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ORIGINAL RESEARCH

Age-Related Associations of Low-Density Lipoprotein Cholesterol and Atherosclerotic Cardiovascular Disease: A Nationwide Population-Based Cohort Study

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BACKGROUND: The relationship between low-density lipoprotein cholesterol (LDL-C) and atherosclerotic cardiovascular disease (ASCVD) according to age remains undetermined. Thus, this study aimed to investigate the age-related association of LDL-C and ASCVD.

METHODS AND RESULTS: Data from the Korean NHIS-HEALS (National Health Insurance Service-National Health Screening Cohort) were analyzed. Individuals previously diagnosed with cardiovascular disease or taking lipid-lowering drugs were excluded. Age-specific association between LDL-C and ASCVD was calculated using adjusted Cox proportional hazards models. During a median follow-up of 6.44 years for 285 119 adults, ASCVD developed in 8996 (3.2%). All age groups showed positive associations between LDL-C and ASCVD risk, mostly with statistical significance from LDL-C of 160 mg/dL onward. ASCVD risk did not differ significantly between the age groups (*P* for interaction=0.489). Correspondingly, subgroup analysis in type 2 diabetes exhibited no difference in the age-specific association of LDL-C and ASCVD (*P* for interaction=0.784).

CONCLUSIONS: The study demonstrated that people aged ≥75 years with higher LDL-C at baseline still presented increased ASCVD risk, which was not significantly different from the younger groups. These findings support the importance of managing LDL-C for the prevention of primary ASCVD in the growing elderly population.

Key Words: age ■ atherosclerotic cardiovascular disease ■ low-density lipoprotein cholesterol

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 United States 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 have validated the advantage of statin treatment exclusively in primary prevention settings.[6–11]

In contrast, a consensus has not been made on 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

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CLINICAL PERSPECTIVE

What Is New?

- Despite the highest prevalence and socioeconomic burden of atherosclerotic cardiovascular disease in the older population, there is no completed prospective statin trial specifically involving the elderly, and retrospective studies with older subjects or age-specific secondary analyses of previous statin trials showed conflicting outcomes, resulting in heterogeneous major guidelines for lipid management.
- Based on data from 285 119 adults in the Korean NHIS-HEALS (National Health Insurance Service-National Health Screening Cohort), excluding those who were previously diagnosed with cardiovascular disease or taking lipid-lowering drugs, the current study revealed that subjects aged ≥70 years showed a similar level of atherosclerotic cardiovascular disease risk elevation following increasing low-density lipoprotein cholesterol compared with the younger age groups.

What Are the Clinical Implications?

- Considering the growing population of older adults who are apparently healthy, current findings urge the need for intensive lipid management in the elderly to prevent primary atherosclerotic cardiovascular disease.

Nonstandard Abbreviations and Acronyms

NHIS-HEALS	National Health Insurance Service-Health Screening Cohort
T2D	type 2 diabetes

statistical significance even vanishing in some studies.[12–16] Randomized controlled trials that aim to elucidate the pros and cons of lowering LDL-C limited to the elderly have 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 being based on similar landmark studies.[20–25]

The aging population is rapidly expanding worldwide, with the proportion of people aged ≥65 years 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 because of the greatest increase in subjects aged ≥65 years, in contrast to relatively steady numbers in those aged <65 years.[27] Notably, ≈80% and 50% of the cardiovascular fatalities 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 among each age groups was proposed in the current study.

METHODS

Data Source

Anonymized data and materials have been made publicly available at the National Health Insurance Sharing Service and can be accessed at https://nhiss.nhis.or.kr/bd/ab/bdaba006cv.do#. Data in the present study were provided by the Korean NHIS-HEALS (National Health Insurance Service-Health Screening Cohort), 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 health care use including the diagnosis, treatment, health care facilities, demographic factors, cause of mortality and date, questionnaires on health problems and risk factors, and laboratory data. The robustness with low attrition rate from 2002 to 2015 and the coverage of the whole population are the major strengths of the NHIS, making it a representative database in various studies. [30–32] The NHIS-HEALS was organized in 2015, comprising 514 866 individuals who were a random selection of 10% of all of the subjects that participated in NHIS health screening between 2002 and 2003. [29]

This investigation was conducted following the guidelines of the Declaration of Helsinki. Ethics approval was permitted by the Asan Medical Center Institutional Review Board (institutional review board number 2020-0852), Seoul, Korea. Informed consent was not necessary because 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 the NHIS added the biochemical data including triglycerides and high-density lipoprotein cholesterol 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 died before 2011, with preexisting CVD, no examination from 2009 to 2010, body mass index (BMI) ≥40 kg/m², no data on LDL-C or triglycerides at baseline, or taking lipid-lowering drugs at baseline (statins, fibrates, or ezetimibe, as presented in Table S1) were excluded. Four authors (H.N.J., M.-J. K., Y.-J.K., and C.H.J.) had full access to the data of this study and are responsible for their integrity.

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, hospitalization for heart failure, 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 hospitalization for heart failure was defined as at least 1 new admission with the primary or subsidiary diagnostic code of corresponding disorders. These definitions on the basis of *ICD-10-CM* codes have been used in previous studies.[33,34] Detailed definitions of the outcomes are described in Table S2.

Baseline Covariates

Baseline covariates were age, sex, systolic and diastolic blood pressure, BMI, fasting plasma glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate, smoking pack-years, use of antihypertensive drugs, and comorbidities including type 2 diabetes (T2D), hypertension, and Charlson Comorbidity Index.[35] The average number of packs smoked each day was multiplied by the total number of years smoked during a lifetime to compute smoking pack-years. Smokers were divided into 4 groups: light smokers (0.025–5 smoking pack-years), medium smokers (5–14 smoking pack-years), heavy smokers (14–26 smoking pack-years), and extreme smokers (>26 smoking pack-years). Subcategories of antihypertensive drugs and the definitions of T2D and hypertension are listed in Tables S1 and S2, respectively. Estimated glomerular filtration rate was computed from serum creatinine level following the Chronic Kidney Disease Epidemiology Collaboration equation (estimated glomerular filtration rate in milliliters per minute per 1.73 m^2=141×min [serum creatinine/*k*, 1]^a×max [serum creatinine/*k*, 1]$^{-1.209}$×0.993^{age}×1.018 [if female sex], where *k* is 0.7 for women and 0.9 for men, *a* is −0.329 for women and −0.411 for men, and min signifies the minimum of serum creatinine/*k* or 1, whereas max signifies the maximum).[36]

Statistical Analysis

The participants were categorized based on their LDL-C levels at baseline into 1 of the 6 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 number and percentage, and continuous variables as mean and SD. To compare the baseline characteristics of the study participants based on their low-density lipoprotein levels, analysis of variance or χ^2 test was used in addition to post hoc analysis with Bonferroni adjustment.

