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ORIGINAL INVESTIGATIONS

Effect of Statin Therapy on Cognitive Decline and Incident Dementia in Older Adults

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ABSTRACT

BACKGROUND The neurocognitive effect of statins in older adults remain uncertain.

OBJECTIVES The aim of this study was to investigate the associations of statin use with cognitive decline and incident dementia among older adults.

METHODS This analysis included 18,846 participants ≥65 years of age in a randomized trial of aspirin, who had no prior cardiovascular events, major physical disability, or dementia initially and were followed for 4.7 years. Outcome measures included incident dementia and its subclassifications (probable Alzheimer's disease, mixed presentations); mild cognitive impairment (MCI) and its subclassifications (MCI consistent with Alzheimer's disease, other MCI); and changes in domain-specific cognition, including global cognition, memory, language and executive function, psychomotor speed, and the composite of these domains. Associations of baseline statin use versus nonuse with dementia and MCI outcomes were examined using Cox proportional hazards models and with cognitive change using linear mixed-effects models, adjusting for potential confounders. The impact of statin lipophilicity on these associations was further examined, and effect modifiers were identified.

RESULTS Statin use versus nonuse was not associated with dementia, MCI, or their subclassifications or with changes in cognitive function scores over time ($p > 0.05$ for all). No differences were found in any outcomes between hydrophilic and lipophilic statin users. Baseline neurocognitive ability was an effect modifier for the associations of statins with dementia (p for interaction < 0.001) and memory change (p for interaction $= 0.02$).

CONCLUSIONS In adults ≥65 years of age, statin therapy was not associated with incident dementia, MCI, or declines in individual cognition domains. These findings await confirmation from ongoing randomized trials.
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ABBREVIATIONS AND ACRONYMS

3MS = Modified Mini-Mental State Examination

AD = Alzheimer's disease

CI = confidence interval

CVD = cardiovascular disease

HR = hazard ratio

LDL-C = low-density lipoprotein cholesterol

MCI = mild cognitive impairment

Cognitive decline and dementia are major health concerns in older patients, affecting approximately 10% of people > 60 years of age (1,2). Hydroxymethylglutaryl coenzyme A reductase inhibitors ("statins") are a cornerstone treatment for prevention of primary and secondary cardiovascular disease (CVD) events. Nonetheless, any drug use comes with risks. The U.S. Food and Drug Administration released a warning in 2012 about cases of apparent short-term cognitive impairment with statin use that had been reported to its adverse drug reaction reporting system, while acknowledging that the cardiovascular benefits outweigh these risks (3).

Despite the warning from the U.S. Food and Drug Administration, 2 recent systematic reviews have concluded that there is insufficient evidence to determine the effects of lipid-lowering agents (predominantly statins) on cognitive function or dementia (4,5). The uncertainty comes from mixed findings in previous studies, with some revealing a beneficial neurocognitive effect of statins (6,7) and others reporting a null effect (8–10). Meanwhile, there is evidence that lipophilic and hydrophilic statins categorized by tissue selectivity may have varying effects on cognition and dementia (11,12). Lipophilic statins, which have a greater blood-brain barrier penetrance than hydrophilic statins, may be more likely to have an impact (13). A neurocognitive effect of statins has also been suggested, which can be modified by patient characteristics such as age, race, comorbid diseases, and genetic factors (14–17). Therefore, it is imperative for clinical research to characterize the effect modifiers of statins to avoid misleading information in certain patient groups (14–16).

Preventive medication is best justified when its use to prevent one condition does not come at the expense of causing, or worsening, another. Older people may be more susceptible to any adverse cognitive effects of statins, because of their age and the presence of other risk factors for neurocognitive disorders. A forecasting study by Odden et al. (18) projected that even a small increased risk for cognitive impairment relating to statin use may counterbalance its cardiovascular benefits in primary prevention in adults ≥75 years of age. Given that statins have already been widely used among older adults and that the prevalence of statin use is expected to continue to rise, ascertaining the effects of statin therapy on cognition in older patients is important for helping clinicians weigh their benefits against associated risks (19). Using the comprehensive cognitive data systematically collected in the ASPREE (Aspirin in Reducing Events in the Elderly) trial (20–22), we undertook an observational study within this large-scale community-based older cohort. The aim of the study was to: 1) determine the prospective associations of baseline statin use with incident dementia, mild cognitive impairment (MCI), and change in cognition over time; 2) assess the role of statin lipophilicity in mediating any statin-related neurocognitive effects; and 2) identify potential effect modifiers of the statin-related changes.

