Table 4. Hazard ratios for cardiovascular mortality in 27,385 men and 39,207 women grouped according to blood pressure and smoking habit (EPOCH-JAPAN)

	Men						Women					
	normal blood pressure			hypertension[a]			normal blood pressure			hypertension[a]		
	never-smoker	former smoker	current smoker	never-smoker	former smoker	current smoker	never-smoker	former smoker	current smoker	never-smoker	former smoker	current smoker
Participants, n	3,999	3,363	9,091	2,656	2,658	5,618	24,373	313	1,289	12,393	203	636
Person-years of follow-up	39,718	30,933	91,722	26,210	24,779	57,108	248,032	3,083	13,902	127,784	1,972	6,788
Cardiovascular disease												
Cases, n	67	74	203	121	130	393	284	10	32	507	17	55
Adjusted HR[b]	1.00	1.07	1.43	1.52	1.70	2.83	1.00	1.49	1.70	1.69	2.56	2.70
95% CI	ref.	0.76–1.50	1.08–1.89	1.13–2.06	1.25–2.31	2.17–3.69	ref.	0.79–2.81	1.18–2.46	1.45–1.98	1.56–4.20	2.00–3.64
PAF[c], %		0.5	6.2	4.2	5.4	25.7		0.4	1.5	22.9	1.1	3.8
	p value for interaction[d] = 0.22						p value for interaction[d] = 0.96					
Coronary heart disease												
Cases, n	17	16	55	19	22	87	44	3	7	89	4	19
Adjusted HR[b]	1.00	0.90	1.58	1.00	1.12	2.57	1.00	2.96	2.43	1.86	3.86	6.14
95% CI	ref.	0.45–1.82	0.91–2.74	0.52–1.95	0.59–2.16	1.51–4.38	ref.	0.91–9.60	1.09–5.42	1.27–2.72	1.36–10.97	3.49–10.79
PAF[c], %		NC	9.3	NC	1.1	24.6		1.2	2.5	24.8	1.8	9.6
	p value for interaction[d] = 0.40						p value for interaction[d] = 0.71					
Stroke												
Cases, n	28	30	85	64	67	189	138	6	16	247	6	17
Adjusted HR[b]	1.00	1.04	1.43	1.86	2.10	3.19	1.00	1.99	1.81	1.76	1.97	1.82
95% CI	ref.	0.61–1.76	0.93–2.20	1.19–2.92	1.33–3.31	2.12–4.78	ref.	0.88–4.53	1.08–3.05	1.41–2.19	0.86–4.50	1.09–3.04
PAF[c], %		0.2	5.5	6.4	7.6	28.0		0.7	1.7	24.8	0.7	1.8
	p value for interaction[d] = 0.77						p value for interaction[d] = 0.21					
Cerebral infarction												
Cases, n	15	23	44	35	45	110	65	4	6	104	4	10
Adjusted HR[b]	1.00	1.38	1.45	1.61	2.29	3.28	1.00	2.30	1.33	1.25	1.92	1.61
95% CI	ref.	0.71–2.68	0.80–2.63	0.87–2.98	1.25–4.18	1.89–5.71	ref.	0.83–6.36	0.58–3.09	0.90–1.73	0.69–5.36	0.81–3.18
PAF[c], %		2.3	5.0	4.9	9.3	28.1		1.2	0.8	10.8	1.0	2.0
	p value for interaction[d] = 0.49						p value for interaction[d] = 0.86					
Intracerebral hemorrhage												
Cases, n	10	3	24	23	15	40	24	2	3	70	0	1
Adjusted HR[b]	1.00	0.30	1.04	2.23	1.58	2.00	1.00	4.23	2.08	3.33	0.00	0.75
95% CI	ref.	0.08–1.11	0.49–2.19	1.04–4.75	0.69–3.63	0.98–4.07	ref.	0.99–18.08	0.62–6.95	2.04–5.44		0.10–5.63
PAF[c], %		NC	NC	NC	NC	NC		NC	NC	NC	NC	NC
	p value for interaction[d] = 0.29						p value for interaction[d] = 0.01					

HR = Hazard ratio; CI = confidence interval; NC = not calculated; ref = reference.

[a] Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg.[b] From a Cox proportional hazards regression model with multivariate adjustment for age, body mass index, serum total cholesterol and cohort. [c] PAFs were calculated as proportion × (HR – 1)/HR, using the proportion of deaths in each smoking group and the HR. [d] The interaction between smoking habit and blood pressure was assessed using likelihood ratio tests.

Table 5. Hazard ratios for cardiovascular mortality in 27,385 men and 39,207 women grouped according to serum total cholesterol and smoking habit (EPOCH-JAPAN)

	Men						Women					
	normal serum cholesterol			high serum cholesterol[a]			normal serum cholesterol			high serum cholesterol[a]		
	never-smoker	former smoker	current smoker	never-smoker	former smoker	current smoker	never-smoker	former smoker	current smoker	never-smoker	former smoker	current smoker
Participants, n	6,030	5,387	13,559	625	634	1,150	30,513	392	1,622	6,253	124	303
Person-years of follow-up	59,933	49,733	137,259	5,996	5,979	11,571	313,809	3,860	17,556	62,007	1,195	3,133
Cardiovascular disease												
Cases, n	177	181	552	11	23	44	646	18	71	145	9	16
Adjusted HR[b]	1.00	1.06	1.63	0.81	1.28	1.94	1.00	1.27	1.58	0.97	1.74	1.87
95% CI	ref.	0.86–1.31	1.37–1.94	0.44–1.49	0.82–1.98	1.39–2.71	ref.	0.80–2.04	1.23–2.03	0.81–1.17	0.90–3.37	1.14–3.09
PAF[c], %		1.0	21.6	NC	0.5	2.2		0.4	2.9	NC	0.4	0.8
	p value for interaction[d] = 0.48						p value for interaction[d] = 0.60					
Coronary heart disease												
Cases, n	32	32	124	4	6	18	103	3	21	30	4	5
Adjusted HR[b]	1.00	1.02	1.96	1.56	1.77	4.19	1.00	1.38	3.04	1.30	5.17	3.90
95% CI	ref.	0.62–1.69	1.32–2.91	0.55–4.44	0.73–4.28	2.33–7.53	ref.	0.43–4.36	1.89–4.90	0.86–1.97	1.88–14.18	1.57–9.67
PAF[c], %		0.3	28.1	0.7	1.2	6.3		0.5	8.5	4.2	1.9	2.2
	p value for interaction[d] = 0.82						p value for interaction[d] = 0.40					
Stroke												
Cases, n	99	87	263	4	10	11	320	8	26	65	4	7
Adjusted HR[b]	1.00	1.04	1.60	0.59	1.17	1.02	1.00	1.19	1.20	0.88	1.61	1.70
95% CI	ref.	0.76–1.41	1.25–2.06	0.22–1.62	0.60–2.26	0.54–1.91	ref.	0.59–2.41	0.80–1.80	0.67–1.15	0.60–4.33	0.80–3.61
PAF[c], %		0.7	21.3	NC	0.3	0.05		0.3	1.0	NC	0.4	0.7
	p value for interaction[d] = 0.40						p value for interaction[d] = 0.49					
Cerebral infarction												
Cases, n	49	63	145	1	5	9	144	6	13	25	2	3
Adjusted HR[b]	1.00	1.35	1.73	0.28	1.10	1.72	1.00	1.73	1.20	0.79	1.67	1.60
95% CI	ref.	0.92–1.99	1.24–2.42	0.04–2.03	0.44–2.78	0.84–3.52	ref.	0.76–3.93	0.68–2.13	0.51–1.21	0.41–6.77	0.51–5.05
PAF[c], %		6.0	22.5	NC	0.2	1.4		1.3	1.1	NC	0.4	0.6
	p value for interaction[d] = 0.39						p value for interaction[d] = 0.75					
Intracerebral hemorrhage												
Cases, n	30	13	64	3	5	0	76	1	4	18	1	0
Adjusted HR[b]	1.00	0.46	1.04	1.26	1.66	0.00	1.00	0.68	0.83	1.01	1.76	0.00
95% CI	ref.	0.24–0.90	0.66–1.62	0.38–4.16	0.63–4.36		ref.	0.09–4.88	0.30–2.29	0.60–1.70	0.24–12.78	
PAF[c], %		NC	NC	NC	NC	NC		NC	NC	NC	NC	NC
	p value for interaction[d] = 0.001						p value for interaction[d] = 0.39					

HR = Hazard ratio; CI = confidence interval; NC = not calculated; ref. = reference.

