High-Density Lipoprotein Cholesterol and Risk of Stroke in Japanese Men and Women

The Oyabe Study

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Background and Purpose—Evidence of an inverse relationship between serum high-density lipoprotein cholesterol (HDL-C) and the risk of stroke is sparse in Asians and in women. The purpose of this investigation was to examine the relationship in a long-term cohort study of Japanese men and women among whom stroke occurrence is higher than in Western countries.

Methods—A prospective cohort study was performed involving 4989 participants (1523 men, 3466 women) 35 to 79 years of age at baseline with ≈10 years of follow-up in a rural area of Japan. End points included all stroke incidence and ischemic stroke incidence.

Results—During follow-up, 132 participants developed stroke, including 81 ischemic stroke cases. Age-adjusted incidence rates per 10 000 person-years for all stroke in subjects with low HDL-C (<30 mg/dL [0.78 mmol/L]) were 103.4 in men and 49.3 in women, which were remarkably higher than in subjects with high HDL-C (≥60 mg/dL [1.56 mmol/L]) (26.4 in men and 15.5 in women). A similar relationship was observed for ischemic stroke. Multivariate-adjusted relative risks for all stroke incidence and ischemic stroke incidence were 2.89 (95% CI, 1.35 to 6.20) and 2.92 (95% CI, 1.17 to 7.32), respectively, for low versus high HDL-C participants. The relationships were independent of sex, age, body mass index, blood pressure, serum total cholesterol, alcohol consumption, and smoking.

Conclusions—This 10-year follow-up study of Japanese men and women demonstrated that lower HDL-C levels were related significantly and independently to increased risk of all stroke incidence and ischemic stroke incidence. (Stroke. 2003;34:863-868.)

Key Words: cohort studies ■ lipoproteins, HDL cholesterol ■ risk factors ■ stroke

Many epidemiological investigations have provided evidence regarding the risk factors for stroke to accomplish primary prevention of the disease.1–6 For example, blood pressure, diabetes mellitus, atrial fibrillation, and cigarette smoking were found to be major risk factors. As for serum lipids, the association between total cholesterol concentration and risk of stroke has been examined in several prospective studies,7–13 and a positive relation to ischemic stroke and an inverse relation to hemorrhagic stroke were reported. On the other hand, although lower levels of serum high-density lipoprotein cholesterol (HDL-C) have repeatedly been shown to be a significant risk factor for coronary heart disease,14–17 whether lower HDL-C levels increase the risk of stroke remains unclear. A few recent cohort studies, mainly in Western men,18–22 have shown an inverse relationship between HDL-C and stroke; however, evidence in women and in Asian people is sparse. The goal of this research was to determine whether HDL-C predicts long-term incidence of stroke in Japanese men and women, an Asian population in which stroke occurrence is higher than in Western countries.

Methods

Study Population
The city of Oyabe, which covers an area of 134.1 km², is located in the Toyama Prefecture in the central part of Japan. Oyabe has ≈35 000 residents. It includes semi-industrial and agricultural areas. Oyabe is one of the districts demonstrating stroke mortality relatively higher than the national rate in Japan.23

This population-based cohort study, which was performed as part of the Oyabe Study, consisted of 5074 residents (1569 men, 3505 women) 35 to 79 years of age who received medical check-ups available for the population of Oyabe from May 1988 through...
November 1988. All participants were invited via letter to the medical check-up on a specific date. Twenty-five percent of all residents 35 to 79 years of age participated in the baseline examination. The response rate was lower in men because many men working in big companies did not respond.

Baseline Examination
Data collected at baseline included age, sex, height, weight, blood pressure, serum total cholesterol, serum HDL-C, smoking status, and alcohol consumption. A single blood pressure measurement was obtained from subjects after a 5-minute rest period while in the seated position by trained staff using a random-zero sphygmomanometer. Blood samples were obtained via cubital vein puncture without regard to the time of the previous meal. Standard enzymatic methods were used to determine serum total cholesterol level with an automatic analyzer (Hitachi-736, Hitachi Ltd), and dextran sulfate methods were used to determine serum HDL-C level with an automatic analyzer (ACA8000, Olympus Ltd). The questionnaire administered by trained staff included medical history, subjective symptoms, and the status of cigarette smoking and alcohol consumption. The status of alcohol consumption was divided into 3 categories: nondrinkers, occasional drinkers, and daily drinkers.

