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Very high high-density lipoprotein cholesterol is associated with increased all-cause mortality in South Koreans

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HIGHLIGHTS

- Although people with very high HDL cholesterol had higher risk of all-cause mortality compared to control group, it seems to be partly attributed to increased mortality from external causes.
- Very high HDL cholesterol was not associated with increased cardiovascular mortality in Korean people, unlike western counterparts, suggesting ethnic differences.

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ABSTRACT

Background and aims: Our study aimed to investigate the association between high-density lipoprotein cholesterol (HDL-C) and all-cause and cause-specific mortality in Korean adults.
Methods: A total of 365,457 participants aged ≥40 years were selected from the Korean National Health Insurance Service–National Sample Cohort from 2009 to 2015. HDL-C level was categorized into < 1.0, 1.0–1.19, 1.2–1.39, 1.4–1.59, 1.6–1.79 (reference), 1.8–1.99, 2.0–2.19 and ≥ 2.20 mmol/L. Cox proportional hazard models were used to examine the association between HDL-C level and mortality risk.
Results: In a median 3.5-year follow-up period, 9,350 participants (2.6%) died. Men with HDL-C level of 1.6–1.79 mmol/L and women with HDL-C level of 1.4–1.59 mmol/L had the lowest age-standardized mortality rates for all-cause death. However, for cardiovascular death, men with HDL-C level ≥2.20 mmol/L and women with HDL-C level of 1.8–1.99 mmol/L showed the lowest mortality rate. After adjusting for multiple covariates, the hazard ratios for all-cause and cancer deaths showed a U-shaped relationship with HDL-C level for both sexes. However, there were heterogenetic associations between HDL-C level and mortality risk of subtypes of cardiovascular disease by sex. For other causes of death except for cardiovascular and cancer death, elevated mortality risk was mainly due to external causes (ICD-10 code, S00-T98).
Conclusions: In South Korea, very high HDL-C level was associated with increased risk of all-cause death. However, the increased all-cause mortality risk in people with very high HDL-C level was partly due to mortality risk from external causes.

1. Introduction

The Framingham heart study has shown that elevated high-density lipoprotein (HDL) level could lower the risk of coronary heart disease [1]. However, a series of randomized clinical trials have failed to prove that an increase in HDL cholesterol (HDL-C) could reduce the risk of cardiovascular mortality [2]. Indeed, recent cohort studies have demonstrated that HDL-C level was not inversely associated with all-cause and cardiovascular mortality but showed a U-shaped dose-response relationship with mortality risk. In a prospective study of 1,764,986 US veterans, there was a U-shaped relationship between HDL-C level and all-cause mortality [3]. In Canada, people with HDL-C level > 90 mg/

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dL were associated with high risk of all-cause mortality [4]. In two prospective cohort studies in Denmark, HDL-C levels ≥3.5 mmol/L and < 1.0 mmol/L were associated with high all-cause mortality and high cardiovascular mortality, respectively, in 116,000 people [5].

In genetic studies, it is also suggested that high HDL levels may be associated with cardiovascular disease or increased risk of cardiovascular disease. In a Mendelian randomization study, genetic variants, which increase plasma HDL-C level, were not significantly associated with decreased risk of myocardial infarction [6]. Recently, a study on loss-of-function mutation in scavenger receptor B type 1 (SCARB1), one of the major receptors of HDL, showed that high HDL-C level could induce atherosclerosis [7]. In addition, recent *in vitro* and in vivo studies have shown that high HDL-C level promotes senescence and interferes with the formation of vascular endothelial progenitor cells [8].

However, the association between HDL-C level and risk of cardiovascular disease was complex and varied by ethnicity, race, or genetic factors [9]. Depending on race or ethnicity, the composition and size of lipoprotein also varied [10,11]. Indeed, African-American women had larger HDL particles compared to white American women, and black male children had smaller VLDL particles and black female children had larger HDL particles compared to white children in the United States [11,12]. Furthermore, polymorphism of *SCARB1*, which is a well-known HDL receptor gene, also differed according to ethnicity or race [13–17].

Therefore, it is still unclear whether very high HDL-C level is associated with increased risk of all-cause mortality or cardiovascular mortality especially in the Asian population, including Korean people. Our study aimed to investigate the association between HDL-C level and all-cause and cause-specific mortality among Korean adults using the National Health Insurance Service–National Sample Cohort (NHIS-NSC), which is a large-scale, nationally representative retrospective cohort study.

2. Materials and methods

2.1. Data sources

The national health insurance system covers over 97% of the entire population living in South Korea, suggesting that the database of the national health insurance system can represent the medical service usage of the entire Korean population [18]. Information on medical health checkups was collected and stored by the National Health Insurance Corporation (NHIC) in South Korea. In recent years, the national health insurance system in South Korea has provided the sampled database for research purposes after deleting the personal identification information. The sampled database provided by the NHIC includes the information of health checkups, linked with the causes of death in Statistics Korea. This database, which was named NHIS, can be accessed by a researcher after receiving approval from the institutional review board (IRB) through internal evaluation and revision of the research proposal. This study was approved by Kyung Hee University (IRB; KHSIRB-17-081).

2.2. Study participants

A total of 587,305 participants who underwent medical health checkup between 2009 and 2015 were included in the National Health Information Database (Fig. S1). Of these, we initially excluded 155,816 individuals aged < 40 years. In addition, 569 people whose age was not recorded were excluded. To rule out the past history of cardiovascular disease, we excluded 17,779 participants who previously had heart disease or stroke, based on the questionnaire. Of the 413,856 eligible participants, 48,399 were excluded for missing covariates. In addition, participants whose follow-up periods were less than 6 months were excluded from the study, because these cases were potentially affected by factors other than HDL-C itself [19]. Finally, 365,457 individuals were included in the final analysis.