[a] High serum cholesterol was defined as serum total cholesterol ≥6.21 mmol/l. [b] From a Cox proportional hazards regression model with multivariate adjustment for age, body mass index, systolic blood pressure and cohort. [c] PAFs were calculated as proportion × (HR – 1)/HR, using the proportion of deaths in each smoking group and the HR. [d] The interaction between smoking habit and serum total cholesterol was assessed using likelihood ratio tests.

that were current smokers and had high serum cholesterol were 4.19 (2.33–7.53) and 3.90 (1.57–9.67), respectively. Interaction was absent between smoking habit and serum total cholesterol for coronary heart disease and cerebral infarction in both sexes; however, there was interaction for intracerebral hemorrhage in men but not in women.

The fraction of deaths due to cardiovascular disease attributable to the coexistence of current smoking and high serum cholesterol was 2.2% for men and 0.8% for women. The corresponding fraction of deaths due to coronary heart disease was 6.3% for men and 2.2% for women.

Discussion

The present study demonstrated that current smoking significantly increased the risk of mortality from both coronary heart disease and cerebral infarction in Japanese men and women, even after adjustment for other major cardiovascular risk factors. These significant increments in risk were observed regardless of age, but were more pronounced in middle-aged than in elderly individuals. However, smoking had little adverse effect on mortality from intracerebral hemorrhage. Because of the high prevalence of smoking among Japanese men, approximately one-fourth of the total cardiovascular deaths in the male study population were attributable to ever smoking (current and former smoking combined), and this is important from a public health perspective. There was a further increase in coronary risk in current smokers who also had hypertension or high serum cholesterol. In addition, hypertensive smokers were at further elevated risk of cerebral infarction. Neither hypertension nor high serum cholesterol modified the adverse effects of smoking on coronary heart disease and cerebral infarction.

The results of a meta-analysis based on a systematic review of the relevant Japanese literature showed that the hazard ratios (95% confidence interval) in current smokers compared with never-smokers were 2.60 (2.19–3.09) for coronary heart disease and 1.39 (1.20–1.62) for total stroke [11], and these risks were broadly comparable with our results although these estimates are for men and women combined. Honjo et al. [5] conducted a pooled analysis similar to ours and reported that the hazard ratios for cardiovascular mortality in male and female current smokers were 2.19 (1.79–2.67) and 2.84 (2.24–3.60) for coronary heart disease and 1.15 (0.94–1.39) and 1.33 (0.99–1.81) for cerebral infarction, respectively, with adjustment only for age and cohort. Although their study lacked adjustment for important confounders such as blood pressure and serum cholesterol, their results are also comparable with our results for coronary heart disease in both sexes and for cerebral infarction in women but are lower than our results for cerebral infarction in men. However, their results are inconsistent with our results for intracerebral hemorrhage. Honjo et al. [5] reported that smoking significantly increased the risk of mortality from intracerebral hemorrhage, with a hazard ratio of 1.27 (1.00–1.62) for men and 1.87 (1.34–2.60) for women; however, our study showed a nonsignificant increment in the corresponding risk. Our results are in accordance with the results of the Japan Public Health Center Study [38] and the results of the previous Korean male study [10] that found that smoking, even heavy smoking, had little effect on incident intracerebral hemorrhage. We suggest that the discrepant results of intracerebral hemorrhage come from the inappropriate adjustment for confounders in their study.

In previous studies [4], as well as in our study, the impact of smoking on the global burden of total deaths from cardiovascular disease largely differed between sexes due to the much higher prevalence of smoking among men than women. A previous Japanese study estimated that the PAF of total cardiovascular deaths due to ever smoking was 23.0% in Japanese men and 8.0% in women [4], and these estimates were similar to ours. However, the estimated burden of coronary heart disease and stroke deaths in men differed between that study and ours. We observed a larger burden of stroke deaths (23.9 vs. 10.4%), especially cerebral infarction deaths (32.6 vs. 9.9%), due to ever smoking in men, but a smaller burden of coronary deaths (34.3 vs. 44.1%) compared with the previous Japanese study [4]. Although these discrepant results may have resulted in part from different characteristics of the two study populations, our results suggest a potentially larger burden of stroke deaths, especially cerebral infarction deaths, due to smoking in Japanese men than previously reported. Our estimated PAF of stroke due to smoking among Japanese men is comparable to the corresponding PAF in Korean men [8, 10], but is larger than the corresponding PAF in Chinese men (approximately 10%) [6, 7]. Although this may be due to the large proportion of fatal intracerebral hemorrhage among total strokes in China [7], and to a difference in background mortality rate between Japanese and Chinese never-smokers [6, 35], this international comparison indicates the importance of tobacco control for preventing stoke in Japan.

Although the methodology (e.g. the type of endpoint and the definition of nonsmokers, hypertension and high serum cholesterol) was not exactly the same between studies, our results are consistent with the results of the first cohort of the Hisayama study [32], which only investigated the effects of these risk factors on coronary heart disease and cerebral infarction. The coexistence of smoking and hypertension increased the risk of incident coronary heart disease by approximately 5-fold and the risk of incident nonembolic cerebral infarction by approximately 4-fold, compared with the absence of these two risk factors in a Japanese population [32]. In addition, the coexistence of smoking and high serum cholesterol increased coronary risk by approximately 4-fold [32]. Our large-scale study provided reliable information on this topic, emphasizing the need to consider concomitant hypertension or high serum cholesterol on the cardiovascular risks of smoking. Smokers with high serum cholesterol were broadly comparable to hypertensive smokers only for coronary mortality risk, as there is evidence that high serum cholesterol has little effect on cerebral infarction in the Japanese [18, 39]. However, unlike our study and the first cohort of the Hisayama study [32], the third cohort of the Hisayama study [33] recently reported that the risk of incident ischemic stroke was higher in smokers with than without hypercholesterolemia. Despite the absence of interaction between smoking habit and blood pressure or serum total cholesterol for coronary heart disease and cerebral infarction, there was some evidence of an interaction between smoking habit and blood pressure for intracerebral hemorrhage. However, it is difficult to explain the observed interaction (i.e. synergistic or otherwise) and the pathophysiological mechanisms responsible for the interaction. Furthermore, the power of this analysis could have been limited by an insufficient number of intracerebral hemorrhage deaths in hypertensive smokers and in hypercholesterolemic smokers. As a consequence, these results regarding intracerebral hemorrhage may have been due to chance.

Our PAF estimates suggest that male hypertensive smokers are special targets for reducing the global burden of premature death and disability due to cardiovascular disease in the Japanese population because of the large contribution of these smokers to the burden of cardiovascular disease deaths among men. NIPPON DATA80 [20] estimated that the PAF of cardiovascular disease due to the coexistence of current smoking and hypertension in Japanese men was 42.4% for those less than 60 years and 18.6% for those 60 years or older, but did not estimate the PAF for coronary heart disease and stroke separately. Our study indicates that male hypertensive smokers contribute significantly to the burden of deaths from both coronary heart disease and stroke. However, hypercholesterolemic smokers contribute less than hypertensive smokers to the total burden of cardiovascular disease deaths because of the lower prevalence of hypercholesterolemic smokers among Japanese men and their lower risk of cardiovascular mortality.

