tween participants and nonparticipants, because the main denial reason for participation in this study was not a health problem. Age- and sex-adjusted systolic blood pressures were 127 mm Hg for participants and 128 mm Hg for nonparticipants (P=0.08). To achieve a minimum of failure study subjects, we performed close follow-up with health questionnaires annually and health checkups every 2 years.

In conclusion, high-normal blood pressure is a risk factor for MI and stroke in general Japanese urban men. Approximately 20% and 8% of CVD incidences can be attributed to normal and high-normal blood pressure in both men and women, respectively. To prevent the incidence of CVD, it is necessary for subjects with high-normal blood pressure to attempt to control these values through lifestyle modifications.

Perspectives

Although it is well accepted that hypertension is a strong risk factor for total mortality and CVD all over the world, only a few studies have addressed the absolute and relative risks of CVD for the population with blood pressure values in the high-normal range. In this study, the impact of high-normal blood pressure on the incidence of CVD was examined in a general urban population cohort in Japan. Blood pressure categories were defined on the basis of the ESH-ESC 2007 criteria. In 64 391 person-years of follow-up, 346 CVD events were identified. Compared with the optimal blood pressure group, the multivariable HR of CVD for high-normal blood pressure was 2.5 times in men but was not statistically significant in women. This might be due to a postmenopausal effect, higher frequency of controlled or medication for hypertension, and white coat hypertension in women compared with those in men, but it should be researched further whether these reasons can be applied in women. The risks of MI and stroke for each blood pressure category were similar to those of CVD. Approximately 20% and 8% of CVD incidences can be attributed to prehypertension in men and women, respectively. It is a remarkable finding that one fifth of CVD incidence is derived from prehypertension in men. Our results suggest that it is necessary for subjects with high-normal blood pressure to attempt to control blood pressure through lifestyle modifications to prevent the incidence of CVD.

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Disclosures

None.

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Low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort study: The Suita study

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ABSTRACT

Objective: Only a small number of population-based cohort studies have directly compared the predictive value of low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDLC) for coronary artery disease in Asian populations, such as Japan.
Methods: We performed an 11.9-year cohort study of 4694 men and women, aged 30–74 years, selected randomly from an urban general population in Japan. Baseline LDL-C levels were estimated using the Friedewald formula. The predictive values of LDL-C and non-HDLC for myocardial infarction (MI) and stroke were compared.
Results and conclusion: During the follow-up period, there were 80 incident cases of MI and 139 of stoke, comprised of 23 intracerebral hemorrhages, 85 cerebral infarctions and 31 other types of stroke. The Hazard ratio (HR) for MI was highest in the top quintile of LDL-C (HR: 3.03, 95% CI, 1.32–6.96) when male and female data were combined. The HR for MI was also highest in the top quintile of non-HDLC (HR: 2.97, 95% CI, 1.26–6.97). Analysis of trends showed a significant positive relationship between MI incidence and serum LDL-C and non-HDLC levels (both $P = 0.02$). However, there was no relationship between the incidence of any subtype of stroke and either LDL-C or non-HDLC. The predictive value of LDL-C and non-HDLC for MI, assessed by calculating the differences in the −2 logarithm likelihood (−2 ln [L]) and area under the curve (AUC), were almost similar.

1. Introduction

The causal relationship between high levels of serum low-density lipoprotein cholesterol (LDL-C) and coronary artery disease (CAD) is well established [1–5]. Blood LDL-C levels are therefore the main target for lipid management in the majority of guidelines of developed countries for preventing atherosclerotic disease [3–5]. Some US cohort studies have also suggested that non-high-density lipoprotein (non-HDLC) may be a better predictor of CAD [6,7]. However, to our knowledge, only one population-based cohort study has directly compared the predictive value of these lipid markers for CAD in an Asian population [8], which have a lower incidence of coronary artery disease, but a higher risk of stroke than Western populations [9–12]. Furthermore, although it has not been shown that there is a positive relationship between the risk of any type of stroke and high serum levels of total cholesterol (TC) in the Japanese population [9,10], the effects on stroke incidence of the closely related lipid fractions, LDL-C and non-HDLC, have not been evaluated.

The purpose of this study was therefore to investigate the predictive value of LDL-C and non-HDLC for the incidence of CAD and stroke in a Japanese urban population over an 11.9-year period. Our *a priori* hypothesis was that both LDL-C and non-HDLC may be useful predictors of CAD risk, but not of stroke risk.

2. Methods

2.1. Populations

The Suita study [13,14], a cohort study of cardiovascular disease, was established in 1989 and included 12,200 Japanese urban residents of Suita City, Osaka. The participants, aged 30–79 years,

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were selected randomly from the municipality population registry. Of these, 6485 men and women had a baseline medical examination at the National Cardiovascular Center between September 1989 and March 1994 (participation rate: 53.2%). Of the 6485 participants, a total of 1791 were excluded for the following reasons: past history of coronary heart disease or stroke ($n = 208$), nonperiodical participation in baseline survey ($n = 79$), aged 75 or older ($n = 343$), non-fasting visit ($n = 153$), use of lipid-lowering agents such as statins ($n = 106$), serum triglyceride $\geq$4.5 mmol/l (400 mg/dl) ($n = 98$) and missing information at the baseline survey or lost to follow-up ($n = 804$). The data of the remaining 4694 participants (2169 men and 2525 women) were then analyzed. Informed consent was obtained from all participants. This cohort study was approved by the Institutional Review Board of the National Cardiovascular Center.

2.2. Baseline examination

Blood samples were collected at the National Cardiovascular Center (NCVC) after the participants had fasted for at least 12 h. The samples were centrifuged immediately and a routine blood examination that included serum total cholesterol (TC), HDL cholesterol, triglyceride and glucose levels then carried out. LDL-C was estimated using the Friedewald formula [15]. Non-HDLC was calculated by subtracting HDL-C from TC.

Blood pressures were measured in triplicate on the right arm in the seated position after 5 min rest by well-trained physicians using a standard mercury sphygmomanometer. The average of the second and third measurements was used in the analyses. Hypertension was defined as either a systolic blood pressure $\geq$140 mmHg, a diastolic blood pressure $\geq$90 mmHg or the use of antihypertensive agents. Diabetes was defined as a fasting serum glucose $\geq$7.0 mmol/l (126 mg/dl), the use of anti-diabetic agents, or both. Height in stockings and weight in light clothing were measured. Public health nurses obtained information on the smoking, drinking and medical histories of the participants.

2.3. Endpoint determination

The participants were followed until December 31, 2005. The first step in the survey involved checking the health status of all participants by repeated clinical visits every 2 years and yearly questionnaires sent by mail or conducted by telephone. Informed consent for review of in-hospital medical records was obtained from 86.2% participants who were suspected of having had a myocardial infarction (MI) or stroke. The medical records were reviewed by registered hospital physicians or research physicians who were blinded to the baseline information.

The criteria for definite and probable MI were defined according to the criteria of the MONICA (Monitoring Trends and Determinants of Cardiovascular Disease) project [16], which requires evidence from an electrocardiogram (ECG), cardiac enzymes and/or autopsy. Stroke was defined according to the National Survey of Stroke criteria [17], which requires the rapid onset of a constellation of neurological deficits lasting at least 24 h or until death. The strokes were classified as either ischemic stroke (thrombotic or embolic), intracerebral hemorrhage, subarachnoid hemorrhage or undetermined type. A definite stroke was defined by autopsy or on the basis of diagnostic imaging, such as computed tomography or magnetic resonance imaging.

Cases with typical clinical symptoms, detected in the clinical visit during follow-up surveillance, but without informed consent for an in-hospital medical records survey, were defined as possible MI or stroke. Furthermore, to complete the surveillance for fatal MI and stroke, we conducted a systematic search for death certificates. All death certificates in Japan are forwarded to the Ministry of Health, Welfare, and Labor and coded for National Vital Statistics. We classified fatal MI and stroke listed on the death certificate, but not registered on our surveillance system, as possible MI and stroke.

2.4. Statistical analysis

Sex-specific analysis was performed. We set the cut-off points for serum LDL-C and non-HDLC according to the quintile ranges. For baseline characteristics, analysis of variance for means or Chi-square tests for proportions were used. The multivariable-adjusted hazard ratio (HR) of LDL-C and non-HDLC for MI or stroke was calculated using proportional hazards model adjusted for age, hypertension, diabetes, HDL-C, body mass index (BMI), smoking (never-smoked; ex-smoker; current smoker) and drinking (never-drank; ex-drinker; regular drinker). Sex-combined analysis with further adjustment for sex was also carried out.

Separate models with LDL-C or non-HDLC levels as ordinal variables (median of LDL-C or non-HDLC quintile) were fitted to the other risk factor adjusted models (test for trend). The differences between the -2 logarithm likelihood (-2 ln [L]) in each lipid added model and the -2 ln [L] in other risk factor adjusted models were calculated. These differences had an approximate χ^2 distribution with 1 d.f. These χ^2 values assess which lipid had the greatest predictive value in other risk factor adjusted models. The ability to predict which people developed cardiovascular disease was also assessed by calculating the area under the receiver-operating characteristic (ROC) curve (AUC). This curve showed the predictive probability of the variables using logistic regression analysis and the same covariates used in the multivariable model of test for trend. Furthermore, the predictive values of the ratio of LDL-C to HDL-C (LDL-C/HDL-C) and the ratio of non-HDLC to HDL-C (non-HDLC/HDL-C) for myocardial infarction (MI) and stroke were also compared.

All confidence intervals were estimated at the 95% level and significance was set at a P value of <0.05. The Statistical Package for the Social Sciences (SPSS Japan Inc. version 15.0J, Tokyo, Japan) was used for all the analyses.

3. Results

The mean and standard deviation of serum LDL-C in the baseline survey was 3.23 $\pm$ 0.82 mmol/l (124.9 $\pm$ 31.7 mg/dl) in men and 3.49 $\pm$ 0.90 mmol/l (134.8 $\pm$ 34.9 mg/dl) in women. The mean baseline serum non-HDLC was 3.90 $\pm$ 0.89 mmol/l (151.1 $\pm$ 34.5 mg/dl) in men and 4.01 $\pm$ 1.01 mmol/l (155.2 $\pm$ 39.1 mg/dl) in women.