2.3. Health survey examinations and laboratory measurements

The general health checkup of NHIC was conducted through 2 stages. The first stage examination is a massive screening test to determine the presence or absence of disease among the general population without symptom. The second stage examination is the consultation for screening test and a more detailed examination to confirm the presence of disease. These health examinations also included a questionnaire for lifestyle or past medical histories.

The information about smoking history, alcohol intake, physical activity, and past history of medical conditions, such as heart disease or stroke, was obtained from the questionnaire of the NHIC. Alcohol intake was categorized into not drinking, 1–4 times per week, and more than 5 times per week. Physical activity was defined as conducting moderate-intensity physical activity for at least 30 min per day for more than 5 days per week or vigorous-intensity physical activity for at least 20 min per day for more than 3 days per week [20].

2.4. Categorization of HDL-C levels

In order to analyze the dose-response relationship between HDL-C level and risk of cause-specific mortality, HDL-C level was categorized into < 1.0, 1.0–1.19, 1.2–1.39, 1.4–1.59, 1.6–1.79, 1.8–1.99, 2.0–2.19, and ≥2.20 mmol/L. Low-density lipoprotein (LDL) cholesterol and triglyceride levels were also selected for covariate adjustment [5].

2.5. All-cause and cause-specific deaths

The NHIS-NSC database was linked to the cause of death data from Statistics Korea. In this study, the entry date was the first health checkup since 2009, and the last follow-up date for death was December 31, 2015. The cause of death was recorded using ICD-10 code [21]. All-cause deaths were defined as death from any cause from the entry date to end date of the study. Death from cancer was defined as death from ICD-10 codes “C00–C97,” and death from cardiovascular disease was defined as death from ICD-10 codes “I00–I99” [5]. In the subgroup for cardiovascular disease death, death from coronary artery disease was defined as death from “I20–I25,” death from overall stroke was defined as death from “I60–I69,” death from ischemic stroke was defined as death from “I63,” and death from hemorrhagic stroke was defined as death from “I60–I62” according to the ICD-10 code. Death due to other causes were classified as other deaths. In subgroup for other causes of death, external causes of death were defined as death from “injury, poisoning and certain other consequences of external causes: S00–T98,” death from respiratory disease was defined as death from “J00–J99,” and death from diabetes mellitus was defined as death from “E10–E14,” according to the ICD-10 code. People who died from other causes or those who were alive until December 31, 2015 were censored.

2.6. Statistical analysis

The baseline characteristics of study participants were presented according to the HDL-C level. Continuous variables have been expressed as mean (standard deviation), and categorical variables have been expressed as number (percentage). The differences in distribution of continuous and categorical variables were tested using independent *t*-test and chi-square test, respectively. In order to know the differences in the cause-specific death rates according to the HDL-C level, the age-standardized mortality rates were calculated as the sum of weighted incidence rate for each 5-year age group using the World Health Organization (WHO) standard population [22]. The age-standardized mortality rates for all-cause, cardiovascular, cancer, and other deaths are expressed as number of cause-specific deaths per 100,000 people.

To examine the association between HDL-C level and risk of cause-specific deaths, the Cox proportional hazard models were used after adjusting for age, smoking status, alcohol intake, physical activity, body mass index (BMI), systolic blood pressure, fasting blood glucose level, triglyceride level, and LDL cholesterol level by sex. Likelihood ratio tests were used to assess trends in hazard ratios (HRs) for ordinal variables (HDL-C levels).

p-values < 0.05 were considered statistically significant. All statistical analyses were performed using SAS Enterprise Guide (version 7.1, SAS Institute, Cary, NC, USA) and Stata 12.0 (StataCorp LP, TX, USA) software.

3. Results

When comparing patients excluded from the study due to past history of cardiovascular disease and study participants, the patients with past history of cardiovascular disease were older and had higher BMI, waist circumference, fasting blood glucose level, triglyceride level, and systolic and diastolic blood pressures than our study participants (Supplementary Table 1). However, the patients with past history of cardiovascular disease had lower total cholesterol, HDL-C, and LDL cholesterol levels. The proportion of overall deaths and cardiovascular disease deaths among patients with past history of cardiovascular disease was higher compared to that in our study participants.

Of 365,457 participants, 9350 (2.6%) died from 2008 to 2015 (Table 1). Of 9350 deaths, 1585 participants (16.9%) died from cardiovascular disease, and 3750 participants (40.1%) died from cancer. The median follow-up period was 3.46 years. The mean age of study participants was 55.6 (11.2) years. The mean HDL-C level was 1.43 (0.59) mmol/L. Except for deaths due to cardiovascular disease, men who have HDL-C level of 1.6–1.79 mmol/L showed the lowest proportion of overall deaths and cancer deaths. In contrast, participants who have HDL-C level ≥2.20 mmol/L showed the lowest mortality proportion from cardiovascular disease.

