Original research

Low-density lipoprotein cholesterol levels and risk of incident dementia: a distributed network analysis using common data models

Minwoo Lee ,[1] Kyung Joo Lee,[2] Jinseob Kim,[3] Dong Yun Lee,[4,5] Rae Woong Park,[4] Sang Youl Rhee,[6] Jae Myung Cha,[7] Hyeon-Jong Yang,[8] Jae-Won Jang,[9] Seunguk Jung,[10] Jeeun Lee,[11] Sang-Hwa Lee,[12] Chulho Kim ,[12] Jong-Seok Bae,[13] Yeo Jin Kim,[13] Ju-Hun Lee,[13] Hyoeun Bae,[13] Yerim Kim [13]

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/jnnp-2024-334708).

For numbered affiliations see end of article.

Correspondence to
Dr Yerim Kim; brainyrk@hallym.ac.kr

Received 24 July 2024
Accepted 3 February 2025

To cite: Lee M, Lee KJ, Kim J, *et al*. *J Neurol Neurosurg Psychiatry* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jnnp-2024-334708

ABSTRACT

Background The link between low-density lipoprotein cholesterol (LDL-C) levels and dementia risk is poorly understood, with conflicting evidence on the role of LDL-C and the impact of statin therapy on cognitive outcomes. Thus, we aimed to examine the association between low-density LDL-C levels and the risk of dementia and assess the influence of statin therapy.

Methods We retrospectively analysed data from 11 university hospitals participating in the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). Participants with a prior diagnosis of dementia or those with <180 days of observation before cohort inclusion, and those included in both cohorts were excluded. The primary outcome was all-cause dementia, with the secondary outcome being Alzheimer's disease-related dementia (ADRD). The study utilised 1:1 propensity score matching to compare individuals with LDL-C levels below 70 mg/dL (1.8 mmol/L) against those with levels above 130 mg/dL (3.4 mmol/L), resulting in a primary analysis cohort of 108 980 matched patients. Secondary analyses further examined LDL-C thresholds below 55 mg/dL (1.4 mmol/L) and the influence of statin use.

Results The LDL-C levels below 70 mg/dL (1.8 mmol/L) were associated with a 26% reduction in the risk of all-cause dementia and a 28% reduction in the risk of ADRD, compared with levels above 130 mg/dL (3.4 mmol/L). For LDL-C levels below 55 mg/dL (1.4 mmol/L), there was an 18% risk reduction for both outcomes. Among those with LDL-C <70 mg/dL (<1.8 mmol/L), statin use was associated with a 13% reduction in all-cause dementia risk and a 12% decrease in ADRD risk compared with non-users.

Conclusion Low LDL-C levels (<70 mg/dL (<1.8 mmol/L)) are significantly associated with a reduced risk of dementia, including ADRD, with statin therapy providing additional protective effects. These findings support the necessity of targeted lipid management as a preventive strategy against dementia, indicating the importance of personalised treatment approaches.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The relationship between low-density lipoprotein cholesterol (LDL-C) levels and dementia risk remains controversial, with inconsistent evidence from prior studies.
⇒ Recent large clinical trials have shown that lowering LDL-C to very low levels does not increase dementia risk, challenging earlier concerns.
⇒ The role of statin therapy in modulating cognitive outcomes remains debated, with some studies suggesting potential neuroprotective effects.

WHAT THIS STUDY ADDS

⇒ LDL-C levels below 70 mg/dL (1.8 mmol/L) are associated with a significant reduction in the risk of all-cause dementia (26%) and Alzheimer's disease-related dementia (28%).
⇒ Statin use contributes additional protection against dementia in individuals with LDL-C levels below 70 mg/dL (1.8 mmol/L), highlighting a synergistic effect.
⇒ Very low LDL-C levels (<30 mg/dL (<0.8 mmol/L)) do not reduce dementia risk further, suggesting a threshold effect for optimal cognitive benefit.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings emphasize the importance of targeted LDL-C management as part of dementia prevention strategies, with potential integration into clinical guidelines.
⇒ The results support the use of statin therapy within specific LDL-C ranges for both cardiovascular and cognitive health benefits.
⇒ Future research may focus on refining LDL-C thresholds and exploring mechanisms linking lipid metabolism to cognitive decline.

INTRODUCTION

The clear link between high, low-density lipoprotein cholesterol (LDL-C) levels[1] and future cardiovascular events underscores the importance of lowering LDL-C to prevent such incidents.[2] However, the relationship between LDL-C levels and dementia is complex.[3–6] Historical concerns regarding the potential risks associated with very low LDL-C levels and cognitive decline led to

cautious guidance from health authorities, including the US Food and Drug Administration.[7] This caution arose from observational studies and pharmacological interventions suggesting a paradoxical relationship between lowering LDL-C and cognitive health.[2–7]

Recent developments have challenged these concerns. Comprehensive meta-analyses and significant randomised clinical trials, such as FOURIER and ODYSSEY, show that significant LDL-C reduction, even to 30 mg/dL (0.8 mmol/L), does not increase the risk of dementia or other adverse cognitive outcomes.[8 9] These findings have prompted a guideline re-evaluation, presenting a more refined understanding of the role of LDL-C in dementia risk.[10 11] However, the exact LDL-C threshold that may potentially alter cognitive decline risk remains undefined, highlighting the need for targeted studies in this area.

Therefore, this study aims to explore the correlation between LDL-C levels and the risk of developing dementia, encompassing all-cause and Alzheimer's disease-related dementia (ADRD), within a large observational cohort recruited from 11 university-affiliated hospitals. By examining the influence of LDL-C levels and statin therapy, this research aims to assess the implications of conventional LDL-C cut-off points on dementia risk. This study could be particularly significant for clinical practice guidelines, suggesting that optimising LDL-C levels and statin therapy could serve as key elements in dementia prevention strategies.

METHODS

Data source

In this study, we utilised retrospective cohort data from patients across 11 medical centres. All relevant data were derived from the Observational Health Data Sciences and Informatics (OHDSI) network and the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). This included Ajou University Medical Centre (AUMC, n=2 959 803), Kangdong Sacred Heart Hospital (KDH, n=1 209 068), Gangdong Kyung Hee University Hospital (KHNMC, n=880 275), Kyung Hee University Hospital (KHMC, n=1 222 935), Gyeongsang National University Changwon Hospital (GNUCH, n=333 345), Kangwon National University Hospital (KWMC, n=569 218), Myungji Hospital (MJH, n=1 039 519), Soon Chun Hyang University Hospital Bucheon (SCHBC, n=1 301 117), Soon Chun Hyang University Hospital Cheonan (SCHCA, n=987 701), Soon Chun Hyang University Hospital Gumi (SCHGM, n=632 252), and Soon Chun Hyang University Hospital Seoul (SCHSU, n=1 098 041 participants). Figure 1 shows all the data adapted to the OMOP CDM.

