High-Density Lipoprotein Cholesterol and Premature Coronary Heart Disease in Urban Japanese Men

Akihiko Kitamura, MD; Hiroyasu Iso, MD; Yoshihiko Naito, MD; Minoru Iida, MD; Masamitsu Konishi, MD; Aaron R. Folsom, MD; Shinichi Sato, MD; Masahiko Kiyama, MD; Masakazu Nakamura, PhD; Tomoko Sankai, MD; Takashi Shimamoto, MD; Yoshio Komachi, MD

Background The objective of this study was to examine the relation of high-density lipoprotein cholesterol (HDL-C) to coronary heart disease in Japanese men whose serum total cholesterol is low by Western standards.

Methods and Results A prospective, observational study based on 7.7 years of follow-up for incidence of coronary heart disease and stroke was conducted. The subjects were 6408 middle-aged male workers aged 40 to 59 years at baseline in urban companies in Osaka, Japan, whose mean serum total cholesterol was 5.10 mmol/L. Mean HDL-C adjusted for age, total cholesterol, systolic blood pressure, alcohol intake, cigarette smoking, and body mass index was 1.27 to 1.28 mmol/L for men who developed coronary heart disease (n=46) or definite myocardial infarction (n=21) compared with 1.46 mmol/L for those free of cardiovascular disease (n=6256; difference, $P<.01$). There was no significant difference in mean HDL-C between stroke cases (n=33) and those free of cardiovascular disease. The incidence rates of coronary heart disease and definite myocardial infarction, adjusted for the other risk factors, were three to four times higher in the lowest HDL-C quartile (<1.24 mmol/L) than the highest quartile (≥1.66 mmol/L), and there was a significant dose response for definite myocardial infarction. Serum total cholesterol was positively and significantly associated with coronary heart disease incidence. Furthermore, the inverse association for HDL-C was apparent among men with total cholesterol <5.69 mmol/L (mean total cholesterol, 4.76 mmol/L) and men with total cholesterol ≥5.69 mmol/L (mean total cholesterol, 6.26 mmol/L).

Conclusions Coronary heart disease incidence is inversely related to HDL-C in urban Japanese middle-aged men, whose mean total cholesterol (5.10 mmol/L) is relatively low. (***Circulation.* 1994;89:2533-2539.**)

Key Words • epidemiology • cholesterol • stroke

Prospective studies in Europe and the United States have shown that serum total cholesterol concentration is positively associated with the subsequent risk of coronary heart disease,[1-3] whereas high-density lipoprotein cholesterol (HDL-C) concentration is inversely associated with the risk.[4-10] Three prospective studies in Japan have shown a direct association between serum total cholesterol and coronary heart disease incidence in Japan.[11-13] A study of Chinese workers also showed a direct association between serum total cholesterol and mortality from coronary heart disease.[14] Other small prospective studies of rural Japanese have failed to show an association between serum total cholesterol and coronary heart disease.[15] The small number of publications on blood lipids and coronary heart disease associations in Japan and other Asian countries is in part due to the low incidence and mortality of coronary heart disease[14,16-18] and low population level of serum total cholesterol.[14,15,18]

The contribution of HDL-C to coronary heart disease when total cholesterol is low, as in Japan and China, is uncertain because no prospective study in these countries has been reported. Studies in Western countries have not provided sufficient data on the relation between HDL-C and coronary heart disease at a low total cholesterol level, for example, <5.2 mmol/L (200 mg/dL), because the prevalence of such low cholesterol levels is relatively small.

To examine the association between HDL-C and incident coronary heart disease at low total cholesterol levels, an 8-year prospective study was conducted among 6408 middle-aged male workers in urban companies, in which approximately 80% of the subjects had total cholesterol concentrations <5.2 mmol/L. The relation between HDL-C and stroke was also examined.

Methods

The subjects were 6624 male workers of 13 industrial companies in Osaka, Japan, 40 to 59 years old, who participated in cardiovascular risk surveys between 1979 and 1986 and had no history of coronary heart disease or stroke. Of these 6624 men, 6408 (97%) who had HDL-C measured were included into the analysis. Eighteen subjects (0.3%) using drugs affecting lipid levels were included in the analysis because doing so had little impact on results. Intake of selected nutrients in this population was as follows: calories

Received January 12, 1994; revision accepted February 10, 1994.

From the Department of Epidemiology and Mass Examination (A.K., Y.N., M.I., S.S., M. Kiyama, M.N.), the Center for Adult Diseases, Osaka, Japan; the Institute of Community Medicine (H.I., T. Sankai, T. Shimamoto), University of Tsukuba, Japan; the National Cardiovascular Center (M. Konishi), Suita, Japan; the Division of Epidemiology (A.R.F.), School of Public Health, University of Minnesota, Minneapolis; and the Osaka Prefectural Institute of Public Health (Y.K.).

