-term cohort study, hypercholesterolemia was shown to be significantly associated with an increased risk of death due to CVD, especially CHD and CHD plus HF, in both sexes among middle-aged and elderly community-dwelling Japanese individuals. The estimated PAFs of these diseases due to hypercholesterolemia were lower than those noted in Western countries and the values for other traditional risk factors. Nevertheless, we believe than managing hypercholesterolemia in Japanese is necessary in order to prevent the development of CVD in these populations.

Declaration

Dr. Sugiyama had full access to all of the data in this study and takes responsibility for the integrity of the data collection and the accuracy of the data analysis.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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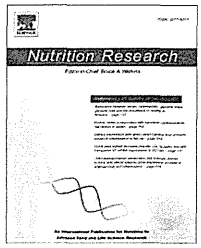

The reasonable reliability of a self-administered food frequency questionnaire for an urban, Japanese, middle-aged population: the Suita study☆,☆☆

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ABSTRACT

Because few studies have developed food frequency questionnaires (FFQ) and examined their reliability for Japanese urban populations, FFQ developed for urban Japanese populations may show reasonable reliability for estimating intakes of nutrients and food groups. Therefore, the objective of this study was to examine the reliability of an FFQ developed for a prospective cohort study in a Japanese urban area. A total of 29 men and 29 women aged 47 to 78 years were selected from participants in the Suita study from February 1997 to February 1998. Seven-consecutive-day dietary records (DR) was collected in each season (28-day DR). The FFQ were administered 3 times in total in each season, except in autumn. We calculated Spearman correlation coefficients to assess the validation of the first and third FFQ compared with 28-day DR and to assess the repeatability for 3-, 6-, and 9-month intervals. Reasonable validity of each FFQ compared with 28-day DR were observed for energy intake and for 27 nutrients, and 11 food groups were selected. Median (range) Spearman rank correlation coefficients for energy-adjusted nutrient and food group intakes of the first FFQ were 0.52 (0.14-0.88) and 0.53 (0.24-0.74), and those of the third FFQ were 0.51 (0.07-0.84) and 0.57 (0.16-0.75), respectively. The repeatability of each interval was relatively good; median (range) Spearman correlation coefficients of nutrients for 3-, 6-, and 9-month intervals were 0.67 (0.40-0.85), 0.63 (0.25-0.93), and 0.62 (0.31-0.87), respectively; those for food groups were 0.58 (0.42-0.76), 0.56 (0.24-0.80), and 0.65 (0.30-0.76), respectively. In conclusion, this FFQ is useful for evaluating the associations of nutrient and food intakes with cardiovascular diseases and their risk factors in Japanese urban populations.

Abbreviations: DR, dietary records; FFQ, food frequency questionnaires.

☆ Conflict of interest: None.

☆☆ Author contributions: K.M. participated in the study analysis, interpretation of data, and drafting of the manuscript and provided statistical expertise. Y.K. participated in the study concept and design, acquisition of data and interpretation of data, and critical revision of the manuscript. Y.M., T.O., M.W., and H.I. participated in acquisition and interpretation of data and critical revision of the manuscript. T.Y. participated in the interpretation of data.

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1. Introduction

The food frequency questionnaire (FFQ) is one of the most commonly used assessment tools for diet. A large number of FFQ have been developed to adapt characteristics of study populations for most epidemiological studies.

Compared with the Western diet, the Japanese diet is characterized by higher intakes of salt, fish, rice, and soy foods and lower intakes of dietary fats and dairy products (eg, calcium-rich food) [1–4]. Furthermore, high-carbohydrate and high-salt intakes are associated with increased risk of all-cause mortality and lifestyle-related diseases [5–7], although intakes of those nutrients have decreased during the last 3 decades [8]. Most FFQ for Japanese have relatively high validity for estimating those nutrients [9].

On the other hand, there are also region-specific dietary habits in Japan. The National Health and Nutrition Survey in Japan [8] showed that the largest metropolitan areas tended to have higher intakes of saturated fatty acids, bread, and meats while tending to have lower intakes of n-3 unsaturated fatty acids, vitamin D, rice, and fish compared with other areas.