The age-standardized mortality rates for Korean men and women were presented according to the HDL-C level (Supplementary Table 2). The HDL-C level was categorized into < 1.0, 1.0–1.19, 1.2–1.39, 1.4–1.59, 1.6–1.79, 1.8–1.99, 2.0–2.19, and ≥2.20 mmol/L, and the reference value was set at 1.6–1.79 mmol/L. The age-standardized mortality rates per 100,000 person-years for all-cause deaths were 100.7 (95% CI, 97.9–103.6) for men and 45.8 (95% CI, 44.1–47.4) for women. Men with HDL-C level of 1.6–1.79 mmol/L showed the lowest age-standardized mortality rates, while women with HDL-C level of 1.4–1.59 mmol/L showed the lowest age-standardized mortality rates for all-cause deaths. Similarly, mortality rate for cancer deaths was the lowest in men with HDL-C levels of 1.6–1.79 mmol/L and the lowest in women with HDL-C level of 1.4–1.59 mmol/L. However, mortality rates due to cardiovascular disease showed a different pattern. The mortality rates due to cardiovascular deaths was the lowest in men with HDL-C level ≥2.20 mmol/L and the lowest in women with HDL-C level of 1.8–1.99 mmol/L.

Adjusted HRs and 95% CIs for all-cause deaths according to the HDL-C level are shown in Table 2 and Fig. 1. The adjusted HRs for all-cause deaths showed a U-shaped relationship according to the HDL-C level. Men with HDL-C level < 1.0 mmol/L had the highest HR of 1.59 (95% CI, 1.45–1.76) compared to men with HDL-C level of 1.6–1.79 mmol/L. Men with HDL-C level ≥2.20 mmol/L showed marginally significant higher mortality risk of all-cause death compared to men with HDL-C level of 1.6–1.79 mmol/L. Women with HDL-C level < 1.0 mmol/L had the highest HR of 1.52 (95% CI, 1.34 to 1.73) compared to women with HDL-C level of 1.6–1.79 mmol/L.

The dose-response relationship of HR for cardiovascular mortality on the HDL-C level differed from that of all-cause deaths (Table 3, Fig. 1). In both men and women, there were negative relationships: the HR of death due to cardiovascular disease increased with decrease in HDL-C level (p for trend < 0.01 for men, p for trend < 0.01 for women). Indeed, the participants with HDL-C level ≥2.20 mmol/L had the lowest HRs for cardiovascular deaths.

A subgroup analysis was also performed for cardiovascular disease. Regarding overall stroke and ischemic stroke, the risk of mortality has decreased with increasing HDL-C level (Table 4). However, there was no significant dose-response relationship between HDL-C level and hemorrhagic stroke. The point estimates of HR for death from coronary artery disease were different between men and women. The HR for death from coronary artery disease among men with HDL-C level ≥2.20 mmol/L was 1.70 (95% CI, 0.68–5.30), whereas the HR for death from coronary artery disease among women with HDL-C level ≥2.20 mmol/L was 0.90 (95% CI, 0.22–2.52).

The HRs and 95% CIs for cancer deaths according to the HDL-C level was also examined (Supplementary Table 3). Similar to the hazards ratio for all-cause deaths, the association between HDL-C level and HR for cancer mortality showed a U-shaped relationship.

We additionally analyzed the association between HDL-C level and mortality risk by alcohol intake. A subgroup analysis was performed by alcohol intake frequency (0 time per week, 1–4 times per week, ≥5 times per week) (Supplementary Tables 4–6). Among nondrinkers, there was no significant dose-response relationship between HDL-C level and mortality risk from external causes. Interestingly, the HR for cardiovascular disease among men with HDL-C level ≥2.20 mmol/L showed decreasing trends with decreasing frequency of alcohol intake (HR, 1.02 for men who drink ≥5 times/week; HR, 0.73 for men who drink 1–4 times/week; HR, 0.39 for men who do not drink) compared to men with HDL-C level of 1.6–1.79 mmol/L. These results suggest that alcohol intake may be an effect modifier in the association between high HDL-C level and mortality risk for cardiovascular disease.

In the proportion of cause of death among total deaths, the proportion of mortality due to cardiovascular disease (10.3%) among participants with HDL-C level ≥2.20 mmol/L was smaller than those of other deaths due to cancer (37.9%) or external cause of injury, poisoning, and other consequences (18.5%) (Supplementary Table 7). In contrast, the proportion of mortality due to external cause of injury, poisoning, and other consequences (18.5%) among participants with HDL-C level ≥2.20 mmol/L was especially higher than those of other groups except for cancer deaths. After age standardization using WHO standard population, the age-standardized mortality rates from external cause of injury, poisoning, and other consequences for HDL-C level ≥2.20 mmol/L were relatively higher compared to those for HDL-C level of 1.6–1.79 mmol/L (Supplementary Table 8).

4. Discussion

In this study, the HDL-C level showed a U-shaped relationship with all-cause mortality, similar to the results of previous cohort studies. However, the dose-response relationships between HDL-C level and risk of mortality varied, depending on the cause of death in this study. HDL-C levels showed a U-shaped relationship with cancer and other causes of death, whereas there was a clear inverse linear relationship between HDL-C level and the mortality risk for overall cardiovascular disease. However, HDL cholesterol levels showed heterogenetic associations with risk of mortality according to the subtypes of cardiovascular disease and sex.

Previously, one prospective study in old Japanese-American men reported that the HDL-C level had an inverse linear association with cardiovascular mortality, but there was no significant linear association between HDL-C level and cardiovascular mortality [23]. Consistently, a study reported that Korean patients with increased HDL-C level had lower rates of major adverse cardiac events compared to patients with decreased HDL-C level, during the 1-year follow-up period with acute myocardial infarction [24]. In addition, some Japanese studies investigated the relationship between HDL-C level and risk of mortality [25,26]. The prospective cohort study consisted of 7019 Japanese adults and showed that very high HDL-C level (≥2.07 mmol/L) was not

Table 1
Baseline characteristics of the study participants by HDL cholesterol level.