Correspondence to Akihiko Kitamura, MD, Department of Epidemiology and Mass Examination, Center for Adult Diseases, Osaka, 1-3-3 Nakamichi, Higashinariku, Osaka 537, Japan.

TABLE 1. Age-Specific and Age-Adjusted Mean Values of Risk Characteristics at Baseline for Men Who Withdrew From the Study Because of Retirement or Quitting and Men Who Did Not

Age at entry, y	40-44		45-49		50-54		55-59		Age-Adjusted	
Withdrawal	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Number	137	2441	192	1715	536	620	506	188	1371	4964
Age, y	41.8	41.8	47.5*	46.7	52.1*	51.4	56.6*	56.4	. . .	. . .
HDL cholesterol, mmol/L	1.46	1.46	1.43	1.45	1.44*	1.50	1.47	1.44	1.42	1.44
Serum total cholesterol, mmol/L	5.05	5.03	5.06	5.16	5.15	5.16	5.07*	5.30	5.03*	5.12
Systolic blood pressure, mm Hg	120.6	121.5	121.6	122.7	126.1	125.1	128.5*	124.9	123.9	123.1
Diastolic blood pressure, mm Hg	75.9	76.1	79.7	78.1	80.4	79.7	80.8	80.0	78.3	77.9
Body mass index, kg/m^2	22.2	22.5	22.8	22.6	22.5	22.7	22.1	22.3	22.4	22.5
Number of cigarettes per day	20.6*	15.2	12.9	14.2	12.9	13.4	12.3	12.3	14.7	14.2
Usual alcohol intake, g/day	37.9	35.8	35.1	34.1	28.8*	34.4	25.8*	30.9	31.5*	34.3

HDL indicates high-density lipoprotein.
Test for differences between men who withdrew from the study and men who did not: *$P<.05$.

from fat, 19% to 23%; ratio of dietary polyunsaturated to saturated fatty acids, 1.1:1.2; cholesterol intake, 430 to 490 mg per day. Details of the nutrition data were published previously.[19]

Baseline Examination

The baseline examination for a participant was defined as the first survey with an HDL-C measurement, with a single blood sample used to define lipid levels. A total of 4009 (63%) of the 6408 participants were fasting at least 8 hours.

Blood was obtained from an antecubital vein, and serum was separated. After precipitation by heparin-manganese, HDL-C was measured by the Liebermann-Burchard method on an AutoAnalyzer II (Technicon).[20] Serum total cholesterol was measured colorimetrically and serum triglyceride fluorimetrically using the Liebermann-Burchard reaction on an AutoAnalyzer II.[20] Between 1975 and 1990, our laboratory successfully met the criteria of precision and accuracy for the measurement of HDL-C and serum total cholesterol under the World Health Organization/Centers for Disease Control Cooperative Cholesterol and Triglyceride Standardization Program (Laboratory No. CT680567) and the Centers for Disease Control/National Heart, Lung, and Blood Institute Lipid Standardization Program (Laboratory No. INT-113).[21] Performance against reference samples indicated that our mean HDL-C values had a bias of <1.0%; coefficient variation was <3.0%.

For fasting participants (n=4009), low-density lipoprotein cholesterol (LDL-C) was calculated[22] as the total cholesterol value minus the HDL-C value minus the value (triglyceride/5).

First- and fifth-phase blood pressures were measured one or two times by trained observers using a standard mercury sphygmomanometer with the patient in the sitting position after at least a 5-minute rest. The first reading of blood pressures was used for the analysis. Body mass index was computed as weight (kilograms) divided by squared height (meters squared). Daily smoking habit and weekly alcohol intake were obtained by well-trained nurse interviewers.

Ascertainment of Incident Cardiovascular Disease and Death

Subjects with HDL-C measured were followed up to determine coronary heart disease and stroke end points through 1991. Follow-up was terminated at noncardiovascular death (n=73) or retirement (leaving the company) (n=1371). The age distribution at retirement for the 1371 men who left the company was 40 to 44 years, 4%; 45 to 49 years, 7%; 50 to 54 years, 13%; 55 to 59 years, 46%; 60 to 64 years, 29%; and 65 to 69 years, 1%.

Men who retired and those who did not had no consistent differences in age-specific mean values of HDL-C and other risk characteristics (Table 1). The age-adjusted mean value of HDL-C for men aged 40 to 59 years was similar between the two groups, whereas the mean value of serum total cholesterol and usual alcohol intake was slightly lower in men who retired than in men who did not.

