J Lipid Atheroscler. 2021 Jan;10(1):74-87
https://doi.org/10.12997/jla.2021.10.1.74
pISSN 2287-2892·eISSN 2288-2561

JLA Journal of Lipid and Atherosclerosis

Original Article

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High-Density Lipoprotein Cholesterol and the Risk of Myocardial Infarction, Stroke, and Cause-Specific Mortality: a Nationwide Cohort Study in Korea

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OPEN ACCESS

Received: Sep 5, 2020
Revised: Nov 5, 2020
Accepted: Nov 18, 2020

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Funding
This study was supported by the big data analysis grant from The Korean Society of Lipid and Atherosclerosis.

ABSTRACT

Objective: We aimed to investigate the relationship between high-density lipoprotein cholesterol (HDL-C) level and the risk of myocardial infarction (MI), stroke, and cause-specific mortality.
Methods: Using the Korean National Health Insurance Service-National Sample Cohort, we identified 343,687 subjects (men, 176,243; women, 167,444) aged ≥20 years who underwent health examinations between 2009 and 2012. HDL-C levels were categorized based on the concentration with 10 mg/dL intervals, starting from levels <30 mg/dL, with levels ≥90 mg/dL considered the highest. The endpoints of the study were newly-diagnosed MI, stroke, or mortality. We used the Cox proportional hazards model with restricted cubic splines.
Results: During a median follow-up of 6.0 years, the number of cases of death, MI, and stroke were 6,617, 4,064, and 3,435 in men and 3,677, 2,804, and 2,891 in women, respectively. The risk of all-cause mortality, cancer mortality, other mortality, and stroke was the lowest at HDL-C concentrations of 57–76 mg/dL in the spline curves; inverse associations with increased risk were observed at the lower HDL-C levels. In contrast, the lowest risk of cardiovascular mortality and MI was observed at the extreme high end. In men, there was a significant inverse and graded increase in hazard ratios of all outcomes in the lower HDL-C categories compared to the reference group (50–59 mg/dL). In the higher HDL-C categories, no significant increase in outcomes was observed. Women showed similar trends.
Conclusion: The risk of mortality, MI, and stroke was high at low HDL-C levels in the Korean general population. However, extremely high HDL-C levels were not associated with an increased risk of mortality, MI, and stroke.

Keywords: Cholesterol, HDL; Mortality; Myocardial infarction; Stroke

Conflicts of Interest
The authors have no conflicts of interest to declare.

Author Contributions
Conceptualization: Yang Y; Formal analysis: Han K, Park SH; Funding acquisition: Lee SH; Investigation: Yang Y, Lee SH; Methodology: Han K, Park SH, Lee SH; Project administration: Lee SH; Supervision: Lee SH; Writing - original draft: Yang Y; Writing - review & editing: Kim MK, Yoon KH, Lee SH.

INTRODUCTION

The inverse association between high-density lipoprotein cholesterol (HDL-C) concentration and cardiovascular disease (CVD) risk has been well-demonstrated by previous observational epidemiologic studies.[1,2] These studies consistently have shown a strong inversely linear and graded relationship irrespective of sex, race, and ethnicity, giving HDL-C the reputation of being the "good" cholesterol. However, randomized controlled pharmacological trials have failed to show any benefit of elevating the HDL-C level, raising doubts of low HDL-C being a causal risk factor.[3,4]

Recent genetic studies have shown that some genetic variants in the *CETP* gene and HDL receptor, related to high levels of HDL-C, are instead associated with a high risk of CVD.[5,6] In addition, a few recent large-scale cohort studies that investigated the whole general population, and covered the entire range of HDL-C levels, have suggested that an extremely high level of HDL-C is associated with the increased risk of mortality.[7,8] A U-shaped risk pattern between HDL-C level and all-cause mortality was observed, leading to a new insight that extremely high HDL-C levels may be a CVD risk factor, similar to low HDL-C levels.

Nevertheless, we should be aware that lipid profiles and the risk of CVD and mortality are largely affected by demographic and lifestyle factors, which might differ across different ethnicities. Thus, further studies based on Asians are needed in determining whether the U-shaped risk pattern of HDL-C level is a universal finding. In this study, we aimed to investigate the relationship between HDL-C level and the risk of myocardial infarction (MI), stroke, and cause-specific mortality in the Korean general population using the nationwide cohort that covers the whole population and the whole range of HDL-C levels.

MATERIALS AND METHODS

This study was performed according to the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement reporting guidelines (www.strobe-statement.org).

1. Data source and study population

We conducted the study based on data from the National Health Insurance Service-National Sample Cohort (NHIS-NSC), a population-based cohort established by the NHIS in South Korea.[9] As a single insurer managed by the government, the NHIS administers a mandatory universal insurance system for all residents in South Korea. The National Health Insurance (NHI) system consists of two major health care programs for universal coverage of all residents of Korea: NHI covers approximately 97% of the population and medical aid (MA) covers the remaining 3%. Since 2014, the NHIS has released nationally representative sample databases that include nearly the entire Korean population and is open to all researchers whose study protocols are approved by an official review committee.

The NHIS-NSC corresponds to 1,000,000 individuals selected through stratified random sampling based on sex, age group, residential area, and income level from nearly 48 million individuals in 2006. All subjects were followed-up until 2015 unless an individual's eligibility was disqualified because of death or emigration. Information of MA beneficiaries has been incorporated into a single NHIS database since 2006. In addition to total cholesterol,

https://doi.org/10.12997/jla.2021.10.1.74

triglyceride, HDL-C, and low-density lipoprotein (LDL) cholesterol levels were measured in the basic blood tests during general health examination since 2008.[10] The cohort comprises four databases as follows: participants' insurance eligibility database (e.g., age, sex, socioeconomic variables, type of eligibility, and income level), a medical procedure and treatment database (based on the medical bills that were claimed by medical service providers for their medical expense), a health examination database (results of general health examinations and questionnaires on lifestyle and behavior), and a medical care institution database (types of medical care institutions, location, equipment, and the number of physicians).

Among 426,978 subjects (age ≥20 years) who underwent health examinations between 2009 and 2012 (index year), we excluded 30,920 subjects with missing data on at least one variable. We excluded those having HDL-C ≥200 mg/dL, considering the possibility of data error (n=767). Subjects who had a history of MI (International Classification of Disease, 10th Revision [ICD-10] codes: I21, I22), stroke (ICD-10 codes: I63, I64), or cancer (ICD-codes: C00-C97) before the index year were also excluded (n=51,604). Finally, a total of 343,687 subjects were analyzed. This study was approved by the Institutional Review Board of The Catholic University of Korea (No. KC18EESI0429). The need for informed consent was waived because anonymous and de-identified information was used for the analyses.

2. Measurements and definitions

Body mass index (BMI) was calculated as the subject's weight (kg) divided by the square of the subject's height (m^2). Information on smoking status, alcohol consumption, and degree of exercise were obtained by a questionnaire from the health examination database: alcohol intake was categorized into <30 g/day and ≥30 g/day; regular exercise was defined as performing >20 minutes of strenuous physical activity at least thrice per week or >30 minutes of moderate physical activity at least five times per week. Household income level was dichotomized at the lower 25%. Blood samples were drawn after an overnight fast for the measurement of blood glucose and serum lipid levels. Hospitals wherein these health examinations were performed were certified by the NHIS and subjected to regular quality control.

