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Article

Atorvastatin or Rosuvastatin Monotherapy vs. Ezetimibe Monotherapy Among Patients With Hyperlipidaemia on Risks of Cognitive Dysfunctions: A Real-World Retrospective Study Using Target Trial Emulation

Minjie Yuan[1,*,†], Junbo Wei[1,†], Shuai Li[1], Jianmin Wang[2], Yun Shen[3]

[1]Department of Cardiology, Renhe Hospital, 200431 Shanghai, China
[2]Department of Neurology, Renhe Hospital, 200431 Shanghai, China
[3]Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, LA 70808, USA
*Correspondence: mj_yuan1988@163.com (Minjie Yuan)
[†]These authors contributed equally.

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Abstract

Aims/Background: Meta-analyses of observational studies suggest that statin use may be associated with a lower risk of dementia, whereas randomised trials show no effect. Most observational studies compared users with non-users, a design prone to confounding by indication. We compared the risk of incident cognitive dysfunction between statin and ezetimibe monotherapy in adults aged 65 years or older with hyperlipidaemia. **Methods:** Single-centre retrospective cohort study using electronic health records from a Shanghai general hospital (2016 to 2024), analysed within the target trial emulation framework with an active comparator, new-user design. Of 22,837 eligible patients, 10,288 were matched 1:1 on a propensity score from 35 covariates. The primary outcome was incident cognitive dysfunction, defined by two or more diagnosis codes on separate dates. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox models with robust variance. **Results:** Over 52,416 person-years of intention-to-treat follow-up, cognitive dysfunction occurred in 322 statin and 324 ezetimibe recipients (12.3 per 1000 person-years in each group; HR 1.00, 95% CI 0.86 to 1.17; p = 0.987). The per-protocol estimate was identical (HR 1.00, 95% CI 0.86 to 1.18). Estimates were consistent across subtypes, sensitivity analyses, and subgroups. Statin use was associated with new-onset diabetes (HR 1.94, 95% CI 1.65 to 2.29), an anticipated positive control finding. **Conclusion:** Among older Chinese adults with hyperlipidaemia, statin and ezetimibe monotherapy were associated with comparable risks of incident cognitive dysfunction. The findings do not establish equivalence but give no reason for cognitive concerns to guide the choice between these agents.

Keywords: target trial emulation; statins; ezetimibe; cognitive dysfunction; elderly

1. Introduction

Cognitive dysfunction is among the most consequential public health challenges of the twenty-first century, and China bears the heaviest absolute burden worldwide. A recent nationwide cross-sectional study reported a crude dementia prevalence of 9.1% (95% confidence interval 8.7% to 9.5%) among Chinese adults aged 65 years or older, of which Alzheimer's disease (AD) accounted for 6.0% and vascular dementia for 1.4% [1]. Mild cognitive impairment (MCI) is more common still. The annual societal cost of AD alone reached US $167.74 billion in 2015 and is projected to exceed $500 billion by 2030 [2]. Effective prevention strategies are urgently needed. The 2024 Lancet standing Commission estimated that approximately 45% of dementia cases worldwide are attributable to potentially modifiable risk factors and, for the first time, identified elevated midlife low-density lipoprotein cholesterol as one of them, which places lipid-lowering therapy squarely within the debate on dementia prevention [3].

Statins, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are the most widely prescribed lipid-lowering drugs globally. Their relationship with cognition remains contentious. In 2012, the US Food and Drug Administration (FDA) added warnings to all statin labels regarding post-marketing reports of memory loss and confusion [4]. Yet large meta-analyses of observational studies have consistently shown a 14–30% reduction in dementia risk among statin users [5,6,7]. In particular, a systematic review and meta-analysis of observational studies reported that statin use was associated with a lower risk of dementia and of Alzheimer's disease [7]. Randomised controlled trials, by contrast, have detected neither benefit nor harm [8]. This discrepancy likely reflects residual confounding, healthy-user bias, and the short follow-up typical of trials designed for cardiovascular endpoints.

Biological plausibility supports a neuroprotective role. Statins exhibit pleiotropic effects beyond cholesterol

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reduction, including anti-inflammatory activity, enhanced endothelial nitric oxide synthase expression, and modulation of amyloid-beta processing [9]. Lipophilic statins such as atorvastatin can cross the blood-brain barrier (BBB), whereas hydrophilic statins have limited central nervous system (CNS) penetration [9]. Whether these mechanisms translate into clinically meaningful cognitive protection in older adults remains an open question.

Most observational studies compare statin users with non-users. This design is vulnerable to confounding by indication: healthier patients may be more likely to receive statins and less likely to develop dementia. The active comparator new-user (ACNU) design mitigates this bias by comparing two drugs sharing the same indication [10]. Ezetimibe inhibits Niemann-Pick C1-Like 1-mediated intestinal cholesterol absorption, acts predominantly at the enterocyte brush border, and has no established central nervous system activity, which makes it a mechanistically distinct yet clinically interchangeable comparator [11,12].

The Target trial emulation (TTE) framework, formalized by Hernán and Robins [13], offers a structured approach for causal inference from observational data. It requires investigators to explicitly specify each component of a hypothetical randomised trial, thereby preventing common biases such as immortal time bias. We conducted a real-world retrospective cohort study using electronic health record (EHR) data from a Chinese hospital, applying the TTE framework to compare atorvastatin or rosuvastatin monotherapy with ezetimibe monotherapy for the prevention of cognitive dysfunction in patients aged 65 years or older with hyperlipidaemia. We hypothesised that statins and ezetimibe would be associated with similar risks of incident cognitive dysfunction, consistent with the null findings of prior TTE analyses using non-user comparators [14,15].

2. Methods

2.1 Study Design, Data Source and Analytical Framework

This was a single-centre, real-world retrospective cohort study using EHR data from a general hospital in Shanghai, China. The study period spanned January 1, 2016 to December 31, 2024. We adopted the target trial emulation (TTE) framework as our analytical approach to estimate the comparative effectiveness of statin monotherapy (atorvastatin or rosuvastatin) versus ezetimibe monotherapy on the risk of incident cognitive dysfunction among patients aged 65 years or older with hyperlipidaemia [13,16]. This framework explicitly specifies each component of a hypothetical randomised trial, eligibility, treatment strategies, assignment, follow-up, outcomes, causal contrasts, and analysis plan, and maps how each was operationalised with the observational data. The ACNU design was employed to reduce confounding by indication [10]. This study followed the Transparent Reporting of Observational Studies Emulating a Target Trial (TARGET) reporting guideline [17] as well as the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies [18].

The database contained structured data on demographics, diagnoses (coded using International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10-CM]), laboratory results, prescription records, and vital signs. All medications were extracted using Chinese generic drug names from the hospital information system (**Supplementary Table 1**). The study was approved by the institutional ethics committee. We used de-identified data so the informed consents were waived.

2.2 Study Population

We identified new users of atorvastatin, rosuvastatin, or ezetimibe monotherapy from a screening pool of 100,962 patients (49,524 statin; 51,438 ezetimibe). Eligibility was assessed using only information recorded on or before the index date, so that no post-index information contributed to the definition of the baseline cohort. The inclusion criteria were:

(1) age 65 years or older at the index date;

(2) a recorded diagnosis of hyperlipidaemia (International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM]: E78.0–E78.5, E78.8, E78.9);

(3) a new prescription for atorvastatin, rosuvastatin, or ezetimibe monotherapy, the date of which defined time zero; and

(4) at least 12 months of continuous EHR activity before the index date.

