

# Association between lipoprotein cholesterol and future cardiovascular disease and mortality in older adults: a Korean nationwide longitudinal study

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## Research

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# **Abstract**

## **Background**

Dyslipidemia is considered as an independent health risk factor of cardiovascular disease (CVD), a leading cause of mortality in older adults. Despite its importance, however, there have been few reports on the association between lipoprotein cholesterol and future CVD and cardiovascular (CV) mortality among elderly Asians. This study investigated the association between lipoprotein cholesterol and future CVD and CV mortality in an elderly Korean population using a large nationwide sample.

## **Methods**

From the cohort database of the Korean National Health Insurance Service, a total of 62,604 adults aged 65 years or more (32,584 men and 30,020 women) were included. High-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) values were categorized by quartiles. Cox proportional hazard models and linear regression analyses were used to assess the association between the quartiles of lipoprotein cholesterol and CV events or CV mortality.

## **Results**

The mean follow-up period was 3.3 years. The incidence rates of ischemic heart disease and ischemic brain disease were 0.97 and 0.61 per 1,000 person-years, and the mortality rates from these diseases were 0.22 and 0.34 per 1,000 person-years. In a completely adjusted model, high HDL-C and LDL-C levels were not associated with the total CV events and deaths from CVD. However, high LDL-C levels were significantly associated with a lower incidence of ischemic brain disease. Furthermore, diabetic patients with high LDL-C were more likely to have higher CV mortality, whereas non-smokers with high LDL-C were less likely to be at risk of CV events.

## **Conclusions**

Neither high LDL-C nor HDL-C was significantly associated with future CV mortality in older adults aged  $\geq 65$  years. High LDL-C seems not a risk factor for CVD in the elderly, and further studies are needed.

## **Background**

Cardiovascular disease (CVD) is the most common cause of death globally [1]. According to the recently published data from the Organisation for Economic Co-operation and Development (OECD) Health Statistics 2020, the overall cardiovascular (CV) mortality rate for OECD member countries was 274.2 per 100,000 people, significantly higher than that from cancer [2]. Dyslipidemia is considered as an independent risk factor for CVD. Low-density lipoprotein cholesterol (LDL-C) has been reported as the most atherogenic lipoprotein and interventional studies showed that LDL-C lowering by statin therapy reduces CV events [3]. All cardiovascular guidelines highlight the evidence that LDL-C is a major cause of CVD and a primary target of lipid-lowering therapy [4]. However, increased high-density lipoprotein

cholesterol (HDL-C) is not always associated with a positive effect and the influence of lowering HDL-C remains a matter of debate [3].

As the elderly population has increased worldwide [5], CVD and its risk factors are important health problems for the elderly. Although CVD is a leading cause of mortality in older adults [6], there have been only a few studies assessing the associations between lipoprotein cholesterol and future CVD incidence or CV mortality in older populations. In some studies on older adults, low HDL-C and high LDL-C levels were associated with an increase in CV events or CV mortality [7, 8]. In other studies, low HDL-C level was significantly associated with the risk of stroke or CV mortality in the elderly, regardless of the LDL-C value [9, 10]. However, recent studies have shown a lack of or an inverse association between LDL-C and mortality among older adults [11-14].

These studies were limited to specific populations or a small number of participants, and even within the elderly population, the age range of the participants varied. There are relatively few studies assessing the association between lipoprotein cholesterol and future CVD and CV mortality in older Asian adults. In a Taiwanese study, elderly women with low total cholesterol, low LDL-C, or low HDL-C level had higher CV mortality [15]; however, these results were inconsistent with those of a recent American study that showed that LDL-C was not associated with CVD risk among adults aged  $\geq 75$  years [16]. Therefore, more Asian studies are needed to confirm the association between lipoprotein cholesterol and future CVD and CV mortality in the elderly population. This study aimed to evaluate these associations in individuals aged  $\geq 65$  years without past medical history of both dyslipidemia and CVD using a nationwide representative sample of the Korean elderly.

## Methods

The Korean National Health Service provides universal health insurance to almost all Koreans except approximately 2.8% of medical aid beneficiaries. The Korean National Health Insurance Service (KNHIS) provides the National Screening Program (NSP) biennially. The KNHIS established the National Health Information Database (NHID), including data from the results of NSP and variables related to sociodemographic characteristics and Korean mortality [17].

### Data sources and study population

In the National Health Insurance Service–National Health Screening Cohort database of the KNHIS, 515,867 participants were included. This population was randomly selected from health screening participants aged 40–79 years between 2002 and 2003. After excluding participants without HDL-C and LDL-C data, those younger than 65 years, those who had a medical history of dyslipidemia (including those who had taken medication), and those with a past medical history of CVD, 62,604 participants were included in the analysis of this study (Figure 1).

This study protocol was approved by the Institutional Review Board (IRB) of Asan Medical Center (IRB No. 2020-0649), and the need for informed consent was waived.

## **Variables**

### *Independent variable*

#### Lipoprotein cholesterol

Lipids were assayed from an 8-hour fasting serum sample of participants in each community hospital. HDL-C was obtained as a measured value. LDL-C was calculated in specimens with triglycerides < 400 mg/dL using the Friedewald formula [18], and it was obtained as a measured value in those with triglycerides  $\geq$  400 mg/dL as in a previous Korean study on LDL-C [19]. HDL-C and LDL-C values were categorized by quartiles.

### *Outcome variables*

#### Cardiovascular (CV) events and deaths from cardiovascular disease (CVD).

The International Classification of Diseases 10th Revision codes were reviewed for the classification of diagnosis and causes of death [20]. CVD was defined as ischemic heart disease (I20-25) and ischemic brain disease (I63). CV events or deaths from CVD were defined as diagnoses of or deaths caused by ischemic heart diseases or ischemic brain diseases, including angina pectoris, acute or subsequent myocardial infarction, certain current complications following acute myocardial infarction, other acute or chronic ischemic heart diseases, and cerebral infarction.

Data regarding the diagnosis and date of CVD event and cause and date of death were collected from the KNHIS cohort database during the 2007–2015 period. As all participants were enrollees of the National Health Insurance or medical aid beneficiaries in Korea, dropout was almost impossible for reasons other than death.

The follow-up time for CV event was calculated as the time from the date of health examination in the NSP to the date of first diagnosis of CVD or to the date of December 31, 2015 for participants who did not have events. The observation time for CV mortality was defined as the time from the date of medical examination in the NSP to the date of death from CVD or to the end of 2015 for participants not reported date of death.

## **Potential confounders**

Age, sex, cigarette smoking status, and body mass index (BMI) were evaluated. Concerning cigarette smoking status, participants were classified as non-smokers, ex-smokers, or current smokers. Non-smokers were defined as adults who had not smoked at least 100 cigarettes in their lifetime, ex-smokers were defined as adults who had smoked at least 100 cigarettes but were not currently smoking, and current smokers were defined as adults who had smoked at least 100 cigarettes and were currently smoking. BMI was defined as the body weight divided by the square of the height ( $\text{kg}/\text{m}^2$ ). According to the definition of obesity for Asians [21], BMI was categorized into normal ( $\text{BMI} < 23 \text{ kg}/\text{m}^2$ ), overweight

(BMI 23–25 kg/m<sup>2</sup>), and obese (BMI ≥ 25 kg/m<sup>2</sup>). Data of hypertension and diabetes were collected using the questionnaire. If participants reported that they took medication for hypertension or diabetes, they were considered to have the diseases. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg; diabetes was defined as a serum concentration of fasting glucose ≥ 126 mg/dL. Each chronic disease was defined as described [22].