Diabetes mellitus was defined based on the presence of at least one claim per year under ICD-10 codes E10-14 and at least one claim per year for the prescription of anti-diabetic medications, or fasting blood glucose (FBG) level ≥126 mg/dL. Hypertension was defined based on the presence of at least one claim per year under ICD-10 codes I10 or I11 and at least one claim per year for the prescription of antihypertensive agents, or systolic/diastolic blood pressure (BP) ≥140/90 mmHg. Dyslipidemia was defined based on the presence of at least one claim per year under ICD-10 code E78 and at least one claim per year for the prescription of a lipid-lowering agent, or total cholesterol ≥240 mg/dL. Metabolic syndrome was diagnosed if at least three of the following conditions were met: i) waist circumference (WC) ≥90 cm for men or ≥85 cm for women (using modified WC criteria for abdominal obesity of the Korean Society for the Study of Obesity[11]); ii) serum triglyceride level ≥150 mg/dL or use of lipid-lowering medications; iii) HDL-C level <40 mg/dL for men or <50 mg/dL for women, or use of lipid-lowering medications; iv) systolic BP ≥130 mmHg, diastolic BP ≥85 mmHg, or use of an antihypertensive drug; and v) FBG level ≥100 mg/dL or use of anti-diabetic medications.

3. Categorization of HDL-C levels

HDL-C levels were categorized into eight groups based on the plasma HDL-C concentration with 10 mg/dL intervals, starting from levels <30 mg/dL, ≥90 mg/dL as a highest (**Table 1**). We

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Table 1. Baseline characteristics of study participants according to the HDL-C categories

Characteristics	HDL-C (mg/dL)							
	<30	30–39	40–49	50–59	60–69	70–79	80–89	≥90
Men								
No.	1,817	22,010	56,703	50,826	27,985	11,113	3,797	1,992
Age (yr)	59.4 ± 9.0	58.2 ± 8.6	57.7 ± 8.4	57.5 ± 8.3	57.8 ± 8.4	57.9 ± 8.4	58.1 ± 8.6	58.1 ± 8.3
BMI (kg/m^2)	24.9 ± 2.8	24.9 ± 2.7	24.5 ± 2.7	24.1 ± 2.7	23.5 ± 2.8	23.1 ± 2.8	22.8 ± 2.8	22.4 ± 2.9
WC (cm)	87.1 ± 7.3	86.8 ± 7.0	85.6 ± 7.1	84.3 ± 7.3	83.0 ± 7.4	81.9 ± 7.5	81.3 ± 7.6	80.6 ± 7.9
Systolic BP (mmHg)	126.4 ± 14.6	126.3 ± 14.5	126.1 ± 14.5	126.4 ± 14.8	126.5 ± 15.1	126.8 ± 15.3	127.1 ± 15.0	127.8 ± 15.5
Diastolic BP (mmHg)	78.4 ± 9.9	78.6 ± 9.8	78.7 ± 9.7	78.9 ± 9.9	78.8 ± 9.9	79.1 ± 10.1	79.3 ± 9.9	79.5 ± 9.9
FBG (mg/dL)	107.7 ± 34.5	105.2 ± 29.8	103.9 ± 27.7	102.9 ± 26.1	102.1 ± 25.2	101.8 ± 25.2	102.8 ± 27.2	101.5 ± 27.1
Total cholesterol (mg/dL)	169.4 ± 38.5	183.9 ± 36.0	192.7 ± 35.4	198.8 ± 35.2	202.4 ± 35.4	207.0 ± 35.9	211.2 ± 37.1	215.9 ± 36.5
Triglyceride (mg/dL)	199 (137–287)	170 (120–240)	139 (100–197)	118 (85–167)	104 (75–146)	95 (68–133)	88 (64–126)	84 (60–119.5)
HDL-C (mg/dL)	25.2 ± 3.6	34.9 ± 2.6	43.7 ± 2.8	53.1 ± 2.8	62.8 ± 2.8	72.6 ± 2.8	82.7 ± 2.8	99.2 ± 12.8
LDL-C (mg/dL)	96.6 ± 37.3	109.8 ± 36.7	116.7 ± 35.1	118.2 ± 35.6	115.3 ± 37.1	112.0 ± 34.8	107.6 ± 35.1	97.3 ± 44.3
Current smoker	705 (38.8)	7,667 (34.8)	18,182 (32.1)	15,190 (29.9)	8,286 (29.6)	3,236 (29.1)	1,114 (29.3)	636 (31.9)
Alcohol (≥30 g/day)	105 (5.8)	1,259 (5.7)	4,116 (7.3)	4,605 (9.1)	3,010 (10.8)	1,337 (12.0)	536 (14.1)	283 (14.2)
Regular exercise	367 (20.2)	4,858 (22.1)	13,592 (24.0)	12,821 (25.2)	7,447 (26.6)	3,148 (28.3)	1,047 (27.6)	571 (28.7)
Household income (lower 25%)	138 (7.6)	1,392 (6.3)	3,459 (6.1)	2,914 (5.7)	1,771 (6.3)	718 (6.5)	251 (6.6)	140 (7.0)
Diabetes	456 (25.1)	4,503 (20.5)	9,534 (16.8)	7,297 (14.4)	3,611 (12.9)	1,300 (11.7)	468 (12.3)	226 (11.4)
Hypertension	908 (50.0)	10,204 (46.4)	24,404 (43.0)	20,866 (41.1)	11,053 (39.5)	4,398 (39.6)	1,497 (39.4)	785 (39.4)
Dyslipidemia	292 (16.1)	4,018 (18.3)	11,578 (20.4)	11,360 (22.4)	6,626 (23.7)	2,878 (25.9)	1,097 (28.9)	623 (31.3)
On lipid-lowering agent	242 (13.3)	3,008 (13.7)	7,627 (13.5)	6,697 (13.2)	3,577 (12.8)	1,441 (13.0)	514 (13.5)	244 (12.3)
Metabolic syndrome	1,483 (81.6)	16,936 (77.0)	29,628 (52.3)	21,817 (42.9)	10,805 (38.6)	3,997 (36.0)	1,354 (35.7)	686 (34.4)
Women								
Number	878	10,976	38,416	51,713	37,373	17,729	6,946	3,413
Age (yr)	63.9 ± 9.7	62.4 ± 9.6	61.1 ± 9.2	59.8 ± 9.0	58.9 ± 8.9	58.0 ± 8.6	57.7 ± 8.4	57.5 ± 8.6
BMI (kg/m^2)	24.7 ± 3.1	24.6 ± 3.0	24.4 ± 3.1	24.1 ± 3.0	23.7 ± 3.1	23.3 ± 3.0	23.0 ± 3.0	22.8 ± 3.0
WC (cm)	82.1 ± 7.9	81.3 ± 7.9	80.6 ± 8.0	79.4 ± 8.0	78.1 ± 8.1	77.0 ± 8.2	76.1 ± 8.2	75.6 ± 8.4
Systolic BP (mmHg)	126.4 ± 16.4	125.9 ± 15.9	125.3 ± 15.9	124.3 ± 15.8	123.4 ± 15.6	122.9 ± 16.0	122.6 ± 15.4	122.7 ± 15.5
Diastolic BP (mmHg)	77.2 ± 10.3	76.9 ± 9.9	76.7 ± 10.0	76.2 ± 10.0	75.9 ± 9.9	75.9 ± 10.1	75.8 ± 10.1	76.0 ± 10.2
FBG (mg/dL)	103.2 ± 34.3	101.7 ± 27.7	100.0 ± 24.5	98.3 ± 22.2	97.2 ± 20.9	96.3 ± 19.6	95.9 ± 19.8	96.5 ± 21.2
Total cholesterol (mg/dL)	176.8 ± 42.2	188.6 ± 37.9	198.7 ± 37.4	204.9 ± 37.1	210.3 ± 36.7	216.5 ± 37.0	221.4 ± 36.2	228.8 ± 39.0
Triglyceride (mg/dL)	182.5 (123–260)	162 (113–228)	134 (97–185)	111 (82–151)	97 (72–131)	86 (64–117)	80 (60–108)	77 (57–106)
HDL-C (mg/dL)	25.1 ± 4.0	35.0 ± 2.5	44.0 ± 2.8	53.4 ± 2.8	63.0 ± 2.8	72.8 ± 2.8	82.6 ± 2.8	97.9 ± 10.9
LDL-C (mg/dL)	108.6 ± 43.5	116.9 ± 37.7	124.3 ± 36.1	126.4 ± 37.0	125.5 ± 36.6	123.9 ± 35.5	120.4 ± 34.6	113.4 ± 42.6
Current smoker	22 (2.5)	248 (2.3)	700 (1.8)	854 (1.7)	585 (1.6)	260 (1.5)	97 (1.4)	69 (2.0)
Alcohol (≥30 g/day)	1 (0.1)	14 (0.1)	47 (0.1)	115 (0.2)	107 (0.3)	65 (0.4)	38 (0.6)	34 (1.0)
Regular exercise	133 (15.2)	1,701 (15.5)	6,629 (17.3)	9,532 (18.4)	7,293 (19.5)	3,690 (20.8)	1,462 (21.1)	765 (22.4)
Household income (lower 25%)	99 (11.3)	1,149 (10.5)	3,974 (10.3)	5,225 (10.1)	3,879 (10.4)	1,818 (10.3)	770 (11.1)	397 (11.6)
Diabetes	191 (21.8)	2,031 (18.5)	5,532 (14.4)	5,786 (11.2)	3,383 (9.1)	1,297 (7.3)	463 (6.7)	240 (7.0)
Hypertension	483 (55.0)	5,719 (52.1)	17,920 (46.7)	21,473 (41.5)	13,833 (37.0)	6,082 (34.3)	2,286 (32.9)	1,113 (32.6)
Dyslipidemia	192 (21.9)	2,721 (24.8)	10,817 (28.2)	15,890 (30.7)	12,187 (32.6)	6,339 (35.8)	2,724 (39.2)	1,539 (45.1)
On lipid-lowering agent	155 (17.7)	2,134 (19.4)	7,730 (20.1)	10,395 (20.1)	7,401 (19.8)	3,477 (19.6)	1,432 (20.6)	741 (21.7)
Metabolic syndrome	707 (80.5)	8,326 (75.9)	26,733 (69.6)	26,280 (50.8)	16,127 (43.2)	7,052 (39.8)	2,706 (39.0)	1,398 (41.0)