Characteristics	Overall (n = 365,457)	HDL-C (mmol/L)							
		< 1.0 (n = 35,697)	1.0–1.19 (n = 73,145)	1.2–1.39 (n = 88,050)	1.4–1.59 (n = 65,948)	1.6–1.79 (n = 51,133)	1.8–1.99 (n = 27,645)	2.0–2.19 (n = 13,197)	≥2.20 (n = 10,642)
Continuous variables									
Age (years)	55.6 (11.2)	57.7 (11.8)	56.5 (11.4)	55.8 (11.1)	55.2 (11.0)	54.8 (10.9)	54.2 (10.6)	53.9 (10.5)	54.0 (10.5)
BMI (kg/m^2)	23.9 (6.1)	25.0 (16.9)	24.6 (3.1)	24.2 (3.1)	23.7 (3.1)	23.3 (3.1)	22.9 (3.0)	22.6 (3.0)	22.3 (3.0)
Waist circumference (cm) (n = 365,402)	81.0 (9.0)	85.0 (8.3)	83.6 (8.4)	81.7 (8.6)	80.0 (8.7)	78.6 (8.7)	77.2 (8.6)	76.5 (8.6)	76.0 (8.7)
Fasting glucose level (mg/dL)	100.9 (26.4)	105.5 (32.4)	103.3 (28.7)	101.2 (26.1)	99.5 (24.4)	98.4 (23.5)	97.7 (23.0)	97.5 (22.8)	98.4 (25.2)
(mmol/L)	5.60 (1.47)	5.86 (1.80)	5.74 (1.59)	5.62 (1.45)	5.52 (1.36)	5.46 (1.31)	5.42 (1.27)	5.41 (1.27)	5.46 (1.40)
Total cholesterol (mg/dL)	198.6 (40.4)	183.9 (57.3)	192.6 (37.1)	197.7 (36.7)	200.5 (36.6)	203.8 (38.1)	207.7 (35.9)	212.1 (43.2)	218.1 (37.7)
(mmol/L)	5.14 (1.04)	4.76 (1.48)	4.99 (0.96)	5.12 (0.95)	5.19 (0.95)	5.28 (0.99)	5.38 (0.93)	5.49 (1.12)	5.64 (0.98)
HDL cholesterol (mg/dL)	55.3 (22.9)	34.2 (3.8)	42.8 (2.2)	50.5 (2.3)	57.9 (2.0)	65.1 (2.3)	73.0 (2.3)	81.0 (2.3)	111.5 (99.0)
(mmol/L)	1.43 (0.59)	0.88 (0.10)	1.11 (0.06)	1.31 (0.06)	1.50 (0.05)	1.68 (0.06)	1.89 (0.06)	2.09 (0.06)	2.88 (2.56)
LDL cholesterol (mg/dL)	117.7 (55.5)	111.8 (107.7)	118.3 (55.4)	120.5 (39.5)	119.5 (41.3)	117.7 (41.2)	115.6 (40.1)	113.0 (50.0)	110.6 (81.2)
(mmol/L)	3.05 (1.44)	2.90 (2.79)	3.06 (1.43)	3.12 (1.02)	3.10 (1.07)	3.05 (1.07)	2.99 (1.04)	2.92 (1.30)	2.86 (2.10)
Triglyceride (mg/dL)	135.0 (98.8)	200.8 (147.5)	162.7 (99.8)	136.1 (80.5)	117.8 (70.1)	106.4 (62.4)	96.9 (57.9)	93.1 (58.3)	110.5 (214.8)
(mmol/L)	1.53 (1.12)	2.27 (1.67)	1.84 (1.13)	1.54 (0.91)	1.33 (0.79)	1.20 (0.70)	1.10 (0.65)	1.05 (0.66)	1.25 (2.43)
Systolic blood pressure (mmHg)	123.7 (15.4)	125.1 (15.0)	124.9 (15.2)	124.0 (15.4)	123.3 (15.5)	122.7 (15.6)	122.0 (15.8)	122.2 (15.8)	122.4 (16.0)
Diastolic blood pressure (mmHg)	76.8 (10.2)	77.5 (10.0)	77.5 (10.1)	77.0 (10.2)	76.6 (10.2)	76.3 (10.3)	75.9 (10.3)	76.0 (10.4)	76.3 (10.6)
Categorical variables (n, %)									
Sex									
Men	172,347 (47.2)	23,812 (66.7)	42,999 (58.8)	43,447 (49.3)	27,530 (41.8)	18,576 (36.3)	8733 (31.6)	3984 (30.2)	3266 (30.7)
Women	193,110 (52.8)	11,885 (33.3)	30,146 (41.2)	44,603 (50.7)	38,418 (58.3)	32,557 (63.7)	18,912 (68.4)	9213 (69.8)	7376 (69.3)
Smoking history									
Never-smoker	234,131 (64.1)	18,205 (51.0)	41,338 (56.5)	55,385 (62.9)	44,753 (67.9)	36,548 (71.5)	20,437 (73.9)	9751 (73.9)	7714 (72.5)
Past smoker	55,518 (15.2)	6775 (19.0)	13,143 (18.0)	14,085 (16.0)	9354 (14.2)	6457 (12.6)	3067 (11.1)	1448 (11.0)	1189 (11.2)
Current smoker	75,808 (20.7)	10,717 (30.0)	18,664 (25.5)	18,580 (21.1)	11,841 (18.0)	8128 (15.9)	4141 (15.0)	1998 (15.1)	1739 (16.3)
Alcohol drinking									
No	213,819 (58.5)	22,289 (62.4)	43,607 (59.6)	51,863 (58.9)	38,535 (58.4)	29,524 (57.7)	15,516 (56.1)	7115 (53.9)	5370 (50.5)
1–4 times/week	134,069 (36.7)	12,018 (33.7)	26,646 (36.4)	32,348 (36.7)	24,212 (36.7)	18,864 (36.9)	10,451 (37.8)	5188 (39.3)	4342 (40.8)
≥5 times/week	17,569 (4.8)	1390 (3.9)	2892 (4.0)	3839 (4.4)	3201 (4.9)	2745 (5.4)	1678 (6.1)	894 (6.8)	930 (8.7)
Physical activity[a]									
Yes	41,929 (11.5)	3631 (10.2)	7853 (10.7)	9829 (11.2)	7570 (11.5)	6230 (12.2)	3589 (13.0)	1749 (13.3)	1478 (13.9)
No	323,528 (88.5)	32,066 (89.8)	65,292 (89.3)	78,221 (88.8)	58,378 (88.5)	44,903 (87.8)	24,056 (87.0)	11,448 (86.8)	9164 (86.1)
Hypertension									
Yes	113,176 (31.0)	13,431 (37.6)	25,467 (34.8)	28,043 (31.9)	19,196 (29.1)	14,002 (27.4)	6992 (25.3)	3320 (25.2)	2725 (25.6)
No	252,281 (69.0)	22,266 (62.4)	47,678 (65.2)	60,007 (68.2)	46,752 (70.9)	37,131 (72.6)	20,653 (74.7)	9877 (74.8)	7917 (74.4)
Diabetes mellitus									
Yes	43,767 (12.0)	7101 (19.9)	11,360 (15.5)	10,697 (12.2)	6425 (9.7)	4401 (8.6)	2063 (7.5)	907 (6.9)	813 (7.6)
No	321,690 (88.0)	28,596 (80.1)	61,785 (84.5)	77,353 (87.9)	59,523 (90.3)	46,732 (91.4)	25,582 (92.5)	12,290 (93.1)	9829 (92.4)
All-cause death	9350 (2.6)	1568 (4.4)	2100 (2.9)	2190 (2.5)	1430 (2.2)	1069 (2.1)	492 (1.8)	258 (2.0)	243 (2.3)
Cardiovascular death	1585 (0.43)	275 (0.77)	372 (0.51)	392 (0.45)	231 (0.35)	176 (0.34)	76 (0.27)	38 (0.29)	25 (0.23)
Cancer death	3750 (1.03)	615 (1.72)	836 (1.14)	918 (1.04)	563 (0.85)	417 (0.82)	206 (0.75)	103 (0.78)	92 (0.86)