Table 1 shows the baseline characteristics of the participants in each LDL-C quintile. In both sexes, there were significant differences in the mean values for age, non-HDLC, HDL-C and BMI. These variables, with the exception of HDL-C, tended to be higher in the higher LDL-C groups. Serum HDL-C levels were lower in the higher LDL-C groups. There was no significant difference in the prevalence of hypertension and diabetes in the quintiles for men, whereas the prevalence of these conditions in women was higher in the higher LDL-C groups. In both sexes, the proportion of current drinkers was lower in the higher LDL-C groups, whereas the proportion of current smokers was highest in the lowest LDL-C group. The relationships between non-HDLC quintiles and the above-mentioned baseline characteristics were almost similar (data not shown in the table).

The total person-years studied was 56,196 (25,420 for men and 30,776 for women), with a mean follow-up period of 11.9 years. During the follow-up period, there were 80 incident cases of MI (41 definite and 39 probable MIs) and 139 of stoke (102 definite and 37

Table 1
Sex-specific mean and prevalence of risk characteristics at baseline in an 11.9-year prospective study of 4694 Japanese men and women

LDL cholesterol quintiles	Q1	Q2	Q3	Q4	Q5	*P*-values
Men						
Numbers	447	435	427	438	422	
LDL cholesterol (Stratum Mean), mmol/l	2.13	2.80	3.22	3.66	4.40	
Age, year	54.0 (12.7)	53.8 (12.6)	52.5 (12.4)	54.7 (12.1)	55.6 (11.0)	0.005
Non-HDL cholesterol, mmol/l	2.84 (0.52)	3.44 (0.39)	3.87 (0.34)	4.31 (0.32)	5.13 (0.56)	<0.001
HDL cholesterol, mmol/l	1.33 (0.39)	1.29 (0.36)	1.29 (0.32)	1.26 (0.30)	1.21 (0.28)	<0.001
BMI, kg/m^2	22.1 (2.9)	22.6 (2.8)	22.9 (2.8)	23.2 (2.6)	23.4 (2.7)	<0.001
Hypertension, %	29.5	27.4	30.4	31.3	33.6	0.364
Diabetes, %	8.1	4.6	4.4	4.6	5.9	0.091
Drinking						
Usual/ex-/never-, %	81.9/2.7/15.4	78.2/2.8/19.1	79.6/1.6/18.7	71.7/5.3/23.1	70.4/4.7/24.9	<0.001
Smoking						
Current/ex-/never-, %	59.3/25.5/15.2	55.4/26.9/17.7	46.6/31.1/22.2	46.6/31.1/22.4	48.1/31.8/20.1	0.002
Women						
Numbers	524	498	513	498	492	
LDL cholesterol (Stratum Mean), mmol/l	2.33	2.98	3.44	3.92	4.82	
Age, year	45.5 (11.4)	49.9 (11.9)	52.7 (11.3)	56.3 (10.6)	57.8 (9.1)	<0.001
Non-HDL cholesterol, mmol/l	2.77 (0.42)	3.47 (0.32)	3.96 (0.31)	4.50 (0.32)	5.46 (0.71)	<0.001
HDL cholesterol, mmol/l	1.54 (0.36)	1.49 (0.36)	1.48 (0.35)	1.45 (0.33)	1.40 (0.31)	<0.001
BMI, kg/m^2	21.0 (2.7)	21.8 (3.2)	22.3 (3.3)	22.6 (3.2)	23.2 (3.3)	<0.001
Hypertension, %	12.8	19.3	23.4	29.9	37.8	<0.001
Diabetes, %	1.5	2.8	3.1	4.0	4.7	0.050
Drinking						
Usual/ex-/never-, %	41.8/2.3/55.9	36.5/1.0/62.4	32.7/1.4/65.9	28.3/1.8/69.9	29.1/1.6/69.3	<0.001
Smoking						
Current/ex-/never-, %	16.4/4.6/79.0	12.7/3.8/83.5	9.6/2.1/88.3	10.8/3.4/85.7	11.6/3.7/84.8	0.015

HDL means high-density lipoprotein. LDL means low-density lipoprotein. S.D. means standard deviations. Brackets indicate standard deviation. Analysis of variance was used for comparisons of multiple group means and the Chi-square test was used to compare frequencies.

probable strokes), comprised of 23 intracerebral hemorrhages, 85 cerebral infarctions and 31 other types of stroke.

Table 2 shows the number of incident cases and multivariable-adjusted HRs for MI and cerebral infarction stratified by LDL-C quintile. In women, the bottom and second quintiles and the third and fourth quintiles were combined into two categories due to the small number of cardiovascular events. In both sexes, the HR for MI was highest in the top quintile of LDL-C, although the value in women was not statistically significant (HR 3.73; 95% CI 1.25–11.1 for men: HR 1.78; 95% CI 0.66–4.77 for women). In the test for trend, serum LDL-C showed a significant positive association with MI when the data from men and women were combined

Table 2
The numbers of cases and multivariable-adjusted HRs and 95% C.I.s for myocardial infarction and cerebral infarction according to serum LDL cholesterol level in an 11.9-year prospective study of 4694 Japanese men and women

LDL cholesterol quintiles	LDL-C range (mmol/l)	No. of persons	Person-years	Myocardial infarction			Cerebral infarction		
				No. of events	HR[a]	95% C.I.	No. of events	HR[a]	95% C.I.
Men									
Q1	<2.54	447	5,129	4	1.00		14	1.00	
Q2	2.54–3.03	435	5,122	15	3.56	1.18, 10.8	9	0.61	0.26, 1.42
Q3	3.04–3.43	427	4,945	9	2.60	0.80, 8.5	15	1.31	0.63, 2.72
Q4	3.44–3.90	438	5,201	10	2.25	0.70, 7.2	13	0.90	0.42, 1.94
Q5	3.91–	422	5,023	18	3.73	1.25, 11.1	6	0.42	0.16, 1.10
					P for trend	0.08		*P* for trend	0.22
Women									
Q1 + Q2[b]	<3.21	1022	12,473	6	1.00		7	1.00	
Q3 + Q4[b]	3.22–4.22	1011	12,279	5	0.45	0.14, 1.49	11	0.82	0.31, 2.15
Q5	4.23	492	6,023	13	1.78	0.66, 4.77	10	1.13	0.42, 3.02
					P for trend	0.14		*P* for trend	0.88
Men and women combined									
Q1		971	11,548	7	1.00		19	1.00	
Q2		933	11,176	18	2.37	0.97, 5.61	11	0.53	0.25, 1.12
Q3	[c]	940	11,102	11	1.57	0.61, 4.08	18	0.95	0.49, 1.82
Q4		936	11,323	13	1.40	0.56, 3.55	21	0.84	0.44, 1.59
Q5		914	11,046	31	3.03	1.32, 6.96	16	0.63	0.32, 1.24
					P for trend	0.02		*P* for trend	0.47

LDL means low-density lipoprotein.

[a] HR means hazard ratio and 95% C.I. means 95% confidence interval. The HR was adjusted for age, body mass index, diabetes, HDL cholesterol, cigarette smoking category and alcohol intake category by a Cox proportional hazard model. Sex was also adjusted in the men and women combined model.

[b] These groups were combined due to small number of cardiovascular event. The cut-off points were 2.73 between Q1 and Q2, and 3.68 between Q3 and Q4, respectively.

[c] Sex-specific quintiles were used for analysis.

Table 3
The numbers of cases and multivariable-adjusted HRs and 95% C.I.s for myocardial infarction and cerebral infarction according to serum non-HDL cholesterol level in an 11.9-year prospective study of 4694 Japanese men and women

Non-HDL cholesterol quintiles	Non-HDLC range (mmol/l)	No. of persons	Person-years	Myocardial infarction			Cerebral infarction		
				No. of events	HR[a]	95% C.I.	No. of events	HR[a]	95% C.I.
Men									
Q1	<3.18	445	5,123	6	1.00		11	1.00	
Q2	3.18–3.68	450	5,195	14	2.34	0.89, 6.16	13	1.21	0.54, 2.73
Q3	3.69–4.12	426	5,077	7	1.21	0.40, 3.64	12	1.26	0.54, 2.91
Q4	4.13–4.63	428	5,041	10	1.49	0.53, 4.16	11	0.97	0.41, 2.31
Q5	4.64	420	4,982	19	2.61	1.00, 6.80	10	0.98	0.40, 2.40
					P for trend	0.12		*P* for trend	0.79
Women									
Q1 + Q2[b]	<3.70	1043	12,821	4	1.00		7	1.00	
Q3 + Q4[b]	3.71–4.87	1010	12,205	7	0.76	0.21, 2.72	11	0.67	
Q5	4.88	472	5,750	13	1.77	0.50, 6.25	10	0.80	
					P for trend	0.10		*P* for trend	
Men and women combined									
Q1		998	11,931	7	1.00		15	1.00	
Q2		940	11,208	17	2.35	0.97, 5.69	16	1.03	0.50, 2.10
Q3	[c]	947	11,412	11	1.38	0.53, 3.60	14	0.83	0.40, 1.76
Q4		917	10,911	13	1.40	0.55, 3.57	20	1.03	0.51, 2.06
Q5		892	10,732	32	2.97	1.26, 6.97	20	0.99	0.48, 2.03
					P for trend	0.02		*P* for trend	0.96

HDL means high-density lipoprotein.

[a] HR means hazard ratio and 95% C.I. means 95% confidence interval. The HR was adjusted for age, body mass index, hypertension, diabetes, HDL cholesterol, cigarette smoking category and alcohol intake category by a Cox proportional hazard model. Sex was also adjusted in the men and women combined model.

[b] These groups were combined due to small number of cardiovascular event. The cut-off points were 3.21 between Q1 and Q2, and 4.26 between Q3 and Q4, respectively.

[c] Sex-specific quintiles were used for analysis.

($P=0.02$). A similar trend was observed when the endpoint was limited to definite MIs by the criteria of the MONICA project ($P=0.01$, data not shown in the table). The incidence for cerebral infarction was not related to LDL-C levels in either sex. The incidences of intra-cerebral hemorrhage, other types of stroke and total stroke were also not associated with LDL-C levels (data not shown in the table).

Table 3 shows the results stratified by non-HDLC. The HR for MI was highest in the top quintile of non-HDLC in both sexes, although in women the value did not reach statistical significance (HR 2.61; 95% CI 1.00–6.8 for men: HR 1.77; 95% CI 0.50–6.25 for women). In men, the HR for MI was highest in the top quintile of non-HDLC (HR 2.61; 95% CI 1.00–6.80). In the test for trend, serum non-HDLC showed a significant positive association with MI when the data of men and women were combined ($P=0.02$). A similar trend was observed when the endpoint was limited to define MIs ($P=0.01$, data not shown in the table). The incidence of cerebral infarction was not associated with non-HDLC levels in either sex. The other types of stroke and total stroke were also not associated with non-HDLC level (data not shown in the table).

