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Association analysis of LDL cholesterol and atherosclerotic cardiovascular disease according to age: a nationwide population-based cohort study

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Abstract

Background: It remains undetermined if the relationship between LDL cholesterol (LDL-C) and atherosclerotic cardiovascular disease (ASCVD) changes with age. Thus, this study aimed to investigate whether the association of LDL-C and ASCVD may be affected by the subject's age.

Methods: Data from the Korean National Health Insurance Service-National Health Screening Cohort were analyzed. Individuals previously diagnosed with cardiovascular disease (CVD) or taking lipid-lowering drugs were excluded. Age-specific association between LDL-C and ASCVD was calculated using adjusted Cox proportional hazards models.

Results: During a median follow-up of 6.44 years, ASCVD developed in 8,996 (3.2%) among 285,119 Korean adults. All age groups showed positive associations between LDL-C and ASCVD risk with a statistical significance from LDL-C of ≥ 160 mg/dL. The risk of ASCVD did not significantly differ between the age groups (P for interaction = 0.62). With a reference to the ASCVD risk in the group of LDL-C 70-99 mg/dL, the ASCVD risk in the group of highest LDL-C (≥190 mg/dL) was similar between the subjects of age <50 and those of age ≥70 years (adjusted hazard ratio [aHR], 1.90 [95% confidence interval (CI), 1.52-2.38] vs. 1.86 [95% CI, 1.30-2.68]). Consistently, the subgroup analysis in subjects with type 2 diabetes exhibited no difference in the association of LDL-C and ASCVD between different age groups (P for interaction = 0.31).

Conclusions: A nationwide population-based cohort study of individuals who had no prior CVD history and were not on lipid-lowering drugs, demonstrated that elderly Korean subjects (>70 years of age) still presented increased ASCVD risk if they had higher LDL-C at baseline. Thus, the association of LDL-C and ASCVD in elderly Korean population did not significantly differ from that in the younger groups. These findings support the importance of managing LDL-C for the purpose of primary prevention of ASCVD in the elderly population.

Keywords: LDL cholesterol; atherosclerotic cardiovascular disease; age.

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Introduction

Cardiovascular disease (CVD), including coronary heart disease and stroke, is a leading cause of disabilities and premature deaths. Cardiovascular mortality was responsible for 15.6 million global mortalities in 2010 [1], accounting for approximately one-third of all mortalities in the USA and 45% in Europe [2, 3]. Essential CVD mechanisms incorporate atherosclerosis, which progresses age-dependently to impair vascular function [4]. Low-density lipoprotein cholesterol (LDL-C) is one of the classic risk factors of atherosclerotic cardiovascular disease (ASCVD) [5]. Apart from well accepted use in patients who already experienced CVD, several randomized controlled trials (RCT) have validated the advantage of statin treatment exclusively in primary prevention settings [6-11].

In contrast, consensus has not been made upon lowering LDL-C to prevent primary ASCVD in the older population. Preceding investigations on the associations between LDL-C and ASCVD risk asserted that the correlation diminished in older adults with the statistical significance vanishing in some studies [12-16]. RCT that aims to elucidate the pros and cons of lowering LDL-C limited to the elderly has yet to be concluded. To make it more complicated, secondary analyses of statin outcome trials with older participants displayed contradictory results [17-19]. Consequently, major international lipid management guidelines are discordant despite their bases on similar landmark studies [20-25].

An elderly population is rapidly expanding worldwide with the proportion of people aged ≥65 years being expected to increase from 8.5% in 2015 to 12% in 2030 [26]. In parallel with longer life expectancy, the prevalence and economic burden of ASCVD in the elderly are tremendous [27]. The incident cases of coronary heart disease are growing overall due to the greatest increase in subjects aged ≥65 years in contrast to relatively steady numbers in those aged <65 years [27]. Notably, approximately 80% and 50% of the cardiovascular fatality occurred in patients aged ≥65 and ≥85 years, respectively [28]. Hence, establishing definite recommendations on LDL-C targets for the elderly is strongly required. Considering the paucity of prior studies on age-specific investigation of LDL-C and incident ASCVD, evaluating whether ASCVD risk according to increasing LDL-C differs between each age group was proposed in the current study.

Methods

Source of data

Data in the present study was obtained by the Korean National Health Insurance Service-Health Screening Cohort (NHIS-HEALS), which is a large nationwide cohort composed of populations participating in the NHIS health screening programs in the Republic of Korea [29]. All Korean nationals are required to register for national health care insurance under the Korean NHIS. A general health screening program is available to insured individuals biennially. The NHIS database encompasses a wide range of information on healthcare utilization including the diagnosis, treatment, healthcare facilities, demographic factors, cause of mortality and date, questionnaires on health problems and risk factors, and laboratory data. The NHIS-HEALS cohort was organized in 2015, comprising 514,866 individuals who were a random selection of 10% of the entire population that participated in the NHIS health screening between 2002 and 2003 [29]. The robustness with low attrition rate from 2002 to 2015 and the coverage of the whole population are the major strengths of NHIS-HEALS, making it a representative database used in various studies. This investigation was conducted following the guidelines of the Declaration of Helsinki. Ethics approval was permitted by the Asan Medical Center Institutional Review Board (IRB-No 2020-0852), Seoul, Korea. Informed consent was not necessary as the data used anonymized individual keys.

Study population

Baseline was determined as the first examination in health screening programs between January 1, 2009 and December 31, 2010, because NHIS added the biochemical data including triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) in 2009 [29]. Participants were followed up from January 1, 2011 to December 31, 2015. The study included people aged ≥18 years at baseline. Subjects who passed away before 2011, with preexisting CVD, no examination from 2009 to 2010, body mass index (BMI) ≥40 kg/m², no data on LDL-C or TG at baseline, or taking lipid-lowering drugs at baseline (statin, fibrates, or ezetimibe, as

presented in Table 1) were excluded.

Study outcome

The primary outcome was the ASCVD incidence, defined as the composite of myocardial infarction (MI) and stroke. The secondary outcomes were the respective incidence of MI, stroke, heart failure (HF), and CVD-related mortality. Diagnosis of each outcome was made with the diagnostic codes based on the *International Classification of Diseases, Tenth Edition, Clinical Modification* (ICD-10-CM). Incident MI, stroke, or HF was defined as at least one new admission with the primary or subsidiary diagnostic code of corresponding disorders. Detailed definitions of the outcomes are described in Table 2.

Baseline covariates

Baseline covariates were age, sex, systolic and diastolic blood pressure, BMI, fasting plasma glucose, total cholesterol, HDL-C, TG, estimated glomerular filtration rate (eGFR), current smoking status, the use of antihypertensive drugs, and comorbidities including type 2 diabetes mellitus (T2DM), hypertension, and Charlson comorbidity index [30]. Subcategories of antihypertensive drugs and the definitions of T2DM and hypertension are listed in Table 1 and 2, respectively. eGFR was computed from serum creatinine (Scr) level following the Chronic Kidney Disease Epidemiology Collaboration equation (eGFR in milliliter per minute per 1.73 m^2 = 141 × min [Scr/k, 1]^a × max [Scr/k, 1]$^{-1.209}$ × 0.993^{age} × 1.018 [if female], where k is 0.7 for females and 0.9 for males, a is –0.329 for females and –0.411 for males, and min signifies the minimum of Scr/k or 1, whereas max signifies the maximum) [31].

Statistical analysis

The participants were categorized based on their LDL-C levels at baseline into one of the six groups (<70, 70–99, 100–129, 130–159, 160–189, and ≥190 mg/dL). Multiple imputation techniques were conducted to manage the missing variables. Added with the imputed data, baseline characteristics were documented in descriptive statistics according to each LDL-C subcategory. Categorical variables were presented as numbers and percentages, and continuous variables as means and

standard deviation (SD). To compare the baseline characteristics of the study participants based on their LDL levels, analysis of variance (ANOVA) or chi-square test was used in addition to post-hoc analysis with Bonferroni's adjustment.

Incidence rates were presented as events per 1,000 person-years with the estimation of a 95% confidence interval (CI). Multivariable Cox proportional hazard regressions were performed to evaluate the relationship between LDL-C and incidence rates of each outcome, adjusting for age (continuously), sex, current smoking status, systolic and diastolic blood pressure (continuously), BMI (continuously), eGFR (continuously), Charlson comorbidity index (continuously), and the use of antihypertensive drugs at baseline. A subgroup with LDL-C levels of 70–99 mg/dL was selected as the reference group.