The OHDSI initiative, a global partnership, facilitates open-source analysis of extensive health data networks worldwide. Although Korean medical centres widely use electronic health records (EHRs), several medical codes related to diagnoses, medications and procedures are incompatible with global coding standards. The OMOP CDM harmonises data across research networks using a uniform structure and analysis software among diverse entities.[12 13] This study was approved by the Institutional Review Board of Kangdong Sacred Heart Hospital (IRB No. 2023-09-002) and adhered to the ethical guidelines outlined in the Declaration of Helsinki.

Study design and cohort characteristics

This study was a retrospective, observational, comparative cohort analysis of outpatient individuals aged ≥18 years from November 1986 to December 2020. The index date was set as the day on which the LDL-C level was measured. Both cohorts

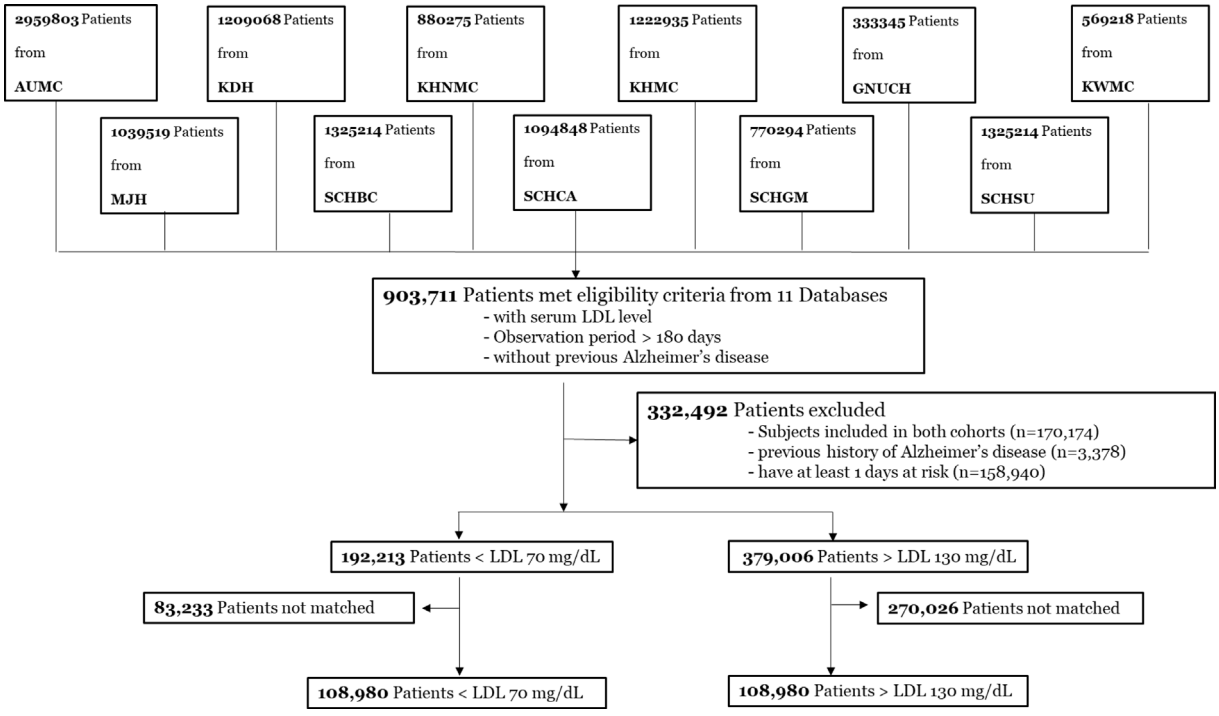

Figure 1 Flowchart of patient selection for the retrospective cohort study from 11 medical centres. AUMC, Ajou University Medical Centre; KDH, Kangdong Sacred Heart Hospital; KHNMC, Gangdong Kyung Hee University Hospital; KHMC, Kyung Hee University Hospital; GNUCH, Gyeongsang National University Changwon Hospital; KWMC, Kangwon National University Hospital; MJH, Myungji Hospital; SCHBC, Soon Chun Hyang University Hospital Bucheon; SCHCA, Soon Chun Hyang University Hospital Cheonan; SCHGM, Soon Chun Hyang University Hospital Gumi; SCHSU, Soon Chun Hyang University Hospital Seoul; LDL, low density lipoprotein.

Table 1 Distribution of baseline characteristics across 11 databases between the LDL-C ≥130 mg/dL (≥3.4 mmol/L) group and the comparative group (LDL-C <70 mg/dL (<1.8 mmol/L)) in the overall population before and after 1:1 propensity score matching