Continuous variables were expressed as means (standard deviation) and categorical variables were expressed as number (percentages).
[a] Physical activity was defined as moderate to vigorous intensity physical activity at least 30 min per day of moderate to vigorous intensity aerobic activity at least 5 days per week.

Table 2
Hazard ratio (95% confidence intervals) for all-cause mortality among Korean men and women aged ≥40 years old according to the HDL-cholesterol level.

	HDL-C (mmol/L)							
	< 1.0	1.0–1.19	1.2–1.39	1.4–1.59	1.6–1.79	1.8–1.99	2.0–2.19	≥2.20
Men								
Age-adjusted model[a]	1.38 (1.25–1.53)	1.07 (0.97–1.18)	1.04 (0.95–1.15)	1.06 (0.96–1.17)	1.00 (Reference)	1.03 (0.90–1.19)	1.18 (0.99–1.41)	1.27 (1.06–1.53)
Age and life style covariates adjusted model[b]	1.33 (1.21–1.46)	1.03 (0.94–1.12)	1.01 (0.92–1.11)	1.06 (0.96–1.17)	1.00 (Reference)	1.08 (0.94–1.23)	1.26 (1.06–1.48)	1.34 (1.13–1.59)
Multi-variables adjusted model[c]	1.59 (1.45–1.76)	1.19 (1.08–1.30)	1.11 (1.01–1.22)	1.10 (1.00–1.22)	1.00 (Reference)	1.00 (0.88–1.14)	1.14 (0.96–1.35)	1.17 (0.99–1.39)
Women								
Age-adjusted model[a]	1.50 (1.31–1.71)	1.09 (0.96–1.22)	1.07 (0.95–1.20)	0.90 (0.79–1.02)	1.00 (Reference)	0.94 (0.80–1.11)	1.07 (0.87–1.32)	1.14 (0.91–1.42)
Age and life style covariates adjusted model[b]	1.52 (1.34–1.72)	1.06 (0.95–1.19)	1.06 (0.95–1.18)	0.89 (0.79–1.01)	1.00 (Reference)	0.91 (0.78–1.07)	1.03 (0.84–1.27)	1.16 (0.94–1.43)
Multi-variables adjusted model[c]	1.52 (1.34–1.73)	1.08 (0.96–1.21)	1.07 (0.95–1.19)	0.90 (0.80–1.02)	1.00 (Reference)	0.91 (0.77–1.06)	1.03 (0.84–1.26)	1.12 (0.91–1.38)

Cox-proportional hazard models were used to examine the association of HDL-cholesterol with risk of all-cause mortality.
[a] Model 1 was adjusted for age.
[b] Model 2 was adjusted for age, frequency of alcohol intake, smoking history and physical activity.
[c] Model 3 was adjusted for age, systolic blood pressure, BMI, fasting blood glucose, triglyceride, LDL cholesterol frequency of alcohol intake, smoking history and physical activity.

significantly associated with elevated coronary heart disease and other cause-specific mortality in a 20-year follow-up period [25]. In the Japan Public Health Center-based prospective study, there was inverse relationship between HDL-C level and incidental risk of coronary heart disease and cerebral infarction among 30,736 Japanese adults in a 15-year follow-up period [26]. Collectively, our finding indicates that there is a principal difference with those of previous studies, in which the participants were mainly Caucasian [4,5].