Age-specific adjusted hazard ratios (aHRs) and 95% CI for risk of ASCVD and CVD-related mortality in association with baseline LDL-C were also calculated via Cox regression. Subjects were divided into four age groups (<50, 50-59, 60-69, and ≥70 years) for the assessment of age-related risk. We assessed interaction of sex, current smoking status, BMI (<25 and ≥25kg/m²), the use of antihypertensive drugs, and Charlson comorbidity index (<4 and ≥4). Lastly, subgroup analyses in patients with T2DM were conducted for the incidence rates and aHRs of outcomes according to the categorization of LDL-C.

Data were analyzed with a statistical significance level of P-value <0.05. All analyses were performed using the SAS Enterprise Guide software (version 7.1, SAS Institute, Inc., Cary, NC, USA).

Results

Baseline clinical and biochemical characteristics of the study populations

The final cohort composed of 285,119 Korean adults who satisfied the inclusion criteria, as shown in Figure 1. 21,334 subjects were excluded because they had already been diagnosed CVD. 75,128 subjects were excluded as they were taking lipid-lowering drugs. The baseline characteristics of the overall population categorized by LDL-C are summarized in Table 3. A subgroup with LDL-C ≥190 mg/dL accounted for 2.4% (n = 6,718), 160–189 mg/dL for 9.0% (n = 25,687), 130–159 mg/dL for 26.6% (n = 75,981), 100–129 mg/dL for 37.2% (n = 105,952), 70–99 mg/dL for 20.2% (n = 57,562), and <70 mg/dL for 4.6% (n = 13,219) of the total participants. The mean age was 58.4 years (SD, 8.7). The overall proportion of men was 55.2% which tended to be lower in the subgroup of higher LDL-C (68.8% in LDL-C <70 mg/dL vs. 39.8% in LDL-C ≥190 mg/dL). The average of baseline LDL-C level was 121.5 mg/dL (SD, 36.4). Patients with T2DM comprised 7.5% (n = 21,258) of the entire population. Unexpectedly, individuals with the lowest LDL-C levels displayed significantly higher T2DM proportion than any other group (13.6% in LDL-C <70 mg/dL vs. 6.0% in LDL-C ≥190 mg/dL). Likewise, the percentages of other comorbidities and current smokers were the largest in the least LDL-C group.

The risk of primary and secondary outcomes

The incidence rates and aHRs of ASCVD, MI, stroke, HF, and CVD-related mortality classified by LDL-C are demonstrated in Table 4. During a median follow-up of 6.44 years, the first ASCVD developed in 8,996 participants (3.2%) with incidence rates of 5.63 (95% CI, 5.37–5.89) and 7.48 (95% CI, 6.65–8.39) per 1,000 person-years for individuals with LDL-C 70–99 and ≥190 mg/dL, respectively. The incidence rates between LDL-C subgroups showed significant differences overall for every outcome. Surprisingly, subjects with LDL-C <70 mg/dL presented non-significant but greater risk compared with the reference group of LDL-C 70–99 mg/dL for all the outcomes. Excluding the least LDL-C group, the risk of ASCVD and each of its components exhibited generally upward trends following increasing LDL-C.

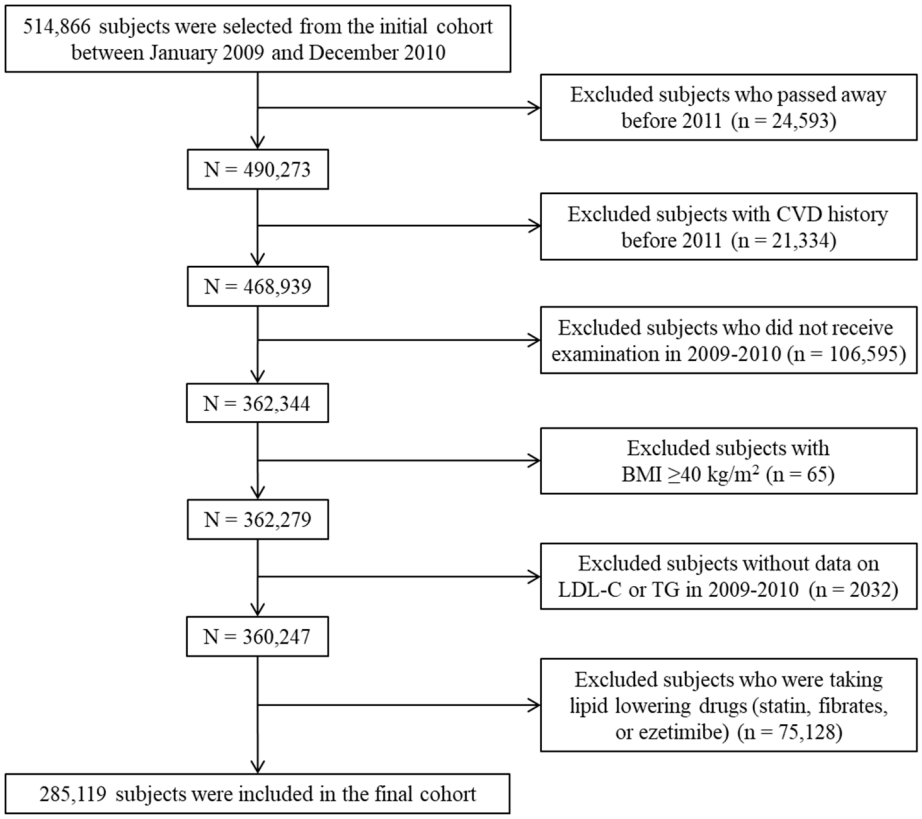

Figure 1. Flow diagram of selection of the study population from the Korean NHIS-HEALS database.

CVD, cardiovascular disease; BMI, body mass index; LDL-C, LDL cholesterol; TG, triglycerides.

Subgroup analysis

Subgroup analysis indicated that sex, current smoking status, and the use of antihypertensive drugs were significantly associated with ASCVD risk concerning LDL-C as described in Table 5. In contrast, the difference in ASCVD risk among the age groups was not significant (*P* for interaction = 0.62; Table 5 and Figure 2). All age groups displayed predominantly positive relationships between LDL-C and ASCVD risk with statistical significance from LDL-C of ≥160 mg/dL, excluding subjects with LDL-C <70 mg/dL whose risk was equal to or nonsignificantly higher than the reference group. Compared with the reference group, the risk of ASCVD in the subgroup of highest LDL-C was similar between the subjects aged <50 years and the subjects aged ≥70 years (aHR, 1.90 [95% CI, 1.52–2.38] and aHR, 1.86 [95% CI, 1.30–2.68], respectively). The association of CVD-related mortality and LDL-C was significantly affected by sex and BMI but not by age (Table 6). Unlike ASCVD risk, the risk of CVD-related mortality did not differ following LDL-C in almost all age categories.

Subgroup analysis in T2DM patients

The baseline characteristics of 21,258 patients with T2DM are summarized in Table 7. The proportion of individuals with LDL-C ≥190 mg/dL was 1.9% (n = 404), that with 160–189 mg/dL was 20.9% (n = 4,441), that with 130–159 mg/dL was 6.8% (n = 1,443), that with 100–129 mg/dL was 36.0% (n = 7,654), that with 70–99 mg/dL was 26.0% (n = 5,523), and that with <70 mg/dL was 8.4% (n = 1,793). The mean age and average LDL-C level were 62.6 ± 8.9 years and 113.7 ± 37.0 mg/dL, respectively. In addition, 1,520 patients with T2DM (7.2%) experienced ASCVD during the follow-up period (Table 8). The incidence rate of ASCVD was significantly higher in the subgroup with LDL-C ≥190 mg/dL than in the reference group (19.83 [95% CI, 14.52–26.45] vs. 12.05 [95% CI, 10.86–13.33] per 1,000 person-years). The outcomes that displayed significant associations between the incidence risk and baseline LDL-C in overall were ASCVD, MI, and HF, although no LDL-C subgroup of HF significantly differed from the reference group. In line with the findings in the overall population, T2DM patients with LDL-C <70 mg/dL had greater incidence rates compared to the reference group for all outcomes except the CVD-related mortality. Similar to the total participants,

age-specific association of ASCVD risk and LDL-C in T2DM patients displayed no difference (*P* for interaction = 0.31; Table 9 and Figure 2). Furthermore, none of the other factors did affect the association of ASCVD risk and LDL-C.