The exclusion criteria were:

(1) any prescription for a lipid-lowering medication (statin, ezetimibe, fibrate, bile acid sequestrant, niacin, or protein convertase subtilisin/kexin type 9 (PCSK9) inhibitor) during the 12-month washout period before the index date;

(2) pre-existing cognitive dysfunction, defined as two or more ICD-10-CM codes for dementia or MCI on separate dates before the index date, consistent with the primary outcome algorithm;

(3) concurrent prescriptions for both a statin and ezetimibe at baseline, defined as both agents dispensed on the index date or within the 30 days preceding it, such that the patient could not be classified as a monotherapy initiator;

(4) a baseline prescription for a cholinesterase inhibitor or memantine; and

(5) incomplete data on any of the four variables required to define eligibility and time zero (age, sex, index prescription date, and treatment assignment).

The numbers excluded at each step are shown in Fig. 1: 10,218 for pre-existing cognitive dysfunction, 13,856 for a lipid-lowering prescription during the washout period, 11,730 for concurrent statin and ezetimibe at baseline, 22,423 for fewer than 12 months of EHR activity, and 19,898 for incomplete eligibility-defining data, giv-

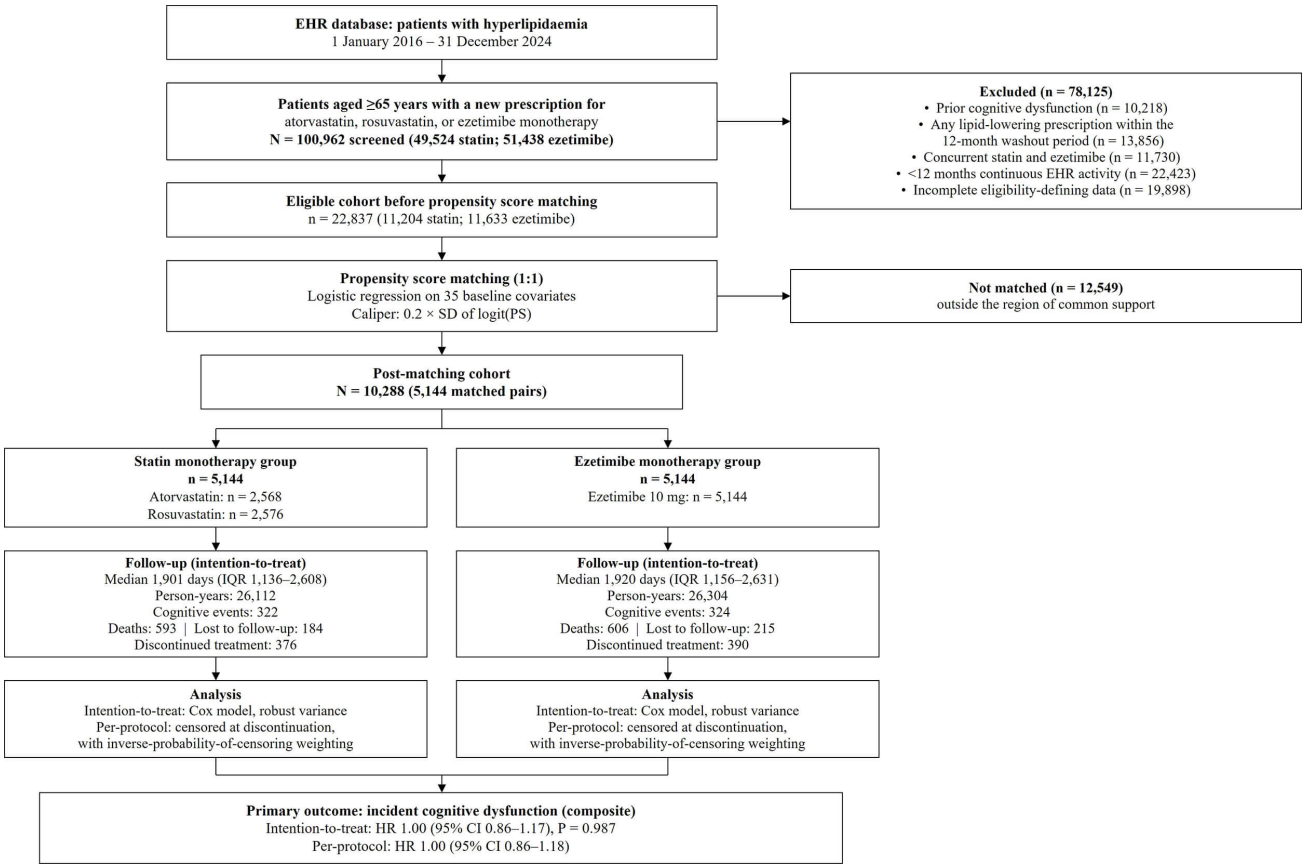


Fig. 1. Study flow diagram.

ing 78,125 exclusions and 22,837 eligible patients who entered propensity score matching. Addition of the comparator agent, or any other change of lipid-lowering treatment, after the index date was not an exclusion criterion. Such changes are treatment deviations that occur after time zero; they were handled by censoring in the per-protocol analysis, while the intention-to-treat analysis retained patients in their originally assigned group, as the target trial emulation framework requires. Missingness in baseline covariates other than the four eligibility-defining variables did not lead to exclusion and was addressed by multiple imputation, so that the eligibility criteria and the missing-data strategy operate on disjoint sets of variables. Patients with a single historical MCI code who did not meet the two-code threshold were retained; the presence of such a code was recorded as a baseline covariate and included in the propensity score model. Detailed eligibility criteria are presented in **Supplementary Methods, Section 1**.

2.3 Treatment Strategies and Time Zero

The two treatment strategies were: (1) initiate atorvastatin or rosuvastatin monotherapy, or (2) initiate ezetimibe monotherapy. Time zero (baseline) was defined as the date of the first prescription fill, at which point eligibility, treatment assignment, and start of follow-up were simultaneously aligned to prevent immortal time bias [19]. The ACNU design was chosen because ezetimibe shares the same indication as statins but acts through a distinct mechanism without direct central nervous system (CNS) effects, thereby reducing confounding by indication [10]. Treatment intensity was classified according to the 2023 Chinese guideline for lipid management [20]: atorvastatin 10–20 mg and rosuvastatin 5–10 mg daily were classified as moderate-intensity, and atorvastatin 40–80 mg and rosuvastatin 20 mg daily as high-intensity. Ezetimibe was prescribed at the single licensed dose of 10 mg daily. The modal daily dose was 20 mg for atorvastatin and 10 mg for rosuvastatin, and 91.2% of statin recipients began moderate-intensity therapy, consistent with prescribing practice in China. Index prescription dose, computed treatment intensity, and the median duration of continuous therapy are reported by agent in **Supplementary Table 2**. Because dose-level changes after the index prescription could not be reliably reconstructed from dispensing records, exposure was characterised at initiation only, and cumulative or time-varying dose effects were not evaluated.

2.4 Outcomes

The primary outcome was incident cognitive dysfunction, a composite defined as two or more ICD-10-CM diagnosis codes recorded on separate dates for any of the following: AD (G30.x and F02.8x), vascular dementia (F01.x),

unspecified dementia (F03.x), MCI (G31.84), or cognitive symptoms (R41.x). Dementia-specific medication prescriptions were used to supplement case ascertainment. Requiring at least two diagnosis codes on separate dates improves the specificity and positive predictive value (PPV) of code-based dementia algorithms relative to a single-code definition, at some cost to sensitivity [21]. The complete diagnosis and medication code lists are provided in **Supplementary Table 1**. Each patient contributed at most one event to the composite, at the date of the second qualifying code. The cognitive subtypes reported as secondary outcomes are components of this composite rather than separate outcomes, and were assigned operationally according to the diagnosis recorded at the qualifying event: AD, vascular dementia, and Lewy body dementia are reported by first recorded aetiological diagnosis; "all-cause dementia" aggregates those three categories; and "MCI alone" denotes patients whose qualifying diagnosis was MCI and who did not receive a dementia code during follow-up. So defined, the categories partition the composite without overlap: the 646 composite events comprise 163 AD, 82 vascular dementia, 29 Lewy body dementia, and 372 MCI alone, and no patient contributed to more than one subtype. This is an operational partition of first recorded diagnoses, not a claim that these are mutually exclusive clinical entities, since AD, vascular dementia, and Lewy body dementia frequently coexist pathologically and a patient classified by an early code may later meet criteria for another subtype. Because components of a composite outcome may differ in frequency and severity, each component is reported separately alongside the composite [22].