## Statistical analyses

In baseline characteristics, continuous variables were presented as mean ± standard deviation and categorical variables were presented in terms of frequencies and percentages.

Proportions of CV event and CV death were calculated according to quartiles of lipoprotein cholesterol. Cox proportional hazard models and linear regression analyses were used to investigate the association between the quartiles of lipoprotein cholesterol and CV events or CV mortality. Four models were constructed for analyses, a crude model and three adjusted models. Model 1 was adjusted for age and sex, and in Model 2, cigarette smoking status was added to Model 1. In Model 3, hypertension, diabetes, and BMI were added to Model 2. In Cox proportional hazard model, participants who did not have CV events but died before December 31, 2015 were right-censored. Hazard ratios (HRs) and 95% confidence intervals (CIs) were obtained by Cox proportional hazard models and beta coefficient ( $\beta$ ) and P-values were calculated by linear regression analyses. To exclude reverse causality, an additional analysis was performed in Model 3 excluding the elderly who died within 1 year from the time of study.

Participants with risk of future CVD event or CV death were assessed by stratified analyses in Model 3, stratified by sex, cigarette smoking, hypertension, diabetes, and obesity. The purpose of this stratified analysis was to explore any effect modifier (interaction).

Statistical analyses were performed using STATA software (version 16.1; StataCorp, College Station, Texas). A P-value of < 0.05 was considered significant.

# Results

## Baseline characteristics of participants

Of the 62,604 participants included, 32,584 were men and 30,020 were women. There were 323 CV events and 114 CV deaths during the follow-up period, with a mean follow-up period of 3.3 ± 2.1 years (maximum: 9.0 years). The mean values of LDL-C of the 1st, 2nd, 3rd, and 4th quartiles were 73.2 ± 15.1 mg/dL, 103.5 ± 6.5 mg/dL, 125.6 ± 6.9 mg/dL, and 161.6 ± 25.0 mg/dL and those of HDL-C of the 1st, 2nd, 3rd, and 4th quartiles were 38.7 ± 4.5 mg/dL, 48.5 ± 2.3 mg/dL, 56.7 ± 2.6 mg/dL, and 73.8 ± 30.2 mg/dL, respectively. The mean BMI of the participants was 24.1 ± 3.0 kg/m<sup>2</sup>, with 22,633 (36.2%) being classified as obese (BMI ≥ 25.0 kg/m<sup>2</sup>). Of the total number of participants, 11.9% were current smokers, and 59.2% and 17.9% had been diagnosed with hypertension and diabetes, respectively. Each basic characteristic of participants had a significant sex-difference (Table 1).

## CV events and CV mortality

During the observation period of 204,025.6 person-years, the incidence rates of ischemic heart disease and ischemic brain disease were 0.97 and 0.61 per 1,000 person-years, respectively. The mortalities from these diseases were 0.22 and 0.34 per 1,000 person-years, during the observation period of 204,058.7 person-years (Table 2).

## Association between quartiles of low-density lipoprotein cholesterol and CVD

Proportions of CV event and CV death according to the quartiles of LDL-C are presented in Figure 2. The proportion of CV event was the highest in participants with LDL-C from the 1st quartile, and it decreased as the quartile of LDL-C increased. However, CV death rate showed no specific pattern in accordance with the quartile of LDL-C.

In the crude model (Table 2), the incidence of ischemic brain disease was 20% lower in participants with LDL-C from the 4th quartile (HR: 0.80, 95% CI: 0.68–0.94) compared to those with LDL-C from the 1st quartile, while its mortality was not significantly related to the LDL-C levels (HR: 0.90, 95% CI: 0.73–1.12). However, neither ischemic heart disease event nor its mortality was significantly associated with high levels of LDL-C. The total CV events were 17% lower in participants with LDL-C from the 4th quartile (HR: 0.83, 95% CI: 0.75–0.92) than in those with LDL-C from the 1st quartile, while there was no significant association between the total CV mortality and high levels of LDL-C (HR: 0.89, 95% CI: 0.76–1.06). The incidences of ischemic heart disease ( $\beta = -4.17 \times 10^{-4}$ ,  $p = 0.041$ ), ischemic brain disease ( $\beta = -4.02 \times 10^{-4}$ ,  $p = 0.013$ ), and total CV event ( $\beta = -8.19 \times 10^{-4}$ ,  $p = 0.002$ ) had negative correlations with LDL-C levels in the crude model by linear regression analysis.

In Model 1 and Model 2, the incidence of ischemic brain disease was 17% lower in participants with LDL-C from the 4th quartile (HR: 0.83, 95% CI: 0.70–0.98 in both models) compared to those with LDL-C from the 1st quartile, while its mortality was not significantly associated with LDL-C levels (HR: 0.93, 95% CI: 0.75–1.16 in both models). However, neither ischemic heart disease event nor its mortality was significantly related to high levels of LDL-C. In Model 1, the total CV events were 13% lower in participants with LDL-C from the 4th quartile (HR: 0.87, 95% CI: 0.79–0.97) than in those with LDL-C from the 1st quartile, while the relationship between them was not significant in Model 2 (HR: 0.90, 95% CI: 0.81–1.01). Total CV mortality was not associated with high levels of LDL-C (HR: 0.95, 95% CI: 0.80–1.13 in both models). The incidences of ischemic brain disease and total CV event had negative correlations with LDL-C levels in Model 1 and Model 2 by linear regression analyses.

In Model 3, the incidence of ischemic brain disease was 16% lower in participants with LDL-C from the 4th quartile (HR: 0.84, 95% CI: 0.70–1.00) than in those with LDL-C from the 1st quartile, while its mortality was not significantly associated with LDL-C levels (HR: 0.95, 95% CI: 0.74–1.22). There was no significant association between the incidence of an ischemic heart disease event or its mortality and high levels of LDL-C and total CV event or its mortality and high levels of LDL-C. The total number of participants who died was 202 and CV deaths were 22 within 1 year from the study. The results from the

analysis of Model 3, excluding the elderly who died within 1 year from the time of study, were not different; both total CV event and CV death were not significantly associated with LDL-C levels.

### **Association between quartiles of high-density lipoprotein cholesterol and CVD**

Proportions of CV event and CV death according to quartiles of HDL-C are presented in Figure 2. The proportion of CV event was the lowest in participants with HDL-C from the 4th quartile, while U-shaped association was observed between the proportions of CV death and HDL-C levels.

In the crude model (Table 3), ischemic heart disease events were 12% lower in participants with HDL-C from the 4th quartile (HR: 0.88, 95% CI: 0.77–1.00) compared to those with HDL-C from the 1st quartile, while its mortality was not significantly lowered (HR: 0.79, 95% CI: 0.61–1.04). However, neither an ischemic brain disease event (HR: 0.95, 95% CI: 0.82–1.12) nor its mortality (HR: 1.04, 95% CI: 0.84–1.28) was significantly associated with high levels of HDL-C. Total CV events were 9% lower in participants with HDL-C from the 4th quartile (HR: 0.91, 95% CI: 0.82–1.00) than in those with HDL-C from the 1st quartile, while there was no significant association between total CV mortality and high levels of HDL-C (HR: 0.93, 95% CI: 0.79–1.10). The incidence of total CV event had negative correlation with HDL-C level ( $\beta = -4.57 \times 10^{-4}$ ,  $p = 0.041$ ) in the crude model by linear regression analysis.