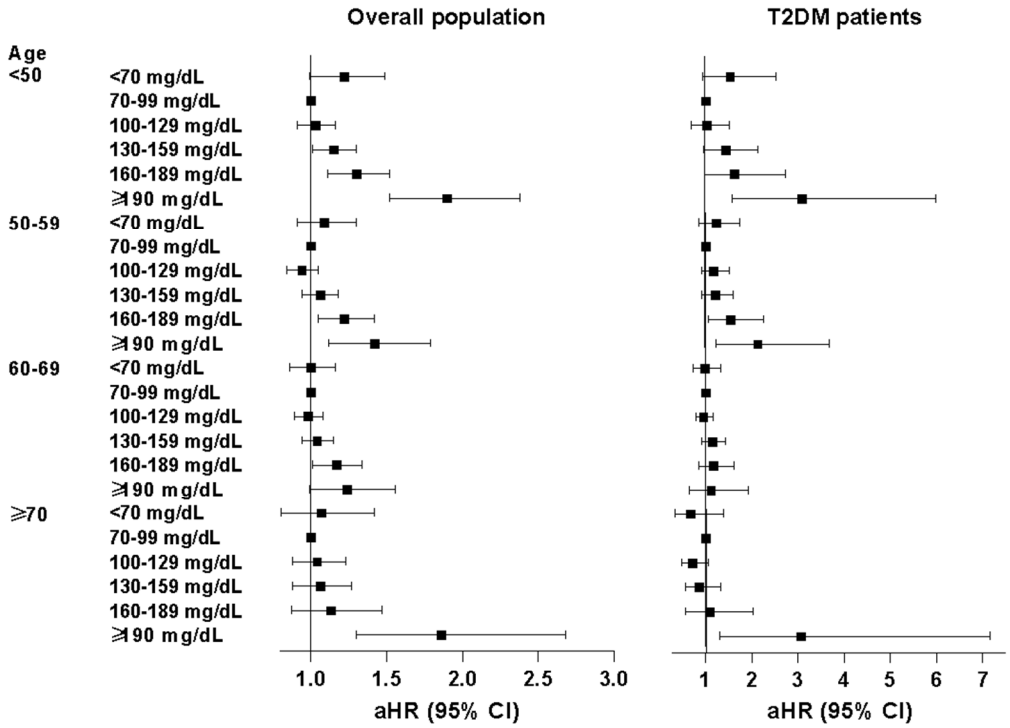

Figure 2. Age-specific aHR for risk of ASCVD with increasing LDL-C in the overall population and T2DM patients by using multivariable Cox regressions.

HR was adjusted for age, sex, smoking status, systolic/diastolic blood pressure, body mass index, estimated glomerular filtration rate, Charlson comorbidity index, and the use of antihypertensive drugs. P for interaction was 0.620 and 0.306 for the overall population and T2DM patients, respectively. aHR, adjusted hazard ratio; ASCVD, atherosclerotic cardiovascular disease; LDL-C, LDL cholesterol; T2DM, type 2 diabetes mellitus.

Discussion

A large-scale cohort study representative of contemporary Korean nationals demonstrated that a higher risk of ASCVD according to increasing LDL-C was not different between people aged >70 years and younger adults, in subjects without CVD history and not taking lipid-lowering drugs. A subgroup analysis in patients with T2DM reiterated the result. The finding of the current study conflicts with previous studies that refuted the increased risk of ASCVD in the elderly with elevated cholesterol levels. A prospective cohort study of 997 participants aged >70 years manifested that high total cholesterol along with low HDL-C had no significant relationship with cardiovascular outcomes [12]. Likewise, only individuals aged <70 years exhibited a significant association between high total cholesterol and elevated MI risk in a population-based case-control study in Sweden [13]. LDL-C was rather inversely correlated with all-cause mortality in 92% of cohorts in a meta-analysis with individuals aged ≥60 years [14]. Several studies have reported that the relationship degree gradually abated with increasing age even if the positive association of total cholesterol or LDL-C with ASCVD risk did exist in older people [15-16]. The Copenhagen City Heart Study indicated that total cholesterol-related risk of ischemic heart disease (IHD) diminished following increasing age, resulting in no significant association in subjects aged >80 years [15]. Likewise, a meta-analysis of 61 prospective studies conducted by the Prospective Studies Collaboration demonstrated that every 1.0 mmol/L (equivalent to approximately 18 mg/dL) decrease in total cholesterol correlated with 56%, 34%, and 17% lower IHD-related mortality in participants aged 40–49, 50–69, and 70–89 years, respectively [16].

The reason for the disagreement between the result of the current and previous studies regarding cholesterol-related ASCVD risk in the elderly has yet to be clarified. One of the possible explanations may be the enhancement in medical characteristics of the older age groups. Contemporary populations with the same age group display prolonged life expectancy and fewer morbidities. Indeed, age-specific analysis of the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY OUTCOMES) trial, which evaluated the prevention of major adverse cardiovascular event (MACE) with alirocumab between 2012 and 2018, displayed

that MACE was further reduced with advancing age without compromising safety profile [32].

No completed RCT exclusively incorporating the elderly has addressed the benefit of statin treatment for primary prevention until now. Therefore, age-specific secondary analysis of landmark studies has been the alternative for clinical evidence in the aged. A post hoc analysis with the extraction of people aged ≥65 years without ASCVD history was conducted from the Lipid-Lowering Trial (LLT) component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized experiment performed at 513 centers comparing the effect of pravastatin and placebo from 1994 to 2002 [17]. Consequently, no cardiovascular advantage was identified in the pravastatin group. However, a considerable crossover rate of 29% from the placebo to the statin group in ALLHAT-LLT would have mitigated the difference between the two groups. Counteracting this finding, Paul et al. reported that rosuvastatin ameliorated ASCVD risk by 26% in adults aged >70 years through age-stratified analysis of the two primary prevention statin trials, Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin and Heart Outcomes Prevention Evaluation [18]. An individual-level meta-analysis of 28 RCTs also validated that participants aged 65–70 years benefited from statin with 39% risk reduction of major vascular events per 1 mmol/L lower levels of LDL-C even though the effect was nonsignificant in adults aged >70 years [19]. The efficacy of lipid-lowering drugs including statin as well as ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor for the prevention of major vascular events similarly had no difference between subjects aged ≥75 years and those aged <75 years, which was corroborated in a meta-analysis by Gencer et al. [33].

The scarcity of explicit evidence on lowering LDL-C to prevent primary ASCVD in the elderly has led to remarkably heterogeneous recommendations among five major guidelines of statin treatment. Although the 2018 American Heart Association/American College of Cardiology (AHA/ACC) Cholesterol Guidelines suggested that risk assessment and statin use may be considered in adults aged ≥75 years with a class IIb recommendation [20], the 2019 ACC/AHA Primary Prevention Guidelines withdrew from approving statin therapy in similar age group [21]. The 2016 US Preventive Services Task Force (USPSTF) also

opposed statin use for people aged ≥75 years [22]. Contrarily, the recent Canadian Cardiovascular Society Guidelines in 2021 and 2019 European Society of Cardiology/European Atherosclerosis Society Guidelines supported maintaining low cholesterol levels regardless of age [23, 24]. The 2014 UK National Institute for Health and Care Excellence Guidelines further strongly emphasized the reduction of cholesterol up to 84 years of age and still with a class IIa recommendation in people aged ≥85 years [25]. This obvious variation of guidance extends to disorganized cholesterol management for the elderly in actual practice.

Population-based studies implemented between the late 1990s and early 2010s in the UK, USA, and the Netherlands have established that the prescription rate of lipid-lowering drugs decreased after 75 years of age not only without prior CVD event but also with CVD history [34-36]. Despite the higher ASCVD incidence rate in older patients [37], the general reluctance of using lipid-lowering drugs in this population may be explained by skepticism about gains and losses. Distinct features of the elderly (e.g., intrinsically limited life expectancy, various comorbidities, polypharmacy causing drug–drug interaction, and concerns about adverse reactions due to impaired metabolism) are clinical hurdles for pursuing low cholesterol levels. Nevertheless, the current study substantiated that elevated ASCVD risk owing to high LDL-C persisted in adults aged >70 years. The relative risk of ASCVD in the highest LDL-C concerning lower LDL-C was comparable between the <50- and ≥70-year-old groups. This result may bring into a higher absolute burden of ASCVD in combination with a greater occurrence rate in older age groups [37]. Furthermore, doubts regarding the side effects of lipid-lowering drugs for the elderly are questionable. No additional safety issue was found with ezetimibe or ezetimibe plus statin treatment in subjects aged ≥75 years compared with their younger counterparts [38]. A meta-analysis of adults aged ≥65 years determined that statin did not raise the risk of myalgia and rhabdomyolysis compared with placebo [39]. Individuals aged ≥75 years were observed to have even fewer events of myalgia than younger individuals in community practice in the USA [40]. Accumulating evidence has also confirmed no significant statin influence on cognitive function in elderly people [41-43]. Lastly, the association between LDL-C levels and ASCVD risk in older people is not as strong as in younger groups possibly due to the poor nutrition and comorbidities in the elderly

[44]. Altogether, maintaining low LDL-C levels to avoid ASCVD still matters in the older population that is at least equivalent to younger individuals.

