Original Article

# The Relationship between Very High Levels of Serum High-Density Lipoprotein Cholesterol and Cause-Specific Mortality in a 20-Year Follow-Up Study of Japanese General Population

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***Aims*: There is no community-based cohort study to examine the effect of very high level of high-density lipoprotein cholesterol (HDL-C) on coronary heart disease (CHD) and other cause-specific mortality. Therefore, we investigated the relationship between HDL-C including very high level and cause-specific mortality in a 20-year cohort study of the representative sample of Japanese.**

***Methods*: We followed 7,019 individuals from the Japanese general population (2,946 men and 4,073 women). We defined HDL-C levels as follow: low (HDL-C <1.04 mmol/L), reference (1.04−1.55 mmol/L), high (1.56−2.06 mmol/L), very high (≥2.07 mmol/L). The multivariate adjusted hazard ratio (HR) for all-cause or cause-specific mortality was calculated using a Cox proportional hazards model adjusted for other traditional risk factors.**

***Results*: During follow-up, we observed 1,598 deaths. No significant association was observed between HDL-C and all-cause mortality. Serum HDL-C also showed no association with stroke. In contrast, the risk for CHD among high HDL-C was lower than reference, HRs were 0.51 [95% confidence interval (CI): 0.21−1.23] in men, 0.33 (95% CI: 0.11−0.95) in women, and 0.41 (95% CI: 0.21−0.81) when men and women were combined. However, very high HDL-C did not show significant association with CHD and other cause-specific mortality.**

***Conclusions*: HDL-C was not associated with all-cause and stroke mortality. In contrast, high serum HDL-C levels, at least up to 2.06 mmol/L, were protective against CHD, although further high levels were not. However, sample size of cause-specific death in very high HDL-C group was not enough even in this 20-year follow-up of 7,019 Japanese; larger cohort studies should be warranted.**

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**Key words:** High-density lipoprotein cholesterol, Mortality, Risk factors, Cohort studies

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## Introduction

Serum high-density lipoprotein cholesterol (HDL-C) is known as a protective factor for coronary heart disease (CHD)[1-9]. In some cohort studies, serum HDL-C is also inversely associated with all-cause mortality[10-12]. However, it is still unclear whether very

high HDL-C levels are beneficial for community dwellers or not. To date, there are no community-based cohort studies concerning the relationship between very high serum levels of HDL-C and CHD or cause-specific mortality. It is very difficult to set a very high HDL-C group in a cohort study[13]. Although our previous study tried to examine the relationship between very high HDL-C levels and cause-specific mortality[14], we did not set a very high HDL-C group because of small number of events.

Accordingly, we investigated the relationship between serum HDL-C categories that included very high HDL-C group and cause-specific and all-cause mortality using data of population samples with long-term follow-up period. This study extended the follow-up period of our previous study[14] from 10 to 20 years. Because Japanese population has more individuals with very high HDL-C levels than Western populations[15], it is suitable to investigate the effect of very high HDL-C levels on cause-specific mortality.

## Methods

### Study Participants

National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged (NIPPON DATA) are the cohort studies that are based on the National Survey on Circulatory Disorders, Japan. NIPPON DATA included two long-term cohort studies. The baseline surveys were performed in 1980 and in 1990 (NIPPON DATA80 and NIPPON DATA90), and the details of these cohorts have been reported[14, 16-19]. In this study, we analyzed data from NIPPON DATA90 because the baseline survey of NIPPON DATA80 did not include the measurement of serum HDL-C.

A total of 8,383 residents (3,504 men and 4,879 women, aged ≥30 years) from 300 randomly selected districts participated in the survey and were followed until 15 November 2010. The participation rate in this survey was 76.5%. Of the 8,383 participants, 1,364 were excluded. The reasons were as follows: history of CHD or stroke ($n$=248), the use of lipid-lowering agents ($n$=267), information missing at the baseline survey ($n$=662), and failure to access because of incomplete residential access information at the second survey ($n$=304). The remaining 7,019 participants (2,946 men and 4,073 women) were included in the analysis.

### Follow-Up Survey

The underlying cause of death in the National Vital Statistics was coded according to the *ICD-9* until the end of 1994 and the *ICD-10* from the start of 1995 until the end of 2010. Details of these classifications are described elsewhere[14, 16-19]. This study was approved by the Institutional Review Board of Shiga University of Medical Science (No.12−18, 2000; No.17−21-1, 2010).