In Models 1, 2, and 3, the incidence of CV events and CV mortality were not significantly associated with high levels of HDL-C. The result from the analysis of Model 3, excluding the elderly who died within 1 year from the time of study, was not different; both total CV event and CV death were not significantly associated with HDL-C levels.

### **Stratified analysis**

In a stratified analysis of the association between LDL-C and CV events, the risk of CV events in non-smokers with LDL-C from the 4th quartile was significantly reduced (adjusted hazard ratio, aHR: 0.84, 95% CI: 0.73–0.96) (Figure 3 a). In a stratified analysis of the association between LDL-C and CV death, CV mortality in diabetic patients with LDL-C from the 4th quartile increased significantly (aHR: 1.47, 95% CI: 1.05–2.05) (Figure 3 b). Stratified analysis could not find any strata with a significant association between HDL-C and CV event or CV death (Figure 3 c, d).

## **Discussion**

This study examined the association between lipoprotein cholesterol and future CVD and death from CVD using a nationwide large sample of an Asian country. In a completely adjusted model, HDL-C level was not associated with the incidences of CVD or CV mortality. However, high LDL-C level was significantly associated with a lower incidence of ischemic brain disease, although it was not associated with ischemic heart disease events or CV death. In stratified analyses, diabetic patients with high LDL-C level had a higher CV mortality, and non-smokers with high LDL-C level were significantly associated with a lower risk of CV events, showing interactions of LDL-C level, diabetes and smoking.

There was no significant association between LDL-C level and CV mortality, which was robust in stratified analysis, consistent with the results of other studies in older adults [10, 11, 23, 24]. This finding is in contrast with those from studies of younger adults, in which high LDL-C and low HDL-C levels were associated with increased risk of CV mortality [25]. It may be due to biological differences according to the age gap and age-related confounding factors that could explain these inconsistent outcomes between two populations [26]. One of the possible reasons why studies of younger people have shown an association between LDL-C level and CVD is that younger people are more stressed than retired older people, and stress may increase cholesterol level by up to 40% [27]. Moreover, other mechanisms that increase cholesterol level may cause CVD [28]. Cholesterol levels tend to decrease with age [29], suggesting that the role of cholesterol in determining the risk of CVD may become less relevant in a more aged population [23]. In addition, HDL-C was not associated with the incidence of CVD and CV mortality in this study, which is consistent with previous findings [11, 30]. These results differ from those of other studies showing that increased HDL-C level was associated with a reduced risk of CVD in the elderly [31], presumably because the effect of other variables affecting CVD was greater than that of HDL-C in this study. The association between HDL-C level and CV events was attenuated after the adjustment for CV risk factors, which suggests that their observed association could be the result of residual confounding as in a prior study [11].

Consistent with most of the previous results in the elderly, the finding that high levels of LDL-C and HDL-C were not significantly associated with total CV events and CV mortality can be reinforced by this nationwide longitudinal study in a large number of Korean elderly population aged  $\geq 65$  years. Furthermore, this finding is consistent with that of a previous study suggesting that lowering LDL-C via statin therapy was not effective in the primary prevention of CV events or CV death in older adults aged 70 years or more [32].

High LDL-C level was significantly associated with a lower incidence of ischemic brain disease in older adults, which contrasts with the hypothesis that cholesterol, particularly LDL-C, is inherently atherogenic. A systematic review demonstrated that elevated LDL-C level was inversely associated with all-cause mortality, and CV mortality was significantly higher in the lowest LDL-C quartile in older adults [12]. One of the possible reasons for these findings is that elevated cholesterol level could be protective in weak older survivors. As cholesterol has various physiological functions including nerve conduction, intracellular transport, as a part of all cell membranes, and as a precursor for the synthesis of substances vital for the organism [33], elevated LDL-C level may have played a role in protecting frail individuals and in those with other catabolic states. Another possible explanation is that healthy elderly survivors may have been less susceptible to the negative effects of high LDL-C [34], and, rather, higher LDL-C level is likely to be significantly associated with healthy survival as in a recent study [11]. One study suggested that low total cholesterol level may be a biomarker for malnutrition-related illness in older persons [35], and higher cholesterol level was associated with better outcomes in late-life physical function and the ability to recover from illnesses [36, 37]. For the other possible reason of the inverse association between CVD and LDL-C level, it has been suggested that CVD may be caused by infections, and high LDL-C level may be beneficial in that LDL is involved in the individuals' immune system by adhering to and

inactivating all kinds of microorganisms and their toxic products [38, 39]. Moreover, the mean value of LDL-C in the 4th quartile of the current study population was  $161.6 \pm 25.0$  mg/dL, which was relatively lower than that of LDL-C of the highest quartile in most studies showing no association between high LDL-C level and CV mortality [10, 11, 23, 26, 40] because older adults who had a medical history of dyslipidemia (including those who had taken medication for dyslipidemia) were excluded in this study. It seems that LDL-C levels in this range were protective for older people, reducing the incidence of ischemic brain disease.

Although the risk of death from CVD was not significantly associated with high LDL-C level in older adults without diabetes, it was significantly increased in diabetic patients with high LDL-C level, showing an interaction between LDL-C level and diabetes. Older adults with diabetes are at particularly high risk of mortality from CVD. Elderly patients with diabetes may have less end organ reserve due to aging and comorbidity, which could result in more abrupt and severe CVD [41]. A previous study reported that an increased LDL-C level was associated with an increased risk for CVD mortality in people with type 2 diabetes [42]. However, more studies have shown that LDL-C is not associated with mortality among diabetic patients [43-46], and a systematic review has shown that treatment of dyslipidemia is unable to prevent CVD in diabetics [47]. These suggest that adding treatment of dyslipidemia to patients who already experience diabetes cannot be beneficial to prevent death from CVD, and that diabetes, not high LDL-C, is a major predictor of CV mortality in diabetic patients.

Non-smokers with high LDL-C level were significantly associated with lower risk of CV events; however, the association between LDL-C and future CVD was not significant in ex- and current smokers. Thus, there was an interaction between smoking and LDL-C. Smoking has been reported as an independent predictor of CV incidence in older and middle-aged population, and there was nearly a twofold increase in its absolute risk in the elderly [48]. There was an inverse association between LDL-C and risk of future CVD in non-smokers.

### **Study strengths and limitations**

This study has the strengths. This was a nationwide longitudinal study comprising a large number of the elderly population. Moreover, in this study, the main CV risk factors were adjusted. Nevertheless, this study has several limitations. The mean follow-up time of 3.3 years was relatively shorter than that of other studies reporting future CV morbidity and mortality. It is possible that other confounding factors affecting CVD have not been considered. Furthermore, due to the exclusion of the elderly with dyslipidemia to rule out the effect of statins, future CV incidence and CV mortality in older adults with higher LDL-C levels or taking statins could not be identified. Considering the participants were all elderly Koreans, it is difficult to generalize the results to other elderly populations. With the cohort effect that only relatively healthy older adults survive to significantly old age, the results should be interpreted carefully considering survivor bias.