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METHODS

This study was exempt from ethics review, as only existing nonidentifiable data were used.

DATA SOURCE AND STUDY PARTICIPANTS. ASPREE was a large, prospective, randomized, placebo-controlled trial of daily low-dose aspirin (enteric-coated 100 mg) (20–22). The ASPREE cohort included 19,114 participants ≥70 years of age (≥65 years if U.S. minorities), with no prior CVD events, dementia, or major physical disabilities, who were recruited between 2010 and 2014 from Australia (87% of participants) and the United States (13%). One of the key selection criteria of ASPREE was that participants had to have a score of ≥78 on the Modified Mini-Mental State Examination (3MS) at enrollment (23). In the present study, we excluded participants with missing values for cognitive test scores (n = 222) and/or covariates (n = 94) at baseline, resulting in 18,846 participants' being included in the present analysis.

EXPOSURE TO STATINS. Participants were asked to bring all currently used medications or a list of these to their study visits. Data for baseline and in-trial statin use were obtained predominantly in this way, but when not possible, data were obtained by self-report and subsequent confirmation via primary care practice records. In this study, participants were grouped by their baseline statin use. Given a putative role of statin lipophilicity on neurocognitive outcomes, we also performed comparisons between hydrophilic (pravastatin and rosuvastatin) and lipophilic (atorvastatin, simvastatin, fluvastatin, lovastatin, pitavastatin) statin users (24).

STUDY OUTCOMES. Incident dementia. Dementia was defined according to the *Diagnostic and Statistical Manual for Mental Disorders*, Fourth Edition, criteria (25). Diagnostic features of dementia include memory impairment and at least 1 of the following: aphasia, apraxia, agnosia, and disturbances in

TABLE 1 Baseline Characteristics of Study Participants by Statin Use at Baseline

	Total (N = 18,846)	No Statin (n = 12,948 [68.7%])	Statin (n = 5,898 [31.3%])	p Value
Demographics				
Age, yrs	74.0 (71.6–77.7)	74.0 (71.6–77.8)	74.0 (71.6–77.5)	0.23
Female	10,622 (56.4)	7,032 (54.3)	3,590 (60.9)	<0.001
Country				
Australia	16,458 (87.3)	11,384 (87.9)	5,074 (86.0)	<0.001
United States	2,388 (12.7)	1,564 (12.1)	824 (14.0)	
Ethnicity/race				<0.001
White	17,202 (91.3)	11,932 (92.2)	5,270 (89.4)	
Black	892 (4.7)	570 (4.4)	322 (5.5)	
Hispanic/Latino	482 (2.6)	292 (2.3)	190 (3.2)	
Other	270 (1.4)	154 (1.2)	116 (2.0)	
Education ≥12 yrs	10,477 (54.8)	7,388 (56.3)	3,089 (51.6)	<0.001
Clinical characteristics				
Smoking				0.25
Never	10,447 (55.4)	7,230 (55.8)	3,217 (54.5)	
Former	7,678 (40.7)	5,230 (40.4)	2,448 (41.5)	
Current	721 (3.8)	488 (3.8)	233 (4.0)	
Alcohol use				<0.001
Never	3,278 (17.4)	2,159 (16.7)	1,119 (19.0)	
Former	1,121 (6.0)	745 (5.8)	376 (6.4)	
Current	14,447 (76.7)	10,044 (77.6)	4,403 (74.7)	
BMI categories				<0.001
Underweight	356 (1.9)	303 (2.3)	53 (0.9)	
Normal	4,555 (24.2)	3,472 (26.8)	1,083 (18.4)	
Overweight	8,373 (44.4)	5,736 (44.3)	2,637 (44.7)	
Obese	5,562 (29.5)	3,437 (26.5)	2,125 (36.0)	
Family history of dementia	4,727 (25.1)	3,325 (25.7)	1,402 (23.8)	0.005
Chronic kidney disease				<0.001
None	12,858 (68.2)	9,066 (70.0)	3,792 (64.3)	
Yes	4,671 (24.8)	2,969 (22.9)	1,702 (28.9)	
Uncertain	1,317 (7.0)	913 (7.1)	404 (6.9)	
Diabetes status				<0.001
None	16,833 (89.3)	12,121 (93.6)	4,712 (79.9)	
Yes (on medication)	1,147 (6.1)	366 (2.8)	781 (13.2)	
Yes (not on medication)	866 (4.6)	461 (3.6)	405 (6.9)	
Hypertension status				<0.001
None	4,919 (25.8)	3,858 (29.4)	1,061 (17.7)	
Yes (on medication)	10,036 (52.5)	5,959 (45.4)	4,077 (68.2)	
Yes (not on medication)	4,153 (21.7)	3,310 (25.2)	843 (14.1)	
Number of concomitant medications used				<0.001
0 or 1	6,136 (32.1)	4,894 (37.3)	1,242 (20.7)	
2–4	8,744 (45.8)	5,829 (44.4)	2,915 (48.7)	
≥5	4,234 (22.2)	2,404 (18.3)	1,830 (30.6)	
Other lipid-lowering agents	860 (4.5)	483 (3.7)	377 (6.3)	<0.001
CES-D score	3.2 ± 3.3	3.1 ± 3.3	3.3 ± 3.4	0.002

