



Differential Associations of Lipid Profiles with Dementia and Cardiovascular Disease: Findings from the UK Biobank Cohort

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Purpose: Lowering low-density lipoprotein cholesterol (LDL-C) is crucial for cardiovascular disease (CVD) prevention, but its impact on cognitive function—and the potential differences by dementia subtype and cholesterol-lowering medication use—remain unclear. This study aimed to examine the associations between lipid levels and dementia and CVD risks, considering dementia subtypes and cholesterol-lowering medication use.

Materials and Methods: A prospective cohort study was conducted using UK Biobank data. Serum lipid levels, including LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides, total cholesterol, and remnant cholesterol, were categorized into clinically relevant ranges. Accounting for cholesterol-lowering medication use, the primary outcomes were incident all-cause dementia, Alzheimer's dementia (AD), vascular dementia (VD), and CVD.

Results: High LDL-C (≥ 160 mg/dL) increased AD risk across all groups {hazard ratio (HR): 1.23 [95% confidence interval (CI): 1.10–1.38], $p < 0.001$; HR: 1.45 (95% CI: 1.08–1.93), $p = 0.013$; HR: 1.25 (95% CI: 1.10–1.42), $p < 0.001$, respectively}, whereas low LDL-C (< 70 mg/dL) showed higher VD risk in those not taking cholesterol-lowering medication [HR: 3.02 (95% CI: 1.73–5.27), $p < 0.001$]. Low HDL-C (≤ 40 mg/dL) was associated with increased AD and VD risk in non-users. High LDL-C (≥ 160 mg/dL) was associated with increased CVD risk in those taking cholesterol-lowering medication.

Conclusion: This study underscores the differential associations of lipid levels with dementia and CVD risk, depending on dementia subtype and cholesterol-lowering medication use. High LDL-C was linked to increased AD risk, whereas low LDL-C was linked to increased VD risk in those not taking cholesterol-lowering medication.

Key Words: Lipid profile, cholesterol-lowering medication, dementia, cardiovascular disease, low-density lipoprotein cholesterol

INTRODUCTION

Lipid management is a cornerstone of preventing atherosclerotic cardiovascular disease (CVD), with low-density lipopro-

tein cholesterol (LDL-C) being the primary target for reducing risk.¹ Aggressive LDL-C lowering, even to levels as low as 55 mg/dL, substantially reduces major cardiovascular events in high-risk individuals.^{2,3} The benefits of low LDL-C levels in CVD prevention are well established; however, the relationship between lipid levels and cognitive health remains controversial, with conflicting evidence on whether lipid-lowering strategies influence dementia risk.^{4,5}

In aging populations, cognitive decline is a growing concern, and emerging evidence indicates a complex interplay between lipid homeostasis and cognitive function.⁵ Cholesterol plays a crucial role in maintaining neuronal membranes, synaptic plasticity, and myelination, with the brain containing approximately 25% of the body's total cholesterol (TC).⁶ Although brain cholesterol is mainly synthesized in situ due to the constraints

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of the blood–brain barrier (BBB), systemic lipid dysregulation may still affect neurovascular health, inflammation, and BBB integrity.^{6,7} As dementia is a heterogeneous syndrome comprising distinct subtypes—most notably Alzheimer’s disease (AD) and vascular dementia (VD)—with differing underlying pathophysiology, the impact of lipid profiles on dementia risk may vary by subtype.⁸ AD is primarily driven by neurodegenerative processes such as amyloid-beta accumulation and tau pathology, whereas VD is associated with cerebrovascular damage and impaired cerebral perfusion.^{6,9} Thus, distinguishing between AD and VD is critical for accurately evaluating the lipid-related mechanisms underlying cognitive decline.

Epidemiological studies on lipid levels and dementia risk have produced mixed results.^{4,5,10} Some meta-analyses imply that higher TC and LDL-C levels increase AD risk, whereas low LDL-C likely has no clear impact on cognitive disorders.^{11,12} An analysis of high-density lipoprotein cholesterol (HDL-C), LDL-C, and TC in the UK Biobank dataset suggests that their relationships with dementia risk follow a U-shaped pattern when modeled by quartiles.¹³ Although these results accounted for cholesterol-lowering medication use in statistical adjustments, the potential modifying effects of these therapies on the associations remain uncertain. A U.S. cohort study of 184367 older adults revealed that every 10 mg/dL increase in LDL-C was associated with a higher dementia risk in statin users but a lower risk in non-users, with extreme HDL-C levels also linked to elevated dementia risk.¹⁴

Similarly, a longitudinal Korean cohort study reported an inverse J-shaped association between LDL-C and dementia in statin non-users, whereas higher LDL-C was linked to elevated dementia risk in statin users.¹⁵ These results suggest that lipid levels may differentially influence CVD and dementia risk, with potential modification by cholesterol-lowering therapy. The effects of LDL-C reduction on dementia risk remain elusive while its benefits in CVD prevention are well established. Therefore,

this study examined the association between lipid levels and the risk of incident dementia and CVD, considering the modifying role of cholesterol-lowering medications. Using data from the UK Biobank cohort, we determined whether lipid profiles differentially influence these outcomes and examined how cholesterol-lowering therapy impacts these relationships. Furthermore, given the distinct pathophysiological mechanisms of AD and VD, we explored whether the associations between lipid profiles and dementia risk varied by dementia subtype.

MATERIALS AND METHODS

Study design and population

This study analyzed data from the UK Biobank, a longitudinal cohort study of >500000 participants (age range: 37–73 years at baseline), recruited between 2006 and 2010. Fig. 1 is a flowchart illustrating the process of participant selection to analyze dementia presence. A total of 502369 participants were included in the baseline survey, from which those with dementia or mild cognitive impairment (MCI) at baseline (n=338), incomplete data at baseline (n=77928), and implausible values for remnant cholesterol (RC) (n=522) were excluded. Thus, a total of 423652 participants were included in the final analysis for dementia. The Institutional Review Board of Yongin Severance Hospital approved the protocol of this study (IRB number: 9-2023-0256). All participants provided written informed consent before enrollment. Furthermore, a separate analysis was performed to assess CVD presence. From the original 502369 participants, those with pre-existing CVD at baseline (n=57158), incomplete baseline data (n=77928), and implausible RC values (n=522) were excluded (Supplementary Fig. 1, only online). This led to a final analytical sample of 376223 participants for the CVD analysis.

To address the potential for reverse causality—specifically,

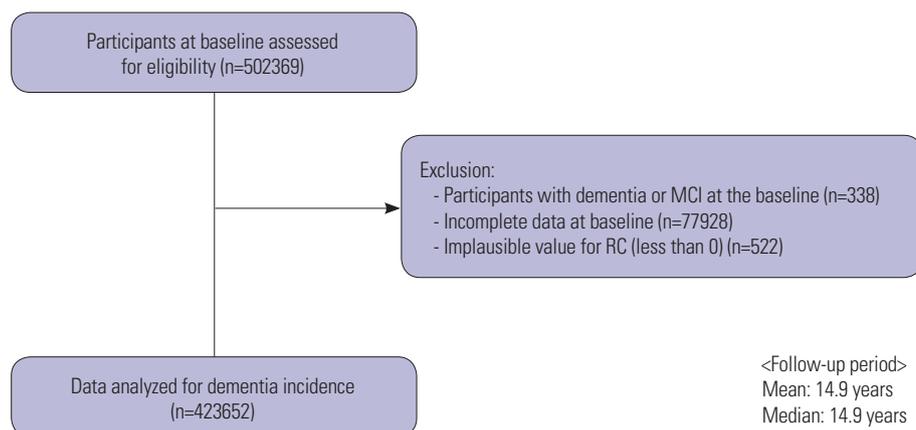


Fig. 1. Flowchart of study population selection for dementia analysis. This flowchart shows the stepwise selection process of participants included in the dementia analysis. The initial cohort consisted of 502369 UK Biobank participants. Exclusion criteria included individuals with pre-existing dementia at baseline, incomplete baseline data, and implausible RC values. A total of 423652 participants were included in the final analysis of incident dementia. RC, remnant cholesterol; MCI, mild cognitive impairment.

that undiagnosed prodromal AD might have affected cholesterol-lowering medication compliance—we excluded participants with MCI at baseline. Additionally, landmark analyses were conducted by excluding all-cause dementia cases diagnosed within the first 1, 2, and 3 years of follow-up to further minimize the influence of preclinical cognitive decline on lipid levels or medication adherence.

