Association of Lipoprotein Cholesterol With 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 an independent health risk of cardiovascular disease (CVD), a leading cause of mortality in older adults. Despite their importance, there have been few reports on the association between lipoprotein cholesterol and future CVD and cardiovascular (CV) mortality among elderly Asians. This longitudinal study investigated the correlations in an elderly Korean population by using a large nationwide sample.

Methods

Among participants in the cohort database of the Korean National Health Insurance Service who completed the National Screening Program, a total of 62,604 adults aged 65 years or older (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 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, while the mortality rates from these diseases were 0.22 and 0.34 per 1,000 person-years, respectively. In a fully adjusted model, high HDL-C and LDL-C levels were not associated with the total CV events and CV mortality; 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 ≥65 years. Older adults with diabetes were significantly associated with a higher risk of CV mortality in high LDL-C levels.

Background

Cardiovascular disease (CVD) is the most common cause of death globally, with an estimated 17.9 million CVD related deaths in 2016, representing 31% of all global deaths [1]. Dyslipidemia is one of the independent risk factors for atherosclerosis and CVD. An elevated level of total cholesterol is widely considered a primary cause of CVD [2]. Numerous studies have shown the associations of reduced high-density lipoprotein cholesterol (HDL-C) and increased low-density lipoprotein cholesterol (LDL-C) with a greater risk of cardiovascular (CV) mortality in adult populations [3, 4].
As the elderly population has increased worldwide [5], CVD and its risk factors, including dyslipidemia, 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 on the relationships between lipoprotein cholesterol and future CVD incidence or CV mortality in older populations, and they give inconsistent results. In some studies of older adults, low HDL-C and high LDL-C was associated with an increase of CV events or CV mortality [7, 8]. In others, low HDL-C 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 inverse association between LDL-C and mortality among older adults [2, 11].

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. To our knowledge, no research has assessed the association of lipoprotein cholesterol with future CVD and CV mortality in older Asian adults. Therefore, this study aimed to evaluate these relationships in individuals aged ≥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 is a public health insurance (i.e., Korean National Health Insurance Service, KNHIS), and provides universal health coverage to almost all Koreans except Medicaid beneficiaries who account for less than 3% of the population. The KNHIS provides the National Screening Program (NSP), a biennial health screening program. KNHIS created the National Health Information Database (NHID), which includes data on health screening results in the NSP, sociodemographic variables, and mortality for over 50 million individuals in Korea. The details of the NHID have been described elsewhere [12].

**Data sources and study population**

We used the National Health Insurance Service-National Health Screening Cohort database of the NHID, in which 515,867 participants were included. This represents 10% of a randomly selected population from the total of Korean participants aged between 40–79 years who participated in the NSP at least once between 2002 and 2003. After excluding participants without data of HDL-C and LDL-C, those younger than 65 years, and those who had a medical history of dyslipidemia and CVD, 62,604 participants were included in the analysis of the current study (Figure 1).

The database included demographic data of the participants, survey data regarding past medical history and health behaviors, and screening results including height, weight, and laboratory tests.

This study protocol was approved by Institutional Review Board of Asan Medical Center (IRB No. 2020-0649), and the requirement for informed consent was waived because the KNHIS database was constructed after anonymization according to strict confidentiality guidelines.
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[13], while it was obtained as a measured value in those with triglycerides ≥400 mg/dL. HDL-C and LDL-C values were categorized by quartiles.

Outcome variables

CV events and CV mortality

Definition of CV events and CV mortality have been described elsewhere [14]. Data concerning the diagnosis of a CV event, date of the event, cause of death, and date of death were obtained from the KNHIS cohort database during the 2007–2015 period. This analysis assumed that there was no censoring other than death or an event. Because all participants are supposed to be beneficiaries of the National Health Insurance or Medical Aid Program in Korea, a dropout for reasons other than death is virtually impossible. Furthermore, because claims for all medical events experienced should be submitted to the KNHIS by healthcare providers for reimbursement, every CV event should be included in the database. The database was reviewed for International Classification of Diseases 10th Revision (ICD-10) codes for diagnosis and cause of death. CV events or death was defined as a diagnosis of or death caused by ischemic heart diseases (I20-25) or ischemic brain diseases (I63). The follow-up time was calculated as the time from the date they received examination in the NSP to the date of first diagnosis of CVD for its events or to the date of December 31, 2015 for participants who did not experience events, and to the date of death for CVD. If there was no date of death in the database, the participant was considered alive at the end of 2015.