## **Conclusions**

Neither high LDL-C nor HDL-C was significantly associated with future CV death in older adults aged  $\geq 65$  years, except high LDL-C level, which was significantly associated with a lower incidence of ischemic brain disease. In stratified analysis, high LDL-C was associated with an increased risk of CV mortality in older adults with diabetes. However, according to several previous studies, there was a lack of an association between high LDL-C and mortality in diabetics and cholesterol-lowering trial was unable to reduce mortality in people with diabetes. Further study is needed to confirm whether there is benefit of lowering LDL-C in older adults with diabetes.

## List Of Abbreviations

CVD: cardiovascular disease; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; CV: cardiovascular; KNHIS: Korean National Health Insurance Service; NSP: National Screening Program; NHID: National Health Information Database; BMI: body mass index; HR: hazard ratio; aHR: adjusted hazard ratio; CI: confidence interval

## Declarations

### Ethics approval and consent to participate

This study protocol was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2020-0649). The requirement for informed consent was waived because the KNHIS database was constructed after anonymization according to strict confidentiality guidelines. Administrative permission to access the NHID was obtained from the National Health Insurance Sharing Service (NHIS-2017-2-336).

### Consent for publication

Not applicable.

### Availability of data and materials

The dataset supporting the findings of this article are available in the National Health Insurance Sharing Service, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available upon request.

The information on how to request for database is in <https://nhiss.nhis.or.kr/bd/ab/bdaba021eng.do>.

The database used for this study can be requested in <https://nhiss.nhis.or.kr/bd/ay/bdaya001iv.do>.

The questionnaire used in this study is available for download in <http://www.law.go.kr/admRulLsInfoP.do?chrClsCd=&admRulSeq=2200000012541#AJAX>.

### Competing interests

The authors declare that they have no competing interests.

## Funding

Not applicable.

## Authors' contributions

Study concept and design: KYS. Acquisition of data: KYS. Analysis and interpretation of data: KYS, SHK. Drafting of the manuscript: SHK. Critical revision of the manuscript: KYS. All authors read and approved the final manuscript.

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## Tables

Table 1. Basic characteristics of participants

	Total	Men	Women	P-value
	N = 62604 (%)	N = 32584 (%)	N = 30020 (%)	
BMI (kg/m <sup>2</sup> )	24.1 ± 3.0	23.9 ± 2.8	24.4 ± 3.1	
<23	22395 (35.8)	12090 (37.1)	10305 (34.3)	< 0.001
23–25	17576 (28.1)	9543 (29.3)	8033 (26.8)	
≥25	22633 (36.2)	10957 (33.6)	11682 (38.9)	
Cigarette smoking				
Non-smoker	42630 (68.1)	13161 (40.4)	29469 (98.2)	< 0.001
Ex-smoker	12510 (20.0)	12331 (37.9)	179 (0.6)	
Current smoker	7439 (11.9)	7072 (21.7)	367 (1.2)	
LDL-C (mg/dL)	117.8 ± 35.3	112.0 ± 33.5	124.1 ± 36.1	
1st quartile	73.2 ± 15.1	72.4 ± 15.6	74.5 ± 14.1	< 0.001
2nd quartile	103.5 ± 6.5	103.3 ± 6.6	103.7 ± 6.5	
3rd quartile	125.6 ± 6.9	125.6 ± 6.9	126.3 ± 6.8	
4th quartile	161.6 ± 25.0	159.3 ± 21.9	163.2 ± 26.8	
HDL-C (mg/dL)	53.9 ± 19.9	52.3 ± 18.9	55.7 ± 20.8	
1st quartile	38.7 ± 4.5	38.4 ± 4.6	39.1 ± 4.3	< 0.001
2nd quartile	48.5 ± 2.3	48.4 ± 2.3	48.6 ± 2.3	
3rd quartile	56.7 ± 2.6	56.6 ± 2.6	56.8 ± 2.6	
4th quartile	73.8 ± 30.2	73.7 ± 29.8	73.9 ± 30.5	
Hypertension	29755 (59.2)	15568 (59.6)	14187 (58.7)	0.049
Diabetes mellitus	11205 (17.9)	6665 (20.5)	4540 (15.1)	< 0.001
Cardiovascular disease	323 (0.5)	211 (0.7)	112 (0.4)	
Ischemic heart disease	198 (0.3)	132 (0.4)	66 (0.2)	< 0.001
Ischemic brain disease	125 (0.2)	79 (0.2)	46 (0.2)	0.012
Cardiovascular death	114 (0.2)	80 (0.3)	34 (0.1)	
Ischemic heart disease	45 (0.1)	38 (0.1)	7 (0.02)	< 0.001
Ischemic brain disease	69 (0.1)	42 (0.1)	27 (0.1)	0.027

\*Abbreviation: BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density

lipoprotein cholesterol

P-values were calculated by chi-square test for categorical variables and by t-test for continuous variables.

Table 2. Association between quartiles of low-density lipoprotein cholesterol and cardiovascular disease

Event	Duration (PYs)	Incidence rate	Crude	Model 1	Model 2	Model 3	
			HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
			$\beta \times 10^4$ (P-value)	$\beta \times 10^4$ (P-value)	$\beta \times 10^4$ (P-value)	$\beta \times 10^4$ (P-value)	
<b>Cardiovascular event</b>							
Ischemic heart disease	198	204025.6	0.970	0.90 (0.79–1.03)	0.90 (0.79–1.03)	0.95 (0.83–1.09)	0.95 (0.83–1.09)
				<b>-4.170 (0.041)</b>	-2.874 (0.164)	-2.874 (0.165)	-1.159 (0.633)
Ischemic brain disease	125	204025.6	0.613	0.80 (0.68–0.94)	0.83 (0.70–0.98)	0.83 (0.70–0.98)	0.84 (0.70–1.00)
				<b>-4.019 (0.013)</b>	<b>-3.450 (0.036)</b>	<b>-3.454 (0.036)</b>	-3.389 (0.078)
Total	323	204025.6	1.583	0.83 (0.75–0.92)	0.87 (0.79–0.97)	0.90 (0.81–1.01)	0.90 (0.81–1.01)
				<b>-8.189 (0.002)</b>	<b>-6.324 (0.017)</b>	<b>-6.328 (0.016)</b>	-4.548 (0.142)
<b>Cardiovascular death</b>							
Ischemic heart disease	45	204058.7	0.221	0.88 (0.68–1.16)	0.99 (0.75–1.29)	0.99 (0.75–1.29)	1.13 (0.83–1.54)
				<b>-0.708 (0.467)</b>	<b>-0.017 (0.986)</b>	<b>-0.022 (0.982)</b>	0.961 (0.381)
Ischemic brain disease	69	204058.7	0.338	0.90 (0.73–1.12)	0.93 (0.75–1.16)	0.93 (0.75–1.16)	0.95 (0.74–1.22)
				<b>0.572 (0.543)</b>	<b>0.934 (0.327)</b>	<b>0.932 (0.329)</b>	1.709 (0.103)
Total	114	204058.7	0.559	0.89 (0.76–1.06)	0.95 (0.80–1.13)	0.95 (0.80–1.13)	1.01 (0.84–1.23)
				<b>-1.617 (0.297)</b>	<b>-0.655 (0.677)</b>	<b>-0.663 (0.673)</b>	-0.701 (0.687)
Model 1: age, sex							

Model 2: Model 1 + cigarette smoking

Model 3: Model 2 + hypertension, diabetes mellitus, body mass index

\*Abbreviation: PY, person-year; HR, hazard ratio; CI, confidence interval

Bold-faced value indicates statistical significance (p-value < 0.05).

