The Journal of Prevention of Alzheimer's Disease 13 (2026) 100555

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Original Article

Hypolipidemics reduce the rate of Alzheimer's disease development and dementia progression: A cohort study linked with genetic and neuropathological analyses

Zohi Sternberg [a,*], Rebecca E. Podolsky [b], Jihnhee Yu [c], Shuangcheng Hua [c], Stanley Halvorsen [d], Bernhard J. Schaller [e]

[a] Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, Buffalo Medical Center, Buffalo, NY, USA
[b] Boston, MA, USA
[c] Department of Biostatistics, University at Buffalo, Buffalo, NY, USA
[d] Department of Pharmacology and Toxicology, Jacobs School of Medicine & Biomedical Sciences, USA
[e] Institute of Physiopathology, Department of Pathology, University of Buenos Aires, Argentina

ARTICLE INFO

Keywords:
Alzheimer's disease
Cognition
Cohort study
Disease progression
Hypolipidemic
Neuropathology
Total cholesterol

ABSTRACT

Background: High cholesterol contributes to the development and progression of dementia due to both Alzheimer's disease (A.D.) and vascular pathology. However, the effects of lipid-lowering regimen (LLR) on cognitive dysfunction and brain neuropathology are unknown.
Objective: To investigate the effect of LLR on the conversion from normal to mild cognitive impairment (MCI), indicated by CDR-SOB of >0–2.5 (MCI), and the progression to dementia, indicated by CDR-SOB =>3 (10-year follow-up) and LLR effect on the rate of survival (15-year follow-up). Participants were stratified by age (≤70 years and >70 years), gender, and the presence of at least one copy of the APOE4 allele. We also analyzed the effect of LLR on brain neuropathology in participants, indicated by Braak staging, hippocampal atrophy, and CSF levels of total Tau. The differential effect of LLR, with or without cerebrovascular disease, lacunar infarct, or cystic infarction in the cognitive network, was analyzed.
Methods: We have analyzed the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS).
Results: In participants with CDR-SOB of >0–2.5, the use of hypolipidemic agents was associated with a reduced yearly increase in the CDR-SOB scores by 0.0088 (0.0038, 0.0138) unit ($P < 0.001$). This effect was more pronounced in participants with CDR-SOB =>3 showing a reduced yearly increase in the CDR-SOB scores by 0.1733 (0.1441, 0.2025) unit ($P < 0.001$) in LLR-users compared to non-users, and an increased rate of survival [HR: 0.822 (0.746, 0.906). $P = 0.001$]. The pattern persisted when participants were stratified based on age, gender, and the presence of APOE4. LLR had no significant effect on Braak staging scores, hippocampal atrophy, and total CSF Tau level, and was independent of the presence or absence of cerebrovascular disease, lacunar infarct, and cystic infarction in cognitive network.
Conclusion: Our results have implications for delaying cognitive dysfunction and halting the progression of dementia, regardless of the etiology being related to AD or vascular pathology.

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia, with genetic and environmental factors interacting in a complex manner to the development and progression of the disease. The combined global percentage of individuals across AD continuum presented with AD dementia, prodromal AD [mild cognitive impairment (MCI)], and preclinical AD (asymptomatic clinical presentation, with changes in

Abbreviations: AD, Alzheimer disease; ADRC, Alzheimer's Disease Research Centers; Aβ, β-amyloid; CDR®, Dementia Staging Instrument; CDR-SOB, Clinical Dementia Rating Scale Sum of Boxes; MCI, Mild Cognitive Impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NACC, National Alzheimer's Coordinating Center; N.I.A, National Institute on Aging; NFT, Neurofibrillary Tangles; UDS, Uniform Data Set.

* Corresponding author at: Clinical Associate Professor of Neurology, Buffalo Medical Center, Buffalo, NY 14203.
E-mail address: zs2@buffalo.edu (Z. Sternberg).

https://doi.org/10.1016/j.tjpad.2026.100555
Received 20 October 2025; Received in revised form 1 February 2026; Accepted 16 March 2026
Available online 13 April 2026
2274-5807/© 2026 The Authors. Published by Elsevier Masson SAS on behalf of SERDI Publisher. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

biomarkers), is estimated to be 22 % (416 million) of all persons aged 50 and above [1]. AD involves a progressive cognitive decline, including memory, language, and executive function, and is characterized by the abnormal aggregation and accumulation of beta-amyloid (Aβ) in the form of extracellular plaques and aggregation of hyper-phosphorylated tau protein in the formation of intracellular neurofibrillary tangles (NFT) [2].

The initial decline in cognitive function is often subtle, and not readily recognized in MCI subjects due to an overlap between what could be due to physiological aging and the underlying AD pathophysiology [3,4]. MCI is heterogeneous in clinical presentation; most present with the amnestic (aMCI) subtype which involves deficits in episodic memory as single or most prominent characteristic and non-amnestic (na) MCI patients, where the memory remains intact, whereas other cognitive abilities such as executive function, attention, language, could be affected in a single or multiple domains [5]. The aMCI patients are more likely to develop AD at follow up [6]. Surrogates of cognitive functions such as neuropsychological testing, biomarkers, neuroimaging, or a combination of these measures are used to define the various stages of the disease [3,7].

Similar to MCI development, the progression to A.D. varies depending on several factors, including age, the presence of the APOE4 allele [8], CSF levels of tau [9], and hippocampal atrophy [10] among others. Longitudinal SPECT studies in A.D. patients have shown an inverse correlation between age and cognitive deterioration, assessed by the mean annual changes in the mini-mental state examination (MMSE) test scores [11] Hippocampal atrophy also correlate with cognitive dysfunction [12], and a relationship between baseline tau-PET and subsequent atrophy has been observed, particularly in younger patients [13].

Vascular risk factors are known to be associated with both development and progression of AD [14]. This study is one in series investigating the effects of cardiovascular drugs on the conversion of normal to MCI and the rate of dementia progression and survival, taking into consideration both AD and cognitive dysfunction resulting from vascular factors among patients with Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) of 0–2.5 (MCI) and CDR-SOB =>3 (dementia), stratified by age, gender, and the presence of APOE4 allele, during a long term follow-up.

Recently, we have reported the beneficial effects of antihypertensives on delaying the rate of conversion from normal to MCI [15] and delaying the rate of dementia progression [15], demonstrating that these beneficial effects are dependent on the class of antihypertensives and are modulated by age, gender, and APOE4 allele.

Another vascular risk factor associated with cognitive dysfunction is hypercholesterolemia. A longitudinal study of a large population-based sample of apparently normal older community-dwelling persons followed for 13 years report an association between higher baseline total cholesterol serum levels and increased risk of cognitive dysfunction [16]. A meta-analysis of 17 studies reports a relationship between total cholesterol in midlife and higher risk of AD [17]. However, other studies in humans do not support an association between serum cholesterol and increased risk of AD [18,19].

A High cholesterol diet in rodents also has shown adverse effects inducing significant cognitive impairment and Alzheimer's-like disease [20,21]. These effects have been associated with accelerating intraneuronal Aβ accumulation [22] and increasing hippocampal hyperphosphorylated tau [23]. Similar relationships between hypercholesterolemia and all AD neuropathological outcomes, including NFT, have been observed in the analysis of neuropathological and clinical data from NACC participants [24].

Although several observational studies have examined lipid-lowering regimens (LLRs) in relation to Alzheimer's disease [25–27], the evidence remains heterogeneous and often limited by narrow inclusion criteria, short follow-up, or incomplete adjustment for major confounders. The present study extends this literature by leveraging one of the largest, prospectively collected, clinically adjudicated datasets available, enabling a comprehensive evaluation of LLR exposure across the full spectrum of cognitive decline. By incorporating broad real-world treatment patterns, stratifying by age, sex, and APOE4 genotype, and integrating neuropathological outcomes, this analysis provides a more granular understanding of the potential role of lipid-lowering therapy in modulating disease trajectories. While the magnitude of effect is expected to be modest in population-based cohorts, even small annual differences may accumulate to clinically relevant delays in progression at the population level.

2. Methods

The study was approved by the Internal Review Board of the State University of New York at Buffalo, Buffalo, NY, U.S.A., and all participants' information were de-identified in the data set received from the National 'Alzheimer's Coordinating Center (NACC). Written informed consent is obtained from all participants and co-participants.

2.1. Study design

All data were obtained only from and validated by the NACC. From September 2005 to the specific data freeze of March 2020 (containing data on to Feb 2020) Alzheimer's Disease Research Centers (ADRCs) across the U.S.A. have been contributing data to the UDS, using a prospective, standardized, and longitudinal clinical evaluation of the subjects in the National Institute on Aging's (N.I.A.'s) ADRC program. In each subject's approximate annual UDS visit, the clinician completes data collection forms, covering topics from subject demographics to neurological examination findings, neuropsychological test results and psychiatric symptoms or other diagnoses issues on individuals with normal cognition, MCI, and dementia. For each ADRC visit, a multidisciplinary team or a single clinician determines a clinical diagnosis based on established (national) guidelines. LLR exposure was modeled as a time-varying covariate to reflect real-world treatment patterns.