	Before PS adjustment			After PS adjustment		
	LDL <70 mg/dL (<1.8 mmol/L)	LDL ≥130 mg/dL (≥3.4 mmol/L)	SMD	LDL <70 mg/dL (<1.8 mmol/L)	LDL ≥130 mg/dL (≥3.4 mmol/L)	SMD
Age group (years)						
25–29	3.1	4.9	−0.09	4.8	4.7	0.01
30–34	3.2	8.7	−0.24	4.9	4.8	0.01
35–39	3.7	10.0	−0.25	5.5	5.4	0.00
50–54	9.2	14.3	−0.16	10.7	11.1	−0.01
55–59	11.2	11.8	−0.02	11.6	11.6	0.00
60–64	12.2	9.0	0.11	11.6	11.4	0.01
70–74	11.3	4.3	0.26	8.8	9.1	−0.01
75–79	9.6	2.7	0.29	6.5	7.0	−0.02
80–84	6.4	1.4	0.26	3.8	4.0	−0.01
85–89	2.8	0.5	0.18	1.5	1.4	0.01
Gender: female	36.0	46.9	−0.22	40.9	42.6	−0.04
Medical history: general						
Acute respiratory disease	3.5	2.0	0.09	2.6	2.6	0.00
Chronic obstructive lung disease	2.5	0.6	0.16	1.6	1.6	0.00
Diabetes mellitus	23.7	4.7	0.57	14.4	15.6	−0.03
Gastro-oesophageal reflux disease	10.0	4.2	0.22	6.5	6.7	−0.01
Gastrointestinal haemorrhage	2.7	0.5	0.17	1.3	1.2	0.00
Hyperlipidaemia	23.4	8.3	0.42	17.9	18.7	−0.02
Hypertensive disorder	36.9	10.9	0.64	26.1	27.8	−0.04
Liver lesion	6.1	1.3	0.26	3.7	3.6	0.00
Obesity	0.4	0.6	−0.03	0.6	0.6	−0.01
Renal impairment	10.0	1.5	0.37	5.1	5.6	−0.02
Medical history: cardiovascular disease						
Atrial fibrillation	3.4	0.6	0.20	2.2	2.4	−0.01
Cerebrovascular disease	8.2	2.1	0.28	5.6	5.8	−0.01
Heart disease	34.0	6.2	0.74	20.3	22.1	−0.04
Heart failure	6.1	0.9	0.29	3.2	3.5	−0.02
Ischaemic heart disease	21.3	2.5	0.61	10.3	11.5	−0.04
Medical history: neoplasms						
Malignant neoplastic disease	8.8	4.6	0.17	6.8	7.1	−0.01
Medication use						
Agents acting on the renin-angiotensin system	37.4	9.2	0.71	25.5	27.5	−0.05
Antibacterials for systemic use	31.4	14.9	0.40	23.7	24.2	−0.01
Antidepressants	14.6	7.2	0.24	11.6	11.9	−0.01
Antiepileptics	11.4	5.2	0.23	8.9	9.1	−0.01
Anti-inflammatory and antirheumatic products	48.2	20.5	0.61	37.0	38.6	−0.03
Antineoplastic agents	6.3	3.5	0.13	5.4	5.6	−0.01
Antipsoriatics	1.4	0.7	0.08	1.1	1.2	0.00
Antithrombotic agents	50.6	13.1	0.88	34.4	37.0	−0.05
Drugs for acid-related disorders	54.2	35.0	0.39	44.1	45.0	−0.02
Drugs used in diabetes	32.7	6.0	0.72	20.3	22.0	−0.04
Lipid-modifying agents	53.1	11.3	1.00	36.6	39.7	−0.06
Psycholeptics	28.6	26.6	0.05	25.4	25.5	0.00
Psychostimulants, agents used for ADHD and nootropics	3.7	1.7	0.13	3.0	3.1	−0.01

Because thousands of diseases and medications are matched between 2 groups, we cannot show all factors in table 1.
ADHD, attention deficit hyperactivity disorder; LDL-C, low-density lipoprotein cholesterol; PS, propensity score; SMD, standardised mean difference.

underwent a 180-day observation period to minimise biases such as immortal time bias and duplication.

Time-at-risk (TAR) was set to 1 day post-index date, with TAR starts set at 180 days from the beginning of the cohort. TAR ended at 99 999 days for extended follow-up until the observation period ended. Figure 1 depicts the cohort selection methodology across 11 databases. Exclusion criteria included individuals with a history of ADRD, those with <180 days of observation before cohort inclusion, and those included in both cohorts.

The primary cohort comprised 192 213 patients with LDL-C <70 mg /dL (<1.8 mmol/L) and 379 006 patients with LDL-C >130 mg/dL (>3.4 mmol/L) for comparison group. The timing of LDL-C measurements was the first value recorded in the patient's data, and the observation

period had to be at least 180 days. After 1:1 propensity score matching, 108 908 patients were matched in each group (LDL-C <70 mg/dL (<1.8 mmol/L) vs LDL-C >130 mg/dL (>3.4 mmol/L)).

Outcomes

The primary outcome was all-cause dementia, with the secondary outcome being ADRD. Definitions for all-cause dementia (F00-F03) and ADRD (F00 and G30) were based on diagnosis codes from the 10th edition of the International Classification of Diseases (ICD-10). The use of ICD-10 codes for defining all-cause dementia and ADRD has been validated in previous studies, demonstrating high positive predictive value and reliability.[14–16]

Covariates

The OMOP-CDM tool facilitated Cox proportional hazards models for large-scale propensity score matching. Covariates employed for extensive propensity score matching between the target and comparator cohorts included age, sex, index year, all recorded comorbidities, prescribed drugs within 365 days before the index date, smoking history, alcohol use, and Charlson comorbidity index. Overall, 4306 covariates were matched using 1:1 or 1:4 propensity score matching with a calliper of 0.2 on the logit scale. The greedy matching algorithm was employed in this analysis. Propensity score distribution and covariate balance were summarised using mean values. Standardised mean differences were <0.1 post-matching (table 1).

Statistical analysis

The OHDSI analysis tools, integrated within the ATLAS platform and the OHDSI Methods Library R packages, are accessible at OHDSI GitHub. In this study, ATLAS version 2.12.0 was utilised alongside FEEDER-NET, a health big-data platform based on OMOP-CDM and supported by a Korean national project. A Cox proportional hazards analysis was conducted to determine the hazard ratio (HR) for the two cohorts. Cumulative incidence rates of the two groups were compared using the log-rank test. A two-sided p value <0.05 was deemed statistically significant for all tests. The calliper width for propensity score (PS) matching was set at 0.2 times the pooled standard deviation of the logit-transformed PS.

Statistical heterogeneity was assessed using χ^2 and I^2 statistics. A fixed-effect model was used when heterogeneity was absent ($p<0.05$, $I^2>50\%$), while a random-effect model was used when heterogeneity was present.

The primary analysis was conducted to compare incident all-cause dementia risk in patients with baseline LDL-C<70 mg/dL (<1.8 mmol/L) to those with LDL-C >130 mg/dL (>3.4 mmol/L). A secondary outcome was ADRD. LDL-C levels <55 mg/dL (<1.4 mmol/L) and 30 mg/dL (0.8 mmol/L) were additional target groups to assess the potential influence of varying LDL-C levels on dementia risk. The cut-offs for LDL-C in this study (<30, 55, 70, and 130 mg/dL (<0.8, 1.4, 1.8 and 3.4 mmol/L)) were divided by using the Korean guidelines for the Management of Dyslipidaemia, fourth edition, from the Korean Society of Lipid and Atherosclerosis and other previous articles.[17–20]

The analysis of the primary study was replicated with a subset of patients who were prescribed any type or dosage of statin to investigate the influence of LDL-C levels. Statin users and non-users were compared to assess the influence of statins on dementia risk across three predefined groups: LDL-C <55 mg/dL (<1.4 mmol/L), LDL-C <70 mg/dL (<1.8 mmol/L), and LDL-C >130 mg/dL (>3.4 mmol/L). Only individuals who were prescribed statins before measuring LDL-C were included in this study.