Values are median (interquartile range), n (%), or mean ± SD. Differences in baseline characteristics between statin users and nonusers were compared using independent-sample Student's *t*-tests or Wilcoxon rank sum test for continuous variables and chi-square tests for categorical variables. Ethnicity/race "other" includes Australian aborigine/Torres Strait islander, native American, more than one race, native Hawaiian/Pacific Islander, and those who were not Hispanic and who did not state their ethnicity/race. BMI was calculated as weight in kilograms divided by height in meters squared and categorized into underweight (<20 kg/m^2), normal (20 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2), and obese (≥30 kg/m^2). Diabetes was defined from self-report or fasting glucose ≥126 mg/dl or using any glucose-lowering medication (on medication) at baseline. Chronic kidney disease was defined as estimated glomerular filtration rate <60 ml/min/1.73 m^2 or urinary albumin-to-creatinine ratio ≥3 mg/mmol. Participants with missing values for chronic kidney disease were assigned to the "uncertain" category. Hypertension was defined as blood pressure >140/90 mm Hg or using any blood pressure–lowering medication (on medication) at baseline. Number of concomitant medications used was defined as the number of concomitant prescription medications taken by participants at baseline (statins were not counted).

BMI = body mass index; CES-D = Centre for Epidemiologic Studies Depression Scale.

TABLE 2 Risk for Incident Dementia and Its Subclassifications Between Statin Users and Nonusers and Between Hydrophilic and Lipophilic Statin Users

	Dementia			Dementia, Probable Alzheimer's Disease			Dementia, Mixed Presentations		
	Cases/Total (Incidence Rate*)	Adjusted HR (95% CI)†	p Value	Cases/Total (Incidence Rate*)	Adjusted HR (95% CI)†	p Value	Cases/Total (Incidence Rate*)	Adjusted HR (95% CI)†	p Value
No statin	382/12,948 (6.48)	Reference	0.11	156/12,948 (2.65)	Reference	0.05	226/12,948 (3.84)	Reference	0.67
Statin	184/5,898 (6.91)	1.16 (0.97–1.40)		79/5,898 (2.97)	1.33 (1.00–1.77)		105/5,898 (3.94)	1.06 (0.82–1.35)	
Lipophilic statin	132/4,051 (7.14)	Reference	0.75	57/4,051 (3.08)	Reference	0.75	75/4,051 (4.06)	Reference	0.84
Hydrophilic statin	51/1,842 (6.27)	0.95 (0.68–1.32)		22/1,842 (2.71)	0.92 (0.56–1.53)		29/1,842 (3.57)	0.95 (0.62–1.48)	

*Event rate per 1,000 person-years. †Adjustment was made for all baseline covariates listed in Table 1, 4 individual cognitive test scores, and ASPREE (Aspirin in Reducing Events in the Elderly) randomized treatment (aspirin or placebo).

CI = confidence interval; HR = hazard ratio.

executive functioning (assessed via dementia assessment visit). In addition, the cognitive impairments needed to be severe enough to cause impairment in social and occupational functioning and represent a decline from a previously higher level of functioning. Dementia diagnoses were adjudicated by an endpoint committee blinded to treatment assignment (26).