2.2. Study population

The UDS reflects the total enrollment of the N.I.A.'s ADRCs from 2005 up to the data freeze of March 2020. Each Center enrolls its participants according to its protocol — e.g., clinician referral, self-referral by participants or family members, active recruitment in the community organizations, etc. Most centers also enroll volunteers with normal cognition and highly educated. Overall, participants are enrolled using different methods and for different research purposes at the N.I.A.'s ADRCs.

In this large prospective, standardized clinical case series rather than a longitudinal study in a strict sense, the analysis is based on complete covariates cases assuming that the missing patterns in covariates are random and do not depend on observed or unobserved observations. Loss of follow-up is right-censored data, incorporated in the data analysis.

2.3. Inclusion/Exclusion criteria

Inclusion criteria: (i) Participants with CDR-SOB>0–2.5 and CDR-SOB≥3; (ii) Participants who took any hypolipidemic drugs at least once.

Exclusion criteria: (i) Participants older than 90 years; (ii) Participants with no or incomplete records of hypolipidemic use for analysis; (iii) participants who died at their first record of CDR-SOB, with no follow-up. Participants with incomplete medication records were excluded to minimize exposure misclassification (v) Participants using antihypertensive or antidiabetic medications were excluded because the use of antidiabetic [28] and antihypertensives [15] medications independently influence cognitive outcomes and would introduce substantial

confounding if retained.

The results were limited to a 10-year follow-up for assessing the effect of LLR on transition to MCI and on disease progression, and 15-year follow-up for assessing LLR effect on the rate of survival. LLR exposure was determined using a NACC code indicating current use of prescription antihyperlipidemic medications including statins, fibric acid derivatives, bile acid sequestrants, cholesterol absorption inhibitors, although the data doesn't differentiate between classes of LLRs. The possible use of LLR was documented at each clinical visit as part of the standardized UDS medication assessment. The LLR exposure was treated as a time-varying covariate in our analysis.

The results were corrected for mental disease signs indicated by the use of antipsychotic drugs, due to a relationship between psychiatric diseases and cognitive deficit [29], Parkinson's disease (P.D.), history of traumatic brain injury (T.B.I.), alcohol abuse, active depression in the last two years, heart attack/cardiac arrest, education history, and history of smoking.

2.4. PICO framework

To ensure clinical evidence, a PICO framework [30] was applied with a population consisting of an ADRC data pool. Interventions consisting of hypolipidemics treatments/prophylaxis focused primarily on A.D. progression.Comparisons between clinical and pathological A.D. progression in different subgroups and outcomes vary but are based on neuropsychological tests.

2.5. Data collection

The UDS data, from the whole ADRCs data pool are collected using different standardized evaluations of participants enrolled in ADRC clinics. Data is recorded directly on UDS forms (hard copy or electronic) during the evaluation process. Information is collected during in-person office visits, home visits, and telephone calls. In addition, Milestone Forms are used to document participant death and drop-out. The UDS is longitudinal, and its protocol requires an approximate annual follow-up for as long as the participant can be involved. Late-stage participants forced to drop out due to health may continue to be followed strictly for autopsy purposes. Trained clinicians and clinic personnel collect data from participants and their co-participants (usually close friends or family members). Depending on a given and validated ADRC protocol, diagnosis is made by either the consensus of the involved team or clinicians.

Although the focus of the ADRCs is A.D., the Centers also collect data on various associated disorders, such as vascular dementia, Lewy body dementia, and frontotemporal lobar degeneration (FTLD). Furthermore, the use of medications — e.g., antihypertensives, hypolipidemics, antidiabetics, antidepressants, and antipsychotics is documented at each visit and during follow-up. However, completing the form assessing the participant's use of medications is optional; therefore, completing the record of adherence to the treatment regimen may be incomplete.

2.6. Data management

To ensure patient privacy, the stored and transmitted data are de-identified at the participants and organization level. Structured data recorded in the electronic health records are assimilated into the database need, not meeting the data to standard and controlled clinical terms. A rigorous data quality assessment excludes records that do not meet quality standards and basic formatting requirements for adequate data representation. Missingness patterns were evaluated, and missing baseline covariates were addressed using the first non-missing value from repeated measures.

2.7. Further diagnostic evaluation

For some UDS patients, CSF values are available for A-β_{42}, T-tau and P-181 tau, and were used for the current study. In the presented dataset here, genotypic data (i.e., APOE status) is available at NACC for 75 % of UDS participants, as well as genetic information on whether the participant or their family has any known A.D. or FTLD mutations.

2.8. Psychiatric assessment

Psychiatric symptom data included (i) a history of depression (coded as consulting a clinician, (ii) being prescribed medication or receiving a diagnosis related to depressed mood), (iii) a depressive symptoms scale (Geriatric Depression Scale-Short Form), (iv) history of pseudobulbar affect, and (v) history of substance use disorder and the Neuropsychiatric Inventory Questionnaire (NPI-Q) assessing presence/absence of 12 neurobehavioral symptoms Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory.

2.9. Neurological examination

For this study, we have used a cohort of participants from NACC-UDS, limiting it to patients who enrolled having CDR-SOB of >0 as indicator of transition from normal to MCI and CDR-SOB of =>3, indicator of progression to dementia, as assessed by Dementia Staging Instrument, with a follow-up of 10 years during disease development and progression and follow-up of 15 years for assessing survival with the possibility of death. In addition, we have provided the values for the group differences in CDR®, MMSE scores and Montreal cognitive assessment (MoCA) scores.

2.10. Statistical analysis

The S.A.S. (Version 9.4) and R 4.0.2 software were used for all statistical analyses. We created the time from CDR-SOB of >0–2.5 (MCI) and of CDR-SOB of =>3 to death with a follow-up of 10 years. The rate of survival was assessed at 15-year follow-up, and the data was censored for patients still alive at the end of 15-year. Normal conversion to MCI was defined as an increase in CDR-SOB of >0–2.5 and disease progression was defined as an increase in the CDR-SOB scores to 3 or higher. In case of missing baseline demographics data, the first non-missing value from the repeated measure data was used. We differentiated between hypolipidemic-users (minimum of one-time use) and non-users, with further stratifications based on age, gender, and at least one copy of the APOE4 allele. We used $\chi 2$ tests for categorical variables and independent sample *t*-test for continuous variables for univariate data analysis. For the regression model for including various covariates, we fitted a logistic model for binary outcomes and multiple regression or the mixed effects model for numeric outcomes.

The primary objective was the group differences in the rate of disease development and progression indicated by the increase in CDR-SOB scores between hypolipidemic-users and non-users. The rate of disease development and progression were corrected for the systolic and diastolic B.P. values, in both lipid lowering regimen (LLR)-users and non-users. The date of the initial visit, when the participant was diagnosed with CDRSOB of >0–2.5, and of CDRSOB =>3, were defined as starting point or disease development and disease progression respectively and analyzed during 10-year follow up. The secondary objective was the proportion of patients' survival from CDRSOB of =>3 to death during 15-year follow up. These unadjusted survival analyses were carried out using the log-rank test and Kaplan-Meier (K.M.) curve, and participants ending the follow-up period still alive produced censored observations.

We performed the adjusted survival analysis using the additive hazards regression model incorporating covariates of interest and interactions when moderating effects of covariates are suspected. The additive hazard model describes the association between the covariates

and time to event regarding the absolute change in the risk. Several important covariates including P.D. status, history of T.B.I., vitamin B12 deficiency, alcohol abuse, smoking, education, cardiovascular disease, depression, and any antipsychotic drugs usage during the follow-up. Loss of follow-up is considered right-censored data and incorporated in the data analysis. Covariate selection and model specification were informed by a prespecified causal framework based on established literature.

2.11. Statistical approach

2.11.1. Justification for the additive hazards model

The additive hazards model was selected for survival analyses because it estimates absolute risk differences, which are more clinically interpretable than relative hazards in the context of chronic neurodegenerative diseases. This model does not rely on proportional hazards assumptions, which are unlikely to hold in heterogeneous aging cohorts, and it accommodates time-varying exposures without inducing structural bias. The choice of this model aligns with the study's objective of quantifying the magnitude of survival differences attributable to LLR exposure.

2.11.2. Time-varying modeling of LLR exposure

LLR use was modeled as a time-varying covariate to reflect real-world treatment patterns and to avoid immortal-time bias. Participants frequently initiate, discontinue, or modify lipid-lowering therapy during follow-up; treating exposure as fixed would misclassify treatment windows and artificially inflate effect estimates. The time-varying structure ensures that person-time is correctly attributed to the exposed or unexposed category only during periods in which LLR use was documented.

2.11.3. Exposure misclassification minimization

To reduce exposure misclassification, LLR use was defined strictly based on documented medication records at each visit. Participants with incomplete or inconsistent medication histories were excluded. Modeling LLR as a time-varying exposure further minimized misclassification by ensuring that treatment status reflected the actual timing of documented use rather than baseline assignment.