Data collection

Participants were assessed at one of the 22 centers throughout the UK, where they completed an extensive baseline assessment.¹⁶ At the baseline visit, biological samples of the participants were collected, and each participant completed a touchscreen questionnaire with assistance from trained staff and underwent a physical assessment. The questionnaire encompassed lifestyle and medical history, which included smoking status, alcohol intake, physical activity, and a history of diabetes or hypertension diagnosed by a doctor. Additionally, information on family history of illnesses such as stroke, heart disease, and AD/dementia was included in the touchscreen questionnaire. Smoking status was categorized into three groups: current smoker, previous smoker, or never smoker. Furthermore, alcohol intake was categorized into three groups: never drinker, previous drinker, or current drinker. Regular exercise included moderate or vigorous physical activity for ≥ 10 min for at least 1 day per week in the previous 4 weeks. Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, and body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2). The values of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were obtained from automated readings using an Omron device (measurement range 0–255 mm Hg). Fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), TC, HDL-C, triglycerides (TG), and LDL-C levels were measured. RC was calculated as TC minus LDL-C minus HDL-C.¹⁷

Hypertension was defined as SBP of ≥ 140 mm Hg, DBP of ≥ 90 mm Hg, or the current use of antihypertensive medication.¹⁸ Type 2 diabetes was defined as FPG level of ≥ 126 mg/dL, HbA1c level of $\geq 6.5\%$, insulin use, or diabetes diagnosed by a doctor.¹⁹ Whether participants were taking cholesterol-lowering medication was determined based on their responses to the questionnaire at the baseline visit. However, the specific medication types or classes were not detailed in the questionnaire. Cerebrovascular accident (CVA) history was defined as having been diagnosed with intracranial hemorrhage, cerebral infarction, stroke not specified as hemorrhage or infarction, or occlusion and stenosis of precerebral or cerebral arteries not leading to cerebral infarction, as reported from primary care data, hospital admission data, self-reports, death register, or other sources, based on previous studies.^{20,21}

The cut-off criteria for each lipid component (LDL-C, HDL-C, TG, and TC) were established as follows: <70 , 70–99, 100–129, 130–159, ≥ 160 mg/dL for LDL-C; ≤ 40 , 41–59, 60–79, ≥ 80 mg/dL

for HDL-C; <150 , 150–199, ≥ 200 mg/dL for TG; and <100 , 100–199, 200–239, ≥ 240 mg/dL for TC referring to the clinical guidelines on dyslipidemia treatment goals.^{1,22,23} RC was analyzed in quartiles.

We identified non-linear associations between lipid profiles and incident dementia and CVD using restricted cubic spline (RCS) curve analysis (Supplementary Fig. 2, only online). Based on these results, we set the reference categories as follows: LDL-C, 100–129 mg/dL; HDL-C, 41–59 mg/dL; TG, <150 mg/dL; TC, 200–239 mg/dL; and RC, 18.9–25.2 mg/dL.

Definition of dementia and CVD

Incident dementia was defined based on the International Classification of Diseases, Tenth Revision (ICD-10) codes, in line with previous studies using the UK Biobank dataset.^{24,25} All-cause dementia included any first recorded diagnosis of F00 (dementia in Alzheimer's dementia), F01 (vascular dementia), F02 (dementia in other diseases classified elsewhere), F03 (unspecified dementia), or G30 (Alzheimer's dementia). Diagnoses were identified using multiple data sources, including primary care records, hospital admissions, death registries, and participant self-reports. The earliest recorded date from any of these sources was used to define disease onset. For subtype analyses, AD was defined as the first report of G30 or F00, while VD was defined as the first report of F01. These subtypes were treated as distinct outcomes in secondary analyses to account for differences in underlying pathophysiology.

New-onset CVD was defined as diagnosis of heart failure, myocardial infarction, angina pectoris, other ischemic heart diseases, peripheral vascular diseases, arterial or venous embolism and thrombosis, or other disorders of arteries, arterioles, or veins. These diagnoses were also identified using ICD codes and were captured from the same composite of data sources: primary care data, hospital admission records, death registries, and self-reports, based on validated definitions used in previous studies.^{26,27}

History of CVA was determined using ICD codes indicative of intracranial hemorrhage, cerebral infarction, unspecified stroke, or occlusion/stenosis of precerebral or cerebral arteries, based on any of the available data sources. CVA was incorporated into the composite definition of CVD to provide a more comprehensive assessment of vascular risk.

Statistical analysis

All data are presented as means \pm standard deviations and numbers (percentages) for continuous and categorical variables, respectively. Differences between the two groups were examined using independent t-tests and chi-square tests for continuous and categorical variables, respectively. Multivariate Cox proportional hazards regression was performed to calculate hazard ratios (HRs) with 95% confidence intervals (CIs), using pre-specified lipid-level ranges for LDL-C, HDL-C, TG, TC, and RC, to evaluate the associations between lipid levels and dementia

Table 1. Baseline Characteristics of the Study Population according to the Presence of New-Onset Dementia

Characteristic	Overall	New-onset dementia		p
		Yes	No	
N (%)	423652	7458 (1.8)	416194 (98.2)	
LDL-C (mg/dL)	137.7±33.6	133.0±37.4	137.8±33.5	<0.001
LDL-C ranges				<0.001
<70	5311 (1.3)	209 (2.8)	5102 (1.2)	
70–99	48950 (11.6)	1312 (17.6)	47638 (11.4)	
100–129	126585 (29.9)	2134 (28.6)	124451 (29.9)	
130–159	139223 (32.9)	2100 (28.2)	137123 (32.9)	
≥160	103583 (24.5)	1703 (22.8)	101880 (24.5)	
HDL-C (mg/dL)	56.0±14.8	5 4.8±15.4	56.0±14.7	<0.001
HDL-C ranges				<0.001
≤40	51973 (12.3)	1205 (16.2)	50768 (12.2)	
41–59	223989 (52.9)	3842 (51.5)	220147 (52.9)	
60–79	119380 (28.2)	1932 (25.9)	117448 (28.2)	
≥80	28310 (6.7)	479 (6.4)	27831 (6.7)	
TG (mg/dL)	154.8±90.9	158.8±89.7	154.7±90.9	<0.001
TG ranges				<0.001
<150	252566 (59.6)	4190 (56.2)	248376 (59.7)	
150–199	76772 (18.1)	1546 (20.7)	75226 (18.1)	
≥200	94314 (22.3)	1722 (23.1)	92592 (22.2)	
TC (mg/dL)	220.3±44.2	214.0±50.2	220.4±44.1	<0.001
TC ranges				<0.001
<100	438 (0.1)	27 (0.4)	411 (0.1)	
100–199	140152 (33.1)	3014 (40.4)	137138 (33.0)	
200–239	150306 (35.5)	2217 (29.7)	148089 (35.6)	
≥240	132756 (31.3)	2200 (29.5)	130556 (31.4)	
RC (mg/dL)	26.6±11.6	26.1±11.6	26.6±11.6	0.002
RC ranges				0.023
≤18.9	106049 (25.0)	1950 (26.1)	104099 (25.0)	
18.9–25.2	106113 (25.0)	1889 (25.3)	104224 (25.0)	
25.2–32.7	105794 (25.0)	1859 (24.9)	103935 (25.0)	
>32.7	105696 (24.9)	1760 (23.6)	103936 (25.0)	
Age (yr)	56.5±8.1	64.5±4.5	56.4±8.1	<0.001
Sex				<0.001
Male	228176 (53.9)	3567 (47.8)	224609 (54.0)	
Female	195476 (46.1)	3891 (52.2)	191585 (46.0)	
BMI (kg/m ²)	27.4±4.8	27.8±4.9	27.4±4.8	<0.001
Smoking status				<0.001
Never-smoker	231576 (54.7)	3476 (46.6)	228100 (54.8)	
Ex-smoker	147324 (34.8)	3212 (43.1)	144112 (34.6)	
Current smoker	44752 (10.6)	770 (10.3)	43982 (10.6)	
Alcohol intake				<0.001
Never drinker	18523 (4.4)	508 (6.8)	18015 (4.3)	
Ex-drinker	15139 (3.6)	496 (6.7)	14643 (3.5)	
Current drinker	389990 (92.1)	6454 (86.5)	383536 (92.2)	
Regular exercise	362500 (85.6)	6055 (81.2)	356445 (85.6)	<0.001
Diabetes	30299 (7.2)	1231 (16.5)	29068 (7.0)	<0.001
Hypertension	205989 (48.6)	4545 (60.9)	201444 (48.4)	<0.001

Table 1. Baseline Characteristics of the Study Population according to the Presence of New-Onset Dementia (Continued)

Characteristic	Overall	New-onset dementia		p
		Yes	No	
Cholesterol-lowering medication	73832 (17.4)	2721 (36.5)	71111 (17.1)	<0.001
CVD history	47613 (11.2)	1792 (24.0)	45821 (11.0)	<0.001
Illnesses of father				
Stroke	23993 (5.7)	493 (6.6)	23500 (5.6)	<0.001
Heart disease	54842 (12.9)	1021 (13.7)	53821 (12.9)	0.055
AD/dementia	13812 (3.3)	380 (5.1)	13432 (3.2)	<0.001
Illnesses of mother				
Stroke	20830 (4.9)	497 (6.7)	20333 (4.9)	<0.001
Heart disease	27383 (6.5)	606 (8.1)	26777 (6.4)	<0.001
AD/dementia	28624 (6.8)	1021 (13.7)	27603 (6.6)	<0.001
Illnesses of siblings				
Stroke	3841 (0.9)	117 (1.6)	3724 (0.9)	<0.001
Heart disease	13454 (3.2)	337 (4.5)	13117 (3.2)	<0.001
AD/dementia	1494 (0.4)	135 (1.8)	1359 (0.3)	<0.001

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; RC, remnant cholesterol; BMI, body mass index; CVD, cardiovascular disease; AD, Alzheimer’s disease. Data are presented as mean±standard deviation or n (%).

and CVD incidence. The analysis was adjusted for age, sex, BMI, smoking status, alcohol intake, regular exercise, and the presence of diabetes and hypertension, as well as cholesterol-lowering medication use. Kaplan–Meier estimators and log-rank tests were used to compare the cumulative incidence rates of new-onset dementia and CVD across various lipid-level categories.