Values are mean±standard deviation, %, or median (interquartile range).
HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; WC, waist circumference; FBG, fasting blood glucose; LDL-C, low-density lipoprotein cholesterol; BP, blood pressure.

also categorized HDL-C levels based on percentiles with 20% intervals, and the lowest group (<5%) as well as the highest group (≥95%) were additionally divided (**Supplementary Table 1**).

4. Study outcomes and follow-up

The study outcomes were newly-diagnosed MI, stroke, and cause-specific mortalities. MI was defined as the recording of ICD-10 codes I21 or I22 during hospitalization or these codes having been recorded at least twice. Stroke was defined as the recording of ICD-10 codes I63 or I64 during hospitalization with claims for brain magnetic resonance imaging or brain computerized tomography. During the follow-up period, subjects without MI or stroke were considered to have completed the study at the date of their death or at the end of follow-up,

https://doi.org/10.12997/jla.2021.10.1.74

whichever came first. Cause of death was classified according to the diagnostic codes of the ICD-10. All-cause mortality (any codes) was categorized into cardiovascular mortality (I00-I99), cancer mortality (C00-C97), and other-cause mortality (codes other than I00–I99 and C00–C97). The study population was followed from baseline to the date of death or cardiovascular events or until December 31, 2015, whichever came first.

5. Statistical analysis

Baseline characteristics are presented as mean±standard deviation (SD), median (interquartile range), or number (%). The incidence rate of outcomes was calculated by dividing the number of incident cases by the total follow-up duration (person-years). The survival and disease-free probability of primary outcomes according to the HDL-C categories were calculated using the Kaplan-Meier curves, and the log-rank test was performed to analyze differences among the groups. Hazard ratios (HRs) and 95% confidence interval values of cause-specific mortality, MI, and stroke were analyzed using the Cox proportional hazards model. The multivariable-adjusted proportional hazards model was applied: Model 1 was not adjusted (crude); Model 2 was adjusted for age, sex, BMI, alcohol consumption, smoking, regular exercise, and income status; Model 3 was further adjusted for the presence of diabetes mellitus, hypertension, triglycerides, and use of lipid-lowering agents. The association between each endpoint and HDL-C on a continuous scale was examined using restricted cubic splines incorporated in the Cox proportional hazards model (Model 3). We set the HRs of restricted cubic spline transformation of continuous confounders with 10 knots, according to the 10 percentiles of each follow-up duration. The concentration of HDL-C associated with the lowest HR of each endpoint was the reference value in the spline Cox regression. In addition, sensitivity analysis was performed after excluding subjects with hypertension, diabetes mellitus, and dyslipidemia because these individuals may have had different levels of risk for CVD or mortality. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and a p-value <0.05 was considered to indicate statistical significance.

RESULTS

1. Baseline characteristics

Baseline characteristics of 176,243 men and 167,444 women according to HDL-C categories are presented in **Table 1**. We found that 39.3% of women and 25.5% of men had HDL-C ≥60 mg/dL, showing a higher proportion of women in the high HDL-C categories compared to men. Men in the higher HDL-C groups had lower BMI, WC, and FBG, and a lower prevalence of diabetes, hypertension, and metabolic syndrome. Subjects in the higher HDL-C groups had higher levels of total cholesterol but lower levels of triglyceride, and lower number of individuals were on lipid-lowering agents. The proportion of subjects performing regular exercise and showing heavy alcohol consumption was higher in the high HDL-C groups. A similar pattern was noted in women.