Cardiovascular disease end points were ascertained via four sources: death certificates, absenteeism reports due to sickness, insurance claims to companies, and annual risk factor surveys. To validate the diagnosis, all living patients were visited or invited to risk factor surveys; study physicians obtained medical history, a standard ECG for coronary heart disease patients, and a neurological examination for stroke patients. For deaths, histories were obtained from the patient's family and/or colleagues who observed the incident. For both fatal and nonfatal cases, medical records at company clinics and/or local hospitals also were reviewed.

The criteria for coronary heart disease were modified from those of a World Health Organization Expert Committee.[23] Painless types of coronary heart disease were not investigated because of difficulty with ascertainment. "Definite" myocardial infarction was indicated by typical chest pain (lasting for 30 minutes or longer) with the appearance of abnormal and persistent Q or QS waves or changes in cardiac enzyme activity or both. "Suspect" myocardial infarction was indicated by typical chest pain without positive ECG and enzyme activity findings. Angina pectoris was defined as repeated episodes of chest pain during effort, especially when walking, usually disappearing rapidly after the cessation of effort or on use of sublingual nitroglycerin. Definite or suspect myocardial infarction and angina pectoris were combined and presented as coronary heart disease. The criteria[24] for stroke and type of stroke were modified criteria of Millikan,[25] which we described in detail elsewhere.[18]

Statistical Analysis

Mean values of baseline characteristics were compared between men who developed coronary heart disease, definite myocardial infarction, or stroke and men who remained free of cardiovascular disease using the t test or ANCOVA. The incidence rates per 1000 person-years for coronary heart disease and for stroke were calculated by quartiles of serum total cholesterol and HDL-C. The incidence rates were adjusted by the direct method of standardization to the age distribution of the total 6408 subjects analyzed.

Proportional hazards regression models[26] were used to examine the relations of these serum lipids with the incidence

TABLE 2. Means and Standard Errors of Risk Characteristics at Baseline for Those Developing Coronary Heart Disease or Stroke or Remaining Free of Cardiovascular Disease: Men Aged 40 to 59 Years

	Free of CVD (n=6256)	Coronary Heart Disease (n=46)	Difference From Free of CVD (*P*)	Stroke (n=33)	Difference From Free of CVD (*P*)
Age, y	46.8 (0.07)	46.8 (0.71)	.97	48.1 (0.84)	.15
HDL cholesterol, mmol/L	1.46 (0.004)	1.22 (0.04)	<.0001	1.39 (0.05)	.25
Serum total cholesterol, mmol/L	5.09 (0.01)	5.82 (0.16)	<.001	5.25 (0.20)	.42
Systolic blood pressure, mm Hg	123.1 (0.20)	128.0 (2.26)	.02	133.9 (2.74)	<.001
Diastolic blood pressure, mm Hg	77.9 (0.15)	81.0 (1.71)	.07	83.9 (1.73)	.005
Body mass index, kg/m^2	22.5 (0.03)	23.7 (0.39)	.002	22.9 (0.48)	.40
Number of cigarettes per day	14.2 (0.17)	20.6 (1.79)	.002	24.1 (3.22)	.004
Usual alcohol intake, g/day	33.7 (0.39)	25.3 (3.99)	.06	37.2 (5.64)	.51

CVD indicates cardiovascular disease; HDL, high-density lipoprotein.
Number of cigarettes and alcohol intake are mean values among all subjects.

of coronary heart disease and stroke, controlling for age, systolic blood pressure, body mass index, cigarette smoking, and alcohol intake. The hazard rate ratio was calculated as exponential of $\beta*\Delta x$, where β is the regression coefficient and Δx is a difference for the variable in question. The regression coefficients for serum total cholesterol and HDL-C also were converted to a percent increment in risk corresponding to a 0.026 mmol/L (1 mg/dL) in serum total cholesterol or HDL-C as follows[27]: excess risk=$100*(e^{\beta*0.026}-1)$. All probability values for statistical significance were two tailed.

Results

During 7.7 years of follow-up, there were 46 incident cases of coronary heart disease (21 definite myocardial infarction, 11 suspect myocardial infarction, 14 angina pectoris) and 33 of stroke (7 cerebral hemorrhage, 20 cerebral infarction, and 6 other types of stroke). Among the fasting participants (n=4009), there were 35 cases of coronary heart disease and 24 cases of stroke.

Table 2 shows mean values of risk characteristics at baseline for coronary heart disease and stroke cases and for those who remained free of cardiovascular disease. Compared with men free of cardiovascular disease, those with incident coronary heart disease had a significantly lower mean value of HDL-C and higher mean values of serum total cholesterol, systolic and diastolic blood pressures, and body mass index. The number of cigarettes smoked per day was higher and mean alcohol intake was lower in men developing coronary heart disease than in those free of cardiovascular disease. Adjustment for age did not alter these findings.