Meanwhile, the group with the least LDL-C showed not only the highest percentages of comorbidities and current smokers but also a nonsignificantly greater risk of all outcomes than the reference group in the current study. An analogous phenomenon was identified in subgroup analysis with T2DM patients. This result partly conforms to the analysis of electronic health records in Vanderbilt University Medical Center, which revealed that people with LDL-C ≤60 mg/dL in the absence of statin were more likely to suffer from T2DM than those with higher LDL-C [45]. More studies are needed concerning causality whether unrecorded characteristics (e.g., poor nutritional status and health behavior) contributed to low LDL-C levels or low LDL-C itself is related to the progression of morbidities, which is beyond the scope of the current study.

This study has some limitations. First, a retrospective study design has made it available to only assume associations. However, implementing a prospective trial neglecting untreated LDL-C to examine its causative role in ASCVD development is impractical. Alternatively, the STAtins for Reducing Events in the Elderly trial is currently in progress to evaluate the efficacy and safety of atorvastatin in adults aged ≥70 years for primary prevention. Second, these results may not be generalizable for every nation with varying socioeconomic conditions. Nevertheless, this report is worthy because of the few studies concerning the age-specific analysis of LDL-C and CVD outcomes based on robust nationwide cohorts, especially in the Asian population. Third, the follow-up period was relatively short. However, the duration was supposed to be sufficient to compare the trends between the age groups because most age groups already showed significant differences in the primary outcome between LDL-C subcategories. Fourth, the diagnosis of morbidities and medications were defined by ICD-10-CM codes, which may have been incorrectly categorized.

Despite the limitations, the strength of this research is that it used a large-scale, population-based dataset of 285,119 subjects including 8,629 adults aged ≥70 years. Moreover, participants were restricted to the primary prevention group for whom the unified recommendation has not been established. Furthermore, individuals taking lipid-lowering drugs were excluded to eliminate the effect of related agents.

Lastly, a subgroup analysis was performed in T2DM patients who are classified to the high-risk groups of CVD in lipid management guidelines.

Conclusively, this nationwide cohort study of adults who had no previous CVD history and were not prescribed lipid-lowering drugs determined that elevated LDL-C was significantly correlated with a greater risk of ASCVD in people aged ≥70 years, which was comparable with the risk in younger adults. This finding spotlights the necessity of settling intensive guidance on LDL-C levels for primary CVD prevention in the elderly. Overlooking high LDL-C because of the advanced chronological age should no longer be taken for granted even though weighing risk and benefit is imperative for managing lipid profile particularly in the older population.

Table 1. Subcategories of lipid-lowering and antihypertensive drugs

Lipid lowering drugs	Statins	Simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, rosuvastatin, and pitavastatin
	Ezetimibe	
	Fibrates	Bezafibrate, ciprofibrate, clinofibrate, etofibrate, and fenofibrate
Antihypertensive drugs	Angiotensin receptor blockers	Losartan, eprosartan, valsartan, irbesartan, candesartan, telmisartan, olmesartan, and fimasartan
	Angiotensin-converting enzyme inhibitors	Captopril, enalapril, lisinopril, perindopril, ramipril, quinapril, benazepril, cilazapril, fosinopril, moexipril, temocapril, zofenopril, and imidapril
	Beta-blockers	Propranolol, carteolol, metoprolol, atenolol, S-atenolol, betaxolol, bevantolol, bisoprolol, celiprolol, nebivolol, and carvedilol
	Calcium-channel blockers	S-amlodipine, amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, lacidipine,

	nilvadipine, manidipine, lercanidipine, cilnidipine, benidipine, efonidipine, and barnidipine
Diuretics	Furosemide, hydrochlorothiazide, chlorthalidone, metolazone, indapamide, triamterene, and spironolactone

Table 2. Definitions of outcomes and covariates

	ICD-10-CM codes	Diagnostic definition
MI	I21–I23	Admission ≥1
Stroke	I60–I64, I690–I694, G45	Admission ≥1
HF	I50	Admission ≥1
CVD-related mortality	I00–I99	
T2DM	E11–14	Admission or outpatient department ≥1 and antidiabetic medication (sulfonylureas, biguanides, α-glucosidase inhibitors, thiazolidinediones, meglitinide, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and insulin)
Hypertension	I10–15	Admission or outpatient department ≥1 and antihypertensive medication (angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, beta blockers, calcium-channel blockers, and diuretics)

The diagnostic code is based on ICD-10-CM. ICD-10-CM, *International Classification of Diseases, Tenth Edition, Clinical Modification*; MI, myocardial infarction; HF, heart failure; CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus.

Table 3. Baseline characteristics classified by LDL-C in the overall population

	Baseline LDL-C (mg/dL)						
	<70	70–99	100–129	130–159	160–189	≥190	Overall
	(n = 13,219)	(n = 57,562)	(n = 105,952)	(n = 75,981)	(n = 25,687)	(n = 6,718)	P-value
Age, years	59.7 (9.2)	58.9 (9.1)	58.3 (8.7)	58.0 (8.4)	57.9 (8.3)	58.3 (8.4)	<0.001
<50, N (%)	6,096 (46.1)	29,086 (50.5)	56,496 (53.3)	41,510 (54.6)	14,171 (55.2)	3,584 (53.3)	
50–59, N (%)	3,783 (28.6)	15,851 (27.5)	29,286 (27.6)	21,515 (28.3)	7,366 (28.7)	1,941 (28.9)	
60–69, N (%)	2,801 (21.2)	10,496 (18.2)	17,005 (16.0)	10,980 (14.5)	3,524 (13.7)	999 (14.9)	
≥70, N (%)	539 (4.1)	2,129 (3.7)	3,165 (3.0)	1,976 (2.6)	626 (2.4)	194 (2.9)	
Men, N (%)	9,096 (68.8)	34,732 (60.3)	59,693 (56.3)	39,270 (51.7)	12,002 (46.7)	2,671 (39.8)	<0.001
Women, N (%)	4,123 (31.2)	22,830 (39.7)	46,259 (43.7)	36,711 (48.3)	13,685 (53.3)	4,047 (60.2)	<0.001
SBP, mmHg	127.3 (16.1)	125.5 (15.7)	125.8 (15.2)	126.5 (15.3)	127.0 (15.0)	127.7 (15.9)	<0.001
DBP, mmHg	78.8 (10.3)	77.8 (10.2)	78.2 (10.1)	78.7 (10.0)	79.0 (9.9)	79.3 (10.2)	<0.001
BMI, kg/m²	23.5 (3.1)	23.5 (2.9)	23.8 (2.8)	24.1 (2.8)	24.4 (2.8)	24.5 (2.8)	<0.001
FPG, mg/dL	104.0 (29.6)	100.7 (25.0)	100.5 (23.4)	101.0 (23.0)	102.0 (24.1)	104.0 (27.2)	<0.001
TC, mg/dL	150.3 (28.8)	169.1 (20.0)	194.2 (17.6)	221.9 (17.0)	251.2 (17.4)	287.1 (33.7)	<0.001
LDL-C, mg/dL	55.3 (13.9)	87.4 (8.3)	114.8 (8.5)	142.7 (7.4)	171.1 (8.2)	221.2 (97.2)	<0.001
HDL-C, mg/dL	55.5 (33.6)	53.9 (22.5)	53.5 (22.3)	53.5 (25.1)	53.4 (23.0)	55.7 (36.8)	<0.001
TG, mg/dL	203.9 (167.8)	141.6 (98.3)	132.8 (79.1)	135.6 (73.1)	141.0 (72.5)	149.9 (82.5)	<0.001

eGFR, mL/min/1.73 m²	82.5 (18.9)	81.5 (18.8)	80.5 (19.2)	79.6 (19.3)	78.9 (19.1)	78.5 (18.3)	<0.001
Medical history, N (%)							
T2DM	1,793 (13.6)	5,523 (9.6)	7,654 (7.2)	4,441 (5.8)	1,443 (5.6)	404 (6.0)	<0.001
Hypertension	4,843 (36.6)	18,162 (31.6)	30,777 (29.0)	21,072 (27.7)	6,751 (26.3)	1,871 (27.9)	<0.001
Current smoker	3,449 (26.1)	11,311 (19.7)	18,984 (17.9)	12,950 (17.0)	4,338 (16.9)	1,069 (15.9)	<0.001
Charlson comorbidity index	1.34 (1.7)	1.08 (1.50)	0.94 (1.35)	0.86 (1.26)	0.85 (1.25)	0.89 (1.28)	<0.001
Antihypertensive drugs	5,521 (41.8)	20,958 (36.4)	35,822 (33.8)	24,809 (32.7)	8,066 (31.4)	2,222 (33.1)	<0.001

Data are expressed in mean (SD) unless otherwise indicated. LDL-C, LDL cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FPG, fasting plasma glucose; TC, total cholesterol; HDL-C, HDL cholesterol; TG, triglycerides; eGFR, estimated glomerular filtration rate; T2DM, type 2 diabetes mellitus.