Those differences between areas may affect differences in lifestyle-related disease incidents between both areas. The secular trend of incidence of coronary heart disease was higher in urban than in rural areas; urban areas have experienced an increase in incidence, whereas rural areas have experienced a decrease [10]. In addition, the incidence of stroke was approximately twice as high as that of coronary heart disease in urban areas, whereas it was 2 to 4 times that in rural areas [10–13].

Several studies in Japan have examined the reliability of the FFQ among Japanese rural populations [9]. However, few FFQ have been developed for Japanese urban populations [14–17]. Furthermore, most other validation studies in Japan do not include urban populations or mixed areas [9] despite that food distribution and urbanization include large metropolitan areas and rural areas in Japan [8]. Therefore, FFQ developed for rural areas could not estimate the nutrient and food intakes for urban populations correctly.

The hypothesis of this study was that the FFQ developed for urban Japanese populations have reasonable reliability for estimating intakes of energy, nutrient, and food groups. Because few FFQ were developed and their reliability for urban Japanese populations was confirmed, the objective of this study was to examine the validity and repeatability of a self-administered FFQ developed for a middle-aged population from prospective cohort studies in Japanese urban areas.

2. Methods and materials

2.1. Study design and subjects

The subjects were recruited from participants of the Suita study. The Suita study is a prospective cohort study conducted in a Japanese urban area, the details of which can be found elsewhere [11,12,18–21]. In brief, this cohort, which is supported by the National Cerebral and Cardiovascular Center, has approximately 6500 men and women aged 30 to 79 years who live in Suita City, an urban area located on the north side of Osaka Prefecture (its population was approximately 345 000 in 1990). This cohort was established in 1989 to focus on protection for cardiovascular diseases.

All study participants underwent regular health checkups between September 1989 and March 1994. Participants continued to visit the National Cerebral and Cardiovascular Center every 2 years since then for regular health checkups. At baseline and at regular health checkup surveys, the participants were evaluated in terms of potential risk factors, including anthropometric indices, blood pressure, blood sample test results, and electrocardiogram results, and their lifestyles were assessed. After the baseline survey, the participants were followed up and cardiovascular events were assessed (ie, stroke and coronary heart disease).

To validate the FFQ for the Suita study, 31 married couples (31 men and 31 women) aged 47 to 78 years were selected from participants of this study. They also participated in the validation study for FFQ of the Japan Public Health Center–Based Prospective Study Cohort II [22,23]. We excluded 2 men and 2 women from the analysis because they did not completely answer the 28-day dietary records (DR); thus, we included 58 men and women for this analysis. Figure shows the timeline of this study. Seven-consecutive-day DR were administered to each subject in each of the 4 seasons. The FFQ was also collected in each season, except in autumn (November 1997). This study was approved by the Institutional review board of the National Cerebral and Cardiovascular Center, and informed consent was obtained from each participant.

2.2. Dietary records

Because the participants also participated in the validation study for the FFQ of the Japan Public Health Center–Based Prospective Study Cohort II, information in the DR for this study was the same. The data collection procedure for the DR

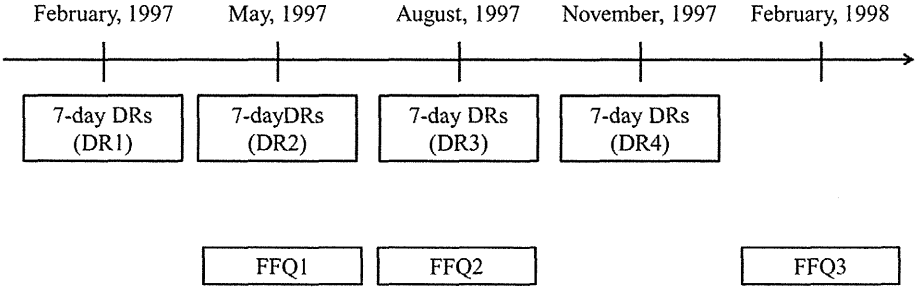

Figure – Timeline of the study for reliability of the self-administered FFQ. The 7-day DR and FFQ were conducted at almost the same time in each season, except for the lack of the FFQ in November 1997.

methodology is described in detail elsewhere [22,23]. In brief, 7-consecutive-day DR were collected in each of the 4 seasons, which were then used as 28-day DR for 1 year. The subjects received the booklet for recording, and local dietitians instructed them how to record. We asked the subjects to record all foods in detail, including seasonings and beverages, method of preparation, and names of dishes, and to measure the weight or size of each food. Local dietitians collected and then checked their DR by the end of each season. We averaged all food intakes in each 28-day period and then considered them as the individual's habitual food intake. Daily energy and major nutrients intakes were calculated by using the *Standard Tables of Food Composition in Japan (Fifth Revised and Enlarged Edition)*[24]. Daily food intakes were also calculated, and all foods were categorized into 18 food groups based on standard tables.