Potential confounders

Sex, cigarette smoking status, and body mass index (BMI) were evaluated. Information on cigarette smoking was collected by a self-administered questionnaire at the time of the NSP, with participants 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 calculated as weight divided by height squared (kg/m^2). According to Asian-specific criteria [15], BMI was categorized into within normal (BMI <23 kg/m^2), overweight (BMI 23–25 kg/m^2), and obese (BMI ≥25 kg/m^2).

Hypertension and diabetes were included in the analysis as CV risk factors. We collected hypertension and diabetes data by using the questionnaire. If participants answered that they took medication for
hypertension or diabetes, they were considered to have the diseases. Hypertension was defined as a systolic blood pressure (SBP) ≥ 140 mmHg or a diastolic blood pressure (DBP) ≥ 90 mmHg; diabetes as a serum concentration of fasting glucose ≥ 126 mg/dL. Each chronic disease was defined as described[16].

**Statistical analysis**

In baseline characteristics, continuous variables were reported as mean ± SD and categorical variables as frequencies and percentages.

The incidence rates of CVD and CV mortality were calculated according to quartiles of lipoprotein cholesterol. Cox proportional hazard models were used to evaluate the association between the quartiles of lipoprotein cholesterol and CV events or CV mortality. Four models were built for survival analyses, a crude model and three adjusted models. Model 1 was adjusted for 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. Adjusted Hazard ratios (aHR) and 95% confidence intervals (CI) were calculated for each model.

Participants at risk of a CVD event or death were identified by stratified analyses in Model 3, stratified by sex, cigarette smoking, hypertension, diabetes, and obesity.

Statistical analyses were performed using STATA software (version 16.1; STATA. Corp, 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 of a mean 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/m², with 22,633 (36.2%) being classified as obese (BMI ≥ 25.0 kg/m²). 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 (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 mortality rates from these diseases were 0.22 and 0.34 per 1,000 person-years, respectively, during the observation period of 204,058.7 person-years (Table 2).

**Association between quartiles of HDL-C and CVD**
Incidence rates of CVD and CV mortality according to quartiles of HDL-C are presented in Figure 2. Incidence rate of CVD was the lowest in participants with HDL-C from the 4th quartile, while U-shaped association was observed between CV mortality rates and HDL-C levels.

In the crude model (Table 2), 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), while its associated 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: 1.03, 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), while there was no significant relationship between total CV mortality and high levels of HDL-C.

In Models 1, 2, and 3, the incidence of CV events and CV mortality was not significantly associated with high levels of HDL-C.

**Association between quartiles of LDL-C and CVD**

Incidence rates of CVD and CV mortality according to the quartiles of LDL-C are presented in Figure 2. The incidence rate of CVD 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 according to the quartile of LDL-C.

In the crude model (Table 3), the incidence of ischemic brain disease was 10% lower in participants with LDL-C from the 4th quartile (HR: 0.90, 95% CI: 0.68–0.94), 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), while there was no significant relationship between total CV mortality and high levels of LDL-C (HR: 0.89, 95% CI: 0.76–1.06).

In Model 1 and 2, the incidence of ischemic brain disease was 17% lower in participants with LDL-C from the 4th quartile (aHR: 0.83, 95% CI: 0.70–0.98 in both models), while its mortality was not significantly associated with LDL-C levels (aHR: 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. The total CV events were 13% lower in participants with LDL-C from the 4th quartile (aHR: 0.87, 95% CI: 0.79–0.97 in both models), while total CV mortality was not significantly associated with high levels of LDL-C (aHR: 0.95, 95% CI: 0.80–1.13 in both models).