End Points
Vital status and the incidence of stroke were ascertained through the end of 1998, with a follow-up of ~10 years. Stroke events were assessed from the population-based stroke registration system of Oyabe. Details of this registration system are given elsewhere. In brief, this stroke registration system has been continuously active for the prevention of stroke and for rehabilitation since 1967. Information regarding stroke was documented mainly for hospitalized patients and outpatients by physicians of all general hospitals and by general practitioners in Oyabe and general hospitals in neighboring cities. Physicians reported the events in a prescribed format that included items related to neurological deficit, trends of symptom, and history. The type of stroke was classified according to the criteria of the Stroke Committee established by the Japanese Ministry of Education, which modified the diagnostic criteria of the ad hoc committee established by the Advisory Council for the National Institute of Neurological Diseases and Blindness, Public Health Service. Registered cases included ischemic stroke, hemorrhagic stroke, and subarachnoid hemorrhage; patients suffering transient ischemic attacks and those presenting with asymptomatic lesions detected by brain imaging were not included. Hospitals equipped with x-ray CT scanners reported at least 85% of registered cases.

To complete the registration, stroke information was gathered from death certificates. Death events from death certificates were coded by trained doctors according to the International Classification of Diseases, Ninth Revision (ICD-9). For this report, the underlying cause of death was used. Mortality from stroke was defined as ICD-9 code 430 to 438. Information was obtained from the Oyabe resident-based register regarding withdrawn participants, including relocation from the city or death from other causes during the observation period.

Exclusions
Participants presenting with a history of stroke (n=65) and those lacking baseline examination data (n=20) were excluded from the cohort. Thus, the report was based on a total of 4989 participants (1523 men, 3466 women).

Statistical Analysis
Crude and age-adjusted rates per 10 000 person-years of follow-up were computed for all stroke incidence and ischemic stroke incidence. Age-adjusted rates were calculated by the direct method from the overall cohort age distribution. Incidence rate was calculated for 5 categories of HDL-C: <30 mg/dL (0.78 mmol/L), 30 to 39 mg/dL (0.78 to 1.03 mmol/L), 40 to 49 mg/dL (1.04 to 1.29 mmol/L), 50 to 59 mg/dL (1.30 to 1.55 mmol/L), and ≥60 mg/dL (1.56 mmol/L). Rates were also calculated for 5 categories of total cholesterol.

Table 1 presents data with respect to baseline variables. Mean age in men was 2.6 years higher than in women; additionally, mean values of blood pressure in men were higher than those in women. Mean values of body mass index, serum total cholesterol, and HDL-C were significantly higher in women than in men.

During follow-up, 63 men and 69 women developed a first-ever stroke event, including 46 men and 35 women who developed ischemic stroke. Twenty-five men and 26 women died as a result of stroke, whereas a total of 388 participants died as a result of all causes. Ninety-two participants were withdrawn because of geographic relocation. Mean age at the first occurrence of stroke in these cohorts was 71.5 years in men and 69.4 years in women. Crude rates for all stroke incidence per 10 000 person-years were 43.0 in men and 19.8 in women. Crude rates for all stroke incidence and ischemic stroke incidence increased as baseline age rose in both sexes (data not shown).

Table 2 shows age-adjusted rates per 10 000 person-years for 2 end points according to HDL-C levels and total cholesterol levels in men. Age-adjusted incidence rates for all stroke increased continuously and markedly as HDL-C levels.
declined. The age-adjusted incidence rate of all stroke for HDL-C of <30 mg/dL (0.78 mmol/L) was nearly 4 times higher compared with that for HDL-C of ≥60 mg/dL (1.56 mmol/L). For ischemic stroke incidence, rates were also highest in men with HDL-C of <30 mg/dL (0.78 mmol/L). Rates of 2 end points were highest in men exhibiting serum total cholesterol of ≥220 mg/dL (5.72 mmol/L) and lowest in men with serum total cholesterol of 200 to 219 mg/dL (5.20 to 5.71 mmol/L).

Age-adjusted rates for 2 end points in women are presented in Table 3. Age-adjusted incidence rate for all stroke was markedly high in women with HDL-C of <30 mg/dL (0.78 mmol/L), although the relationship was less continuous than that in men. The relationship of HDL-C to all stroke mortality was not clear, probably because of the smaller number of events. The relationship of total cholesterol to all stroke and ischemic stroke incidence resembled a U-shaped curve with the bottom between total cholesterol values of 180 and 220 mg/dL (4.68 and 5.72 mmol/L).