2.3. *Food frequency questionnaire*

The developed self-administered FFQ consisted of a number of questions and included items under 50 types of food, 6 alcohol beverages, 8 dishes, 10 salty food and dishes, as well as 7 questions concerning the fat content of milk and types of meat, fish, and oil consumed (see Supplementary data). Three questions assessed dietary habits (eg, seasoning and noodle soup) to estimate salt intake. We asked for the weekly or monthly frequency of consumption of 49 foods (excluding salty food and dishes) and 6 alcohol beverages, whereas for vegetable consumption, we asked for the daily frequency in an open-ended style.

The frequency of dry fish was grouped into 5 categories: "rarely," "once or twice per week," "every other day," "once per day," and "twice per day." Almost all food and alcohol beverages, excluding rice, bread, and beer, were shown as a standard portion size in the FFQ. Portion sizes of beer were categorized into "large (633 mL)," "medium (500 mL)," "small (350 mL)," and "glass (200 mL)."

In addition, we asked for the frequencies of principal foods at each mealtime (breakfast, lunch, dinner, or snack), including rice, bread, noodles, sweet buns, and cereal, because habitual intake of principal food at each mealtime may reflect their dietary habit. It may also be useful to estimate cereal and carbohydrate intakes more correctly. Portion sizes of rice were grouped into 4 categories: "large (200 g)," "medium (standard; 150 g)," "small (110 g)," and "other (open-ended)." Bread portions were categorized into "quarter of a loaf," "one-fifth of a loaf," "one-sixth of a loaf," and "one-eighth of a loaf."

The amount of each food intake was calculated by multiplying the standard or selected portion size by the frequency (per day). For milk, meat, fish, and oil, answers to 7 questions that asked the fat content of those foods assessed the weight of the food components. Salt intake was also weighted by answers to 3 questions related to salt intake (seasoning and noodle soup). The estimated daily energy and major nutrients intakes in the FFQ were calculated by using the *Standard Tables of Food Composition in Japan (Fifth Revised and Enlarged Edition)*[24]. Daily food intakes were also all calculated, and all foods were categorized on the basis of the standard tables.

2.4. *Selected foods and nutrients*

Intakes of 11 food groups were categorized on the basis of the standard tables, and energy and 27 nutrients were calculated. We also estimated the intake of animal and plant protein, animal and plant fat, calcium from milk and dairy products, and caffeine because those nutrients could be estimated by using the standard tables. Those nutrients have been shown to be associated with risk of cardiovascular diseases and their risk factors [25–27].

2.5. *Statistical analyses*

All nutrient and food group intakes in men and women were adjusted for energy intake by residual methods [28] using linear regression analysis after logarithmic transformation. We calculated the means and SDs for energy, for each nutrient, and for food groups of 28-day DR and respective FFQ (FFQ1, FFQ2, and FFQ3) and presented them as means ± SD. To assess the validation of the FFQ compared with 28-day DR, we calculated the Spearman correlation coefficients of 28-day DR with FFQ1 and FFQ3. We also divided the subjects into tertiles according to intakes for energy, energy-adjusted nutrients, and food groups for 28-day DR, FFQ1, and FFQ3, respectively, and then calculated the percentages of the same and extreme categories for energy, energy-adjusted nutrient, and food group intakes. To assess the repeatability, we calculated Spearman correlation coefficients among respective FFQ at 3-, 6-, and 9-month intervals. SAS Statistical Package version 9.4 (Statistical Analysis System Inc, Cary, NC, USA) was used for analyses.

3. Results

3.1. *Validation of FFQ*

Table 1 shows the means and correlations of nutrient intakes between the 28-day DR and the FFQ. Most of the mean crude intakes of energy and nutrients calculated by the FFQ were systematically lower than those calculated by the 28-day DR, excluding sodium, calcium, polyunsaturated fatty acids, vitamin D, and ethanol.