2.11.4. Confounding control strategy

Covariate selection was guided by a prespecified causal framework informed by established literature linking cardiovascular, metabolic, and neurodegenerative pathways. Adjustment variables included demographic factors (age, sex, education), APOE4 genotype, vascular comorbidities, psychiatric symptoms, blood pressure, smoking, alcohol use, and neurological conditions known to influence cognitive trajectories. Exclusion of participants using antihypertensive or antidiabetic medications was implemented to reduce confounding from two major cardiometabolic pathways independently associated with cognitive decline. This strategy was designed to block major backdoor paths and minimize residual confounding.

2.11.5. Handling of missing data

Missing baseline demographic variables were addressed by carrying forward the first non-missing value from repeated measures, consistent with the structure of the NACC dataset. Missingness was assumed to be missing at random (MAR), as most missing data resulted from administrative rather than clinical factors. Participants with incomplete medication records or missing outcome data at baseline were excluded according to predefined criteria to preserve internal validity. The proportion of missingness for key covariates was quantified and reported.

2.11.6. Assumptions and model diagnostics

Model assumptions were evaluated to ensure validity of the analytical approach. For the additive hazards model, cumulative regression functions were inspected for stability over time. For mixed-effects models, residual distributions and random-effects structures were examined to confirm appropriate fit. No major violations of model assumptions were detected. Proportional hazards assumptions were not required due to the use of an additive hazards framework.

Together, these methodological choices were designed to maximize internal validity, reduce structural bias, and provide clinically interpretable estimates of the association between LLR exposure and cognitive outcomes.

3. Results

Table 1A presents patients' demographics stratified by CDR-SOB scores of >0–2.5 and CDR-SOB scores of ≥ 3, W/LLR and WO/ LLR usage. LLR-users were older in CDR-SOB >0–2.5 (72.2± 8 years vs. 69.5 ±11 years) and CDR ≥ 3 (73.7±8 years vs. 71.8±10 years) compared to non-users (Ps < 0.001). The systolic blood pressure was significantly higher, and diastolic blood pressure was significantly lower in LLR-users compared to non-users, in both CDR-SOB >0–2.5 and CDR-SOB ≥ 3 subgroups (Ps < 0.001) resulting in significantly lower mean blood pressure in LLR-users compared to non-users (P < 0.001).

Table 1B presents the results of neuropsychological tests stratified by the use of LLR. The response of participants with the CDR-SOB >0–2.5 to LLR was opposite to participants with CDR-SOB ≥ 3. The participants who used LLR with CDR-SOB >0–2.5 showed higher CDR, CDR-SOB and lower MoCA and MMSE scores compared to LLR non-users (P values < 0.001). In contrast, The CDR-SOB ≥ 3 subgroup on LLR had lower CDR, CDR-SOB (P values < 0.001) and higher MoCA (P = 0.042) and MMSE (P = 0.130) scores compared to LLR non-users.

3.2. Hypolipidemics and cognitive dysfunction-development and progression

Fig. 1 presents the effect of LLR on the conversion from normal to MCI stratified by age (1A), gender (1B), and the presence of at least one copy of APOE4 (1C) in a sample size of 28,372 participants. The use of LLR reduced the increase in CDR-SOB scores by 0.0088 (0.0038, 0.0138) unit per year (P < 0.001) compared to LLR-non-users. The average

Table 1A
Patients' demographics stratified by CDR-SOB scores of 0≥ 2.5 and CDR-SOB scores of ≥ 3, W/LLR and WO/ LLR. P < 0.05 is statistically significant.

	CDR-SOB >0–2.5			CDR-SOB≥ 3		
Pt's demographics	**W/LLR**	**W/O LLR**	**P-value**	**W/ LLR**	**W/O LLR**	**P-Value**
N (%)	11,790 (41.5)	16,582 (58.5)		9803 (57.0)	7417 (43.0)	**N/A**
Age (years, mean±SD)	72.2 (8.1)	69.5 (11.0)	<0.001	73.7 (8.49)	71.8 (10.8)	<0.001
ApoE4 (1 or 2 copies)			<0.001			<0.001
Yes **(%)**	3285 (45.0)	3955 (55.0)		3027 (47.0)	3445 (53.0)	
No **(%)**	5199 (40.0)	7926 (60.0)		2431 (40.0)	3636 (60.0)	
Missing data **(%)**	3306 (41.0)	4701 (59.0)		4345 (50.0)	4336 (50.0)	
BP [median]						
Systolic (mmHg)	135 [123,150]	133 [120, 150]	<0.001	136 [122, 150]	135 [120, 152]	<0.001
Diastolic (mmHg)	76 [69, 83]	78 [70, 85]	<0.001	75 [68, 83]	78 [70, 85]	<0.001
Mean (mmHg)	95 [88, 104]	96 [87, 105]	<0.001	95 [87, 104]	96 [87, 106]	<0.001

Abbreviations: BP: blood pressure; CDR-SOB: clinical dementia rating-sum of boxes; LLR: lipid lowering regimen.

Table 1B
Neuropsychological tests in participants stratified by CDR-SOB scores and LLR.

Variables	CDR-SOB >0–2.5			CDR-SOB ≥3		
Neropsychological tests	W LLR	W/O LLR	P-value	W LLR	W/O LLR	P-value
CDR (mean±SD)	0.238 (0.255)	0.198 (0.250)	<0.001	0.981 (0.561)	1.07 (0.628)	<0.001
CDR-SOB (mean±SD)	0.668 (0.916)	0.552 (0.873)	<0.001	5.74 (3.04)	6.25 (3.43)	<0.001
MoCA (raw)	25.1 (8.62)	26.00 (9.28)	<0.001	21.1 (18.8)	22.6 (21.8)	0.0422
MMSE (mean±SD)	28.5 (6.94)	29.1 (8.55)	<0.001	23.4 (13.4)	23.0 (14.9)	0.1302

Abbreviations: as in Table 1A and CDR: clinical dementia rating; MMSE: mini mental test examination; MoCA: Montreal cognitive assessment.

yearly proportion of MCI participants (0 > CDR-SOB ≤ 2.5) who transitioned to CDR-SOB≥3 during the 10-year follow up was 1.48 % for LLR-users compared to 1.83 % for LLR non-users.

This trend continued when participants were stratified by age [≤ 70 (n = 13,327) 0.0128 (0.0066, 0.0190, P < 0.001)] and >70 (n = 15,045) 00.0089 (0.0014, 0.0164), P = 0.02)] (Fig. 1A); in male (n = 11,527) 0.0204 (0.0117, 0.0290) P < 0.001)] but not in female [(n = 16,845) 0.0018 (-0.0042, 0.0079, P = 0.555)] gender (Fig. 1B); and in participants with at least one APOE4 allele [(n = 7240) 0.0185 (0.0085, 0.0286) (P < 0.001)], but not in those without APOE4 allele [(n = 13,125) 0.0044 (-0.0015, 0.0104) (P = 0.145)] presence (Fig. 1C).

Fig. 2 presents the effect of LLR on the progression of dementia. The results are stratified by age (2A), gender (2B), and the presence of at least one copy of APOE4 (2C) in a sample size of 17,183 participants. The use of LLR reduced the increase in CDR-SOB scores by 0.1733 (0.1441, 0.2025) unit per year (P < 0.001) compared to LLR-non-users. The average yearly proportion of participants with CDR-SOB ≥ 3 who transitioned to CDR-SOB = 18 during the 10-year follow up was 0.53 % for LLR-users compared to 1.50 % for LLR non-users.

This trend continued when participants were stratified by age [≤ 70 (n = 6517) 0.2238 (0.1730, 0.2747), P < 0.001)] [>70 [(n = 10,666) 0.1376 (0.1021, 0.1731), P < 0.001] (Fig. 2A). LLR had similar effects when participants were stratified by gender [female (n = 8725) 0.1259 (0.0843, 0.1676, P < 0.001)] [male (n = 8458) 0.2153 (0.1743, 0.2564), P < 0.001] (Fig. 2B) and in participants with [(n = 6464) 0.1579 (0.1168, 0.1990) (P < 0.001)] and without [(n = 6041) 0.2167 (0.1686, 0.2647), P < 0.001] (Fig. 2C) the presence of APOE4 allele. Further stratification of participants to ≤50 years vs. >50 years and ≤60 years vs. >60 years showed that the LLR benefit on CDR-SOB is mostly apparent in participants >50 years old (P < 0.001) and is absent in participants <50 years old (n = 268) (P = 0.660). Nevertheless, 31 participants in the <50 years old subgroup eventually reached CDR-SOB = 18.

3.3. Hypolipidemics and rate of survival in participants progressing to dementia

Fig. 3 presents the effect of LLR on the rate of survival in participants who progressed to dementia (CDRSOB of =>3), stratified by age (3A), gender (3B) and the presence of one or two APOE4 allele (3C). LLR use increased the rate of survival in participants who progressed to dementia [HR: 0.822 (0.746, 0.906). P = 0.001] (Fig. 3). This pattern was similar after participants' stratification based on age [≤ 70: 10.828 (0.714, 0.961), P = 0.01] [> 70: 0.843 (0.741, 0.959), P = 0.01] (Fig. 3A). Further stratification of participants to ≤50 years vs. >50 years and ≤60 years vs. >60 years showed that the LLR benefit on survival rate is mostly apparent in participants >50 years old (n = 268) (P < 0.001) and is absent in participants ≤50 years old (P = 0.90).