To determine the predictive values of LDL-C and non-HDLC, the difference between the −2 ln [L] of model including each lipid and the −2 ln [L] of other variable-adjusted models was calculated. The χ^2 values for LDL-C and non-HDLC were almost the same at 5.71 ($P=0.02$) for LDL-C and 5.49 ($P=0.02$) for non-HDLC. Furthermore, the AUC of the ROC curves based on predictive probability targeting for MI were also estimated. The AUC of LDL-C and non-HDLC were the same at 0.82.

We calculated the hazard ratios of LDL-C/HDL-C and non-HDLC/HDL-C, and compared the predictive values of these for the incidence of MI and stroke. Both ratios were significantly associated with the increased risk for MI but not with any types of stroke. The multivariable HRs of LDL-C/HDL-C and non-HDLC/HDL-C for MI were 1.32 [95% CI, 1.07–1.61] and 1.25 [95% CI, 1.07–1.47], respectively. Furthermore, the χ^2 values between the −2 ln (L) of each lipid added model and non-added model for LDL-C/HDL-C and non-HDLC/HDL-C were almost the same at 7.34 ($P=0.01$) for LDL-C/HDL-C and 7.06 ($P=0.01$) for non-HDLC/HDL-C. The AUC of the ROC curves based on predictive probability were also the same. Apparently, because non-HDLC/HDLC was expressed as [(TC/HDLC) − 1], the HR and predictive value for TC/HDLC were just the same as those of non-HDLC/HDLC.

When the participants were divided in two groups using the median value of serum triglycerides (1.12 mmol/l, 99 mg/dl), the results of all the analyses listed above were similar.

4. Discussion

This 11.9-year cohort study of a Japanese urban population showed a positive association between serum LDL-C or non-HDLC levels and increased risk of MI, but not with any type of stroke. Furthermore, we found there was no substantial difference in the predictive value for MI incidence between LDL-C and non-HDLC. To our knowledge, this is the first cohort study in an urban Japanese population on the relationship between serum lipids and cardiovascular events.

The role of LDL-C in the development of atherosclerosis and the beneficial effect of LDL-C lowering therapy are well established, especially in Western populations [1–4] Our study indicated there is also a positive relationship between serum LDL-C and CAD events in community-dwelling Japanese with no history of cardiovascular disease or use of lipid-lowering agents, such as statins. A recent large clinical trial in Japan [18], the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA study), also have shown an 18% reduction in mean LDL-C (from 4.05 mmol/l to 3.31 mmol/l) was associated with a 33% decreased risk for CAD. These results suggested strongly that management of serum LDL-C levels is as effective for reducing CAD in Japan as it is in Western countries.

Non-HDLC levels are thought to be an alternative predictor that can substitute for LDL-C in patients with hypertriglycemia

[3]. Non-HDLC reflects the total cholesterol concentration of all atherogenic lipoproteins. Several previous studies in US communities [6,7,9,19,20] or patients with type 2 diabetes [21,22] showed that the non-HDLC level was a stronger predictor for CAD risk than LDL-C. In the Lipid Research Clinics Program Follow-up Study [6], differences of 0.78 mmol/l (30 mg/dl) in non-HDLC and LDL-C levels corresponded to increases in CVD risk of 19% and 15% in men, and 11% and 8% in women, respectively. In contrast, Chien et al. showed that the hazard ratio of the top quintile and area under the ROC curve for CAD incidence were almost similar for LDL-C and non-HDLC in ethnic Chinese living in Taiwan [8].

Our results are consistent with the Taiwan study described above [8], which to date represents the only report from a non-Western community. As we calculated serum LDL-C levels using the Friedewald formula, our results were not applicable to the population with serum triglyceride levels equal to or greater than 4.5 mmol/l (≥400 mg/dl). However, even if the predictive values of LDL-C and non-HDLC are similar in the Japanese population, non-HDLC may be the more convenient indicator to use for primary prevention in the community. Both TC and HDL-C are included in routine biochemistry measurements because of convenience and low cost, and can be measured directly even in non-fasting serum. Accordingly, non-HDLC may be a good serum marker for risk assessment of CAD in a community-based setting.

In the present study, the positive association between serum lipids levels and MI in women was less evident than that in men. We believe it was mainly due to small number of MI in women. Continued community surveillance in Japan showed that incidence of MI for women was about one third of men [23]. In the present study, incidence of MI for women was only 0.78 per 1000 person-years. Because most MI cases (22 of 24) were post-menopausal women, the low incidence of MI in pre-menopausal women was one reason for sex-difference. However, it was difficult to perform further analysis because of small sample size of MI cases.

Similar to previous studies that have explored the relationship between TC and stroke in Japan [9,24,25], we found no association between LDL-C or non-HDLC levels and stroke events. A large meta-analysis of individual data from 61 prospective studies [26], the majority of which were from the US, European and Japanese populations, showed an absence of an independent positive association between TC or non-HDLC and ischemic and total stroke mortality. Recently, the death probability over a 10-year period due to MI and stroke have been calculated and displayed as color risk score charts by combining 10-year age, systolic blood pressure, smoking, and serum total cholesterol and glucose levels by NIPPON DATA (National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged) Research group [27]. NIPPON DATA Risk chart for MI clearly showed the positive relationship between TC and MI, however, the risk chart for stroke showed the color gradient, which was shown death probability, for stroke was not affected by TC levels.

The lack of a relationship between TC and ischemic stroke in Japanese studies may be due to a lower prevalence of thrombotic type cortical infarctions (large-artery occlusive) than in Western populations [28], a condition that is associated with atherosclerosis secondary to hypercholesterolemia. Furthermore, the Atherosclerosis Risk in Communities (ARIC) Study also indicated that TC was associated with increased risk of non-lacunar, non-embolic stroke (thrombotic type cortical infarction), but not with lacunar or embolic stroke [29]. The effect of LDL-C or non-HDLC on ischemic stroke may be weak in populations with a low prevalence of large-artery occlusive infarctions, such as in Japan. However, a meta-analysis of randomized control trials by statin therapy has indicated a reduction of stroke [30]. Even in Japanese patients with hypercholesterolemia, statin therapy showed a non-significant but inverse association with cerebral infarction [18]. Accordingly, high serum levels of LDLC or non-HDLC should be dealt with caution as a potential risk factor for ischemic stroke.

Previous studies indicated that CAD or MI morality in Japanese people was still lower than in Westerners [9–12]. However, recently, there were evidences that serum levels of TC and LDL-C in Japanese were as high as those reported in the US population [31]. However, CAD mortality has been shown to be higher in large urbanized areas in Japan such as Tokyo and Osaka compared to the rest of Japan [32]. These two cities are among the most urbanized areas in Asia. The present study therefore provides additional evidence supporting the usefulness of LDL-C and non-HDLC as predictors of future risk for MI in screening of the urbanized Japanese population. Although in Asian countries hypertension rather than LDL-C remains the most important manageable cardiovascular risk factor [33], the present study showed that, at least in urbanized areas, lowering of LDL-C levels should also be considered as an important public health issue.

The present study had some limitations. Firstly, the single LDL-C or non-HDLC measurement at the baseline survey may have underestimated the relationship between these lipids and CAD due to regression dilution bias. Secondly, we did not measure serum apolipoprotein B (apoB), which some previous studies have shown as a stronger predictor for CAD than non-HDLC [8,20]. Furthermore, measurement of apoB is not required fasting status and is estimated to be cost-efficient [34]. Further cohort studies with measurement of apoB are needed in Japanese community-dwelling populations. Thirdly, in order to accurately compare the predictive value of non-HDLC and LDL-C, serum levels of LDL-C should be measured by direct measurement of LDL-C, rather than by the Friedewald formula. Exclusion of participants with a high serum triglyceride level (≥400 mg/dl) may reduce the predictive potential of non-HDLC. Finally, the relationship between serum lipids and cerebral infarction warrants further investigation, as we did not evaluate the effect of serum LDL-C and non-HDLC on each subtype of cerebral infarction due to small sample size, especially for thrombotic type cortical infarctions.

In conclusion, higher levels of serum LDL-C and non-HDLC are both associated with an increased risk of MI, but not with cerebral infarction in a Japanese urban population. Although the predictive value of non-HDLC for MI is almost similar to that of LDL-C calculated by the Friedewald formula, non-HDLC may be recommended as an alternative screening marker for primary prevention of CAD in the community, as it is less expensive and more convenient.

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Secular Trends in the Incidence of and Risk Factors for Ischemic Stroke and Its Subtypes in Japanese Population

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Background—The study of long-term trends in the incidence of and risk factors for ischemic stroke subtypes could offer insights into primary and secondary prevention.

Methods and Results—We established 3 cohorts of residents ≥40 years of age in 1961, 1974, and 1988 in the Japanese community of Hisayama. Morphological examinations by autopsy or brain imaging were performed on most of the ischemic stroke cases developed in these cohorts. When 13-year follow-up data were compared, the age-adjusted incidence of ischemic stroke and lacunar infarction declined significantly from the first to the third cohort for both sexes, whereas the incidences of atherothrombotic and cardioembolic infarction did not change during this period. Hypertension was a powerful risk factor for the development of ischemic stroke, and improvement of hypertension control would have largely influenced this declining trend: The age- and sex-adjusted hazard ratio of hypertension decreased from 3.25 (95% CI 2.17 to 4.86) in the first cohort to 1.83 (1.29 to 2.58) in the third cohort. A rapid increase in the prevalence of metabolic disorders may have offset the impact of improvements in hypertension control and resulted in a slowdown of the decline in the incidence of ischemic stroke in the cohorts in the present study; however, hypertension still makes a large contribution to the development of ischemic stroke.