Spearman correlation coefficients between the FFQ and the 28-day DR were calculated to examine the validity of the FFQ. Median and range values of Spearman correlation coefficients for crude intakes of energy and nutrients estimated by FFQ1 were 0.47 and 0.07 (soluble fiber) and 0.89 (ethanol). After adjustment for energy intake, intakes for nutrients were 0.52 and 0.14 (caffeine) and 0.88 (ethanol), and crude intakes of those estimated by FFQ3 were 0.44 and 0.19 (polyunsaturated fatty acids) and 0.84 (ethanol). After adjustment for energy intake, those for intakes of nutrients were 0.51 and 0.07 (caffeine) and 0.84 (ethanol) (Table 1).

Percentages of joint classifications of energy and energy-adjusted nutrient intakes by tertiles between 28-day DR and FFQ are shown in Table 2. Similar trends in Spearman correlation coefficients were observed. Ethanol, carbohydrate, and calcium intakes have relatively high percentage of the same category and low percentage of the extreme category. In contrast, caffeine, α-tocopherol, and n-3 polyunsaturated

Table 1 – Nutrient intakes for 28-day DR with FFQ1 and FFQ3

	Nutrient intakes			Spearman correlation coefficients			
				DR vs FFQ1		DR vs FFQ3	
	28-d DR	FFQ1	FFQ3	Crude	Energy adjusted	Crude	Energy adjusted
Energy (kcal)	2043 ± 323	1907 ± 329	1847 ± 300	0.58		0.45	–
Total protein (g)	78.6 ± 12.4	76.5 ± 17.9	76.6 ± 15.3	0.53	0.48	0.47	0.54
Plant protein (g)	37.0 ± 6.3	35.4 ± 6.6	35.7 ± 8.1	0.60	0.65	0.53	0.71
Animal protein (g)	41.6 ± 9.3	41.1 ± 13.7	40.9 ± 11.9	0.41	0.41	0.43	0.43
Total fat (g)	54.7 ± 10.3	53.3 ± 15.9	52.1 ± 12.8	0.56	0.57	0.44	0.66
Plant fat (g)	26.9 ± 6.4	28.7 ± 9.7	27.7 ± 8.5	0.46	0.42	0.22	0.38
Animal fat (g)	27.7 ± 7.3	24.5 ± 9.0	24.3 ± 7.3	0.54	0.63	0.62	0.75
Carbohydrate (g)	286.7 ± 49.7	252.8 ± 51.0	242.8 ± 43.8	0.71	0.76	0.59	0.80
Energy from protein (%energy)	15.5 ± 1.6	16.1 ± 2.8	16.7 ± 2.6	–	0.61	–	0.61
Energy from fat (%energy)	24.2 ± 3.5	25.0 ± 5.7	25.4 ± 4.8	–	0.61	–	0.65
Energy from carbohydrate (%energy)	56.2 ± 5.5	53.4 ± 8.3	52.9 ± 7.1	–	0.65	–	0.75
Sodium (mg)	3793 ± 763	4258 ± 1240	3863 ± 996	0.32	0.48	0.39	0.43
Potassium (mg)	3065 ± 485	2454 ± 527	2501 ± 510	0.46	0.47	0.49	0.53
Calcium (mg)	664 ± 189	724 ± 257	719 ± 261	0.68	0.69	0.48	0.54
Calcium from milk and dairy products (mg)	230 ± 161	267 ± 181	262 ± 181	0.85	0.74	0.75	0.69
Magnesium (mg)	320 ± 51	300 ± 72	304 ± 73	0.55	0.59	0.51	0.60
Retinol (μg)	320 ± 286	352 ± 340	316 ± 224	0.46	0.50	0.40	0.46
β-Carotene (μg)	3866 ± 1369	2940 ± 1027	3005 ± 1061	0.47	0.58	0.29	0.29
Retinol equivalent (μg)	689 ± 315	643 ± 370	617 ± 265	0.53	0.55	0.33	0.36
Vitamin D (μg)	8.59 ± 3.03	11.48 ± 6.51	10.66 ± 5.19	0.28	0.23	0.28	0.20
α-Tocopherol (mg)	8.15 ± 1.46	6.92 ± 1.68	6.81 ± 1.47	0.36	0.25	0.24	0.16
Vitamin K (μg)	251 ± 77	227 ± 66	241 ± 90	0.47	0.54	0.40	0.43
Vitamin B_6 (mg)	1.49 ± 0.27	1.32 ± 0.32	1.32 ± 0.28	0.36	0.43	0.44	0.54
Vitamin B_{12} (μg)	9.91 ± 5.30	8.80 ± 4.04	8.21 ± 3.16	0.26	0.23	0.27	0.36
Folic acid (μg)	457 ± 94	312 ± 86	314 ± 81	0.51	0.58	0.31	0.35
Vitamin C (mg)	150.3 ± 34.2	94.8 ± 34.4	101.2 ± 25.2	0.61	0.59	0.46	0.47
Saturated fatty acids (g)	15.7 ± 3.8	15.2 ± 5.1	14.7 ± 4.2	0.73	0.74	0.69	0.83
Monounsaturated fatty acids (g)	18.2 ± 3.9	17.2 ± 5.4	16.7 ± 4.3	0.51	0.47	0.44	0.66
Polyunsaturated fatty acids (g)	13.0 ± 2.4	13.5 ± 4.3	13.6 ± 3.7	0.37	0.31	0.19	0.25
n-3 polyunsaturated fatty acids (g)	2.5 ± 0.5	2.6 ± 1.0	2.6 ± 0.8	0.20	0.15	0.33	0.22
n-6 polyunsaturated fatty acids (g)	10.4 ± 2.1	10.9 ± 3.6	11.0 ± 3.3	0.44	0.35	0.22	0.34
Cholesterol (mg)	331 ± 98	298 ± 124	299 ± 101	0.61	0.60	0.52	0.64
Dietary fiber (g)	16.9 ± 2.9	12.5 ± 2.8	2.8 ± 0.7	0.40	0.46	0.45	0.50
Soluble fiber (g)	3.8 ± 0.8	2.8 ± 0.6	9.5 ± 2.1	0.07	0.20	0.36	0.33
Insoluble fiber (g)	12.3 ± 2.1	9.5 ± 2.2	12.4 ± 2.8	0.45	0.49	0.49	0.55
Caffeine (g)	0.19 ± 0.07	0.02 ± 0.02	0.02 ± 0.04	0.16	0.14	0.25	0.07
Ethanol (g)	10.0 ± 15.4	12.6 ± 21.7	11.4 ± 18.6	0.89	0.88	0.84	0.84
Median				0.47	0.52	0.44	0.51