Interaction analysis was conducted to assess whether the association between lipid levels and dementia risk varied by cholesterol-lowering medication use. Additionally, to account for the potential competing risk of death from non-dementia causes such as CVD, particularly in individuals with high LDL-C who were not taking cholesterol-lowering medication, we performed sensitivity analyses using the Fine–Gray hazard model.

All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R (version 4.1.1; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p<0.05$.

RESULTS

Baseline characteristics of the study population

Table 1 presents the baseline characteristics of the study population according to the presence of new-onset dementia. Among the 423652 participants included in the analysis, 7458 (1.8%) individuals developed dementia, of which 3567 (47.8%) were male. Those with incident dementia were substantially older (64.5±4.5 years vs. 56.4±8.1 years). TC, LDL-C, HDL-C, and RC were considerably lower, whereas TG was markedly higher in

individuals who developed dementia. Additionally, the proportions of individuals exhibiting the presence of diabetes, hypertension, or those taking cholesterol-lowering medication were substantially higher in the incident dementia group. Furthermore, the proportions of individuals with a history of CVD or a family history of stroke, heart disease, or dementia were substantially higher in the incident dementia group.

Supplementary Table 1 (only online) lists the baseline characteristics of the study population according to the presence of new-onset CVD. Among the 376223 participants, 58249 (15.5%) individuals developed CVD, of which 25776 (44.3%) were male. Furthermore, those with incident CVD were substantially older (59.7 ± 7.2 years vs. 55.4 ± 8.1 years).

Interaction analysis by cholesterol-lowering medication use

Supplementary Table 2 (only online) shows statistical interactions between lipid profiles and cholesterol-lowering medication use in relation to both dementia and CVD outcomes. Significant interactions ($p < 0.01$) were found for LDL-C, HDL-C, and TC with both all-cause dementia and CVD (all p for interaction < 0.01), supporting the use of stratified analyses based on cholesterol-lowering medication use. Although TG and RC showed no significant interaction with dementia ($p = 0.898$ and $p = 0.063$, respectively), TG showed a significant interaction with CVD ($p = 0.014$). Therefore, we presented stratified results accordingly.

Sensitivity analyses

In landmark analyses, the associations between lipid levels and all-cause dementia risk remained consistent across in direction across all time points. Notably, key findings such as the elevated risk associated with low LDL-C (< 70 mg/dL) and TC (< 100 mg/dL) in participants not taking cholesterol-lowering medication persisted even after excluding cases within the first 3 years, as shown in Supplementary Table 3 (only online).

The results of competing risk analyses, shown in Supplementary Table 4 (only online), were generally consistent with our main findings based on Cox proportional hazards models. Notably, in the group with high LDL-C (≥ 160 mg/dL) not taking cholesterol-lowering medication, the competing risk of CVD was not significantly elevated [HR: 0.94 (95% CI: 0.82–1.08), $p = 0.394$], suggesting that the lack of association between high LDL-C and dementia in this group is unlikely to be explained by differential cardiovascular mortality.

Association between lipid profile and new-onset dementia

Table 2 presents the links between lipid profile ranges and incident dementia—including all-cause dementia, AD, and VD—based on both crude and multivariable-adjusted HRs with 95% CIs in the total population. Regarding all-cause dementia, LDL-C < 70 mg/dL was associated with a significantly increased risk

among the overall population and those not taking cholesterol-lowering medication [HR: 1.16 (95% CI: 1.00–1.34), $p = 0.047$; HR: 1.93 (95% CI: 1.43–2.61), $p < 0.001$, respectively], whereas LDL-C ≥ 160 mg/dL was associated with increased risk only among medication users [HR: 1.46 (95% CI: 1.23–1.73), $p < 0.001$]. HDL-C ≤ 40 mg/dL was consistently associated with higher risk across all groups [HR: 1.14 (95% CI: 1.06–1.22), $p < 0.001$; HR: 1.11 (95% CI: 1.01–1.22), $p = 0.039$; HR: 1.19 (95% CI: 1.08–1.30), $p < 0.001$, respectively], and HDL-C ≥ 80 mg/dL was also linked to increased risk only among medication users [HR 1.27 (95% CI: 1.04–1.56), $p = 0.017$]. TC < 100 mg/dL showed the highest hazard ratio among non-users [HR: 4.37 (95% CI: 2.34–8.15), $p < 0.001$]. In contrast, TC ≥ 240 mg/dL was significantly associated with increased dementia risk among medication users [HR: 1.34 (95% CI: 1.14–1.57), $p < 0.001$]. TG ≥ 200 mg/dL was inversely associated with all-cause dementia risk across all groups. Fig. 2 presents a forest plot summarizing these associations by cholesterol-lowering medication use.

When stratified by dementia subtype, differing patterns emerged. For AD, LDL-C ≥ 160 mg/dL was consistently associated with increased risk in all three groups [HR: 1.23 (95% CI: 1.10–1.38), $p < 0.001$; HR: 1.45 (95% CI: 1.08–1.93), $p = 0.013$; HR: 1.25 (95% CI: 1.10–1.42), $p < 0.001$, respectively]. HDL-C ≤ 40 mg/dL was significantly associated with increased AD risk among the overall population and non-users [HR: 1.17 (95% CI: 1.04–1.32), $p = 0.008$; HR: 1.24 (95% CI: 1.06–1.46), $p = 0.007$, respectively], but not among those taking medication. TC ≥ 240 mg/dL was significantly associated with increased AD risk in all groups [HR: 1.16 (95% CI: 1.05–1.27), $p = 0.002$; HR: 1.33 (95% CI: 1.01–1.74), $p = 0.039$; HR: 1.15 (95% CI: 1.04–1.27), $p = 0.008$, respectively]. No significant associations were found for TG or RC in AD.

For VD, TC < 100 mg/dL showed the strongest association with increased risk in the overall population [HR: 2.88 (95% CI: 1.52–5.46), $p = 0.001$]. Among medication users, LDL-C ≥ 160 mg/dL and TC ≥ 240 mg/dL were significantly associated with increased VD risk [HR: 2.05 (95% CI: 1.49–2.82), $p < 0.001$; HR: 1.81 (95% CI: 1.31–2.48), $p < 0.001$, respectively]. Among non-users, LDL-C < 70 mg/dL, TC < 100 mg/dL, and HDL-C ≤ 40 mg/dL were significantly associated with elevated VD risk [HR: 3.02 (95% CI: 1.73–5.27), $p < 0.001$; HR: 8.70 (95% CI: 2.76–27.40), $p < 0.001$; HR: 1.29 (95% CI: 1.02–1.63), $p = 0.030$, respectively]. For TG and RC, no significant association was found after adjusting for confounders.

Association between lipid profile and new-onset CVD

Fig. 3 illustrates a forest plot of incident CVD from the fully adjusted models in the subgroup analysis of participants taking and not taking cholesterol-lowering medication. For participants taking cholesterol-lowering medication, higher CVD risk was observed with higher LDL-C (≥ 160 mg/dL and 130–159 mg/dL) [HR: 1.37 (95% CI: 1.23–1.53), $p < 0.001$; HR: 1.15 (95% CI: 1.04–1.27), $p = 0.005$, respectively]. No significant link was noted for LDL-C for those not taking cholesterol-lowering medica-

Table 2. Cox Proportional Hazards Regression Models for (A) All-Cause Dementia, (B) AD, and (C) VD according to Lipid Profile Ranges