Mean HDL-C levels also were compared between men with coronary heart disease and men free of cardiovascular disease after adjustment for age, total serum cholesterol, body mass index, cigarette smoking, and alcohol intake. Adjusted mean values of HDL-C were 1.28 mmol/L for coronary heart disease and 1.46 mmol/L for men free of cardiovascular disease (difference, P=.0002). Among subtypes of coronary heart disease, adjusted mean values of HDL-C did not vary: 1.27 mmol/L for definite myocardial infarction (n=21), 1.29 mmol/L for suspect myocardial infarction (n=11), and 1.30 mmol/L for angina pectoris (n=14).

Men with incident stroke had significantly higher mean values of systolic and diastolic blood pressures and number of cigarettes smoked than those who remained free of cardiovascular disease. There were no significant differences in mean levels of HDL-C, serum total cholesterol, body mass index, or alcohol intake between men with stroke and those free of cardiovascular disease. Adjusted mean values of HDL-C did not vary either: 1.44 mmol/L for stroke and 1.46 mmol/L for those free of cardiovascular disease (P=.70). Among subtypes of stroke, adjusted mean values of HDL-C were 1.40 mmol/L for cerebral hemorrhage (n=7), 1.46 mmol/L for cerebral infarction (n=20), and 1.41 mmol/L for other types of stroke (n=6).

Table 3 provides the number of cases, age-adjusted incidence rates (per 1000 person-years), and multivariate-adjusted relative risks of coronary heart disease, definite myocardial infarction, and stroke by quartiles of serum total cholesterol concentration. For both coronary heart disease and definite myocardial infarction, the age-adjusted incidence rate and the relative risk were lowest in the lowest cholesterol quartile (<4.50 mmol/L) and increased with higher serum total cholesterol quartiles. According to a proportional hazards regression model adjusting for age, HDL-C, systolic blood pressure, body mass index, number of cigarettes, and usual alcohol intake, this positive association was statistically significant for both coronary heart disease and definite myocardial infarction. Multivariate-adjusted relative risk (95% confidence interval [CI]) in the highest cholesterol quartile compared with the lowest was 4.89 (1.84 to 12.9) for coronary heart disease and 5.14 (1.12 to 23.6) for definite myocardial infarction. Stated differently, a 0.026-mmol/L (1 mg/dL) greater serum total cholesterol concentration was associated with 1.9% greater absolute risk of both coronary heart disease and definite myocardial infarction. On the other hand, there was a U-shaped relation between serum total cholesterol and stroke incidence: The incidence rates and relative risks were higher in both the lowest and highest cholesterol quartiles than the middle quartiles.

Table 4 shows the HDL-C data. For both coronary heart disease and definite myocardial infarction, the incidence rate was highest in the lowest HDL-C quartile (<1.24 mmol/L) and decreased significantly with higher HDL-C quartiles. Multivariate-adjusted relative risk (95% CI) in the lowest quartile of HDL-C with the

TABLE 3. Age-Adjusted Incidence Rates of Coronary Heart Disease, Definite Myocardial Infarction, and Stroke During 7.7-Year Follow-up and Adjusted Relative Risk Estimates by Quartile of Serum Total Cholesterol Levels: Men Aged 40 to 59 Years

Serum Total Cholesterol Quartiles, mmol/L	Not at Risk	Person-Years of Follow-up	Coronary Heart Disease (n=46) No.	Age-Adjusted Rate*	Adjusted Relative Risk†	Definite Myocardial Infarction (n=21) No.	Age-Adjusted Rate	Adjusted Relative Risk	Stroke (n=33) No.	Age-Adjusted Rate	Adjusted Relative Risk
<4.50	1620	12 158	5	0.46	1.00	2	0.18	1.00	11	0.93	1.00
4.50-5.06	1579	12 047	7	0.58	1.48	3	0.26	1.53	2	0.17	0.19
5.07-5.63	1633	12 632	9	0.71	1.93	5	0.38	2.58	7	0.55	0.62
≥5.64	1576	12 200	25	2.02	4.89	11	0.89	5.14	13	1.02	1.13
P†					.001			.04			.78
Regression coefficient (SE)‡				.724 (.128)			.710 (.186)			.177 (.199)	
P				<.0001			.0001			.37	

*Rates are per 1000 person-years, adjusted by the direct method according to the age distribution of all men examined.

†Significance of the relative risk at the highest quartile of serum total cholesterol level to the lowest quartile, with use of a proportional hazards regression model with three indicator variables for total cholesterol level adjusting for age, high-density lipoprotein cholesterol level, systolic blood pressure, body mass index, number of cigarettes smoked per day, and usual alcohol intake.