Subclassifications of dementia. Dementia was subclassified as follows: 1) probable Alzheimer's disease (AD) (the most common cause of dementia), diagnosed according to the 2012 criteria of Jack et al. (27); or 2) mixed presentations, referring to other forms of dementia that did not meet the criteria of probable AD, which included possible AD (meeting the core AD criteria but without evidence of gradual cognitive decline), etiologic mixed presentations including those with neuroimaging consistent with moderate or marked cerebrovascular pathology and small vessel ischemia, and those with non-AD causes (26).

Mild cognitive impairment. MCI was considered present when after a dementia trigger, participants were subsequently adjudicated as not reaching the dementia endpoint by the dementia adjudication committee (26,28). (In ASPREE, the definition of MCI was more equivalent to cognitive impairment with no dementia.) Dementia triggers included a 3MS score <78 or a decrease over time by more than 10.15 points, adjusted for age and level of education, or as noted on the participant's medical records, a clinician diagnosis of dementia, or prescription of cholinesterase inhibitors (26).

Subclassifications of MCI. MCI was subclassified as follows: 1) MCI consistent with AD; or 2) other MCI, defined as evidence of functional decline or MCI not consistent with AD or insufficient information to diagnose AD (26,28).

Change in cognitive function. Cognitive function was assessed at baseline, at years 1, 3, and 5, and at a final visit. This occurred after early cessation of the trial in June 2017 and hence in 1 of years 3 to 7, depending on when, during the 2010 to 2014 recruitment phase, the participant had been randomized.

A battery of cognitive tests was administered, including the 3MS (23) to measure global cognition, the Symbol Digit Modalities Test (29) to measure psychomotor speed, the Hopkins Verbal Learning Test-Revised (30) delayed recall task to measure episodic memory, and the single letter (F) Controlled Oral Word Association Test to measure language and executive function (31). To reduce floor and ceiling effects and other forms of measurement error in the individual tests, a composite cognitive z score was computed by standardizing the raw score for each individual cognitive domain to a z score and then taking the mean of the z scores for the 4 cognitive tests. For all tests, a higher score indicates better cognition.

ASSESSMENT OF COVARIATES. Potential baseline confounders were selected on the basis of known associations with neurocognitive outcomes and their potential interaction with statins. These included age, sex, years of education, country, race/ethnicity, smoking status, alcohol consumption, body mass index, family history of dementia, chronic kidney disease, diabetes, hypertension, number of concomitant medications used (to take into account the impact of polypharmacy on cognition), use of other lipid-lowering agents, and depression score measured using the Center for Epidemiologic Studies Depression Scale (31). Procedures for assessment of covariates can be found in the ASPREE protocol (32,33).

STATISTICAL ANALYSES. Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) with 95% confidence intervals (CIs) for dementia and MCI outcomes with statin use, adjusted for baseline covariates, 4 domain-specific cognitive

TABLE 3 Risk for MCI and Its Subclassifications Between Statin Users and Nonusers and Between Hydrophilic and Lipophilic Statin Users

	MCI			MCI Consistent With Alzheimer's Disease			Other MCI		
	Cases/Total (Incidence Rate*)	Adjusted HR (95% CI)†	p Value	Cases/Total (Incidence Rate*)	Adjusted HR (95% CI)†	p Value	Cases/Total (Incidence Rate*)	Adjusted HR (95% CI)†	p Value
No statin	262/12,948 (4.48)	Reference	0.81	51/12,948 (0.87)	Reference	0.13	211/12,948 (3.60)	Reference	0.26
Statin	118/5,898 (4.47)	0.97 (0.77–1.22)		33/5,898 (1.24)	1.44 (0.90–2.29)		85/5,898 (3.21)	0.86 (0.66–1.12)	
Lipophilic statin	82/4,051 (4.47)	Reference	0.72	25/4,051 (1.36)	Reference	0.38	57/4,051 (3.10)	Reference	0.40
Hydrophilic statin	36/1,842 (4.47)	1.07 (0.72–1.61)		8/1,842 (0.99)	0.69 (0.30–1.58)		28/1,842 (3.47)	1.22 (0.77–1.94)	

*Event rate per 1,000 person-years. †Adjustment was made for all baseline covariates listed in Table 1, 4 individual cognitive test scores, and ASPREE (Aspirin in Reducing Events in the Elderly) randomized treatment (aspirin or placebo).