### Baseline Examination

Nonfasting blood samples were obtained from all participants, and blood samples were shipped to the commissioned clinical laboratory (SRL, Tokyo, Japan) for blood measurement after they were preprocessed. Serum total cholesterol and triglyceride (TG) were measured by enzymatic methods. HDL-C was measured by the precipitation method using heparin-calcium. Lipid measurement was standardized by the Centers for Disease Control/National Heart, Lung, and Blood Institute Lipid Standardization Program[20]. Plasma glucose was measured enzymatically.

Public health nurses obtained information about lifestyle factors such as the current use of medication, the extent of smoking and alcohol consumption, physical activity, and history of cardiovascular disease (CVD). The body mass index (BMI) was calculated as the weight (kg) divided by the height squared ($m^2$). Baseline blood pressure was measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated subjects.

We defined the metabolic syndrome based on the criteria defined by the joint committee of eight Japanese medical societies; visceral obesity (waist ≥85 cm in men, ≥90 cm in women) plus ≥2 items of the following three components: (1) HDL-C <1.04 mmol/L (40 mg/dl) or TG ≥1.70 mmol/L (150 mg/dl) or medication for hyperlipidemia, (2) blood pressure ≥130/85 mmHg or taking an antihypertensive, (3) fasting blood glucose ≥6.10 mmol/L (110 mg/dl) or medication for diabetes. In this study, we substitute BMI (≥25 kg/$m^2$) for waist and nonfasting blood glucose (≥7.77 mmol/L, 140 mg/dl) for fasting blood glucose. In addition, we defined diabetes as serum glucose ≥11.1 mmol/L, a history of diabetes, or both and hypertension as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, the use of antihypertensive agents, or any combination of these.

### Statistical Analysis

We divided all participants into four HDL-C categories according to the definition in a large previous cross-sectional study in Japan[21], which was as follows: low [HDL-C <1.04 mmol/L (<40 mg/dl)], reference [1.04−1.55 mmol/L (40−59 mg/dl)], high [1.56−2.06 mmol/L (60−79 mg/dl)], very high

[≥2.07 mmol/L (≥80 mg/dl)]. Then, we performed analysis of variance to compare multiple group means and the $\chi^2$ test to compare frequencies.

The multivariate adjusted hazard ratio (HR) of each HDL-C category for all-cause or cause-specific mortality, i.e., CVD, CHD, stroke, cerebral infarction, cerebral hemorrhage, was calculated using the Cox proportional hazards model. In model 1, we adjusted for age, in model 2, we adjusted for age, BMI, hypertension, diabetes, smoking category (never-smoked, ex-smoker, current smoker; ≤20 and ≥21 cigarettes/day), drinking category (never-drinker, ex-drinker, and current drinker), non-HDL cholesterol and TG (log-transformed). Sex was also adjusted in sex-combined analysis. Wald's tests were used to test for significance of HR in each HDL-C categories compared with the reference group[22]. The model with continuous serum HDL-C values instead of HDL-C categories was also examined to clarify the linear trend between HDL-C and mortality. The proportional hazard assumption was checked by the schoenfeld residuals plot. In addition, we performed analysis using the same cut points as our former study[14]: very low [HDL-C <0.91 mmol/L (<35 mg/dl)], low [0.91−1.03 mmol/L (35−39 mg/dl)], reference [1.04−1.55 mmol/L (40−59 mg/dl)], high [1.56−1.81 mmol/L (60−69 mg/dl)], and very high [≥1.82 mmol/L (≥70 mg/dl)].

We performed additional analysis stratified by hypertension (with/without), smoking (with/without), drinking (with/without), diabetes (with/without), high serum levels of non-HDL-C (with/without, defined by median; ≥3.62, <3.62), hypertriglyceridemia (with/without, defined by median; ≥1.21, <1.21) examine certainty of the results for CVD and all-cause mortality. Sensitivity analysis for each cause of death was not performed due to small numbers of each cause-specific event.

All CIs were estimated at the 95% level. *P*-value <0.05 was considered significant. Statistical analysis was performed with IBM SPSS Statistics Ver. 22.

## Results

Total person-years were 126,481 (51,356 in men and 75,122 in women), and the mean follow-up period was 18.0 years. During follow-up, 1,598 participants died, of which 450 died due to CVD. **Table 1** shows the baseline characteristics of the study participants according to HDL-C category.

**Table 2** shows the number of deaths; multiple adjusted HRs; and 95% CIs for all-cause, CVD, and CHD mortality. In age-adjusted model, we did not observe any linear association between HDL-C categories and each cause of death. The risk for all-cause mortality did not show statistical difference among the four HDL-C categories. As a result of testing for the proportional hazard assumption using the schoenfeld residuals plot, the assumption was not violated for any variables. In addition, we observed an inverse relationship between HDL-C and all-cause mortality similar to that of our previous study in the same cut points as our former study (data not shown).