Sex- and age-adjusted and multivariate-adjusted RRs calculated by Cox proportional-hazard analyses are presented in Table 4. Analyses were performed in all subjects. RRs were adjusted for sex, age, body mass index, systolic blood pressure, serum total cholesterol, smoking habits, and alcohol consumption in multivariate-adjusted models. Because the relationship between stroke events and serum total cholesterol did not show a linear trend, adjustment was performed with

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**TABLE 2. Relationship of Baseline HDL-C and Total Cholesterol to Age-Adjusted Person-Year Rates for All Stroke Incidence and Ischemic Stroke Incidence in Men**

<table>
<thead>
<tr>
<th>Serum HDL-C, mg/dL (mmol/L)</th>
<th>All Stroke Incidence</th>
<th>Ischemic Stroke Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men, n</td>
<td>Age-Adjusted Rate per 10 000 Person-Years</td>
</tr>
<tr>
<td>&lt;30 (&lt;0.78)</td>
<td>118  (11)</td>
<td>103.4</td>
</tr>
<tr>
<td>30– (0.78–)</td>
<td>424  (19)</td>
<td>46.7</td>
</tr>
<tr>
<td>40– (1.04–)</td>
<td>511  (20)</td>
<td>42.4</td>
</tr>
<tr>
<td>50– (1.30–)</td>
<td>289  (8)</td>
<td>33.5</td>
</tr>
<tr>
<td>60– (1.56–)</td>
<td>181  (5)</td>
<td>26.4</td>
</tr>
</tbody>
</table>

Serum total cholesterol, mg/dL (mmol/L)

| <160 (<4.16)              | 391  (19)           | 45.5                      | 13  | 32.0 |
| 160– (4.16–)              | 377  (17)           | 48.4                      | 12  | 35.2 |
| 180– (4.68–)              | 334  (12)           | 39.5                      | 8   | 27.0 |
| 200– (5.20–)              | 235  (7)            | 30.2                      | 6   | 25.3 |
| 220– (5.72–)              | 186  (8)            | 61.8                      | 7   | 56.0 |

Total 1523  (63)       | 46                        | 46                        |

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**TABLE 3. Relationship of Baseline HDL-C and Total Cholesterol to Age-Adjusted Person-Year Rates for All Stroke Incidence and Ischemic Stroke Incidence in Women**

<table>
<thead>
<tr>
<th>Serum HDL-C, mg/dL (mmol/L)</th>
<th>All Stroke Incidence</th>
<th>Ischemic Stroke Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women, n</td>
<td>Age-Adjusted Rate per 10 000 Person-Years</td>
</tr>
<tr>
<td>&lt;30 (&lt;0.78)</td>
<td>131  (8)</td>
<td>49.3</td>
</tr>
<tr>
<td>30– (0.78–)</td>
<td>643  (11)</td>
<td>15.9</td>
</tr>
<tr>
<td>40– (1.04–)</td>
<td>1246 (21)</td>
<td>17.0</td>
</tr>
<tr>
<td>50– (1.30–)</td>
<td>926  (22)</td>
<td>24.9</td>
</tr>
<tr>
<td>60– (1.56–)</td>
<td>520  (7)</td>
<td>15.5</td>
</tr>
</tbody>
</table>

Serum total cholesterol, mg/dL (mmol/L)

| <160 (<4.16)              | 429  (7)            | 23.2                      | 4   | 12.3 |
| 160– (4.16–)              | 636  (14)           | 26.4                      | 7   | 13.0 |
| 180– (4.68–)              | 746  (11)           | 14.9                      | 7   | 9.4  |
| 200– (5.20–)              | 719  (15)           | 20.4                      | 4   | 5.4  |
| 220– (5.72–)              | 936  (22)           | 19.2                      | 13  | 11.7 |

Total 3466  (69)       | 35                      | 35                        |
4 dummy variables for 5 categories of total cholesterol. Adjustment for alcohol consumption was also conducted with 2 dummy variables. Compared with participants with HDL-C of ≥60 mg/dL (1.56 mmol/L) as the reference level, adjusted RR for all stroke incidence and ischemic stroke incidence were 3 times higher in those with HDL-C <30 mg/dL (0.78 mmol/L), a finding that was statistically significant. Relationships were not clear in participants with HDL-C of ≥30 mg/dL (0.78 mmol/L). When analyzed for each sex separately, the relationships were similar, and multivariate-adjusted RRs for all stroke incidence were the highest in subjects with HDL-C <30 mg/dL (0.78 mmol/L) compared with the reference level (3.02 [P = 0.057] in men and 2.89 [P = 0.053] in women). Results were also similar when RR were calculated according to quintiles of HDL-C in men and women. (Data are shown in Tables A through D, which are available online at http://stroke.ahajournals.org.) Multivariate-adjusted RRs were not significantly different among the 5 categories of total cholesterol level (data not shown).