Additionally, lipophilic statins and hydrophilic statins were compared regarding their impact on dementia risk. To strengthen the reliability of the results, PS matching ranging from 1:1 to 1:4 was utilised.

RESULTS

Of 12 233 274 individuals across 11 cohorts, 903 711 patients fulfilled the eligibility criteria. After excluding 332 492 patients enrolled in both cohorts or with an ADRD history and who had at least 1 day at risk, the study focused on 192 213 participants with LDL-C levels <70 mg/dL (<1.8 mmol/L) and 379 006 patients with LDL-C levels >130 mg/dL (>3.4 mmol/L). After PS matching, the study included 108 980 matched pairs in each group (figure 1). Table 1 details the baseline characteristics of the participants.

Analysis I: LDL-C level association with dementia risk in the overall population

Cox proportional hazards regression analyses were conducted to compare all-cause dementia and ADRD risk between groups with LDL-C levels <70 mg/dL (<1.8 mmol/L) and those ≥130 mg/dL (≥3.4 mmol/L) within the overall population. Figure 2 illustrates the Kaplan-Meier curve from the primary analysis, evaluating all-cause dementia risk across LDL-C levels <70 mg/dL (<1.8 mmol/L) and those ≥130 mg/dL (≥3.4 mmol/L) at each participating centre. LDL-C levels <70 mg/dL (<1.8 mmol/L) were linked to a 26% decreased risk of all-cause dementia and a 28% decreased risk of ADRD, compared with having LDL-C levels ≥130 mg/dL (≥3.4 mmol/L) in cohorts matched at 1:1 ratio (HR 0.74, 95% CI 0.70 to 0.78 for all-cause dementia, and HR 0.72, 95% CI 0.67 to 0.77 for ADRD) (table 2 and figure 3). Furthermore, LDL-C levels <55 mg/dL (<1.4 mmol/L) were linked to an 18% reduced risk of all-cause dementia and ADRD compared with LDL-C levels ≥130 mg/dL (>3.4 mmol/L) (HR 0.82, 95% CI 0.77 to 0.88, and HR 0.82, 95% CI 0.76 to 0.89, respectively) (table 2 and online supplemental figure S1). These findings were consistent in the 1:4 PS-matching groups. However, LDL-C levels <30 mg/dL (<0.8 mmol/L) did not exhibit reduced dementia risk compared with the LDL-C ≥130 mg/dL (≥3.4 mmol/L) group (table 2 and online supplemental figure S2).

Analysis II: LDL-C level association with dementia risk in statin user population

Cox proportional hazards regression analyses were conducted among the statin-using population to assess all-cause dementia risks and ADRD, comparing the LDL-C <70 mg/dL (<1.8 mmol/L) group to the LDL-C ≥130 mg/dL (≥3.4 mmol/L) group, with PS matching at 1:1 and 1:4 ratios. In 1:1 matched cohort, LDL-C <70 mg/dL (<1.8 mmol/L) was linked to a 13% reduced risk of all-cause dementia and a 14% reduced risk of ADRD, relative to levels of ≥130 mg/dL (≥3.4 mmol/L) (HR 0.87, 95% CI 0.80 to 0.94, and HR 0.86, 95% CI 0.78 to 0.94, respectively) (online supplemental table S1 and figure S3). This trend persisted in the 1:4 PS-matched groups. However, LDL-C levels <55 mg/dL (<1.4 mmol/L) (HR 0.94, 95% CI 0.85 to 1.03, and HR 0.95, 95% CI 0.85 to 1.05, respectively) and 30 mg/dL (0.8 mmol/L) (HR 0.93, 95% CI 0.75