The risks for CHD among high HDL-C category (1.56−2.06 mmol/L) were lower than those among reference category (1.01−1.55 mmol/L). HRs were 0.33 (95% CI: 0.11−0.95) in women and 0.41 (95% CI: 0.21−0.81) when men and women were combined, and the risk in men was also lower (HR: 0.51, HR 0.21−1.23) although it did not reach statistical significance ($p=0.14$). We did not observe lower risk for CHD in very high HDL-C category compared with the reference group. The results were almost similar after multivariable adjustment.

**Table 3** shows the number of deaths, multiple adjusted HRs, and 95% CIs for stroke and its subtypes (cerebral infarction and intracerebral hemorrhage). We did not observe any significant difference in the risk for each subtype of stroke among the four HDL-C categories. We did not also observe any linear association between HDL-C categories and stroke mortality.

The results of stratification by the existence of hypertension, smoking, alcohol drinking, diabetes, high serum level of non-HDL-C, hypertriglyceridemia for CVD, and all-cause mortality showed substantially similar results shown in **Table 2** (data not shown).

## Discussion

In our 20-year follow-up study, serum HDL-C levels did not show significant association with all-cause and stroke mortality in this Japanese general population. Furthermore, the high HDL-C category (1.56−2.06 mmol/L) showed significant inverse association with CHD mortality; however, the very high HDL-C category (≥2.07 mmol/L) did not show significant relationship with CHD. Consequently, there is no inverse relationship between HDL-C levels and cardiovascular mortality because major subtype of CVD in Japan is stroke[13, 23]; in fact, the proportion of stroke within CVD (39%) was twice as large as that of CHD (21%) in the present study.

In this same cohort, we have already reported an inverse relationship between HDL-C and all-cause mortality at 10-year follow-up[14]. In the present study,

**Table 1.** Baseline characteristics stratified by HDL cholesterol level at the baseline survey in 1990, NIPPON DATA90

| Risk charasteristics | Baseline HDL-C range, mmol/L (mg/dl) | | | | *P*-values |
|---|---|---|---|---|---|
| | Low<br><1.04<br>(<40) | Reference<br>1.04-1.55<br>(40-59) | High<br>1.56-2.06<br>(60-79) | Very high<br>2.07+<br>(80+) | |
| Men | | | | | |
| Number of subjects | 702 | 1554 | 554 | 136 | |
| HDL-cholesterol (mmol/L) | 0.87 ± 0.12 | 1.26 ± 0.14 | 1.74 ± 0.14 | 2.32 ± 0.28 | <0.001 |
| Age (years) | 52.5 ± 13.7 | 52.7 ± 13.4 | 53.5 ± 13.3 | 51.7 ± 13.0 | 0.048 |
| BMI (kg/m$^2$) | 24.2 ± 2.9 | 22.9 ± 3.0 | 21.7 ± 2.6 | 21.3 ± 3.0 | <0.001 |
| Total cholesterol (mmol/L) | 5.12 ± 1.04 | 5.06 ± 0.92 | 5.21 ± 0.88 | 5.43 ± 0.91 | <0.001 |
| Non-HDL cholesterol (mmol/L) | 4.24 ± 1.04 | 3.81 ± 0.93 | 3.47 ± 0.87 | 3.10 ± 0.93 | <0.001 |
| Triglycerides (mmol/L)[§] | 2.07 | 1.34 | 1.04 | 0.92 | <0.001 |
| Hypertension (%) | 46.0 | 46.5 | 48.6 | 42.6 | 0.612 |
| Diabetes (%) | 9.4 | 6.2 | 6.7 | 8.8 | 0.040 |
| Metabolic syndrome (%) | 26.9 | 11.5 | 2.5 | 2.9 | <0.001 |
| Smoking | | | | | |
| Never-smoker (%) | 20.5 | 20.1 | 22.4 | 22.1 | |
| Ex-smoker (%) | 19.2 | 23.9 | 25.6 | 23.5 | <0.001 |
| Current smoker (≦20 cigarettes/day)(%) | 34.6 | 37.0 | 37.0 | 44.1 | |
| Current smoker (≧21 cigarettes/day)(%) | 25.6 | 18.9 | 15.0 | 10.3 | |
| Alcohol drinking | | | | | |
| Never-drinker (%) | 52.1 | 32.1 | 25.1 | 11.8 | |
| Ex-drinker (%) | 8.4 | 5.7 | 3.8 | 3.7 | <0.001 |
| Current drinker (%) | 39.5 | 62.2 | 71.1 | 84.6 | |
| Women | | | | | |
| Number of subjects (proportion, %) | 425 | 2009 | 1341 | 298 | |
| HDL-cholesterol (mmol/L) | 0.89 ± 0.11 | 1.30 ± 0.15 | 1.75 ± 0.14 | 2.29 ± 0.22 | <0.001 |
| Age (years) | 57.7 ± 13.9 | 52.4 ± 13.8 | 49.4 ± 13.1 | 49.7 ± 12.9 | <0.001 |
| BMI (kg/m$^2$) | 24.4 ± 3.1 | 23.3 ± 3.3 | 21.9 ± 3.1 | 21.2 ± 2.6 | <0.001 |
| Total cholesterol (mmol/L) | 5.27 ± 1.09 | 5.24 ± 0.99 | 5.34 ± 0.88 | 5.72 ± 0.87 | <0.001 |
| Non-HDL cholesterol (mmol/L) | 4.38 ± 1.09 | 3.94 ± 1.00 | 3.59 ± 0.89 | 3.43 ± 0.82 | <0.001 |
| Triglyceride (mmol/L)[§] | 1.99 | 1.25 | 0.93 | 0.77 | <0.001 |
| Hypertensions (%) | 47.1 | 45.0 | 45.9 | 43.0 | 0.694 |
| Diabetes (%) | 6.1 | 4.4 | 2.1 | 1.7 | <0.001 |
| Metabolic syndrome (%) | 30.8 | 9.2 | 2.4 | 1.3 | <0.001 |
| Smoking | | | | | |
| Never-smoker (%) | 84.7 | 88.4 | 90.2 | 88.3 | |
| Ex-smoker (%) | 2.1 | 2.4 | 2.8 | 2.7 | 0.005 |
| Current smoker (≦20 cigarettes/day)(%) | 10.8 | 8.4 | 6.6 | 8.4 | |
| Current smoker (≧21 cigarettes/day)(%) | 2.4 | 0.8 | 0.4 | 0.7 | |
| Drinking | | | | | |
| Never-drinker (%) | 95.1 | 94.0 | 91.1 | 85.6 | |
| Ex-drinker (%) | 1.2 | 0.8 | 1.2 | 0.3 | <0.001 |
| Current drinker (%) | 3.8 | 5.2 | 7.8 | 14.1 | |