Incidence rates were presented as events per 1000 person-years with the estimation of a 95% 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, smoking pack-years, systolic blood pressure (continuously), BMI (continuously), estimated glomerular filtration rate (continuously), Charlson Comorbidity Index (continuously), and the use of antihypertensive drugs at baseline. A subgroup with LDL-C levels of 70 to 99 mg/dL was selected as a reference group.

Age-specific adjusted hazard ratio 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 4 age groups (<55, 55–64, 65–74, and ≥75 years) for the assessment of age-related risk. We assessed interaction of sex, smoking pack-years, BMI (<25 and ≥25 kg/m²), the use of antihypertensive drugs, and Charlson Comorbidity Index (<4 and ≥4). Lastly, subgroup analyses in patients with T2D were conducted for the incidence rates and adjusted hazard ratio of outcomes according to the categorization of LDL-C.

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

RESULTS

Baseline Clinical and Biochemical Characteristics of the Study Populations

The final cohort was composed of 285 119 participants who satisfied the inclusion criteria as shown in Figure 1. Among those who were excluded, 21 334 subjects had already been diagnosed with CVD at baseline, and 75 128 were taking lipid-lowering drugs. The baseline characteristics of the overall population categorized by LDL-C are summarized in Table 1. A subgroup with LDL-C ≥190 mg/dL accounted for 2.4%

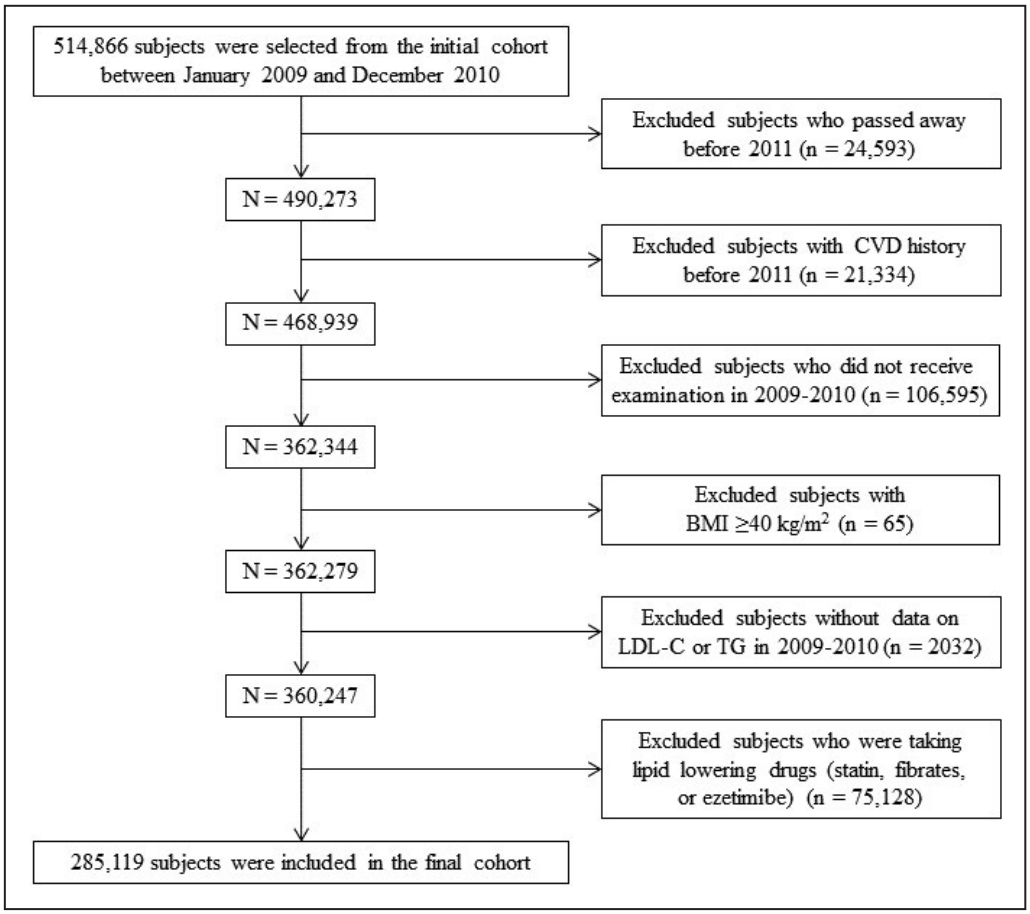

Figure 1. Flow diagram of the study population from the Korean NHIS-HEALS (National Health Insurance Service-National Health Screening Cohort) database.
BMI indicates body mass index; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; and TG, triglycerides.

(n=6718), 160 to 189 mg/dL for 9.0% (n=25 687), 130 to 159 mg/dL for 26.6% (n=75 981), 100 to 129 mg/dL for 37.2% (n=105 952), 70 to 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 years). The overall proportion of men was 55.2%, but it tended to be lower as LDL-C increased (68.8% in LDL-C <70 mg/dL versus 39.8% in LDL-C ≥190 mg/dL). The average baseline LDL-C level was 121.5 mg/dL (SD, 36.4 mg/dL). Patients with T2D comprised 7.5% (n=21 258) of the entire population. Unexpectedly, individuals with the lowest LDL-C levels displayed significantly higher T2D proportion than any other group (13.6% in LDL-C <70 mg/dL versus 6.0% in LDL-C ≥190 mg/dL). Likewise, the percentages of subjects with other comorbidities or a smoking history of >5 pack-years were the largest in the least LDL-C group.