Variable	Unadjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	p						
A. All-cause dementia								
a. Total participants								
LDL-C								
<70	2.37 (2.05–2.73)	<0.001	1.53 (1.33–1.77)	<0.001	1.46 (1.27–1.69)	<0.001	1.16 (1.00–1.34)	0.047
70–99	1.60 (1.49–1.71)	<0.001	1.25 (1.17–1.34)	<0.001	1.22 (1.14–1.31)	<0.001	1.06 (0.99–1.14)	0.101
100–129	Reference							
130–159	0.89 (0.84–0.95)	<0.001	0.91 (0.85–0.96)	0.001	0.92 (0.86–0.97)	0.005	1.01 (0.95–1.08)	0.687
≥160	0.97 (0.91–1.04)	0.417	0.92 (0.86–0.98)	0.012	0.93 (0.87–0.99)	0.033	1.06 (0.99–1.13)	0.118
HDL-C								
≤40	1.35 (1.27–1.44)	<0.001	1.30 (1.22–1.39)	<0.001	1.23 (1.15–1.32)	<0.001	1.14 (1.06–1.22)	<0.001
41–59	Reference							
60–79	0.94 (0.89–1.00)	0.041	0.97 (0.91–1.03)	0.275	1.00 (0.94–1.06)	0.976	1.03 (0.97–1.09)	0.295
≥80	0.99 (0.90–1.09)	0.833	0.99 (0.89–1.09)	0.808	1.04 (0.94–1.15)	0.482	1.06 (0.96–1.17)	0.231
TG								
<150	Reference							
150–199	1.22 (1.15–1.29)	<0.001	1.00 (0.94–1.06)	0.915	0.99 (0.93–1.05)	0.623	0.98 (0.93–1.04)	0.578
≥200	1.10 (1.04–1.16)	<0.001	0.96 (0.90–1.02)	0.152	0.94 (0.88–0.99)	0.023	0.92 (0.86–0.97)	0.003
TC								
<100	4.27 (2.92–6.24)	<0.001	2.67 (1.83–3.91)	<0.001	2.42 (1.66–3.55)	<0.001	1.71 (1.16–2.50)	0.006
100–199	1.46 (1.39–1.55)	<0.001	1.26 (1.19–1.34)	<0.001	1.23 (1.16–1.30)	<0.001	1.04 (0.98–1.11)	0.170
200–239	Reference							
≥240	1.12 (1.06–1.19)	<0.001	1.02 (0.96–1.08)	0.478	1.03 (0.97–1.09)	0.350	1.07 (1.01–1.14)	0.024
RC								
≤18.9	1.03 (0.97–1.10)	0.306	1.10 (1.04–1.18)	0.002	1.10 (1.03–1.17)	0.004	1.03 (0.97–1.10)	0.348
18.9–25.2	Reference							
25.2–32.7	0.99 (0.93–1.05)	0.673	0.95 (0.90–1.02)	0.156	0.96 (0.90–1.02)	0.166	1.00 (0.94–1.07)	0.967
>32.7	0.93 (0.87–1.00)	0.036	0.95 (0.89–1.01)	0.090	0.94 (0.88–1.00)	0.058	1.01 (0.95–1.08)	0.763
b. Participants taking cholesterol-lowering medication								
LDL-C								
<70	1.32 (1.12–1.56)	<0.001	1.28 (1.09–1.52)	0.003	1.23 (1.04–1.45)	0.014	1.07 (0.90–1.27)	0.430
70–99	1.17 (1.08–1.28)	<0.001	1.12 (1.03–1.22)	0.011	1.10 (1.01–1.20)	0.029	1.04 (0.95–1.13)	0.407
100–129	Reference							
130–159	0.98 (0.87–1.11)	0.773	1.09 (0.96–1.23)	0.169	1.09 (0.97–1.23)	0.164	1.12 (0.99–1.26)	0.076
≥160	1.16 (0.97–1.37)	0.097	1.42 (1.20–1.68)	<0.001	1.41 (1.19–1.67)	<0.001	1.46 (1.23–1.73)	<0.001
HDL-C								
≤40	1.12 (1.02–1.23)	0.014	1.23 (1.12–1.36)	<0.001	1.18 (1.07–1.30)	<0.001	1.11 (1.01–1.22)	0.039
41–59	Reference							
60–79	1.10 (0.99–1.21)	0.071	1.04 (0.94–1.15)	0.474	1.07 (0.96–1.19)	0.212	1.10 (0.99–1.22)	0.069
≥80	1.25 (1.03–1.52)	0.022	1.21 (0.99–1.47)	0.066	1.25 (1.03–1.53)	0.026	1.27 (1.04–1.56)	0.017
TG								
<150	Reference							
150–199	0.98 (0.89–1.08)	0.660	1.00 (0.91–1.10)	0.971	0.99 (0.90–1.09)	0.837	0.98 (0.89–1.08)	0.642
≥200	0.85 (0.77–0.93)	<0.001	0.95 (0.87–1.05)	0.319	0.94 (0.86–1.03)	0.180	0.91 (0.83–1.00)	0.045
TC								
<100	1.66 (1.03–2.70)	0.039	1.69 (1.04–2.74)	0.034	1.54 (0.95–2.50)	0.082	1.25 (0.77–2.03)	0.376
100–199	1.17 (1.07–1.29)	0.001	1.08 (0.98–1.20)	0.104	1.06 (0.96–1.17)	0.224	1.00 (0.90–1.10)	0.969
200–239	Reference							
≥240	1.19 (1.02–1.40)	0.031	1.33 (1.14–1.56)	<0.001	1.33 (1.13–1.56)	<0.001	1.34 (1.14–1.57)	<0.001

Table 2. Cox Proportional Hazards Regression Models for (A) All-Cause Dementia, (B) AD, and (C) VD according to Lipid Profile Ranges (Continued)

Variable	Unadjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
RC								
≤18.9	1.05 (0.96–1.15)	0.302	1.01 (0.92–1.11)	0.772	1.02 (0.93–1.12)	0.725	0.99 (0.91–1.09)	0.907
18.9–25.2	Reference							
25.2–32.7	0.85 (0.76–0.96)	0.006	0.90 (0.80–1.01)	0.066	0.90 (0.81–1.01)	0.073	0.91 (0.82–1.02)	0.113
>32.7	0.87 (0.76–0.98)	0.021	1.06 (0.94–1.20)	0.366	1.05 (0.93–1.19)	0.423	1.07 (0.94–1.21)	0.307
c. Participants not taking cholesterol-lowering medication								
LDL-C								
<70	2.40 (1.78–3.23)	<0.001	2.27 (1.68–3.06)	<0.001	2.18 (1.62–2.94)	<0.001	1.93 (1.43–2.61)	<0.001
70–99	1.07 (0.94–1.22)	0.327	1.33 (1.17–1.52)	<0.001	1.29 (1.14–1.47)	<0.001	1.25 (1.09–1.42)	0.001
100–129	Reference							
130–159	1.18 (1.10–1.28)	<0.001	0.96 (0.89–1.04)	0.350	0.98 (0.90–1.05)	0.512	0.99 (0.91–1.06)	0.710
≥160	1.36 (1.26–1.46)	<0.001	1.00 (0.92–1.08)	0.995	1.01 (0.93–1.09)	0.861	1.02 (0.94–1.10)	0.611
HDL-C								
≤40	1.21 (1.10–1.33)	<0.001	1.29 (1.17–1.41)	<0.001	1.22 (1.11–1.34)	<0.001	1.19 (1.08–1.30)	<0.001
41–59	Reference							
60–79	1.03 (0.97–1.10)	0.335	0.97 (0.91–1.04)	0.452	1.01 (0.94–1.08)	0.875	1.01 (0.94–1.08)	0.798
≥80	1.10 (0.99–1.23)	0.082	0.97 (0.86–1.08)	0.563	1.02 (0.90–1.14)	0.800	1.01 (0.90–1.14)	0.819
TG								
<150	Reference							
150–199	1.22 (1.14–1.32)	<0.001	1.00 (0.93–1.08)	0.959	0.99 (0.91–1.06)	0.701	0.98 (0.91–1.06)	0.632
≥200	1.08 (1.01–1.16)	0.033	0.95 (0.88–1.03)	0.202	0.93 (0.86–1.00)	0.046	0.91 (0.85–0.98)	0.015
TC								
<100	6.78 (3.64–12.63)	<0.001	5.31 (2.85–9.89)	<0.001	4.98 (2.67–9.28)	<0.001	4.37 (2.34–8.15)	<0.001
100–199	0.93 (0.87–1.01)	0.086	1.17 (1.08–1.27)	<0.001	1.14 (1.06–1.24)	<0.001	1.11 (1.03–1.20)	0.007
200–239	Reference							
≥240	1.24 (1.16–1.32)	<0.001	1.05 (0.99–1.12)	0.123	1.06 (0.99–1.13)	0.093	1.06 (0.99–1.13)	0.080
RC								
≤18.9	0.85 (0.78–0.93)	<0.001	1.08 (0.99–1.18)	0.091	1.08 (0.98–1.17)	0.110	1.07 (0.98–1.17)	0.150
18.9–25.2	Reference							
25.2–32.7	1.16 (1.07–1.25)	<0.001	1.04 (0.96–1.12)	0.379	1.03 (0.95–1.12)	0.449	1.04 (0.96–1.12)	0.375
>32.7	1.13 (1.04–1.22)	0.003	1.01 (0.93–1.10)	0.779	1.00 (0.92–1.08)	0.911	1.00 (0.92–1.08)	0.968
B. AD								
a. Total participants								
LDL-C								
<70	1.82 (1.38–2.39)	<0.001	1.25 (0.95–1.64)	0.115	1.22 (0.92–1.60)	0.165	1.02 (0.77–1.35)	0.870
70–99	1.47 (1.30–1.66)	<0.001	1.18 (1.05–1.33)	0.007	1.17 (1.03–1.32)	0.013	1.04 (0.91–1.18)	0.565
100–129	Reference							
130–159	1.03 (0.93–1.14)	0.564	1.03 (0.93–1.13)	0.626	1.03 (0.93–1.14)	0.527	1.13 (1.02–1.25)	0.023
≥160	1.20 (1.08–1.33)	<0.001	1.09 (0.99–1.21)	0.089	1.10 (0.99–1.22)	0.064	1.23 (1.10–1.38)	<0.001
HDL-C								
≤40	1.22 (1.09–1.36)	<0.001	1.26 (1.12–1.42)	<0.001	1.23 (1.09–1.38)	<0.001	1.17 (1.04–1.32)	0.008
41–59	Reference							
60–79	1.08 (0.99–1.18)	0.073	1.02 (0.93–1.12)	0.682	1.04 (0.94–1.14)	0.445	1.05 (0.96–1.16)	0.263
≥80	1.18 (1.02–1.36)	0.030	1.03 (0.88–1.20)	0.726	1.05 (0.90–1.23)	0.507	1.07 (0.92–1.25)	0.398
TG								
<150	Reference							
150–199	1.14 (1.03–1.26)	0.008	0.97 (0.88–1.07)	0.559	0.97 (0.88–1.07)	0.492	0.97 (0.87–1.06)	0.478
≥200	1.02 (0.93–1.12)	0.716	0.95 (0.86–1.05)	0.310	0.94 (0.85–1.03)	0.206	0.93 (0.84–1.02)	0.134