[§]geometric mean

The value were expressed as the means±srandard deviation (SD) for continuous variables, and as percentages for categorical variables. Analysis of variance was used for comparisons of multiple group means and the $\chi^2$-test was used to compare proportions.

**Table 2.** The number of death and multivariate-adjusted HR (95% CIs) for all-cause and cardiovascular deaths according to serum HDL cholesterol

Table 2A [Model 1]

| Baseline HDL cholesterol level, mmol/L (mg/dl) | No. of persons | Person-years | All-cause | | | | Cardiovascular disease | | | | Coronary heart disease | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No. of deaths | HR (95% CI) | *P* | *P*¶ | No. of deaths | HR (95% CI) | *P* | *P*¶ | No. of deaths | HR (95% CI) | *P* | *P*¶ |
| Men | | | | | | | | | | | | | | |
| <1.04 (<40) | 702 | 12152 | 217 | 1.10 (0.94, 1.30) | 0.24 | | 60 | 1.12 (0.82, 1.53) | 0.46 | | 18 | 1.31 (0.73, 2.34) | 0.37 | |
| 1.04-1.55 (40-59) | 1554 | 27119 | 443 | 1.00 | | 0.34 | 120 | 1.00 | | 0.26 | 31 | 1.00 | | 0.52 |
| 1.56-2.06 (60-79) | 554 | 9677 | 160 | 0.95 (0.80, 1.14) | 0.61 | | 36 | 0.79 (0.54, 1.15) | 0.21 | | 6 | 0.51 (0.21, 1.23) | 0.14 | |
| 2.07+ (80+) | 136 | 2408 | 38 | 1.11 (0.79, 1.54) | 0.56 | | 10 | 1.09 (0.57, 2.08) | 0.79 | | 2 | 0.80 (0.19, 3.36) | 0.77 | |
| Women | | | | | | | | | | | | | | |
| <1.04 (<40) | 425 | 7483 | 122 | 1.00 (0.81, 1.22) | 0.97 | | 46 | 1.27 (0.89, 1.79) | 0.19 | | 5 | 0.62 (0.24, 1.64) | 0.34 | |
| 1.04-1.55 (40-59) | 2009 | 36829 | 377 | 1.00 | | 0.82 | 106 | 1.00 | | 0.79 | 24 | 1.00 | | 0.71 |
| 1.56-2.06 (60-79) | 1341 | 25255 | 195 | 1.00 (0.84, 1.19) | 0.97 | | 56 | 1.07 (0.77, 1.48) | 0.68 | | 4 | 0.33 (0.11, 0.95) | 0.04 | |
| 2.07+ (80+) | 298 | 5555 | 46 | 1.14 (0.84, 1.54) | 0.42 | | 16 | 1.46 (0.86, 2.47) | 0.16 | | 5 | 1.94 (0.74, 5.09) | 0.18 | |
| Men and women combined§ | | | | | | | | | | | | | | |
| <1.04 (<40) | 1127 | 19636 | 339 | 1.07 (0.94, 1.21) | 0.32 | | 106 | 1.21 (0.96, 1.52) | 0.11 | | 23 | 1.07 (0.66, 1.74) | 0.79 | |
| 1.04-1.55 (40-59) | 3563 | 63949 | 820 | 1.00 | | 0.51 | 226 | 1.00 | | 0.43 | 55 | 1.00 | | 0.71 |
| 1.56-2.06 (60-79) | 1895 | 34933 | 355 | 0.98 (0.86, 1.11) | 0.69 | | 92 | 0.92 (0.72, 1.17) | 0.50 | | 10 | 0.41 (0.21, 0.81) | 0.01 | |
| 2.07+ (80+) | 434 | 7963 | 84 | 1.12 (0.90, 1.40) | 0.32 | | 26 | 1.28 (0.85, 1.92) | 0.23 | | 7 | 1.39 (0.63, 3.06) | 0.41 | |