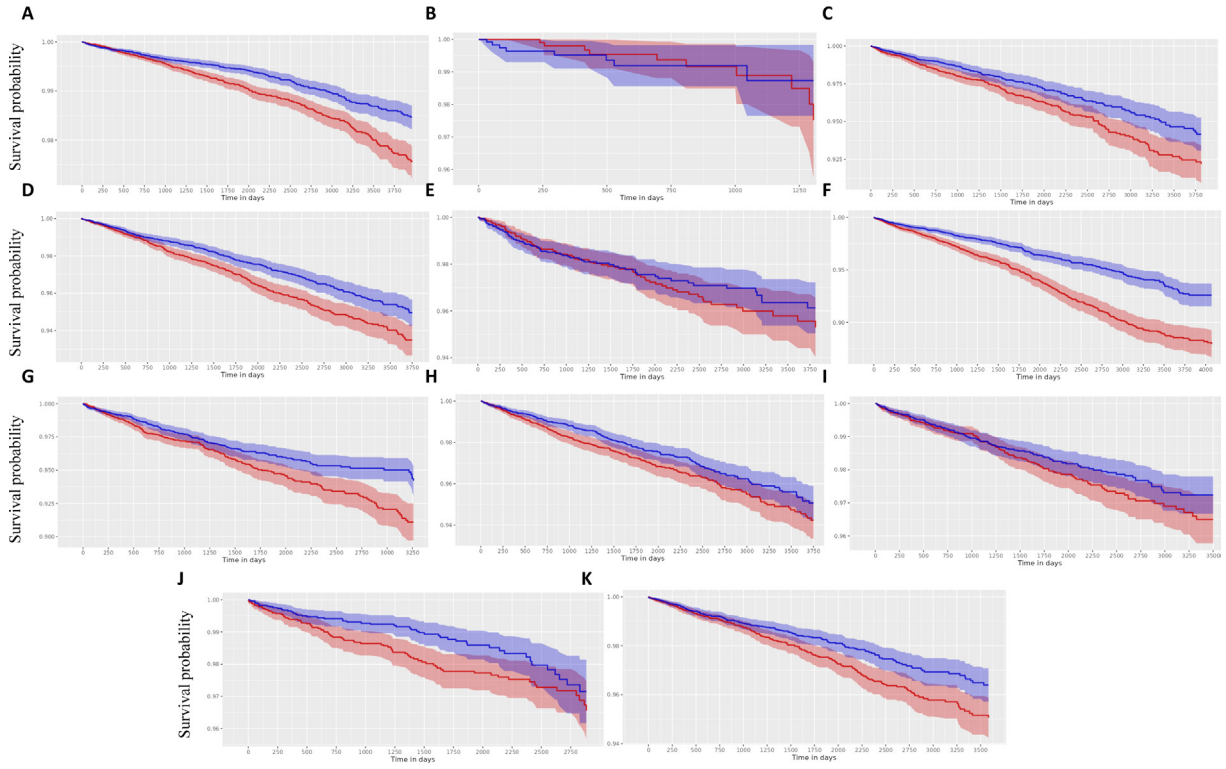

Figure 2 Kaplan-Meier curves for the risk of all-cause dementia between the group with LDL-C <70 mg/dL (<1.8 mmol/L) and LDL-C >130 mg/dL (>3.4 mmol/L). (A) AUMC, (B) GNUCH, (C) KDH, (D) KHMC, (E) KHNMC, (F) KWMC, (G) MJH, (H) SCHBC, (I) SCHCA, (J) SCHGM, (K) SCHSU. AUMC, Ajou University Medical Centre; GNUCH, Gyeongsang National University Changwon Hospital; KDH, Kangdong Sacred Heart Hospital; KHMC, Kyung Hee University Hospital; KHNMC, Gangdong Kyung Hee University Hospital; KWMC, Kangwon National University Hospital; MJH, Myungji Hospital; SCHBC, Soon Chun Hyang University Hospital Bucheon; SCHCA, Soon Chun Hyang University Hospital Cheonan; SCHGM, Soon Chun Hyang University Hospital Gumi; SCHSU, Soon Chun Hyang University Hospital Seoul; LDL-C, low-density lipoprotein cholesterol.

to 1.16, and HR 0.89, 95% CI 0.69 to 1.14, respectively) did not exhibit a statistically significant reduction in dementia risk compared with the LDL-C ≥130 mg/dL (≥3.4 mmol/L) category (online supplemental table S1).

Analysis III: statin use association with dementia risk across LDL-C level categories

Using LDL-C level categories, Cox proportional hazard regression analyses were conducted to evaluate the influence of statin use on dementia risk. Statin use did not reduce dementia risk in the LDL-C <55 mg/dL (<1.4 mmol/L) group. However, among those with LDL-C <70 mg/dL (<1.8 mmol/L), statin use was associated with a 13% reduction in all-cause dementia risk and a 12% decrease in ADRD risk compared with non-users. Statin use among individuals with LDL-C levels >130 mg/dL (>3.4 mmol/L) was also associated with a 7% reduction in all-cause dementia risk and a 10% decrease in ADRD risk compared with non-users. However, the slight reduction in dementia risk associated with statin use was not replicated in sensitivity analyses using a 1:4 PS ratio (online supplemental table S2 and figure S4).

Analysis IV: association of statin type with dementia risk

In 1:1 matched cohort, lipophilic statin users showed no more decreased dementia risk than the hydrophilic statin users, consistent with findings from 1:4 ratio sensitivity analyses. Similar results were found when examining drug prescription periods of 180 days and 365 days (online supplemental figure S5).

DISCUSSION

Utilising the OMOP-CDM framework across 11 academic hospital-based cohorts, this collaborative study revealed a significant association between baseline LDL-C levels and the risk of developing incident dementia. LDL-C levels <70 mg/dL (<1.8 mmol/L) or 55 mg/dL (1.4 mmol/L) showed a significant reduction in both all-cause dementia and ADRD compared with levels >130 mg/dL (>3.4 mmol/L). This reduction is evident regardless of statin use, highlighting the intrinsic importance of LDL-C management in reducing dementia risk. The protective effect of statins on dementia risk was evident at LDL-C levels <70 mg/dL (<1.8 mmol/L) and >130 mg/dL (>3.4 mmol/L), indicating a complex relationship between lipid levels and statin therapy in cognitive health. These findings emphasise the importance of achieving specific LDL-C thresholds for dementia prevention. Furthermore, it suggests a potential synergistic benefit of statin use within this optimal range.

The primary findings of this study highlight the critical importance of LDL-C levels in dementia risk, emphasising the critical importance of these levels irrespective of statin use. Lower LDL-C levels are directly associated with reduced dementia incidence, supporting cholesterol management as fundamental in preventing dementia. The findings of this study contrast with those of recent studies that found no association between LDL-C levels and dementia risk. For example, a study involving 184 367 participants from Kaiser Permanente Northern California health plan found no overall association between LDL-C levels and dementia risk,

Table 2 Comparative risk of all-cause dementia and Alzheimer's disease-related dementia in the overall population: LDL <70 mg/dL (<1.8 mmol/L) group and LDL ≥130 mg/dL (≥3.4 mmol/L) group; LDL <55 mg/dL (<1.4 mmol/L) group versus LDL ≥130 mg/dL (>3.4 mmol/L) group; and LDL <30 mg/dL (<0.8 mmol/L) group versus LDL ≥130 mg/dL (≥3.4 mmol/L) group

LDL <70 mg/dL (<1.8 mmol/L) vs LDL ≥130 mg/dL (>3.4 mmol/L)	LDL <70 mg/dL (<1.8 mmol/L)		LDL ≥130 mg/dL (>3.4 mmol/L)		
	Subjects	Event	Subjects	Event	HR
All-cause dementia					
1:1 PS time at risk 180	108 786	2318	108 786	3055	0.74 (0.70–0.78)
1:4 PS time at risk 180	108 786	2318	259 530	5317	0.78 (0.73–0.83)
Alzheimer's disease-related dementia					
1:1 PS time at risk 180	108 980	1754	108 980	2381	0.72 (0.67–0.77)
1:4 PS time at risk 180	108 980	1754	259 848	4056	0.75 (0.69–0.81)
LDL <55 mg/dL (<1.4 mmol/L) vs LDL ≥130 mg/dL (>3.4 mmol/L)	**LDL <55 mg/dL (<1.4 mmol/L)**		**LDL ≥130 mg/dL (>3.4 mmol/L)**		
	Subjects	Event	Subjects	Event	HR
All-cause dementia					
1:1 PS time at risk 180	52 169	1399	52 169	1758	0.82 (0.77–0.88)
1:4 PS time at risk 180	52 169	1399	139 968	3889	0.82 (0.75–0.89)
Alzheimer's disease-related dementia					
1:1 PS time at risk 180	52 269	1095	52 269	1388	0.82 (0.76–0.89)
1:4 PS time at risk 180	52 269	1095	140 172	3040	0.79 (0.72–0.86)
LDL <30 mg/dL (<0.8 mmol/L) vs LDL ≥130 mg/dL (≥3.4 mmol/L)	**LDL <30 mg/dL (<0.8 mmol/L)**		**LDL ≥130 mg/dL (≥3.4 mmol/L)**		
	Subjects	Event	Subjects	Event	HR
All-cause dementia					
1:1 PS time at risk 180	7603	208	7603	233	0.97 (0.80–1.17)
1:4 PS time at risk 180	7603	208	22 400	682	1.00 (0.82–1.22)
Alzheimer's disease-related dementia					
1:1 PS time at risk 180	7613	158	7613	177	1.01 (0.82–1.25)
1:4 PS time at risk 180	7613	158	22 420	536	1.04 (0.83–1.29)