Table 4. The numbers, incidence rates, and aHRs of ASCVD, MI, stroke, HF, and CVD-related mortality classified by LDL-C

	Baseline LDL-C (mg/dL)						
	<70 (n = 13,219)	70–99 (n = 57,562)	100–129 (n = 105,952)	130–159 (n = 75,981)	160–189 (n = 25,687)	≥190 (n = 6,718)	Overall (N = 285,119)
ASCVD							
Number of events (%)	537 (4.1)	1,878 (3.3)	3,115 (2.9)	2,311 (3.0)	863 (3.4)	292 (4.3)	8,996 (3.2)
Incidence per 1,000 person-years (95% CI)	7.04 (6.45–7.66)	5.63 (5.37–5.89)	5.06 (4.88–5.24)	5.22 (5.01–5.44)	5.77 (5.39–6.16)	7.48 (6.65–8.39)	
aHR (95% CI)*	1.08 (0.98–1.18)	1.00 (ref)	0.98 (0.93–1.04)	1.07 (1.01–1.14)	1.21 (1.12–1.31)	1.52 (1.34–1.72)	
P-value	0.137	<0.001†	0.558	0.030	<0.001	<0.001	
MI							
Number of events (%)	78 (0.6)	253 (0.4)	486 (0.5)	424 (0.6)	197 (0.8)	82 (1.2)	1,520 (0.5)
Incidence per 1,000 person-years (95% CI)	1.01 (0.80–1.26)	0.75 (0.66–0.85)	0.78 (0.71–0.85)	0.95 (0.86–1.04)	1.30 (1.13–1.50)	2.07 (1.65–2.57)	
aHR (95% CI)*	1.10 (0.85–1.42)	1.00 (ref)	1.17 (1.00–1.36)	1.53 (1.31–1.79)	2.23 (1.85–2.69)	3.62 (2.82–4.66)	
P-value	0.458	<0.001†	0.049	<0.001	<0.001	<0.001	
Stroke							
Number of events (%)	467 (3.5)	1,644 (2.9)	2,660 (2.5)	1,916 (2.5)	675 (2.6)	214 (3.2)	7,576 (2.7)
Incidence per 1,000 person-years (95% CI)	6.11 (5.57–6.69)	4.92 (4.68–5.16)	4.31 (4.15–4.48)	4.32 (4.13–4.52)	4.50 (4.16–4.85)	5.46 (4.75–6.24)	

aHR (95% CI)*	1.08 (0.97–1.20)	1.00 (ref)	0.96 (0.90–1.02)	1.00 (0.94–1.07)	1.06 (0.97–1.16)	1.23 (1.06–1.42)	
P-value	0.143	<0.001†	0.140	0.929	0.205	0.005	
HF							
Number of events (%)	101 (0.8)	318 (0.6)	478 (0.5)	289 (0.4)	96 (0.4)	42 (0.6)	1,324 (0.5)
Incidence per 1,000 person-years (95% CI)	1.31 (1.06–1.59)	0.94 (0.84–1.05)	0.77 (0.70–0.84)	0.65 (0.57–0.73)	0.63 (0.51–0.77)	1.06 (0.76–1.43)	
aHR (95% CI)*	1.19 (0.95–1.48)	1.00 (ref)	0.92 (0.80–1.06)	0.82 (0.70–0.97)	0.82 (0.65–1.03)	1.25 (0.90–1.73)	
P-value	0.137	<0.001†	0.230	0.019	0.082	0.182	
CVD-related mortality							
Number of events (%)	101 (0.8)	337 (0.6)	470 (0.4)	330 (0.4)	142 (0.6)	41 (0.6)	1,421 (0.5)
Incidence per 1,000 person-years (95% CI)	1.30 (1.06–1.58)	1.00 (0.89–1.11)	0.75 (0.69–0.83)	0.74 (0.66–0.82)	0.94 (0.79–1.10)	1.03 (0.74–1.40)	
aHR (95% CI)*	1.07 (0.86–1.34)	1.00 (ref)	0.89 (0.78–1.03)	0.99 (0.85–1.15)	1.33 (1.09–1.62)	1.39 (1.00–1.92)	
P-value	0.546	<0.001†	0.118	0.866	0.005	0.049	

aHR, adjusted hazard ratio; ASCVD, atherosclerotic cardiovascular disease; MI, myocardial infarction; HF, heart failure; CVD, cardiovascular disease; LDL-C, LDL cholesterol.

*Adjusted for age, sex, smoking status, systolic/diastolic blood pressure, body mass index, estimated glomerular filtration rate, Charlson comorbidity index, and the use of antihypertensive drugs.

†P-value of reference group (LDL-C of 70–99 mg/dL) signifies the overall P-value of differences among LDL-C groups.

Table 5. Risk of ASCVD with categorization of baseline LDL-C by age, sex, smoking status, BMI (<25 and ≥25 kg/m²), the use of antihypertensive drugs, and Charlson comorbidity index (<4 and ≥4)

	Baseline LDL-C (mg/dL)												
	<70		70–99		100–129		130–159		160–189		≥190		P for interaction
	aHR (95% CI)*	P-value	aHR (95% CI)*	P-value†	aHR (95% CI)*	P-value	aHR (95% CI)*	P-value	aHR (95% CI)*	P-value	aHR (95% CI)*	P-value	
Age, years													0.620
<50	1.22 (0.99–1.49)	0.061	1.00 (ref)	<0.001	1.03 (0.91–1.16)	0.672	1.15 (1.01–1.30)	0.029	1.30 (1.11–1.52)	0.001	1.90 (1.52–2.38)	<0.001	
50–59	1.09 (0.91–1.30)	0.365	1.00 (ref)	<0.001	0.94 (0.84–1.05)	0.252	1.06 (0.94–1.18)	0.361	1.22 (1.05–1.42)	0.009	1.42 (1.12–1.79)	0.004	
60–69	1.00 (0.86–1.16)	0.981	1.00 (ref)	0.064	0.98 (0.89–1.08)	0.663	1.04 (0.94–1.15)	0.450	1.17 (1.01–1.34)	0.031	1.24 (0.99–1.56)	0.066	
≥70	1.07 (0.80–1.42)	0.660	1.00 (ref)	0.034	1.04 (0.88–1.23)	0.666	1.06 (0.88–1.27)	0.573	1.13 (0.87–1.47)	0.353	1.86 (1.30–2.68)	0.001	
Sex													<0.001
Men	1.13 (1.01–1.27)	0.031	1.00 (ref)	<0.001	1.02 (0.95–1.10)	0.556	1.18 (1.09–1.27)	<0.001	1.38 (1.24–1.54)	<0.001	2.08 (1.76–2.46)	<0.001	
Women	0.98 (0.82–1.17)	0.809	1.00 (ref)	0.445	0.91 (0.83–1.00)	0.042	0.91 (0.83–1.01)	0.070	1.01 (0.89–1.14)	0.942	1.08 (0.90–1.30)	0.406	
Current smoker													0.001
No	1.07 (0.95–1.20)	0.284	1.00 (ref)	<0.001	0.97 (0.91–1.04)	0.378	1.02 (0.95–1.10)	0.524	1.16 (1.05–1.27)	0.003	1.33 (1.14–1.54)	<0.001	
Yes	1.12 (0.93–1.34)	0.226	1.00 (ref)	0.001	1.01 (0.89–1.14)	0.933	1.22 (1.08–1.39)	0.002	1.41 (1.19–1.67)	<0.001	2.33 (1.83–2.96)	<0.001	