‡Regression coefficients are derived from a proportional hazards regression model with a linear term for total cholesterol level adjusting for these covariates.

highest quartile was 4.17 (1.37 to 12.7) for coronary heart disease and 3.39 (0.68 to 16.8) for definite myocardial infarction. A 0.026-mmol/L (1 mg/dL) greater HDL-C concentration was associated with a 5.7% lower risk of coronary heart disease and a 6.4% lower risk of definite myocardial infarction. No association was evident between HDL-C and the incidence of stroke.

In a subsample analysis using only fasting participants controlling for age, systolic blood pressure, body mass index, number of cigarettes, usual alcohol intake, and LDL-C, the regression coefficients (SE) for HDL-C in relation to coronary heart disease and definite myocardial infarction were −2.28 (0.77) (*P*=.003) and −2.39 (1.17) (*P*=.04), respectively. The results adjusted for LDL-C were similar to the nonadjusted data of the total sample.

The inverse association of HDL-C level with the incidence of coronary heart disease and definite myocardial infarction was apparent both among men with serum total cholesterol <5.69 mmol/L (mean total cholesterol, 4.76 mmol/L) and with serum total cholesterol level ≥5.69 mmol/L (mean total cholesterol, 6.26 mmol/L) (Table 5). The inverse association was statistically significant and the magnitude of the association was similar in both the lower and higher total cholesterol subgroups. No interaction was found between HDL-C and total cholesterol in relation to the diseases according to the proportional hazards model (*P*=.88 for

TABLE 4. Age-Adjusted Incidence Rates of Coronary Heart Disease, Definite Myocardial Infarction, and Stroke During 7.7-Year Follow-up and Adjusted Relative Risk Estimates by Quartile of HDL Cholesterol Levels: Men Aged 40 to 59 Years

HDL Cholesterol Quartiles, mmol/L	Not at Risk	Person-Years of Follow-up	Coronary Heart Disease (n=46) No.	Age-Adjusted Rate*	Adjusted Relative Risk†	Definite Myocardial Infarction (n=21) No.	Age-Adjusted Rate	Adjusted Relative Risk	Stroke (n=33) No.	Age-Adjusted Rate	Adjusted Relative Risk
<1.24	1702	13 252	28	2.09	4.17	12	0.89	3.39	12	0.90	1.31
1.24-1.44	1579	12 035	7	0.64	1.61	4	0.36	1.82	9	0.77	1.23
1.45-1.65	1506	11 552	7	0.61	1.80	3	0.26	1.54	4	0.35	0.59
≥1.66	1621	12 198	4	0.33	1.00	2	0.17	1.00	8	0.64	1.00
P†					.01			.14			.60
Regression coefficient (SE)‡				−2.25 (.63)			−2.56 (.95)			−.522 (.588)	
P				.0003			.007			.37	

HDL indicates high-density lipoprotein.

*Rates are per 1000 person-years, adjusted by the direct method according to the age distribution of all men examined.

†Significance of the relative risk at the highest quartile of HDL cholesterol level to the lowest quartile, with use of a proportional hazards regression model with three indicator variables for HDL cholesterol level adjusting for age, serum total cholesterol level, systolic blood pressure, body mass index, number of cigarettes smoked per day, and usual alcohol intake.

‡Regression coefficients are derived from a proportional hazards regression model with a linear term for HDL cholesterol levels adjusting for these covariates.

TABLE 5. Age-Adjusted Incidence Rates of Coronary Heart Disease and Definite Myocardial Infarction According to Serum Total Cholesterol and HDL Cholesterol Levels: Men Aged 40 to 59 Years

Serum Total Cholesterol, mmol/L	HDL Cholesterol, mmol/L	Not at Risk	Person-Years of Follow-up	Coronary Heart Disease			Definite Myocardial Infarction		
				No.	Age-Adjusted Rate*	Adjusted Relative Risk	No.	Age-Adjusted Rate	Adjusted Relative Risk
<5.69	<1.42	2366	18 227	16	0.89	2.46	8	0.45	4.00
	≥1.42	2604	19 709	6	0.31	1.00	2	0.11	1.00
P†						.08			.09
Regression coefficient (SE)‡					−2.12 (.87)			−2.62 (1.33)	
P					.02			.049	
≥5.69	<1.42	677	5252	19	3.59	2.58	7	1.49	1.55
	≥1.42	761	5849	5	0.87	1.00	2	0.54	1.00
P†						.08			.55
Regression coefficient (SE)‡					−2.69 (.94)			−2.90 (1.44)	
P					.004			.04	

HDL indicates high-density lipoprotein.

*Rates are per 1000 person-years, adjusted by the direct method according to the age distribution of all men examined.