Several limitations should be acknowledged in the present study. First, to maximize the availability of data on smoking habits from potentially participating cohorts, we defined the three categories of smoking habits without considering the number of cigarettes smoked. Second, we assumed that the smoking habit at baseline remained unchanged throughout the follow-up period although it is likely that some current smokers quit smoking during the follow-up period. Moreover, extensive passive exposure to environmental tobacco smoke either at home or in the workplace may have been common, due to the high prevalence of smoking among Japanese men [20] and insufficient restriction of smoking in public places at that time. These limitations may have led to an underestimation of the true harm of active smoking [40]. Third, both hypertension and high serum cholesterol were defined without considering the use of medications that lower blood pressure or serum cholesterol. Furthermore, the levels of blood pressure and serum total cholesterol could have changed due to lifestyle modification and/or prescribed medications over the follow-up period although this was also present in other prospective studies in which the baseline levels of these factors were assumed to remain unchanged throughout the follow-up period. As a whole, these limitations may also have led to misclassification of the blood pressure and serum cholesterol categories, which may have resulted in an underestimation of the cardiovascular mortality risk due to the coexistence of smoking and hypertension or high serum cholesterol. Fourth, we could not calculate hazard ratios for subarachnoid hemorrhage mortality because there were only 75 documented deaths due to this subtype (20 in men and 55 in women). Fifth, we could not determine the cardiovascular mortality risk in smokers who had both hypertension and high serum cholesterol, because of the small number of cardiovascular deaths in this group. Finally, due to limited baseline information, no adjustment was made for diabetes in our analyses. However, this may not have had a large effect on our results because of the low prevalence of diabetes at that time in Japan [41].

In conclusion, smoking is definitely an undesirable habit that can lead to an increased risk of mortality from

both coronary heart disease and cerebral infarction. Furthermore, smoking increases the burden of cardiovascular disease in Japan due to its high popularity. Particular attention should be given to smokers who have another cardiovascular risk factor, such as hypertension or high serum cholesterol, because the combination of these risk factors substantially increases the mortality risk from coronary heart disease and cerebral infarction. Therefore, smokers with a concomitant risk factor should have rigorous counseling for smoking cessation and other lifestyle modifications. From a public health perspective in Japan, priority should be given to hypertensive smokers since this group makes a large contribution to the burden of both coronary deaths and cerebral infarction deaths.

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Disclosure Statement

None declared.

Appendix

The EPOCH-JAPAN Research Group

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ORIGINAL RESEARCH

American Heart Association | American Stroke Association.

Relation Between Serum Total Cholesterol Level and Cardiovascular Disease Stratified by Sex and Age Group: A Pooled Analysis of 65 594 Individuals From 10 Cohort Studies in Japan

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Background—The relation between serum total cholesterol (TC) and cardiovascular disease in women and in the elderly is unclear, especially in Asian populations.

Methods and Results—We examined this relation in the largest-scale pooled analysis of the Japanese population, the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN) study. A total of 65 594 participants who were 40 to 89 years of age and did not have a past history of cardiovascular disease were examined. Cox proportional-hazards models were used to estimate hazard ratios for death from total stroke, cerebral infarction, intracranial cerebral hemorrhage, or coronary heart disease. The mean follow-up period was 10.1 years, with the number of deaths from total stroke, cerebral infarction, cerebral hemorrhage, and coronary heart disease being 875, 457, 212, and 374, respectively. The participants were divided into 2 age groups: middle-aged (40 to 69 years; mean age 55 years) and elderly (70 to 89 years; mean age 75 years). In men, the multivariate-adjusted hazard ratios for coronary heart disease in the highest TC category (≥6.21 mmol/L) compared with the lowest category (<4.14 mmol/L) were 2.52 (95% confidence interval: 1.15–5.07) in middle-aged participants and 2.77 (1.09–7.03) in elderly participants. In women, the hazard ratios of the highest TC category (≥6.72 mmol/L) compared with the lowest category (<4.66 mmol/L) were 3.20 (1.44–7.09) in middle-aged participants and 1.02 (0.42–2.49) in elderly participants. TC levels were not associated with cerebral infarction in any age or sex group and were associated negatively with total stroke and cerebral hemorrhage.

Conclusion—High serum TC levels are associated with coronary heart disease in middle-aged Japanese men and women, but evidence in elderly Japanese individuals is still limited. **(*J Am Heart Assoc.* 2012;1:e001974 doi: 10.1161/JAHA.112.001974)**

Key Words: cholesterol • coronary heart disease • pooled analysis • stroke

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Hypercholesterolemia is a well-documented and established risk factor for coronary heart disease (CHD).[1,2] However, evidence of this association is mainly from middle-aged or relatively young elderly men <70 years of age, whereas evidence from women or the elderly, especially in Asian populations, is scarce. One large meta-analysis based on observational studies found that high levels of serum total cholesterol (TC) were associated with an increased CHD mortality rate in both men and women.[3] However, this study was stratified only by age and sex and was not adjusted for other confounders. Another meta-analysis based on observational studies showed a weaker association between TC and CHD in women and in participants ≥75 years of age.[4] To our knowledge, no observational study has demonstrated a clear positive relation between serum TC levels and death from CHD in women and the elderly specific to Asian populations.[1] Furthermore, less evidence is available on the influence of serum TC on stroke than on CHD.

We therefore investigated the associations between serum TC level and death due to cardiovascular disease (CVD), such as CHD and stroke, after stratification by sex and age in the largest-scale pooled analysis carried out in the Japanese population. Our a priori hypothesis is that a high serum TC level is a risk factor for CVD in Japanese after stratification by both sex and age.

Methods

Study Design

This study was part of a pooled project called EPOCH-JAPAN (Evidence for Cardiovascular Prevention from Observational Cohorts in Japan), which incorporates a meta-analysis of individual participant data from 13 cohorts across Japan. The project was designed to conduct pooled analyses and examine the relation between cause-specific mortality rate and various exposures, including laboratory measures and lifestyle factors. The guidelines for a cohort recruitment of EPOCH-JAPAN were as follows: collection of health examination measures, >1000 participants, and >10 years of follow-up (although each cohort's collaborator had discretion to choose the size of his or her data set for pooling). Both nationwide and regional cohort studies were included. We have reported the detailed characteristics of each cohort previously.[5]

Study Population

Of the 13 cohorts, 10 provided data on the cause of death (n=90 528).[5] The people who were (1) <40 or ≥90 years of age (n=10 528), (2) had past history of CVD (n=7422), and (3) lacked data on TC level (n=2122) at the baseline survey were removed. Moreover, 4862 participants were removed because of missing data for at least one of the following covariates: sex, age, body mass index, blood pressure, and smoking and drinking status. Finally, a total of 65 594 participants were included in the analysis. The levels of serum TC were measured enzymatically in all the cohorts, with the exception of the NIPPON DATA80 cohort, in which TC was measured by the Lieberman-Burchard direct method.

Ascertainment of Death

The causes of death were sought in great detail from the available sources in each cohort study. In most studies, death certificates were reviewed or the National Vital Statistics were used after permission had been obtained. Other sources used in some studies included autopsy reports, medical records, health examinations, and questionnaires. The underlying cause of death was coded according to the *International Classification of Diseases* (*ICD*) for National Vital Statistics based on the criteria proposed by the World Health Organization.[6] These classifications were based on the *ICD-9* until the end of 1994 and on the *ICD-10* from the beginning of 1995. The respective classification codes for *ICD-9* and *ICD-10* used in the study were as follows: death from CVD (390 to 459; I00 to I99), total stroke (TS) (410 to 414 or 430 to 438; I20 to I25 or I60 to I69), cerebral infarction (433 or 434 or 437.8; I63 or I69.3), intracranial cerebral hemorrhage (431 to 432; I61 or I69.1), and CHD (410 to 414; I20 to I25).