BMI, kg/m²												0.439
<25	1.09 (0.97–1.23)	0.128	1.00 (ref)	<0.001	0.98 (0.92–1.05)	0.604	1.07 (0.99–1.16)	0.079	1.19 (1.08–1.32)	0.001	1.68 (1.44–1.96)	<0.001
≥25	1.04 (0.87–1.23)	0.680	1.00 (ref)	0.001	0.99 (0.89–1.09)	0.769	1.07 (0.96–1.19)	0.209	1.23 (1.08–1.40)	0.002	1.30 (1.06–1.60)	0.012
Antihypertensive drugs												0.019
No	1.01 (0.86–1.19)	0.866	1.00 (ref)	<0.001	1.07 (0.98–1.17)	0.134	1.12 (1.02–1.23)	0.016	1.35 (1.20–1.52)	<0.001	1.70 (1.42–2.04)	<0.001
Yes	1.10 (0.98–1.24)	0.108	1.00 (ref)	<0.001	0.92 (0.86–1.00)	0.036	1.04 (0.96–1.13)	0.376	1.10 (0.98–1.23)	0.095	1.38 (1.17–1.64)	<0.001
Charlson comorbidity index												0.554
<4	1.08 (0.97–1.21)	0.141	1.00 (ref)	<0.001	0.99 (0.93–1.06)	0.792	1.07 (1.00–1.15)	0.041	1.21 (1.11–1.32)	<0.001	1.53 (1.34–1.75)	<0.001
≥4	1.04 (0.84–1.29)	0.728	1.00 (ref)	0.067	0.94 (0.81–1.09)	0.374	1.08 (0.92–1.28)	0.352	1.22 (0.97–1.54)	0.094	1.41 (0.98–2.03)	0.062

ASCVD, atherosclerotic cardiovascular disease; LDL-C, LDL cholesterol; BMI, body mass index; aHR, adjusted hazard ratio.

*Adjusted for age, sex, smoking status, systolic/diastolic blood pressure, body mass index, estimated glomerular filtration rate, Charlson comorbidity index, and the use of antihypertensive drugs.

†P-value of reference group (LDL-C of 70–99 mg/dL) signifies the overall P-value of differences among LDL-C groups.

Table 6. Risk of CVD-related mortality with categorization of baseline LDL-C by age, sex, smoking status, BMI (<25 and ≥25 kg/m²), the use of antihypertensive drugs, and Charlson comorbidity index (<4 and ≥4)

	Baseline LDL-C (mg/dL)												
	<70		70–99		100–129		130–159		160–189		≥190		P for interaction
	aHR (95% CI)*	P-value	aHR (95% CI)*	P-value †	aHR (95% CI)*	P-value	aHR (95% CI)*	P-value	aHR (95% CI)*	P-value	aHR (95% CI)*	P-value	
Age, years													0.917
<50	1.07 (0.53–2.15)	0.842	1.00 (ref)	0.161	0.81 (0.53–1.21)	0.305	1.02 (0.67–1.55)	0.910	1.55 (0.95–2.54)	0.081	0.94 (0.33–2.62)	0.901	
50–59	1.26 (0.75–2.13)	0.382	1.00 (ref)	0.297	0.85 (0.60–1.21)	0.374	1.11 (0.78–1.59)	0.558	1.36 (0.86–2.16)	0.193	0.96 (0.38–2.39)	0.922	
60–69	0.97 (0.69–1.36)	0.866	1.00 (ref)	0.043	0.87 (0.70–1.08)	0.209	0.97 (0.76–1.23)	0.779	1.31 (0.97–1.79)	0.083	1.55 (0.96–2.50)	0.075	
≥70	1.16 (0.77–1.75)	0.485	1.00 (ref)	0.354	1.00 (0.77–1.29)	0.997	0.90 (0.67–1.21)	0.489	1.17 (0.78–1.74)	0.447	1.67 (0.94–2.99)	0.083	
Sex													0.035
Men	1.13 (0.87–1.46)	0.356	1.00 (ref)	<0.001	0.89 (0.75–1.05)	0.165	1.08 (0.89–1.30)	0.165	1.66 (1.30–2.13)	<0.001	1.73 (1.11–2.71)	0.017	
Women	0.94 (0.59–1.49)	0.786	1.00 (ref)	0.758	0.89 (0.70–1.13)	0.336	0.83 (0.64–1.08)	0.169	0.94 (0.68–1.31)	0.724	1.07 (0.66–1.73)	0.785	
Current smoker													0.675
No	1.11 (0.84–1.46)	0.469	1.00 (ref)	0.025	0.95 (0.80–1.12)	0.503	0.95 (0.79–1.14)	0.572	1.34 (1.06–1.69)	0.013	1.26 (0.85–1.87)	0.249	
Yes	1.05 (0.71–1.56)	0.800	1.00 (ref)	0.036	0.82 (0.62–1.08)	0.162	1.04 (0.78–1.41)	0.777	0.40 (0.95–2.08)	0.091	1.74 (0.93–3.26)	0.084	

BMI, kg/m²													0.005
<25	1.12 (0.88–1.43)	0.342	1.00 (ref)	0.009	0.81 (0.69–0.95)	0.010	0.93 (0.78–1.11)	0.435	1.08 (0.85–1.38)	0.535	1.28 (0.86–1.90)	0.228	
≥25	0.82 (0.46–1.46)	0.501	1.00 (ref)	<0.001	1.26 (0.93–1.70)	0.139	1.24 (0.90–1.71)	0.189	2.19 (1.53–3.14)	<0.001	1.84 (1.03–3.28)	0.040	
Antihypertensive drugs													0.065
No	1.25 (0.87–1.79)	0.230	1.00 (ref)	0.002	0.78 (0.61–0.99)	0.039	1.08 (0.85–1.38)	0.515	1.40 (1.02–1.91)	0.035	0.96 (0.50–1.83)	0.904	
Yes	0.98 (0.74–1.31)	0.914	1.00 (ref)	0.018	0.96 (0.81–1.15)	0.679	0.93 (0.76–1.13)	0.434	1.28 (0.99–1.65)	0.059	1.62 (1.11–2.37)	0.013	
Charlson comorbidity index													0.071
<4	1.22 (0.96–1.56)	0.101	1.00 (ref)	0.001	0.90 (0.77–1.05)	0.163	1.04 (0.88–1.23)	0.641	1.32 (1.06–1.64)	0.012	1.33 (0.93–1.92)	0.122	
≥4	0.57 (0.32–1.04)	0.065	1.00 (ref)	0.025	0.91 (0.66–1.26)	0.562	0.71 (0.47–1.07)	0.097	1.41 (0.87–2.28)	0.161	1.71 (0.82–3.56)	0.150	

CVD, cardiovascular disease; LDL-C, LDL cholesterol; BMI, body mass index; aHR, adjusted hazard ratio.

*Adjusted for age, sex, smoking status, systolic/diastolic blood pressure, body mass index, estimated glomerular filtration rate, Charlson comorbidity index, and the use of antihypertensive drugs.

† P-value of reference group (LDL-C of 70–99 mg/dL) signifies the overall P-value of differences among LDL-C groups.

Table 7. Baseline characteristics classified by LDL-C in T2DM patients

	Baseline LDL-C (mg/dL)						
	<70	70–99	100–129	130–159	160–189	≥190	Overall
	(n = 1,793)	(n = 5,523)	(n = 7,654)	(n = 4,441)	(n = 1,443)	(n = 404)	P-value
Age, years	62.7 (8.7)	63.2 (8.8)	62.7 (8.9)	62.2 (8.9)	61.5 (9.0)	61.7 (8.9)	<0.001
<50, N (%)	523 (29.2)	1,497 (27.1)	2,302 (30.1)	1,483 (33.4)	526 (36.5)	143 (35.4)	
50–59, N (%)	639 (35.6)	2,032 (36.8)	2,746 (35.9)	1,541 (34.7)	478 (33.1)	142 (35.1)	
60–69, N (%)	547 (30.5)	1,682 (30.5)	2,169 (28.3)	1,169 (26.3)	372 (25.8)	102 (25.2)	
≥70, N (%)	84 (4.7)	312 (5.6)	437 (5.7)	248 (5.6)	67 (4.6)	17 (4.2)	
Men, N (%)	1,288 (71.8)	3,765 (68.2)	4,905 (64.1)	2,564 (57.7)	725 (50.2)	159 (39.4)	<0.001
Women, N (%)	505 (28.2)	1,758 (31.8)	2,749 (35.9)	1,877 (42.3)	718 (49.8)	245 (60.6)	<0.001
SBP, mmHg	129.9 (16.5)	129.3 (15.3)	129.8 (15.4)	130.8 (15.5)	131.0 (15.5)	131.4 (16.3)	<0.001
DBP, mmHg	78.9 (10.3)	78.5 (9.9)	79.1 (10.0)	80.0 (9.9)	80.2 (10.0)	79.9 (10.0)	<0.001
BMI, kg/m²	24.3 (3.2)	24.5 (3.1)	24.6 (3.1)	24.9 (3.0)	25.1 (3.1)	25.2 (3.1)	<0.001
FPG, mg/dL	140.4 (50.9)	139.1 (47.8)	141.8 (48.6)	146.2 (49.9)	148.9 (55.1)	158.3 (59.4)	<0.001
TC, mg/dL	149.1 (32.4)	167.9 (22.2)	193.2 (19.2)	221.6 (19.2)	253.1 (21.6)	293.3 (38.9)	<0.001