LLR had similar effects when participants were stratified by gender [female: 0.858 (0.751, 0.981), P = 0.02] [male: 0.812 (0.704, 0.936), P = 0.004] (Fig. 3B) and the existence [0.818, (0.707, 0.944), P = 0.006] or absence [0.832 (0.706, 0.979), P = 0.03] of at least one copy of APOE4 allele (Fig. 3C).

3.4. LLR and post-mortem AD brain neuropathology

We compared the severity of brain neuropathology between LLR-users and non-users by analyzing the group differences in Braak staging, and hippocampal atrophy. Among participants, 22.4 % (n = 1697) LLR-users, and 28.4 % (n = 2431) non-users had postmortem autopsy. The severity of Braak staging (I+II, III+IV, V+VI) (Fig. 4A) and hippocampal atrophy (none, mild, moderate, severe) (Fig. 4B) were not different between LLR-users and non- users (P > 0.05). Similar analysis of 142 "pure AD" LLR-users, and 219 "pure AD" LLR-non-users did not show statistically significant differences in the severity of Braak staging and hippocampal atrophy between subgroups (results not shown). No significant differences in total CSF Tau levels were observed between LLR-users and non-users (P > 0.05). Using generalized linear mixed model, the LLR effect did not vary in the presence of other brain neuropathology, including cerebrovascular disease, lacunar infarct, and cystic infarction in cognitive network.

4. Discussion

This study should be interpreted within the context of literature that has repeatedly explored the association between LLR and cognitive outcomes. While conceptual overlap is unavoidable, the present analysis contributes incremental but meaningful evidence by examining a broader and more heterogeneous cohort than most prior studies, applying inclusive exposure definitions that reflect real-world prescribing patterns, and integrating long-term clinical and neuropathological endpoints. The breadth of the inclusion strategy enhances generalizability, whereas the exclusion of individuals receiving antihypertensive or antidiabetic therapy reduces confounding from two major cardiometabolic pathways known to influence cognitive decline. This balance between inclusiveness and specificity strengthens the interpretability of the observed associations.

We have conducted exhaustive analysis of NACC participants' dataset showing that LLR have the potential to delay the conversion of normal to MCI as well as impede the progression of dementia increasing survival. The same pattern was observed after participants' stratification by age, gender, and the existence of at least one copy of APOE4 allele. Nevertheless, the clinical effects of LLR seem to be more pronounced in the progressive stage of the disease compared to the initial stages. Our results agree with a systematic review and metanalyses of 36 observational studies reporting associations between statins and decreased risk of dementia and AD with no gender differences [31]. However, the LLR clinical effect is apparent in participant above 50 years old and is absent in younger participants. This age-dependent pattern aligns with findings from recent studies suggesting that statins and other lipid-lowering agents may exert neuroprotective effects primarily in older adults [32]. Moreover, a longitudinal cohort study demonstrated that statin use was associated with slower cognitive decline in patients with Alzheimer's disease and mixed dementia, with a dose-response relationship favoring older user [33]. Our results suggest that the LLR effect on cognitive function is complex and may be both age- and stage-dependent [34], echoing broader evidence that peripheral hypercholesterolemia in midlife is linked to late-life cognitive decline [33].

One can argue that the beneficial effects of statins stem from their

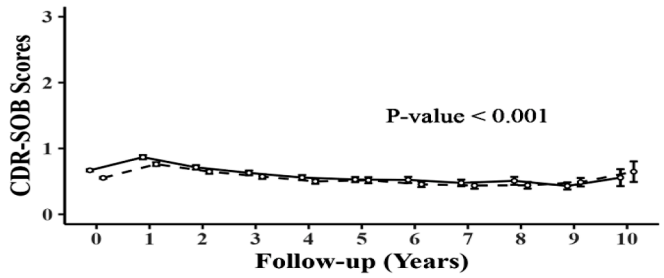


Figure 1

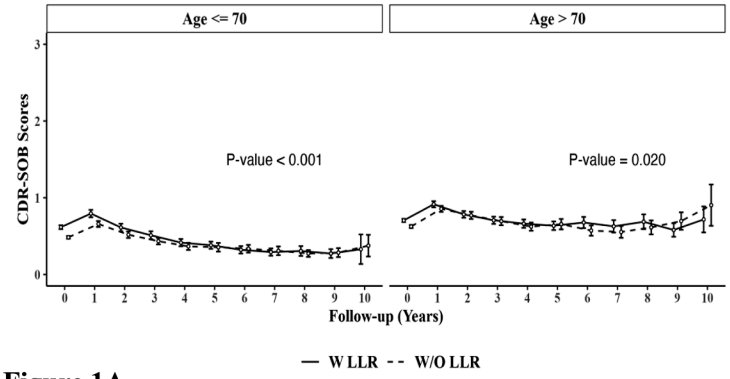


Figure 1A

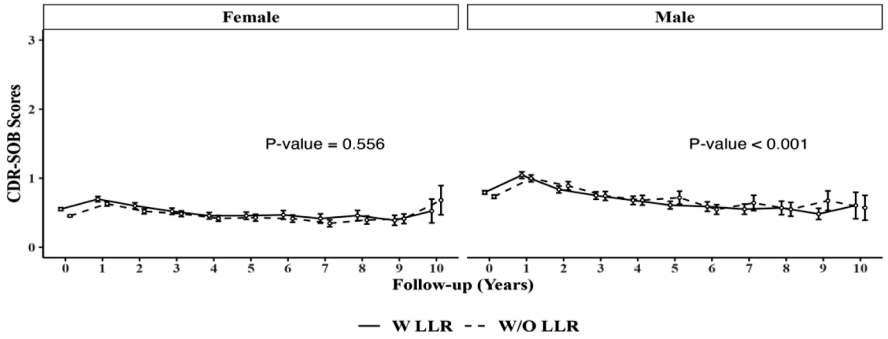


Figure 1B

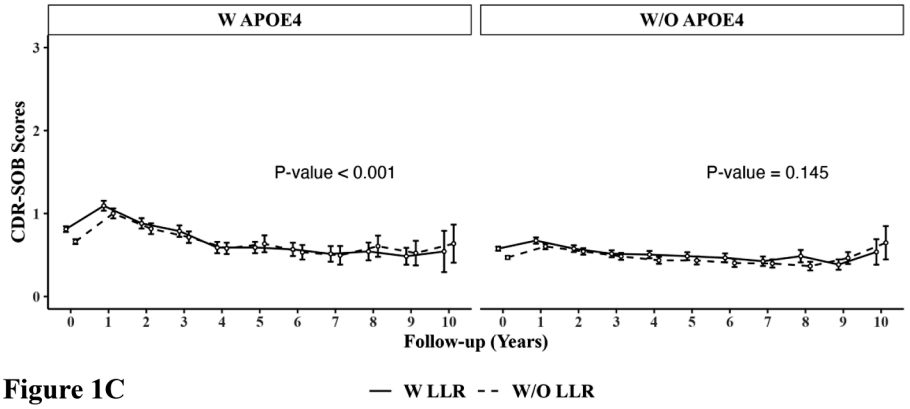


Figure 1C

Fig. 1. Presents the effect of LLR on the CDR-SOB scores on the conversion from normal to MCI. Results are stratified by age (1A), gender (1B), and the existence of at least one copy of APOE4 allele (1C). The results are shown for 10-year follow-up. $P < 0.05$ is statistically significant.
Abbreviation: LLR: Lipid Lowering Regimen Fig. 1.