The genetic differences in HDL-C level by races or ethnic groups could be considered regarding the association between HDL-C level and cardiovascular disease mortality. A study by Helgadottir et al. showed that the HDL-raising mutation of SCARB1 variants was not associated with risk of coronary artery disease [27], whereas the study by Zanoni et al. reported that SCARB1 variants were significantly associated with elevated risk of coronary artery disease [7]. These controversial findings might be explained by the different ethnic structures [27]. C allele variants of the SCARB1 rs5888 were more common in the South Korean population than in the Caucasian population [13,15–17]. The variants of the C allele in SCARB1 rs5888 were associated with reduced risk of coronary artery disease and ischemic stroke [28,29]. Indeed, the strength of association of high HDL-C level ≥60 mg/dL and reduced risk of coronary heart disease was different between Framingham Heart Study and Korean Heart Study. In previous studies, people with HDL-C level ≥60 mg/dL had no significant or marginally weak association with reduced risk of coronary heart disease for men and women [30,31]. However, there was prominent and coherent association between HDL-C level ≥60 mg/dL and reduced risk of coronary heart disease for Korean men and women compared to those with HDL-C level < 35 mg/dL [32].

The second possible explanation is that eating habits, prevalence of obesity, and lifestyle in East Asia are very different from those of Western countries. Especially, obesity, insulin resistance, and metabolic disorder are closely related with dysfunctional HDL-C [33]. The prevalence of obesity in South Korea was 5.3% in 2015, which was 7.2 times lower than 38.2% in the United States. The percentage of people who consumed fruits (66.4%) and vegetable (99.1%) daily in South Korea was also higher than those in the United States [34]. For these reasons, the ratio of dysfunctional HDL-C in Korean individuals is estimated to be lower than that in the people in the United States. In fact, the mortality rate from ischemic heart disease in South Korea (38 per 100,000 population) is the lowest among Organization for Economic Co-operation and Development (OECD) countries except for Japan [34].

It was notable that the high all-cause mortality among people with HDL-C level ≥2.20 mmol/L was mainly due to deaths from external cause of injury, poisoning, and other consequences. Previous cohort studies also showed that people with very high HDL-C level had higher non-cancer/non-cardiovascular disease, but they did not perform the subgroup analysis by causes of death. However, there is a lack of evidence or controversies whether high HDL-C levels were associated with risk of suicide or external injury [35,36]. In contrast, high mortality rate from external cause of injury, poisoning, and other consequences among people with high HDL-C level may be confounded by frequent alcohol intake [37,38]. However, there was no elevated risk of mortality in men with high HDL-C level in our study. Instead, alcohol intake seems to be an effect modifier in the association between high HDL-C level and mortality risk of cardiovascular disease. The mortality risk from cardiovascular disease in men with HDL-C level ≥2.20 mmol/L showed decreasing trends with decreasing frequency of alcohol intake.

The previous randomized clinical trials showed that the HDL-C level could not be a good target biomarker for cardiovascular disease [2,39]. However, HDL-C level is still useful in the clinical field, because HDL-C is simple and easy to measure than HDL function or particles. In addition, there was no gold standard for HDL function to predict the cardiovascular mortality [40,41], whereas HDL-C has good predictability for cardiovascular disease mortality [42].