†Significance of the relative risk for the higher HDL cholesterol level compared with the lower level, with use of a proportional hazards regression model with indicator variables for HDL cholesterol level adjusting for age, serum total cholesterol level, systolic blood pressure, body mass index, number of cigarettes smoked per day, and usual alcohol intake.

‡Regression coefficients are derived from a proportional hazards regression model with a linear term for HDL cholesterol levels adjusting for these covariates.

coronary heart disease and $P=.98$ for definite myocardial infarction).

In the subsample of fasting participants with control for LDL-C, the regression coefficient (SE) of HDL-C (mmol/L) for coronary heart disease was −2.89 (1.13) ($P=.01$) in men with serum total cholesterol <5.69 mmol/L and −2.23 (1.06) ($P=.04$) in those with serum total cholesterol ≥5.69 mmol/L. The respective regression coefficients (SE) of HDL-C for definite myocardial infarction were −2.86 (1.84) ($P=.12$) and −2.60 (1.55) ($P=.09$). The results adjusted for LDL-C were similar to the nonadjusted data of the total sample.

Discussion

The present study showed that serum HDL-C and total cholesterol were inversely and independently associated with the incidence of coronary heart disease in middle-aged Japanese men. These results are consistent with other epidemiological studies in the United States and European countries.[2-8] Chen et al[14] reported a positive relation between serum total cholesterol and mortality from coronary heart disease below the range of cholesterol values generally seen in Western populations. Our study confirms that serum total cholesterol concentration is positively associated with coronary heart disease incidence even at low cholesterol levels.

The uniqueness of this study is that the protective association of HDL-C with coronary heart disease was found in men whose level of serum total cholesterol is relatively low. Mean serum total cholesterol in this sample was 5.10 mmol/L, which is 0.34 to 1.24 mmol/L lower than levels previously reported for US and European men.[27-30] This study suggests that a 0.026-mmol/L (1 mg/dL) greater HDL-C concentration was associated with a 5.7% to 6.4% lower incidence rate of coronary heart disease and definite myocardial infarction. When controlling for LDL-C in the subsample analysis of the fasting participants, the corresponding risk decrement was similar. These estimates are higher than the estimate of 1.9% to 2.3% from four prospective American studies,[27] although the CI includes the estimate of the American studies. There is no obvious explanation for a stronger inverse association of HDL-C with coronary heart disease in the Japanese study than in the American studies; yet, it is noteworthy that American women, who have a lower incidence of coronary heart disease than American men, showed a higher estimate of risk (3.2% per 1 mg/dL HDL-C) than American men.[27]

Furthermore, the protective association of HDL-C with coronary heart disease was observed in men with serum total cholesterol <5.69 mmol/L as well as those with values ≥5.69 mmol/L. That is, the magnitude of the inverse association of HDL-C with coronary heart disease and definite myocardial infarction did not vary according to total cholesterol concentration. A similar finding was reported from two US studies.[31,32]

The current screening recommendation of the US National Cholesterol Education Program is to measure lipoproteins when total cholesterol is either >6.21 mmol/L or lies within 5.17 to 6.21 mmol/L in the presence of two or more risk factors.[33] This study suggests that, even at lower levels of total cholesterol, screening of HDL-C might be valuable to indicate persons at greater risk of coronary heart disease. However, the cost-benefit of such measurement to prevent coronary heart disease is, of course, not established.

There was no association evident between HDL-C and stroke. A prospective study[29] of Japanese living in Hawaii reported an insignificant inverse association between HDL-C and stroke. Several clinical and pathological studies reported that HDL-C levels were lower in patients with cerebral infarction in cortical artery regions than in those with no stroke or cerebral infarction in penetrating artery regions.[34-36] The present

sample size, however, did not allow us to examine relations of HDL-C to subtype of cerebral infarction.

A drawback of this study is that we did not identify cardiovascular disease events after men left employment in the participating companies. However, there were no apparent differences in age-specific or age-adjusted mean values of baseline coronary risk factors, including HDL-C, between men who left employment and men who did not. Thus, the withdrawal of these men is unlikely to affect the results substantially.

Survey follow-up was terminated mostly between ages 55 and 64 years, meaning the results are generalizable primarily to "premature" coronary heart disease in urban Japanese men. As premature coronary heart disease has a large impact on years of productivity, the findings are important.

Conclusions

The present study indicated an independent inverse relation of HDL-C and total cholesterol with coronary heart disease in a population with low total serum cholesterol concentrations. Because cigarette smoking, body mass index, and physical activity were strongly correlated with HDL-C, as reported previously in our study[37,38] and in other studies,[4,6,10,39,40] smoking cessation, weight control, and exercise probably would be helpful in the prevention of coronary heart disease in Japanese as well as US and European men.

Acknowledgments

The authors thank Dr David R. Jacobs, Division of Epidemiology, University of Minnesota, for valuable comments on the manuscript.