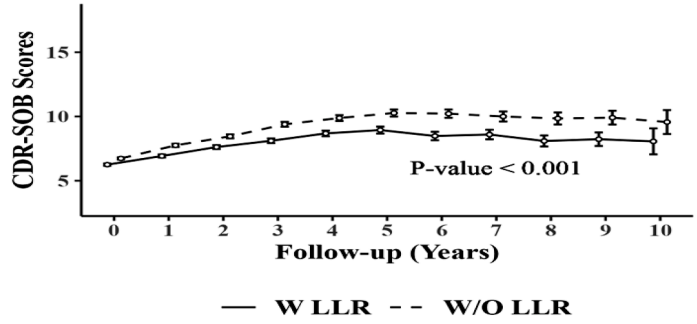


Figure 2

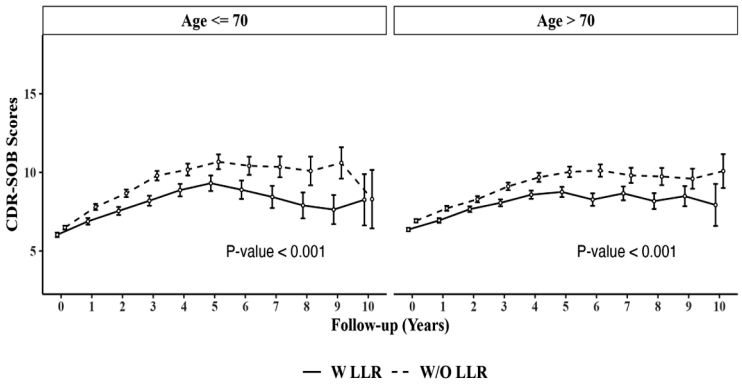


Figure 2A

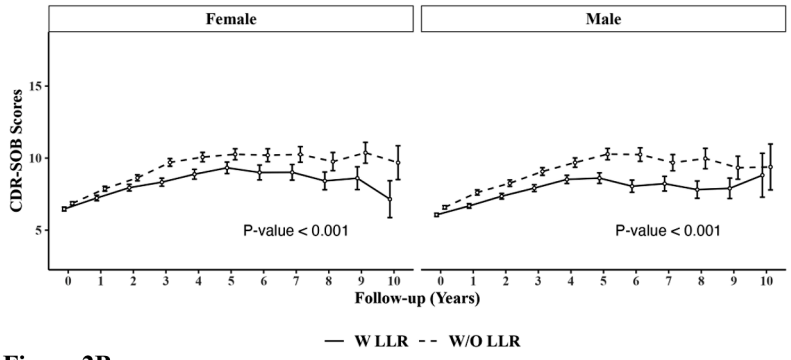


Figure 2B

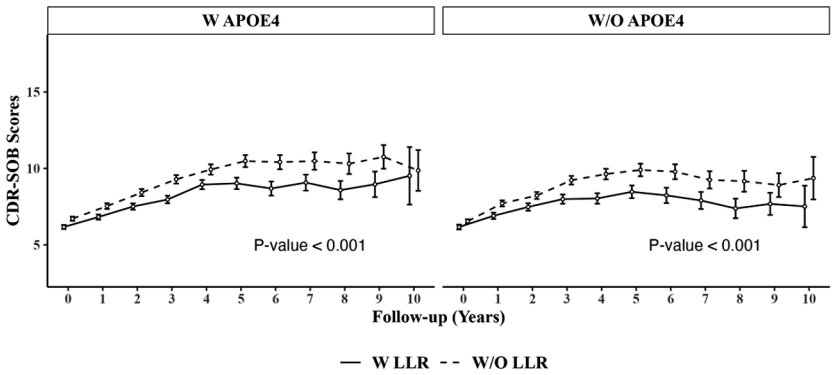


Figure 2C

Fig. 2. Presents the effect of LLR on the CDR-SOB scores indicating the progression of dementia. Results are stratified by age (2A), gender (2B), and the existence of at least one copy of APOE4 allele (2C). The results are shown for 10-year follow-up. $P < 0.05$ is statistically significant. Abbreviation: as in Fig. 1.

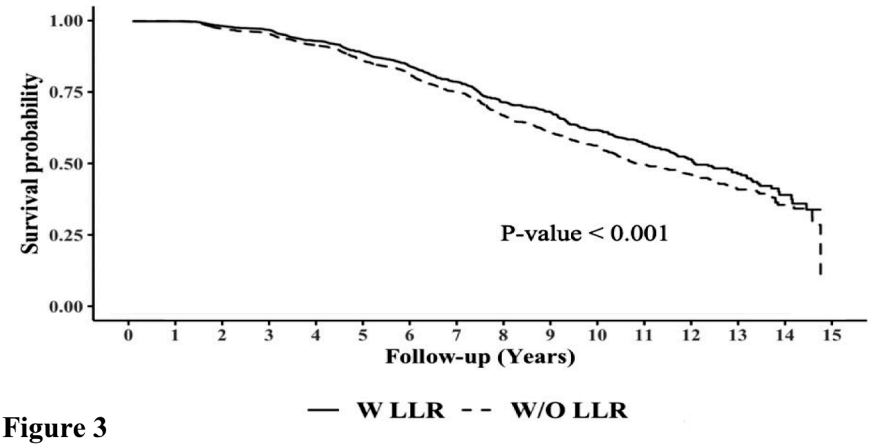


Figure 3

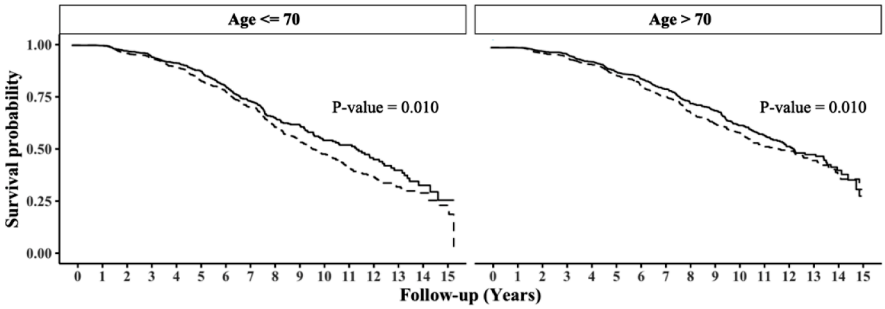


Figure 3A

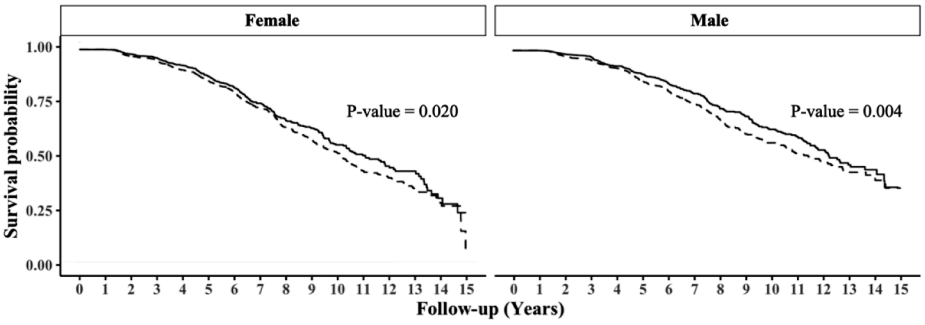


Figure 3B

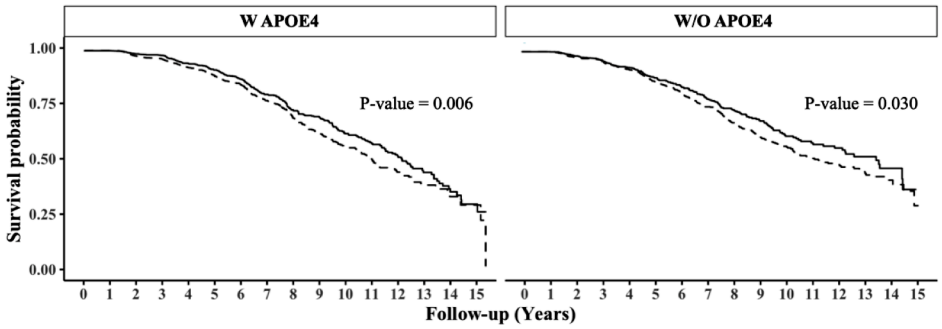


Figure 3C

Fig. 3. Presents the effect of LLR on the rate of survival in participants who progressed to dementia (CDRSOB of =>3), stratified b age (3A), gender (3B), and the existence of APOE4 allele (3C) (1 or 2 copies) during 15-year follow-up.
$P < 0.05$ is statistically significant Fig. 3.

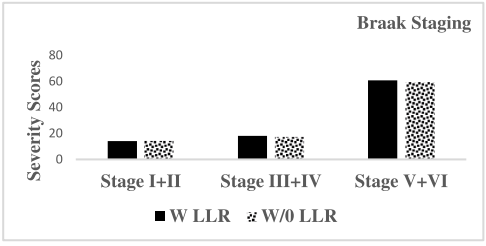


Fig. 4A. Presents the differences in Braak staging between LLR-users and non-users Fig. 4A.
$P > 0.05$.

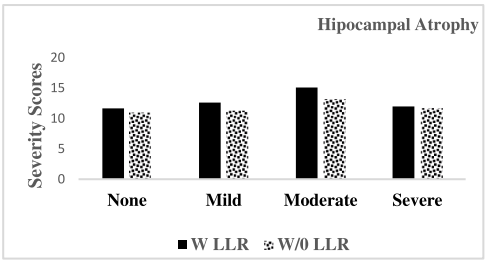


Fig. 4B. Presents the differences in hippocampal atrophy between LLR-users and non-users Fig. 4B.
$P > 0.05$.

pleiotropic effects including anti-inflammatory effects [35]. Nevertheless, in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial of 5804 elderly individuals aged 70–82 years with a history of, or risk factors for, vascular disease, reported no effect of pravastatin on cognitive function despite cardiovascular benefits among the study participants [36]. Thus, although the pleiotropic effects of statins remain biologically plausible mechanisms for cognitive protection, current evidence does not support their use for this purpose in older adults without clear indications for lipid-lowering therapy.