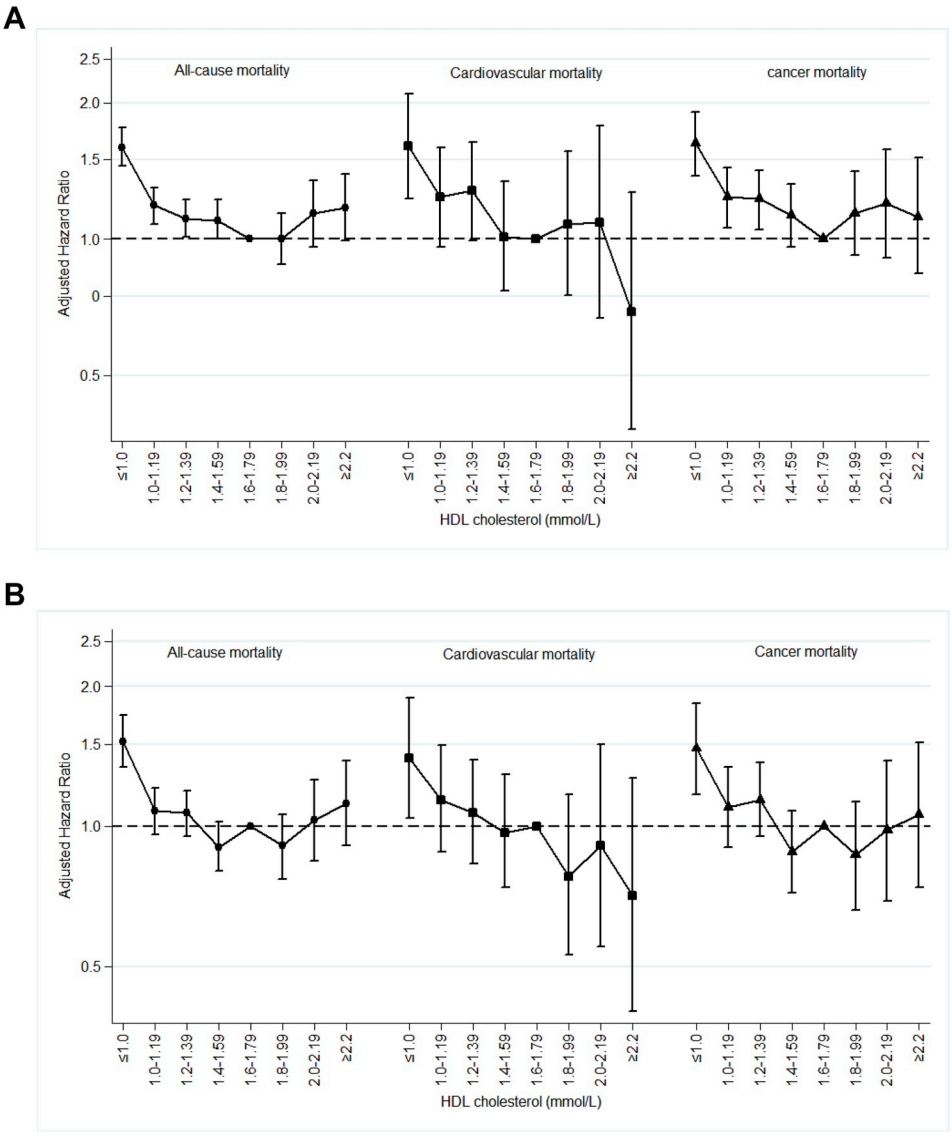

Fig. 1. Hazard ratios for mortality.
(A) Among Korean men according to the HDL cholesterol level. The Cox proportional hazard models were used after adjusting for age, smoking status, alcohol intake, physical activity, BMI, systolic blood pressure, fasting blood glucose, triglycerides level, LDL cholesterol by sex. Death from cancer was defined as ICD-10 code "C00-C97" and death from cardiovascular disease was defined as ICD-10 code "I00-I99".[5] Death due to other causes was classified as other deaths. (B) Among Korean women according to the HDL cholesterol level. The Cox proportional hazard models were used after adjusting for age, smoking status, alcohol intake, physical activity, BMI, systolic blood pressure, fasting blood glucose, triglycerides level, LDL cholesterol by sex. Death from cancer was defined as ICD-10 code "C00-C97" and death from cardiovascular disease was defined as ICD-10 code "I00-I99".[5] Death due to other causes was classified as other deaths.

Our study has several limitations, which should be considered in interpreting the results. First, the median follow-up period was 3.5 years, which is not long enough. Therefore, the number of deaths was relatively small, and the statistical power might be weak. Due to the small number of deaths, death from cardiovascular disease could not be divided into subcategories. Second, the study was not conducted through randomized controlled trials; therefore, it was not possible to infer the causal relationship between HDL-C level and risk of mortality. Although patients with previous history of cardiovascular disease and those with cardiovascular disease within 6 months after the study enrollment were excluded, but there would be residual confounding factor in the association between HDL-C level and risk of cardiovascular disease. In addition, selection bias may occur due to different participation rate of health screening program by age or occupation. Third, serum HDL-C level was collected from various medical centers or hospitals across the country, and therefore, it was not standardized. However, serum HDL-C level was included as one of the items in the national health screening program. Korean Centers for Disease Control and Prevention operates the committee for the criteria and quality control of the Korea National Health Screening Program (KNHSP) and conducts standard management for the KNHSP. Fourth, some risk factors such as socioeconomic status or use of lipid-lowering drugs were not considered in this study. People with high HDL-C level ≥2.2 mmol/L were unlikely to have low socioeconomic status, given the low prevalence of current smoker and low BMI. Fifth, there might be a risk where the classification of the causes of deaths may be inaccurate. However, we used the cause of death data since 2009, and therefore, we anticipate that the effect of the misclassification of the cause of death will be minor and insignificant in this study. Sixth, we did not consider the use of medication such as lipid-lowering drug. Use of prescription medications such as statins may be associated with lower cardiovascular mortality. Lastly, the number of deaths from specific causes among people with very high HDL-C level was small. This small sample size could reduce the power and increase the uncertainty of estimation.

Despite these limitations, our study finding shows that the low HDL-C level could still significantly predict the increased risk of cardiovascular mortality and all-cause mortality in the South Korean population. Unlike their white-skinned counterparts in the previous studies, there was no notable increase in the cardiovascular mortality among Korean individuals with very high HDL-C level. On the contrary, the all-cause mortality was significantly higher among Korean men with high HDL-C level ≥2.2 mmol/L than those with HDL-C level of 1.6–1.79 mmol/L. However, these increases in all-cause mortality were due to other causes of death, mainly due to increase in the mortality risk from external causes of injury or poisoning, not due to internal causes. Further studies will be required to understand which function of HDL-C or

Table 3
Hazard ratio (95% confidence intervals) for cardiovascular mortality among Korean men and women aged ≥40 years according to the HDL-cholesterol level.