LDL-C, low-density lipoprotein cholesterol; PS, propensity score.

suggesting statin use could qualitatively alter this relationship.[3] Similarly, a study from Korea observed an inverted J-shaped relationship between LDL-C levels and dementia risk, highlighting the highest risk within the lowest LDL-C docile levels (LDL-C <75 mg/dL (<1.9 mmol/L)).[5] Our findings support the notion of an inverted J-shaped relationship, as we observed that LDL-C levels below 30 mg/dL (0.8 mmol/L) did not show a reduced risk of dementia compared with levels >130 mg/dL (>3.4 mmol/L), contrary to what is typically observed with LDL-C levels <55 mg/dL (<1.4 mmol/L) or 70 mg/dL (1.8 mmol/L). This finding suggests that LDL-C levels <30 mg/dL (<0.8 mmol/L) do not significantly increase dementia risk. However, if there is any protective effect, it appears to be minimal, thereby validating the consistency observed in the results.

The observed risk reduction in dementia associated with LDL-C levels <70 mg/dL (<1.8 mmol/L) or 55 mg/dL (1.4 mmol/L), compared with higher LDL-C levels, suggests a clear threshold effect, emphasising the potential effectiveness of targeted lipid management in reducing cognitive decline risk. These findings highlight the potential for LDL-C as a modifiable risk factor in dementia prevention, reinforcing the necessity of including LDL-C targets in preventive guidelines.

In populations using statins, the analysis underscores the importance of achieving specific LDL-C thresholds in reducing dementia risk. Lower LDL-C levels are associated with decreased dementia risk, supporting the primary hypothesis that LDL-C levels significantly influence dementia risk. This finding underscores the concept that while statins may offer additional neuroprotective benefits through mechanisms beyond lowering cholesterol, maintaining specific LDL-C levels is crucial for managing dementia risk.

Within comparable LDL-C level categories, statin use significantly reduced dementia risk in groups with LDL-C levels <70 mg/dL (<1.8 mmol/L) and >130 mg/dL (>3.4 mmol/L). This observation suggests that the effectiveness of statins in preventing dementia may not only depend on achieving specific LDL-C thresholds. However, the reduced effectiveness of statins when LDL-C levels are <55 mg/dL (<1.4 mmol/L) remains unexplained, with factors such as well-managed health behaviours and nutritional status possibly playing a role. This insightful understanding of how statin use interacts with LDL-C levels emphasises the need for personalised statin prescriptions, focusing on achieving LDL-C levels that offer the maximum cognitive benefits.

The biological mechanisms connecting LDL-C levels to dementia risk warrant detailed investigation. High LDL-C levels may influence cognitive health through several pathways, such as brain cholesterol homeostasis balance,[21 22] inflammation,[23–26] and oxidative stress,[27–29] all implicated in dementia development. Lower LDL-C levels can also reduce the risk of cerebrovascular disease, a known dementia risk factor, by preventing atherosclerosis.[30 31] Moreover, statins