Incidence rate is for the total participants.

HR is for the 4th quartile compared to the 1st quartile.

Table 3. Association between quartiles of high-density lipoprotein cholesterol and cardiovascular disease

	Event	Duration (PYs)	Incidence rate	Crude	Model 1	Model 2	Model 3
				HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
				$\beta \times 10^4$ (P-value)	$\beta \times 10^4$ (P-value)	$\beta \times 10^4$ (P-value)	$\beta \times 10^4$ (P-value)
<b>Cardiovascular event</b>							
Ischemic heart disease	198	204025.6	0.970	<b>0.88 (0.77–1.00)</b>	0.90 (0.80–1.03)	0.90 (0.80–1.03)	0.95 (0.83–1.09)
				-3.789 (0.057)	-2.804 (0.163)	-2.832 (0.159)	-1.293 (0.585)
Ischemic brain disease	125	204025.6	0.613	0.95 (0.82–1.12)	0.98 (0.83–1.14)	0.98 (0.84–1.15)	0.94 (0.79–1.12)
				-0.784 (0.621)	-0.292 (0.855)	-0.262 (0.870)	-0.960 (0.610)
Total	323	204025.6	1.583	<b>0.91 (0.82–1.00)</b>	0.93 (0.85–1.03)	0.93 (0.85–1.03)	0.95 (0.85–1.05)
				<b>-4.573 (0.041)</b>	-3.096 (0.164)	-3.094 (0.165)	-2.252 (0.633)
<b>Cardiovascular death</b>							
Ischemic heart disease	45	204058.7	0.221	0.79 (0.61–1.04)	0.84 (0.65–1.10)	0.85 (0.65–1.11)	0.82 (0.60–1.11)
				-1.543 (0.105)	-1.041 (0.278)	-0.993 (0.301)	-1.237 (0.248)
Ischemic brain disease	69	204058.7	0.338	1.04 (0.84–1.28)	1.06 (0.86–1.31)	1.06 (0.86–1.31)	1.10 (0.87–1.40)
				-1.121 (0.223)	-0.881 (0.342)	-0.846 (0.361)	-0.551 (0.591)
Total	114	204058.7	0.559	0.93 (0.79–1.10)	0.98 (0.83–1.15)	0.98 (0.83–1.15)	0.98 (0.81–1.19)
				-1.043 (0.491)	-0.312 (0.838)	-0.222 (0.884)	-0.113 (0.947)
Model 1: age, sex							

Model 2: Model 1 + cigarette smoking

Model 3: Model 2 + hypertension, diabetes mellitus, body mass index

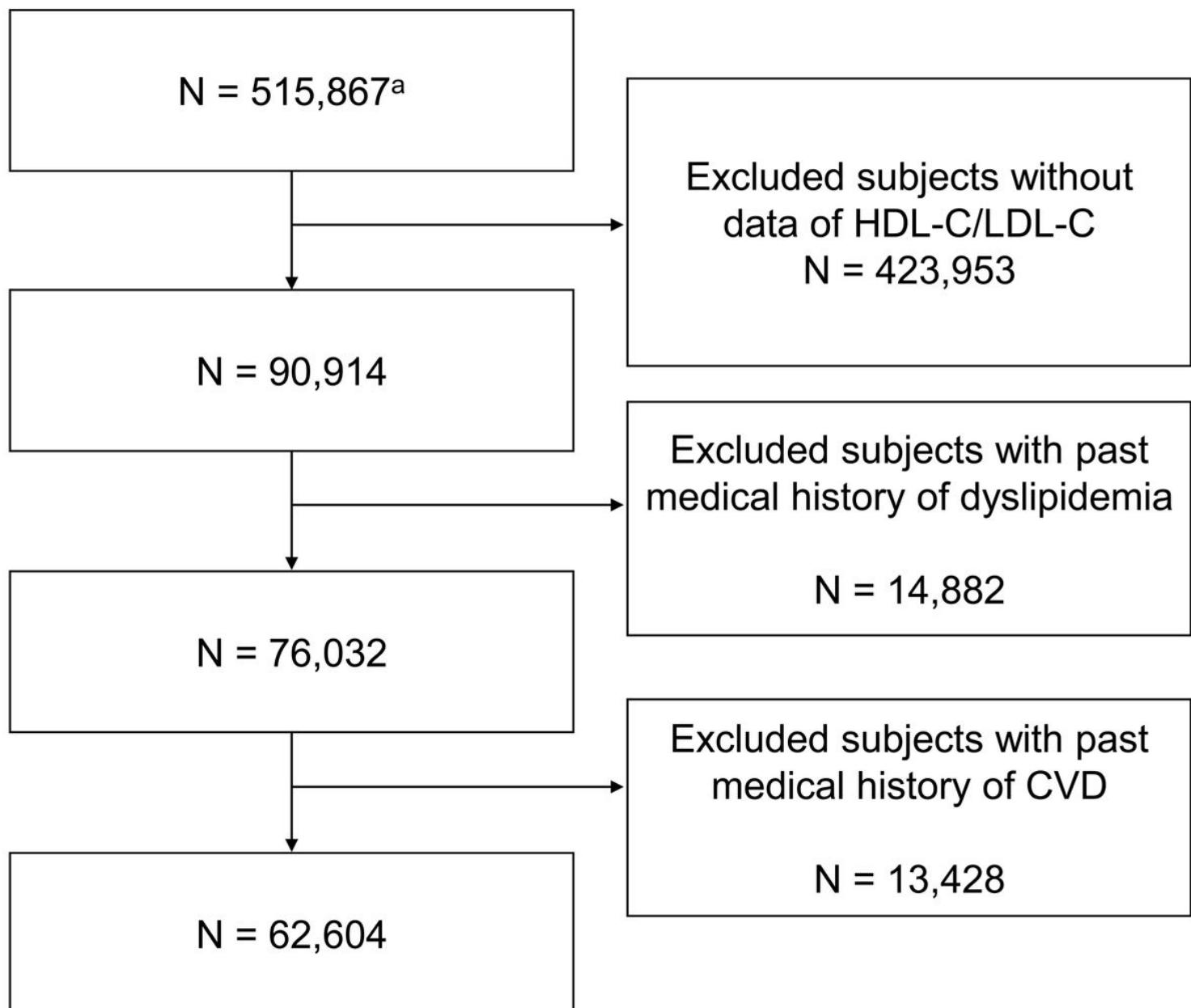
\*Abbreviation: PY, person-year; HR, hazard ratio; CI, confidence interval

Bold-faced value indicates statistical significance (p-value < 0.05).

Incidence rate is for the total participants.

HR is for the 4th quartile compared to the 1st quartile.