HR: hazard ratio, 95% CI: 95% confidence interval
The HR was calculated using a Cox proportional hazard model. The Wald's test was used to examine the difference in the HR of each HDL-C category compared with the reference group.
¶Continuous serum HDL-C value used in the proportional hazard model.
Model 1: adjusted for age (+sex§)

Table 2B [Model 2]

| Baseline HDL cholesterol level, mmol/L (mg/dl) | No. of persons | Person-years | All-cause | | | | Cardiovascular disease | | | | Coronary heart disease | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No. of deaths | HR (95% CI) | *P* | *P*¶ | No. of deaths | HR (95% CI) | *P* | *P*¶ | No. of deaths | HR (95% CI) | *P* | *P*¶ |
| Men | | | | | | | | | | | | | | |
| <1.04 (<40) | 702 | 12152 | 217 | 1.13 (0.94, 1.35) | 0.19 | | 60 | 1.12 (0.79, 1.59) | 0.51 | | 18 | 1.70 (0.89, 3.27) | 0.11 | |
| 1.04-1.55 (40-59) | 1554 | 27119 | 443 | 1.00 | | 0.16 | 120 | 1.00 | | 0.38 | 31 | 1.00 | | 0.43 |
| 1.56-2.06 (60-79) | 554 | 9677 | 160 | 0.90 (0.74, 1.10) | 0.25 | | 36 | 0.78 (0.53, 1.14) | 0.20 | | 6 | 0.46 (0.19, 1.12) | 0.09 | |
| 2.07+ (80+) | 136 | 2408 | 38 | 1.02 (0.73, 1.43) | 0.91 | | 10 | 1.08 (0.55, 2.09) | 0.83 | | 2 | 0.77 (0.18, 3.34) | 0.73 | |
| Women | | | | | | | | | | | | | | |
| <1.04 (<40) | 425 | 7483 | 122 | 1.09 (0.87, 1.35) | 0.46 | | 46 | 1.40 (0.97, 2.04) | 0.07 | | 5 | 0.68 (0.25, 1.88) | 0.46 | |
| 1.04-1.55 (40-59) | 2009 | 36829 | 377 | 1.00 | | 0.12 | 106 | 1.00 | | 0.55 | 24 | 1.00 | | 0.97 |
| 1.56-2.06 (60-79) | 1341 | 25255 | 195 | 0.93 (0.78, 1.12) | 0.46 | | 56 | 1.01 (0.72, 1.42) | 0.95 | | 4 | 0.31 (0.11, 0.93) | 0.04 | |
| 2.07+ (80+) | 298 | 5555 | 46 | 0.96 (0.69, 1.32) | 0.79 | | 16 | 1.20 (0.68, 2.11) | 0.52 | | 5 | 1.72 (0.60, 4.90) | 0.31 | |
| Men and women combined§ | | | | | | | | | | | | | | |
| <1.04 (<40) | 1127 | 19636 | 339 | 1.12 (0.98, 1.29) | 0.11 | | 106 | 1.27 (0.99, 1.63) | 0.07 | | 23 | 1.29 (0.76, 2.20) | 0.35 | |
| 1.04-1.55 (40-59) | 3563 | 63949 | 820 | 1.00 | | 0.06 | 226 | 1.00 | | 0.25 | 55 | 1.00 | | 0.47 |
| 1.56-2.06 (60-79) | 1895 | 34933 | 355 | 0.93 (0.81, 1.05) | 0.24 | | 92 | 0.89 (0.69, 1.14) | 0.36 | | 10 | 0.38 (0.19, 0.75) | 0.01 | |
| 2.07+ (80+) | 434 | 7963 | 84 | 1.01 (0.80, 1.27) | 0.95 | | 26 | 1.14 (0.74, 1.74) | 0.55 | | 7 | 1.23 (0.54, 2.79) | 0.62 | |