Secondary outcomes comprised the cognitive subtypes described above, cardiovascular events, mortality, and safety outcomes. The cardiovascular endpoints were myocardial infarction, ischaemic stroke, hemorrhagic stroke, transient ischaemic attack (TIA), heart failure hospitalisation, and major adverse cardiovascular events (MACE). MACE was defined operationally as the composite of cardiovascular death, myocardial infarction, or ischaemic stroke. TIA was not a component of MACE and was analysed only as a separate endpoint, consistent with standardized cardiovascular endpoint definitions, which treat TIA as a distinct cerebrovascular entity rather than a completed stroke [23], and with a systematic review of MACE definitions in administrative data, in which TIA is not an enumerated component [24]. Hemorrhagic stroke was likewise analysed separately and was not included in the MACE composite; we note that some definitions of MACE incorporate stroke of any type, and this narrower specification should be borne in mind when comparing our estimate with others [24]. Mortality outcomes were all-cause and cardiovascular death, the latter being a subset of the former. Safety outcomes were new-onset diabetes, liver enzyme elevation, and myopathy or myalgia. Event dates were ascertained by a single rule for each outcome class. For the primary composite and its cognitive subtypes, the event date was the date of the second qualifying diagnosis code. For myocardial infarction, ischaemic stroke, hemorrhagic stroke, TIA, and heart failure hospitalisation, the event date was the admission date of the first hospitalisation carrying a qualifying diagnosis in the principal position; for the small number of qualifying events recorded only in the outpatient setting, the date of the first qualifying diagnosis code was used. MACE was dated at the earliest of its component events. For all-cause and cardiovascular death, the event date was the date of death recorded in the death record, not the date on which the record was entered. For new-onset diabetes, the event date was the earliest of the first qualifying diagnosis code, the first prescription for an antidiabetic medication, or the first glycated haemoglobin value of 6.5% or higher. For liver enzyme elevation, the event date was the date of the first qualifying laboratory result, and for myopathy the date of the first qualifying diagnosis code. In every case, only the first event of each type contributed to the analysis. Follow-up began at time zero and ended at the earliest of the outcome of interest, death, loss to follow-up, or 31 December 2024. Patients lost to follow-up, defined as having no clinical contact recorded for more than 12 consecutive months before the administrative end of the study, were right-censored at the date of their last recorded encounter and contributed person-time up to that date; they were not excluded.

2.5 Covariates

Baseline covariates were measured during the 12 months preceding and including the index date. These comprised age, sex, calendar year of the index date, body mass index (BMI), systolic and diastolic blood pressure, the lipid panel (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides), glycated haemoglobin (HbA1c), fasting plasma glucose (FPG), estimated glomerular filtration rate (eGFR), serum creatinine (SCr), alanine aminotransferase (ALT), aspartate aminotransferase (AST), nine comorbidities, five concomitant medication classes, smoking status, alcohol consumption, the Charlson Comorbidity Index (CCI), the number of healthcare visits in the preceding 12 months, and the number of unique medications. The propensity score model therefore contained 35 covariates, each of which is listed individually in **Supplementary Table 3**.

2.6 Statistical Analysis

Continuous variables are summarised as mean ± standard deviation (SD) when approximately normally distributed and as median (interquartile range, IQR) otherwise; categorical variables are summarised as n (%). We used propensity score matching (PSM; 1:1 nearest-neighbour matching without replacement, caliper 0.2 × SD of the logit of the propensity score) to balance measured baseline co-

variates between treatment groups. The propensity score was estimated by multivariable logistic regression including all 35 covariates. Model discrimination was acceptable in the eligible cohort (C-statistic 0.701) and, as expected after successful matching, close to chance in the matched cohort (C-statistic 0.511), indicating that treatment assignment was no longer predictable from measured covariates. Covariate balance was assessed using standardized mean differences (SMD), with an absolute value below 0.1 considered adequate [25]; balance is displayed in **Supplementary Fig. 1** and the distribution of the propensity score before and after matching in **Supplementary Fig. 2**. Baseline characteristics of the eligible cohort before matching are presented in **Supplementary Table 4**. Normality of every continuous covariate was assessed using the Shapiro–Wilk test together with visual inspection of histograms and quantile–quantile plots, with the results reported in **Supplementary Table 5**. Missing baseline covariate data were handled by multiple imputation with chained equations (MICE) using a random forest algorithm (m = 20 imputations) [26,27]; a random forest imputation model was chosen because it accommodates non-linear relationships and interactions among covariates without requiring these to be specified in advance [27]. Baseline characteristics in Table 1 are summarised from the imputed data pooled across the 20 imputations, so that the denominator for every variable is the full matched cohort of 5144 per group; observed missingness before imputation is reported in **Supplementary Table 6**. The primary analysis estimated the intention-to-treat (ITT) effect using Cox proportional hazards models with robust (sandwich) variance estimation to account for the within-matched-pair correlation induced by matching, reporting hazard ratios (HRs) with 95% confidence intervals (CIs) [28,29]. For every outcome the time scale was time from the index date to that outcome, so that person-time was censored at the outcome of interest rather than at the end of total follow-up; incidence rates are therefore outcome-specific. The proportional hazards assumption was assessed using scaled Schoenfeld residuals (**Supplementary Fig. 3**). The per-protocol analysis censored patients at treatment discontinuation, defined as a prescription gap exceeding 90 days or a switch to the comparator. Censoring of this kind is informative if the reasons for discontinuation are associated with the outcome. We therefore did two things. First, we compared baseline characteristics between patients who discontinued and those who continued (**Supplementary Table 7**). Second, we repeated the per-protocol analysis with stabilised inverse probability of censoring weights estimated from a logistic model for remaining uncensored that included all 35 baseline covariates, following the approach recommended for per-protocol effects in pragmatic trials and target trial emulations [30,31] (**Supplementary Table 8**). Death is a competing risk for cognitive dysfunction. Because the complement of the Kaplan–Meier estimator overestimates cumulative incidence when a competing risk is present [32,33], cumulative incidence was estimated using the Aalen–Johansen estimator of the cause-specific cumulative incidence function, which is what Fig. 2 and **Supplementary Fig. 4** display. Fine–Gray subdistribution hazard models were fitted as a complementary regression analysis [34]. To assess outcome misclassification, a random 20% sample of the matched cohort underwent independent manual review of the electronic record by two clinicians blinded to treatment assignment, with disagreements resolved by a third reviewer; sensitivity, specificity, PPV, and Cohen's κ were computed for the International Classification of Diseases, 10th Revision (ICD-10)-based MACE algorithm against the chart-adjudicated reference standard, and the Cox model was refitted using chart-confirmed events (**Supplementary Table 9**). All analyses were performed in Python version 3.11.8 (Python Software Foundation, Wilmington, DE, USA) using the lifelines package version 0.30.3 for survival analysis, scikit-learn version 1.4.2 for propensity score estimation, and SciPy (version 1.13.0, NumFOCUS, Texas, US) for distributional testing. Two-sided p values below 0.05 were considered statistically significant. Detailed statistical methods are provided in **Supplementary Methods, Section 2**.