In Model 3, the incidence of ischemic brain disease was 16% lower in participants with LDL-C from the 4th quartile (aHR: 0.84, 95% CI: 0.70–1.00), while its mortality was not significantly associated with LDL-C levels (aHR: 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, as well as total CV event or its mortality and high LDL-C.

**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 (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 failed to identify any strata with a significant association between HDL-C and CV events or CV death (Figure 3 c, d).

**Discussion**

This large longitudinal study evaluated the association between lipoprotein cholesterol and future incidence of CVD and CV mortality using a nationally representative sample of an Asian country. Using a fully adjusted model, HDL-C was not associated with the incidences of CVD or CV mortality. However, high LDL-C 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 had a higher CV mortality, whereas non-smokers with high LDL-C were significantly associated with a lower risk of CV events.

There was no significant association between LDL-C and CV mortality, which was robust in stratified analysis, consistent with other studies in older adults [10, 11, 17, 18]. This finding contrasts 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 [19]. 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 [20]. Cholesterol levels tend to decrease with age [21], suggesting that the role of cholesterol in determining the risk of CVD may become less relevant in a more aged population [17]. In addition, HDL-C was not related to the incidence of CVD and CV mortality in this study, which is in line with previous findings [11, 22]. These results differ from those of other studies showing that increased HDL-C was associated with a reduced risk of CVD in the elderly [23], presumably because the effect of other variables affecting CVD was greater than that of HDL-C in our study. Relationship between HDL-C and CV events was attenuated after adjustment for CV risk factors, which suggests 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 ≥65 years. Furthermore, this finding is in line with a previous study suggesting that
lowering LDL-C via statin therapy was not effective in primary prevention of CV events or CV death in older adults aged 70 years or older [24].

High LDL-C was significantly associated with a lower incidence of ischemic brain disease in older adults, which contrasts with the cholesterol hypothesis that cholesterol, particularly LDL-C, is inherently atherogenic. A systematic review demonstrated that elevated LDL-C was inversely associated with all-cause mortality, and CV mortality was significantly higher in the lowest LDL-C quartile in older adults [2]. One reason for these findings may be that elevated cholesterol 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 [25], elevated LDL-C 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 [26] and rather, higher LDL-C is likely to be significantly associated with healthy survival as in a recent study [11]. One study suggested that low total cholesterol may be a biomarker for malnutrition-related illness in older persons [27], and higher cholesterol was associated with better outcomes in late-life physical function and the ability to recover from illnesses [28, 29]. For the other possible reasons of the inverse association between CVD and LDL-C level, it has been suggested that CVD may be caused by infections, and LDL-C directly inactivates almost all types of microorganisms and their toxic products [30, 31]. Moreover, the mean value of LDL-C in the 4th quartile of the current study population was 161.6 ± 25.0 mg/dL, which was relatively lower than that of LDL-C of the highest quartile in most studies showing no relationship between high LDL-C and CV mortality [10, 11, 17, 20, 32] because older adults with 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 CV mortality was not significantly associated with LDL-C in the entire study population, CV mortality rate was higher in diabetic patients with high LDL-C, suggesting that diabetes is a strong risk of CV mortality in the elderly. Older adults with diabetes are at particularly high risk of mortality from CVD. Elderly patients with abnormal glucose metabolism may have less end organ reserve due to aging and comorbidity, which could result in more abrupt and severe CVD [33]. The deleterious effect of hyperglycemia itself and lipid abnormalities in diabetic patients are likely to play an important role in the development of atherogenesis [34]. In diabetes with dyslipidemia, insulin resistance increases the production of small, dense LDL-C and promotes increased deposition of cholesterol within the arterial wall, progressing atherosclerosis, which is significantly associated with the incidence of CVD [35]. Therefore, older adults with diabetes and dyslipidemia were more likely to be vulnerable to CV related death.

Non-smokers with high LDL-C were significantly associated with lower risk of CV events, suggesting that smoking is stronger risk factor of CV morbidity in the elderly than serum cholesterol level. Smoking has been reported as an independent predictor of CV incidence in older population as well as in middle-aged population, and there was nearly a two-fold increase in its absolute risk in the elderly [36]. In the elderly, a
high LDL-C and refraining from smoking positively interacted to a healthy survival, which would have resulted in a significant reduction in CV morbidity.