**Discussion**

This community-based 10-year follow-up study in Japanese men and women indicated that low HDL-C levels (<30 mg/dL [0.78 mmol/L]) led to significantly and independently increased risk of stroke. Participants with low HDL-C levels showed 3-fold-higher risk of all stroke and ischemic stroke incidence after multivariate adjustment.

Although reliable evidence exists regarding the inverse relation of HDL-C and the risk of coronary heart disease, the relation to stroke has not been identified sufficiently. A few prospective studies have addressed this issue in Western men; however, evidence in women or in Asian populations has been sparse. The first detailed description of the association between stroke and HDL-C derives from the Framingham Heart Study, which documented an inverse relation between HDL-C and the incidence of atherothrombotic brain infarction. However, this relation was weak and not significant. The Copenhagen City Heart Study revealed that HDL-C included as a continuous variable in a Cox proportional-hazard model negatively associated with non-hemorrhagic stroke incidence (RR, 1.18 with a decrease of 10 mg/dL [0.26 mmol/L]). In a 21-year prospective study of Israeli men ≥42 years of age, decreasing rates of ischemic stroke mortality were observed with increasing serum HDL-C level or percentage of serum cholesterol contained in the HDL fraction. Recently, a cohort study in middle-aged British men reported that higher HDL-C levels were associated with a significantly lower risk of nonfatal stroke even after adjustment for potential confounders; the RR was 0.59 in men with HDL-C of ≥51.2 mg/dL (1.33 mmol/L) compared with men with HDL-C of <35.8 mg/dL (0.93 mmol/L). A case-control study among Hispanic, black, and white men and women in the United States reported that increased HDL-C levels (≥35 mg/dL [0.91 mmol/L]) are associated with a reduced risk of ischemic stroke in the elderly (odds ratio, 0.53). A cohort study in urban Japanese men reported no significant relationship of HDL-C to stroke incidence, but that cohort was younger and the mean HDL-C level was higher than in our study. The present study is, as far as we know, one of the first investigations involving Japanese and Asian populations, in which stroke occurrence is high and coronary heart disease occurrence is low compared with Western countries. Also, our results are important because they demonstrate a clear relationship between HDL-C and stroke in women; previously, this relation had not been clearly shown in Western populations.

Effect of serum total cholesterol on stroke is important when considering the effects of HDL-C. The relation of the serum total cholesterol to stroke has been investigated repeatedly, but the subject remains unclear and controversial. However, several studies documented a positive relationship between total cholesterol and ischemic stroke; in contrast, other investigations reported an inverse relationship between total cholesterol and hemorrhagic stroke. In the present study, the relation of total cholesterol to all stroke and ischemic stroke appeared U shaped. The relation of HDL-C to stroke changed little after adjustment for total cholesterol, which was included as 4 dummy variables to adjust for the nonlinear relation in Cox models. Consequently, our results regarding HDL-C and stroke would not be affected by baseline total cholesterol level. On the other hand, the number of hemorrhagic stroke events in our study was not high enough to analyze the relationship of HDL-C or total cholesterol to the risk of hemorrhagic stroke.

A recent clinical trial revealed that selective increases in HDL-C with gemfibrozil resulted in a significant reduction in the combined outcome of death from coronary heart disease, nonfatal myocardial infarction, and stroke in men with low low-density lipoprotein cholesterol (LDL-C); therefore,

### TABLE 4. Adjusted RRs for All Stroke Incidence and Ischemic Stroke Incidence According to Baseline HDL-C in All Participants