LDL-C, mg/dL	54.4 (15.0)	86.5 (8.4)	114.2 (8.5)	142.1 (8.4)	170.9 (8.2)	224.7 (93.6)	<0.001
HDL-C, mg/dL	52.4 (39.8)	49.9 (20.8)	49.8 (24.6)	49.8 (21.0)	51.9 (32.3)	55.7 (45.3)	<0.001
TG, mg/dL	226.6 (188.2)	161.0 (107.5)	151.6 (89.0)	153.4 (81.9)	163.9 (94.2)	171.1 (97.0)	<0.001
eGFR, mL/min/1.73 m²	79.0 (19.6)	78.1 (19.3)	77.4 (19.8)	76.8 (19.9)	77.1 (19.3)	77.2 (19.3)	<0.001
Medical history, N (%)							
Hypertension	1,213 (67.7)	3,504 (63.4)	4,626 (60.4)	2,590 (58.3)	823 (57.0)	229 (56.7)	<0.001
Current smoker	423 (23.6)	1,102 (20.0)	1,550 (20.3)	834 (18.8)	255 (17.7)	63 (15.6)	<0.001
Charlson comorbidity index	3.39 (2.1)	3.16 (1.9)	2.97 (1.8)	2.88 (1.9)	2.82 (1.8)	2.84 (1.9)	<0.001
Antihypertensive drugs	1,296 (72.3)	3,708 (67.1)	4,908 (64.1)	2,756 (62.1)	894 (62.0)	252 (62.4)	<0.001

Data are expressed in mean (SD) unless otherwise indicated. T2DM, type 2 diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FPG, fasting plasma glucose; TC, total cholesterol; HDL-C, HDL cholesterol; TG, triglycerides; eGFR, estimated glomerular filtration rate.

Table 8. The numbers, incidence rates, and aHRs of ASCVD, MI, stroke, HF, and CVD-related mortality classified by LDL-C in T2DM patients

	Baseline LDL-C (mg/dL)						
	<70 (n = 1,793)	70–99 (n = 5,523)	100–129 (n = 7,654)	130–159 (n = 4,441)	160–189 (n = 1443)	≥190 (n = 404)	Overall (N = 21,258)
ASCVD							
Number of events (%)	135 (7.5)	378 (6.8)	510 (6.7)	334 (7.5)	117 (8.1)	46 (11.4)	1,520 (7.2)
Incidence per 1,000 person-years (95% CI)	13.42 (11.25–15.88)	12.05 (10.86–13.33)	11.63 (10.64–12.69)	13.15 (11.78–14.64)	14.18 (11.73–16.99)	19.83 (14.52–26.45)	
aHR (95% CI)*	1.09 (0.89–1.32)	1.00 (ref)	0.99 (0.87–1.13)	1.16 (1.00–1.34)	1.32 (1.07–1.63)	1.82 (1.34–2.48)	
P-value	0.407	<0.001†	0.868	0.055	0.010	<0.001	
MI							
Number of events (%)	26 (1.5)	55 (1.0)	89 (1.2)	71 (1.6)	34 (2.4)	16 (4.0)	291 (1.4)
Incidence per 1,000 person-years (95% CI)	2.52 (1.65–3.69)	1.72 (1.29–2.23)	1.99 (1.60–2.45)	2.73 (2.13–3.44)	4.02 (2.79–5.62)	6.69 (3.82–10.86)	
aHR (95% CI)*	1.42 (0.89–2.27)	1.00 (ref)	1.21 (0.87–1.70)	1.75 (1.23–2.50)	2.75 (1.79–4.24)	4.68 (2.67–8.22)	
P-value	0.141	<0.001†	0.265	0.002	<0.001	<0.001	
Stroke							
Number of events (%)	111 (6.2)	329 (6.0)	430 (5.6)	268 (6.0)	84 (5.8)	31 (7.7)	1253 (5.9)
Incidence per 1,000 person-years (95% CI)	10.99 (9.04–13.24)	10.45 (9.35–11.64)	9.77 (8.87–10.74)	10.50 (9.28–11.83)	10.09 (8.05–12.49)	13.17 (8.95–18.69)	

aHR (95% CI)*	1.03 (0.83–1.28)	1.00 (ref)	0.95 (0.83–1.10)	1.06 (0.90–1.24)	1.07 (0.84–1.36)	1.36 (0.94–1.97)	
P-value	0.795	0.417†	0.511	0.523	0.597	0.102	
HF							
Number of events (%)	27 (1.5)	72 (1.3)	81 (1.1)	41 (0.9)	13 (0.9)	8 (2.0)	242 (1.1)
Incidence per 1,000 person-years (95% CI)	2.62 (1.73–3.81)	2.25 (1.76–2.83)	1.81 (1.44–2.25)	1.57 (1.13–2.13)	1.53 (0.82–2.62)	3.31 (1.43–6.51)	
aHR (95% CI)*	1.16 (0.74–1.81)	1.00 (ref)	0.83 (0.60–1.14)	0.74 (0.50–1.09)	0.76 (0.42–1.38)	1.62 (0.78–3.38)	
P-value	0.513	<0.001†	0.249	0.124	0.367	0.198	
CVD-related mortality							
Number of events (%)	18 (1.0)	70 (1.3)	86 (1.1)	42 (0.9)	21 (1.5)	8 (2.0)	245 (1.2)
Incidence per 1,000 person-years (95% CI)	1.74 (1.03–2.75)	2.18 (1.70–2.75)	1.91 (1.53–2.36)	1.61 (1.16–2.17)	2.46 (1.52–3.77)	3.30 (1.42–6.49)	
aHR (95% CI)*	0.76 (0.45–1.27)	1.00 (ref)	0.90 (0.66–1.24)	0.82 (0.56–1.21)	1.40 (0.85–2.28)	1.74 (0.84–3.64)	
P-value	0.292	<0.001†	0.525	0.321	0.183	0.139	

aHR, adjusted hazard ratio; ASCVD, atherosclerotic cardiovascular disease; MI, myocardial infarction; HF, heart failure; CVD, cardiovascular disease; LDL-C, LDL cholesterol; T2DM, type 2 diabetes mellitus.

*Adjusted for age, sex, smoking status, systolic/diastolic blood pressure, body mass index, estimated glomerular filtration rate, Charlson comorbidity index, and the use of antihypertensive drugs.

† P-value of reference group (LDL-C of 70–99 mg/dL) signifies the overall P-value of differences among LDL-C groups.