References

1. Kannel WB, Castelli WP, Gordon T, Mcnamara PM. Serum cholesterol, lipoproteins, and the risk of coronary heart disease: the Framingham Study. *Ann Intern Med.* 1971;74:1-12.
2. The Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the Pooling Project. *J Chron Dis.* 1978;31:201-306.
3. WHO Expert Committee on Prevention of Coronary Heart Disease. *Prevention of Coronary Heart Disease: World Health Organization Technical Report Series 678.* Geneva: World Health Organization, 1982.
4. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease: the Framingham Study. *Am J Med.* 1977;62:707-714.
5. Miller NE, Forde OH, Thelle DS, Mjos OD. The Tromso Heart Study: high-density lipoprotein and coronary heart disease: a prospective case-control study. *Lancet.* 1977;1:965-968.
6. Goldbourt U, Medalie JH. High density lipoprotein cholesterol and incidence of coronary heart disease: the Israeli Ischemic Heart Disease Study. *Am J Epidemiol.* 1979;109:296-308.
7. Enger SC, Hjermann I, Foss OP, Helgeland A, Holme I, Leren P, Norum KR. High density lipoprotein cholesterol and myocardial infarction or sudden coronary death: a prospective case-control study in middle-aged men of the Oslo study. *Artery.* 1979;5:170-181.
8. Keys A. Alpha lipoprotein(HDL) cholesterol in the serum and the risk of coronary heart disease and death. *Lancet.* 1980;2:603-606.
9. Yaari S, Goldbourt U, Even-Zohar S, Neufeld HN. Associations of serum high density lipoprotein and total cholesterol with total, cardiovascular, and cancer mortality in a 7-year prospective study of 10,000 men. *Lancet.* 1981;1:1011-1015.
10. Jacobs DR Jr, Mebane IL, Bangdiwala SI, Criqui MH, Tyroler HA. High density lipoprotein cholesterol as a predictor of cardiovascular disease mortality in men and women: the follow-up study of the Lipid Research Clinics Prevalence Study. *Am J Epidemiol.* 1990;131:32-47.
11. Konishi M, Iida M, Naito Y, Terao A, Takayama Y, Ito H, Yutani C, Ito M, Kojima S, Shimamoto T, Inada H, Doi M, Iso H, Sato S, Kitamura A, Komachi Y. The trend of coronary heart disease and its risk factors based on epidemiological investigations. *Jpn Circ J.* 1987;51:319-324.
12. Kiyohara Y, Ueda K, Fujishima M. Smoking and cardiovascular disease in the general population in Japan. *J Hypertens.* 1990;8(suppl 5):S9-S15.
13. Kodama K, Sasaki H, Shimizu Y, Kato H, Akahoshi M, Hosoda Y. *Cholesterol and Coronary Heart Disease in a Japanese Population: A 26-Year Follow-up Study.* Second International Conference on Preventive Cardiology and the 29th Annual Meeting of the AHA Council on Epidemiology. 1989:A64. Abstract.
14. Chen Z, Peto R, Collins R, MacMahon S, Lu J, Li W. Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. *BMJ.* 1991;303:276-282.
15. Komachi Y, Kojima S, Sakuma M, Isomura K, Iida M, Tanaka H, Tsunetoshi Y, Hiwada K, Takahashi H, Handa K. *A Collaborative Study on Geographical and Occupational Differences in Nutrition Intake and Its Relation to Stroke and Coronary Heart Disease* [in Japanese]. Annual Report of the Research on Cardiovascular Diseases 1983, Osaka, National Cardiovascular Center; 1984:14-25.
16. Pisa Z, Uemura K. Trends of mortality from ischaemic heart disease and other cardiovascular diseases in 27 countries, 1968-1977. *World Health Stat Q.* 1982;35:11-47.
17. Robertson TL, Kato H, Rhoads GG, Kagan A, Marmot M, Syme SL, Gordon T, Worth RM, Belsky JL, Dock DS, Miyanishi M, Kawamoto S. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California: incidence of myocardial infarction and death from coronary heart disease. *Am J Cardiol.* 1977;39:239-243.
18. Shimamoto T, Komachi Y, Inada H, Doi M, Iso H, Sato S, Kitamura A, Iida M, Konishi M, Nakanishi N, Terao A, Naito Y, Kojima S. Trends for coronary heart disease and stroke and their risk factors in Japan. *Circulation.* 1989;79:503-515.
19. Ueshima H, Iida M, Shimamoto T, Konishi M, Tanigaki M, Doi M, Nakanishi N, Takayama Y, Ozawa H, Komachi Y. Dietary intake and serum total cholesterol level: their relationship to different lifestyles in several Japanese populations. *Circulation.* 1982;66:519-526.
20. Lipid Research Clinics Program. *Manual of Laboratory Operations, Lipid and Lipoprotein Analysis.* US Dept of Health, Education, and Welfare publication No. 75-628 (revised). Washington, DC: US Government Printing Office; 1982.
21. Nakamura M, Morita M, Yabuuchi E, Yukami M, Kuruma S, Kuritani C, Kanatsu Y, Nishiwaki E, Ueshima H, Iida M, Komachi Y. The evaluation and the results of cooperative cholesterol and triglyceride standardization program by WHO-CDC [in Japanese]. *Rinsho Byori.* 1982;30:325-332.
22. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* 1972;18:499-502.
23. WHO Expert Committee. *Arterial Hypertension and Ischemic Heart Disease, Preventive Aspects.* Geneva: WHO Technical Report Series No. 231; 1962.
24. The Ministry of Education Study Group, Okinaka S (chairman). *Characteristics of Stroke in Japan and Standardized Criteria for Stroke Diagnosis* [in Japanese]. Tokyo: The Ministry of Education; 1963.
25. Millikan CH. A report by an ad hoc committee established by the Advisory Council for the National Institute of Neurological Disease and Blindness, Public Health Service: a classification and outline of cerebrovascular diseases. *Neurology.* 1958;8:393-433.
26. Cox DR. Regression models and life-tables. *J R Stat Soc [B].* 1972;34:187-220.
27. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, Jacobs DR, Bangdiwala S, Tyroler A. High-density lipoprotein cholesterol and cardiovascular disease: four prospective American studies. *Circulation.* 1989;79:8-15.
28. Sprafka JM, Burke GL, Folsom AR, Luepker RV, Blackburn H. Continued decline in cardiovascular disease risk factors: results of the Minnesota Heart Survey, 1980-1982 and 1985-1987. *Am J Epidemiol.* 1990;132:489-500.
29. Reed D, Yano K, Kagan A. Lipids and lipoproteins as predictors of coronary heart disease, stroke, and cancer in the Honolulu Heart Program. *Am J Med.* 1986;80:871-878.
30. National Center for Health Statistics-National Heart, Lung, and Blood Institute Collaborative Lipid Group. Trends in serum cho-