Statistical Methods

Sex-specific analysis was performed. TC was categorized into 7 categories (<4.14, 4.14 to 4.65, 4.66 to 5.16, 5.17 to 5.68, 5.69 to 6.20, 6.21 to 6.71, and ≥6.72 mmol/L) in accordance with a previous Japanese cohort study,[7] which had provided key evidence for the guidelines of the Japan Atherosclerosis Society for diagnosis and prevention of atherosclerotic CVD for Japanese.[8] However, because only a small number of participants had TC levels ≥6.72 mmol/L in men and <4.14 mmol/L in women, with the number of events in these participants being limited, we decided to combine these TC levels into the adjacent category (6.21 to 6.71 mmol/L in men and 4.14 to 4.65 mmol/L in women). The lowest level in both sexes (men, <4.14 mmol/L; women, <4.65 mmol/L) served as the reference group.

The study population was divided into 2 age groups in both men and women: middle-aged (40 to 69 years; mean age 55 years) and elderly (70 to 89 years; mean age 75 years). Age group– and sex-specific analyses were performed. Cox proportional-hazards models stratified by cohorts[9] were used to estimate the hazard ratios (HRs) for cardiovascular outcomes according to baseline TC. Deaths from CHD and from TS and its subtypes (cerebral infarction and cerebral hemorrhage) were used in the analysis. In the Cox model, age, body mass index, systolic blood pressure, smoking status (current smoker, ex-smoker, never-smoker), and drinking status (current drinker, ex-drinker, never-drinker) were used as confounding variables.

All confidence intervals were estimated at the 95% level, and the significance level was set at P=0.05. All the statistical analyses were performed in Statistical Analysis System release 9.13 (SAS Institute, Inc., Cary, NC).

Results

The baseline characteristics of the participants in the 10 cohorts are shown in Table 1. Each baseline survey was performed between 1977 and 1990, with the number of participants ranging from 1608 in the Tanno-Sobetsu cohort

Table 1. Baseline Characteristics of the Study Participants in Each Cohort

Cohort Name	Geographic Location (Prefecture)	Year of Baseline Survey	Follow-Up Periods, y, Average ±SD	No. Participants	Age at Study Entry, y, Average±SD	Serum Total Cholesterol, mmol/L, Average±SD	Systolic Blood Pressure, mm Hg, Average±SD	Diastolic Blood Pressure, mm Hg, Average± SD	Body Mass Index, kg/m^2, Average± SD	Smoking*Status			Drinking† Status		
										Never	Ex-	Current	Never	Ex-	Current
Men															
Tanno-Sobetsu	Hokkaido	1977	18.5±3.7	742	50.5±6.9	4.81±1.06	131±19	82±10	23.1±2.7	226	0	516	212	0	530
Osaki	Miyagi	1994	6.0±1.4	6142	62.1±10.0	5.02±0.88	132±17	80±11	23.6±2.9	1335	1811	2996	966	473	4703
Ohasama	Iwate	1987	9.9±2.6	877	59.4±10.9	4.84±0.88	134±17	76±11	23.1±2.8	435	0	442	341	0	536
Oyabe	Ishikawa	1988	9.6±2.1	1461	60.4±10.3	4.71±0.85	131±20	79±11	22.6±2.7	661	0	800	374	0	1087
YKK workers	Toyama	1990	10.7±2.8	1970	47.3±5.4	5.22±0.88	121±16	76±12	22.7±2.6	545	303	1122	359	30	1581
RERF cohort	Hiroshima	1986	15.4±3.5	619	54.5±10.8	5.12±0.88	122±13	80±8	21.7±2.7	95	182	342	112	35	472
Hisayama	Fukuoka	1988	10.7±2.8	1106	58.3±11.6	5.10±1.06	135±20	81±11	22.8±3.0	226	327	553	369	69	668
JACC study	Nationwide‡	1988–1990	9.4±2.1	8988	57.9±9.9	4.86±0.91	135±19	81±11	22.8±2.8	2048	2163	4777	1760	436	6792
NIPPON DATA80	Nationwide‡	1980	16.5±4.7	2737	55.5±10.7	4.84±0.88	142±21	85±12	22.5±2.9	492	556	1689	556	164	2017
NIPPON DATA90	Nationwide‡	1990	9.4±1.9	2412	57.0±11.3	5.15±0.96	140±20	85±12	23.0±3.0	524	597	1291	820	156	1436
Total			9.9±4.1	27 054	57.7±10.7	4.95±0.91	134±19	81±12	23.0±2.9	6587	5939	14 528	5869	1363	19 822
Women															
Tanno-Sobetsu	Hokkaido	1977	18.7±3.6	866	50.3±6.7	5.02±0.91	133±20	82±10	24.2±3.4	801	0	65	790	0	76
Osaki	Miyagi	1994	6.0±1.5	6612	61.2±9.2	5.48±0.88	130±18	78±11	24.1±3.2	6195	106	311	5049	183	1380
Ohasama	Iwate	1987	10.7±2.2	1363	58.4±9.3	5.30±0.93	129±16	73±11	23.9±3.3	1329	0	34	1280	0	83
Oyabe	Ishikawa	1988	10.1±1.4	3166	58.0±9.5	5.22±0.93	126±20	75±11	23.2±3.1	3085	0	81	2729	0	437
YKK workers	Toyama	1990	11.0±2.6	1036	47.2±5.4	5.30±0.96	117±16	72±12	22.3±2.7	1025	2	9	825	2	209
RERF cohort	Hiroshima	1986	16.2±2.6	1342	57.3±9.9	5.56±0.98	121±14	76±9	22.3±3.3	1168	35	139	803	17	522
Hisayama	Fukuoka	1988	11.3±2.2	1513	59.4±11.8	5.53±1.06	133±22	76±11	22.9±3.3	1378	31	104	1363	17	133
JACC study	Nationwide‡	1988–1990	9.6±1.9	15 952	56.5±9.5	5.25±0.93	132±19	78±11	23.3±3.2	15 213	182	557	12 800	155	2997
NIPPON DATA80	Nationwide‡	1980	17.3±4.0	3415	55.8±10.7	5.04±0.88	138±22	81±12	23.1±3.4	3052	73	290	2753	42	620
NIPPON DATA90	Nationwide‡	1990	9.6±1.5	3275	56.8±11.5	5.48±0.98	137±20	81±12	23.1±3.3	2925	72	278	3055	26	194
Total			10.3±3.9	38 540	57.2±10.1	5.33±0.96	131±20	78±11	23.4±3.2	36 171	501	1868	31 447	442	6651

*In the studies of Tanno-Sobetsu, Ohasama, and Oyabe, ex-smokers were classified as nonsmokers.
†In the studies of Tanno-Sobetsu, Ohasama, and Oyabe, ex-drinkers were classified as nondrinkers.
‡In this nationwide cohort study, the participants were from all areas of Japan.

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to 24 940 in the Japan Collaborative Cohort (JACC) study. Mean age ranged from 47 years in the YKK cohort to 61 years in the Osaki cohort.

The number of total participants was 65 594 (27 054 men and 38 540 women), and the mean age was 57 years. The mean ± standard deviation (SD) serum TC level of the total participants was 4.95±0.91 mmol/L for men and 5.33±0.96 mmol/L for women. The levels were lowest in the Oyabe cohort for men (4.71 mmol/L) and in the Tanno-Sobetsu cohort for women (5.02 mmol/L) and were highest in the YKK cohort for men (5.22 mmol/L) and in the Radiation Effects Research Foundation (RERF) cohort for women (5.56 mmol/L). The mean follow-up period was ≈10.1 years, with the number of deaths from TS, cerebral infarction, cerebral hemorrhage, and CHD being 875, 457, 212, and 374, respectively.

In the Cox regression models, the relation between serum TC levels and CHD death was continuous and positive overall, with the exception of elderly women. However, when TC level was treated as a continuous variable, the relation was not significant in elderly men (Table 2). In middle-aged men, the multivariate-adjusted HR of the highest TC category (≥6.21 mmol/L) for CHD was 2.52 (95% confidence interval [CI]: 1.15–5.07) compared with the lowest TC category (<4.14 mmol/L), and the multivariate-adjusted HR for a 1-SD increment in serum TC level (0.98 mmol/L) was 1.26 (95% CI: 1.11–1.42). In elderly men, the multivariate-adjusted HR of the highest TC category for CHD was 2.77 (95% CI: 1.09–7.03) compared with the lowest TC category. The multivariate-adjusted HR for a 1-SD increment in serum TC level in these participants was 1.23 (95% CI: 0.96–1.56).