Risk of Primary and Secondary Outcomes

The incidence rates and adjusted hazard ratios of ASCVD, MI, stroke, hospitalization for heart failure, and CVD-related mortality classified by LDL-C are demonstrated in Table 2. During a median follow-up of 6.44 years, the first ASCVD developed in 8996 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 1000 person-years for individuals with LDL-C 70 to 99 and ≥190 mg/dL, respectively. The incidence rates among LDL-C subgroups showed significant differences overall for every outcome. Surprisingly, subjects with LDL-C <70 mg/dL presented nonsignificant but greater risk than the reference group with LDL-C 70 to 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.

Subgroup Analysis

Subgroup analysis indicated that sex, a smoking history of >14 pack-years, and the use of antihypertensive drugs were significantly associated with ASCVD risk in regard to LDL-C as described in Table 3. In contrast,

Table 1. Baseline Characteristics Classified by LDL-C in the Overall Population

Characteristic	Baseline LDL-C, mg/dL						
	<70	70–99	100–129	130–159	160–189	≥190	
	n=13 219	n=57 562	n=105 952	n=75 981	n=25 687	n=6718	Overall *P* value
Age, y	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
<55, n (%)	5085 (38.5)	24 213 (42.1)	46 651 (44.0)	33 750 (44.4)	11 350 (44.2)	2912 (43.3)	
55–64, n (%)	4068 (30.8)	17 885 (31.1)	33 963 (32.1)	25 697 (33.8)	8994 (35.0)	2297 (34.2)	
65–74, n (%)	3201 (24.2)	12 012 (20.9)	20 059 (18.9)	13 262 (17.5)	4284 (16.7)	1181 (17.6)	
≥75, n (%)	865 (6.5)	3452 (6.0)	5279 (5.0)	3272 (4.3)	1059 (4.1)	328 (4.9)	
Men, n (%)	9096 (68.8)	34 732 (60.3)	59 693 (56.3)	39 270 (51.7)	12 002 (46.7)	2671 (39.8)	<0.001
SBP, mm Hg	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, mm Hg	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/m^2	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 per 1.73 m^2	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 (%)							
T2D	1793 (13.6)	5523 (9.6)	7654 (7.2)	4441 (5.8)	1443 (5.6)	404 (6.0)	<0.001
Hypertension	4843 (36.6)	18 162 (31.6)	30 777 (29.0)	21 072 (27.7)	6751 (26.3)	1871 (27.9)	<0.001
Smoking pack-years, n (%)*							
Nonsmokers	6831 (51.7)	33 692 (58.5)	64 023 (60.4)	47 390 (62.4)	16 590 (64.6)	4593 (68.4)	<0.001
Light smokers	735 (5.6)	3395 (5.9)	6004 (5.7)	4184 (5.5)	1282 (5.0)	300 (4.5)	<0.001
Medium smokers	1034 (7.8)	4130 (7.2)	7711 (7.3)	5273 (6.9)	1590 (6.2)	349 (5.2)	<0.001
Heavy smokers	1898 (14.4)	7172 (12.5)	12 804 (12.1)	8610 (11.3)	2871 (11.2)	676 (10.1)	<0.001
Extreme smokers	2293 (17.3)	7485 (13.0)	12 353 (11.7)	8443 (11.1)	2736 (10.7)	641 (9.5)	<0.001
Nonresponders	428 (3.2)	1688 (2.9)	3057 (2.9)	2081 (2.7)	618 (2.4)	159 (2.4)	<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	5521 (41.8)	20 958 (36.4)	35 822 (33.8)	24 809 (32.7)	8066 (31.4)	2222 (33.1)	<0.001

Data are expressed in mean (SD) unless otherwise indicated. BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; T2D, type 2 diabetes; TC, total cholesterol; and TG, triglycerides.

*Calculated as the average number of packs smoked per day multiplied by the total number of years smoked during a lifetime. Smokers were classified into 4 categories: light smokers (0.025–5 smoking pack-years), medium smokers (5–14 smoking pack-years), heavy smokers (14–26 smoking pack-years), and extreme smokers (>26 smoking pack-years).

the difference in ASCVD risk among the age groups was not significant (*P* for interaction=0.489; Table 3 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 onward, excluding subjects with LDL-C <70 mg/dL, whose risk was nonsignificantly higher than the reference group. The risk of CVD-related mortality with increasing LDL-C had a significant correlation with sex, BMI, and Charlson Comorbidity Index of >4, whereas age was not a significant factor (Table 4). Unlike ASCVD risk, the oldest group was the only age category that showed a significant difference in the risk of CVD-related mortality following LDL-C.

Subgroup Analysis in Patients With T2D

The baseline characteristics of 21 258 patients with T2D are summarized in Table S3. The proportion of individuals was 1.9% (n=404), 6.8% (n=1443), 20.9% (n=4441), 36.0% (n=7654), 26.0% (n=5523), and 8.4% (n=1793) in LDL-C ≥190, 160 to 189, 130 to 159, 100 to 129, 70 to 99, and <70 mg/dL, respectively. The mean age and average LDL-C level were 62.6 years (SD, 8.9 years) and 113.7 mg/dL (SD, 37.0 mg/dL), respectively.