Table 9. Risk of ASCVD with categorization of baseline LDL-C by age, sex, smoking status, BMI (<25 and ≥25 kg/m²), use of antihypertensive drugs, and Charlson comorbidity index (<4 and ≥4) in T2DM patients

	Baseline LDL-C (mg/dL)												
	<70		70–99		100–129		130–159		160–189		≥190		P for interaction
	aHR (95% CI)*	P-value	aHR (95% CI)*	P-value†	aHR (95% CI)*	P-value	aHR (95% CI)*	P-value	aHR (95% CI)*	P-value	aHR (95% CI)*	P-value	
Age, years													0.306
<50	1.53 (0.93–2.53)	0.096	1.00 (ref)	0.004	1.02 (0.69–1.51)	0.912	1.44 (0.97–2.14)	0.074	1.62 (0.97–2.72)	0.066	3.08 (1.58–5.99)	0.001	
50–59	1.23 (0.86–1.75)	0.268	1.00 (ref)	0.059	1.18 (0.92–1.51)	0.189	1.21 (0.92–1.61)	0.173	1.54 (1.06–2.26)	0.025	2.13 (1.24–3.67)	0.006	
60–69	0.99 (0.74–1.32)	0.938	1.00 (ref)	0.542	0.96 (0.79–1.16)	0.662	1.15 (0.92–1.43)	0.215	1.17 (0.85–1.62)	0.330	1.12 (0.65–1.93)	0.678	
≥70	0.68 (0.33–1.39)	0.293	1.00 (ref)	0.021	0.72 (0.49–1.06)	0.099	0.86 (0.56–1.32)	0.490	1.08 (0.57–2.03)	0.815	3.06 (1.31–7.16)	0.010	
Sex													0.169
Men	1.04 (0.82–1.34)	0.733	1.00 (ref)	0.001	1.08 (0.92–1.28)	0.360	1.25 (1.04–1.52)	0.020	1.55 (1.17–2.05)	0.002	2.08 (1.32–3.28)	0.002	
Women	1.18 (0.85–1.64)	0.311	1.00 (ref)	0.034	0.84 (0.67–1.05)	0.119	1.00 (0.79–127)	0.972	1.06 (0.78–1.45)	0.715	1.54 (1.01–2.35)	0.043	
Current smoker													0.776
No	1.17 (0.93–1.46)	0.179	1.00 (ref)	0.002	0.98 (0.84–1.14)	0.771	1.17 (0.99–1.39)	0.065	1.28 (1.00–1.62)	0.046	1.77 (1.24–2.52)	0.002	
Yes	0.86 (0.56–1.32)	0.498	1.00 (ref)	0.416	0.95 (0.71–1.27)	0.725	1.09 (0.79–1.51)	0.594	1.45 (0.92–2.28)	0.112	1.32 (0.58–3.03)	0.510	

BMI, kg/m²													0.790
<25	1.04 (0.80–1.34)	0.782	1.00 (ref)	0.001	0.96 (0.81–1.14)	0.659	1.10 (0.91–1.34)	0.331	1.38 (1.05–1.81)	0.021	2.04 (1.37–3.05)	0.001	
≥25	1.17 (0.86–1.60)	0.328	1.00 (ref)	0.177	1.03 (0.83–1.27)	0.782	1.23 (0.98–1.55)	0.070	1.25 (0.91–1.73)	0.175	1.58 (0.98–2.56)	0.060	
Antihypertensive drugs													0.720
No	0.81 (0.48–1.36)	0.421	1.00 (ref)	0.079	1.05 (0.79–1.39)	0.740	1.26 (0.93–1.70)	0.144	1.42 (0.93–2.16)	0.103	2.01 (1.07–3.79)	0.030	
Yes	1.14 (0.92–1.41)	0.224	1.00 (ref)	0.003	0.97 (0.84–1.13)	0.712	1.13 (0.95–1.34)	0.166	1.29 (1.01–1.64)	0.038	1.77 (1.24–2.51)	0.002	
Charlson comorbidity index													0.775
<4	1.10 (0.83–1.46)	0.523	1.00 (ref)	0.002	1.03 (0.86–1.24)	0.714	1.23 (1.01–1.50)	0.043	1.29 (0.97–1.70)	0.078	2.13 (1.44–3.15)	<0.001	
≥4	1.07 (0.81–1.41)	0.627	1.00 (ref)	0.109	0.94 (0.77–1.15)	0.533	1.08 (0.86–1.35)	0.511	1.39 (1.02–1.90)	0.038	1.47 (0.89–2.42)	0.131	

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; T2DM, type 2 diabetes mellitus; aHR, adjusted hazard ratio.

*Adjusted for age, sex, smoking status, systolic/diastolic blood pressure, body mass index, estimated glomerular filtration rate, Charlson comorbidity index, and use of antihypertensive drugs.

† P-value of reference group (LDL-C of 70–99 mg/dL) signifies overall P-value of differences among LDL-C groups.

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국문요약

연령에 따른 저밀도지단백-콜레스테롤과 죽상경화성 심혈관계질환의 연관성 연구

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정한나

연구배경 및 목적

심근경색과 뇌졸중을 포함하는 죽상경화성 심혈관계질환 (ASCVD)은 전 세계적으로 주요한 사망 원인이며, 연령이 증가할수록 ASCVD의 발생률과 유병률은 증가한다. 저밀도지단백-콜레스테롤 (LDL-C)의 상승은 ASCVD의 주요한 위험인자로 알려져 있다. ASCVD의 이차예방뿐만 아니라 일차예방을 목적으로 statin을 사용하여 LDL-C을 낮추면 ASCVD 발생이 감소한다는 사실이 많은 무작위-대조군 연구를 통하여 입증되었다. 반면, 고령 환자에서는 이전 ASCVD 병력이 없을 경우 LDL-C을 낮게 유지하는 것의 이득이 입증되지 않았다. 따라서, 심뇌혈관질환 과거력과 지질강하제 사용력이 없는 한국인 성인에서 연령에 따라 LDL-C 수치와 ASCVD 위험 간의 연관성이 달라지는지 알아보기 위해 본 연구를 진행하였다.

연구대상 및 방법

국민건강보험자료 (Korean National Health Insurance Service)-National Health Screening Cohort (NHIS-HEALS)를 이용하여 후향적 코호트 연구를 시행하였다. NHIS-HEALS 는 2002 년에서 2015 년까지 전체 인구에서 약 10%에 해당하는 514,866 명의 다양한 건강정보자료를 제공한다. 중성지방과 고밀도지단백-콜레스테롤 (HDL-C)을 비롯한 생화학 지표는 NHIS-HEALS 에 2009 년부터 추가되었으므로 본 연구는 2009 년 1 월 1 일부터 2010 년 12 월

31 까지의 2 년 자료를 기저 수준으로 설정하였다. 본 연구의 분석에 2009 년 시점의 나이가 18 세 이상인 성인을 포함시켰다. 2011 년 이전 심혈관질환, 즉 심근경색, 심부전, 또는 뇌졸중을 진단받은 적이 있거나, 2011 년 이전 사망했거나, statin, fibrates, ezetimibe 로 특정한 지질강하제의 복용력이 있는 환자는 분석에서 제외하였다.

연구 결과로는, 2011 년 1 월 1 일부터 2015 년 12 월 31 일까지 연령에 따라 기저 LDL-C 수치와 이후 ASCVD 발생 간의 상관성을 분석하였다. 또한 LDL-C 수치에 따른 심근경색, 뇌졸중, 심부전 각각 및 심혈관질환과 관련된 사망 (심근경색, 뇌졸중, 혹은 심부전과 관련된 사망으로 정의)의 발생 빈도와 위험도를 계산하였다. 추가적으로 제 2 형 당뇨병 환자에서 하위분석을 시행하였다. 위험도 산출은 연령, 성별, 흡연 상태, 혈압, 체질량지수, 사구체여과율, Charlson 동반질환 지수 (Charlson Comorbidity Index), 그리고 고혈압 약제 사용 유무로 보정하여 다변량 Cox 비례위험 회귀분석을 진행하였다.

연구결과

성인 285,119명을 대상으로 6.44년의 중간 추적 기간 동안 8996명 (3.2%)에서 ASCVD가 발생했다. 모든 연령대에서 LDL-C과 ASCVD 위험도는 양성 연관성을 보였으며 LDL-C 160 mg/dL 이상에서는 대부분 통계적으로 유의했다. ASCVD 위험도는 고령 인구와 젊은 연령에서 유의한 차이가 없었다 (P for interaction = .62). LDL-C이 70-99 mg/dL인 군의 ASCVD 위험도와 비교하여 LDL-C이 190 mg/dL 이상으로 가장 높은 군의 위험도 비는, 연령 50세 미만과 70세 이상인 대상자에서 유사한 결과를 보였다 (각각의 aHR 1.90 [95% CI, 1.52-2.38], 1.86 [95% CI, 1.30-2.68]). 마찬가지로 2형 당뇨병 환자를 대상으로 시행한 하위분석 결과 LDL-C과 ASCVD 위험도 사이의 관계는 연령에 따른 차이가 없었다 (P for interaction = .31).

결론

이전 심뇌혈관질환 이력이 없고 지질강하제를 복용하지 않았던 성인을

대상으로 한 전국 인구 기반 코호트 연구 결과, 70세 이상의 고령 인구에서 높은 LDL-C은 여전히 ASCVD 위험도 증가와 유의한 연관성을 보였으며, 이는 젊은 연령에서와 차이가 없었다. 이러한 연구 결과는 증가하는 노인 인구에서 ASCVD의 일차적 예방을 위한 LDL-C 관리의 중요성을 뒷받침한다.

중심단어: 저밀도지단백-콜레스테롤, 죽상경화성 심혈관계질환, 연령