In middle-aged women, the multivariate-adjusted HR of the highest TC category (≥6.72 mmol/L) for CHD was 3.20 (95% CI: 1.44–7.09) compared with the lowest TC category (<4.66 mmol/L), whereas the multivariate-adjusted HR for a 1-SD increment in serum TC (0.98 mmol/L) was 1.36 (95% CI: 1.12–1.66). However, in elderly women, the multivariate-adjusted HR of the highest TC level for CHD was 1.02 (95% CI: 0.42–2.49), and the multivariate-adjusted HR for a 1-SD increment in serum TC was 1.02 (95% CI: 0.82–1.27).

On the other hand, serum TC levels were not associated with cerebral infarction in any age or sex group and were associated negatively with cerebral hemorrhage and TS. The multivariate-adjusted HRs for cerebral infarction for a 1-SD increment in serum TC were 0.92 (95% CI: 0.74–1.14) in middle-aged men, 1.04 (95% CI: 0.87–1.24) in elderly men, 1.08 (95% CI: 0.83–1.39) in middle-aged women, and 0.97 (95% CI: 0.80–1.16) in elderly women. The multivariate-adjusted HR for cerebral hemorrhage for a 1-SD increment in serum TC was 0.84 (95% CI: 0.72–0.97) in the combined participants. The multivariate-adjusted HR for TS for a 1-SD increment in serum TC was 0.93 (95% CI: 0.862–0.997) in the combined participants. The Figure 1 summarizes the associations with CHD and cerebral infarction by sex and age groups.

Although 52% (n=34 379) of the participants in the present study had information on antihypertensive medication, the relations between TC and death from CVD (HRs) did not change substantially when use of hypertension medication (16%) was added as a covariate. In the subgroup analysis of participants with information on self-reported diabetes (n=28 793) or casual blood glucose (n=32 384), the relations between TC and death from CVD also were not altered when diabetes was added as a covariate. Because it is likely that there were time period differences in CVD event rates, we reanalyzed the data excluding 2 cohorts with earlier baseline surveys (Tanno-Sobetsu [1977] and NIPPON DATA80 [1980] cohorts). This analysis showed that the relations between TC and death from CVD (HRs) did not change substantially (data not shown).

Discussion

In this large cohort study in Japan, we found a positive relation between serum TC level and CHD death in both middle-aged women and middle-aged men. We also observed that the highest TC group (≥6.21 mmol/L) had an increased risk for CHD in elderly men, although the multivariate-adjusted HR did not reach a statistically significant level when TC level was treated as a continuous variable. There was also no relation between TC and CHD in elderly women. Except for elderly women, our results are similar to those reported in 2 previous large-scale studies.[3,4] To our knowledge, this is the first finding from a large-scale study specific to an Asian population that demonstrates a positive relation between hypercholesterolemia and CHD in middle-aged women with a mean age of 55 years. On the other hand, serum TC levels were not associated with cerebral infarction in any age or sex group and were associated negatively with TS and cerebral hemorrhage death.

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study, which included participants between 70 and 82 years of age with prior vascular disease (mean age 75 years), showed that pravastatin reduced the risk of CHD events.[10] In addition, the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study showed that pravastatin reduced the risk of CHD in Japanese participants ≥60 years of age without a history of CHD or stroke.[11] The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study also showed that rosuvastatin reduced the incidence of major cardiovascular events, including CHD, in people ≥70 years of age without prior vascular disease who had an elevated high-sensitivity C-reactive protein without apparent hyperlipidemia.[12] However, observational studies on

Table 2. The Number of Deaths, Crude Mortality Rate, and Multivariate-Adjusted HRs for CVD Death According to Total Cholesterol Levels

	Age Category, years		Total Cholesterol, mmo/L							
			<4.14	4.14 to 4.65	4.66 to 5.16	5.17 to 5.68	5.69 to 6.20	6.21 to 6.71	≥6.72	For 1 SD* Increasing
Men										
Coronary heart disease	40 to 69	Number of participants	3956	4805	5339	4276	2597	2111		
		Number of deaths	16	30	24	25	19	17		
		Crude mortality rate†	0.39	0.60	0.44	0.57	0.72	0.82		
		HR (95% CI)‡	1	1.56 (0.85 to 2.87)	1.20 (0.64 to 2.28)	1.71 (0.91 to 3.24)	2.26 (1.14 to 4.45)	2.52 (1.15 to 5.07)		1.26 (1.11 to 1.42)
	70 to 89	Number of participants	871	860	892	694	380	273		
		Number of deaths	11	21	18	11	10	8		
		Crude mortality rate†	1.70	3.18	2.69	2.11	3.45	5.08		
		HR (95% CI)‡	1	1.95 (0.93 to 4.06)	1.73 (0.81 to 3.67)	1.49 (0.64 to 3.48)	2.31 (0.96 to 5.53)	2.77 (1.09 to 7.03)		1.23 (0.96 to 1.56)
Cerebral infarction	40 to 69	Number of participants	3956	4805	5339	4276	2597	2111		
		Number of deaths	16	34	25	14	9	7		
		Crude mortality rate†	0.39	0.67	0.45	0.32	0.34	0.32		
		HR (95% CI)‡	1	1.78 (0.98 to 3.23)	1.26 (0.67 to 2.37)	1.05 (0.51 to 2.16)	1.13 (0.49 to 2.59)	1.11 (0.45 to 2.73)		0.92 (0.74 to 1.14)
	70 to 89	Number of participants	871	860	892	694	380	273		
		Number of deaths	37	32	43	28	14	8		
		Crude mortality rate†	5.73	4.85	6.43	5.38	4.82	6.47		
		HR (95% CI)‡	1	0.85 (0.53 to 1.38)	1.25 (0.80 to 1.96)	1.25 (0.76 to 2.07)	0.94 (0.50 to 1.77)	0.78 (0.36 to 1.69)		1.04 (0.87 to 1.24)
Women										
Coronary heart disease	40 to 69	Number of participants	8566		7230	7240	5359	3159	2502	
		Number of deaths	12		16	15	15	8	15	
		Crude mortality rate†	0.13		0.21	0.20	0.28	0.25	0.59	
		HR (95% CI)‡	1		1.37 (0.65 to 2.90)	1.21 (0.56 to 2.61)	1.56 (0.72 to 3.36)	1.45 (0.58 to 3.59)	3.20 (1.44 to 7.09)	1.36 (1.12 to 1.66)
	70 to 89	Number of participants	945		884	968	789	482	416	
		Number of deaths	20		19	17	11	9	7	
		Crude mortality rate†	2.37		2.46	2.02	1.64	2.15	1.92	
		HR (95% CI)‡	1		1.08 (0.57 to 2.03)	0.95 (0.49 to 1.82)	0.83 (0.40 to 1.75)	1.06 (0.48 to 2.37)	1.02 (0.42 to 2.49)	1.02 (0.82 to 1.27)