Table 2. Number, Incidence Rate, and aHR of ASCVD, MI, Stroke, HHF, and CVD-Related Mortality Classified by LDL-C

	Baseline LDL-C, mg/dL						
	Overall	<70	70–99	100–129	130–159	160–189	≥190
	n=285 119	n=13 219	n=57 562	n=105 952	n=75 981	n=25 687	n=6718
ASCVD							
Events, n (%)	8996 (3.2)	537 (4.1)	1878 (3.3)	3115 (2.9)	2311 (3.0)	863 (3.4)	292 (4.3)
Incidence*		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†		1.09 (0.99–1.20)	1.00 (ref)‡	0.98 (0.93–1.04)	1.07 (1.01–1.14)	1.21 (1.12–1.32)	1.53 (1.35–1.73)
MI							
Events, n (%)	1520 (0.5)	78 (0.6)	253 (0.4)	486 (0.5)	424 (0.6)	197 (0.8)	82 (1.2)
Incidence*		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†		1.12 (0.87–1.45)	1.00 (ref)‡	1.16 (1.00–1.36)	1.53 (1.31–1.79)	2.24 (1.85–2.70)	3.67 (2.86–4.72)
Stroke							
Events, n (%)	7576 (2.7)	467 (3.5)	1644 (2.9)	2660 (2.5)	1916 (2.5)	675 (2.6)	214 (3.2)
Incidence*		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†		1.09 (0.99–1.21)	1.00 (ref)‡	0.96 (0.90–1.02)	1.01 (0.94–1.07)	1.07 (0.97–1.17)	1.24 (1.07–1.43)
HHF							
Events, n (%)	1324 (0.5)	101 (0.8)	318 (0.6)	478 (0.5)	289 (0.4)	96 (0.4)	42 (0.6)
Incidence*		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†		1.20 (0.96–1.50)	1.00 (ref)‡	0.92 (0.80–1.06)	0.83 (0.71–0.97)	0.82 (0.65–1.03)	1.26 (0.91–1.74)
CVD-related mortality							
Events, n (%)	1421 (0.5)	101 (0.8)	337 (0.6)	470 (0.4)	330 (0.4)	142 (0.6)	41 (0.6)
Incidence*		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†		1.10 (0.88–1.37)	1.00 (ref)‡	0.90 (0.78–1.03)	1.00 (0.85–1.16)	1.34 (1.10–1.63)	1.41 (1.02–1.96)

The interval expressed between parentheses signifies a 95% CI. aHR indicates adjusted hazard ratio; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; HHF, hospitalization for heart failure; LDL-C, low-density lipoprotein cholesterol; and MI, myocardial infarction.

*Indicated as a rate per 1000 person-years.

†Adjusted for age, sex, smoking pack-years, systolic blood pressure, body mass index, estimated glomerular filtration rate, Charlson Comorbidity Index, and the use of antihypertensive drugs.

‡*P* value of the reference group (LDL-C of 70–99 mg/dL), which signifies the overall *P* value of multivariable Cox regressions was <0.01.

In addition, 1520 patients with T2D (7.2%) experienced ASCVD during the follow-up period (Table S4). The incidence rate of ASCVD in the subgroup with LDL-C ≥190 mg/dL was significantly higher than in the reference group (19.83 [95% CI, 14.52–26.45] versus 12.05 [95% CI, 10.86–13.33] per 1000 person-years). The outcomes that displayed significant associations between the incidence risk and baseline LDL-C overall were ASCVD and MI. Similar to the overall population, patients with T2D with LDL-C <70 mg/dL had greater incidence rates than the reference group for every outcome other than CVD-related mortality. Age-specific association of ASCVD risk and LDL-C in patients with T2D displayed no difference, in line with the total participants (*P* for interaction=0.784; Table 5 and Figure 2). Furthermore, none of the other factors had a significant relationship with ASCVD risk with respect to LDL-C.

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 ≥75 years and younger adults and in subjects without CVD history and not taking lipid-lowering drugs. A subgroup analysis in patients with T2D 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 reproted 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

Table 3. Risk of Atherosclerotic Cardiovascular Disease With Categorization of Baseline LDL-C by Age, Sex, Smoking Pack-Years, BMI (<25 and ≥25 kg/m²), 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	
	aHR (95% CI)*	aHR (95% CI)*	*P* value†	aHR (95% CI)*	aHR (95% CI)*	aHR (95% CI)*	aHR (95% CI)*	*P* for interaction
Age, y								0.489
<55	1.17 (0.92–1.49)	1.00 (ref)	<0.001	1.04 (0.91–1.20)	1.17 (1.01–1.35)	1.34 (1.11–1.60)	2.02 (1.57–2.61)	
55–64	1.16 (0.97–1.40)	1.00 (ref)	<0.001	0.93 (0.83–1.04)	1.06 (0.94–1.19)	1.19 (1.03–1.39)	1.47 (1.16–1.85)	
65–74	1.05 (0.91–1.22)	1.00 (ref)	0.032	0.96 (0.88–1.06)	1.04 (0.94–1.15)	1.16 (1.01–1.33)	1.23 (0.98–1.54)	
≥75	1.01 (0.80–1.27)	1.00 (ref)	0.005	1.06 (0.93–1.21)	1.06 (0.91–1.23)	1.23 (1.01–1.51)	1.75 (1.30–2.34)	
Sex								<0.001
Men	0.87 (0.77–0.97)	1.00 (ref)	<0.001	1.02 (0.95–1.10)	1.18 (1.09–1.28)	1.39 (1.24–1.55)	2.12 (1.79–2.50)	
Women	0.98 (0.82–1.18)	1.00 (ref)	0.08	0.91 (0.83–1.00)	0.91 (0.83–1.01)	1.01 (0.89–1.14)	1.09 (0.90–1.30)	
Heavy smokers‡								<0.001
No	1.01 (0.89–1.15)	1.00 (ref)	<0.001	0.98 (0.91–1.05)	1.03 (0.96–1.11)	1.13 (1.03–1.25)	1.35 (1.16–1.57)	
Yes	1.25 (1.06–1.46)	1.00 (ref)	<0.001	0.98 (0.88–1.09)	1.16 (1.03–1.30)	1.44 (1.24–1.68)	2.15 (1.71–2.71)	
BMI, kg/m²								0.461
<25	1.11 (0.99–1.25)	1.00 (ref)	<0.001	0.98 (0.91–1.05)	1.07 (0.99–1.16)	1.20 (1.08–1.33)	1.69 (1.44–1.97)	
≥25	1.05 (0.88–1.25)	1.00 (ref)	<0.001	0.99 (0.89–1.09)	1.07 (0.97–1.19)	1.24 (1.09–1.41)	1.32 (1.08–1.62)	
Antihypertensive drugs								0.023
No	1.03 (0.87–1.21)	1.00 (ref)	<0.001	1.07 (0.98–1.16)	1.12 (1.02–1.23)	1.35 (1.20–1.52)	1.70 (1.42–2.04)	
Yes	1.12 (1.00–1.26)	1.00 (ref)	<0.001	0.93 (0.86–1.00)	1.05 (0.96–1.13)	1.11 (0.99–1.24)	1.41 (1.19–1.67)	
Charlson Comorbidity Index								0.959
<4	1.10 (0.99–1.22)	1.00 (ref)	<0.001	0.93 (0.93–1.05)	1.07 (1.00–1.15)	1.21 (1.11–1.32)	1.55 (1.36–1.77)	
≥4	1.07 (0.86–1.33)	1.00 (ref)	0.067	0.95 (0.82–1.10)	1.10 (0.93–1.30)	1.26 (1.00–1.59)	1.40 (0.96–2.03)	