HR: hazard ratio, 95% CI: 95% confidence interval
The HR was calculated using a Cox proportional hazard model. The Wald's test was used to examine the difference in the HR of each HDL-C category compared with the reference group.
¶Continuous serum HDL-C value used in the proportional hazard model.
Model 2: adjusted for age + bmi + triglyceride (log-transformed) + non-hdl + hypertension + diabetes + smoking + drinking (+sex§)

**Table 3.** The number of deaths and multivariate-adjusted HR (95% CIs) for subgroups of stroke death according to serum HDL cholesterol level

Table 3A [Model 1]

| Baseline HDL cholesterol level, mmol/L (mg/dl) | No. of persons | Person-years | Stroke | | | | Cerebral Infarction | | | | Cerebral Hemorrhage | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No. of deaths | HR (95% CI) | *P* | *P*¶ | No. of deaths | HR (95% CI) | *P* | *P*¶ | No. of deaths | HR (95% CI) | *P* | *P*¶ |
| Men | | | | | | | | | | | | | | |
| <1.04 (<40) | 702 | 12152 | 18 | 0.86 (0.50, 1.48) | 0.59 | | 12 | 0.95 (0.49, 1.87) | 0.89 | | 3 | 0.48 (0.14, 1.68) | 0.25 | |
| 1.04-1.55 (40-59) | 1554 | 27119 | 47 | 1.00 | | 0.22 | 29 | 1.00 | | 0.96 | 14 | 1.00 | | 0.28 |
| 1.56-2.06 (60-79) | 554 | 9677 | 20 | 1.12 (0.67, 1.89) | 0.67 | | 11 | 1.00 (0.50, 2.01) | 0.99 | | 4 | 0.76 (0.25, 2.32) | 0.64 | |
| 2.07+ (80+) | 136 | 2408 | 7 | 1.98 (0.89, 4.39) | 0.09 | | 4 | 2.09 (0.73, 6.00) | 0.17 | | 2 | 1.68 (0.38, 7.39) | 0.49 | |
| Women | | | | | | | | | | | | | | |
| <1.04 (<40) | 425 | 7483 | 19 | 1.34 (0.77, 2.31) | 0.30 | | 12 | 1.22 (0.62, 2.41) | 0.57 | | 5 | 2.52 (0.76, 8.32) | 0.13 | |
| 1.04-1.55 (40-59) | 2009 | 36829 | 41 | 1.00 | | 0.96 | 27 | 1.00 | | 0.71 | 6 | 1.00 | | 0.83 |
| 1.56-2.06 (60-79) | 1341 | 25255 | 21 | 1.06 (0.62, 1.80) | 0.83 | | 14 | 1.16 (0.60, 2.22) | 0.66 | | 5 | 1.61 (0.49, 5.30) | 0.43 | |
| 2.07+ (80+) | 298 | 5555 | 6 | 1.44 (0.61, 3.39) | 0.41 | | 2 | 0.76 (0.18, 3.21) | 0.71 | | 2 | 3.11 (0.63, 15.4) | 0.17 | |
| Men and women combined § | | | | | | | | | | | | | | |
| <1.04 (<40) | 1127 | 19636 | 37 | 1.07 (0.73, 1.57) | 0.74 | | 24 | 1.07 (0.67, 1.73) | 0.77 | | 8 | 1.05 (0.46, 2.38) | 0.92 | |
| 1.04-1.55 (40-59) | 3563 | 63949 | 88 | 1.00 | | 0.44 | 56 | 1.00 | | 0.81 | 20 | 1.00 | | 0.42 |
| 1.56-2.06 (60-79) | 1895 | 34933 | 41 | 1.07 (0.74, 1.55) | 0.73 | | 25 | 1.07 (0.67, 1.71) | 0.79 | | 9 | 0.99 (0.45, 2.19) | 0.99 | |
| 2.07+ (80+) | 434 | 7963 | 13 | 1.69 (0.94, 3.04) | 0.08 | | 6 | 1.34 (0.58, 3.13) | 0.49 | | 4 | 2.07 (0.71, 6.07) | 0.19 | |