2.7 Sensitivity and Subgroup Analyses

Seven pre-specified sensitivity analyses were performed: excluding the first year of follow-up to address detection bias; restricting the outcome to dementia excluding MCI; analysing atorvastatin and rosuvastatin separately versus ezetimibe; extending the washout period to 730 days; complete-case analysis; and excluding patients who carried a single historical MCI code at baseline. E-values were calculated to assess robustness to unmeasured confounding [35]. Negative control outcomes (urinary tract infection, appendicitis, fracture) and positive control outcomes (new-onset diabetes, LDL-C reduction ≥30%) were pre-specified to detect residual confounding. Subgroup analyses were stratified by age (65–74, 75–84, ≥85 years), sex, diabetes mellitus (DM), hypertension (HTN), and cardiovascular disease (CVD); effect modification was formally assessed by including a treatment-by-subgroup product term in the Cox model and reporting the corresponding p value for interaction. A head-to-head comparison of atorvastatin versus rosuvastatin within the statin group was also performed. Subgroup and secondary analyses were not adjusted for multiplicity and are interpreted as exploratory.

3. Results

3.1 Study Population and Baseline Characteristics

From the screening pool of 100,962 patients (49,524 statin; 51,438 ezetimibe), 78,125 were excluded and 22,837 met all eligibility criteria (11,204 statin; 11,633 ezetimibe). One-to-one propensity score matching then yielded 5144 matched pairs, comprising 10,288 patients; the remaining

Table 1. Baseline characteristics of the Post-PSM study population.

Characteristic	Statin group (n = 5144)	Ezetimibe group (n = 5144)	SMD
Age, years, mean ± SD	73.4 ± 5.9	73.2 ± 5.9	0.034
Male sex, n (%)	2670 (51.9)	2716 (52.8)	–0.018
Calendar year of index date, mean ± SD	2018.8 ± 2.2	2018.8 ± 2.2	0.030
BMI, kg/m^2, mean ± SD	24.1 ± 3.1	24.1 ± 3.1	–0.020
SBP, mmHg, mean ± SD	135.1 ± 16.2	134.9 ± 16.3	0.011
DBP, mmHg, mean ± SD	78.3 ± 8.6	78.2 ± 8.6	0.011
TC, mmol/L, mean ± SD	5.1 ± 1.1	5.1 ± 1.1	0.010
LDL-C, mmol/L, mean ± SD	3.0 ± 0.7	3.0 ± 0.7	0.013
HDL-C, mmol/L, mean ± SD	1.3 ± 0.4	1.3 ± 0.4	–0.014
TG, mmol/L, mean ± SD	1.7 ± 0.8	1.7 ± 0.8	0.033
HbA1c, %, mean ± SD	6.3 ± 1.2	6.3 ± 1.2	–0.002
FPG, mmol/L, mean ± SD	6.4 ± 2.2	6.3 ± 2.1	0.028
eGFR, mL/min/1.73 m^2, mean ± SD	63.8 ± 11.2	64.1 ± 11.0	–0.034
SCr, μmol/L, mean ± SD	88.7 ± 24.8	88.5 ± 24.9	0.005
ALT, U/L, mean ± SD	21.8 ± 11.5	21.6 ± 11.6	0.017
AST, U/L, mean ± SD	17.1 ± 7.9	17.0 ± 7.8	0.006
CCI, mean ± SD	1.8 ± 1.3	1.8 ± 1.2	0.016
Healthcare visits, prior 12 months, mean ± SD	9.1 ± 3.0	9.1 ± 3.0	–0.004
Unique medications, n, mean ± SD	6.4 ± 1.4	6.4 ± 1.4	0.015
Diabetes mellitus, n (%)	1916 (37.2)	1910 (37.1)	0.002
Hypertension, n (%)	3500 (68.0)	3491 (67.9)	0.004
Stroke/TIA, n (%)	1053 (20.5)	1073 (20.9)	–0.010
CHD/MI, n (%)	1701 (33.1)	1671 (32.5)	0.012
Heart failure, n (%)	427 (8.3)	382 (7.4)	0.033
Depression, n (%)	650 (12.6)	699 (13.6)	–0.028
Atrial fibrillation, n (%)	301 (5.9)	314 (6.1)	–0.011
CKD, n (%)	740 (14.4)	738 (14.3)	0.001
Baseline single MCI code, n (%)	983 (19.1)	994 (19.3)	–0.005
Antihypertensives, n (%)	3073 (59.7)	2973 (57.8)	0.039
Antidiabetic medications, n (%)	1526 (29.7)	1544 (30.0)	–0.008
Antidepressants, n (%)	330 (6.4)	357 (6.9)	–0.021
Benzodiazepines, n (%)	451 (8.8)	473 (9.2)	–0.015
Antiplatelet/anticoagulants, n (%)	1725 (33.5)	1656 (32.2)	0.029
Current smoker, n (%)	1104 (21.5)	1096 (21.3)	0.004
Former smoker, n (%)	593 (11.5)	649 (12.6)	–0.033
Never smoker, n (%)	3447 (67.0)	3399 (66.1)	0.020
Current drinker, n (%)	913 (17.7)	937 (18.2)	–0.012
Former drinker, n (%)	374 (7.3)	394 (7.7)	–0.015
Never drinker, n (%)	3857 (75.0)	3813 (74.1)	0.020

Values are mean ± SD for continuous variables and n (%) for categorical variables. SMD, standardized mean difference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; HbA1c, glycated haemoglobin; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCI, Charlson Comorbidity Index; CHD, coronary heart disease; MI, myocardial infarction; TIA, transient ischaemic attack; CKD, chronic kidney disease; MCI, mild cognitive impairment; SD, standard deviation.

All percentages use the full matched cohort of 5144 per group as the denominator. Baseline characteristics are summarised from the multiply imputed data, pooled across the 20 imputations, because the imputed data set is the one used for the analysis; every variable therefore has a complete denominator and the three smoking categories and the three alcohol categories each sum to 5144 within a group. Observed missingness before imputation, which was 22.1% and 22.3% for smoking status and 26.4% and 25.5% for alcohol consumption in the statin and ezetimibe groups respectively, is reported in full in **Supplementary Table 6**. This table reports all 35 covariates entered into the propensity score model, with smoking and alcohol each shown as three categories. The corresponding characteristics of the eligible cohort before matching are given in **Supplementary Table 4**. Laboratory values are expressed in International System of Units (SI units).