Continued

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Table 2. Continued

	Age Category, years		Total Cholesterol, mmo/L							
			<4.14	4.14 to 4.65	4.66 to 5.16	5.17 to 5.68	5.69 to 6.20	6.21 to 6.71	≥6.72	For 1 SD*, Increasing
Cerebral infarction	40 to 69	Number of participants	8566		7230	7240	5359	3159	2502	
		Number of deaths	13		13	9	14	8	8	
		Crude mortality rate†	0.14		0.17	0.12	0.26	0.25	0.32	
		HR (95% CI)‡	1		0.97 (0.45 to 2.10)	0.61 (0.26 to 1.44)	1.12 (0.52 to 2.42)	1.11 (0.45 to 2.74)	1.28 (0.51 to 3.22)	1.08 (0.83 to 1.39)
	70 to 89	Number of participants	945		884	968	789	482	416	
		Number of deaths	35		21	27	29	6	7	
		Crude mortality rate†	4.16		2.72	3.21	4.32	1.43	1.92	
		HR (95% CI)‡	1		0.70 (0.41 to 1.21)	0.89 (0.54 to 1.48)	1.39 (0.84 to 2.29)	0.45 (0.19 to 1.07)	0.69 (0.30 to 1.58)	0.97 (0.80 to 1.16)
Men and Women										
Total stroke	40 to 89	Number of participants	8449	11 554	14 345	13 178	9125	5100	3843	
		Number of deaths	147	183	182	160	103	45	55	
		Crude mortality rate†	1.70	1.52	1.25	1.21	1.14	0.89	1.45	
		HR (95% CI)‡	1	0.95 (0.76 to 1.18)	0.82 (0.65 to 1.02)	0.83 (0.66 to 1.05)	0.78 (0.60 to 1.02)	0.60 (0.42 to 0.84)	0.99 (0.72 to 1.37)	0.93 (0.862 to 0.997)
Cerebral hemorrhage	40 to 89	Number of participants	8449	11 554	14 345	13 178	9125	5100	3843	
		Number of deaths	44	41	47	38	15	12	15	
		Crude mortality rate†	0.51	0.34	0.32	0.29	0.17	0.24	0.39	
		HR (95% CI)‡	1	0.71 (0.46 to 1.09)	0.69 (0.46 to 1.05)	0.63 (0.41 to 0.99)	0.37 (0.20 to 0.68)	0.51 (0.27 to 0.99)	0.85 (0.46 to 1.58)	0.84 (0.72 to 0.97)

HR indicates hazard ratio; CVD, cardiovascular disease.

*One SD of total cholesterol was 0.98 mmol/L.

†Crude mortality rate was expressed as per 1000 person-years.

‡HR was adjusted for age, systolic blood pressure, body mass index, smoking categories, and drinking categories. All analyses were stratified by cohort.

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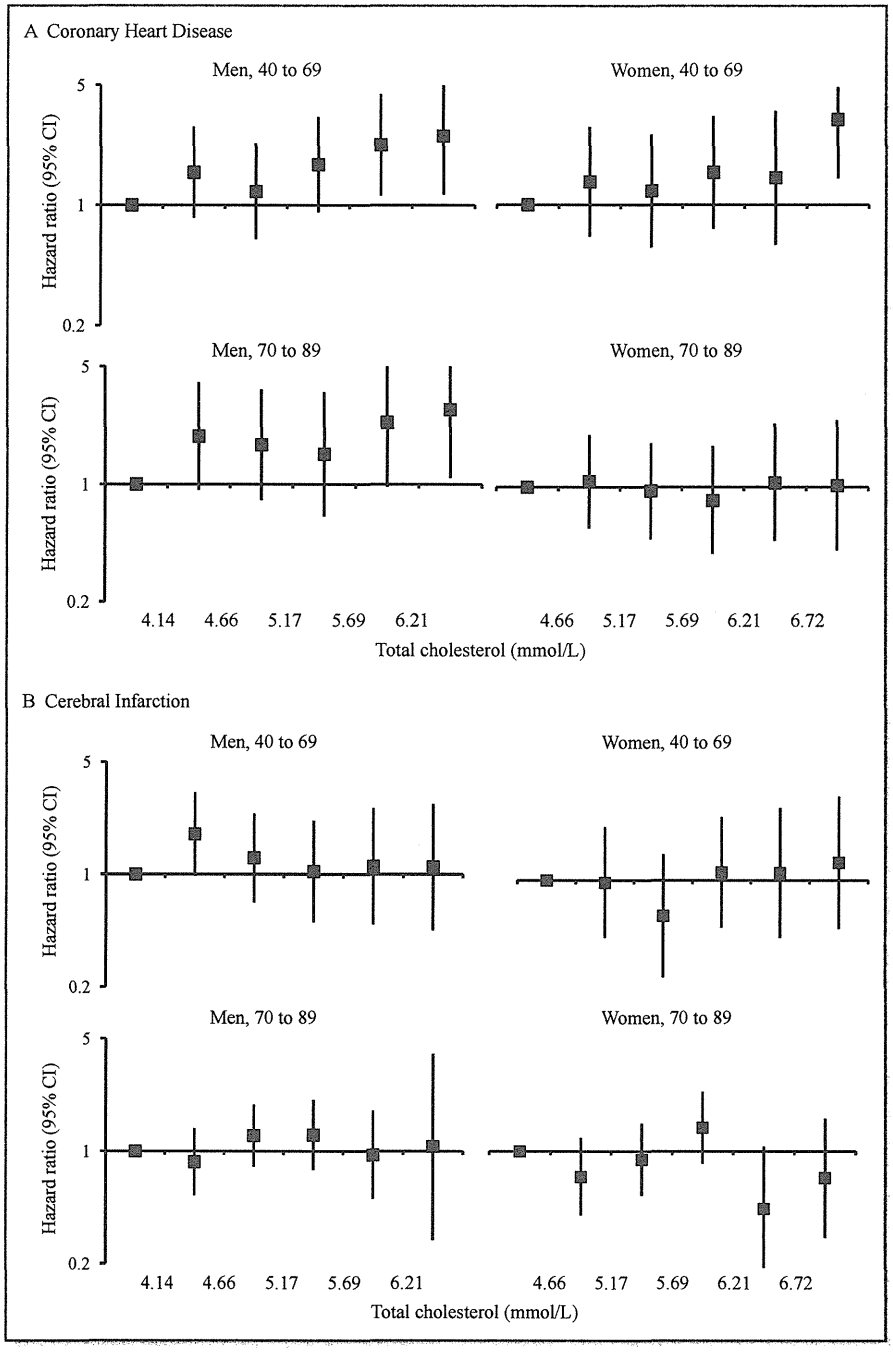

Figure 1. Multivariate-adjusted hazard ratios for death from (A) coronary heart disease and (B) cerebral infarction according to total cholesterol levels. Hazard ratio was adjusted for cohort, age, systolic blood pressure, body mass index, and smoking and drinking categories. CI indicates confidence interval.

elderly people at low risk or in the primary care setting are very rare, and there is little evidence of a sex difference. Moreover, elderly people, especially elderly women, are the dominant population in the currently aging societies of developed countries. Therefore, the sex-specific findings we observed in elderly community dwellers are important and suggest an increased risk for CHD in the highest TC group (≥6.21 mmol/L) in elderly men. However, this relation was not significant when TC level was treated as a continuous variable.

The Seven Countries Study showed that Japan had the lowest CHD mortality rate among developed countries, which was attributed largely to remarkably low serum TC

levels in the 1950s.[13] However, changes in lifestyle toward a Westernized pattern in Japan have resulted in a continuous increase in dietary fat intake and serum TC levels. Moreover, it was reported recently that Japanese born after World War II had serum TC levels similar to those of white men[14] and that the incident rate of CHD in Japan is increasing in some areas.[15,16] In the Western population, a positive relation between TC and CHD was observed in both sexes and in all age groups, although its association was attenuated in the elderly.[3] The weak association or lack of association between serum TC and CHD in elderly Japanese participants could be due to relatively less exposure to hypercholesterolemia in their young and middle-aged periods before the baseline, a time when mean serum TC level was known to be very low.[17,18] Although we do not have information on serum TC levels before the baseline measurements in the present study, elderly Japanese, even those with hypercholesterolemia, might not have had higher serum TC levels throughout their entire lives. Especially for elderly women, the exposure period to high serum TC could be shorter than for men, as serum TC levels in women before menopause are considerably lower than in men. This could be one reason for the lack of relation between serum TC levels and CHD in elderly women. Furthermore, our findings could be explained by survivor bias.[19] In other words, elderly participants in the present study might have some beneficial characteristics that helped them avoid CHD due to hypercholesterolemia.