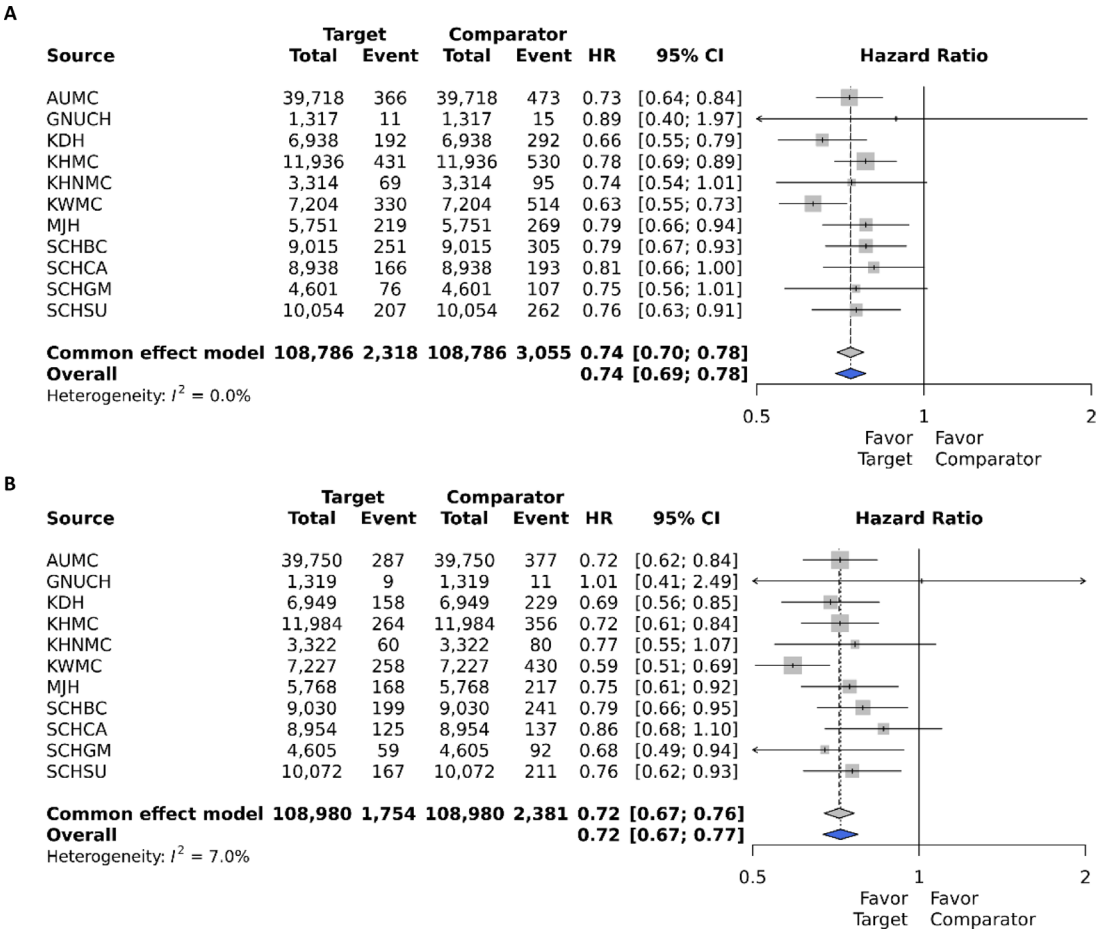

Figure 3 Meta-analysis of the impact of LDL-C levels on (A) all-cause dementia and (B) Alzheimer's disease dementia. In the distributed network analysis with 1:1 propensity score matching, the LDL-C <70 mg/dL (<1.8 mmol/L) compared with LDL-C >130 mg/dL (>3.4 mmol/L) were associated with decreased risk of incident all-cause dementia and Alzheimer's disease dementia. AUMC, Ajou University Medical Centre; KDH, Kangdong Sacred Heart Hospital; KHNMC, Gangdong Kyung Hee University Hospital; KHMC, Kyung Hee University Hospital; GNUCH, Gyeongsang National University Changwon Hospital; KWMC, Kangwon National University Hospital; MJH, Myungji Hospital; SCHBC, Soon Chun Hyang University Hospital Bucheon; SCHCA, Soon Chun Hyang University Hospital Cheonan; SCHGM, Soon Chun Hyang University Hospital Gumi; SCHSU, Soon Chun Hyang University Hospital Seoul; LDL-C, low-density lipoprotein cholesterol.

may exert pleiotropic neuroprotective effects, enhancing endothelial function, reducing neuroinflammation, and regulating amyloid-β metabolism.[32 33] Hence, understanding these mechanisms could clarify the pathophysiological basis of our findings and reveal targets for therapeutic intervention beyond conventional lipid-lowering strategies.

This study has some limitations. The retrospective design introduces the potential for unmeasured confounding factors that could influence the observed associations between LDL-C levels, statin use, and dementia risk. While PS matching was used to mitigate this bias by accounting for various covariates, residual confounding cannot be entirely excluded. Nevertheless, the analysis utilising CDM involved extensive PS matching. The robustness of the findings was validated through consistent outcomes observed in multiple sensitivity analyses. Additionally, relying on electronic health records from individual institutions for outcome identification may lead to variability in diagnostic accuracy and potential underreporting of dementia cases, which could affect the strength of the observed associations. Second, the focus of the study on baseline LDL-C levels, without longitudinal tracking of lipid profiles over time, limits the ability to assess the influence of dynamic changes in LDL-C levels on dementia risk. Third, although our study utilises ICD-10 diagnostic codes to define dementia outcomes, which may inherently limit the granularity of detailed clinical conditions, the likelihood of misclassification is significantly mitigated in the context of South Korea. The assignment of dementia-related F codes is subject to stringent regulatory oversight, as these codes carry considerable implications for insurance eligibility and benefits. Furthermore, the participating institutions in this study are university-affiliated academic hospitals with dedicated neurology and neuropsychiatry departments, where diagnostic processes adhere to rigorous clinical standards. These factors collectively enhance the reliability of ICD-10 codes as a representation of confirmed dementia cases, thereby minimising concerns regarding potential misclassification.

Despite these limitations, the large and diverse cohort enrolled, and the application of rigorous statistical methods, lend robustness to the findings and offer valuable insights into the complex relationship between lipid management and cognitive health. However, future studies are warranted to validate these results and further elucidate the mechanisms underlying the relationship between LDL-C levels, statin therapy, and dementia risk, thus facilitating targeted interventions in dementia prevention.

CONCLUSION

Our study reveals that LDL-C levels <70 mg/dL (<1.8 mmol/L) or 55 mg/dL (1.4 mmol/L) at baseline significantly lower the risk of all-cause and ADRD compared with levels >130 mg/dL (>3.4 mmol/L). The association between LDL-C levels <70 mg/dL (<1.8 mmol/L) and reduced dementia risk remains consistent among statin users. These findings underscore the crucial role of managing LDL-C in lowering dementia risk and highlight the importance of targeted strategies in addressing cardiovascular and cognitive health outcomes by physicians.

Author affiliations
[1]Department of Neurology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea (the Republic of)
[2]Department of Medical Informatics & Statistics, Kangdong Sacred Heart Hospital, Seoul, Korea (the Republic of)
[3]Zarathu Co Ltd, Seoul, Korea (the Republic of)
[4]Department of Biomedical Informatics, Ajou University School of Medicine, Suwon, Korea (the Republic of)
[5]Bongdam forest mental health clinic, Hwaseong, Korea (the Republic of)
[6]Department of Digital Health and Department of Endocrinology and Metabolism, Kyung Hee University College of Medicine, Seoul, Korea (the Republic of)
[7]Department of Internal Medicine, Kyung Hee University Hospital at Gangdong, Kyung Hee University School of Medicine, Seoul, Korea (the Republic of)
[8]Department of Pediatrics, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, Seoul, Korea (the Republic of)
[9]Department of Neurology, Kangwon National University Hospital, Kangwon National University College of Medicine, Chuncheon, Korea (the Republic of)
[10]Department of Neurology, Gyeongsang National University Changwon Hospital, Changwon, Korea (the Republic of)
[11]Department of Neurology, Myongji Hospital, Hanyang University College of Medicine, Goyang, Korea (the Republic of)
[12]Department of Neurology, Chuncheon Sacred Heart Hospital, Hallym University College of Medicine, Chuncheon, Korea (the Republic of)
[13]Department of Neurology, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea (the Republic of)

Contributors YK: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and revision of the manuscript, obtainment of funding, guarantor. ML: drafting of the manuscript, and revision of the manuscript. DYL, RWP, SYR, JMC, H-JY, J-WJ, SJ, JL, S-HL, CK, J-SB, YJK, J-HL, HB: critical revision of the manuscript for important intellectual content. JK and KJL: acquisition of data, analysis and interpretation of data. JK and KJL: statistical analysis. YK, KJL, DYL and JK: technical or material support.

Funding This research was supported by the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Science and ICT (NRF-2022R1F1A1074643). This study was supported by a grant from the Korean Neurological Association (KNA-22_SONGPA-1).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The Institutional Review Board (Kangdong Sacred Heart Hospital IRB no. 2023-09-002) approved the study protocol, and the need for written informed consent was waived due to the use of de-identified data.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Due to existing embargoes on our datasets, the full data from this study cannot be publicly shared. However, anonymised data will be made available upon request to any qualified investigator.