2. HDL-C level and the risk of cause-specific mortality, MI, and stroke

During the median follow-up of 6.0 years (interquartile range 5.2–6.4 years), the number of cases of death, MI, and stroke were 6,617, 4,064, and 3,435 in men and 3,677, 2,804, and 2,891 in women, respectively. The association between HDL-C on a continuous scale and the risk of each outcome in the total population is presented in **Fig. 1**. For all-cause mortality, cancer mortality, other mortality, and stroke, the lowest risk was observed at HDL-C levels of 60, 76,

https://doi.org/10.12997/jla.2021.10.1.74

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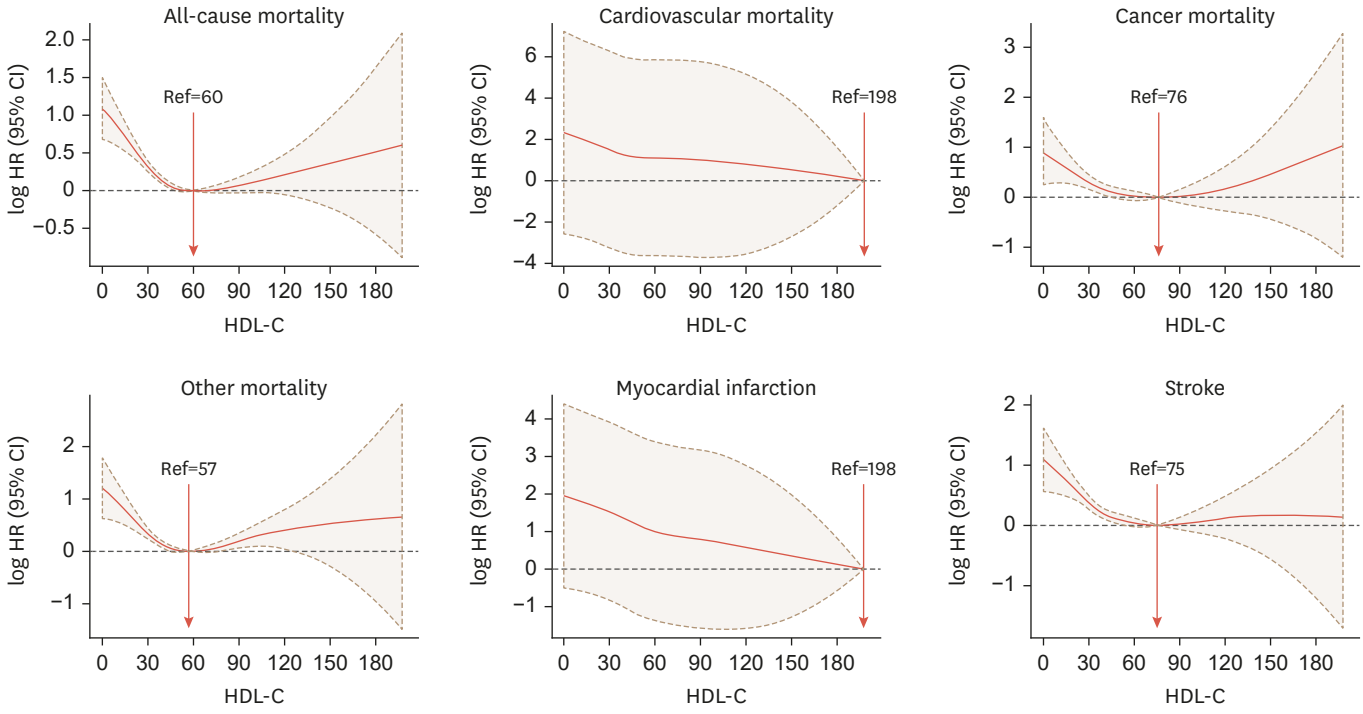

Fig. 1. HDL-C levels on a continuous scale and the risk of each outcome in all subjects.
Hazard ratio (solid line) and 95% confidence interval (dashed lines) from Cox regression using restricted cubic splines. Multivariable adjustment was performed for age, sex, body mass index, alcohol consumption, smoking, regular exercise, income status, diabetes mellitus, hypertension, triglycerides, and use of lipid-lowering agents.
HDL-C, high-density lipoprotein cholesterol.

57, and 75 mg/dL, respectively. In subjects having lower concentrations of HDL-C, an inverse association with increased risk was observed for these outcomes. However, there was no significant increase in the risk in subjects having higher concentrations of HDL-C. In contrast, the lowest risk for cardiovascular mortality and MI was observed at the extreme high end.

Table 2 shows the HRs of each outcome according to the HDL-C concentration-based categories in men. Similar to the spline curve, there was a significant inverse and graded increase in the risk of each outcome in subjects with lower HDL-C levels compared to the reference range (50–59 mg/dL). After multivariable adjustment, the risk of all-cause mortality, MI, and stroke was approximately two times higher in the HDL-C <30 mg/dL group than in the reference group. A significant decrease in risk of MI was observed in the 60–79 mg/dL HDL-C group, compared to the reference group. There was no significant increase in the risk of any outcomes in the high HDL-C range. Similar results were noted with percentile-based analyses. Subjects with HDL-C range of lowest 5th percentile had approximately 50% increased risk of all-cause mortality, MI, and stroke compared to the reference group (40th–60th percentile) (**Supplementary Table 1**). There was no significant U-shape association between HLD-C levels and the risk of all outcomes. In addition, a significantly lower risk of MI was observed at the extreme high HDL-C percentile groups (80th–95th and ≥95th percentile). Kaplan-Meier estimates of survival probability of each outcome showed comparable results (**Fig. 2**).

Table 3 and **Supplementary Table 2** show the HRs of each outcome according to the HDL-C concentration-based and percentile-based categories in women, respectively. Generally,

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Table 2. Hazard ratios of mortality, myocardial infarction, and stroke by HDL-C categories in men