In the present study, serum TC levels were not associated with cerebral infarction in any age or sex group. This finding is different from several other large-scale cohort studies in Western populations, which showed a weak but positive association between serum TC and cerebral infarction,[3,4,20,21] but is similar to previous cohort studies in Japan and some Western countries.[2,22–25] These discrepancies could be due to differences in the prevalence of subtypes of cerebral infarction. Cerebral infarction consists of 3 major pathological subtypes—namely lacunar, atherothrombotic, and cardioembolic infarctions. In some Western populations, atherothrombotic infarctions account for approximately one half of cerebral infarctions,[26] whereas in some Japanese populations, it accounts for only approximately one quarter of cerebral infarctions. Furthermore, cardioembolic infarction is more common than atherothrombotic infarction, accounting for 23% to 38% of cerebral infarctions.[27–30] The Hisayama study in a Japanese community showed that serum low-density lipoprotein cholesterol was associated positively with only atherothrombotic infarctions, whereas it was associated negatively with cardioembolic infarction and showed no association with lacunar infarction.[27] One possible mechanism for the inverse association between low TC and cardioembolic infarction is that low TC increases the occurrence of atrial fibrillation,[31] which is the predominant risk factor for cardioembolic infarction. The aforementioned heterogeneity in pathological background of cerebral infarction might be a major reason for the variation in findings observed among cohort studies.

In the present study, serum TC levels were associated negatively with risk of cerebral hemorrhage death. This result is similar to previous studies in Japan and the United States.[20,32,33] Low serum TC can induce angionecrosis, possibly in coexistence with hypertension. Experimental evidence from one study showed that a hypercholesterolemic diet given to spontaneously hypertensive rats reduced angionecrosis of smooth muscle cells in intracerebral arteries, leading to the occurrence of hemorrhagic stroke.[34] Low serum TC also can reflect nutritional status, which is known to be related to death after onset. Further basic, clinical, and epidemiological studies on these associations are required. Consequently, because TC can be associated inversely with the cardioembolic type of cerebral infarction in addition to cerebral hemorrhage, it is not unexpected that TC was associated inversely with TS death in the present study, similar to another recent report from Japan.[35]

Several limitations need to be considered when these results are interpreted. First, we did not take into account the use or nonuse of cholesterol-lowering therapy, including statins, the main drug used to treat hypercholesterolemia. However, baseline surveys in 7 cohorts of EPOCH-JAPAN were performed before the introduction of the first statin in Japan (1989).[36] Another 3 cohorts were also started around 1990, and therefore it is likely that only a few participants were taking statins at baseline. Consequently, it is not likely that this limitation would have changed our inferences substantially. Second, the results were based on single health examinations and were likely to have underestimated the true association because of regression dilution bias. Third, the participants in the study volunteered to receive their health examinations, and for that reason their characteristics could be somewhat different from those of nonparticipants or the general population. This would influence the absolute measure of effect (mortality rate) and could therefore underestimate the risk. However, these differences have little effect on relative measures of effect, such as HRs. Fourth, the number of deaths from CHD in the study might not be sufficient in elderly women to estimate the association with serum TC.

In conclusion, this largest-scale pooled analysis specific to Asians found a significant positive relation between serum TC and CHD in both middle-aged men and middle-aged women who were 40 to 69 years of age and did not have a past history of CVD, although a similar relation in elderly participants was not confirmed. Further research is therefore warranted in elderly men and women.

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Disclosures

None.

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REVIEW

Blood Cholesterol Level and Risk of Stroke in Community-based or Worksite Cohort Studies: A Review of Japanese Cohort Studies in the Past 20 years

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Evidence of the causal relationship between hypercholesterolemia and coronary artery disease (CAD) has been established worldwide. However, little attention has been paid to the relationship between hypercholesterolemia and stroke, despite stroke being the most common cardiovascular disease in Japan. We therefore reviewed cohort studies that investigated this relationship in the Japanese population over the past 20 years, and compared their findings with clinical trials and cohort studies in Western countries. Fourteen cohort studies were carried out in Japan during this period. The number of subjects in the studies ranged from 1621 to 91,219 and the mean follow-up period ranged from 7.6 to 32 years. The majority of studies showed no association between hypercholesterolemia and total stroke. However, one report showed a positive association between low-density lipoprotein cholesterol and atherothrombotic cerebral infarction. The relationship between hypercholesterolemia and cerebral infarction may be modified by the proportion of atherothrombotic infarctions in the population surveyed. Randomized controlled trials on statins have shown a substantial reduction in cerebral infarction, and so the discrepancy between cohort studies and clinical trials requires further study. However, some studies have reported that subjects with low blood cholesterol are more susceptible to intracerebral hemorrhage. Two hypotheses have been proposed to explain this association between low cholesterol and intracerebral hemorrhage. First, low blood cholesterol may induce angionecrosis, possibly in combination with hypertension, and second, low blood cholesterol may reflect a poor nutritional status. Either way, further continuous research in various fields of medical science is required to clarify the overall effect of blood cholesterol on stroke in humans. (Keio J Med 61 (3) : 79–88, September 2012)

***Keywords*: cholesterol, stroke, cohort studies, cerebral infarction, intracerebral hemorrhage**

Introduction

The causal relationship between coronary artery disease (CAD) and high serum levels of total cholesterol (TC) or low-density lipoprotein cholesterol (LDLC) is well established.[1–4] Serum cholesterol levels are therefore the main target for lipid management and prevention of atherosclerotic disease in the guidelines of the majority developed countries. Furthermore, some U.S. cohort studies have suggested that non-high-density lipoprotein cholesterol (non-HDLC) may be a better predictor of CAD.[5,6] Non-HDLC reflects the total cholesterol concentration of all atherogenic lipoproteins and is calculated by subtracting the level of high-density lipoprotein cholesterol (HDLC) from that of TC. The Health and Medical Service Law for the Elderly was enacted in 1982, and as

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a result, all Japanese citizens aged 40 years and over have had the opportunity to undergo screening for TC from 1986 and screening for HDLC from 1992. Citizens with dyslipidemia are also provided with health services such as health education to prevent CAD. For this screening system, the basis was changed from TC to LDLC in April 2008.

In contrast, little attention has been paid to the relationship between hypercholesterolemia and stroke, despite stroke being the most common cardiovascular disease in Japan.[7] There is evidence that the mean cholesterol level in the Japanese population has been lower than that in most Western countries for many decades and this is associated with a lower CAD mortality than in Western populations.[7] However, to clarify the relationship between hypercholesterolemia and stroke it is necessary to carry out original cohort studies. This review article focuses on a series of cohort studies performed in Japanese community-based or worksite populations. These studies provide evidence that partially establishes the long-held, but unconfirmed, belief that hypercholesterolemia is associated with stroke.

Overview of Japanese Cohort Studies Carried Out in the Past Two Decades

We performed a PubMed literature search of studies published between January 1991 and August 2011. We used the search terms "*cholesterol*" in combination with "*cerebrovascular disease* or *stroke*," "*Japan* or *Japanese*" and "*cohort studies*." Studies were selected using the following criteria: (1) reports were published in English, (2) studies were performed in Japan, (3) studies were of the prospective cohort type (including nested case–control studies), and (4) statistical analyses were carried out on the relationship between cholesterol levels (TC, LDLC, non-HDLC) and stroke endpoint (fatal and/or non-fatal stroke including its subtypes) adjusted at least for age and hypertension (including blood pressure levels). Finally, we selected potentially relevant articles based on the title and the abstract, and obtained the full text of these articles for detailed review.