Our absolute effect sizes—approximately 0.01 CDR-SOB units per year for transition to MCI and 0.17 units per year for progression to dementia—are modest. Such magnitudes are expected in large, heterogeneous cohorts where cognitive decline is multifactorial and gradual. Importantly, small annual differences can accumulate over extended follow-up, potentially delaying clinically significant milestones such as loss of independence or institutionalization. In the context of a disease with limited disease-modifying options, even incremental slowing of decline may have meaningful public health implications, particularly when applied across aging populations with high prevalence of hyperlipidemia.

Emerging evidence highlights cholesterol metabolism as critical mediator of AD pathogenesis. Amyloid PET scan data derived from non-demented participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI) show that higher levels of serum cholesterol accelerate Aβ deposition in the brain [37], suggesting a relationship between hypercholesterolemia and cognitive dysfunction. This relationship may be mediated, in part, through cholesterol oxidation products, such as 24 (S)−hydroxycholesterol (24-OHC) and 27-Hydroxycholesterol (27-OHC). Both levels were significantly higher in the CSF of those diagnosed with early AD compared to the levels in controls [38]. Through passive diffusion, the 27-OHC can enter the CNS, with the potential for increasing Aβ accumulation and deposition [39], and promoting neuroinflammation [40].

High cholesterol, specifically high LDL, also contributes to dementia through increasing cerebral small vessel disease burden [41], therefore linking high cholesterol to both AD and vascular dementia. Consistent with these mechanistic insights our finding demonstrates that LLR is associated with slower cognitive decline, improved survival in dementia, and stage-dependent benefits across APOE4 subgroups, despite no significant difference in classical neuropathological markers. Taken together, these results suggest that cholesterol and its metabolites act as dual drivers of neurodegeneration, while hypolipidemic therapy may mitigate their downstream effects, providing a mechanistic rationale for the observed clinical benefits.

Although our findings demonstrate that LLR use was associated with slower clinical progression and improved survival, no notable differences were observed in neuropathological or fluid biomarkers. Specifically, Braak staging, hippocampal atrophy, and CSF tau concentrations were comparable between LLR-users and non-users. This absence of biomarker effect suggests that the clinical benefits of LLR may not be mediated through direct modification of classical Alzheimer's disease pathology. These results are consistent with large autopsy-based cohorts, such as the Religious Orders Study and the Rush Memory and Aging Project, which reported limited associations between statin exposure and post-mortem indices of amyloid or tau burden [42,43]. The absence of differences in Braak staging, hippocampal atrophy, or CSF tau between LLR users and non-users suggests that the observed clinical benefits may operate through pathways other than core Alzheimer's pathology. Potential mechanisms include vascular stabilization, anti-inflammatory effects, or modulation of peripheral cholesterol metabolism. These findings align with emerging evidence that vascular and metabolic factors contribute substantially to clinical progression even in the presence of established AD pathology.

Recent neuroimaging studies using tau PET have shown heterogeneous patterns of tau accumulation that are not consistently altered by statin use [44]. By contrast, some epidemiological and mechanistic studies have suggested that statins may reduce amyloid deposition or tau phosphorylation, particularly in APOE4 carriers [31,45]. However, these findings have not been reliably replicated in neuropathological analyses, highlighting a divergence between clinical and mechanistic evidence. Meta-analyses of observational studies have further complicated the picture, with some reporting reduced dementia risk among statin users, while others found no significant association [46,47]. The NILVAD trial, for example, observed no biomarker-level differences despite modest clinical benefits in statin-treated patients with mild-to-moderate Alzheimer's disease [42].

Taking it together, our findings support the view that LLR effects may be exerted through pathways other than those that directly modulate amyloid or tau pathology. This dissociation between clinical outcomes and biomarker neutrality underscores the need for future studies that integrate longitudinal biomarker trajectories with clinical endpoints. Such work will clarify whether the protective effects of LLR reflect symptomatic modulation, systemic resilience, or subtle changes below the threshold of current neuropathological detection. By bridging clinical outcomes with mechanistic pathway, our study contributes to a growing body of evidence that positions LLR as a potential adjunct in the management of AD and related dementias.

The more pronounced association observed among APOE4 carriers is consistent with mechanistic evidence implicating cholesterol transport and APOE-dependent pathways in amyloid deposition, neuroinflammation, and synaptic vulnerability. Although the effect remains modest, the genotype-specific signal suggests that lipid-lowering therapy may confer differential benefit in biologically defined subgroups. These findings underscore the need for future studies integrating genetic stratification, lipidomic profiling, and longitudinal biomarker trajectories to clarify whether APOE4 carriers represent a therapeutically responsive subgroup.

The cognitive effects of LLR, particularly statins and PCSK9 inhibitors, remain a subject of ongoing debate. Our findings reveal a complex and seemingly contradictory relationship between LLR use and neuropsychological outcomes in individuals with varying degrees of dementia. In cross-sectional analyses, participants receiving LLR exhibited lower scores on cognitive assessments (MoCA, MMSE)

compared to non-LLR counterparts, particularly within the mild dementia subgroup (CDR >0–2.5). These differences were statistically significant ($P < 0.001$), suggesting a potential association between LLR and reduced cognition. However, this interpretation is complicated by the concurrent observation that this same LLR user group also presented with lower Clinical Dementia Rating (CDR) and CDR-Sum of Boxes (CDR-SOB) scores, indicating less severe clinical dementia at baseline.

Longitudinal data spanning a 10-year follow-up period revealed a more compelling narrative: participants on LLR demonstrated a significantly slower progression of dementia symptoms, as evidenced by consistently lower CDR-SOB scores over time ($P < 0.001$). This suggests that while LLR may not confer immediate cognitive benefits, it could play a protective role in attenuating long-term functional decline, potentially through vascular or anti-inflammatory mechanisms. These findings align with recent meta-analytic evidence from randomized controlled trials, which found no significant reduction in incident cognitive impairment or dementia with LLR use (OR 0.96; 95 % CI: 0.74–1.26) but affirmed the cognitive safety of such therapies [48]. Moreover, a large cohort study from the Swedish SveDem registry demonstrated a dose-response benefit of statins, with simvastatin users showing improved MMSE scores over three years compared to other statin types [33]. Similarly, a multicenter observational study found that LDL-C levels below 70 mg/dL were associated with a 26 % reduction in all-cause dementia risk, with statin use providing additional protective effects [49].

Taken together, these data suggest a nuanced dynamic: (a) Cross-sectional snapshots may reflect transient cognitive fluctuations or confounding by indication (e.g., LLR prescribed to higher-risk individuals). (b) Longitudinal trajectories, however, highlight the potential for LLR to modulate disease progression, especially in early-stage dementia. This apparent contradiction underscores the importance of temporal context in evaluating cognitive outcomes and cautions against relying solely on static cognitive scores. Future research should prioritize longitudinal designs, stratify by dementia subtype and severity, and differentiate between lipid-lowering agents to elucidate their mechanistic impact on neurodegeneration.

4.1. *Strength & limitations*

This study has several strengths. It leverages one of the largest, prospectively collected, clinically adjudicated datasets available for Alzheimer's disease research, enabling evaluation of lipid-lowering regimen (LLR) exposure across the full cognitive continuum. The use of standardized assessments from the National Alzheimer's Coordinating Center (NACC) minimizes diagnostic heterogeneity and ensures consistency in outcome measurement. Modeling LLR exposure as a time-varying covariate reduces immortal-time bias and more accurately reflects real-world treatment patterns. The integration of clinical trajectories, survival outcomes, and neuropathological data provides a uniquely comprehensive view of LLR associations with disease progression. Extensive stratified and sensitivity analyses—across age, sex, APOE4 genotype, and neuropathological subgroups—support the robustness and generalizability of the findings.

Several limitations should be acknowledged. As an observational study, residual confounding cannot be excluded, particularly given the inability to differentiate between classes, doses, or duration of lipid-lowering therapies. Medication adherence was incompletely captured, and treatment exposure may be misclassified despite time-varying modeling. Participants enrolled in ADRCs are not fully representative of the general population, with higher education levels and greater engagement in clinical research, potentially limiting external validity. Missing data, although addressed using predefined rules, may introduce bias if missingness deviates from the assumed missing-at-random mechanism. Neuropathological analyses were restricted to participants who underwent autopsy, a subset that may differ systematically from the broader cohort. Finally, the absence of biomarker-based staging for all participants limits the ability to disentangle AD-specific from vascular or mixed etiologies.

Despite these limitations, the study provides robust, population-level evidence that LLR exposure is associated with slower clinical progression and improved survival, offering insights that may inform future mechanistic and interventional research.

Taken together, the present findings offer moderate but robust incremental evidence that lipid-lowering therapy is associated with slower cognitive decline and improved survival, even in the absence of detectable differences in classical neuropathological markers. The dissociation between clinical benefit and biomarker neutrality highlights the complexity of cholesterol-related mechanisms in neurodegeneration and suggests that LLRs may exert their effects through pathways not captured by traditional AD pathology metrics. These results should be viewed as hypothesis-generating and complementary to existing literature, providing a foundation for more targeted mechanistic and interventional studies. Future studies should incorporate detailed pharmacologic data, longitudinal biomarker tracking, and randomized designs to disentangle the cognitive effects of individual LLRs in hope of optimizing therapeutic strategies.