<table>
<thead>
<tr>
<th>Serum HDL-C, mg/dL (mmol/L)</th>
<th>Sex-, Age-Adjusted RR (95% CI)</th>
<th>Multivariate-Adjusted RR* (95% CI)</th>
<th>P</th>
<th>Sex-, Age-Adjusted RR (95% CI)</th>
<th>Multivariate-Adjusted RR* (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 (&lt;0.78)</td>
<td>3.10 (1.50–6.39)</td>
<td>0.002</td>
<td>2.89 (1.35–6.20)</td>
<td>0.007</td>
<td>3.42 (1.45–8.08)</td>
<td>0.005</td>
</tr>
<tr>
<td>30– (0.78–)</td>
<td>1.27 (0.65–2.49)</td>
<td>0.480</td>
<td>1.20 (0.60–2.41)</td>
<td>0.612</td>
<td>1.21 (0.53–2.76)</td>
<td>0.645</td>
</tr>
<tr>
<td>40– (1.04–)</td>
<td>1.24 (0.65–2.35)</td>
<td>0.519</td>
<td>1.18 (0.61–2.26)</td>
<td>0.627</td>
<td>1.07 (0.48–2.39)</td>
<td>0.862</td>
</tr>
<tr>
<td>50– (1.30–)</td>
<td>1.39 (0.71–2.72)</td>
<td>0.332</td>
<td>1.42 (0.73–2.79)</td>
<td>0.304</td>
<td>0.99 (0.41–2.36)</td>
<td>0.979</td>
</tr>
<tr>
<td>60– (1.56–)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Adjusted for sex, age, body mass index, systolic blood pressure, serum total cholesterol, cigarette smoking, and alcohol consumption.
†Reference level.
HDL-C could have a direct antiatherosclerotic effect.²⁸ It has been suggested that the risk of stroke may decrease as a result of the antiatherosclerotic effects of HDL-C, including the ability to transport cholesterol in a reverse manner from peripheral cells to the liver.²⁹ Furthermore, it has been suggested that HDL-C may prevent atherosclerosis via inhibition of LDL oxidation in artery walls;³⁰ it may exert a direct effect on the release of endothelium-derived relaxing factor.³¹

HDL-C has been reported to relate to several lifestyle factors, e.g., physical activity, obesity, smoking, and alcohol consumption.³²⁻³⁵ In the present study, the association of HDL-C and stroke did not change after adjustment for obesity, cigarette smoking, and alcohol consumption; however, the association was not adjusted for physical activity. Lee et al.³⁶ reported an inverse association between physical activity and stroke; additionally, this work suggested that the association may be mediated through the beneficial effects of higher physical activity on body weight, blood pressure, serum cholesterol, and glucose tolerance. Higher stroke risk by lower HDL-C in the present investigation might be due in part to lower physical activity in participants with low HDL-C levels. Additionally, low HDL-C has been raised as a factor in insulin resistance syndrome, which includes diabetes mellitus as a factor.³⁷,³⁸ This study does not include baseline data regarding blood glucose; consequently, it is not clear how diabetes would confound the results. On the other hand, it should be considered that HDL-C values in the present study might be somewhat lower because of the use of anesthetic agents such as thiopental, which has been shown to decrease HDL-C levels.³⁹

Some studies, but not many as previously noted, in Western men reported a dose-response relationship between HDL-C and the risk of stroke.⁴⁰,⁴¹ The relationship in the present investigation appeared nonlinear; i.e., a marked increase in risk was evident in participants with HDL-C <30 mg/dL (0.78 mmol/L) compared with other categories. The reason for this nonlinear relationship is unclear. Men in the lowest HDL-C category exhibited relatively higher body mass index, and women in this category were older with higher body mass index and higher blood pressure; however, these participants would not be considered a special group.

In conclusion, this population-based 10-year cohort study showed that Japanese men and women with low HDL-C levels (<30 mg/dL [0.78 mmol/L]) had significantly and independently higher risk of stroke, especially ischemic stroke. For the primary prevention of stroke worldwide in men and women, individuals with low HDL-C should be considered a group at high risk of stroke. Therefore, early detection and health education for low HDL-C would be necessary. Moreover, in the course of management of established risk factors such as high blood pressure, low HDL-C could be included as a risk factor for strict management of cardiovascular risk.

Acknowledgments
This study was supported by a grant-in-aid for scientific research (08670459) from the Ministry of Education, Science, and Culture of Japan and the Japan Arteriosclerosis Prevention Fund. We thank the persons in the registration system in the city of Oyabe and the Oyabe Public Health Center, and we acknowledge the general practitioners and hospitals who supported the stroke registry. We also thank Tomiko Yoshii for her important contribution to the registry.

References


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Stroke. 2003;34:863-868; originally published online March 13, 2003; doi: 10.1161/01.STR.0000060869.34009.38
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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