HDL-C categories	Subjects	Event	Incidence rate*	Hazard ratio (95% confidence interval)		
				Model 1	Model 2	Model 3
All-cause mortality						
<30	1,817	147	14.3	2.42 (2.04–2.86)	1.99 (1.68–2.36)	1.86 (1.57–2.21)
30–39	22,010	943	7.6	1.28 (1.18–1.38)	1.24 (1.14–1.34)	1.18 (1.09–1.28)
40–49	56,703	2,097	6.5	1.10 (1.03–1.17)	1.11 (1.04–1.18)	1.09 (1.02–1.16)
50–59	50,826	1,712	5.9	1 (ref.)	1 (ref.)	1 (ref.)
60–69	27,985	1,059	6.7	1.13 (1.04–1.22)	1.04 (0.96–1.12)	1.05 (0.97–1.13)
70–79	11,113	402	6.4	1.08 (0.97–1.20)	0.96 (0.86–1.07)	0.97 (0.87–1.08)
80–89	3,797	177	8.3	1.40 (1.20–1.63)	1.16 (0.99–1.35)	1.17 (1.00–1.36)
90≤	1,992	80	7.0	1.18 (0.94–1.48)	0.96 (0.76–1.20)	0.98 (0.78–1.22)
p for trend				0.0014	<0.0001	<0.0001
Cardiovascular mortality						
<30	1,817	27	2.6	3.24 (2.18–4.83)	2.53 (1.69–3.77)	2.32 (1.55–3.47)
30–39	22,010	150	1.2	1.48 (1.21–1.82)	1.37 (1.11–1.68)	1.29 (1.04–1.59)
40–49	56,703	323	1.0	1.24 (1.05–1.46)	1.22 (1.03–1.45)	1.19 (1.01–1.41)
50–59	50,826	234	0.8	1 (ref.)	1 (ref.)	1 (ref.)
60–69	27,985	158	1.0	1.23 (1.00–1.50)	1.16 (0.94–1.42)	1.17 (0.95–1.43)
70–79	11,113	42	0.7	0.82 (0.59–1.14)	0.76 (0.55–1.06)	0.76 (0.55–1.06)
80–89	3,797	28	1.3	1.62 (1.09–2.39)	1.40 (0.95–2.08)	1.41 (0.95–2.09)
90≤	1,992	9	0.7	0.97 (0.50–1.89)	0.83 (0.43–1.63)	0.85 (0.44–1.66)
p for trend				0.0005	0.0004	0.0052
Cancer mortality						
<30	1,817	50	4.9	1.91 (1.44–2.55)	1.53 (1.15–2.04)	1.50 (1.13–2.01)
30–39	22,010	387	3.1	1.22 (1.08–1.38)	1.15 (1.01–1.30)	1.14 (1.00–1.29)
40–49	56,703	851	2.6	1.04 (0.94–1.14)	1.02 (0.93–1.13)	1.03 (0.93–1.13)
50–59	50,826	737	2.5	1 (ref.)	1 (ref.)	1 (ref.)
60–69	27,985	417	2.6	1.03 (0.91–1.16)	0.97 (0.86–1.09)	0.97 (0.86–1.09)
70–79	11,113	157	2.5	0.98 (0.82–1.16)	0.89 (0.75–1.06)	0.90 (0.76–1.07)
80–89	3,797	62	2.9	1.14 (0.88–1.47)	0.98 (0.76–1.28)	0.98 (0.76–1.27)
90≤	1,992	28	2.5	0.96 (0.66–1.40)	0.82 (0.56–1.19)	0.81 (0.56–1.19)
p for trend				0.0048	0.0006	0.0013
Other mortality						
<30	1,817	70	6.8	2.66 (2.08–3.40)	2.31 (1.81–2.96)	2.07 (1.62–2.65)
30–39	22,010	403	3.2	1.26 (1.12–1.43)	1.28 (1.13–1.44)	1.18 (1.04–1.34)
40–49	56,703	917	2.8	1.11 (1.01–1.23)	1.15 (1.04–1.27)	1.12 (1.01–1.23)
50–59	50,826	738	2.6	1 (ref.)	1 (ref.)	1 (ref.)
60–69	27,985	482	3.0	1.19 (1.06–1.33)	1.07 (0.95–1.20)	1.09 (0.97–1.22)
70–79	11,113	199	3.2	1.24 (1.06–1.45)	1.05 (0.90–1.23)	1.08 (0.92–1.27)
80–89	3,797	87	4.1	1.59 (1.28–1.99)	1.249 (1.00–1.56)	1.27 (1.01–1.58)
90≤	1,992	43	3.8	1.47 (1.08–2.00)	1.121 (0.82–1.53)	1.17 (0.86–1.59)
p for trend				0.8999	0.0007	0.0940
Myocardial infarction						
<30	1,817	75	7.6	2.42 (1.81–3.24)	1.97 (1.47–2.64)	1.97 (1.47–2.65)
30–39	22,010	716	5.9	1.60 (1.41–1.82)	1.45 (1.28–1.65)	1.44 (1.26–1.64)
40–49	56,703	1,434	4.6	1.14 (1.02–1.27)	1.10 (0.99–1.23)	1.10 (0.98–1.22)
50–59	50,826	1,061	3.7	1 (ref.)	1 (ref.)	1 (ref.)
60–69	27,985	511	3.3	0.85 (0.74–0.99)	0.85 (0.73–0.98)	0.85 (0.74–0.98)
70–79	11,113	169	2.7	0.77 (0.62–0.95)	0.77 (0.62–0.95)	0.76 (0.61–0.94)
80–89	3,797	66	3.1	0.93 (0.68–1.29)	0.92 (0.67–1.26)	0.89 (0.65–1.23)
90≤	1,992	32	2.8	0.79 (0.49–1.26)	0.77 (0.48–1.23)	0.75 (0.47–1.21)
p for trend				<0.0001	<0.0001	<0.0001
Stroke						
<30	1,817	75	7.5	2.44 (1.92–3.11)	1.93 (1.52–2.46)	1.86 (1.46–2.38)
30–39	22,010	540	4.4	1.43 (1.29–1.60)	1.30 (1.16–1.45)	1.26 (1.12–1.41)
40–49	56,703	1,143	3.6	1.16 (1.06–1.27)	1.12 (1.03–1.23)	1.11 (1.01–1.21)
50–59	50,826	890	3.1	1 (ref.)	1 (ref.)	1 (ref.)
60–69	27,985	498	3.2	1.04 (0.93–1.17)	1.02 (0.91–1.14)	1.03 (0.92–1.15)
70–79	11,113	186	3.0	0.98 (0.83–1.15)	0.96 (0.81–1.13)	0.95 (0.80–1.11)
80–89	3,797	70	3.3	1.12 (0.88–1.43)	1.06 (0.83–1.35)	1.04 (0.82–1.33)
90≤	1,992	33	2.9	0.99 (0.70–1.41)	0.94 (0.66–1.33)	0.93 (0.66–1.32)
p for trend				<0.0001	<0.0001	<0.0001

Model 1: crude; Model 2: adjusted for age, sex, body mass index, alcohol consumption, smoking, regular exercise, and income status; Model 3: model 2 + further adjusted for diabetes mellitus, hypertension, triglycerides, and use of lipid-lowering agents.
HDL-C, high-density lipoprotein cholesterol.
*per 1,000 person-years.