Table 1 summarizes the cohort studies carried out on Japanese populations over the past 20 years, listed in chronological order of date of publication. Of the 14 studies,[8–21] 2 studies were on worksite populations[8,18] and the remaining 12 studies were on residents of various communities. All but one of the studies were cohort studies, the exception being a nested case–control study.[13] The number of subjects ranged from 1621 to 91,219, and the mean or median follow-up periods ranged from 7.6 to 32 years. In the cohort studies, the endpoint in eight studies was the first occurrence of stroke and/or its subtypes during the follow-up period,[8–10,14–16,18,19] and in six studies, the endpoint was death due to stroke and/or its subtypes.[11–13,17,20,21] Apart from two studies,[10,16] all the investigations also examined the relationship between TC (or LDLC or non-HDLC) and myocardial infarction (MI) or CAD. A positive association between hypercholesterolemia and CAD was shown in all but two of the studies[20,21] (data not shown in the table). In contrast, the majority of studies showed no association between hypercholesterolemia and total stroke events. Furthermore, some studies reported that community residents with low serum TC or LDLC levels were *more* likely to develop intracerebral hemorrhage.[11–13,17,21] Only one recent report from the Hisayama study showed a positive association between LDLC and atherothrombotic cerebral infarction.[15] Several of the above-mentioned studies are discussed in more detail below.

Summary of Key Studies

1. NIPPON DATA80

The cohort studies of the National Survey on Circulatory Disorders, 1980, Japan, are referred to as NIPPON DATA80 (National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged, 1980).[11,12] The baseline surveys were performed in 1980. In 1980 approximately 10,000 community residents aged 30 years or older from 300 randomly selected districts participated in a survey. **Figure 1** shows the relationship between TC and death due to CAD in the 17.3-year follow-up period of NIPPON DATA80.[12] A positive, graded relationship was observed between the two parameters in men. Although a graded relationship was not observed in women, the group with the highest TC had a significantly increased risk of death from CAD. In contrast, there was no association between TC and the risk of stroke mortality (**Fig. 2**). Limited analysis showed there was also no association between TC and death due to cerebral infarction. However, this study had some limitations. The first is the possible misclassification of stroke diagnosis because the endpoints were determined from death certificates. The second is that TC includes HDLC, a protective factor for atherosclerosis. These issues were therefore addressed by other cohort studies.

2. The Suita study

The Suita study was established in 1989 and invited 12,200 Japanese urban residents of Suita City, Osaka, to participate. The participants were 30–79 years old and were selected randomly from the municipal population registry. Of these, 6485 men and women took part in a baseline medical examination at the National Cardiovascular Center between September 1989 and February 1994. The endpoints of this study were the first incidence of MI or stroke. In this study,[14] the relative risk for MI in the top quintile of LDLC (≥151 mg/dl in men and ≥164 mg/dl in

Table 1 Overview of community-based or worksite cohort studies investigating blood cholesterol levels and stroke in Japan published between January 1991 and August 2011*

Author	Study name	Publication year	Number of subjects	Follow-up years	Endpoints for stroke	Results concerning stroke
Kitamura A, et al.[8]	-	1994	6408 men (Worksite)	7.7	Incidence of total stroke.	TC and total stroke: No relationship.
Nakayama T, et al. [9]	Shibata Study	1997	2302 men and women (Community)	15.5	Incidence of total stroke, cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage.	TC and all total stroke: No relationship. TC and cerebral infarction: No relationship. TC and intracerebral hemorrhage: No relationship.
Tanizaki Y, et al. [10]	Hisayama Study	2000	1621 men and women (Community)	32	Incidence of cerebral infarction and its subtypes: cardioembolic, lacunar, and atherothrombotic.	TC and cerebral infarction: No relationship. TC and lacunar type: No relationship. TC and atherothrombotic type: No relationship. TC and cardioembolic type: No relationship. in men and inverse relationship in women.
Okamura T, et al. [11]	NIPPON DATA80	2003	9216 men and women (Community)	13.2	Death due to total stroke, intracerebral hemorrhage, and cerebral infarction.	TC and total stroke: No relationship. TC and cerebral infarction: No relationship. TC and intracerebral hemorrhage: Inverse relationship in men.
Okamura T, et al. [12]	NIPPON DATA80	2007	9216 men and women (Community)	17.3	Death due to total stroke, intracerebral hemorrhage, and cerebral infarction.	TC and total stroke: No relationship. TC and cerebral infarction: No relationship. TC and intracerebral hemorrhage: Inverse relationship.
Cui R, et al. [13]	JACC Study	2007	345 cases and 345 controls from 39,242 men and women of a cohort study. (Community-based nested case–control study)	10	Death due to total stroke, subarachnoid hemorrhage, intracerebral hemorrhage, and cerebral infarction.	TC and total stroke: Inverse relationship. TC and intracerebral hemorrhage: Inverse relationship. TC and subarachnoid hemorrhage: No relationship. TC and cerebral infarction: No relationship.
Okamura T, et al. [14]	Suita Study	2009	4694 men and women (Community)	11.9	Incidence of total stroke and cerebral infarction.	LDLC and total stroke: No relationship. LDLC and cerebral infarction: No relationship. Non-HDLC and total stroke: No relationship. Non-HDLC and cerebral infarction: No relationship.
Imamura T, et al. [15]	Hisayama Study	2009	2351 men and women (Community)	19	Incidence of total stroke, cerebral infarction and its subtypes (cardioembolic, lacunar, and atherothrombotic) and hemorrhagic stroke (subarachnoid hemorrhage and intracerebral hemorrhage).	LDLC and total stroke: No relationship. LDLC and cerebral infarction: No relationship. LDLC and atherothrombotic type: Positive relationship. LDLC and lacunar type: No relationship. LDLC and cardioembolic type: Inverse relationship. LDLC and hemorrhagic stroke: No relationship.

Author	Study name	Publication year	Number of subjects	Follow-up years	Endpoints for stroke	Results concerning stroke
Ishikawa S, et al. [16]	JMS Cohort Study	2009	12,276 men and women (Community)	10.7	Incidence of total stroke and cerebral infarction.	TC and total stroke: No relationship. TC and cerebral infarction: No relationship.
Noda H. et al. [17] **	Ibaraki Prefectural Cohort Study	2009	91,219 men and women (Community)	10.3	Death due to total stroke, intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral infarction.	LDLC and total stroke: Inverse relationship. LDLC and subarachnoid hemorrhage: No relationship. LDLC and intracerebral hemorrhage: Inverse relationship. LDLC and cerebral infarction: No relationship.
Li Q, et al. [18]	YKK study	2010	1794 men (Worksite)	12	Incidence of total stroke.	TC and total stroke: No relationship.
Tanabe N, et al. [19]	JALS Study	2010	22,430 men and women (Community)	7.6	Incidence of total stroke, intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral infarction.	TC and total stroke: No relationship. TC and cerebral infarction: No relationship. TC and intracerebral hemorrhage: No relationship. TC and subarachnoid hemorrhage: No relationship. Non-HDLC and total stroke: No relationship. Non-HDLC and cerebral infarction: No relationship. Non-HDLC and intracerebral hemorrhage: No relationship. Non-HDLC and subarachnoid hemorrhage: No relationship.
Nago N, et al. [20]	JMS cohort study	2011	12,334 men and women (Community)	11.9	Death due to total stroke, hemorrhagic stroke (subarachnoid hemorrhage and intracerebral hemorrhage), and cerebral infarction.	TC and total stroke: No relationship. TC and hemorrhagic stroke: No relationship. TC and cerebral infarction: No relationship.
Tsuji H, et al. [21]	-	2011	16,461 men and women (Community)	10.9	Death due to total stroke, hemorrhagic stroke (subarachnoid hemorrhage and intracerebral hemorrhage), and cerebral infarction.	TC and total stroke: Inverse relationship. TC and hemorrhagic stroke: Inverse relationship. TC and cerebral infarction: Inverse relationship.

* Although the nomenclatures of subtypes of stroke were not unified among the cohort studies, they are unified in this table for the reader's convenience.
**Serum LDLC levels in this cohort were calculated by the Friedewald formula, with the majority of serum samples being collected in the non-fasting state.
NIPPON DATA, National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged; JACC Study: The Japan Collaborative Cohort Study; JMS Cohort Study, Jichi Medical School Cohort Study; JALS Study, Japan Arteriosclerosis Longitudinal Study.
TC, total cholesterol; LDLC, low-density lipoprotein cholesterol; non-HDLC, non-high-density lipoprotein cholesterol.