Nutrient intakes for 28-day DR with FFQ1 and FFQ3 are means ± SD.
Spearman correlation coefficients ≥0.27 ($P < .05$) and ≥0.36 ($P < .01$).

fatty acids, which have lower Spearman correlation coefficients, have relatively low percentage of the same category and high percentage of the extreme category.

We also show in Table 3 the mean and Spearman correlation coefficients of food group intakes between the 28-day DR and FFQ. Similar differences for mean intakes linked with nutrients were observed. Intakes for most of the food groups, excluding pulses (including soy), nuts and seeds, fruits, milk and dairy products, and confectioneries, as calculated by each FFQ, were systematically higher than values calculated by the 28-day DR.

Median and range values of Spearman correlation coefficients between FFQ1 and 28-day DR for intakes of food groups were 0.57 and 0.17 (vegetables) and 0.74 (cereals). After adjustment for energy intake, these were 0.53 and 0.24 (meats) and 0.75 (cereals). Those between FFQ3 and 28-day DR were 0.57 and 0.19 (algae, nuts, and seeds) and 0.74 (cereals). After adjustment for energy intake, these were 0.57 and 0.16 (algae) and 0.78 (cereals).

Percentages of joint classifications of energy-adjusted food group intakes by tertiles between 28-day DR and FFQ were also calculated (Table 4). They showed trends similar to those of Spearman correlation coefficients. Cereal intake comprises a relatively high percentage of the same category and a lower percentage of the extreme category. In contrast, nuts, seeds, and algae have a relatively low percentage of the same category and a high percentage of the extreme category.

3.2. *Repeatability of FFQ*

In this analysis, we administered the FFQ in 3 seasons (ie, at 3-, 6-, and 9-month intervals) to address repeatability. Mean values of