Table 2. Cox Proportional Hazards Regression Models for (A) All-Cause Dementia, (B) AD, and (C) VD according to Lipid Profile Ranges (Continued)

Variable	Unadjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
TC								
<100	1.67 (0.62–4.45)	0.309	1.15 (0.43–3.08)	0.775	1.09 (0.41–2.91)	0.867	0.84 (0.31–2.25)	0.727
100–199	1.23 (1.12–1.35)	<0.001	1.11 (1.01–1.22)	0.034	1.09 (0.99–1.20)	0.074	0.95 (0.86–1.06)	0.367
200–239					Reference			
≥240	1.26 (1.15–1.38)	<0.001	1.11 (1.01–1.22)	0.027	1.12 (1.02–1.23)	0.021	1.16 (1.05–1.27)	0.002
RC								
≤18.9	0.89 (0.80–0.99)	0.040	0.95 (0.85–1.06)	0.349	0.95 (0.85–1.05)	0.317	0.91 (0.81–1.01)	0.074
18.9–25.2					Reference			
25.2–32.7	0.97 (0.87–1.07)	0.533	0.94 (0.85–1.04)	0.252	0.94 (0.85–1.05)	0.260	0.97 (0.87–1.08)	0.566
>32.7	0.95 (0.86–1.05)	0.332	0.98 (0.88–1.09)	0.687	0.98 (0.88–1.08)	0.656	1.03 (0.92–1.14)	0.633
b. Participants taking cholesterol-lowering medication								
LDL-C								
<70	1.07 (0.79–1.45)	0.674	1.09 (0.80–1.49)	0.578	1.07 (0.79–1.46)	0.667	0.99 (0.73–1.36)	0.975
70–99	1.07 (0.92–1.25)	0.366	1.04 (0.89–1.21)	0.607	1.03 (0.89–1.20)	0.671	1.00 (0.86–1.17)	0.974
100–129					Reference			
130–159	0.94 (0.76–1.16)	0.563	1.03 (0.84–1.27)	0.753	1.04 (0.84–1.28)	0.742	1.05 (0.85–1.29)	0.660
≥160	1.16 (0.87–1.55)	0.314	1.41 (1.06–1.88)	0.020	1.42 (1.06–1.90)	0.017	1.45 (1.08–1.93)	0.013
HDL-C								
≤40	1.00 (0.84–1.18)	0.985	1.18 (0.99–1.40)	0.065	1.16 (0.97–1.38)	0.098	1.12 (0.94–1.34)	0.194
41–59					Reference			
60–79	1.24 (1.05–1.47)	0.012	1.09 (0.91–1.29)	0.358	1.09 (0.92–1.30)	0.313	1.11 (0.93–1.32)	0.247
≥80	1.31 (0.94–1.83)	0.106	1.11 (0.79–1.56)	0.532	1.13 (0.80–1.58)	0.487	1.13 (0.81–1.59)	0.465
TG								
<150					Reference			
150–199	0.90 (0.76–1.07)	0.231	0.95 (0.80–1.12)	0.529	0.95 (0.80–1.12)	0.540	0.94 (0.79–1.11)	0.477
≥200	0.74 (0.63–0.86)	<0.001	0.87 (0.74–1.03)	0.105	0.87 (0.74–1.03)	0.102	0.85 (0.72–1.01)	0.060
TC								
<100	0.56 (0.14–2.24)	0.411	0.64 (0.16–2.57)	0.527	0.60 (0.15–2.43)	0.474	0.54 (0.13–2.17)	0.382
100–199	1.08 (0.92–1.28)	0.336	1.05 (0.89–1.24)	0.584	1.04 (0.88–1.23)	0.642	1.01 (0.85–1.19)	0.916
200–239					Reference			
≥240	1.18 (0.90–1.54)	0.235	1.31 (1.00–1.72)	0.049	1.32 (1.01–1.73)	0.043	1.33 (1.01–1.74)	0.039
RC								
≤18.9	0.96 (0.82–1.13)	0.631	0.91 (0.78–1.07)	0.253	0.91 (0.78–1.07)	0.258	0.90 (0.77–1.06)	0.208
18.9–25.2					Reference			
25.2–32.7	0.71 (0.58–0.87)	<0.001	0.76 (0.62–0.92)	0.006	0.76 (0.62–0.93)	0.007	0.76 (0.62–0.93)	0.008
>32.7	0.79 (0.64–0.98)	0.029	0.98 (0.80–1.22)	0.889	0.99 (0.80–1.23)	0.935	0.99 (0.80–1.23)	0.963
c. Participants not taking cholesterol-lowering medication								
LDL-C								
<70	1.42 (0.73–2.74)	0.302	1.42 (0.73–2.75)	0.302	1.39 (0.71–2.68)	0.335	1.30 (0.67–2.53)	0.434
70–99	0.96 (0.76–1.22)	0.761	1.23 (0.97–1.55)	0.087	1.21 (0.95–1.52)	0.117	1.18 (0.94–1.50)	0.159
100–129					Reference			
130–159	1.42 (1.26–1.61)	<0.001	1.15 (1.02–1.30)	0.028	1.16 (1.02–1.31)	0.022	1.16 (1.03–1.32)	0.018
≥160	1.72 (1.51–1.95)	<0.001	1.24 (1.09–1.41)	0.001	1.24 (1.09–1.41)	<0.001	1.25 (1.10–1.42)	<0.001
HDL-C								
≤40	1.14 (0.98–1.33)	0.097	1.30 (1.11–1.52)	0.001	1.26 (1.07–1.47)	0.004	1.24 (1.06–1.46)	0.007
41–59					Reference			
60–79	1.17 (1.05–1.30)	0.003	1.02 (0.92–1.14)	0.686	1.04 (0.94–1.16)	0.446	1.04 (0.94–1.17)	0.435
≥80	1.32 (1.12–1.56)	<0.001	1.04 (0.87–1.24)	0.690	1.07 (0.90–1.28)	0.453	1.07 (0.90–1.27)	0.464

Table 2. Cox Proportional Hazards Regression Models for (A) All-Cause Dementia, (B) AD, and (C) VD according to Lipid Profile Ranges (Continued)