https://doi.org/10.12997/jla.2021.10.1.74

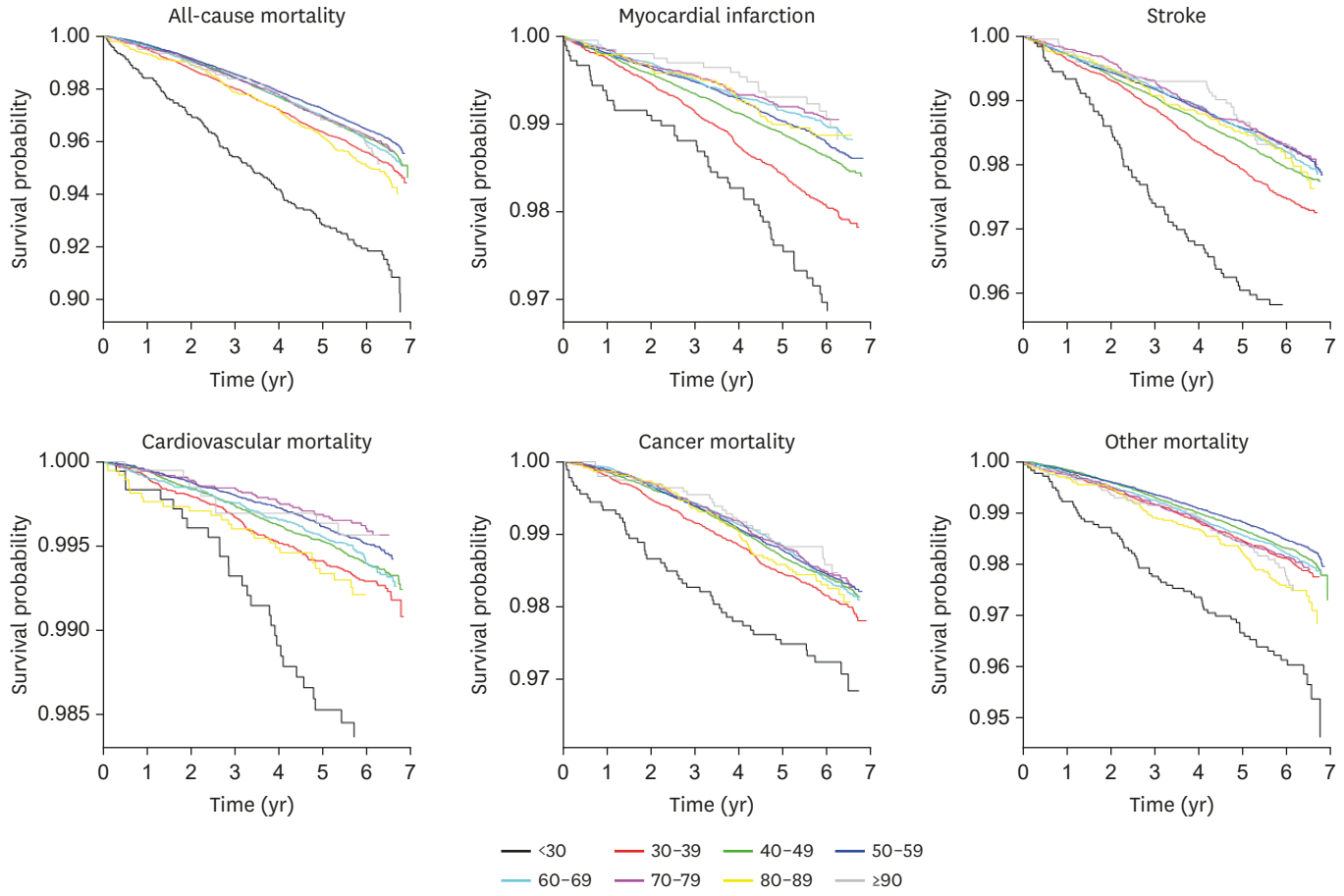

Fig. 2. Kaplan-Meier estimates of survival probability for each outcome according to the high-density lipoprotein cholesterol concentration-based categories in men.

the risk of most outcomes was significantly higher in the lower HDL-C groups than in the reference group, in both analyses. Although significantly higher risk of other mortality was observed at the extreme high concentration (HDL-C ≥90 mg/dL), this was not observed in the percentile-based analysis. Besides, there was no further increase in the risk for all-cause mortality, cardiovascular mortality, cancer mortality, MI, and stroke in the higher HDL-C groups, suggesting no evidence of HDL-C paradox. Kaplan-Meier estimates of survival probability of each outcome showed comparable results (**Fig. 3**).

3. Sensitivity analysis

Sensitivity analysis was performed after excluding subjects with hypertension, diabetes mellitus, and dyslipidemia (**Supplementary Tables 3** and **4**). Although higher HRs of all-cause mortality, other mortality, MI, and stroke were observed in the lower concentrations of HDL-C compared to the reference range, we could not find any significant U-shaped association between HDL-C and all outcomes for both men and women.

DISCUSSION

In this study of the Korean general population, we examined the association between HDL-C levels and the risk of cause-specific mortality, MI, and stroke. Unlike some of the previous reports

https://doi.org/10.12997/jla.2021.10.1.74

Table 3. Hazard ratios of mortality, myocardial infarction, and stroke by HDL-C categories in women

HDL-C categories	Subjects	Event	Incidence rate*	Hazard ratio (95% confidence interval)		
				Model 1	Model 2	Model 3
All-cause mortality						
<30	878	52	10.4	2.91 (2.20–3.85)	1.80 (1.37–2.38)	1.72 (1.30–2.28)
30–39	10,976	425	6.8	1.92 (1.72–2.15)	1.36 (1.22–1.53)	1.30 (1.16–1.46)
40–49	38,416	994	4.5	1.28 (1.18–1.40)	1.10 (1.01–1.20)	1.08 (0.99–1.18)
50–59	51,713	1,040	3.5	1 (ref.)	1 (ref.)	1 (ref.)
60–69	37,373	695	3.3	0.93 (0.84–1.02)	1.00 (0.91–1.10)	1.01 (0.92–1.11)
70–79	17,729	291	2.9	0.82 (0.72–0.93)	0.99 (0.87–1.12)	1.01 (0.89–1.15)
80–89	6,946	113	2.9	0.81 (0.67–0.99)	1.02 (0.84–1.24)	1.05 (0.86–1.27)
90≤	3,413	67	3.4	0.98 (0.76–1.25)	1.19 (0.93–1.52)	1.23 (0.96–1.58)
p for trend				<0.0001	<0.0001	0.0026
Cardiovascular mortality						
<30	878	6	1.2	1.62 (0.72–3.65)	0.95 (0.42–2.13)	0.92 (0.41–2.07)
30–39	10,976	104	1.7	2.27 (1.80–2.87)	1.53 (1.21–1.94)	1.49 (1.17–1.89)
40–49	38,416	173	0.8	1.08 (0.88–1.32)	0.91 (0.74–1.11)	0.89 (0.73–1.09)
50–59	51,713	216	0.7	1 (ref.)	1 (ref.)	1 (ref.)
60–69	37,373	134	0.6	0.86 (0.70–1.07)	0.94 (0.76–1.17)	0.95 (0.76–1.17)
70–79	17,729	69	0.7	0.94 (0.71–1.23)	1.16 (0.88–1.52)	1.18 (0.90–1.55)
80–89	6,946	20	0.5	0.69 (0.44–1.10)	0.90 (0.57–1.42)	0.92 (0.58–1.45)
90≤	3,413	7	0.4	0.49 (0.23–1.04)	0.62 (0.29–1.31)	0.63 (0.30–1.35)
p for trend				<0.0001	0.0633	0.1653
Cancer mortality						
<30	878	12	2.3	1.98 (1.11–3.51)	1.36 (0.76–2.41)	1.30 (0.73–2.32)
30–39	10,976	120	1.9	1.59 (1.29–1.96)	1.22 (0.99–1.50)	1.19 (0.96–1.47)
40–49	38,416	345	1.6	1.31 (1.13–1.52)	1.16 (1.00–1.34)	1.14 (0.98–1.33)
50–59	51,713	355	1.2	1 (ref.)	1 (ref.)	1 (ref.)
60–69	37,373	236	1.1	0.92 (0.78–1.09)	1.00 (0.84–1.17)	1.00 (0.84–1.18)
70–79	17,729	98	1.0	0.81 (0.65–1.01)	0.95 (0.76–1.19)	0.97 (0.77–1.21)
80–89	6,946	40	1.0	0.84 (0.61–1.17)	1.04 (0.75–1.44)	1.06 (0.76–1.47)
90≤	3,413	19	1.0	0.81 (0.51–1.29)	1.00 (0.63–1.58)	1.03 (0.65–1.63)
p for trend				<0.0001	0.0179	0.0630
Other mortality						
<30	878	34	6.8	4.24 (3.00–6.01)	2.51 (1.77–3.56)	2.38 (1.68–3.39)
30–39	10,976	197	3.2	1.99 (1.68–2.35)	1.36 (1.15–1.61)	1.28 (1.08–1.52)
40–49	38,416	471	2.2	1.36 (1.20–1.55)	1.15 (1.01–1.31)	1.12 (0.99–1.28)
50–59	51,713	465	1.6	1 (ref.)	1 (ref.)	1 (ref.)
60–69	37,373	320	1.5	0.96 (0.83–1.10)	1.03 (0.89–1.19)	1.04 (0.90–1.20)
70–79	17,729	122	1.2	0.77 (0.63–0.94)	0.93 (0.76–1.13)	0.96 (0.79–1.17)
80–89	6,946	53	1.3	0.86 (0.64–1.14)	1.07 (0.80–1.42)	1.11 (0.84–1.48)
90≤	3,413	41	2.1	1.34 (0.97–1.84)	1.59 (1.16–2.19)	1.66 (1.20–2.29)
p for trend				<0.0001	0.0017	0.0586
Myocardial infarction						
<30	878	24	4.9	1.52 (0.86–2.69)	1.05 (0.59–1.87)	1.01 (0.57–1.79)
30–39	10,976	327	5.4	1.93 (1.63–2.29)	1.50 (1.27–1.77)	1.41 (1.19–1.67)
40–49	38,416	776	3.6	1.25 (1.10–1.43)	1.11 (0.97–1.26)	1.07 (0.94–1.22)
50–59	51,713	824	2.8	1 (ref.)	1 (ref.)	1 (ref.)
60–69	37,373	539	2.6	0.90 (0.78–1.04)	0.98 (0.85–1.13)	1.01 (0.87–1.16)
70–79	17,729	200	2.0	0.75 (0.61–0.91)	0.89 (0.73–1.09)	0.93 (0.76–1.14)
80–89	6,946	72	1.8	0.67 (0.49–0.92)	0.84 (0.61–1.15)	0.87 (0.63–1.19)
90≤	3,413	42	2.2	0.78 (0.52–1.17)	0.97 (0.64–1.46)	0.98 (0.65–1.48)
p for trend				<0.0001	<0.0001	0.0015
Stroke						
<30	878	47	9.7	2.96 (2.18–4.01)	1.99 (1.46–2.70)	2.03 (1.49–2.77)
30–39	10,976	286	4.6	1.49 (1.30–1.70)	1.12 (0.98–1.29)	1.09 (0.95–1.26)
40–49	38,416	759	3.5	1.12 (1.02–1.24)	0.98 (0.89–1.08)	0.97 (0.88–1.07)
50–59	51,713	900	3.1	1 (ref.)	1 (ref.)	1 (ref.)
60–69	37,373	541	2.6	0.84 (0.75–0.93)	0.91 (0.82–1.02)	0.92 (0.83–1.03)
70–79	17,729	224	2.2	0.74 (0.63–0.85)	0.89 (0.77–1.03)	0.90 (0.78–1.05)
80–89	6,946	81	2.1	0.66 (0.52–0.83)	0.84 (0.66–1.06)	0.84 (0.66–1.06)
90≤	3,413	53	2.7	0.91 (0.68–1.20)	1.15 (0.87–1.53)	1.11 (0.84–1.47)
p for trend				<0.0001	0.0013	0.0079