aHR indicates adjusted hazard ratio; BMI, body mass index; and LDL-C, low-density lipoprotein cholesterol.

*Adjusted for age, sex, smoking pack-years, systolic blood pressure, BMI, estimated glomerular filtration rate, Charlson Comorbidity Index, and the use of antihypertensive drugs.

†*P* value of the reference group (LDL-C of 70–99 mg/dL) signifies the overall *P* value of multivariable Cox regressions.

‡Smokers with a history of >14 smoking pack-years, which are calculated as the average number of packs smoked per day multiplied by the total number of years smoked during a lifetime.

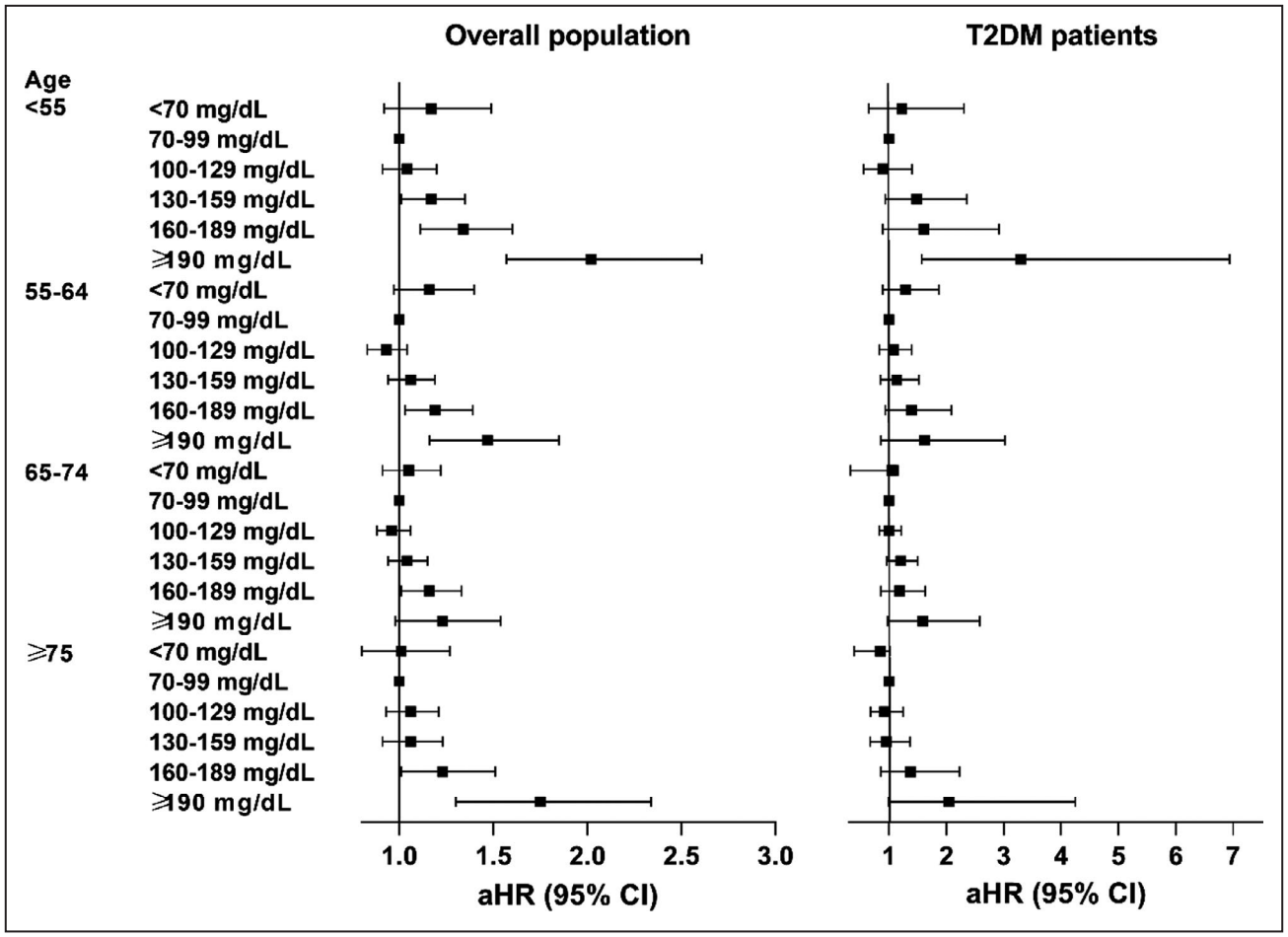

Figure 2. Age-specific adjusted hazard ratio (aHR) for risk of atherosclerotic cardiovascular disease with increasing low-density lipoprotein cholesterol by multivariable Cox regressions in the overall population and patients with type 2 diabetes (T2DM).