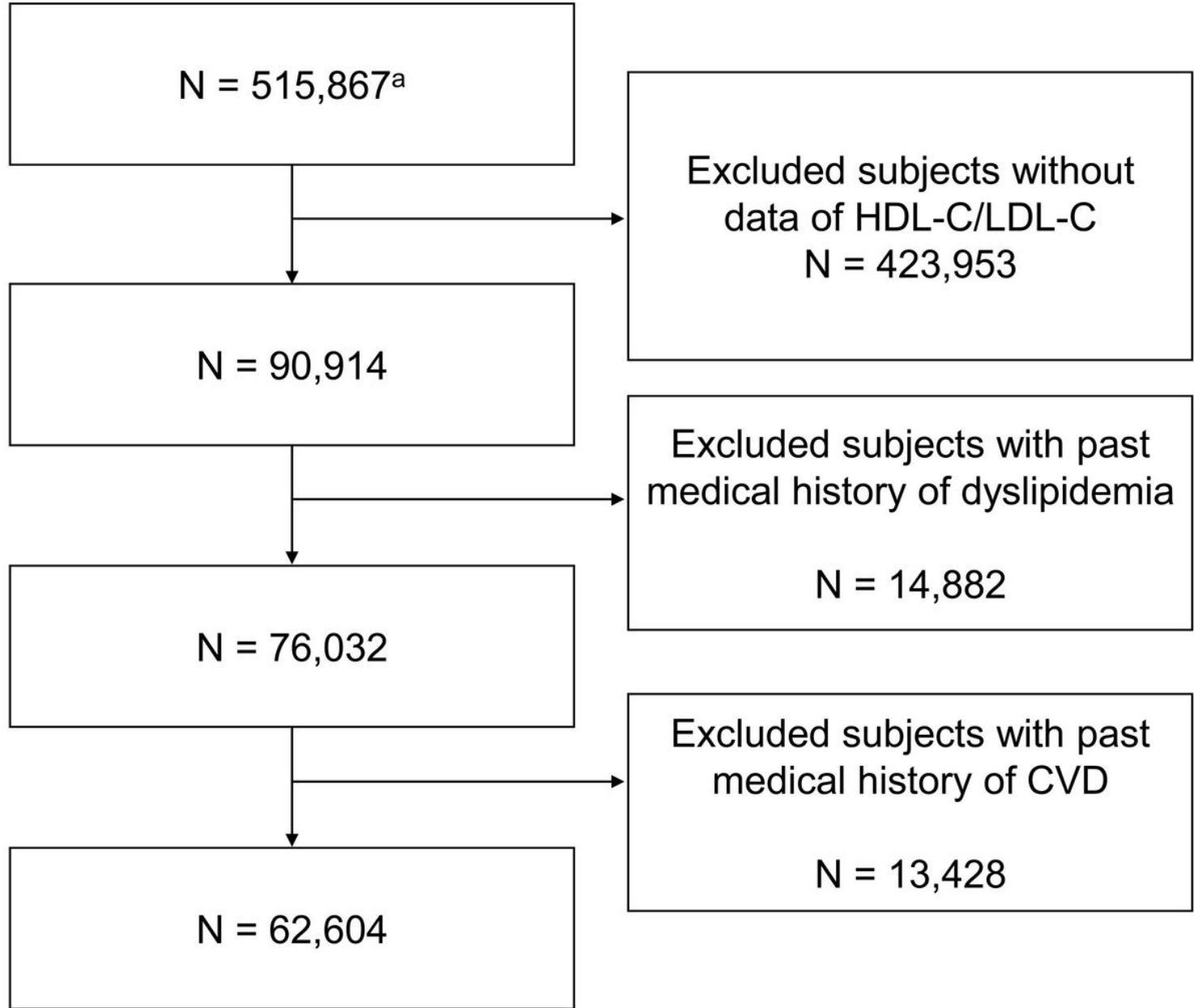
## Figures



**Figure 1**

Participant selection aNumber of individuals in the National Health Insurance Service–National Health Screening Cohort database of the Korean National Health Insurance Service (2002–2015).

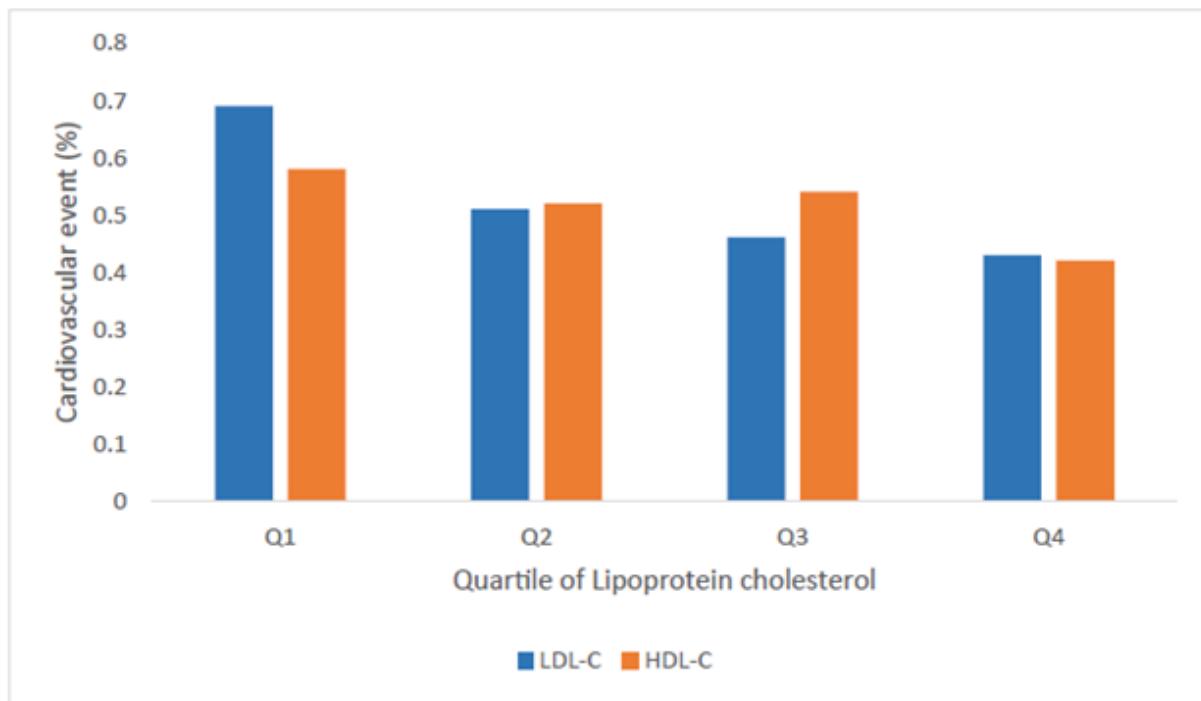
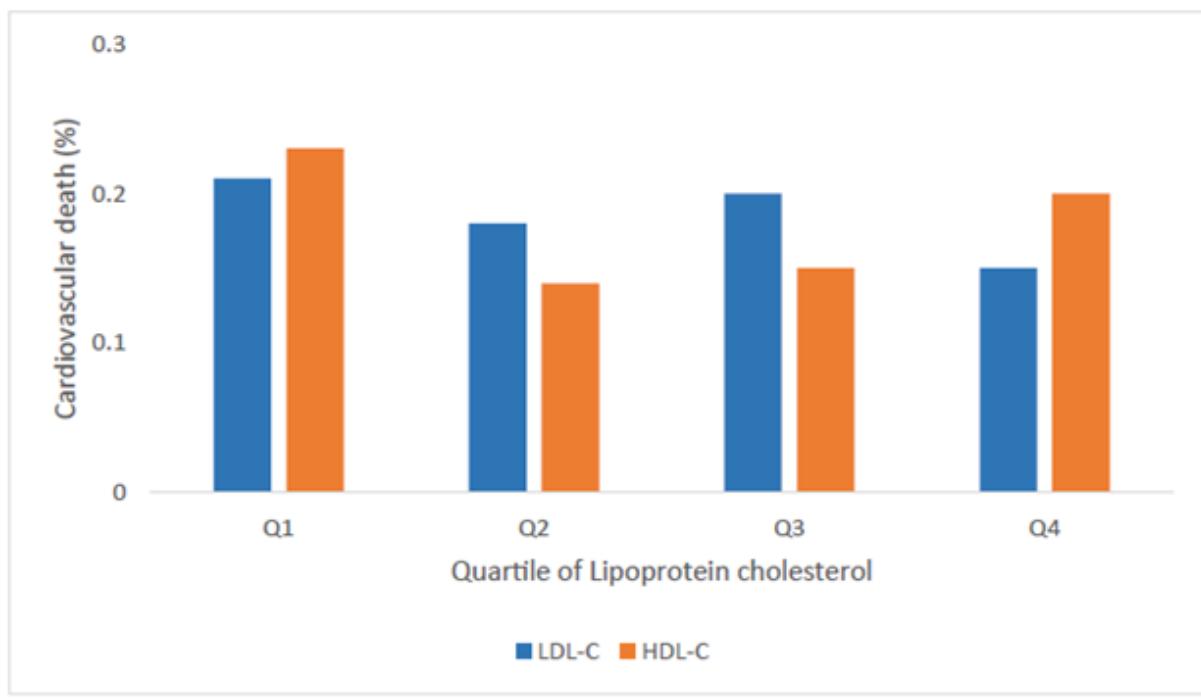
\*Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease



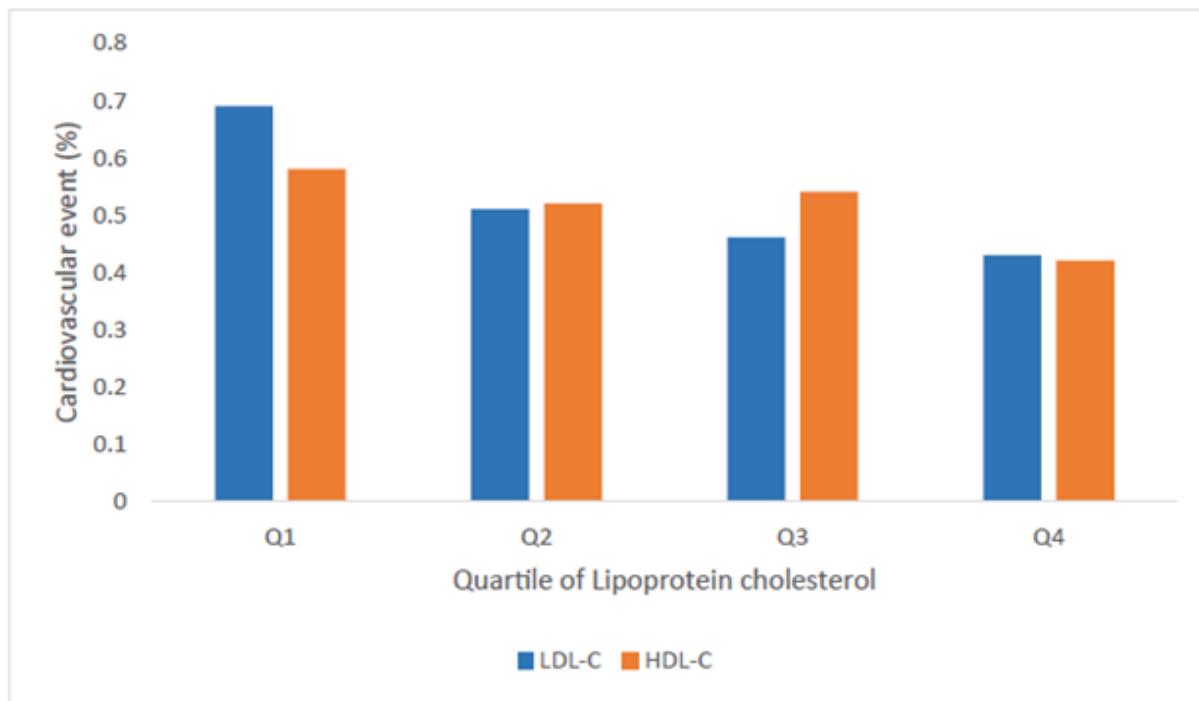
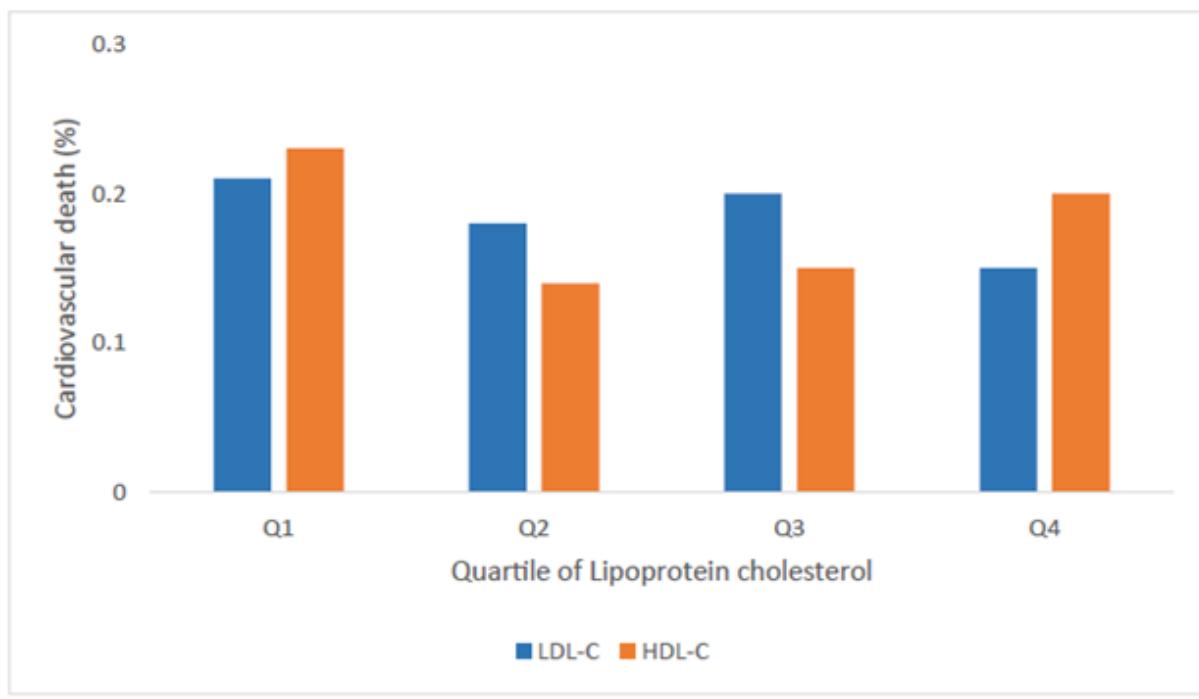
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Participant selection aNumber of individuals in the National Health Insurance Service–National Health Screening Cohort database of the Korean National Health Insurance Service (2002–2015).