Variable	Unadjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
TG								
<150				Reference				
150–199	1.17 (1.04–1.31)	0.011	0.98 (0.87–1.11)	0.777	0.97 (0.86–1.10)	0.678	0.97 (0.86–1.10)	0.654
≥200	1.06 (0.94–1.18)	0.357	0.99 (0.88–1.11)	0.855	0.97 (0.86–1.10)	0.642	0.96 (0.86–1.09)	0.553
TC								
<100	3.49 (0.87–13.98)	0.078	2.98 (0.74–11.96)	0.123	2.86 (0.71–11.46)	0.138	2.67 (0.67–10.74)	0.165
100–199	0.75 (0.66–0.86)	<0.001	0.97 (0.85–1.11)	0.646	0.95 (0.83–1.09)	0.494	0.94 (0.82–1.08)	0.394
200–239				Reference				
≥240	1.38 (1.25–1.53)	<0.001	1.14 (1.03–1.27)	0.010	1.15 (1.04–1.27)	0.008	1.15 (1.04–1.27)	0.008
RC								
≤18.9	0.71 (0.62–0.83)	<0.001	0.89 (0.77–1.04)	0.137	0.89 (0.77–1.03)	0.130	0.89 (0.77–1.03)	0.121
18.9–25.2				Reference				
25.2–32.7	1.17 (1.03–1.32)	0.015	1.06 (0.93–1.20)	0.378	1.05 (0.93–1.19)	0.410	1.06 (0.93–1.20)	0.394
>32.7	1.15 (1.01–1.30)	0.030	1.06 (0.93–1.20)	0.378	1.05 (0.92–1.19)	0.469	1.05 (0.92–1.19)	0.466
C. VD								
a. Total participants								
LDL-C								
<70	3.62 (2.75–4.76)	<0.001	2.09 (1.59–2.75)	<0.001	1.97 (1.50–2.60)	<0.001	1.30 (0.98–1.73)	0.067
70–99	1.89 (1.63–2.21)	<0.001	1.40 (1.20–1.63)	<0.001	1.35 (1.16–1.58)	<0.001	1.04 (0.88–1.21)	0.669
100–129				Reference				
130–159	0.64 (0.55–0.75)	<0.001	0.67 (0.58–0.79)	<0.001	0.69 (0.59–0.80)	<0.001	0.86 (0.73–1.02)	0.077
≥160	0.84 (0.72–0.98)	0.027	0.84 (0.72–0.98)	0.026	0.85 (0.73–1.00)	0.045	1.14 (0.96–1.35)	0.126
HDL-C								
≤40	1.65 (1.43–1.90)	<0.001	1.41 (1.22–1.64)	<0.001	1.31 (1.13–1.52)	<0.001	1.12 (0.96–1.30)	0.142
41–59				Reference				
60–79	0.81 (0.70–0.92)	0.002	0.95 (0.82–1.09)	0.462	0.99 (0.86–1.14)	0.893	1.06 (0.92–1.23)	0.398
≥80	0.71 (0.55–0.93)	0.012	0.89 (0.68–1.17)	0.413	0.95 (0.72–1.25)	0.704	1.01 (0.77–1.33)	0.927
TG								
<150				Reference				
150–199	1.37 (1.19–1.58)	<0.001	1.04 (0.90–1.20)	0.613	1.02 (0.88–1.18)	0.794	1.02 (0.88–1.17)	0.830
≥200	1.44 (1.27–1.64)	<0.001	1.12 (0.98–1.28)	0.091	1.08 (0.95–1.23)	0.251	1.04 (0.91–1.19)	0.565
TC								
<100	11.71 (6.24–21.99)	<0.001	6.09 (3.24–11.47)	<0.001	5.43 (2.88–10.24)	<0.001	2.88 (1.52–5.46)	0.001
100–199	2.33 (2.03–2.67)	<0.001	1.85 (1.61–2.13)	<0.001	1.78 (1.55–2.05)	<0.001	1.28 (1.10–1.49)	0.002
200–239				Reference				
≥240	1.27 (1.08–1.48)	0.003	1.19 (1.02–1.40)	0.028	1.20 (1.03–1.41)	0.022	1.32 (1.13–1.55)	<0.001
RC								
≤18.9	1.19 (1.02–1.38)	0.022	1.28 (1.10–1.49)	0.001	1.28 (1.10–1.48)	0.001	1.12 (0.96–1.30)	0.137
18.9–25.2				Reference				
25.2–32.7	0.93 (0.79–1.09)	0.347	0.89 (0.76–1.04)	0.149	0.89 (0.76–1.05)	0.160	0.99 (0.84–1.16)	0.880
>32.7	0.93 (0.79–1.09)	0.363	0.92 (0.78–1.08)	0.302	0.91 (0.78–1.07)	0.246	1.08 (0.92–1.27)	0.344
b. Participants taking cholesterol-lowering medication								
LDL-C								
<70	1.62 (1.18–2.23)	0.003	1.47 (1.06–2.02)	0.019	1.37 (1.00–1.90)	0.053	1.11 (0.80–1.54)	0.534
70–99	1.18 (0.98–1.42)	0.075	1.10 (0.91–1.32)	0.324	1.07 (0.89–1.29)	0.471	0.97 (0.81–1.17)	0.783
100–129				Reference				
130–159	0.89 (0.68–1.16)	0.377	1.00 (0.76–1.30)	0.981	1.00 (0.76–1.30)	0.973	1.04 (0.79–1.35)	0.795
≥160	1.56 (1.14–2.15)	0.006	1.97 (1.43–2.71)	<0.001	1.94 (1.41–2.66)	<0.001	2.05 (1.49–2.82)	<0.001

Table 2. Cox Proportional Hazards Regression Models for (A) All-Cause Dementia, (B) AD, and (C) VD according to Lipid Profile Ranges (Continued)

Variable	Unadjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
HDL-C								
≤40	1.21 (1.00–1.46)	0.045	1.20 (0.99–1.45)	0.068	1.11 (0.91–1.35)	0.287	1.01 (0.83–1.23)	0.897
41–59					Reference			
60–79	0.99 (0.80–1.24)	0.961	1.06 (0.85–1.33)	0.594	1.11 (0.89–1.40)	0.352	1.17 (0.93–1.47)	0.173
≥80	1.04 (0.67–1.62)	0.857	1.22 (0.78–1.91)	0.387	1.30 (0.83–2.03)	0.260	1.33 (0.85–2.09)	0.214
TG								
<150					Reference			
150–199	1.09 (0.90–1.34)	0.378	1.07 (0.87–1.31)	0.509	1.06 (0.86–1.29)	0.599	1.04 (0.85–1.27)	0.715
≥200	1.00 (0.83–1.20)	0.996	1.04 (0.86–1.26)	0.653	1.02 (0.84–1.23)	0.851	0.98 (0.81–1.18)	0.814
TC								
<100	3.35 (1.56–7.19)	0.002	2.87 (1.33–6.20)	0.007	2.52 (1.17–5.43)	0.019	1.84 (0.85–3.98)	0.124
100–199	1.31 (1.06–1.62)	0.012	1.13 (0.91–1.40)	0.257	1.10 (0.89–1.36)	0.390	0.99 (0.80–1.23)	0.936
200–239					Reference			
≥240	1.59 (1.16–2.18)	0.004	1.79 (1.30–2.47)	<0.001	1.78 (1.29–2.44)	<0.001	1.81 (1.31–2.48)	<0.001
RC								
≤18.9	1.09 (0.90–1.33)	0.376	1.08 (0.89–1.32)	0.431	1.09 (0.89–1.32)	0.400	1.05 (0.86–1.28)	0.626
18.9–25.2					Reference			
25.2–32.7	0.90 (0.71–1.14)	0.403	0.94 (0.75–1.20)	0.636	0.95 (0.75–1.20)	0.658	0.97 (0.76–1.23)	0.790
>32.7	0.93 (0.72–1.20)	0.591	1.11 (0.86–1.44)	0.423	1.10 (0.85–1.42)	0.484	1.12 (0.87–1.45)	0.373
c. Participants not taking cholesterol-lowering medication								
LDL-C								
<70	5.02 (2.91–8.66)	<0.001	4.23 (2.44–7.31)	<0.001	4.00 (2.31–6.93)	<0.001	3.02 (1.73–5.27)	<0.001
70–99	1.41 (1.04–1.92)	0.025	1.74 (1.29–2.36)	<0.001	1.68 (1.24–2.28)	<0.001	1.52 (1.12–2.07)	0.007
100–129					Reference			
130–159	0.94 (0.77–1.16)	0.567	0.76 (0.62–0.93)	0.009	0.77 (0.63–0.95)	0.013	0.79 (0.65–0.97)	0.027
≥160	1.32 (1.08–1.62)	0.006	0.96 (0.79–1.18)	0.720	0.97 (0.79–1.19)	0.759	1.00 (0.82–1.23)	0.979
HDL-C								
≤40	1.50 (1.20–1.87)	<0.001	1.48 (1.18–1.87)	<0.001	1.39 (1.11–1.76)	0.005	1.29 (1.02–1.63)	0.030
41–59					Reference			
60–79	0.94 (0.78–1.12)	0.477	0.96 (0.79–1.16)	0.662	0.99 (0.82–1.20)	0.950	1.00 (0.83–1.21)	0.969
≥80	0.83 (0.60–1.15)	0.272	0.84 (0.60–1.18)	0.320	0.88 (0.63–1.24)	0.478	0.88 (0.62–1.24)	0.463
TG								
<150					Reference			
150–199	1.34 (1.10–1.63)	0.004	1.01 (0.83–1.24)	0.918	0.99 (0.81–1.21)	0.941	0.98 (0.81–1.20)	0.880
≥200	1.48 (1.23–1.77)	<0.001	1.18 (0.98–1.42)	0.084	1.13 (0.94–1.37)	0.187	1.09 (0.90–1.31)	0.384
TC								
<100	17.88 (5.71–55.91)	<0.001	11.84 (3.77–37.13)	<0.001	11.53 (3.67–36.20)	<0.001	8.70 (2.76–27.40)	<0.001
100–199	1.54 (1.27–1.88)	<0.001	1.90 (1.55–2.32)	<0.001	1.85 (1.51–2.26)	<0.001	1.73 (1.41–2.12)	<0.001
200–239					Reference			
≥240	1.51 (1.25–1.81)	<0.001	1.29 (1.07–1.56)	0.007	1.30 (1.08–1.56)	0.006	1.30 (1.08–1.57)	0.005
RC								
≤18.9	0.97 (0.77–1.23)	0.815	1.28 (1.02–1.62)	0.036	1.28 (1.01–1.62)	0.039	1.25 (0.99–1.59)	0.059
18.9–25.2					Reference			
25.2–32.7	1.15 (0.92–1.42)	0.221	0.99 (0.80–1.23)	0.924	0.98 (0.79–1.22)	0.881	1.00 (0.80–1.24)	0.999
>32.7	1.27 (1.03–1.57)	0.027	1.07 (0.86–1.32)	0.538	1.04 (0.84–1.29)	0.693	1.05 (0.85–1.30)	0.622

AD, Alzheimer's disease; VD, vascular dementia; HR, hazard ratio; CI, confidence intervals; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; RC, remnant cholesterol; BMI, body mass index.