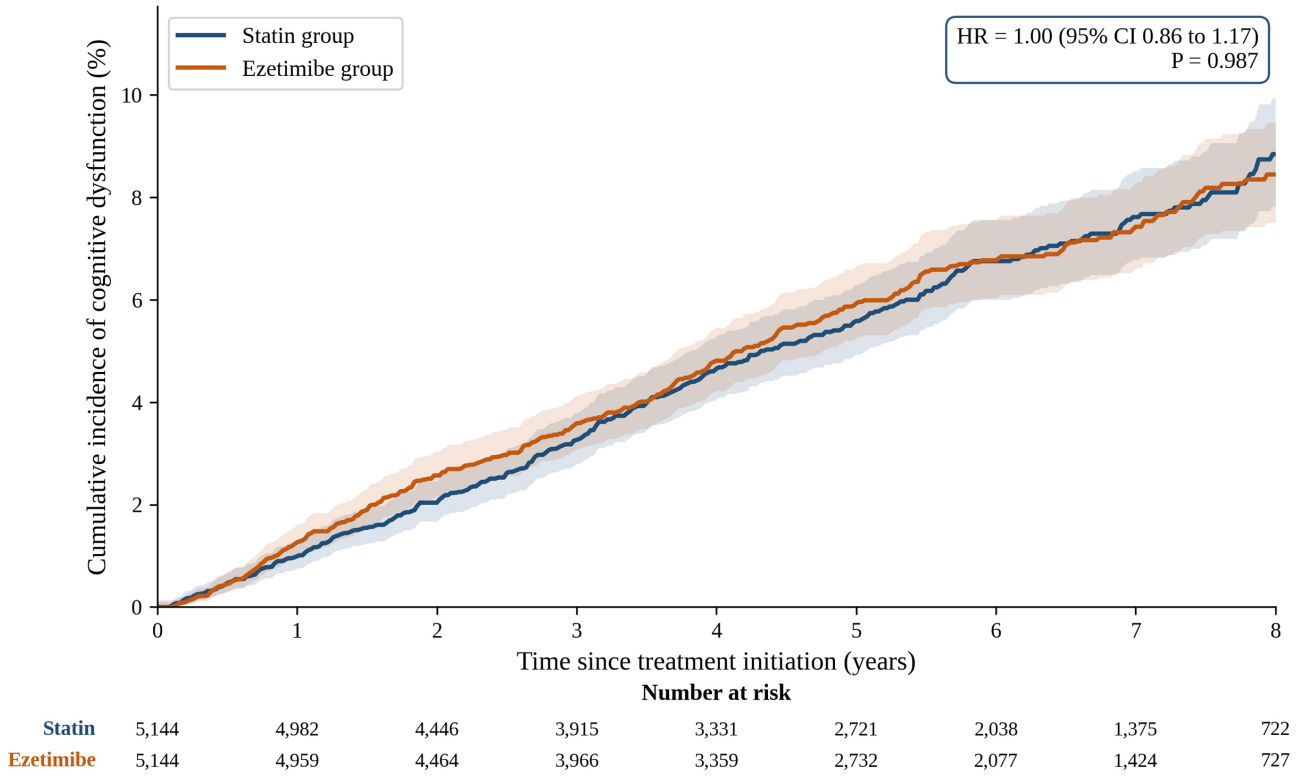


Fig. 2. Cumulative incidence of cognitive dysfunction by treatment group, intention-to-treat analysis.

12,549 eligible patients lay outside the region of common support and were not matched (Fig. 1). Incomplete data on the variables required to define eligibility and time zero was the most frequent reason for exclusion. After matching, 5144 patients were assigned to the statin group (atorvastatin: n = 2568; rosuvastatin: n = 2576) and 5144 to the ezetimibe group. The mean age was 73.3 ± 5.9 years and 52.4% were male. Before matching, 21 of the 39 tabulated baseline characteristics differed between groups by an absolute SMD of 0.1 or more, most prominently age, total cholesterol, LDL-C, eGFR, SCr, and the CCI (**Supplementary Table 4**); after matching, no characteristic exceeded this threshold (Table 1; **Supplementary Fig. 1**). Missing data patterns are summarised in **Supplementary Table 6**.

3.2 Follow-Up

Under the ITT specification, in which follow-up continued irrespective of subsequent treatment changes, the median follow-up was 1901 days (IQR 1136–2608) in the statin group and 1920 days (IQR 1156–2631) in the ezetimibe group, contributing 26,112 and 26,304 person-years of total observation, respectively. Follow-up ended because of the outcome of interest in 322 and 324 patients, death in 593 and 606 patients, loss to follow-up in 184 and 215 patients, and administrative censoring on 31 December 2024 in the remainder (**Supplementary Table 10**). Treatment discontinuation, defined as a prescription gap exceeding 90 days or a switch to the comparator, occurred in 376 statin and 390 ezetimibe recipients. These patients continued to contribute follow-up time in the ITT analysis and were censored at the date of discontinuation only in the per-protocol analysis, which accordingly accrued fewer person-years and fewer events. Patients who discontinued (n = 766; 376 statin and 390 ezetimibe) were closely similar at baseline to those who continued: no characteristic differed by an absolute standardized mean difference of 0.10 or more, and the largest difference was for atrial fibrillation (standardized mean difference –0.095) (**Supplementary Table 7**). One exception is worth stating explicitly: carrying a single historical MCI code at baseline was associated with a modestly higher probability of subsequent discontinuation (adjusted odds ratio 1.27, 95% CI 1.09 to 1.50), so censoring at discontinuation is not strictly non-informative with respect to cognitive status.

3.3 Primary Outcome

In the ITT analysis, incident cognitive dysfunction occurred in 322 patients (12.3 per 1000 person-years) in the statin group and 324 patients (12.3 per 1000 person-years) in the ezetimibe group (HR 1.00, 95% CI 0.86 to 1.17; p = 0.987; Table 2; Fig. 2). In the per-protocol analysis, censoring at treatment discontinuation reduced the number of events to 307 and 307, respectively, and the corresponding estimate was materially unchanged (HR 1.00, 95% CI 0.86 to 1.18; p = 0.954; Table 3; **Supplementary Table 11**). Weighting the per-protocol analysis by stabilised in-

Table 2. Primary and secondary outcomes—intention-to-treat analysis.

Outcome	Statin events	Statin PY	Rate (/ 1000)	Eze events	Eze PY	Rate (/ 1000)	HR (95% CI)	*p*
Primary: Cognitive dysfunction (composite)	322	26,112	12.3	324	26,304	12.3	1.00 (0.86 to 1.17)	0.987
Alzheimer's disease	82	26,112	3.1	81	26,304	3.1	1.02 (0.75 to 1.39)	0.898
Vascular dementia	45	26,112	1.7	37	26,304	1.4	1.23 (0.79 to 1.89)	0.359
All-cause dementia (excl. MCI)	140	26,112	5.4	134	26,304	5.1	1.05 (0.83 to 1.33)	0.670
MCI alone	182	26,112	7.0	190	26,304	7.2	0.96 (0.79 to 1.18)	0.731
Lewy body dementia	13	26,112	0.5	16	26,304	0.6	0.82 (0.39 to 1.70)	0.590
Myocardial infarction	298	25,119	11.9	309	25,320	12.2	0.97 (0.83 to 1.14)	0.714
Ischaemic stroke	423	24,884	17.0	463	24,795	18.7	0.91 (0.80 to 1.04)	0.163
Hemorrhagic stroke	66	25,916	2.5	54	26,121	2.1	1.23 (0.86 to 1.76)	0.258
TIA	125	25,715	4.9	165	25,796	6.4	0.76 (0.60 to 0.96)	0.021
Heart failure hospitalization	272	25,276	10.8	242	25,528	9.5	1.13 (0.95 to 1.35)	0.154
MACE	960	23,951	40.1	1029	23,902	43.1	0.93 (0.85 to 1.02)	0.112
All-cause mortality	593	26,112	22.7	606	26,304	23.0	0.99 (0.88 to 1.10)	0.806
CV mortality	297	26,112	11.4	313	26,304	11.9	0.96 (0.82 to 1.12)	0.576
New-onset diabetes	410	15,097	27.2	223	15,921	14.0	1.94 (1.65 to 2.29)	<0.001
Liver enzyme elevation	79	25,821	3.1	29	26,210	1.1	2.76 (1.80 to 4.22)	<0.001
Myopathy	23	26,045	0.9	4	26,290	0.2	5.81 (2.01 to 16.79)	0.001

PY, person-years; HR, hazard ratio; CI, confidence interval; MCI, mild cognitive impairment; TIA, transient ischaemic attack; MACE, major adverse cardiovascular events; CV, cardiovascular.