5. Conclusion

Our comprehensive analysis of the NACC dataset, supported by converging evidence from observational studies and longitudinal cohorts, underscores the potential of lipid-lowering agents (LLRs)—particularly statins—to mitigate cognitive decline and delay the progression of dementia. Protective effects appear to be both age- and stage-dependent, with older adults and those in advanced stages of cognitive impairment deriving the greatest benefit. These findings align with emerging mechanistic insights linking cholesterol metabolism, oxysterol profiles, and blood–brain barrier integrity to neurodegeneration.

While the pleiotropic properties of statins offer biologically plausible pathways for cognitive protection, their clinical utility remains nuanced. The absence of consistent effects in randomized trials like PROSPER and the lack of differentiation between LLR classes in the NACC dataset highlight the need for more granular research. Future studies should aim to disentangle the contributions of individual LLRs, explore the impact of combination therapies, and assess the role of statin solubility in crossing the BBB.

Taken together, our results contribute to a growing body of evidence suggesting that cholesterol management—particularly in midlife and among high-risk populations—may play a critical role in preserving cognitive health. However, targeted interventions and personalized approaches will be essential to translate these findings into practical clinical strategies.

Use of generative AI and AI-assisted technologies

Generative AI and AI-assisted technologies have not been used in scientific writing and in figures, images, and artwork.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Availability of data and materials

Data and materials can be available upon request.

Ethics approval

This is an observational study. The University at Buffalo Research Ethics Committee has confirmed that no ethical approval is required.

Consent to participate

NA.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

CRediT authorship contribution statement

Zohi Sternberg: Conception, writing, methodology, data interpretation; **Rebecca E. Podolsky:** Revision, intellectual input; **Jihnhee Yu:** Visualization, data analysis, curation; **Shuangcheng Hua:** Visualization, data analysis, curation; **Stanley Halvorsen:** Intellectual input; **Bernhard J. Schaller:** Review, editing, methodology, conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Zohi Sternberg has patent pending to NA. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors thank the National Alzheimer's Coordinating Center (NACC) for providing the Uniform Data Set and Ms. Merilee Taylan and Mr. Zachary Miller for guidance and clarifications related to the data set. We are indebted to the study members and their families for their ongoing commitment and support of NACC's research philosophy.

The NACC database is funded by NIA/NIH Grant U24 AG072122. NACC data are contributed by the NIA-funded ADRCs: P30 AG062429 (PI James Brewer, MD, PhD), P30 AG066468 (PI Oscar Lopez, MD), P30 AG062421 (PI Bradley Hyman, MD, PhD), P30 AG066509 (PI Thomas Grabowski, MD), P30 AG066514 (PI Mary Sano, PhD), P30 AG066530 (PI Helena Chui, MD), P30 AG066507 (PI Marilyn Albert, PhD), P30 AG066444 (PI John Morris, MD), P30 AG066518 (PI Jeffrey Kaye, MD), P30 AG066512 (PI Thomas Wisniewski, MD), P30 AG066462 (PI Scott Small, MD), P30 AG072979 (PI David Wolk, MD), P30 AG072972 (PI Charles DeCarli, MD), P30 AG072976 (PI Andrew Saykin, PsyD), P30 AG072975 (PI David Bennett, MD), P30 AG072978 (PI Neil Kowall, MD), P30 AG072977 (PI Robert Vassar, PhD), P30 AG066519 (PI Frank LaFerla, PhD), P30 AG062677 (PI Ronald Petersen, MD, PhD), P30 AG079280 (PI Eric Reiman, MD), P30 AG062422 (PI Gil Rabinovici, MD), P30 AG066511 (PI Allan Levey, MD, PhD), P30 AG072946 (PI Linda Van Eldik, PhD), P30 AG062715 (PI Sanjay Asthana, MD, FRCP), P30 AG072973 (PI Russell Swerdlow, MD), P30 AG066506 (PI Todd Golde, MD, PhD), P30 AG066508 (PI Stephen Strittmatter, MD, PhD), P30 AG066515 (PI Victor Henderson, MD, MS), P30 AG072947 (PI Suzanne Craft, PhD), P30 AG072931 (PI Henry Paulson, MD, PhD), P30 AG066546 (PI Sudha Seshadri, MD), P20 AG068024 (PI Erik Roberson, MD, PhD), P20 AG068053 (PI Justin Miller, PhD), P20 AG068077 (PI Gary Rosenberg, MD), P20 AG068082 (PI Angela Jefferson, PhD), P30 AG072958 (PI Heather Whitson, MD), P30 AG072959 (PI James Leverenz, MD).

References

[1] Gustavsson A, Norton N, Fast T, Frolich L, Georges J, Holzapfel D, Kirabali T, Krolak-Salmon P, Rossini PM, Ferretti MT, Lanman L, Chadha AS, van der Flier WM. Global estimates on the number of persons across the Alzheimer's disease continuum. Alzheimers Dement 2023;19(2):658–70.

[2] Jagust W. Imaging the evolution and pathophysiology of Alzheimer disease. Nat Rev Neurosci 2018;19(11):687–700.

[3] Schaller BJ. Strategies for molecular imaging dementia and neurodegenerative diseases. Neuropsychiatr Dis Treat 2008;4(3):585–612.

[4] Jacobs AH, Li H, Winkeler A, Hilker R, Knoess C, Ruger A, Galldiks N, Schaller B, Sobesky J, Kracht L, Monfared P, Klein M, Vollmar S, Bauer B, Wagner R, Graf R, Wienhard K, Herholz K, Heiss WD. PET-based molecular imaging in neuroscience. Eur J Nucl Med Mol Imaging 2003;30(7):1051–65.

[5] Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med 2004; 256(3):183–94.

[6] Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B. Current concepts in mild cognitive impairment. Arch Neurol 2001;58(12):1985–92.

[7] Apostolova LG. Alzheimer Disease. Contin (Minneap Minn) 2016;22(2 Dementia): 419–34.

[8] Petersen RC, Smith GE, Ivnik RJ, Tangalos EG, Schaid DJ, Thibodeau SN, Kokmen E, Waring SC, Kurland LT. Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals. JAMA 1995; 273(16):1274–8.

[9] Vermunt L, Sikkes SAM, van den Hout A, Handels R, Bos I, van der Flier WM, Kern S, Ousset PJ, Maruff P, Skoog I, Verhey FRJ, Freund-Levi Y, Tsolaki M, Wallin AK, Olde Rikkert M, Soininen H, Spiru L, Zetterberg H, Blennow K, Scheltens P, Muniz-Terrera G, Visser PJ, Alzheimer Disease Neuroimaging I, Group AR, groups IDs. Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. Alzheimers Dement 2019;15(7):888–98.

[10] Josephs KA, Dickson DW, Tosakulwong N, Weigand SD, Murray ME, Petrucelli L, Liesinger AM, Senjem ML, Spychalla AJ, Knopman DS, Parisi JE, Petersen RC, Jack Jr CR, Whitwell JL. Rates of hippocampal atrophy and presence of post-mortem TDP-43 in patients with Alzheimer's disease: a longitudinal retrospective study. Lancet Neurol 2017;16(11):917–24.

[11] Sakai M, Hanyu H, Kume K, Sato T, Hirao K, Kanetaka H, Abe S, Kanaya K, Sakurai H, Iwamoto T. Rate of progression of Alzheimer's disease in younger versus older patients: a longitudinal single photon emission computed tomography study. Geriatr Gerontol Int 2013;13(3):555–62.

[12] Peng GP, Feng Z, He FP, Chen ZQ, Liu XY, Liu P, Luo BY. Correlation of hippocampal volume and cognitive performances in patients with either mild cognitive impairment or Alzheimer's disease. CNS Neurosci Ther 2015;21(1): 15–22.

[13] La Joie R, Visani AV, Baker SL, Brown JA, Bourakova V, Cha J, Chaudhary K, Edwards L, Iaccarino L, Janabi M, Lesman-Segev OH, Miller ZA, Perry DC, O'Neil JP, Pham J, Rojas JC, Rosen HJ, Seeley WW, Tsai RM, Miller BL, Jagust WJ, Rabinovici GD. Prospective longitudinal atrophy in Alzheimer's disease correlates with the intensity and topography of baseline tau-PET. Sci Transl Med 2020;12 (524).

[14] Wanleenuwat P, Iwanowski P, Kozubski W. Alzheimer's dementia: pathogenesis and impact of cardiovascular risk factors on cognitive decline. Postgr Med 2019; 131(7):415–22.

[15] Sternberg Z, Podolsky R, Yu J, Tian M, Hojnacki D, Schaller B. Delayed decline of cognitive function by antihypertensive agents: a cohort study linked with genotype data. J Prev Alzheimers Dis 2022;9(4):679–91.

[16] Schilling S, Tzourio C, Soumare A, Kaffashian S, Dartigues JF, Ancelin ML, Samieri C, Dufouil C, Debette S. Differential associations of plasma lipids with incident dementia and dementia subtypes in the 3C study: a longitudinal, population-based prospective cohort study. PLoS Med 2017;14(3):e1002265.