MCI = mild cognitive impairment; other abbreviations as in Table 2.

test scores, and the randomized trial intervention (aspirin or placebo). Proportional hazards assumptions were checked by including an interaction term between statin use and time in the model and Schoenfeld residual tests. No violations of the proportional hazards assumption were found. Linear mixed-effects models were used to examine the associations of baseline statin use with changes in the composite cognition (composite *z* score) and 4 individual cognitive domains. The model allowed the comparison of mean cognitive score and slope of cognitive score change between the statin users and nonusers through inclusion of a binary variable to indicate statin users, a continuous variable for the year of cognitive assessment (0 [baseline], 1, 3, 5, etc.), and a statin-by-year interaction. The potential confounders (including baseline covariates and the randomized trial intervention, aspirin or placebo) were fitted as fixed effects; participant-specific intercept and slope were included as random effects to allow the serial correlation between repeated assessments of cognition within the same participant and differential rates of cognition change across visits.

To investigate the impact of statin lipophilicity on statin-related neurocognitive effects, the main analyses were repeated for comparisons between hydrophilic and lipophilic statin users. To identify effect modifiers of the associations between statin use and outcomes, subgroup analyses were performed by age, sex, baseline cognitive ability (composite cognitive *z* score), hypertension, diabetes, smoking status, and randomized treatment allocation to aspirin or placebo (to examine the potential drug interaction between statin and aspirin).

Whether low levels of low-density lipoprotein cholesterol (LDL-C) adversely affect cognitive function remains debatable (34). To answer this question, 2 ancillary analyses were conducted. We first investigated whether there was a differential statin-related effect across participants with different baseline LDL-C levels (by quartiles) and then determined the association between baseline LDL-C and all outcomes within statin users and nonusers, respectively.

In sensitivity analyses, we reanalyzed the time-to-event data using 2 alternative approaches: Fine and Gray competing risk models to consider competing risk events and Cox regression models with inverse probability of treatment weighting to control for confounding adjustment. We also reran the main analyses excluding participants who initiated statins during follow-up. Baseline statin users who temporarily or permanently discontinued treatment during follow-up (11.6%) were not excluded, to avoid reverse causality.

All p values were 2-sided. Bonferroni correction was made for 5 cognitive function tests, such that $p < 0.01$ was considered to indicate statistical significance. For time-to-event analyses and interaction tests, $p < 0.05$ was considered to indicate statistical significance to reduce type II error. Analyses were performed using Stata/SE version 15.0 (StataCorp, College Station, Texas).

RESULTS

BASELINE CHARACTERISTICS. Participant characteristics by baseline statin use are presented in Table 1. Of the 18,846 eligible participants (median age 74.0 years; interquartile range: 71.6 to 77.7 years; 56.4% women) who were followed for a median of 4.7 years, 5,898 (31.3%) were taking statins at baseline. Statin users were more likely to be female, to have a lower average education level and a higher Center for Epidemiologic Studies Depression Scale score, to take more medications at baseline, and to have a higher prevalence of obesity, chronic kidney disease, diabetes, and hypertension. They were less likely to be White, to be current drinkers, or to have family histories of dementia.

STATIN USE AND INCIDENT DEMENTIA. During 85,557 person-years of follow-up, 566 incident cases of dementia were recorded (probable AD, n = 235;

TABLE 4 Changes in Composite Cognition and Domain-Specific Cognition Over Time Between Statin Users and Nonusers and Between Hydrophilic and Lipophilic Statin Users

	Baseline			Cognitive Change Over Time		
	β*	SE	p Value†	β‡	SE	p Value†
Statin users vs. nonusers						
3MS (global function)	-0.303	0.067	<0.001	0.006	0.021	0.79
SDMT (psychomotor speed)	0.053	0.142	0.71	0.033	0.028	0.24
COWAT (language, executive function)	-0.050	0.069	0.47	0.020	0.017	0.22
HVLT-R delayed recall (episodic memory)	-0.166	0.043	<0.001	-0.005	0.010	0.62
Composite *z* score	-0.033	0.010	0.001	0.003	0.002	0.13
Hydrophilic statins vs. lipophilic statins						
3MS (global function)	-0.095	0.118	0.42	-0.001	0.041	0.98
SDMT (psychomotor speed)	-0.159	0.248	0.52	-0.009	0.052	0.86
COWAT (language, executive function)	-0.222	0.119	0.06	-0.005	0.030	0.87
HVLT-R delayed recall (episodic memory)	-0.063	0.073	0.39	0.030	0.019	0.12
Composite *z* score	-0.024	0.018	0.18	0.000	0.003	0.97