HR: hazard ratio, 95% CI: 95% confidence interval
The HR was calculated using a Cox proportional hazard model. The Wald's test was used to examine the difference in the HR of each HDL-C
¶Continuous serum HDL-C value used in the proportional hazard model.
Model 1: adjusted for age (+sex§)

Table 3B [Model 2]

| Baseline HDL cholesterol level, mmol/L (mg/dl) | No. of persons | Person-years | Stroke | | | | Cerebral Infarction | | | | Cerebral Hemorrhage | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No. of deaths | HR (95% CI) | *P* | *P*¶ | No. of deaths | HR (95% CI) | *P* | *P*¶ | No. of deaths | HR (95% CI) | *P* | *P*¶ |
| Men | | | | | | | | | | | | | | |
| <1.04 (<40) | 702 | 12152 | 18 | 0.82 (0.45, 1.48) | 0.50 | | 12 | 0.72 (0.34, 1.53) | 0.40 | | 3 | 0.67 (0.17, 2.61) | 0.57 | |
| 1.04-1.55 (40-59) | 1554 | 27119 | 47 | 1.00 | | 0.29 | 29 | 1.00 | | 0.58 | 14 | 1.00 | | 0.79 |
| 1.56-2.06 (60-79) | 554 | 9677 | 20 | 1.15 (0.66, 1.97) | 0.63 | | 11 | 1.06 (0.52, 2.17) | 0.88 | | 4 | 0.69 (0.22, 2.19) | 0.53 | |
| 2.07+ (80+) | 136 | 2408 | 7 | 1.93 (0.84, 4.44) | 0.12 | | 4 | 2.47 (0.82, 7.46) | 0.11 | | 2 | 1.39 (0.29, 6.71) | 0.68 | |
| Women | | | | | | | | | | | | | | |
| <1.04 (<40) | 425 | 7483 | 19 | 1.42 (0.79, 2.55) | 0.24 | | 12 | 1.31 (0.63, 2.74) | 0.48 | | 5 | 2.50 (0.70, 8.94) | 0.16 | |
| 1.04-1.55 (40-59) | 2009 | 36829 | 41 | 1.00 | | 0.64 | 27 | 1.00 | | 0.43 | 6 | 1.00 | | 0.87 |
| 1.56-2.06 (60-79) | 1341 | 25255 | 21 | 0.96 (0.56, 1.66) | 0.89 | | 14 | 1.01 (0.52, 1.99) | 0.97 | | 5 | 1.54 (0.45, 5.31) | 0.49 | |
| 2.07+ (80+) | 298 | 5555 | 6 | 1.26 (0.52, 3.07) | 0.62 | | 2 | 0.67 (0.15, 2.90) | 0.59 | | 2 | 2.81 (0.50, 15.7) | 0.24 | |
| Men and women combined § | | | | | | | | | | | | | | |
| <1.04 (<40) | 1127 | 19636 | 37 | 1.10 (0.73, 1.67) | 0.65 | | 24 | 0.99 (0.59, 1.68) | 0.98 | | 8 | 1.25 (0.52, 3.04) | 0.62 | |
| 1.04-1.55 (40-59) | 3563 | 63949 | 88 | 1.00 | | 0.76 | 56 | 1.00 | | 0.84 | 20 | 1.00 | | 0.89 |
| 1.56-2.06 (60-79) | 1895 | 34933 | 41 | 1.03 (0.70, 1.52) | 0.87 | | 25 | 1.05 (0.64, 1.70) | 0.86 | | 9 | 0.91 (0.40, 2.05) | 0.81 | |
| 2.07+ (80+) | 434 | 7963 | 13 | 1.53 (0.84, 2.81) | 0.17 | | 6 | 1.33 (0.56, 3.16) | 0.53 | | 4 | 1.62 (0.52, 5.02) | 0.41 | |

HR: hazard ratio, 95% CI: 95% confidence interval
The HR was calculated using a Cox proportional hazard model. The Wald's test was used to examine the difference in the HR of each HDL-C category compared with the reference group.
¶Continuous serum HDL-C value used in the proportional hazard model.
Model 2: adjusted for age + bmi + triglyceride (log-transformed) + non-hdl + hypertension + diabetes + smoking + drinking (+sex§)

we followed up same individuals for 20 years, which was twice the follow-up period of our previous study. As a result, HDL-C levels did not show significant association with all-cause mortality. This result may seem to show different relationship from our previous study[14]. However, the result of the present study does not show variation in these relationships for 20 years because we observed an inverse relationship between HDL-C and all-cause mortality similar to that of our previous study although we used the same cut points, and the proportional hazard assumption was not violated for variables. These findings indicate that the discrepancy among our studies is apparently caused by the difference of cut points, especially because of adding very high HDL-C category. Moreover, because we assessed the effect of HDL-C only based on single measurement at baseline survey, the longer follow-up period was prolonged, the more potential confounding factors, especially during follow-up period, affected the results. For example, statins, which had been launched in 1989, have not expanded yet when baseline surveys started in 1990, however the use of statin has been very popular year by year. Thus, prolongation of follow-up period may strengthen the confounding effect of statin therapy. In addition, change of lifestyle of participants during follow-up period may be another important confounding factor.