Hazard ratios are from Cox proportional hazards models with robust variance estimation; the reference group is ezetimibe monotherapy. Rates are per 1000 person-years. Person-years are outcome-specific: for each endpoint, a patient contributes time from the index date until that endpoint occurs or until censoring, whichever comes first. Person-years consequently differ across endpoints. They are identical for the primary composite and for its mutually exclusive cognitive subtypes because follow-up for every cognitive endpoint terminates at the first qualifying cognitive diagnosis, and identical for all-cause and cardiovascular mortality because follow-up terminates at death with the same risk set termination rule. In this intention-to-treat analysis, follow-up continued irrespective of subsequent treatment discontinuation or switching. New-onset diabetes was analysed only among the 3228 statin and 3234 ezetimibe recipients free of diabetes at baseline, and its person-years reflect that restricted risk set.

verse probability of censoring weights, to address the possibility that discontinuation was informative, left the estimate unchanged (HR 1.00, 95% CI 0.86 to 1.18; $p = 0.968$; **Supplementary Table 8**). A Fine–Gray model treating death as a competing event produced a comparable subdistribution hazard ratio (1.00, 95% CI 0.86 to 1.17; $p = 0.998$; **Supplementary Table 12**). The scaled Schoenfeld residuals provided no evidence against the proportional hazards assumption (global $p = 0.42$; **Supplementary Fig. 3**). Manual chart review of a random 20% sample (2067 patients) showed good agreement between the ICD-10-based MACE algorithm and the adjudicated record (PPV 90.4%, sensitivity 82.7%, Cohen's κ 0.826), and the hazard ratio computed from chart-confirmed events (0.97, 95% CI 0.81 to 1.16; $p = 0.731$) was consistent with that from coded events (0.93, 95% CI 0.85 to 1.02; $p = 0.112$) (**Supplementary Table 9**).

3.4 Secondary Outcomes

Among cognitive subtypes, hazard ratios for AD (HR 1.02, 95% CI 0.75 to 1.39; $p = 0.898$), vascular dementia (HR 1.23, 95% CI 0.79 to 1.89; $p = 0.359$), all-cause dementia excluding MCI (HR 1.05, 95% CI 0.83 to 1.33; $p = 0.670$), MCI alone (HR 0.96, 95% CI 0.79 to 1.18; $p = 0.731$), and Lewy body dementia (HR 0.82, 95% CI 0.39 to 1.70; $p = 0.590$) were all consistent with the primary analysis (Table 2). Cumulative incidence curves for secondary outcomes are shown in **Supplementary Fig. 4**. Because these analyses were not adjusted for multiplicity, they should be regarded as exploratory.

For cardiovascular outcomes, MACE was similar between groups (HR 0.93, 95% CI 0.85 to 1.02; $p = 0.112$), as were myocardial infarction (HR 0.97, 95% CI 0.83 to 1.14; $p = 0.714$), ischaemic stroke (HR 0.91, 95% CI 0.80 to 1.04; $p = 0.163$), hemorrhagic stroke (HR 1.23, 95% CI 0.86 to 1.76; $p = 0.258$), and heart failure hospitalisation (HR 1.13, 95% CI 0.95 to 1.35; $p = 0.154$). Transient ischaemic attack, which was analysed as a separate endpoint and was not a component of MACE, occurred in 125 statin and 165 ezetimibe recipients (4.9 vs. 6.4 per 1000 person-years; HR 0.76, 95% CI 0.60 to 0.96; $p = 0.021$). This was the only cardiovascular secondary endpoint to reach nominal statistical significance. Because 16 secondary outcomes were examined without adjustment for multiplicity, and because the direction was not mirrored in the larger and more

Table 3. Primary and secondary outcomes—per-protocol analysis.

Outcome	Statin Events	Statin PY	Rate (/ 1000)	Eze Events	Eze PY	Rate (/ 1000)	HR (95% CI)	*p*
Primary: Cognitive dysfunction (composite)	307	24,410	12.6	307	24,522	12.5	1.00 (0.86 to 1.18)	0.954
Alzheimer's disease	76	24,410	3.1	77	24,522	3.1	0.99 (0.72 to 1.36)	0.959
Vascular dementia	42	24,410	1.7	33	24,522	1.3	1.28 (0.81 to 2.02)	0.291
All-cause dementia (excl. MCI)	131	24,410	5.4	125	24,522	5.1	1.05 (0.82 to 1.35)	0.680
MCI alone	176	24,410	7.2	182	24,522	7.4	0.97 (0.79 to 1.20)	0.784
Lewy body dementia	13	24,410	0.5	15	24,522	0.6	0.87 (0.41 to 1.83)	0.716
Myocardial infarction	281	23,561	11.9	286	23,698	12.1	0.99 (0.84 to 1.17)	0.888
Ischaemic stroke	400	23,261	17.2	431	23,138	18.6	0.92 (0.81 to 1.06)	0.253
Hemorrhagic stroke	62	24,217	2.6	48	24,377	2.0	1.30 (0.89 to 1.90)	0.171
TIA	119	24,047	4.9	156	24,091	6.5	0.76 (0.60 to 0.97)	0.027
Heart failure hospitalization	256	23,685	10.8	217	23,837	9.1	1.19 (0.99 to 1.42)	0.063
MACE	908	22,456	40.4	966	22,384	43.2	0.94 (0.86 to 1.03)	0.161
All-cause mortality	559	24,410	22.9	586	24,522	23.9	0.96 (0.85 to 1.08)	0.474
CV mortality	281	24,410	11.5	304	24,522	12.4	0.93 (0.79 to 1.09)	0.371
New-onset diabetes	382	14,115	27.1	207	14,791	14.0	1.94 (1.64 to 2.30)	<0.001
Liver enzyme elevation	75	24,198	3.1	27	24,451	1.1	2.81 (1.81 to 4.36)	<0.001
Myopathy	21	24,354	0.9	4	24,511	0.2	5.27 (1.81 to 15.34)	0.002

PY, person-years; HR, hazard ratio; CI, confidence interval; MCI, mild cognitive impairment; TIA, transient ischaemic attack; MACE, major adverse cardiovascular events.

Patients were censored at treatment discontinuation, defined as a prescription gap exceeding 90 days, or at switching to the comparator; the reference group is ezetimibe monotherapy. Person-years are outcome-specific, as defined in the footnote to Table 2. Because this additional censoring removes person-time and the events that would otherwise have occurred after discontinuation, both person-years and event counts are lower than in the corresponding intention-to-treat analysis in Table 2, and every per-protocol event set is a strict subset of the corresponding intention-to-treat event set.

reliably coded ischaemic stroke endpoint, we regard this as a chance finding and it should be treated as hypothesis-generating. All-cause mortality occurred in 593 statin and 606 ezetimibe recipients (HR 0.99, 95% CI 0.88 to 1.10; $p = 0.806$); cardiovascular death, a subset of these events, accounted for 297 and 313 deaths, respectively (HR 0.96, 95% CI 0.82 to 1.12; $p = 0.576$). Among the 3228 statin and 3234 ezetimibe recipients who were free of diabetes at baseline, new-onset diabetes occurred in 410 and 223 patients (HR 1.94, 95% CI 1.65 to 2.29; $p < 0.001$), consistent with the established diabetogenic effect of statins. Liver enzyme elevation (HR 2.76, 95% CI 1.80 to 4.22; $p < 0.001$) and myopathy (HR 5.81, 95% CI 2.01 to 16.79; $p = 0.001$) were also more frequent with statin therapy.

3.5 Sensitivity and Subgroup Analyses

Subgroup analyses showed no evidence of effect modification by age stratum (65–74, 75–84, ≥85 years; p for interaction = 0.269), sex ($p = 0.368$), diabetes ($p = 0.474$), hypertension ($p = 0.848$), or cardiovascular disease ($p = 0.369$); stratum-specific estimates and p values for interaction are reported in **Supplementary Table 13**. Within the statin group, no clinically meaningful difference was observed between atorvastatin and rosuvastatin for the primary outcome (HR 1.06, 95% CI 0.85 to 1.32; $p = 0.597$; **Supplementary Table 14**).