The data were fitted using linear mixed models to investigate the changes in cognitive function scores over time between statin users and nonusers. Year of cognition assessment (year 0 refers to baseline) was treated as a continuous variable representing time. The models were constructed by entering statin use at baseline, year, statin × year interaction, baseline covariates (variables listed in Table 1 plus randomized study treatment [aspirin or placebo]), random intercept, and random slope on time. *The coefficient (β) of the main effect of statin was interpreted as the difference in cognitive scores between statin users and nonusers at baseline. †Significance criterion was $p < 0.01$ on the basis of Bonferroni correction. ‡The coefficient (β) of the statin × year interaction was interpreted as the mean difference in the annual rate of change in cognitive scores between statin users and nonusers.

3MS = Modified Mini-Mental State Examination; COWAT = Controlled Oral Word Association Test; HVLT-R = Hopkins Verbal Learning Test-Revised; SDMT = Symbol Digit Modalities Test; SE = standard error.

mixed presentations, n = 331). Compared with no statin use, statin use was not associated with risk for all-cause dementia (HR: 1.16; 95% CI: 0.97 to 1.40; p = 0.11), probable AD (HR: 1.33; 95% CI: 1.00 to 1.77; p = 0.05), or mixed presentations of dementia (HR: 1.06; 95% CI: 0.82 to 1.35; p = 0.67) (Table 2).

STATIN USE AND MCI. There were 380 incident cases of MCI (MCI consistent with AD, n = 84; other MCI, n = 296). Compared with no statin use, statin use was not associated with risk for MCI (HR: 0.97; 95% CI: 0.77 to 1.22; p = 0.81), MCI consistent with AD (HR: 1.44; 95% CI: 0.90 to 2.29; p = 0.13), or other MCI (HR: 0.86; 95% CI: 0.66 to 1.12; p = 0.26) (Table 3).

STATIN USE AND COGNITIVE CHANGE OVER TIME. At baseline, statin users had significantly lower scores on global cognition (measured by the 3MS), episode memory (Hopkins Verbal Learning Test-Revised delayed recall), and composite cognition compared with nonusers. Over the follow-up period, there was no statistically significant difference in the change of composite cognition and any individual cognitive domains between the 2 groups ($p > 0.01$ for all) (Table 4).

COGNITIVE CHANGE AND DEMENTIA WITH THE USE OF HYDROPHILIC VERSUS LIPOPHILIC STATINS. No significant differences were found in any of the outcomes of interest between users of hydrophilic or lipophilic statins (Tables 2, 3, and 4).