Hazard ratio was adjusted for age, sex, smoking pack-years, systolic blood pressure, body mass index, estimated glomerular filtration rate, Charlson Comorbidity Index, and the use of antihypertensive drugs. *P* for interaction was 0.489 and 0.784 for the overall population and patients with T2DM, respectively.

heart disease 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 ≈18 mg/dL) decrease in total cholesterol correlated with 56%, 34%, and 17% lower ischemic heart disease–related mortality in participants aged 40 to 49, 50 to 69, and 70 to 89 years, respectively.[16]

The reason for the disagreement between the result of the current and previous studies on 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. Age-specific analysis of the ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial, which evaluated the prevention of major adverse cardiovascular events with alirocumab between 2012 and 2018, displayed that adverse cardiovascular events were further reduced with advancing age without compromising the safety profile.[37]

No completed randomized controlled trial 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 LLT (Lipid-Lowering Trial) component of the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), a randomized experiment performed at 513 centers

Table 4. Risk of Cardiovascular Disease–Related Mortality With Categorization of Baseline LDL-C by Age, Sex, Smoking Pack-Years, BMI (<25 and ≥25 kg/m²), 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	
	aHR*	aHR*	*P* value†	aHR*	aHR*	aHR*	aHR*	*P* for interaction
Age, y								0.874
<55	1.09 (0.47–2.50)	1.00 (ref)	0.288	0.73 (0.44–1.20)	1.06 (0.65–1.74)	1.32 (0.71–2.45)	0.32 (0.04–2.38)	
55–64	1.12 (0.62–2.04)	1.00 (ref)	0.177	0.90 (0.63–1.30)	1.08 (0.74–1.57)	1.60 (1.02–2.51)	0.81 (0.29–2.26)	
65–74	1.27 (0.90–1.78)	1.00 (ref)	0.092	0.97 (0.77–1.22)	1.02 (0.79–1.31)	1.30 (0.93–1.82)	1.72 (1.04–2.87)	
≥75	0.94 (0.65–1.37)	1.00 (ref)	0.045	0.87 (0.70–1.09)	0.91 (0.71–1.18)	1.25 (0.90–1.74)	1.68 (1.04–2.72)	
Sex								0.031
Men	1.16 (0.90–1.50)	1.00 (ref)	<0.001	0.89 (0.75–1.06)	1.09 (0.90–1.31)	1.68 (1.31–2.15)	1.77 (1.13–2.76)	
Women	0.95 (0.60–1.50)	1.00 (ref)	0.759	0.89 (0.70–1.13)	0.84 (0.65–1.09)	0.95 (0.68–1.32)	1.08 (0.67–1.75)	
Heavy smokers‡								0.326
No	1.04 (0.77–1.40)	1.00 (ref)	0.097	0.97 (0.82–1.15)	0.96 (0.79–1.16)	1.32 (1.03–1.68)	1.28 (0.85–1.91)	
Yes	1.22 (0.86–1.73)	1.00 (ref)	0.002	0.80 (0.62–1.03)	1.30 (0.79–1.35)	1.50 (1.06–2.12)	1.75 (0.97–3.18)	
BMI, kg/m²								0.005
<25	1.16 (0.91–1.47)	1.00 (ref)	0.006	0.81 (0.69–0.95)	0.94 (0.79–1.12)	1.09 (0.85–1.39)	1.29 (0.87–1.92)	
≥25	0.83 (0.47–1.48)	1.00 (ref)	<0.001	1.26 (0.93–1.70)	1.25 (0.91–1.72)	2.22 (1.54–3.18)	1.89 (1.06–3.38)	
Antihypertensive drugs								0.060
No	1.27 (0.88–1.82)	1.00 (ref)	0.001	0.77 (0.61–0.98)	1.08 (0.85–1.38)	1.41 (1.03–1.92)	0.96 (0.50–1.82)	
Yes	1.01 (0.76–1.35)	1.00 (ref)	0.015	0.97 (0.82–1.16)	0.94 (0.77–1.14)	1.29 (1.00–1.67)	1.67 (1.14–2.44)	
Charlson Comorbidity Index								0.039
<4	1.24 (0.98–1.58)	1.00 (ref)	<0.001	0.89 (0.76–1.04)	1.04 (0.88–1.23)	1.31 (1.05–1.63)	1.33 (0.92–1.91)	
≥4	0.61 (0.34–1.11)	1.00 (ref)	0.011	0.97 (0.70–1.34)	0.70 (0.46–1.08)	1.56 (0.96–2.53)	1.92 (0.92–4.01)	

The interval expressed between parentheses signifies a 95% CI. aHR indicates adjusted hazard ratio; BMI, body mass index; and LDL-C, low-density lipoprotein cholesterol.

*Adjusted for age, sex, smoking pack-years, systolic blood pressure, BMI, estimated glomerular filtration rate, Charlson Comorbidity Index, and the use of antihypertensive drugs.

†*P* value of the reference group (LDL-C of 70–99 mg/dL) signifies the overall *P* value of multivariable Cox regressions.

‡Smokers with a history of >14 smoking pack-years, which are calculated as the average number of packs smoked per day multiplied by the total number of years smoked during a lifetime.

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 2 groups. Counteracting this finding, Ridker et al reported that rosuvastatin ameliorated ASCVD risk by 26% in adults aged >70 years through age-stratified analysis of the 2 primary prevention statin trials, Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin and the Heart Outcomes Prevention Evaluation trial.[18] An individual-level meta-analysis of 28 randomized controlled trials also validated that participants aged 65 to 70 years benefited from statins, with a 39% risk reduction of major vascular events per 1 mmol/L-lower levels of LDL-C, although the effect was nonsignificant in adults aged >70 years.[19] The efficacy of lipid-lowering drugs including statins as well as ezetimibe and proprotein convertase subtilisin/kexin type 9 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.[38]

The scarcity of explicit evidence on lowering LDL-C to prevent primary ASCVD in the elderly has led to remarkably heterogeneous recommendations among 5 major guidelines of statin treatment. Although the 2018 American Heart Association/American College of Cardiology 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 American College of Cardiology/American Heart Association Primary Prevention Guidelines withdrew from approving statin therapy in a similar age group.[21] The 2016 US Preventive Services Task Force

Table 5. Risk of Atherosclerotic Cardiovascular Disease With Categorization of Baseline LDL-C by Age, Sex, Smoking Pack-Years, BMI (<25 and ≥25 kg/m²), the Use of Antihypertensive Drugs, and Charlson Comorbidity Index (<4 and ≥4) in Patients With Type 2 Diabetes