The primary finding was consistent across all seven pre-specified sensitivity analyses (**Supplementary Table 15**). Excluding the first year of follow-up to mitigate detection bias yielded an HR of 1.06 (95% CI 0.89 to 1.25; $p = 0.533$); restricting the outcome to dementia excluding MCI, 1.05 (0.83 to 1.33; $p = 0.670$); analysing atorvastatin alone versus ezetimibe, 1.03 (0.85 to 1.24; $p = 0.757$); rosuvastatin alone versus ezetimibe, 0.97 (0.80 to 1.18; $p = 0.779$); extending the washout period to 730 days, 1.06 (0.88 to 1.28; $p = 0.515$); complete-case analysis, 1.00 (0.74 to 1.35; $p = 1.000$); and excluding the 1977 patients who carried a single historical MCI code at baseline, 0.99 (0.83 to 1.17; $p = 0.875$). The E-value for the point estimate was 1.00, and the E-value for the confidence limit closest to the null was also 1.00, because the point estimate lies at the null and the confidence interval includes it (**Supplementary Table 16**). The E-value framework quantifies the strength of unmeasured confounding that would be required to explain away an observed association; when no association is observed there is nothing to explain away, and the analysis is therefore uninformative here rather than reassuring [35]. We accordingly do not claim that the null result is robust

to unmeasured confounding on this basis. Negative control outcomes showed no association with treatment assignment, whereas both positive controls behaved as anticipated (**Supplementary Table 17**).

4. Discussion

4.1 Principal Findings

In this real-world retrospective cohort study analysed within the target trial emulation framework, we compared statin monotherapy with ezetimibe monotherapy among 10,288 propensity-score-matched patients aged 65 years or older. We found no evidence of a difference in the risk of incident cognitive dysfunction between the two strategies (HR 1.00, 95% CI 0.86 to 1.17). The finding was consistent between the intention-to-treat and per-protocol analyses, across all cognitive subtypes, across seven prespecified sensitivity analyses, and across subgroups defined by age, sex, and comorbidity status. Atorvastatin and rosuvastatin showed comparable cognitive outcomes when compared directly within the statin arm. The confidence interval is nonetheless compatible with a 14% relative reduction or a 17% relative increase in risk, so these data should not be interpreted as demonstrating equivalence.

4.2 Comparison With Existing Literature

Our results align with the two largest prior TTE studies of statins and dementia. Caniglia et al. [15] emulated a sequence of trials within the Rotterdam Study (n = 6373) and reported a risk difference of –0.1% (95% CI –2.3% to 1.8%) for statin initiation versus non-initiation over 10 years. Zimmerman et al. [14] used Kaiser Permanente data (n = 322,358) and found an HR of 1.00 (95% CI 0.99 to 1.01) after excluding the first year of follow-up. An analysis of the aspirin in Reducing Events in the Elderly (ASPREE) trial similarly found no association between statin therapy and incident dementia or cognitive decline in 18,846 older adults [36]. A companion emulated-trial analysis of the same health-care system, comprising 705,061 members, likewise found no association between statin initiation and dementia in any of 32 sociodemographic subgroups [37].

Critically, all three prior studies compared statins with no treatment. Our study advances the methodology by using ezetimibe as an active comparator. This design inherently conditions on the decision to treat, eliminating the healthy-user and confounding-by-indication biases that plague statin-versus-nothing comparisons [10]. The convergence of our null finding with those from non-user comparator studies strengthens the conclusion that statins neither protect against nor accelerate cognitive decline in older adults. We emphasise that ezetimibe was selected as a comparator for methodological rather than therapeutic reasons. Ezetimibe is not a first-line lipid-lowering agent in Chinese or international guidelines, and in this cohort it was typically initiated in patients for whom a statin was considered unsuitable or insufficiently tolerated [20]. Its value here lies in the fact that it shares the indication for lipid lowering, and therefore the clinical decision to treat, while acting peripherally through Niemann-Pick C1-Like 1 inhibition without established central nervous system activity [11,12]. This makes it a mechanistically distinct but clinically interchangeable reference against which any specific cognitive effect of statins would be detectable. The consequence of this design choice is that our estimate contrasts two active treatment strategies as they are used in practice and does not address the separate question of statin therapy versus no lipid-lowering treatment. Because ezetimibe initiators may differ systematically from statin initiators in ways related to statin intolerance, some residual confounding by indication may persist despite matching.

These results also help reconcile the longstanding paradox between observational meta-analyses showing 14–30% reduced dementia risk with statins [5,7] and null randomised trial evidence [8]. The observational signal likely reflects residual confounding: statin users tend to be healthier, more health-conscious, and more engaged with healthcare. Our ACNU design substantially attenuates these biases, and the resulting null estimate aligns with what the randomized evidence would predict. Convergent evidence from randomised trials of other lipid-lowering agents points in the same direction: pooled safety analyses of PCSK9 inhibitors, which achieve far greater reductions in low-density lipoprotein cholesterol than statins, have not detected an excess of neurocognitive adverse events [38].

4.3 Relevance to the Chinese Population

This study is the first TTE of statins and cognition conducted in a mainland Chinese elderly population. Chinese lipid management guidelines recommend moderate-intensity statin therapy as first-line treatment, reflecting the approximately two-fold higher systemic statin exposure in East Asian compared with Caucasian patients due to ATP binding cassette subfamily G member 2 (ABCG2) and solute carrier anion transporter family 1B1 (SLCO1B1) polymorphisms [20,39]. Moderate-intensity statins in Chinese patients may therefore achieve pharmacologic exposures approximating high-intensity regimens in Western populations. Despite this higher effective exposure, we observed no cognitive signal, reinforcing the class-level neutrality of statins on cognition.

The RACING trial demonstrated that moderate-intensity rosuvastatin plus ezetimibe was non-inferior to high-intensity rosuvastatin monotherapy for cardiovascular outcomes in Korean patients [40]. That trial included no cognitive endpoints. Our findings complement the RACING evidence by showing that the choice between statin monotherapy and ezetimibe need not be influenced by cognitive concerns.

4.4 Strengths and Limitations

This study has several strengths. Applying the TTE framework as the analytical approach ensured transparent alignment of time zero, treatment strategies, eligibility, and follow-up, avoiding immortal time bias [13,19]. The ACNU design reduced confounding by indication. PSM on 35 covariates achieved excellent balance, reducing the number of characteristics with an absolute SMD of 0.1 or more from 21 before matching to none afterwards, with the propensity score C-statistic falling from 0.701 to 0.511. Positive and negative control outcome analyses provided empirical support for the analytic approach: the expected excess risk of new-onset diabetes with statins was confirmed (HR 1.94, $p < 0.001$), while negative controls showed null effects. Independent chart review of a random 20% sample confirmed adequate MACE ascertainment (PPV 90.4%, κ 0.826). Censoring at treatment discontinuation was examined directly rather than assumed to be non-informative: baseline characteristics of patients who discontinued and continued were compared, and the per-protocol estimate was reproduced using inverse probability of censoring weights.