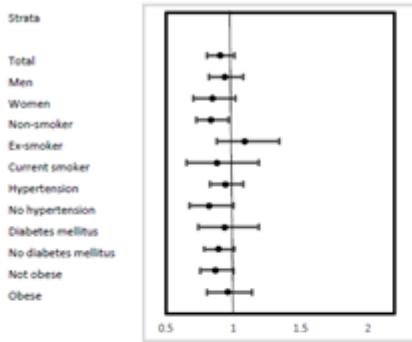
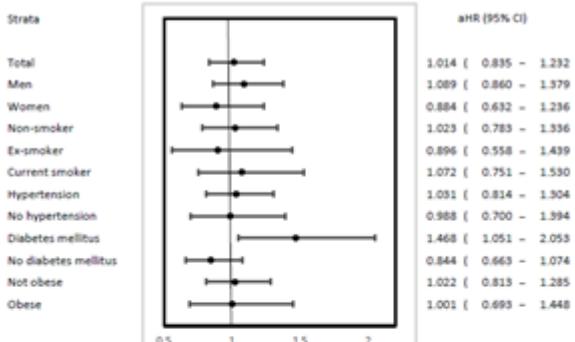
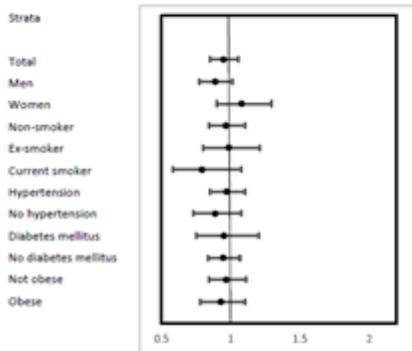
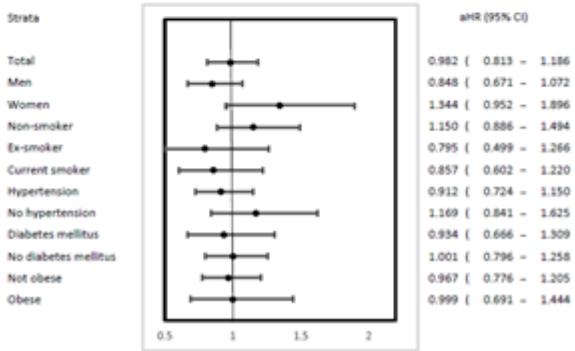
\*Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease

**a****b****Figure 2**

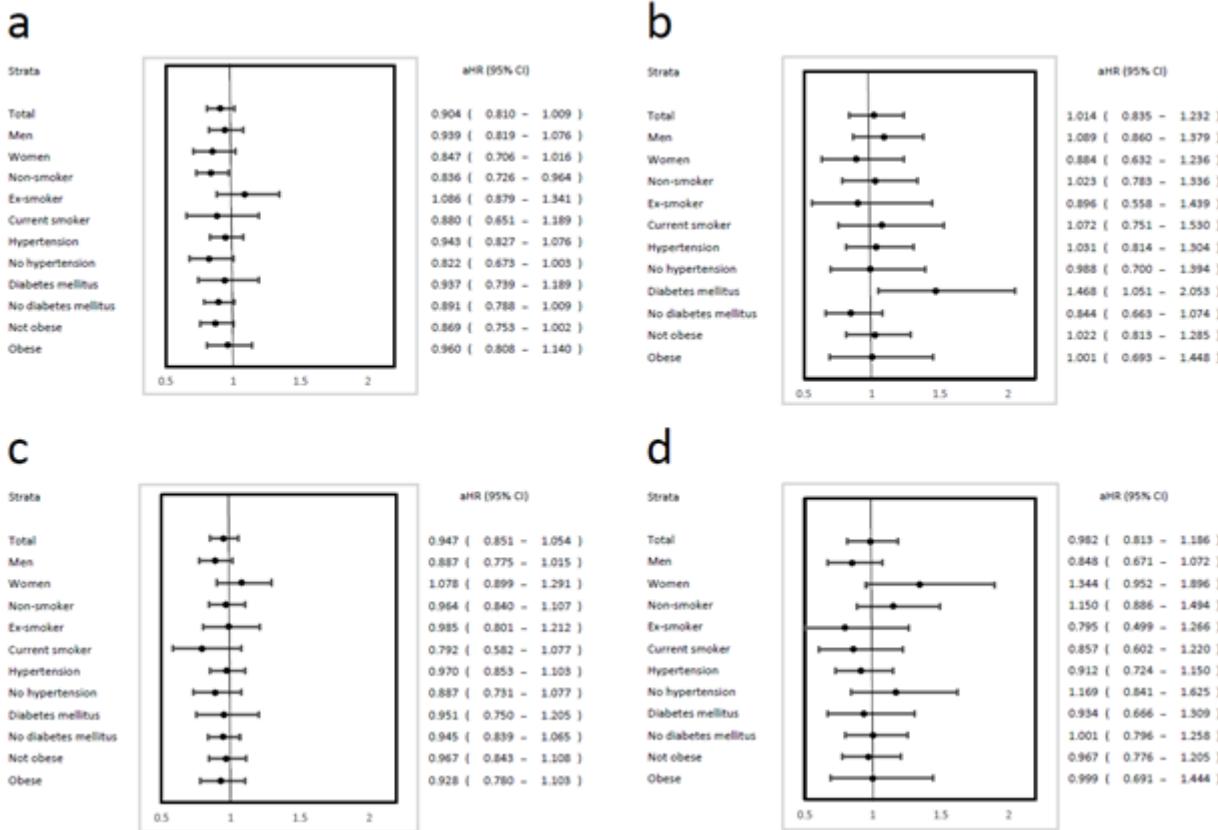
Proportion of cardiovascular event and death according to quartiles of lipoprotein cholesterol  
a) Proportion of cardiovascular event, b) Proportion of cardiovascular death \*Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

**a****b****Figure 2**

Proportion of cardiovascular event and death according to quartiles of lipoprotein cholesterol  
a) Proportion of cardiovascular event, b) Proportion of cardiovascular death \*Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

**a****b****c****d****Figure 3**

Forest plots showing stratified analyses of the association between cholesterol and cardiovascular event and mortality a) LDL-C and cardiovascular event, b) LDL-C and cardiovascular death, c) HDL-C and cardiovascular event, d) HDL-C and cardiovascular death \*Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol  
aHR is for the 4th quartile compared to the 1st quartile.



**Figure 3**

Forest plots showing stratified analyses of the association between cholesterol and cardiovascular event and mortality a) LDL-C and cardiovascular event, b) LDL-C and cardiovascular death, c) HDL-C and cardiovascular event, d) HDL-C and cardiovascular death \*Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol aHR is for the 4th quartile compared to the 1st quartile.