Model 1: crude; Model 2: adjusted for age, sex, body mass index, alcohol consumption, smoking, regular exercise, and income status; Model 3: model 2 + further adjusted for diabetes mellitus, hypertension, triglycerides, and use of lipid-lowering agents.
HDL-C, high-density lipoprotein cholesterol.
*per 1,000 person-years.

https://doi.org/10.12997/jla.2021.10.1.74

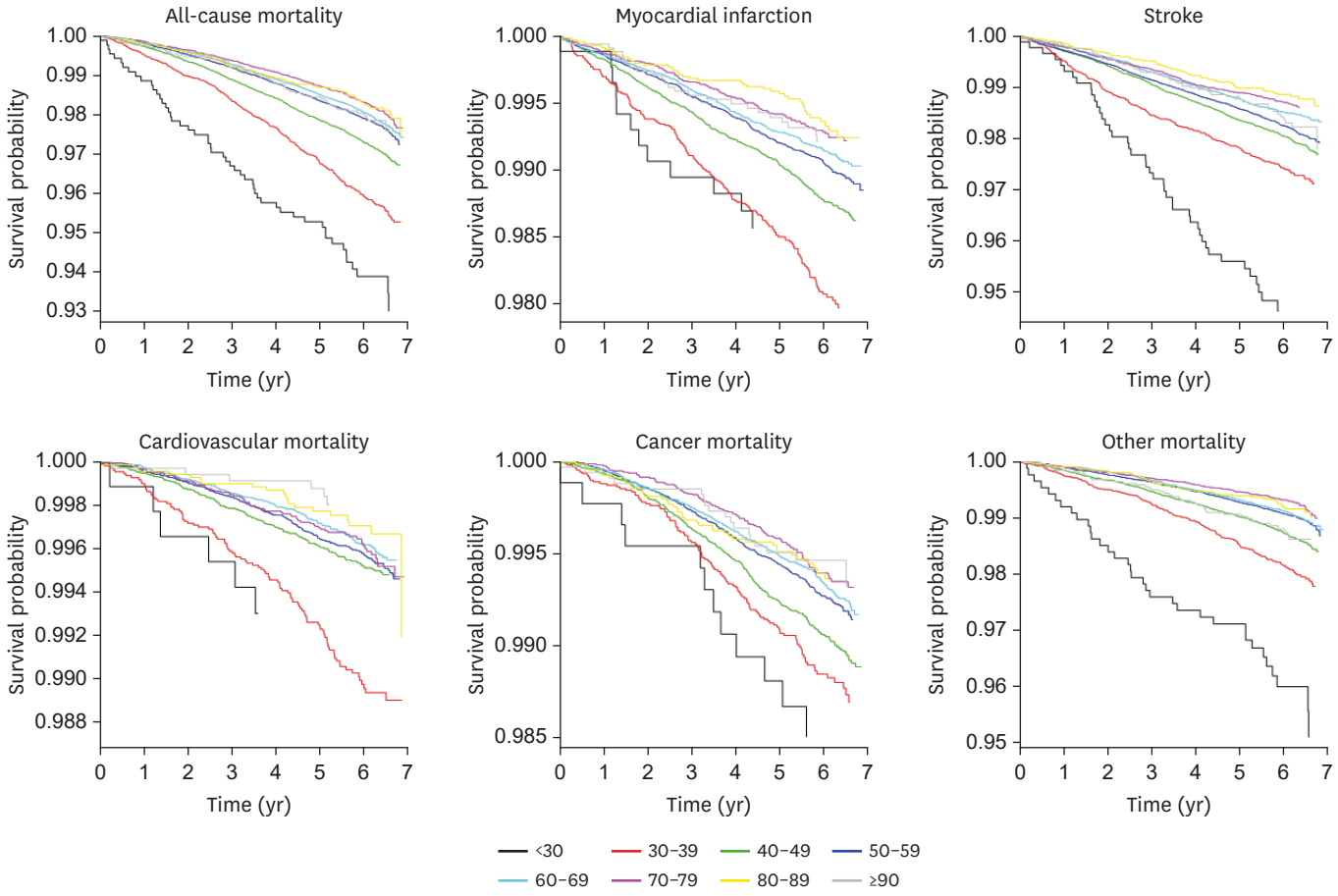

Fig. 3. Kaplan-Meier estimates of survival probability for each outcome according to high-density lipoprotein cholesterol concentration-based categories in women.

mostly based on the western population, we could not observe any significant U-shaped risk association between HDL-C and all outcomes in both men and women. The risk of mortality, MI, and stroke was high at low HDL-C levels in the Korean general population. However, extremely high HDL-C levels were not associated with an increased risk of mortality, MI, and stroke. Rather, the lower risk of cardiovascular mortality and MI was observed at extreme high levels of HDL-C.