	Baseline LDL-C, mg/dL							
	<70	70–99		100–129	130–159	160–189	≥190	
	aHR (95% CI)*	aHR (95% CI)*	*P* value†	aHR (95% CI)*	aHR (95% CI)*	aHR (95% CI)*	aHR (95% CI)*	*P* for interaction
Age, y								0.784
<55	1.23 (0.65–2.31)	1.00 (ref)	0.004	0.89 (0.56–1.41)	1.49 (0.94–2.36)	1.61 (0.89–2.92)	3.30 (1.57–6.94)	
55–64	1.29 (0.89–1.87)	1.00 (ref)	0.384	1.08 (0.83–1.40)	1.14 (0.85–1.52)	1.40 (0.94–2.09)	1.62 (0.86–3.02)	
65–74	1.05 (0.33–1.16)	1.00 (ref)	0.207	1.00 (0.83–1.22)	1.21 (0.97–1.50)	1.19 (0.86–1.64)	1.59 (0.98–2.58)	
≥75	0.85 (0.39–1.02)	1.00 (ref)	0.181	0.92 (0.68–1.25)	0.96 (0.67–1.37)	1.38 (0.86–2.23)	2.05 (0.99–4.25)	
Sex								0.151
Men	1.05 (0.82–1.35)	1.00 (ref)	0.001	1.09 (0.92–1.29)	1.27 (1.05–1.54)	1.56 (1.18–2.06)	2.14 (1.36–3.38)	
Women	1.19 (0.89–1.65)	1.00 (ref)	0.035	0.84 (0.67–1.05)	1.00 (0.79–1.27)	1.06 (0.77–1.45)	1.55 (1.02–2.35)	
Heavy smokers‡								0.931
No	1.15 (0.90–1.46)	1.00 (ref)	0.011	0.99 (0.84–1.17)	1.20 (1.00–1.44)	1.27 (0.99–1.64)	1.68 (1.16–2.43)	
Yes	1.01 (0.71–1.42)	1.00 (ref)	0.172	0.95 (0.74–1.21)	1.08 (0.81–1.42)	1.43 (0.97–2.11)	1.85 (0.94–3.64)	
BMI, kg/m²								0.766
<25	1.04 (0.81–1.35)	1.00 (ref)	0.001	0.97 (0.82–1.15)	1.11 (0.91–1.35)	1.38 (1.05–1.81)	2.07 (1.39–3.09)	
≥25	1.18 (0.86–1.61)	1.00 (ref)	0.149	1.03 (0.84–1.28)	1.24 (0.99–1.56)	1.26 (0.91–1.73)	1.61 (1.00–2.60)	
Antihypertensive drugs								0.726
No	0.81 (0.48–1.37)	1.00 (ref)	0.076	1.05 (0.79–1.39)	1.26 (0.93–1.70)	1.43 (0.94–2.18)	2.03 (1.08–3.82)	
Yes	1.15 (0.93–1.43)	1.00 (ref)	0.003	0.98 (0.84–1.14)	1.14 (0.96–1.35)	1.29 (1.01–1.64)	1.80 (1.26–2.56)	
Charlson Comorbidity Index								0.707
<4	1.10 (0.79–1.46)	1.00 (ref)	0.002	1.05 (0.88–1.26)	1.25 (1.02–1.52)	1.28 (0.97–1.70)	2.14 (1.45–3.17)	
≥4	1.09 (0.83–1.43)	1.00 (ref)	0.081	0.93 (0.76–1.14)	1.07 (0.85–1.34)	1.40 (1.02–1.91)	1.51 (0.92–2.48)	

aHR indicates adjusted hazard ratio; BMI, body mass index; and LDL-C, low-density lipoprotein cholesterol.

*Adjusted for age, sex, smoking pack-years, systolic blood pressure, BMI, estimated glomerular filtration rate, Charlson Comorbidity Index, and the use of antihypertensive drugs.

†*P* value of the reference group (LDL-C of 70–99 mg/dL) signifies the overall *P* value of multivariable Cox regressions.

‡Smokers with a history of >14 smoking pack-years, which are calculated as the average number of packs smoked per day multiplied by the total number of years smoked during a lifetime.

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 age 84 years 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 United Kingdom, United States, and the Netherlands have established that the prescription rate of lipid-lowering drugs decreased after age 75 years, not only without prior CVD event but also with CVD history.[39–41] Despite the higher ASCVD incidence rate in older patients,[42] 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 (eg, intrinsically limited life expectancy, various comorbidities, polypharmacy causing drug–drug interaction, and concerns about adverse reactions caused by impaired metabolism) are clinical hurdles for pursuing low cholesterol levels. Nevertheless, the current study substantiated that elevated ASCVD risk caused by high LDL-C persisted in adults aged ≥75 years. The occurrence rate of ASCVD was higher in the elderly, and our study verified the similar ASCVD risk between the older and the younger age groups. Collectively, an absolute burden of ASCVD may be higher in the elderly.[42] Furthermore, doubts about 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.[43] A meta-analysis of adults aged ≥65 years determined that statin use did not raise the risk of myalgia and rhabdomyolysis compared with placebo.[44] Individuals aged ≥75 years were observed to have even fewer events of myalgia than younger individuals in community practice in the United States.[45] Accumulating evidence has also confirmed no significant statin influence on cognitive function in elderly people.[46–48] Lastly, the association between LDL-C levels and ASCVD risk in older people is not as strong as in younger groups, possibly because of poor nutrition and comorbidities in the elderly.[49] 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 or smokers with >5 pack-years of smoking, 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 of patients with T2D. This result partly conforms to the analysis of electronic health records at the Vanderbilt University Medical Center, which revealed that people with LDL-C ≤60 mg/dL in the absence of statin use were more likely to suffer from T2D than those with higher LDL-C.[50] More studies are needed on causality and whether unrecorded characteristics (eg, 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 about 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 among 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 data set of 285 119 subjects, including 14 255 adults aged ≥75 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 patients with T2D who are classified to the high-risk groups of CVD in lipid-management guidelines.