[17] Anstey KJ, Ashby-Mitchell K, Peters R. Updating the evidence on the association between serum cholesterol and risk of late-life dementia: review and meta-analysis. J Alzheimers Dis 2017;56(1):215–28.

[18] Tan ZS, Seshadri S, Beiser A, Wilson PW, Kiel DP, Tocco M, D'Agostino RB, Wolf PA. Plasma total cholesterol level as a risk factor for Alzheimer disease: the Framingham Study. Arch Intern Med 2003;163(9):1053–7.

[19] Ylilauri MP, Voutilainen S, Lonnroos E, Mursu J, Virtanen HE, Koskinen TT, Salonen JT, Tuomainen TP, Virtanen JK. Association of dietary cholesterol and egg intakes with the risk of incident dementia or Alzheimer disease: the Kuopio Ischaemic Heart Disease Risk Factor Study. Am J Clin Nutr 2017;105(2):476–84.

[20] Mancini G, Dias C, Lourenco CF, Laranjinha J, de Bem A, Ledo A. A high fat/cholesterol diet recapitulates some Alzheimer's disease-like features in mice: focus on hippocampal mitochondrial dysfunction. J Alzheimers Dis 2021;82(4):1619–33.

[21] Ledreux A, Wang X, Schultzberg M, Granholm AC, Freeman LR. Detrimental effects of a high fat/high cholesterol diet on memory and hippocampal markers in aged rats. Behav Brain Res 2016;312:294–304.

[22] Umeda T, Tomiyama T, Kitajima E, Idomoto T, Nomura S, Lambert MP, Klein WL, Mori H. Hypercholesterolemia accelerates intraneuronal accumulation of Abeta oligomers resulting in memory impairment in Alzheimer's disease model mice. Life Sci 2012;91(23-24):1169–76.

[23] Bhat NR, Thirumangalakudi L. Increased tau phosphorylation and impaired brain insulin/IGF signaling in mice fed a high fat/high cholesterol diet. J Alzheimers Dis 2013;36(4):781–9.

[24] Xu C, Apostolova LG, Oblak AL, Gao S. Association of hypercholesterolemia with Alzheimer's Disease pathology and cerebral amyloid angiopathy. J Alzheimers Dis 2020;73(4):1305–11.

[25] Hendrie HC, Hake A, Lane K, Purnell C, Unverzagt F, Smith-Gamble V, Murrell J, Ogunniyi A, Baiyewu O, Callahan C, Saykin A, Taylor S, Hall K, Gao S. Statin use, incident dementia and Alzheimer disease in elderly African Americans. Ethn Dis 2015;25(3):345–54.

[26] Lee JW, Choi EA, Kim YS, Kim Y, You HS, Han YE, Kim HS, Bae YJ, Kim J, Kang HT. Statin exposure and the risk of dementia in individuals with hypercholesterolaemia. J Intern Med 2020;288(6):689–98.
[27] Rajan KB, McAninch EA, Wilson RS, Dhana A, Evans-Lacko S, Evans DA. Statin initiation and risk of incident Alzheimer disease and cognitive decline in genetically susceptible older adults. Neurology 2024;102(7):e209168.
[28] Sood A, Capuano AW, Wilson RS, Barnes LL, Kapasi A, Bennett DA, Arvanitakis Z. Metformin, age-related cognitive decline, and brain pathology. Neurobiol Aging 2024;133:99–106.
[29] Sheffield JM, Karcher NR, Barch DM. Cognitive Deficits in psychotic disorders: a lifespan perspective. Neuropsychol Rev 2018;28(4):509–33.
[30] Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. BMC Med Inf Decis Mak 2007;7:16.
[31] Olmastroni E, Molari G, De Beni N, Colpani O, Galimberti F, Gazzotti M, Zambon A, Catapano AL, Casula M. Statin use and risk of dementia or Alzheimer's disease: a systematic review and meta-analysis of observational studies. Eur J Prev Cardiol 2022;29(5):804–14.
[32] Wang W, Li X. Cognitive function in dyslipidemia patients: exploring the impact of statins. Front Neurol 2024;15:1436010.
[33] Petek B, Habel H, Xu H, Villa-Lopez M, Kalar I, Hoang MT, Maioli S, Pereira JB, Mostafaei S, Winblad B, Gregoric Kramberger M, Eriksdotter M, Garcia-Ptacek S. Statins and cognitive decline in patients with Alzheimer's and mixed dementia: a longitudinal registry-based cohort study. Alzheimers Res Ther 2023;15(1):220.
[34] Alsehli AM, Olivo G, Clemensson LE, Williams MJ, Schioth HB. The cognitive effects of statins are modified by age. Sci Rep 2020;10(1):6187.
[35] Wanamaker BL, Swiger KJ, Blumenthal RS, Martin SS. Cholesterol, statins, and dementia: what the cardiologist should know. Clin Cardiol 2015;38(4):243–50.
[36] Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG, Risk PsgPSoPitEa. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360(9346):1623–30.
[37] Souza PG, J PF, Brum WS, De Bastiani MA, Pascoal TA, Benedet AL. Hypercholesterolemia accelerates aβ deposition in regions associated with early amyloidosis: neuroimaging/optimal neuroimaging measures for tracking disease progression. Alzheimer's Demen J 2020;16.
[38] Wang HL, Wang YY, Liu XG, Kuo SH, Liu N, Song QY, Wang MW. Cholesterol, 24-hydroxycholesterol, and 27-hydroxycholesterol as surrogate biomarkers in cerebrospinal fluid in mild cognitive impairment and Alzheimer's Disease: a meta-analysis. J Alzheimers Dis 2016;51(1):45–55.
[39] Zhang X, Xi Y, Yu H, An Y, Wang Y, Tao L, Wang Y, Liu W, Wang T, Xiao R. 27-hydroxycholesterol promotes Abeta accumulation via altering Abeta metabolism in mild cognitive impairment patients and APP/PS1 mice. Brain Pathol 2019;29(4):558–73.
[40] Yu C, Wang W, Shi L, Ma R, Zhang Y, Zhang C, Wang X, Wang T, Zheng Y, Tian J. 27-Hydroxycholesterol triggers microglial senescence subsequent to iron overloading contributes to brain aging, suppressed by Deferoxamine. NPJ Aging 2025.
[41] Kang SH, Yoo H, Cheon BK, Park YH, Kim SJ, Ham H, Jang H, Kim HJ, Oh K, Koh SB, Na DL, Kim JP, Seo SW. Distinct effects of cholesterol profile components on amyloid and vascular burdens. Alzheimers Res Ther 2023;15(1):197.
[42] Murphy C, Dyer AH, Lawlor B, Kennelly SP. N.s. group, what is the impact of ongoing statin use on cognitive decline and dementia progression in older adults with mild-moderate Alzheimer disease? PLoS One 2023;18(5):e0285529.
[43] St-Onge F, Chapleau M, Breitner JCS, Villeneuve S, Pichet Binette A. Tau accumulation and its spatial progression across the Alzheimer's disease spectrum. Brain Commun 2024;6(1):fcae031.
[44] Macedo AC, Tissot C, Therriault J, Servaes S, Wang YT, Fernandez-Arias J, Rahmouni N, Lussier FZ, Vermeiren M, Bezgin G, Vitali P, Ng KP, Zimmer ER, Guiot MC, Pascoal TA, Gauthier S, Rosa-Neto P. The use of tau PET to stage Alzheimer disease according to the Braak Staging Framework. J Nucl Med 2023;64(8):1171–8.
[45] Du L, Langhough RE, Hermann BP, Jonaitis EM, Betthauser TJ, Rivera-Rivera LA, Cody KA, Chin NA, Cadman RV, Johnson KM, Field AS, Asthana S, Eisenmenger L, Christian BT, Johnson SC. Tau mediates the impact of amyloid and vascular disease burden on the trajectory of clinical symptoms. Alzheimers Dement 2025;21(10):e70831.
[46] Li X, Liu Y, Song T, Wu X, Xing Y. Statins and the risk of dementia: a meta-analysis. Acta Neurol Belg 2025;125(3):699–705.
[47] Qutub Jamali CO. Neuroprotective effects of statins and cyclodextrins: review and potential role in dementia treatment. Cambridge University Press; 2025. Published online by24 June 2025.
[48] Reddin C, Stankard A, Chan KY, Krewer F, Judge C, Canavan M, Davis DHJ, O'Donnell M. Association of lipid-lowering therapy with dementia and cognitive outcomes: a systematic review and meta-analysis. Age Ageing 2025;54(8).
[49] Lee M, Lee KJ, Kim J, Lee DY, Park RW, Rhee SY, Cha JM, Yang HJ, Jang JW, Jung S, Lee J, Lee SH, Kim C, Bae JS, Kim YJ, Lee JH, Bae H, Kim Y. Low-density lipoprotein cholesterol levels and risk of incident dementia: a distributed network analysis using common data models. J Neurol Neurosurg Psychiatry 2025;96(10):981–9.