Conclusions—These findings suggest that in the Japanese population, the incidence of ischemic stroke has declined significantly over the past 40 years, probably owing to better management of hypertension. There is a need for greater primary prevention efforts in the treatment of hypertension and metabolic disorders. (***Circulation***. **2008;118:2672-2678.**)

Key Words: cerebral infarction ■ morbidity ■ risk factors ■ hypertension ■ trend

Stroke continues to be a major public health concern worldwide. In Japan, it is the third leading cause of death and a major neurological cause of long-term disability.[1] The increase in the elderly population that accompanies the improvement in life expectancy is expected to further increase stroke prevalence. On the other hand, there have been major advances in the identification and management of stroke risk factors and the treatment of acute stroke. The study of temporal trends in stroke incidence provides insights into the effect of these factors. Several epidemiological studies have reported that the declining or stable incidence of stroke is likely attributable to better treatment of risk factors over time.[2–8] On the basis of their 50 years of follow-up data, the authors of the Framingham Study recently showed that the age-adjusted incidence of stroke decreased significantly in men and women owing to the improved control of hypertension and smoking.[2] In Japan, the incidence of stroke declined by 60% from 1964 to 1983 in a rural population.[7] We also found in a Japanese urban area that the incidence of ischemic stroke declined markedly between the 1960s and 1970s as a result of hypertension control, but this declining trend was slowed in the late 1980s and 1990s, probably because of an increase in metabolic disorders.[8]

Clinical Perspective p 2678

Because the pathogenesis, prognosis, and treatment differ among ischemic stroke subtypes,[9,10] the evaluation of temporal trends in the incidence of and risk factors for ischemic stroke subtypes may contribute to more effective primary and secondary prevention of ischemic stroke. However, morphological features of the brain were not readily available before the widespread use of computed tomography and magnetic resonance imaging, and the definition of ischemic stroke subtypes was not determined until the early 1990s.[11–13] Therefore, there is little information on the effect of the changes in cardiovascular risk factors on secular trends in the incidence of ischemic stroke and its subtypes.

The Hisayama Study is a population-based study that has established several cohorts at times that correspond to periods of remarkable lifestyle changes in Japan.[8,14–16] One of the

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characteristics of this study is that most of the deceased study subjects underwent autopsy examination from the beginning of the study, and thus, the morphological features of the brains examined by autopsy or brain imaging are available for most of the stroke cases in each cohort.[8,14] Furthermore, study-team physicians performed physical and neurological examinations on the subjects who developed stroke and collected detailed clinical information throughout the study period. These characteristics of the study design enabled us to examine secular trends in the incidence of and risk factors for ischemic stroke subtypes. We previously reported the steadily declining incidence of lacunar infarction (LAI) using 12-year follow-up data of the first 3 cohorts.[17] In this article, we extend the follow-up period of these cohorts to 13 years and compare the impact of cardiovascular risk factors on the incidence of ischemic stroke subtypes.

Methods

Study Population

The Hisayama Study, an epidemiological study of cerebrovascular-cardiovascular diseases, was established in 1961 in Hisayama Town, a suburban community adjacent to Fukuoka City, a metropolitan area on Kyushu Island in southern Japan. The population of the town was ≈8000 in 2007, and full community surveys of the residents have been repeated since 1961. The study design and characteristics of the subject population have been described in detail elsewhere.[14–16] Briefly, we established 4 study cohorts from Hisayama residents ≥40 years of age in 1961, 1974, 1988, and 2002 after screening examinations. In 1961, a total of 1658 subjects in that age group consented to participate in the screening examination (participation rate 90.1%). After the exclusion of subjects with a history of stroke or myocardial infarction and subjects who died or moved out of town during the examination, 1618 subjects were enrolled as the first cohort. Similarly, after excluding subjects with a history of stroke or myocardial infarction, we established a second cohort consisting of 2038 subjects from 2135 participants (participation rate 81.2%) in 1974, a third cohort of 2637 subjects from 2742 participants (participation rate 80.9%) in 1988, and a fourth cohort of 3123 subjects from 3328 participants (participation rate 77.6%) in 2002. The health status of these cohort populations was followed up every year by repeated health examinations or by mail or telephone for any subjects who did not undergo a regular examination or who moved out of town. Only 2 subjects in the first cohort, 2 in the second cohort, and 1 in the third cohort were lost to follow-up. The development of cardiovascular diseases in the study populations was also checked by a daily monitoring system organized by the study team, local physicians, and members of the local health and welfare office. When the subjects died, autopsy examinations were performed at the Department of Pathology, Kyushu University.

Measurement of Cardiovascular Risk Factors

Details of the measurement of cardiovascular risk factors in each cohort were published previously.[8,14–16] In brief, blood pressures were measured 3 times with subjects in a recumbent position in 1961 and in a sitting position in 1974, 1988, and 2002, and hypertension was defined as a mean systolic blood pressure ≥140 mm Hg, a mean diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive agents. Glucose intolerance was defined by an oral glucose tolerance test in subjects with glycosuria in 1961, by fasting and postprandial glucose concentrations in 1974, and by a 75-g oral glucose tolerance test in 1988 and 2002, in addition to medical history of diabetes. Serum cholesterol levels were measured by the Zak-Henly method with the modification by Yoshikawa in 1961, by the Zurkowski method in 1974, and by the enzymatic method in 1988 and 2002. Hypercholesterolemia was defined as total cholesterol ≥5.7 mmol/L (220 mg/dL). Body height and weight were measured with subjects in light clothing without shoes, and obesity was defined as body mass index ≥25.0 kg/m^2. Information on antihypertensive treatment, alcohol intake, and smoking habits was obtained with the use of a standardized questionnaire and was categorized as current habitual use or not. Current drinking was also categorized as light (1 to 33 g/d) or heavy (≥34 g/d) drinking according to daily ethanol intake.

Definition of Ischemic Stroke Subtypes

Stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit that persisted for >24 hours and was classified as ischemic stroke, cerebral hemorrhage, subarachnoid hemorrhage, or undetermined type.[8] The diagnoses of ischemic stroke subtypes were made on the basis of the Classification of Cerebrovascular Disease III proposed by the National Institute of Neurological Disorders and Stroke,[11] as well as on the basis of the diagnostic criteria of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study[12] and Cerebral Embolism Task Force.[13] We classified ischemic stroke subtypes into 4 categories: LAI, atherothrombotic infarction (ATI), cardioembolic infarction (CEI), and undetermined subtype. Details of the diagnostic criteria of ischemic stroke subtypes have been published previously.[10] Briefly, LAI was diagnosed as the presence of a relevant brain stem or subcortical hemispheric lesion with a diameter of <1.5 cm demonstrated on brain imaging or autopsy and no evidence of cerebral cortical or cerebellar impairment. ATI was diagnosed when the subject had significant stenosis (>50%) or occlusion of a major cerebral artery with infarct size ≥1.5 cm on brain imaging or autopsy. The diagnosis of CEI was made on the basis of primary and secondary clinical features suggestive of CEI as reported by the Cerebral Embolism Task Force.[13] The category of undetermined stroke included all ischemic stroke cases for which the subtype could not be determined because of insufficient clinical or morphological information. We considered morphological findings significant and used clinical features as reference information.

During the 13-year follow-up period, first-ever ischemic stroke developed in 134 subjects (83 cases of LAI, 28 of ATI, 17 of CEI, and 6 of undetermined subtype) in the first cohort, in 142 subjects in the second cohort (76 cases of LAI, 29 of ATI, 34 of CEI, and 3 of undetermined subtype), and in 154 subjects in the third cohort (74 cases of LAI, 42 of ATI, 38 of CEI, and 0 of undetermined subtype). Among these, morphological examinations by autopsy or brain imaging were performed on 90.3% (autopsy rate 90.3%) in the first cohort, 97.2% (autopsy rate 87.5%) in the second cohort, and 100.0% (autopsy rate 72.4%) in the third cohort.

Statistical Analysis

The prevalences of possible risk factors were adjusted for age by the direct method and were examined for trends across cohorts by the Cochran-Mantel-Haenszel χ^2 test with 10-year age groupings. Age-adjusted mean values of risk factors were calculated by the covariance method, and their trends were tested by the linear regression model. The incidences of first-ever ischemic stroke and its subtypes were calculated by the person-year method with adjustment for age by the direct method. The world standard population was used as a standard population. The age-adjusted incidences among the first 3 cohorts were compared with the use of the Cox proportional hazards model. Age and sex-adjusted hazard ratios (HRs) and 95% CIs of cardiovascular risk factors for the development of ischemic stroke and its subtypes were estimated by the Cox proportional hazards model in each cohort, and the population attributable risk fraction of each risk factor was calculated.

Ethical Considerations

The study protocol was approved by the Human Ethics Review Committee of the Graduate School of Medical Sciences, Kyushu University.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Table 1. Trends in Age-Adjusted Prevalence of Cardiovascular Risk Factors Among 4 Examinations of the Hisayama Study by Sex

	Men					Women				
Variables	1961 (n=705)	1974 (n=855)	1988 (n=1110)	2002 (n=1315)	*P* for Trend	1961 (n=913)	1974 (n=1183)	1988 (n=1527)	2002 (n=1808)	*P* for Trend
Age, y	55±11	56±11	57±12	60±12	<0.001	57±12	58±12	59±12	62±13	<0.001
Hypertension, %	38.4	43.1	44.1	42.0	0.25	35.9	40.1	35.1	31.3	<0.001
Antihypertensive agents, %	2.0	8.4	13.2	18.2	<0.001	2.1	7.4	13.4	16.6	<0.001
Systolic BP, mm Hg*	162±18	157±18	151±18	148±18	<0.001	163±19	161±19	154±19	149±19	<0.001
Diastolic BP, mm Hg*	91±11	90±11	87±11	89±11	0.011	88±11	87±11	83±11	86±11	<0.001
Glucose intolerance, %	11.6	14.1	39.3	54.5	<0.001	4.8	7.9	30.0	35.5	<0.001
Obesity, %	7.0	11.6	24.1	29.3	<0.001	12.9	21.5	23.8	24.0	<0.001
Body mass index, kg/m^2	21.3±2.8	21.7±2.8	22.8±2.8	23.5±2.8	<0.001	21.7±3.4	22.5±3.3	22.9±3.3	22.9±3.4	<0.001
Hypercholesterolemia, %	2.8	12.2	26.9	25.8	<0.001	6.6	19.9	41.6	41.6	<0.001
Total cholesterol, mmol/L	3.9±0.9	4.7±0.9	5.1±0.9	5.1±0.9	<0.001	4.2±1.0	5.0±1.0	5.5±1.0	5.4±1.0	<0.001
Atrial fibrillation, %	0.7	1.6	1.6	1.1	0.84	0.5	0.4	0.9	0.6	0.55
Current smoking, %	75.0	73.3	50.4	46.9	<0.001	16.6	10.2	6.9	8.5	<0.001
Current drinking, %	69.6	63.8	61.5	71.7	0.043	8.3	5.7	9.5	29.1	<0.001
Light drinking, %	43.4	31.9	29.5	37.7	...	8.2	5.5	8.0	27.1	...
Heavy drinking, %	26.3	31.9	32.0	34.0	...	0.1	0.2	1.5	2.0	...