	HDL-C (mmol/L)							
	< 1.0	1.0–1.19	1.2–1.39	1.4–1.59	1.6–1.79	1.8–1.99	2.0–2.19	≥2.20
Men								
Age-adjusted model[a]	1.58 (1.23–2.05)	1.21 (0.94–1.55)	1.25 (0.98–1.60)	1.01 (0.76–1.33)	1.00 (Reference)	1.12 (0.77–1.61)	1.23 (0.69–1.83)	0.75 (0.41–1.37)
Age and life style covariates adjusted model[b]	1.47 (1.14–1.91)	1.15 (0.90–1.48)	1.23 (0.96–1.57)	1.00 (0.76–1.32)	1.00 (Reference)	1.14 (0.79–1.65)	1.16 (0.71–1.88)	0.76 (0.42–1.40)
Multi-variables adjusted model[c]	1.61 (1.23–2.09)	1.24 (0.96–1.59)	1.28 (0.99–1.64)	1.01 (0.77–1.34)	1.00 (Reference)	1.08 (0.75–1.56)	1.09 (0.67–1.78)	0.69 (0.38–1.27)
Women								
Age-adjusted model[a]	1.46 (1.09–1.95)	1.15 (0.88–1.49)	1.06 (0.82–1.38)	0.96 (0.73–1.27)	1.00 (Reference)	0.79 (0.53–1.18)	0.93 (0.56–1.55)	0.78 (0.44–1.40)
Age and life style covariates adjusted model[b]	1.44 (1.07–1.92)	1.14 (0.88–1.48)	1.06 (0.82–1.37)	0.96 (0.72–1.26)	1.00 (Reference)	0.78 (0.53–1.17)	0.92 (0.56–1.53)	0.77 (0.43–1.37)
Multi-variables adjusted model[c]	1.40 (1.04–1.89)	1.14 (0.88–1.49)	1.07 (0.83–1.39)	0.97 (0.74–1.29)	1.00 (Reference)	0.78 (0.53–1.17)	0.91 (0.55–1.50	0.71 (0.40–1.27)

Cox-proportional hazard models were used to examine the association of HDL-cholesterol with risk of all-cause mortality.
[a] Model 1 was adjusted for age.
[b] Model 2 was adjusted for age, frequency of alcohol intake, smoking history and physical activity.
[c] Model 3 was adjusted for age, systolic blood pressure, BMI, fasting blood glucose, triglyceride, LDL cholesterol frequency of alcohol intake, smoking history and physical activity.

Table 4
Hazard ratio (95% confidence intervals) for death from coronary artery disease and death from stroke among Korean men and women aged ≥40 years old according to the HDL-cholesterol level.

	HDL-C (mmol/L)							
	< 1.0	1.0–1.19	1.2–1.39	1.4–1.59	1.6–1.79	1.8–1.99	2.0–2.19	≥2.20
Men								
Coronary artery disease[a]	2.35 (1.36–4.05)	1.85 (1.10–3.12)	1.52 (0.89–2.58)	1.38 (0.78–2.44)	1.00 (Reference)	2.20 (1.14–4.23)	1.34 (0.50–3.62)	1.70 (0.68–5.30)
Overall stroke[b]	1.46 (0.97–2.21)	1.32 (0.90–1.94)	1.37 (0.94–2.01)	0.89 (0.58–1.38)	1.00 (Reference)	0.88 (0.48–1.61)	1.53 (0.79–2.93)	0.80 (0.34–1.90)
Ischemic stroke[c]	2.41 (1.07–5.43)	2.10 (0.96–4.58)	2.14 (0.99–4.65)	1.05 (0.42–2.60)	1.00 (Reference)	1.90 (0.69–5.25)	0.58 (0.07–4.65)	0.59 (0.07–4.76)
Hemorrhagic stroke[d]	0.99 (0.50–1.93)	0.77 (0.41–1.42)	1.15 (0.65–2.02)	0.77 (0.40–1.48)	1.00 (Reference)	0.23 (0.05–0.98)	2.14 (0.96–4.78)	0.74 (0.22–2.52)
Women								
Coronary artery disease[a]	1.34 (0.77–2.34)	0.97 (0.58–1.60)	0.88 (0.54–1.44)	0.71 (0.41–1.24)	1.00 (Reference)	0.56 (0.24–1.29)	0.50 (0.15–1.67)	0.90 (0.34–2.35)
Overall stroke[b]	1.43 (0.87–2.35)	1.48 (0.97–2.26)	1.39 (0.93–2.10)	1.10 (0.70–1.72)	1.00 (Reference)	0.87 (0.47–1.63)	1.57 (0.81–3.05)	0.70 (0.27–1.80)
Ischemic stroke[c]	1.40 (0.57–3.44)	1.67 (0.77–3.61)	1.67 (0.78–3.56)	1.54 (0.69–3.43)	1.00 (Reference)	0.73 (0.20–2.71)	1.59 (0.43–5.87)	–
Hemorrhagic stroke[d]	0.97 (0.43–2.17)	1.01 (0.53–1.92)	1.19 (0.66–2.15)	0.76 (0.38–1.50)	1.00 (Reference)	1.14 (0.52–2.48)	1.16 (0.43–3.14)	0.79 (0.23–2.70)

The Cox-proportional hazard models were performed after adjusting for age, systolic blood pressure, body mass index, fasting blood glucose, triglyceride, LDL cholesterol frequency of alcohol intake, smoking history and physical activity.
[a] Coronary artery disease was defined as “I20-I25”.
[b] Overall stroke was defined as “I60-I69”.
[c] Ischemic stroke was defined as “I63”.
[d] Hemorrhagic stroke was defined as “I60-I62” according to the ICD-10 code.

which genetic factor causes the differences in association between HDL-C level and risk of cardiovascular mortality, with respect to races or ethnic groups.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

Chang-Mo Oh, MD, PhD, made substantial contributions to the conception of the work, acquisition and interpretation of the data, and data analysis and wrote the manuscript. In-Hwan Oh, MD, PhD, wrote the manuscript and contributed to the study design and interpretation of data. Junho K Hur, PhD; Jae-Hong Ryoo, MD, PhD; Ju Young Jung, MD, PhD; Sung Keun Park, MD, PhD; Hong Jun Yang, MS; Joong-Myung Choi, MD, PhD; Kyu-Won Jung, MS; and Young-Joo Won, PhD, made substantial contributions to the acquisition of the data and critical revision of the study protocol and manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.01.035.

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