Model 1, adjusted for age, sex, and BMI; Model 2, adjusted for age, sex, BMI, smoking status, alcohol intake, and regular exercise; Model 3, adjusted for age, sex, BMI, smoking status, alcohol intake, and regular exercise, presence of diabetes, hypertension, and taking cholesterol-lowering medication.

tion. The lowest HDL-C range of ≤ 40 mg/dL was associated with elevated CVD risk for participants taking and not taking cholesterol-lowering medication [HR: 1.17 (95% CI: 1.12–1.22), $p < 0.001$; HR: 1.16 (95% CI: 1.13–1.19), $p < 0.001$, respectively].

For participants not taking medication, higher HDL-C levels of ≥ 80 mg/dL and 60–79 mg/dL demonstrated protective effects against CVDs [HR: 0.94 (95% CI: 0.90–0.98), $p = 0.002$; HR: 0.92 (95% CI: 0.89–0.94), $p < 0.001$, respectively]. A higher TG

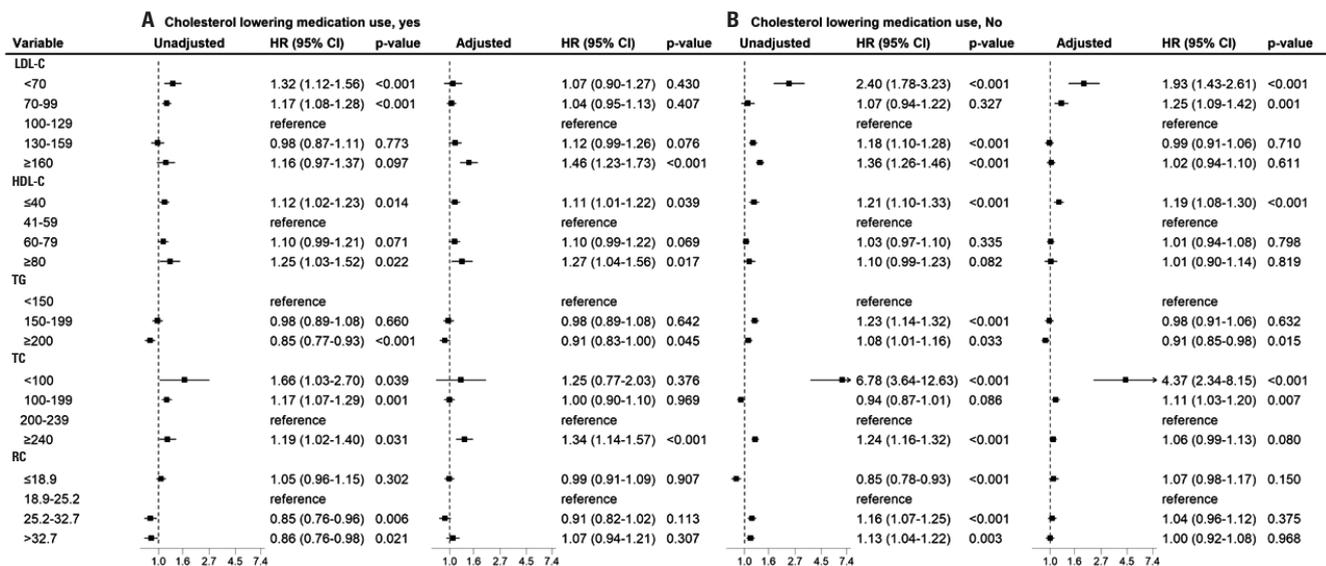


Fig. 2. Forest plot of HRs for all-cause dementia by lipid profile ranges. (A) HRs for incident dementia in participants using cholesterol-lowering medication. (B) HRs for incident dementia in participants not using cholesterol-lowering medication. HRs are presented for various lipid profile ranges, including LDL-C, HDL-C, TG, TC, and RC. Models were adjusted for age, sex, body mass index, smoking status, alcohol intake, regular exercise, diabetes, and hypertension. Error bars indicate 95% CIs. HR, hazard ratio; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; TC, total cholesterol; RC, remnant cholesterol.

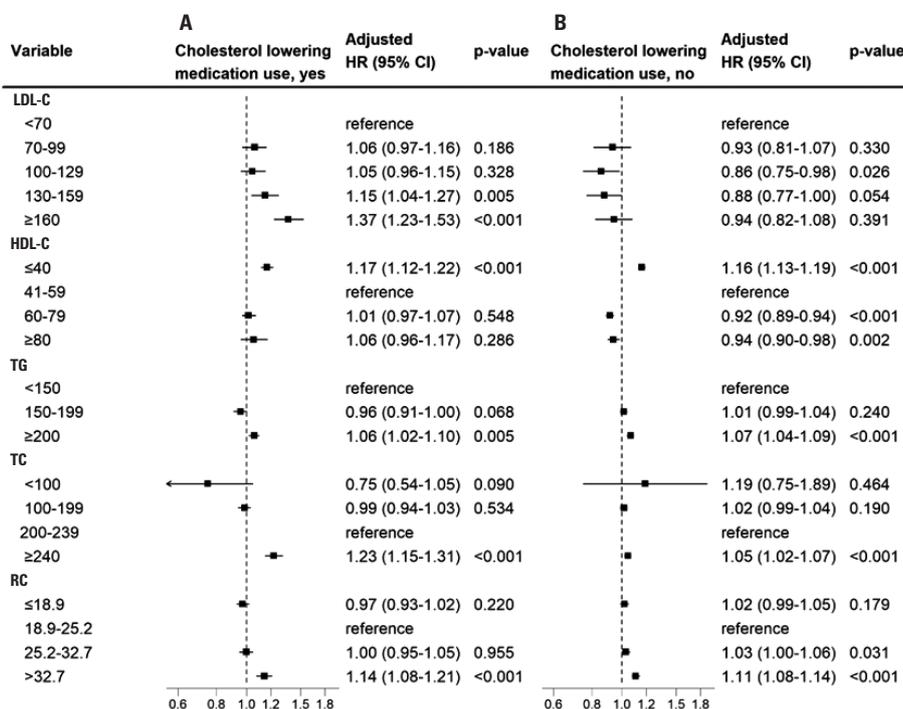


Fig. 3. Forest plot of HRs for incident CVD by lipid profile ranges. (A) HRs for incident CVD in participants using cholesterol-lowering medication. (B) HRs for incident CVD in participants not using cholesterol-lowering medication. HRs are presented for various lipid profile ranges, including LDL-C, HDL-C, TG, TC, and RC. Models were adjusted for age, sex, body mass index, smoking status, alcohol intake, regular exercise, diabetes, and hypertension. Error bars indicate 95% CIs. HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; TC, total cholesterol; RC, remnant cholesterol.

level of ≥ 200 mg/dL was associated with elevated CVD risk for both subgroups [HR: 1.06 (95% CI: 1.02–1.10), $p=0.005$; HR: 1.07 (95% CI: 1.04–1.09), $p<0.001$]. Higher TC (≥ 240 mg/dL) was linked to increased CVD risk for both subgroups [HR: 1.23 (95% CI: 1.15–1.31), $p<0.001$; HR: 1.05 (95% CI: 1.02–1.07), $p<0.001$]. Furthermore, higher RC (>32.7 mg/dL) was linked to increased CVD risk for both subgroups. Supplementary Fig. 3 (only online) shows a forest plot for the incident CVD for the unadjusted models.

DISCUSSION

Our study revealed distinct links between lipid levels and dementia and CVD risks, which differed based on the use of cholesterol-lowering medications and the subtype of dementia. Among individuals on cholesterol-lowering therapy, high LDL-C (≥ 160 mg/dL) and high TC (≥ 240 mg/dL) were consistently linked to elevated risks of all-cause dementia, AD, VD, and CVD. Contrastingly, in individuals not taking medication, low LDL-C (<70 mg/dL), low HDL-C (≤ 40 mg/dL), and low TC (<100 mg/dL) were associated with higher dementia risk, particularly VD; however, no significant link was noted between LDL-C and CVD. Increased TG levels (≥ 200 mg/dL) were protective against all-cause dementia in all groups but were associated with higher CVD risk. Low HDL-C (≤ 40 mg/dL) was also linked to an increased AD risk in the overall population and those not taking medication, as well as a consistently higher CVD risk regardless of medication use. High HDL-C (≥ 60 mg/dL) was protective against CVD in those not taking medication but showed variable associations with dementia. Increased RC (>32.7 mg/dL) consistently indicated a higher CVD risk but was not significantly related to dementia.

One of the key findings of our study is the divergent association of LDL-C with dementia risk depending on dementia subtypes and cholesterol-lowering medication use. Among those not taking cholesterol-lowering medication, low LDL-C (<70 mg/dL) and low TC (<100 mg/dL) were significantly associated with elevated risk of all-cause dementia and VD, suggesting that inadequate systemic cholesterol levels may compromise synaptic integrity and neuroprotection. These findings are in line with prior studies showing that excessively low cholesterol may impair neuronal function and increase neurodegenerative vulnerability.^{28,29} Conversely, among those taking cholesterol-lowering medication, high LDL-C (≥ 160 mg/dL) and high TC (≥ 240 mg/dL) levels were associated with increased risk of AD, VD, and all-cause dementia, supporting the idea that persistent dyslipidemia despite treatment may accelerate neurodegeneration.