BP indicates blood pressure. Hypertension was defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg or current use of antihypertensive agents. Hypercholesterolemia was defined as total cholesterol level ≥5.7 mmol/L (220 mg/dL). Obesity was defined as body mass index ≥25.0 kg/m^2. Current drinking was divided into light (1 to 33 g) and heavy (≥34 g) drinking according to daily ethanol intake.

*Mean systolic and diastolic BPs among hypertensive subjects in each examination.

Results

Trends in Cardiovascular Risk Factors

We compared the age-adjusted prevalence of cardiovascular risk factors at baseline examination among the 4 cohorts by sex (Table 1). During the 40-year period from 1961 to 2002, the populations grew 5 years older in both sexes. The age-adjusted prevalence of hypertension was stable at ≈40% in men (*P* for trend=0.25) and decreased significantly in women (*P* for trend <0.001), whereas the proportion of individuals using antihypertensive agents increased consistently with time in both men and women. As a result, age-adjusted mean blood pressures among hypertensive men and women decreased significantly throughout the study period. In contrast, the age-adjusted prevalence of glucose intolerance and obesity increased greatly over the study period for both sexes. More than half of men and one third of women had glucose intolerance in 2002. The age-adjusted prevalence of hypercholesterolemia increased 10-fold in men and 6-fold in women from 1961 to 1988 but was unchanged in 2002. The age-adjusted prevalence of current smoking for men was 4-fold higher than that for women in 1961, and it decreased significantly with time for both sexes. The prevalence of current drinking increased significantly for both sexes in 2002.

Trends in Incidence of Ischemic Stroke Subtypes

We then compared the age-adjusted incidence of ischemic stroke using the results of a 13-year follow-up in the first 3 cohorts (1st, 2nd, and 3rd cohort). The age-adjusted incidence of ischemic stroke declined significantly for both sexes throughout the cohorts: It significantly declined by 56% for men and by 40% for women from the first to the third cohort (*P* for trend <0.001 for either sex; Table 2). In regard to ischemic stroke subtypes, the age-adjusted incidence of LAI for men declined significantly by 54% from the first to the second cohort, and it continued to decline by 39% from the second to the third cohort (*P* for trend <0.001). The age-adjusted incidence of LAI for women also declined by 25% from the first to the second cohort, and it continued to decline by 17% from the second to the third cohort (*P* for trend=0.003). The age-adjusted incidence of ATI and CEI did not change significantly among the cohorts for either sex.

Trends in Proportion of Ischemic Stroke Subtype

The proportions of ischemic stroke subtypes among the cohorts are shown by sex in the Figure. For men, the proportion of subjects with LAI decreased steadily from the first to the third cohort, whereas the proportions with ATI and CEI increased. For women, the proportion of the subjects with CEI increased slightly from the first to the third cohort, but the proportions of those with the other subtypes were constant among the cohorts.

Trends in the Effect of Cardiovascular Risk Factors on Ischemic Stroke

Because both cardiovascular risk factors and the incidence of ischemic stroke changed dramatically, we compared the impact of cardiovascular risk factors on the development of ischemic stroke among the first 3 cohorts (Table 3). In the first cohort, hypertension was a powerful risk factor for ischemic stroke (age- and sex-adjusted HR 3.25, 95% CI 2.17 to 4.86) and largely contributed to its occurrence (population attributable risk fraction 51%). The impact of hypertension gradually declined during the study period; however, hyper-

Table 2. Age-Adjusted Incidence Rate (per 1000 Person-Years) of Ischemic Stroke and Its Subtypes Among 3 Cohorts of the Hisayama Study by Sex, With a 13-Year Follow-Up in Each Cohort

	Men				Women			
	1st Cohort (7456 PY)	2nd Cohort (9655 PY)	3rd Cohort (12 333 PY)	*P* for Trend	1st Cohort (10 294 PY)	2nd Cohort (13 762 PY)	3rd Cohort (17 953 PY)	*P* for Trend
Ischemic stroke								
No. of events	72	70	70		62	72	84	
Incidence rate	8.73	5.44	3.85	<0.001	4.28	3.06	2.57	<0.001
LAI								
No. of events	48	34	30		35	42	44	
Incidence rate	5.68	2.59	1.59	<0.001	2.41	1.81	1.50	0.003
ATI								
No. of events	14	14	22		14	15	20	
Incidence rate	1.88	1.03	1.23	0.27	0.96	0.61	0.54	0.084
CEI								
No. of events	9	21	18		8	13	20	
Incidence rate	1.08	1.74	1.03	0.43	0.58	0.56	0.53	0.86
Undetermined subtype								
No. of events	1	1	0		5	2	0	
Incidence rate	0.09	0.09	0.00	0.20	0.33	0.08	0.00	0.004

PY indicates person-years.

tension was still a significant risk factor and made the largest contribution to the development of ischemic stroke even in the third cohort (HR 1.83, 95% CI 1.29 to 2.58, population attributable risk fraction 30%). Glucose intolerance was also a significant risk factor for ischemic stroke in the first cohort. The effect of glucose intolerance on the occurrence of ischemic stroke was reduced and was not significant in the second cohort, but it appeared to be a significant risk factor in the third cohort. The population attributable risk fraction for glucose intolerance decreased from 13% in the first cohort to 4% in the second cohort and then increased to 13% in the third cohort. Obesity appeared to be a significant risk factor for ischemic stroke in every cohort, and its population attributable risk fraction was increased gradually from 6% in the first cohort to 9% in the third cohort. Hypercholesterolemia, smoking habits, and alcohol intake were not significant risk factors for ischemic stroke in any of the cohorts. In the multivariate analysis that included all risk factors, hypertension was a significant risk factor for ischemic stroke, and its HR decreased from 2.92 (95% CI 1.93 to 4.41) in the first cohort to 1.71 (95% CI 1.20 to 2.45) in the third cohort. Glucose intolerance was an independent risk factor for ischemic stroke in the first cohort (HR 1.91, 95% CI 1.23 to 2.95) but was not significant in the third cohort (HR 1.28, 95% CI 0.93 to 1.78). Obesity was not a significant risk factor in any of the cohorts after adjustment for other risk factors. We tried to investigate the effect of cardiovascular risk factors on ischemic stroke subtypes, but we could not find reliable evidence of an effect of these risk factors on the development of each subtype, probably because of the small number of events.

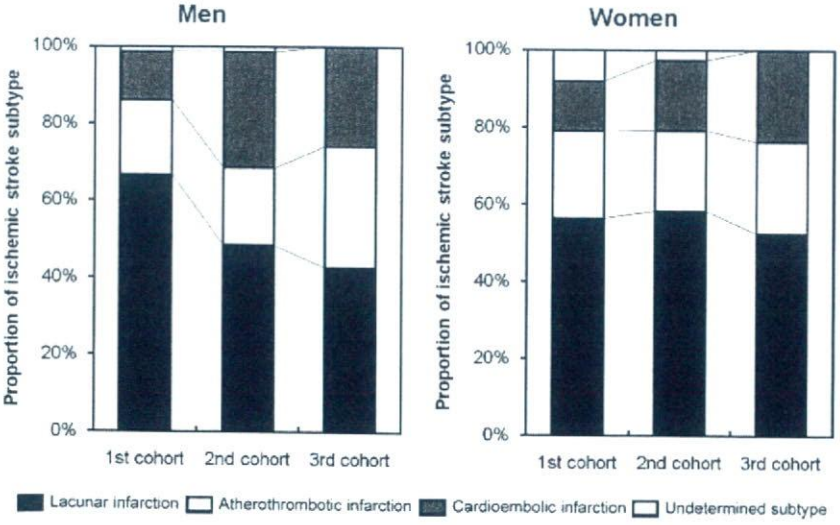

Figure. Proportion of ischemic stroke subtypes among the 3 cohorts of the Hisayama Study by sex.

Table 3. Age- and Sex-Adjusted HRs of Cardiovascular Risk Factors for Ischemic Stroke Among 3 Cohorts of the Hisayama Study

	1st Cohort			2nd Cohort			3rd Cohort		
	HR (95% CI)	*P*	PAF	HR (95% CI)	*P*	PAF	HR (95% CI)	*P*	PAF
Hypertension	3.25 (2.17–4.86)	<0.001	0.51	3.09 (2.05–4.65)	<0.001	0.53	1.83 (1.29–2.58)	<0.001	0.30
Glucose intolerance	2.45 (1.60–3.74)	<0.001	0.13	1.38 (0.87–2.17)	0.17	0.04	1.41 (1.02–1.94)	0.036	0.13
Obesity	1.83 (1.12–3.00)	0.017	0.06	1.63 (1.04–2.57)	0.034	0.07	1.54 (1.07–2.21)	0.021	0.09
Hypercholesterolemia	1.07 (0.50–2.29)	0.87	0.00	1.42 (0.95–2.12)	0.085	0.07	0.96 (0.68–1.35)	0.80	−0.02
Current smoker	1.27 (0.85–1.90)	0.24	0.10	0.83 (0.55–1.24)	0.36	-0.08	1.33 (0.89–1.98)	0.16	0.07
Current drinker	0.99 (0.65–1.51)	0.94	-0.01	1.45 (0.96–2.19)	0.081	0.12	1.09 (0.72–1.64)	0.70	0.02

PAF indicates the population attributable risk fraction.

Discussion

By comparing the incidence of ischemic stroke subtypes among 3 cohorts established at different times in a Japanese community, we demonstrated that the incidence of LAI declined significantly from the first to the third cohort for both sexes, whereas the incidence of ATI and CEI remained stable. During the study period, blood pressure levels among hypertensive subjects decreased significantly with time as a result of the popularization of antihypertensive medication. The prevalence of smoking habits declined steadily for both sexes. Contrary to these declining trends, the prevalence of metabolic disorders, namely, obesity, glucose intolerance, and hypercholesterolemia, increased steeply with time. These changes in cardiovascular risk factors might affect the incidence of ischemic stroke and its subtypes.