In conclusion, 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 ≥75 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, although weighing risk and benefit is imperative for the managing lipid profile particularly in the older population.

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Supplemental Material

Tables S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. 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 S2. Definitions of outcomes and covariates.

	ICD-10-CM codes	Diagnostic definition
MI	I21–I23	Admission ≥1
Stroke	I60–I64, I690–I694, G45	Admission ≥1
HHF	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; HHF, hospitalization for heart failure; CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus.

Table S3. 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**
Number	1,793	5,523	7,654	4,441	1,443	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
<55, N (%)	388 (21.6)	1,122 (20.3)	1,756 (22.9)	1,101 (24.8)	406 (28.1)	108 (26.7)	
55–64, N (%)	634 (35.4)	1,975 (35.8)	2,713 (35.4)	1,597 (36.0)	507 (35.1)	148 (36.6)	
65–74, N (%)	628 (35.0)	1,894 (34.3)	2,468 (32.2)	1,347 (30.3)	412 (28.6)	114 (28.2)	
≥75, N (%)	143 (8.0)	532 (9.6)	717 (9.4)	396 (8.9)	118 (8.2)	34 (8.4)	
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
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
Smoking pack-years, N (%)*							
None-smokers	904 (50.4)	2,952 (53.4)	4,226 (55.2)	2,569 (57.8)	891 (61.7)	275 (68.1)	<0.001
Light smokers	87 (4.9)	301 (5.4)	381 (5.0)	188 (4.2)	57 (4.0)	10 (2.5)	<0.001
Medium smokers	116 (6.5)	347 (6.3)	547 (7.1)	283 (6.4)	92 (6.4)	18 (4.5)	<0.001
Heavy smokers	262 (14.6)	696 (12.6)	958 (12.5)	482 (10.9)	156 (10.8)	39 (9.7)	<0.001
Extreme smokers	343 (19.1)	1,012 (18.3)	1,267 (16.6)	742 (16.7)	202 (14.0)	45 (11.1)	<0.001
Non-responders	81 (4.5)	215 (3.9)	275 (3.6)	177 (4.0)	45 (3.1)	17 (4.2)	<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.

*Calculated as the average number of packs smoked per day multiplied by the total number of years smoked during a lifetime. Smokers were classified into four categories: light smokers (0.025–5 smoking pack-years), medium smokers (5–14 smoking pack-years), heavy smokers (14–26 smoking pack-years), and extreme smokers (more than 26 smoking pack-years).

LDL-C, LDL cholesterol; T2DM, type 2 diabetes mellitus; N, number; 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 S4. Number, incidence rate, and aHR of ASCVD, MI, stroke, HHF, and CVD-related mortality classified by LDL-C in T2DM patients.

		Baseline LDL-C (mg/dL)					
	Overall	**<70**	**70–99**	**100–129**	**130–159**	**160–189**	**≥190**
Number	21,258	1,793	5,523	7,654	4,441	1,443	404
ASCVD							
Events, N (%)	1,520 (7.2)	135 (7.5)	378 (6.8)	510 (6.7)	334 (7.5)	117 (8.1)	46 (11.4)
Incidence*		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†		1.10 (0.90–1.33)	1.00 (ref)‡	0.99 (0.87–1.14)	1.16 (1.00–1.35)	1.32 (1.07–1.63)	1.85 (1.36–2.51)
MI							
Events, N (%)	291 (1.4)	26 (1.5)	55 (1.0)	89 (1.2)	71 (1.6)	34 (2.4)	16 (4.0)
Incidence*		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†		1.41 (0.89–2.25)	1.00 (ref)‡	1.21 (0.87–1.70)	1.76 (1.23–2.51)	2.75 (1.79–4.24)	4.67 (2.66–8.19)
Stroke							
Events, N (%)	1,253 (5.9)	111 (6.2)	329 (6.0)	430 (5.6)	268 (6.0)	84 (5.8)	31 (7.7)
Incidence*		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†		1.04 (0.84–1.29)	1.00 (ref)§	0.96 (0.83–1.11)	1.06 (0.90–1.25)	1.07 (0.84–1.36)	1.39 (0.96–2.01)
HHF							
Events, N (%)	242 (1.1)	27 (1.5)	72 (1.3)	81 (1.1)	41 (0.9)	13 (0.9)	8 (2.0)
Incidence*		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†		1.18 (0.76–1.83)	1.00 (ref)‖	0.84 (0.61–1.15)	0.74 (0.51–1.10)	0.76 (0.42–1.38)	1.64 (0.79–3.43)
CVD-related mortality							

Events, N (%)	245 (1.2)	18 (1.0)	70 (1.3)	86 (1.1)	42 (0.9)	21 (1.5)	8 (2.0)
Incidence[*]		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[†]		0.77 (0.46–1.30)	1.00 (ref)[#]	0.93 (0.68–1.28)	0.85 (0.48–1.25)	1.41 (0.86–2.30)	1.82 (0.87–3.80)

The interval expressed between parentheses signifies a 95% confidence interval. aHR, adjusted hazard ratio; ASCVD, atherosclerotic cardiovascular disease; MI, myocardial infarction; HHF, hospitalization for heart failure; CVD, cardiovascular disease; LDL-C, LDL cholesterol; T2DM, type 2 diabetes mellitus; N, number.

[*]Indicated as a rate per 1,000 person-years.

[†]Adjusted for age, sex, smoking pack-years, systolic blood pressure, body mass index, estimated glomerular filtration rate, Charlson comorbidity index, and the use of antihypertensive drugs.

[‡]P-value of the reference group (LDL-C of 70–99 mg/dL), which signifies the overall P-value of multivariable Cox regressions, was <0.001.

[§]P-value of the reference group (LDL-C of 70–99 mg/dL), which signifies the overall P-value of multivariable Cox regressions, was 0.389.

[‖]P-value of the reference group (LDL-C of 70–99 mg/dL), which signifies the overall P-value of multivariable Cox regressions, was 0.170.

[#]P-value of the reference group (LDL-C of 70–99 mg/dL), which signifies the overall P-value of multivariable Cox regressions, was 0.162.