Major recent population-based cohort studies that investigated the relationship between extremely high HDL-C levels and cardiovascular outcomes are summarized in **Supplementary Table 5**.[7,8,12,14] In a pooled analysis of six community-based cohorts,[12] including the Framingham Heart Study and Atherosclerosis Risk in Communities study (ARIC), both men and women did not show an increased risk of coronary heart disease events and total mortality at high HDL-C levels. Instead, the risk plateaued. In an analysis on the Canadian cohort,[13] men at both the lowest (≤30 mg/dL) and the highest HDL-C categories (>90 mg/dL) showed a significantly higher all-cause mortality rate. The lowest mortality rate was seen at HDL-C levels of 51–70 mg/dL, implying a U-shaped association. In addition, a higher mortality rate than overall was observed in other mortality outcomes among both men and women. However, there was no significant U-shaped association in cardiovascular and cancer mortality. An analysis based on the cohort of Copenhagen City Heart Study (CCHS) and Copenhagen General Population Study (CGPS),[8] which included individuals with White Danish descent alone, showed a significant U-shaped association between HDL-C level and all-cause as well as cardiovascular mortality in both men and women.

https://doi.org/10.12997/jla.2021.10.1.74

The Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH–JAPAN) study examined the impact of extremely high levels of HDL-C on cause-specific CVD mortality using pooled data of nine Japanese cohort studies.[14] In the above study, extremely high levels of HDL-C were found to be significantly associated with an increased risk of death from ischemic stroke in men. However, there was no significant association in cardiovascular and all-cause mortality after multivariable adjustment. Considering the above together, we find that only a few previous studies have demonstrated typical U-shaped risk associations between HDL-C level and related outcomes. In most studies, a significant U-shaped risk pattern was definite only for all-cause mortality. The Copenhagen cohort study alone showed that this U-shaped association was also significantly seen with cardiovascular mortality. Furthermore, no study showed a statistically significant increase in risks of MI or ischemic stroke at extremely high levels of HDL-C.

A possible explanation for the inconsistent findings from previous studies is that high levels of HDL-C have complex heterogeneous causes. Recent human genetic studies have demonstrated that the genetic basis of an extremely high HDL-C concentration is frequently polygenic, with contributions from both rare large-effect and common small-effect variants.[15,16] Several new variants in HDL-C genes that regulate HDL-C metabolism have been discovered with methodologic developments in genotyping and sequencing. Nevertheless, several of these genes were found to lack any association with CVD.[17] In a Mendelian randomization study, some single nucleotide polymorphisms, such as the Asn396Ser variant in the *LIPG* gene, that raise plasma HDL-C concentration did not reduce the risk of MI.[18] In addition, genetic risk score combining 14 variants exclusively related to HDL-C showed no association with the risk of MI, in contrast to the polymorphisms related to plasma LDL cholesterol levels which were consistently associated with the risk of MI.[19] Moreover, the complex association is well-known between HDL-C levels and sociodemographic and lifestyle factors, such as low levels of income, smoking, alcohol consumption, obesity, and limited physical activity in numerous epidemiological studies.[20] There could be additional unknown mechanisms for extreme HDL-C levels, including possible new genes, gene-environment interactions, and nonmendelian influences such as epigenetic effects. These data collectively indicate that plasma HDL-C concentration may be a confounding variable and question the clinical utility of HDL-C level as a specific biomarker of CVD.

With advancements in lipidomics and proteomics, an evolving understanding of the compositional and functional complexity of HDL particles has led to the attention on tests that assess the quality of HDL particles, rather than quantity, such as HDL particle number, functionally significant structural components, and functions.[21-24] One of the functional parameters that have been most intensively studied is serum cholesterol efflux capacity, a functional marker of the ability of HDL to promote the first step of reverse cholesterol transport.[25] Rohatgi et al.[25] demonstrated that cholesterol efflux capacity has a stronger inverse association with the incidence of cardiovascular events than did HDL-C concentration in a population-based cohort. However, cholesterol efflux capacity requires a high-throughput approach that is experimentally measured as the ability of human serum to promote the efflux of cholesterol from loaded macrophages. Thus, this measure still has limitations of cost and time on clinical application.[26]

Previously, Oh et al.[27] reported the relationship between extremely high HDL-C levels and mortality in the Korean population. The authors concluded that the extremely high levels of HDL-C are associated with increased all-cause mortality, although they failed to show its statistical significance after multivariable adjustments, thus only demonstrating a tendency.

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Although the authors used the same database as our study did, there were some differences between their study and ours, especially in the research design. First, Oh et al.[27] excluded subjects aged under 40 years. However, we included subjects aged ≥20 years to consider the possibility that extremely high HDL-C levels are associated with hereditary and premature mortality.[28] Our study has an advantage that we further included MI and stroke in addition to mortality related outcomes. Interestingly, the lower risk of cardiovascular mortality and MI was observed at extreme high levels of HDL-C, but the stroke was not. The causes of ischemic stroke are more diverse compared to MI. In Korea, about 37% of patients with ischemic stroke had large artery atherosclerosis, followed by cardioembolism (22%) and small-vessel occlusion (18%).[29] Therefore, stroke might show different risk patterns with cardiovascular mortality and MI in the study. Lastly, we investigated the complete range of HDL-C concentrations, using spline curves and category-based approach with both concentrations and percentiles.

This study has some limitations that need to be acknowledged. First, discrepancies between the diagnosis of individuals in medical practice and diagnoses based on disease codes from claim data can lead to inaccurate analysis. Second, we could not consider the menopausal status and hormone replacement therapy in women, which could affect the cholesterol levels. Third, the response rate of the self-reported questionnaire in the NHIS was approximately 70%; thus, there might have been possible selection bias. Lastly, since the results were derived from a single country's claim data, our findings cannot be generalized to people of different ethnicities.

In this nationwide cohort study representing the entire population of Korea and the complete range of HDL-C levels, we did not observe any significant U-shaped risk association between HDL-C concentration and mortality outcomes, MI, and stroke in both men and women. Further research is needed to identify more specified prognostic factors that predict adverse outcomes reflecting the dynamic physiologic function of HDL particles rather than simple concentration. This could be achieved by conducting functional and genetic studies on HDL-C, enabling more personalized risk estimation.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Hazard ratios of mortality, myocardial infarction, and stroke by HDL-C percentile categories in men

Click here to view

Supplementary Table 2

Hazard ratios of mortality, myocardial infarction, and stroke in women by HDL-C percentile categories in women

Click here to view

Supplementary Table 3

Hazard ratios of mortality, myocardial infarction, and stroke by HDL-C categories in men (excluding subjects with hypertension, diabetes mellitus, and dyslipidemia)

Click here to view

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Supplementary Table 4

Hazard ratios of mortality, myocardial infarction and stroke by HDL-C categories in women (excluding subjects with hypertension, diabetes mellitus, and dyslipidemia)

Click here to view

Supplementary Table 5

Summary of representative cohort studies on high-density lipoprotein cholesterol and health outcomes

Click here to view

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