Hypertension is the most powerful risk factor for ischemic stroke.[9] In the first cohort, hypertension contributed to approximately half of the occurrence of ischemic stroke. During the study period, the age-adjusted prevalence of hypertension declined in women, and the proportion of all participants receiving hypertensive treatment increased steeply in both sexes. This improvement of hypertension control resulted in a decrease in age-adjusted mean systolic blood pressure level of 14 mm Hg among hypertensive subjects in both sexes. Because of this improved control of hypertension, the impact of the disease on the development of ischemic stroke was seen to weaken in the third cohort. The Framingham Study also showed a decline in the annual incidence of nonembolic stroke during a follow-up period of 50 years or more.[2] During this period, the mean systolic blood pressure level, prevalence of hypertension, and proportion of all participants receiving treatment for hypertension improved significantly. These reductions in the incidence of ischemic stroke and improvements in treatment for hypertension were similar to the findings of the present study. Our previous study showed that the impact of hypertension was similar for all ischemic stroke subtypes.[10] These results suggest that better management of hypertension might have made the biggest contribution to the declining trend in the incidence of ischemic stroke, especially of LAI; however, hypertension was still a significant risk factor in the third cohort and had a large attributable risk fraction for ischemic stroke. Because half of the hypertensive subjects did not undergo treatment for hypertension in the third cohort, there is a need for greater primary prevention efforts to improve the treatment of hypertension.

In subjects in the present study, the age-adjusted prevalence of metabolic disorders, such as obesity, hypercholesterolemia, and glucose intolerance, increased greatly during the past 40 years, probably owing to the westernization of the Japanese lifestyle. When we examined the impact of these metabolic disorders on the development of ischemic stroke, glucose intolerance was a significant risk factor in the first and the third cohort, and the impact of obesity was constant throughout the study period. Both glucose intolerance and body mass index have been shown to be significant risk factors for ischemic stroke and LAI.[10,18] Moreover, obesity is closely related to other cardiovascular risk factors and jointly increases the risk of ischemic stroke.[19] Our previous study also showed that the accumulation of metabolic disorders (that is, metabolic syndrome) was a significant risk factor for the development of ischemic stroke in our third cohort.[20] We speculate that the improved management of hypertension and the worsening of metabolic disorders cancelled each other out and resulted in the slowdown of the declining trend of the incidence of LAI and the sustained incidence of ATI.

Smoking is a widely accepted risk factor for ischemic stroke in Western populations, but this relationship is controversial for Japanese.[10,21,22] In the present study cohorts, the declining prevalence of smoking habits closely mirrored the declining trend in the incidence of ischemic stroke; however, smoking habits had little impact on the incidence of ischemic stroke in the present study cohorts. One possible explanation is that the association between smoking and the risk of ischemic stroke is only evident in populations with moderate to high levels of serum cholesterol.[23] A recent review of cardiovascular mortality trends in Japan[23] showed that the increase in serum cholesterol appeared mainly in young to middle-aged people. In contrast, elderly people, a high-risk group for ischemic stroke, continued to maintain a lower cholesterol level. However, the prevalence of smoking habits is still high in Japanese men, and therefore, the adverse influence of smoking might appear in the current generation of younger men, with a higher cholesterol level to be seen in the future.

LAI is the most common subtype of ischemic stroke in the Japanese population, unlike in Western populations.[1] Among subjects in the present study, because of the decreased incidence of LAI and the sustained incidences of ATI and CEI, the proportion of ischemic stroke subtypes has become closer to that of Western populations in men (Figure).

However, the pattern of ischemic stroke subtypes differed from that of Western populations, with subjects in the present study showing a high proportion of LAI even in recent years (43% for men and 52% for women in the third cohort). A recent hospital-based registration study in an urban area[24] and a study of 16 992 patients with acute ischemic stroke from rural areas in Japan[25] also showed a higher prevalence of LAI than of other subtypes. One possible explanation for this is the racial difference in the genetic susceptibility of LAI. We recently found 2 susceptibility genes for ischemic stroke, *PRKCH* and *AGTRL1*, in a genome-wide association study.[26,27] A single-nucleotide polymorphism in the *PRKCH* gene increased the risk of LAI, but this single-nucleotide polymorphism is specific to Asian populations.[27]

The present study has several limitations. First, the number of events of subtypes other than LAI was relatively small, and therefore, the power to assess trends in the incidence of and risk factors for ischemic stroke subtypes was weak. Second, there were a large number of subjects overlapping among the cohorts. Indeed, 916 of the subjects in the first cohort also accounted for 45% of the population of the second cohort. In addition, a total of 1229 subjects in the second cohort also participated in the third cohort (47% of the third cohort). However, we treated the overlapping subjects as in any life table analysis, establishing every cohort after excluding subjects with prior stroke or myocardial infarction at baseline. Therefore, these overlapping populations were not considered to distort the incidence trends in the present study. Third, the measurement of blood glucose and the criteria for glucose intolerance were different among the cohorts, which suggests an underestimation of the prevalence of glucose intolerance in the former cohorts. Nevertheless, the rapid changes in other risk factors in the present study are in accordance with the results of the National Nutritional Survey and other surveys of Japan.[23] Finally, the methods of case ascertainment and the diagnostic sensitivity of imaging techniques changed dramatically during the study period. The proportion of case subjects with of incident ischemic stroke who received diagnostic imaging tests increased over time. Echocardiography and carotid scanning were rarely performed in the former cohorts (3.0% and 0% in the first cohort, 29.6% and 4.2% in the second cohort, and 61.7% and 27.3% in the third cohort, respectively). Therefore, it is possible that the trends in the incidence of ATI and CEI were less accurate than the trends for LAI. Nonetheless, we believe that the findings of the present study reflect the actual secular trends in the incidence of ischemic stroke subtypes and their risk factors in the Japanese population, because we performed comprehensive surveillance, including autopsy examinations, in most of the cases.

Conclusions

By comparing the incidence of and risk factors for ischemic stroke subtypes among 3 cohorts established at different times in a Japanese community, we demonstrated that the incidence of LAI declined significantly from the 1960s to the late 1990s, but LAI remained the most frequent subtype of ischemic stroke in the Japanese. The improvement in hypertension control might have had a major influence on this declining trend. However, hypertension still has a large impact on ischemic stroke, and the increasing prevalence of metabolic disorders might emerge as an additional risk in future cohorts. The present study indicates the need for continued primary prevention efforts, particularly with respect to hypertension and metabolic disorders.

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Disclosure

None.

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CLINICAL PERSPECTIVE

Stroke continues to be a major public health concern worldwide. Several epidemiological studies have reported that the declining or stable incidence of stroke is most often attributed to better treatment of risk factors over time. Here, by comparing the incidence of and risk factors for ischemic stroke subtypes among 3 cohorts established at different times in a Japanese community, we demonstrate that the age-adjusted incidence of ischemic stroke and of lacunar infarction declined significantly from the 1960s to the late 1990s, but lacunar infarction remains the most frequent subtype of ischemic stroke in the Japanese. Hypertension was a powerful risk factor for the development of ischemic stroke, and improvement of hypertension control would have largely influenced this declining trend: The age- and sex-adjusted hazard ratio of hypertension decreased from 3.25 (95% CI 2.17 to 4.86) in the first cohort to 1.83 (1.29 to 2.58) in the third cohort. However, hypertension still has a large impact on ischemic stroke, and the increase in metabolic disorders might emerge as an additional risk in the third cohort. The present study indicates the need for continued primary prevention efforts, particularly with respect to hypertension and metabolic disorders.

High-Sensitivity C-Reactive Protein and Coronary Heart Disease in a General Population of Japanese

The Hisayama Study

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Objective—The purpose of this study was to investigate the effects of high-sensitivity C-reactive protein (hs-CRP) on the risks of coronary heart disease (CHD) in a general population of Japanese.

Methods and Results—The Hisayama study is a population-based prospective cohort study. A total of 2589 participants aged 40 years or older were followed up for 14 years. Outcomes are incident CHD (myocardial infarction, coronary revascularization, and sudden cardiac death). The median hs-CRP level was 0.43 mg/L at baseline. During the follow-up period, 129 coronary events were observed. Age- and sex-adjusted annual incidence rates of CHD rose progressively with higher hs-CRP levels: 1.6, 3.3, 4.5, and 7.4 per 1000 person-years for quartile groups defined by hs-CRP levels of <0.21, 0.21 to 0.43, 0.44 to 1.02, and >1.02 mg/L, respectively ($P<0.0001$ for trend). The risk of CHD in the highest quartile group was 2.98-fold (95% CI, 1.53 to 5.82) higher than that in the lowest group even after controlling for other cardiovascular risk factors.

Conclusions—hs-CRP levels were clearly associated with future CHD events in a general population of Japanese. In Japanese populations, the hs-CRP cut-off point for high-risk of future development of CHD is likely to be >1.0 mg/L, which is much lower than that for Western populations. (***Arterioscler Thromb Vasc Biol.* 2008;28:1385-1391**)

Key Words: inflammation ■ C-reactive protein ■ coronary heart disease ■ prospective cohort study ■ general population

Coronary heart disease (CHD) is estimated to be one of the leading causes of death in Japan as well as other countries around the world, placing a burden on the community.[1] Although the burden of CHD has been reduced in several developed countries in the past few decades,[2] its incidence rates have not declined in Japan.[3] Effective prevention will require a strategy based on knowledge of the importance of novel and traditional risk factors for CHD in Japan.

See accompanying article on page 1222

Recently, inflammation has emerged as an important factor in atherosclerosis,[4] and high-sensitivity C-reactive protein (hs-CRP) has attracted clinical attention as a novel risk factor for CHD. However, current knowledge of the importance of hs-CRP as a risk factor for CHD is derived mainly from studies done in Western populations,[5–12] and it is unclear to what extent these findings apply to Japanese populations. The Hisayama Study is a prospective cohort study of a general Japanese population. A previous report from the Hisayama Study showed a positive association between hs-CRP levels and the risks of ischemic stroke among Japanese men.[13] The objective of the present analysis is to examine the relationship between serum hs-CRP levels and future development of coronary heat disease in a general population of Japanese.

Methods

Study Design and Participants

Since 1961, we have been conducting a long-term prospective cohort study of cardiovascular disease in the town of Hisayama, a suburb of Fukuoka City in Southern Japan.[3,14] In 1988, a screening survey for the present study was performed in the town. A total of 2736 residents aged 40 years or older (80.9% of the total population of this age group) consented to participate in the examination.[13,15] After the exclusion of 102 subjects with a history of stroke or CHD and 45 subjects whose frozen blood samples were of insufficient quantity for the measurement of serum hs-CRP, the remaining 2589 individuals were enrolled in this study.

The ethics committee of Kyushu University approved this study, participants provided written informed consent, and the procedures followed were in accordance with national guidelines.