ORCID iDs
Minwoo Lee http://orcid.org/0000-0001-8474-5744
Chulho Kim http://orcid.org/0000-0001-8762-8340
Yerim Kim http://orcid.org/0000-0002-7108-6302

REFERENCES

1 Wilson PW, D'Agostino RB, Levy D, *et al*. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837–47.
2 Silverman MG, Ference BA, Im K, *et al*. Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-analysis. *JAMA* 2016;316:1289–97.
3 Ferguson EL, Zimmerman SC, Jiang C, *et al*. Low- and High-Density Lipoprotein Cholesterol and Dementia Risk Over 17 Years of Follow-up Among Members of a Large Health Care Plan. *Neurology (ECronicon)* 2023;101:e2172–84.
4 Williams DM, Finan C, Schmidt AF, *et al*. Lipid lowering and Alzheimer disease risk: a mendelian randomization study. *Ann Neurol* 2020;87:30–9.
5 Lee YB, Kim MY, Han K, *et al*. Association between cholesterol levels and dementia risk according to the presence of diabetes and statin use: a nationwide cohort study. *Sci Rep* 2022;12:19383.
6 Iwagami M, Qizilbash N, Gregson J, *et al*. Blood cholesterol and risk of dementia in more than 1.8 million people over two decades: a retrospective cohort study. *Lancet Healthy Longev* 2021;2:e498–506.
7 Beydoun MA, Beason-Held LL, Kitner-Triolo MH, *et al*. Statins and serum cholesterol's associations with incident dementia and mild cognitive impairment. *J Epidemiol Community Health* 2011;65:949–57.
8 Sabatine MS, Giugliano RP, Keech AC, *et al*. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med* 2017;376:1713–22.
9 Schwartz GG, Steg PG, Szarek M, *et al*. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med* 2018;379:2097–107.
10 Grundy SM, Stone NJ, Bailey AL, *et al*. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;139:e1082–143.
11 Mach F, Baigent C, Catapano AL, *et al*. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111–88.
12 You SC, Rho Y, Bikdeli B, *et al*. Association of Ticagrelor vs Clopidogrel With Net Adverse Clinical Events in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. *JAMA* 2020;324:1640–50.
13 Yoon D, Ahn EK, Park MY, *et al*. Conversion and Data Quality Assessment of Electronic Health Record Data at a Korean Tertiary Teaching Hospital to a Common Data Model for Distributed Network Research. *Healthc Inform Res* 2016;22:54–8.
14 Choi YJ, Kim S, Hwang YJ, *et al*. Prevalence of Dementia in Korea Based on Hospital Utilization Data from 2008 to 2016. *Yonsei Med J* 2021;62:948–53.
15 Phung TKT, Andersen BB, Høgh P, *et al*. Validity of dementia diagnoses in the Danish hospital registers. *Dement Geriatr Cogn Disord* 2007;24:220–8.
16 Shih YJ, Wang JY, Wang YH, *et al*. Analyses and identification of ICD codes for dementias in the research based on the NHIRD: a scoping review protocol. *BMJ Open* 2022;12:e062654.
17 Rhee E-J, Kim HC, Kim JH, *et al*. 2018 Guidelines for the Management of Dyslipidemia in Korea. *J Lipid Atheroscler* 2019;8:78.
18 Karagiannis AD, Mehta A, Dhindsa DS, *et al*. How low is safe? The frontier of very low (<30 mg/dL) LDL cholesterol. *Eur Heart J* 2021;42:2154–69.
19 Furtado RHM, Giugliano RP. What Lessons Have We Learned and What Remains to be Clarified for PCSK9 Inhibitors? A Review of FOURIER and ODYSSEY Outcomes Trials. *Cardiol Ther* 2020;9:59–73.
20 Giugliano RP, Wiviott SD, Blazing MA, *et al*. Long-term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol : A Prespecified Analysis of the IMPROVE-IT Trial. *JAMA Cardiol* 2017;2:547–55.
21 Varma VR, Büşra Lüleci H, Oommen AM, *et al*. Abnormal brain cholesterol homeostasis in Alzheimer's disease-a targeted metabolomic and transcriptomic study. *NPJ Aging Mech Dis* 2021;7:11.
22 Hughes TM, Rosano C, Evans RW, *et al*. Brain cholesterol metabolism, oxysterols, and dementia. *J Alzheimers Dis* 2013;33:891–911.
23 Jukema RA, Ahmed TAN, Tardif JC. Does low-density lipoprotein cholesterol induce inflammation? If so, does it matter? Current insights and future perspectives for novel therapies. *BMC Med* 2019;17:197.
24 Rocha VZ, Santos RD. Cholesterol and inflammation: the lesser the better in atherothrombosis. *Eur J Prev Cardiol* 2018;25:944–7.
25 Thirumangalakudi L, Prakasam A, Zhang R, *et al*. High cholesterol-induced neuroinflammation and amyloid precursor protein processing correlate with loss of working memory in mice. *J Neurochem* 2008;106:475–85.
26 Loera-Valencia R, Goikolea J, Parrado-Fernandez C, *et al*. Alterations in cholesterol metabolism as a risk factor for developing Alzheimer's disease: potential novel targets for treatment. *J Steroid Biochem Mol Biol* 2019;190:104–14.
27 Zarrouk A, Hammouda S, Ghzaiel I, *et al*. Association Between Oxidative Stress and Altered Cholesterol Metabolism in Alzheimer's Disease Patients. *Curr Alzheimer Res* 2020;17:823–34.

28 Pappolla MA, Smith MA, Bryant-Thomas T, *et al*. Cholesterol, oxidative stress, and Alzheimer's disease: expanding the horizons of pathogenesis. *Free Radic Biol Med* 2002;33:173–81.
29 Gamba P, Staurenghi E, Testa G, *et al*. A Crosstalk Between Brain Cholesterol Oxidation and Glucose Metabolism in Alzheimer's Disease. *Front Neurosci* 2019;13:556.
30 Mortensen MB, Dzaye O, Bøtker HE, *et al*. Low-Density Lipoprotein Cholesterol Is Predominantly Associated With Atherosclerotic Cardiovascular Disease Events in Patients With Evidence of Coronary Atherosclerosis: The Western Denmark Heart Registry. *Circulation* 2023;147:1053–63.
31 Ference BA, Ginsberg HN, Graham I, *et al*. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2017;38:2459–72.
32 van der Most PJ, Dolga AM, Nijholt IM, *et al*. Statins: mechanisms of neuroprotection. *Prog Neurobiol* 2009;88:64–75.
33 Vaughan CJ, Delanty N. Neuroprotective properties of statins in cerebral ischemia and stroke. *Stroke* 1999;30:1969–73.