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

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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.

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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 disease14,16-18 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 in 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...
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.21 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 calculated22 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 (the leaving 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%.

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

<table>
<thead>
<tr>
<th>Age at entry, y</th>
<th>40-44</th>
<th>45-49</th>
<th>50-54</th>
<th>55-59</th>
<th>Age-Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Number</td>
<td>137</td>
<td>2441</td>
<td>192</td>
<td>1715</td>
<td>536</td>
</tr>
<tr>
<td>Age, y</td>
<td>41.8</td>
<td>41.8</td>
<td>47.5*</td>
<td>46.7</td>
<td>52.1*</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.46</td>
<td>1.46</td>
<td>1.43</td>
<td>1.45</td>
<td>1.44*</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>5.05</td>
<td>5.03</td>
<td>5.06</td>
<td>5.16</td>
<td>5.15</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>120.6</td>
<td>121.5</td>
<td>121.6</td>
<td>122.7</td>
<td>126.1</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>75.9</td>
<td>76.1</td>
<td>79.7</td>
<td>78.1</td>
<td>80.4</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.2</td>
<td>22.5</td>
<td>22.8</td>
<td>22.6</td>
<td>22.5</td>
</tr>
<tr>
<td>Number of cigarettes per day</td>
<td>20.6*</td>
<td>15.2</td>
<td>12.9</td>
<td>14.2</td>
<td>12.9</td>
</tr>
<tr>
<td>Usual alcohol intake, g/day</td>
<td>37.9</td>
<td>35.8</td>
<td>35.1</td>
<td>34.1</td>
<td>28.8*</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein.

*Test for differences between men who withdrew from the study and men who did not: *P<.05.

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 criteria24 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 models26 were used to examine the relations of these serum lipids with the incidence
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 \( β \Delta x \), 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: excess risk = 100(\( e^{βΔx} - 1 \)). 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

<table>
<thead>
<tr>
<th>Serum Total Cholesterol Quartiles, mmol/L</th>
<th>Coronary Heart Disease (n=46)</th>
<th>Definite Myocardial Infarction (n=21)</th>
<th>Stroke (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age-Adjusted Rate*</td>
<td>Adjusted Relative Risk†</td>
<td>Age-Adjusted Rate</td>
</tr>
<tr>
<td>&lt;4.50</td>
<td>0.46</td>
<td>1.00</td>
<td>2</td>
</tr>
<tr>
<td>4.50-5.06</td>
<td>0.58</td>
<td>1.48</td>
<td>3</td>
</tr>
<tr>
<td>5.07-5.63</td>
<td>0.71</td>
<td>1.93</td>
<td>5</td>
</tr>
<tr>
<td>≥5.64</td>
<td>2.02</td>
<td>4.89</td>
<td>11</td>
</tr>
</tbody>
</table>

Regression coefficient (SE)‡

For HDL-C, the regression coefficients were derived from a proportional hazards regression model with a linear term for HDL 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 ≥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

<table>
<thead>
<tr>
<th>HDL Cholesterol Quartiles, mmol/L</th>
<th>Coronary Heart Disease (n=46)</th>
<th>Definite Myocardial Infarction (n=21)</th>
<th>Stroke (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age-Adjusted Rate*</td>
<td>Adjusted Relative Risk†</td>
<td>Age-Adjusted Rate</td>
</tr>
<tr>
<td>&lt;1.24</td>
<td>2.09</td>
<td>4.17</td>
<td>12</td>
</tr>
<tr>
<td>1.24-1.44</td>
<td>0.64</td>
<td>1.61</td>
<td>4</td>
</tr>
<tr>
<td>1.45-1.65</td>
<td>0.61</td>
<td>1.80</td>
<td>3</td>
</tr>
<tr>
<td>≥1.66</td>
<td>0.33</td>
<td>1.00</td>
<td>2</td>
</tr>
</tbody>
</table>

Regression coefficient (SE)‡

| P| .01                      | .14                              | .60          |

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

<table>
<thead>
<tr>
<th>Serum Total Cholesterol, mmol/L</th>
<th>HDL Cholesterol, mmol/L</th>
<th>Not at Risk</th>
<th>Person-Years of Follow-up</th>
<th>Coronary Heart Disease</th>
<th>Definite Myocardial Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No.</td>
<td>Adjusted Rate*</td>
</tr>
<tr>
<td>&lt;5.69</td>
<td>&lt;1.42</td>
<td>2366</td>
<td>18227</td>
<td>16</td>
<td>0.89</td>
</tr>
<tr>
<td>≥5.69</td>
<td>&lt;1.42</td>
<td>677</td>
<td>5252</td>
<td>19</td>
<td>3.59</td>
</tr>
<tr>
<td>P†</td>
<td></td>
<td></td>
<td></td>
<td>.02</td>
<td>.049</td>
</tr>
<tr>
<td>Regression coefficient (SE)‡</td>
<td></td>
<td></td>
<td></td>
<td>-2.12 (.87)</td>
<td>-2.62 (1.33)</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td>.08</td>
<td>.55</td>
</tr>
<tr>
<td>≥5.69</td>
<td>≥1.42</td>
<td>761</td>
<td>5849</td>
<td>5</td>
<td>0.87</td>
</tr>
<tr>
<td>P†</td>
<td></td>
<td></td>
<td></td>
<td>.08</td>
<td>.55</td>
</tr>
<tr>
<td>Regression coefficient (SE)‡</td>
<td></td>
<td></td>
<td></td>
<td>-2.60 (.94)</td>
<td>-2.90 (1.44)</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td>.004</td>
<td>.04</td>
</tr>
</tbody>
</table>

*Indicates high-density lipoprotein.

†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 al14 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 study29 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,45-58 and in other studies,4-6,10,19,20 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.

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