Follow-Up Survey

The subjects were followed up prospectively from December 1988 to November 2002 by repeated health examinations. A detailed description of the study methods has been published previously.[3,13,15] In

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brief, the health status of any subject who had not undergone a regular examination or who had moved out of town was checked yearly by mail or telephone. We also established a daily monitoring system among the study team and local physicians or members of the town's Health and Welfare Office. When a subject died, an autopsy was performed at the Departments of Pathology of Kyushu University. During the follow-up period, 545 subjects died, of whom 412 (75.6%) underwent autopsy. Only one participant was lost to follow-up.

Outcomes

The primary outcome of the present analysis was CHD. The criteria for a diagnosis of CHD included first-ever acute myocardial infarction (MI), silent MI, sudden cardiac death within 1 hour after the onset of acute illness, or coronary artery disease followed by coronary artery bypass surgery or angioplasty.[3,14] Acute MI was diagnosed when a subject met at least 2 of the following criteria: (1) typical symptoms, including prolonged severe anterior chest pain; (2) abnormal cardiac enzymes more than twice the upper limit of the normal range; (3) evolving diagnostic electrocardiographic (ECG) changes; (4) morphological changes including local asynergy of cardiac wall motion on echocardiography, a persistent perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars >1 cm long accompanied by coronary atherosclerosis at autopsy. Silent MI was defined as myocardial scarring without any historical indication of clinical symptoms or abnormal cardiac enzyme changes. The secondary outcomes of the present investigation were deaths attributable to any cardiovascular disease (ICD-10[16] codes I00-I99), deaths attributable to noncardiovascular disease, and total deaths.

Risk Factors

Plasma glucose levels were determined by the glucose-oxidase method, and diabetes was defined by a 75-g oral glucose tolerance test and by fasting (≥7.0 mmol/L) or postprandial (≥11.1 mmol/L) blood glucose levels or by the use of hypoglycemic agents. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were determined enzymatically. Low-density lipoprotein (LDL) cholesterol level was estimated using the Friedewald formula.[17] Hypercholesterolemia was defined as a serum cholesterol level of 5.69 mmol/L or higher. Serum specimens collected at the time of CRP measurement were stored at −20°C until they were used in 2002. Serum hs-CRP levels were analyzed using a modification of the Behring latex-enhanced CRP assay on a BN-100 nephelometer (Dade Behring) with a 2% interassay coefficient of variation. Sitting blood pressure (BP) was measured 3 times at the right upper arm using a sphygmomanometer after 5 minutes of rest; an average of 3 measurements was used for the analysis. Hypertension was defined as BP levels of ≥140/90 mm Hg or current treatment with antihypertensive agents. The waist circumference was measured at the umbilical level in a standing position. Height and weight were measured in light clothes without shoes, and body mass index (BMI, kg/m^2) was calculated. Obesity was defined as a BMI of ≥25kg/m^2. ECG abnormalities were defined as Minnesota code 3-1 or 4-1,2,3. Information on smoking habits, alcohol intake, and physical activity during leisure time was obtained using a standard questionnaire. Smoking habits and alcohol intake were classified as either current or not. Subjects engaging in sports or other forms of exertion ≥3 times a week during their leisure time made up a regular exercise group. Metabolic syndrome was defined using criteria recommended in the National Cholesterol Education Program Adult Treatment Panel III guideline[18] with a modification of abdominal obesity, which was defined as a waist circumference ≥90 cm in men and ≥80 cm in women according to the International Obesity Task Force central obesity criteria for Asia.[19]

Statistical Analysis

We used quartiles of hs-CRP levels for the analysis of the effects of hs-CRP on the risks of CHD. The contributions of relevant factors to an elevated hs-CRP level, which was defined as the highest quartile, were examined using a logistic regression model, with an estimated odds ratio (OR) and 95% confidence interval (95% CI). The cumulative incidence of CHD was estimated using Cox's proportional hazards model. The incidence rates were calculated by the person-year method and standardized for age and sex distribution of the world standard population by the direct method using 10-year age groupings. The age- and sex-adjusted or multivariate-adjusted hazard ratio (HR) and 95% CI were estimated using Cox's proportional hazard model. Comparison of the effects hs-CRP between participants with and without other cardiovascular risk factors was done, and the probability value for homogeneity was estimated by adding an interaction term to the statistical model. All analyses were performed using the SAS software package (SAS Institute).

Results

Among the 2589 participants, the median hs-CRP level was 0.43 mg/L. The baseline characteristics of the subjects by hs-CRP quartile groups are shown in Table 1. Subjects with higher hs-CRP levels were older and less frequently women. The age- and sex-adjusted logistic regression analysis revealed that hypertension (OR, 1.40; 95% CI, 1.16 to 1.69), diabetes (OR, 1.67; 95% CI, 1.29 to 2.16), obesity (OR, 1.80; 95% CI, 1.47 to 2.22), hypercholesterolemia (OR, 1.32; 95% CI, 1.09 to 1.60), metabolic syndrome (OR, 2.04; 95% CI, 1.67 to 2.50), and smoking habits (OR, 1.96; 95% CI 1.56 to 2.47) were significantly associated with elevated hs-CRP levels, which were defined as the highest quartile (>1.02 mg/L).

During the 14 years of follow up, 129 coronary events were observed. The Figure shows the age- and sex-adjusted cumulative incidence of CHD according to hs-CRP quartiles. The cumulative incidence of CHD clearly increased with rising hs-CRP levels. The age- and sex-adjusted incidence rates of CHD according to hs-CRP quartiles are shown in Table 2. The incidence rates rose progressively with higher hs-CRP levels: 1.6, 3.3, 4.5, and 7.4 per 1000 person-years from the first to the fourth quartile groups, respectively ($P<0.0001$ for trend). Table 2 also shows age- and sex-adjusted and multivariate-adjusted HRs and 95% CIs for the development of CHD according to the hs-CRP quartiles. The risks of CHD significantly increased with rising hs-CRP levels even after controlling for age, sex, systolic BP, ECG abnormalities, diabetes, BMI, total and HDL cholesterol, smoking habits, alcohol intake, and regular exercise ($P=0.0002$ for trend). The risk of CHD in the highest quartile group was significantly higher than that in the lowest group (multivariate-adjusted HR, 2.98; 95% CI, 1.53 to 5.82).

During the follow-up period, 545 participants died (158 died of cardiovascular disease and 387 died of noncardiovascular disease). The age- and sex-adjusted total and cause-specific mortality rates are shown in Table 3. The age-and sex-adjusted all-cause mortality rates rose progressively with higher hs-CRP levels ($P<0.0001$ for trend). The age- and sex-adjusted and multivariate-adjusted HRs also increased with rising hs-CRP levels even after controlling for other risk factors (Table 3; $P<0.0001$ for trend). When causes of death were divided into cardiovascular and noncardiovascular diseases, the relationship of hs-CRP to cardiovascular deaths was stronger than that to noncardiovascular deaths.

Age- and sex-adjusted hazard ratios of hs-CRP (highest versus lowest quartiles) for the development of CHD among

Table 1. Baseline Characteristics by Quartiles of High-Sensitivity C-Reactive Protein

	hs-CRP Levels, mg/L				
	<0.21 (n=648)	0.21 to 0.43 (n=647)	0.44 to 1.02 (n=645)	>1.02 (n=649)	*P* Trend
Age, y	55 (11)	58 (12)	59 (11)	62 (12)	<0.0001
Women, %	64	63	55	51	<0.0001
Systolic blood pressure, mm Hg	128 (20)	132 (22)	136 (21)	138 (21)	<0.0001
Diastolic blood pressure, mm Hg	76 (11)	78 (11)	79 (11)	79 (12)	<0.0001
Hypertension,* %	29	39	45	52	<0.0001
ECG abnormalities,† %	15	15	16	18	0.1
Diabetes,‡ %	6	9	16	17	<0.0001
Waist, cm	77.4 (8.8)	80.6 (9.0)	83.8 (8.8)	83.8 (9.5)	<0.0001
Body mass index, kg/m^2	22 (3)	23 (3)	24 (3)	24 (3)	<0.0001
Total cholesterol, mmol/L	5.21 (1.02)	5.38 (1.09)	5.44 (1.11)	5.40 (1.13)	0.002
Triglycerides, mmol/L	1.15 (0.99)	1.37 (1.22)	1.56 (1.71)	1.48 (1.02)	<0.0001
HDL cholesterol, mmol/L	1.38 (0.30)	1.34 (0.31)	1.27 (0.29)	1.22 (0.30)	<0.0001
LDL cholesterol,§ mmol/L	3.30 (1.01)	3.41 (1.12)	3.46 (1.14)	3.50 (1.09)	0.0009
Metabolic syndrome, %	14	24	33	39	<0.0001
Current smoker, %	19	20	26	35	<0.0001
Current alcohol use, %	27	27	35	33	0.006
Regular exercise, %	10	9	9	12	0.2

Values are means (SD) or frequencies.

hs-CRP indicates high-sensitivity C-reactive protein; ECG, electrocardiographic; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Blood pressure ≥140/90 mm Hg or current use of antihypertensive agents.

†Minnesota codes 3-1 or 4-1,2,3.

‡Fasting glucose e ≥7.0 mmol/L, postprandial blood glucose ≥11.1 mmol/L, or current use of hypoglycemic agents.

§LDL cholesterol level was estimated using the Friedewald formula.

major clinical subgroups defined by the absence or presence of other cardiovascular risk factors are shown in Table 4. There were comparable effects of hs-CRP on the risk of CHD for participants who were and those who were not hypertensive (*P* homogeneity=0.7). Likewise, there were no clear differences in the effects of hs-CRP for participants with and without other cardiovascular risk factors such as diabetes, obesity, hypercholesterolemia, metabolic syndrome, or smoking habits (all *P* homogeneity >0.4).

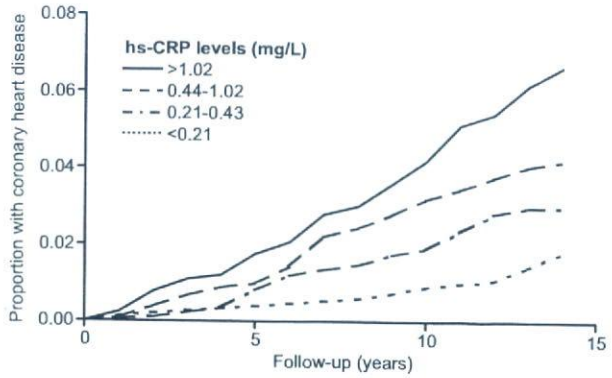

Figure. Age- and sex-adjusted cumulative incidence of coronary heart disease according to quartiles of high-sensitivity C-reactive protein. hs-CRP indicates high-sensitivity C-reactive protein.