In the present study, HDL-C did not show significant association with stroke, even with cerebral infarction. As mentioned above, in Japan, stroke mortality is much higher than CHD mortality[13, 23], and to our knowledge, almost all Japanese cohort studies did not show any positive relationship between TC or LDL-C and cerebral infarction[24, 25]. Even in a large worldwide pooled analysis[26], a weak positive relationship between TC or LDL-C and stroke was only observed. Usually, main biological background of protective effect of HDL-C is explained by reverse-cholesterol transport, which acts in an opposing manner against cholesterol accumulation to artery because of LDL-C. Thus, it is not surprising that there is no association between low HDL-C and cerebral infarction in a population where there is no relationship between high LDL-C and cerebral infarction. A previous study in Japan showed a significant association between low HDL-C and risk of cerebral infarction; however, the definition of low HDL-C was too low [$<$0.78 mmol/L (30 mg/dl)], which suggested other metabolic background such as diabetes or visceral obesity[27].

We found that the high HDL-C category (1.56–2.06 mmol/L) significantly reduces the risk of CHD, whereas the very high HDL-C category ($\geq$2.07 mmol/L) does not. It has been controversial whether very high HDL-C levels prevent CHD. It has been reported that high levels of serum HDL-C *per se* protect against CHD regardless of the cause of HDL-C elevation when high HDL-C was defined as $\geq$1.56 mmol/L[13, 21]. In contrast, pooled analysis of six cohort studies has shown that very high HDL-C defined as $\geq$2.07 mmol/L increased the risk for CHD events[28]. Abnormal HDL-C function raised by cholesterol ester transfer protein (CETP) deficiency leads to lowering of cholesterol efflux, then reverse cholesterol transport was inhibited[29]. A clinical trial using CETP inhibitor has failed to show the protective effect for CHD, although participants in this study showed an extremely HDL-C elevation almost equivalent to very high HDL-C level in our study[30]. Some previous studies have shown mild inverse or no association between HDL-C concentrations and plasma CETP activity[31-33]. Moreover, plasma CETP activity showed inverse correlation with CVD risk independent of HDL-C levels[34]. Furthermore, cholesterol efflux capacity that reflects HDL-C function has shown the inverse relationship with some status of atherosclerosis[35]. These findings indicate that the function as well as quantity of HDL-C is carefully evaluated for an individual with very high HDL-C level. Further studies with information about HDL-C function should be warranted.

Several studies reported that heavy alcohol consumption or alcoholism can be confounding factors of excess death in high HDL-C group[36]. In addition, in the present study, the proportion of drinkers between both men and women in very high HDL-C category was the highest in the four categories. However, the proportions of population with hypertension, diabetes, smoker, and obesity among very high HDL-C categories are not higher compared with those among high HDL-C categories, hence they are not considered to be unhealthy population. In addition, a small percentage of women among very high HDL-C category, which was 14%, were drinker. Therefore, we consider that alcohol consumption was not a confounding factor among very high HDL-C category in the present study.

There are some limitations in this study. First, we did not have any information about participants concerning change in risk characteristics including use of lipid lowering agents during follow-up. Second, causes of death may be misclassified because “heart failure” may include CHD. Accordingly, underestimation of CHD deaths is possible[37]. This should make it more difficult to show an association between HDL-C and death due to CHD; accordingly, we believe our results may be conservative and not to be over-stated. Third,

the number of events among very high HDL-C category was not enough even in our extended 20-year cohort study. In future, larger population study is needed to investigate population with very high HDL-C levels. This result indicates a potential that the function as well as the quantity of HDL-C might be evaluated for individuals with very high HDL-C level.

## Conclusions

A 20-year follow-up study did not show the significant association between serum HDL-C levels and all-cause mortality and stroke. In contrast, high HDL-C level (1.56−2.06 mmol/L) significantly reduced risk for CHD death. However, very high HDL-C level (≥2.07 mmol/L) did not. Because sample size of cause-specific death in very high HDL-C group was not enough even in this 20-year follow-up of 7,019 Japanese, a larger community-based cohort study or a pooled analysis of a number of cohort studies is needed in the future.

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## Appendix

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## Conflicts of Interest

There are no conflicts of interest in the present study.

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