Several limitations warrant consideration, and several correspond to concerns that cannot be resolved with routinely collected data. First, unmeasured confounding cannot be excluded. Apolipoprotein E ε4 genotype, the strongest genetic risk factor for AD, is not captured in routine EHR data, and a population-based cohort has reported that the association between statin initiation and incident Alzheimer disease may differ by apolipoprotein E (APOE) ε4 carriage [41]. Reassuringly, the largest published emulation of this question found that adjustment for APOE ε4 in a genotyped subsample did not materially change the null result [14]. Educational attainment, physical activity, and dietary pattern were likewise unavailable; because these factors are plausibly associated both with cognitive risk and with the decision to prescribe, residual confounding remains possible, although the active comparator, new-user design partially mitigates confounding by indication by conditioning on the clinical decision to treat. Second, 1977 participants (19.2%) carried a single historical MCI code at baseline. These patients did not meet the two-code exclusion threshold and the indicator was included in the propensity score model, but their inclusion could obscure the onset of the outcome if some already had prodromal dementia; a pre-specified sensitivity analysis excluding them gave a materially unchanged estimate. Under-recognition of early cognitive impairment in routine care means the true prevalence of prodromal disease at baseline is likely to have been higher still, and any resulting misclassification would tend to attenuate a true association. Third, this is a single-centre study conducted in one urban tertiary hospital in Shanghai; case mix, prescribing culture, and diagnostic intensity differ across Chinese regions, ethnic groups, and primary care settings, so these findings should not be extrapolated to those populations without further study. Fourth, electronic health record (EHR)-based outcome ascertainment has imperfect sensitivity for cognitive dysfunction, particularly in its early stages; the requirement for two or more diagnosis codes on separate dates improves specificity at the cost of sensitivity, and non-differential misclassification of this kind would bias estimates toward the null. This limitation is not resolved by our validation work. Manual chart adjudication was performed for the ICD-10-based MACE algorithm only, and although it showed good agreement, it provides no direct evidence about the accuracy of the cognitive outcome algorithm, which is the primary endpoint. We relied instead on published validation of two-code dementia algorithms [21], which report positive predictive values in the region of 75 to 80 per cent and sensitivity near 70 per cent against a clinical reference standard. The accuracy of the algorithm in this population is therefore unverified, and independent adjudication of cognitive outcomes should be a priority for future work. Fifth, prescription records document dispensing rather than ingestion, so adherence could not be verified; the per-protocol analysis censors at prescription gaps but cannot distinguish a patient who collects medication without taking it, and this non-differential exposure misclassification would also attenuate any true difference. Sixth, the intention-to-treat analysis classified patients according to the treatment initiated at time zero and retained that classification irrespective of subsequent switching, so a patient who moved from a statin to ezetimibe continued to contribute person-time to the statin group. Treatment discontinuation, a composite of a prescription gap exceeding 90 days and switching to the comparator, occurred in 376 statin (7.3%) and 390 ezetimibe (7.6%) recipients; the dispensing extract did not record the two components separately, so the number who specifically switched cannot be reported. Non-adherence to the assigned strategy of this kind biases an intention-to-treat estimate toward the null, which is the direction of our finding. The per-protocol analysis, which censors such patients and which was additionally reproduced with inverse probability of censoring weights, gave an essentially identical estimate, so the effect of switching on our conclusions appears small; nevertheless, we cannot exclude some attenuation. Seventh, exposure was characterised at initiation only, and dose escalation, de-escalation, or later switching between agents could not be reliably reconstructed, so cumulative dose-response relationships were not examined. Eighth, recent preclinical evidence suggests that ezetimibe may itself possess anti-aggregation properties through a mechanism independent of Niemann-Pick C1-Like 1 [42]; if confirmed, this would complicate the assumption that ezetimibe is cognitively neutral and would bias the comparison toward the null. These findings are preliminary and require replication. Finally, secondary and subgroup analyses were not adjusted for multiple comparisons and are therefore exploratory; the nominal association observed for transient is-

chaemic attack should be regarded as hypothesis-generating rather than confirmatory.

5. Conclusion

In this real-world retrospective cohort study of 10,288 propensity-score-matched patients aged 65 years or older, analysed within the target trial emulation framework, statin monotherapy and ezetimibe monotherapy were associated with comparable risks of incident cognitive dysfunction (HR 1.00, 95% CI 0.86 to 1.17). Although the width of the confidence interval precludes a formal claim of equivalence, these findings provide no evidence that cognitive considerations should influence the choice between these agents for lipid management in older Chinese adults. Multicentre studies incorporating apolipoprotein E genotyping and prospective cognitive assessment are needed to confirm these observations.

Key Points

• Among 10,288 propensity-score-matched adults aged 65 years or older with hyperlipidaemia, statin monotherapy and ezetimibe monotherapy were associated with comparable risks of incident cognitive dysfunction (hazard ratio 1.00, 95% confidence interval 0.86 to 1.17) over 52,416 person-years of follow-up.

• The use of ezetimibe as an active comparator, rather than non-use of lipid-lowering therapy, conditions the analysis on the clinical decision to treat and thereby reduces confounding by indication and healthy-user bias, which have limited the interpretation of most previous observational studies of statins and cognition.

• The null association persisted in the per-protocol analysis, across Alzheimer's disease, vascular dementia, and mild cognitive impairment considered separately, across seven pre-specified sensitivity analyses, and across subgroups defined by age, sex, diabetes, hypertension, and cardiovascular disease.

• Anticipated positive control associations were reproduced, including a higher rate of new-onset diabetes among statin recipients free of diabetes at baseline (hazard ratio 1.94, 95% confidence interval 1.65 to 2.29), whereas negative control outcomes showed no association with treatment assignment.

• Because the confidence interval remains compatible with modest benefit or modest harm, these findings should not be interpreted as establishing equivalence; they indicate only that no clinically meaningful difference in cognitive risk was detected.

• For older Chinese adults requiring lipid-lowering therapy, these data provide no evidence that concern about cognitive outcomes should influence the choice between a statin and ezetimibe; that decision may instead be guided by cardiovascular efficacy, tolerability, and metabolic safety.

Abbreviations

AD, Alzheimer's disease; ACNU, Active comparator new-user; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BBB, Blood-brain barrier; BMI, Body mass index; CCI, Charlson Comorbidity Index; CI, Confidence interval; CNS, Central nervous system; CVD, Cardiovascular disease; DM, Diabetes mellitus; EHR, Electronic health record; eGFR, Estimated glomerular filtration rate; FDA, Food and Drug Administration; HbA1c, Glycated hemoglobin; HDL-C, High-density lipoprotein cholesterol; HMG-CoA, 3-Hydroxy-3-methylglutaryl-coenzyme A; HR, Hazard ratio; HTN, Hypertension; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; IQR, Interquartile range; ITT, Intention-to-treat; LDL-C, Low-density lipoprotein cholesterol; MACE, Major adverse cardiovascular events; MCI, Mild cognitive impairment; MICE, Multiple imputation with chained equations; NPC1L1, Niemann-Pick C1-Like 1; PPV, Positive predictive value; PSM, Propensity score matching; SD, Standard deviation; SMD, Standardized mean difference; TIA, Transient ischaemic attack; TTE, Target trial emulation.

Availability of Data and Materials

The de-identified analytic dataset and statistical analysis code supporting the findings of this study are available from the corresponding author upon reasonable request, subject to institutional data use agreements and approval from the data governance committee of Renhe Hospital. Individual-level electronic health record data cannot be shared publicly due to patient privacy regulations and institutional data security policies.

Author Contributions

MJY: Conceptualization, Funding Acquisition, Project Administration, Writing—Original Draft; JBW: Data Curation, Formal Analysis; SL: Investigation; JMW: Investigation; YS: Methodology; Validation, Visualization. All authors contributed to revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of Renhe Hospital, Shanghai, China (approval number KY2024-09). The approval number carries the institutional prefix for the calendar year in which the application was reviewed. Because the study was a retrospective analysis of de-identified electronic health record data from this single institution, with no direct patient contact and no more than minimal risk to participants, the Institutional Review Board waived the requirement for individual informed

consent in accordance with the applicable Chinese regulations governing the use of existing medical records for scientific research. All procedures were conducted in accordance with the Declaration of Helsinki.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, the authors used an artificial intelligence (AI)-assisted language model (ChatGPT-6.1 sol) for the purposes of improving readability, language editing, and ensuring grammatical accuracy of the text. The authors carefully reviewed and edited all AI-assisted output and take full responsibility for the accuracy, integrity, and authenticity of the content of this manuscript. The AI tool was not used for generating scientific conclusions, interpreting data, or making clinical recommendations.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/BJHM56431.

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