Discussion

The present analysis demonstrated that serum hs-CRP levels were clearly associated with future coronary events in a general population of Japanese. The association between hs-CRP and CHD was strong and continuous down to very low hs-CRP levels of less than 0.21 mg/L. These associations remained strong even after controlling for age, sex, systolic BP, ECG abnormalities, diabetes, BMI, total and HDL cholesterol, smoking habits, alcohol intake, and regular exercise. Furthermore, the effects of hs-CRP were comparable for subjects with and without other cardiovascular risk factors such as hypertension, diabetes, obesity, hypercholesterolemia, metabolic syndrome, and smoking habits.

Large-scale nested case-control studies have reported that participants with incident CHD had higher levels of hs-CRP.[5,6,8–11] Likewise, large-scale cohort studies have clearly demonstrated that hs-CRP levels predicted future coronary events.[7,12] However, these studies were mainly conducted in Western populations, and it is unclear to what extent these associations apply to Japanese populations. The Honolulu Heart Program has reported a clear association between hs-CRP levels and the future development of CHD in a population of Japanese Americans.[20] The present analysis from the Hisayama Study confirmed the results from these previous observational studies in a general population of Japanese, finding that the relative risks of increasing hs-CRP levels for the development of CHD were similar to those

Table 2. Incidence Rates and Adjusted Hazard Ratios for Development of Coronary Heart Disease According to Quartiles of High-Sensitivity C-Reactive Protein

	hs-CRP Levels, mg/L				
	<0.21 (n=648)	0.21 to 0.43 (n=647)	0.44 to 1.02 (n=645)	>1.02 (n=649)	*P* Trend
No. of events/person-years	11/8589	22/8297	36/8073	60/7485	
Crude incidence rate (per 1000 person-years)	1.3	2.7	4.5	8.0	
Age- and sex-adjusted incidence rate (per 1000 person-years)	1.6	3.3	4.5	7.4	
Age- and sex-adjusted hazard ratio (95% CI)	1 (reference)	1.75 (0.85 to 3.61)	2.55 (1.30 to 5.02)	3.96 (2.07 to 7.57)	<0.0001
Multivariate-adjusted hazard ratio* (95% CI)	1 (reference)	1.60 (0.77 to 3.31)	1.97 (0.98 to 3.95)	2.98 (1.53 to 5.82)	0.0002

hs-CRP indicates high-sensitivity C-reactive protein; 95% CI, 95% confidence interval.

*Hazard ratios controlling for age, sex, systolic blood pressure, ECG abnormalities, diabetes, body mass index, total and HDL cholesterol, smoking habits, alcohol intake, and regular exercise.

obtained from other observational studies conducted in Western populations[5–12] or in a population of Japanese Americans.[20] These findings suggest that hs-CRP is an important risk factor for CHD among Japanese as well as among Westerners.

In the present analysis, hs-CRP levels in Japanese (median 0.43 mg/L) were much lower than those in Western populations (median approximately 1.5 to 2.0 mg/L).[21,22] This is consistent with the findings of other cross-sectional studies in which Asian subjects had lower hs-CRP levels compared to Western subjects.[21–24] The reason for this ethnic difference is not clearly resolved, but genetic diversity has been reported to influence hs-CRP levels.[25] The relatively low BMI in Japanese and differences in diet and lifestyle may also have modulated hs-CRP levels.[26] The Honolulu Heart Program reported a median hs-CRP level of 0.54 mg/L among Japa-

Table 3. Mortality Rates and Adjusted Hazard Ratios for Total and Cause-Specific Deaths According to Quartiles of High-Sensitivity C-Reactive Protein

	hs-CRP Levels, mg/L				
	<0.21 (n=648)	0.21 to 0.43 (n=647)	0.44 to 1.02 (n=645)	>1.02 (n=649)	*P* Trend
Total deaths					
No. of events/person-years	79/8624	106/8365	143/8181	217/7626	
Age- and sex-adjusted mortality rate (per 1000 person-years)	12.7	15.2	18.9	23.5	
Age- and sex-adjusted hazard ratio (95% CI)	1 (reference)	1.08 (0.81 to 1.45)	1.30 (0.99 to 1.72)	1.80 (1.39 to 2.34)	<0.0001
Multivariate-adjusted hazard ratio* (95% CI)	1 (reference)	1.13 (0.84 to 1.51)	1.41 (1.06 to 1.87)	1.85 (1.41 to 2.43)	<0.0001
Cardiovascular deaths					
No. of events/person-years	16/8624	28/8365	47/8181	67/7626	
Age- and sex-adjusted mortality rate (per 1000 person-years)	2.2	3.7	6.0	7.2	
Age- and sex-adjusted hazard ratio (95% CI)	1 (reference)	1.38 (0.75 to 2.55)	2.15 (1.22 to 3.80)	2.77 (1.60 to 4.80)	<0.0001
Multivariate-adjusted hazard ratio* (95% CI)	1 (reference)	1.40 (0.75 to 2.60)	2.28 (1.27 to 4.09)	3.00 (1.70 to 5.28)	<0.0001
Noncardiovascular deaths					
No. of events/person-years	63/8624	78/8365	96/8181	150/7626	
Age- and sex-adjusted mortality rate (per 1000 person-years)	10.5	11.5	12.9	16.4	
Age- and sex-adjusted hazard ratio (95% CI)	1 (reference)	1.00 (0.72 to 1.40)	1.09 (0.79 to 1.50)	1.55 (1.15 to 2.08)	0.0004
Multivariate-adjusted hazard ratio* (95% CI)	1 (reference)	1.06 (0.76 to 1.48)	1.18 (0.85 to 1.64)	1.56 (1.14 to 2.13)	0.001

hs-CRP indicates high-sensitivity C-reactive protein; 95% CI, 95% confidence interval.

*Hazard ratios controlling for age, sex, systolic blood pressure, ECG abnormalities, diabetes, body mass index, total and HDL cholesterol, smoking habits, alcohol intake, and regular exercise.

Table 4. Age- and Sex-Adjusted Hazard Ratios of High-Sensitivity C-Reactive Protein (Highest vs Lowest Quartiles) for Development of Coronary Heart Disease Among Major Clinical Subgroups Defined by the Absence or Presence of Other Cardiovascular Risk Factors

	No. of Events/Person-Years			
	Highest Quartile (hs-CRP>1.02 mg/L)	Lowest Quartile (hs-CRP<0.21 mg/L)	Hazard Ratio* (95% CI)	*P* Homogeneity
Hypertension†				
Absent	18/3843	6/6224	3.18 (1.25 to 8.08)	0.7
Present	42/3643	5/2365	4.27 (1.68 to 10.82)	
Diabetes‡				
Absent	45/6276	9/8122	3.73 (1.81 to 7.68)	0.7
Present	15/1210	2/467	2.84 (0.65 to 12.43)	
Obesity§				
Absent	45/5113	10/7412	3.63 (1.81 to 7.28)	0.7
Present	15/2373	1/1177	5.42 (0.71 to 41.35)	
Hypercholesterolemia‖				
Absent	32/4448	5/5975	4.74 (1.83 to 12.26)	0.4
Present	28/3037	6/2614	2.83 (1.16 to 6.88)	
Metabolic syndrome¶				
Absent	27/4340	7/7068	3.34 (1.44 to 7.75)	1.0
Present	29/2631	3/1122	3.31 (1.00 to 10.92)	
Current smoking				
Absent	34/4910	9/7030	3.39 (1.61 to 7.15)	0.5
Present	26/2576	2/1559	5.94 (1.40 to 25.12)	

hs-CRP indicates high-sensitivity C-reactive protein; 95% CI, 95% confidence interval.
*Hazard ratios for the highest vs the lowest quartile of high-sensitivity C-reactive protein.
†Blood pressure ≥140/90 mm Hg or current use of antihypertensive agents.
‡Fasting glucose ≥7.0 mmol/L, postprandial blood glucose ≥11.1 mmol/L, or current use of hypoglycemic agents.
§Body mass index ≥25kg/m^2.
‖Total cholesterol ≥5.69 mmol/L.
¶Defined by the modified National Cholesterol Education Program Adult Treatment Panel III criteria.

nese Americans without CHD,[20] which was lower than that of Western populations but higher than that obtained from the present analysis. These findings suggest that lower hs-CRP levels among Asian populations are derived from differences in genetic factors as well as differences in BMI, diet, and lifestyle.

Another important finding obtained from the present analysis is that the association between hs-CRP levels and CHD was continuous from very low hs-CRP levels and that a slightly elevated hs-CRP level of more than 1 mg/L was clearly associated with increased risk of future coronary events in Japanese. Similar findings were obtained from the Honolulu Heart Program, whose subjects were Japanese American.[20] A low cut-off point of hs-CRP (<1 mg/L) has also been suggested as the target of lipid lowering therapy with statin for maximum reduction of recurrent coronary events or deaths among Western patients with acute coronary syndrome.[27–29] These findings imply that the association between hs-CRP and CHD are likely to be continuous down to very low hs-CRP levels among Asian as well as Western subjects. The American Heart Association and the Centers for Disease Control have recommended categorizing subjects using hs-CRP cut-off points of <1, 1 to 3, and >3 mg/L into low-, average-, and high-risk categories, respectively, based mainly on the findings obtained from studies done in Western populations.[30] Among Asian subjects whose hs-CRP levels are much lower than those of Western subjects, however, an hs-CRP level of >1 mg/L is likely to be the cut-off point for the high-risk category.

In the present analysis, the effects of hs-CRP on the risks of future coronary events were independent of other cardiovascular risk factors and did not differ between participants with and those without traditional risk factors such as hypertension, diabetes, obesity, hypercholesterolemia, metabolic syndrome, or smoking habits. These results suggest that measurement of hs-CRP is likely to provide additional information for the detection of high-risk individuals among subjects without traditional risk factors as well as for the detection of extremely high-risk individuals among those with traditional risk factors. This finding is consistent with other observational studies suggesting that inclusion of hs-CRP into risk prediction models improves the accuracy of cardiovascular risk classification.[31,32]

Several limitations of our study should be discussed. The primary limitation is that we estimated the cut-off point of hs-CRP for detection of high-risk subjects based on analysis using quartile groupings despite continuous relationships between hs-CRP and the risks of CHD. The cut-off point