This study had several limitations. The participants of this study were over 65 years of age; this age group is relatively younger when compared with other previous studies evaluating the relationship between lipoprotein cholesterol and future CV events and CV mortality in the elderly. Moreover, the mean follow-up duration of 3.3 years was relatively shorter than other studies reporting future CV morbidity and mortality. We could not distinguish the possibilities of other potential factors influencing the results, even though we excluded participants with confounding factors that can affect lipoprotein cholesterol and CVD before the analysis. Furthermore, due to the exclusion of the elderly with dyslipidemia, 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 very old age, the results should be interpreted carefully considering survivor bias. Therefore, longer follow-up studies including missing confounders among older elderly populations are needed.

Conclusions

Neither high LDL-C nor HDL-C was significantly associated with future CV mortality in older adults aged ≥ 65 years, except high LDL-C was significantly related to a lower incidence of ischemic brain disease. In stratified analysis, we found that older adults with diabetes showed increased risk of CV mortality in high levels of LDL-C.

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; ICD-10: International Classification of Diseases 10th Revision; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: hazard ratio; aHR: adjusted hazard ratio; CI: confidence interval

Declarations

Ethics approval and consent to participate

This study protocol was approved by 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 acquired by National Health Insurance Sharing Service (NHIS-2017-2-336).

Consent for publication
Not applicable.

**Availability of data and materials**

The dataset generated and analyzed during the current study are available in National Health Insurance Sharing Service. But the authors have no right to share or provide the data. The information of how to request for database is available in https://nhiss.nhis.or.kr/bd/ab/bdaba021eng.do. Detail and cost of the database is described in https://nhiss.nhis.or.kr/bd/ab/bdaba022eng.do. To request the database, visit https://nhiss.nhis.or.kr/bd/ay/bdaya001iv.do. (only available in Korean)

The questionnaire used in this study is not available in English. The Korean version of the questionnaire is available for download at following website: (http://www.law.go.kr/admRulLsInfoP.do?chrClsCd=&admRulSeq=2200000012541#AJAX).

**Competing interests**

The authors declare that they have no competing interests.

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Not applicable.

**Authors' contributions**

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

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Tables

Table 1. Basic characteristics of participants
|                          | Total          | Men             | Women           |
|--------------------------|----------------|-----------------|-----------------|
| N = 62604 (%)            | N = 32584 (%)  | N = 30020 (%)   |                 |
| **BMI (kg/m²)**          |                |                 |                 |
| <23                      | 22395 (35.8)   | 12090 (37.1)    | 10305 (34.3)    |
| 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)    |
| 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)**        |                |                 |                 |
| 1st quartile             | 73.2 ± 15.1    | 72.4 ± 15.6     | 74.5 ± 14.1     |
| 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)**        |                |                 |                 |
| 1st quartile             | 38.7 ± 4.5     | 38.4 ± 4.6      | 39.1 ± 4.3      |
| 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)    |
| **Diabetes mellitus**    | 11205 (17.9)   | 6665 (20.5)     | 4540 (15.1)     |
| **Cardiovascular disease**| 323 (0.5)      | 211 (0.7)       | 112 (0.4)       |
| **Ischemic heart disease**| 198 (0.3)      | 132 (0.4)       | 66 (0.2)        |
| **Ischemic brain disease**| 125 (0.2)      | 79 (0.2)        | 46 (0.2)        |
| **Cardiovascular death** | 114 (0.2)      | 80 (0.3)        | 34 (0.1)        |
| **Ischemic heart disease**| 45 (0.1)       | 38 (0.1)        | 7 (0.02)        |
| **Ischemic brain disease**| 69 (0.1)       | 42 (0.1)        | 27 (0.1)        |
*Abbreviation: BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