Furthermore, low HDL-C (≤ 40 mg/dL) was consistently associated with higher all-cause dementia risk across all groups, higher AD risk in the overall population and those not taking medication, and higher VD risk in those not taking chole-

sterol-lowering medication. Given the role of HDL-C in anti-inflammatory and antioxidant processes, decreased levels may contribute to greater neuroinflammation and impaired amyloid-beta clearance, reinforcing the protective role of HDL-C in cognitive health.³⁰ Increased TG levels (≥ 200 mg/dL) were associated with a lower risk of all-cause dementia in all groups, though no significant association was found with AD or VD specifically. While hypertriglyceridemia is a known risk factor for metabolic syndrome and CVD, some studies have suggested a potential neuroprotective effect of higher TG levels,¹³ likely due to their role in lipid metabolism and brain energy supply,³¹ although further mechanistic research is needed.

Despite extensive research, the role of lipid abnormalities in dementia remains debated, with large cohort studies from the UK Biobank, U.S., Korea, and China reporting U-shaped associations between LDL-C, HDL-C, and TC with dementia risk,^{13–15,32} which we further support by showing subtype-specific patterns and stratification by cholesterol-lowering medication use. A previous study involving Korean adults aged ≥ 40 years similarly reported that higher LDL-C levels correlated with elevated all-cause dementia risk in statin users, whereas in non-users, lower LDL-C levels were associated with a higher risk.¹⁵ Furthermore, findings from the Shanghai Aging Study suggest that among individuals without vascular risk factors, higher TC and LDL-C levels may be inversely associated with all-cause dementia risk, and LDL-C was inversely correlated with incident AD, emphasizing the complex interplay between lipid metabolism and neurodegeneration.³² Partially aligning with prior studies, our findings suggest that high LDL-C and TC levels may increase AD risk regardless of cholesterol-lowering treatment status, whereas very low lipid levels may predominantly contribute to higher VD risk, particularly among individuals not taking cholesterol-lowering medication.

Such differential associations by dementia subtype may reflect underlying pathophysiological differences between AD and VD. AD is characterized by amyloid deposition and neurofibrillary tangles, processes that may be exacerbated by lipid-induced neuroinflammation and oxidative stress,^{6,8} while VD is more tightly linked to vascular pathology, cerebral perfusion, and endothelial function.⁹ As cholesterol is essential for maintaining the structural integrity of vascular endothelial cells—contributing to lipid raft formation, BBB function, and overall vascular stability—insufficient cholesterol may compromise vascular integrity and repair mechanisms, thereby elevating VD risk.^{33,34} The effects of cholesterol-lowering therapy, especially statins, add a further layer of complexity to these associations. While concerns exist about potential cognitive side effects, an elderly Australian cohort study found that statin users did not exhibit accelerated cognitive decline compared to non-users.³⁵ Beyond lowering LDL-C, statins also exert pleiotropic effects that promote neuroprotective actions by reducing inflammation and enhancing endothelial function through nitric oxide synthesis and tumor necrosis factor-alpha suppres-

sion.³⁶ These mechanisms may help mitigate neurovascular dysfunction and neuronal damage, thereby potentially decreasing dementia risk. This could explain why, in our study, low LDL-C levels in statin users were not significantly associated with elevated dementia risk. While aggressive lowering of LDL-C remains necessary for preventing CVD, our results suggest that caution is warranted when aggressively lowering LDL-C in individuals not taking cholesterol-lowering medication, as very low levels may be detrimental to cognitive health. Aging-related BBB dysfunction is another critical factor, as early BBB breakdown in AD can facilitate the entry of peripheral cholesterol into the brain.³⁷ Cholesterol deficiency within the brain may impair synaptic transmission, disrupt membrane integrity, and contribute to neurodegeneration.^{6,37} Thus, maintaining moderate lipid levels in individuals with low metabolic or vascular risk is likely beneficial for cognitive health.

Consistent with established guidelines, our study confirmed that higher LDL-C, lower HDL-C, higher TG, and higher RC levels were associated with an increased CVD risk.^{1,22,23} High LDL-C (≥ 160 mg/dL) was strongly related to an increased CVD risk, especially among individuals on cholesterol-lowering therapy. This result reinforces the well-documented role of LDL-C as a major driver of atherosclerosis and cardiovascular events.¹ Notably, no significant association was observed between LDL-C and CVD risk in individuals not taking cholesterol-lowering medication. This discrepancy may be attributed to overall lower cardiovascular risk profiles in this group, such as healthier lifestyle habits or genetic predispositions, which could mitigate the impact of high LDL-C. Higher RC (>32.7 mg/dL) consistently exhibited a higher CVD risk across all groups, reinforcing its potential as a marker of residual cardiovascular risk beyond traditional lipid measures.³⁸ However, RC was not markedly associated with dementia, suggesting that its impact is more directly related to atherosclerotic disease rather than neurodegenerative processes. Low HDL-C (≤ 40 mg/dL) was a substantial risk factor for CVD across all groups, consistent with its role in reverse cholesterol transport and vascular protection.³⁹

The main strength of this study is its large-scale prospective design using UK Biobank data with long-term follow-up. While associations observed between lipid profiles and CVD risk are consistent with established literature, they primarily serve to support the validity of the stratified analytical approach applied in this study. The expected associations—such as increased CVD risk with high LDL-C, low HDL-C, and elevated RC—confirm the methodological robustness of the analysis. These findings also serve to reinforce the interpretation of the more complex and novel relationships observed between lipid levels and dementia. Furthermore, our study accounted for dementia subtype and cholesterol-lowering medication use altogether, providing valuable insights into their modifying effects on lipid-dementia and lipid-CVD associations.

However, this study had several limitations. First, residual confounding due to unmeasured factors such as diet, genetic

predisposition, and social determinants of health cannot be excluded despite adjustments for major confounders. Second, cholesterol-lowering medication use was based on self-reported data and may not reflect adherence or dose changes. Third, the ICD-10 codes used to define dementia and CVD outcomes may have introduced misclassification bias. In addition, as dementia diagnoses were based on medical records rather than objective cognitive assessments, the possibility of detection bias exists. Participants who are more health-conscious may be more likely to seek medical evaluation, resulting in differential diagnosis rates. This limitation is inherent to large-scale cohort datasets such as the UK Biobank and should be interpreted with caution. Furthermore, while our study identifies associations, causal relationships cannot be inferred, and further mechanistic studies are required.

While reverse causality cannot be completely ruled out, it is unlikely to fully explain the observed associations. Several other explanations may underlie the observation of elevated LDL-C levels among those taking cholesterol-lowering medication. These include suboptimal medication adherence, inadequate dosing, genetic variation affecting statin response, drug-drug interactions, and lifestyle factors such as persistent high-fat diet or sedentary behavior.

In addition, to address the potential competing risk of death—particularly relevant among participants with high LDL-C levels who may have an elevated risk of cardiovascular mortality—we conducted a Fine-Gray competing risk analysis, which yielded comparable hazard estimates. These findings support the robustness of our conclusions and suggest that the lower dementia risk observed in those with high LDL-C in those not taking cholesterol-lowering medication is unlikely to be solely explained by differential censoring due to cardiovascular deaths.

Our results underscore the importance of individualized lipid management strategies based on cardiovascular and cognitive health considerations. While aggressive LDL-C lowering remains critical for CVD prevention, our findings suggest that excessively low LDL-C is related to increased dementia risk in individuals not taking cholesterol-lowering medication, particularly for VD. Moreover, our findings reinforce the importance of maintaining optimal HDL-C levels for cardiovascular and cognitive health. Thus, strategies to improve HDL-C levels, including lifestyle modifications, such as regular physical activity and dietary interventions, should be prioritized.

In conclusion, our findings underscore the complex interplay between lipid levels and risk of dementia and CVDs, with differential effects based on dementia subtype and cholesterol-lowering medication use. While aggressive LDL-C lowering remains crucial for CVD prevention, its implications for cognitive health necessitate careful consideration. Very low LDL-C levels may be detrimental to cognitive function in individuals not taking cholesterol-lowering medication, emphasizing the need for individualized lipid management strategies. Future research should further investigate the causal impact of tailored lipid-

lowering interventions on dementia subtypes, based on individuals' underlying metabolic and vascular risk profiles.

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AUTHOR CONTRIBUTIONS

Conceptualization: all authors. **Data curation:** all authors. **Formal analysis:** all authors. **Funding acquisition:** Yu-Jin Kwon. **Investigation:** all authors. **Methodology:** Seok-Jae Heo. **Project administration:** Yu-Jin Kwon. **Resources:** all authors. **Software:** all authors. **Supervision:** Yu-Jin Kwon. **Validation:** Yu-Jin Kwon and Seok-Jae Heo. **Visualization:** all authors. **Writing—original draft:** Jong Hee Lee, Yu-Jin Kwon, and Seok-Jae Heo. **Writing—review & editing:** all authors. **Approval of final manuscript:** all authors.

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