lesterol levels among US adults aged 20 to 74 years. *JAMA.* 1987; 257:937-942.
31. Abbott RD, Wilson PWF, Kannel WB, Castelli WP. High density lipoprotein cholesterol, total cholesterol screening, and myocardial infarction: the Framingham Study. *Arteriosclerosis.* 1988;8:207-211.
32. Stampfer MJ, Sacks FM, Salvini S, Willett WC, Hennekens CH. A prospective study of cholesterol, apoproteins, and the risk of myocardial infarction. *N Engl J Med.* 1991;325:373-381.
33. Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Report of the National Cholesterol Education Program Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults. *Arch Intern Med.* 1988;148:36-69.
34. Murai A, Tanaka T, Miyahara T, Kameyama M. Lipoprotein abnormalities in the pathogenesis of cerebral infarction and transient ischemic attack. *Stroke.* 1981;12:167-172.
35. Tell GS, Crouse JR, Furberg CD. Relation between blood lipids, lipoproteins, and cerebrovascular atherosclerosis: a review. *Stroke.* 1988;19:423-430.
36. Adams RJ, Carroll RM, Nichols FT, McNair N, Feldman DS, Feldman EB, Thompson WO. Plasma lipoproteins in cortical versus lacunar infarction. *Stroke.* 1989;20:448-452.
37. Iida M, Ueshima H, Terao A, Shimamoto T, Konishi M, Doi M, Nakanishi N, Takayama Y, Naito Y, Tanigaki M, Komachi Y. The effect of HDL-cholesterol on cardiovascular disease in Japan [in Japanese]. *Kousei no Shihyo.* 1981;28:3-10.
38. Miyagaki T, Iso H, Kitamura A, Naito Y, Sankai T, Shimamoto T, Sato S, Kiyama M, Tanigaki M, Iida M, Komachi Y. Physical activity and its relationship to cardiovascular risk factors in rural Japanese men. *J Epidemiol.* 1992;2:97-104.
39. Tyroler HA, guest ed. Epidemiology of plasma high-density lipoprotein cholesterol levels: the Lipid Research Clinics Program Prevalence Study, Lipid Research Clinics Program. *Circulation.* 1980;62(suppl IV):1-136.
40. Linn S, Fulwood R, Rifkind B, Carroll M, Muesing R, Williams OD, Johnson C. High density lipoprotein cholesterol levels among US adults by selected demographic and socioeconomic variables: the second national health and nutrition examination survey 1976-1980. *Am J Epidemiol.* 1989;129:281-294.