Table 2. Association between quartiles of High-density lipoprotein cholesterol and cardiovascular disease
| Event                          | Duration (PYs) | Incidence rate | Crude HR (95% CI) | Model 1 aHR (95% CI) | Model 2 aHR (95% CI) | Model 3 aHR (95% CI) |
|-------------------------------|----------------|----------------|-------------------|----------------------|----------------------|----------------------|
| **Cardiovascular event**     |                |                |                   |                      |                      |                      |
| Ischemic heart disease       | 198            | 204025.6       | 0.970             | 0.88 (0.77 - 1.00)   | 0.90 (0.80 - 1.03)   | 0.90 (0.80 - 1.03)   | 0.95 (0.83 - 1.09)   |
| Ischemic brain disease       | 125            | 204025.6       | 0.613             | 0.95 (0.82 - 1.12)   | 0.98 (0.84 - 1.14)   | 0.98 (0.84 - 1.15)   | 0.94 (0.79 - 1.12)   |
| Total                         | 323            | 204025.6       | 1.583             | 0.91 (0.82 - 1.00)   | 0.93 (0.85 - 1.03)   | 0.93 (0.85 - 1.03)   | 0.95 (0.85 - 1.05)   |
| **Cardiovascular death**     |                |                |                   |                      |                      |                      |                      |
| 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)   |
| Ischemic brain disease       | 69             | 204058.7       | 0.338             | 1.03 (0.84 - 1.28)   | 1.06 (0.85 - 1.31)   | 1.06 (0.86 - 1.31)   | 1.10 (0.87 - 1.40)   |
| Total                         | 114            | 204058.7       | 0.559             | 0.93 (0.79 - 1.10)   | 0.97 (0.82 - 1.14)   | 0.98 (0.83 - 1.15)   | 0.98 (0.81 - 1.19)   |

Model 1: 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; aHR, adjusted hazard ratio  
Bold values were significantly associated (p < 0.05).

Table 3. Association between quartiles of Low-density lipoprotein cholesterol and cardiovascular disease
| Event                          | Duration (PYs) | Incidence Rate | Crude HR (95% CI) | Model 1 aHR (95% CI) | Model 2 aHR (95% CI) | Model 3 aHR (95% CI) |
|-------------------------------|----------------|----------------|-------------------|----------------------|----------------------|----------------------|
| **Cardiovascular event**      |                |                |                   |                      |                      |                      |
| Ischemic heart disease        | 198            | 204025.6       | 0.970             | 0.89 (0.76 - 1.06)   | 0.95 (0.80 - 1.13)   | 0.95 (0.80 - 1.13)   |
|                               |                |                |                   | 1.01 (0.84 - 1.23)   |                      |                      |
| Ischemic brain disease        | 125            | 204025.6       | 0.613             | 0.90 (0.68 - 0.94)   | 0.83 (0.70 - 0.98)   | 0.83 (0.70 - 0.98)   |
|                               |                |                |                   | 0.84 (0.70 - 1.00)   |                      |                      |
| Total                         | 323            | 204025.6       | 1.583             | 0.83 (0.75 - 0.92)   | 0.87 (0.79 - 0.97)   | 0.87 (0.79 - 0.97)   |
|                               |                |                |                   | 0.90 (0.81 - 1.01)   |                      |                      |
| **Cardiovascular death**      |                |                |                   |                      |                      |                      |
| Ischemic heart disease        | 45             | 204058.7       | 0.221             | 0.88 (0.68 - 1.16)   | 0.99 (0.75 - 1.29)   | 0.97 (0.75 - 1.29)   |
|                               |                |                |                   | 1.13 (0.83 - 1.54)   |                      |                      |
| 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)   |                      |                      |
| 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)   |                      |                      |
| Model 1: 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; aHR, adjusted hazard ratio |
| Bold values were significantly associated (p < 0.05). |
Figure 1

Participant selection

Number 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
Figure 2

Cardiovascular event and mortality according to quartiles of lipoprotein cholesterol a) cardiovascular event, b) cardiovascular mortality *Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol
Figure 3

Forest plots showing stratified analyses of the association of cholesterol with cardiovascular event and mortality a) high LDL-C and cardiovascular event, b) high LDL-C and cardiovascular death, c) high HDL-C and cardiovascular event, d) high 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