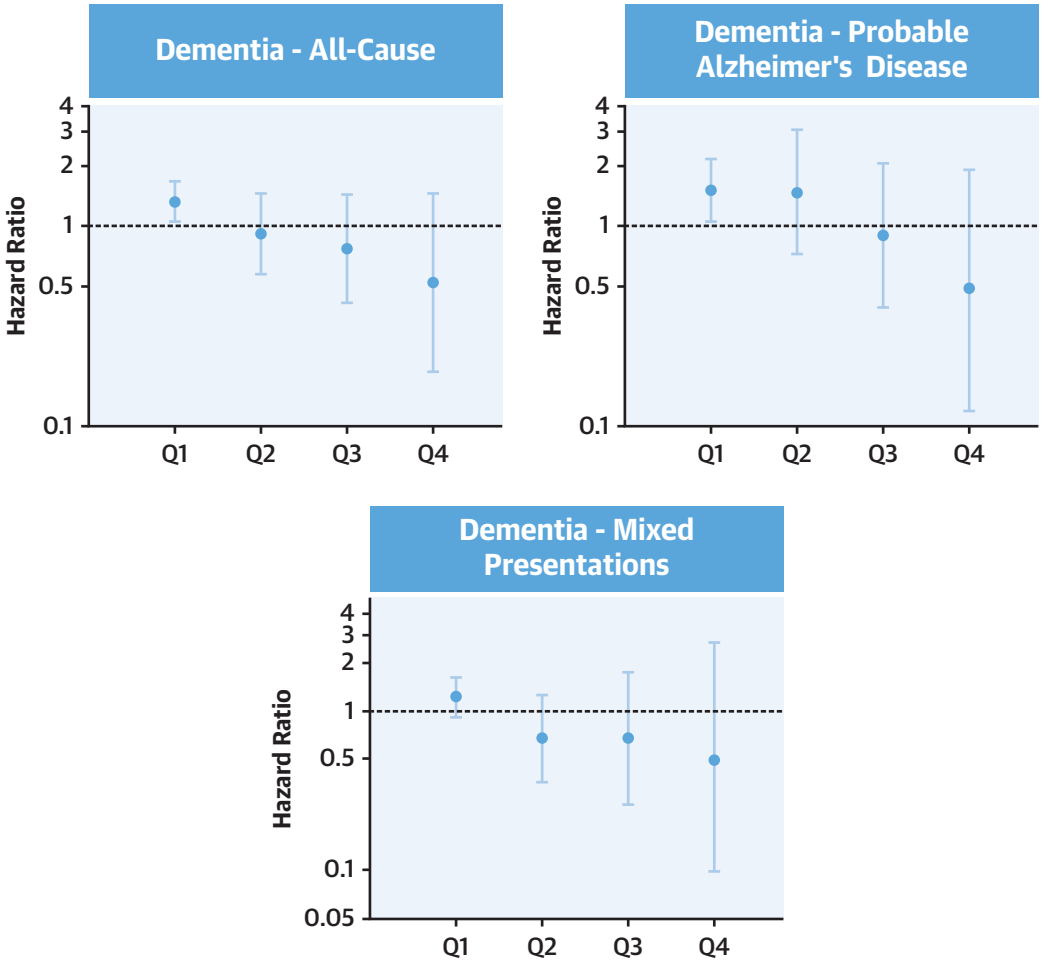
EFFECT MODIFIERS OF THE ASSOCIATIONS OF STATIN USE WITH COGNITION AND DEMENTIA. We found interaction effects between baseline cognitive ability and statin therapy for all dementia outcomes (p for interaction <0.05 for all). To visualize the modifying effect, we calculated the HRs for dementia and its subclassifications for statin use separately, among participant subgroups stratified by the quartile of their baseline composite cognitive *z* score. The data show that the HRs for each outcome decreased in a stepwise manner with increasing quartiles (Central Illustration).

A similar effect modification by baseline composite cognition was also found for the association between statin use and the change in episodic memory (p for interaction = 0.02). To visualize the modifying effect, Figure 1 was plotted to depict the fitted trajectory over time of changes in composite cognition and individual cognitive domains in statin users and nonusers, by baseline composite cognition scores dichotomized at the median. No other interaction effects were found between statin use and selected factors (Supplemental Tables 1 to 3).

LDL-C, COGNITION, AND DEMENTIA. The associations between statin use and all outcomes did not differ significantly across baseline LDL-C quartiles (Supplemental Tables 4 to 6). Compared with the lowest quartile of LDL-C, higher quartiles of LDL-C were not associated with greater or lower risk for any outcome (Supplemental Tables 7 and 8).

SENSITIVITY ANALYSES. Using Fine and Gray competing risk models or Cox regression models with inverse probability of treatment weighting to analyze

CENTRAL ILLUSTRATION **Statin Use, Dementia, and Its Subclassifications, by Baseline Composite Cognition**



Quartiles of Composite Cognitive z Score (Range)	Dementia HR (95% CI)*	Dementia-Probable AD HR (95% CI)*	Dementia-Mixed Presentations HR (95% CI)*
1st quartile (−2.68 to −0.48)	1.34 (1.07-1.68)	1.53 (1.07-2.18)	1.23 (0.92-1.64)
2nd quartile (−0.48 to 0.04)	0.92 (0.58-1.47)	1.50 (0.73-3.07)	0.67 (0.36-1.26)
3rd quartile (0.04 to 0.51)	0.78 (0.42-1.46)	0.90 (0.39-2.07)	0.67 (0.26-1.75)
4th quartile (0.51 to 2.51)	0.53 (0.19-1.49)	0.49 (0.12-1.94)	0.50 (0.10-2.69)
p interaction between statin use and baseline composite cognition (treated as a continuous variable)			
	<0.001	*0.01*	*0.007*

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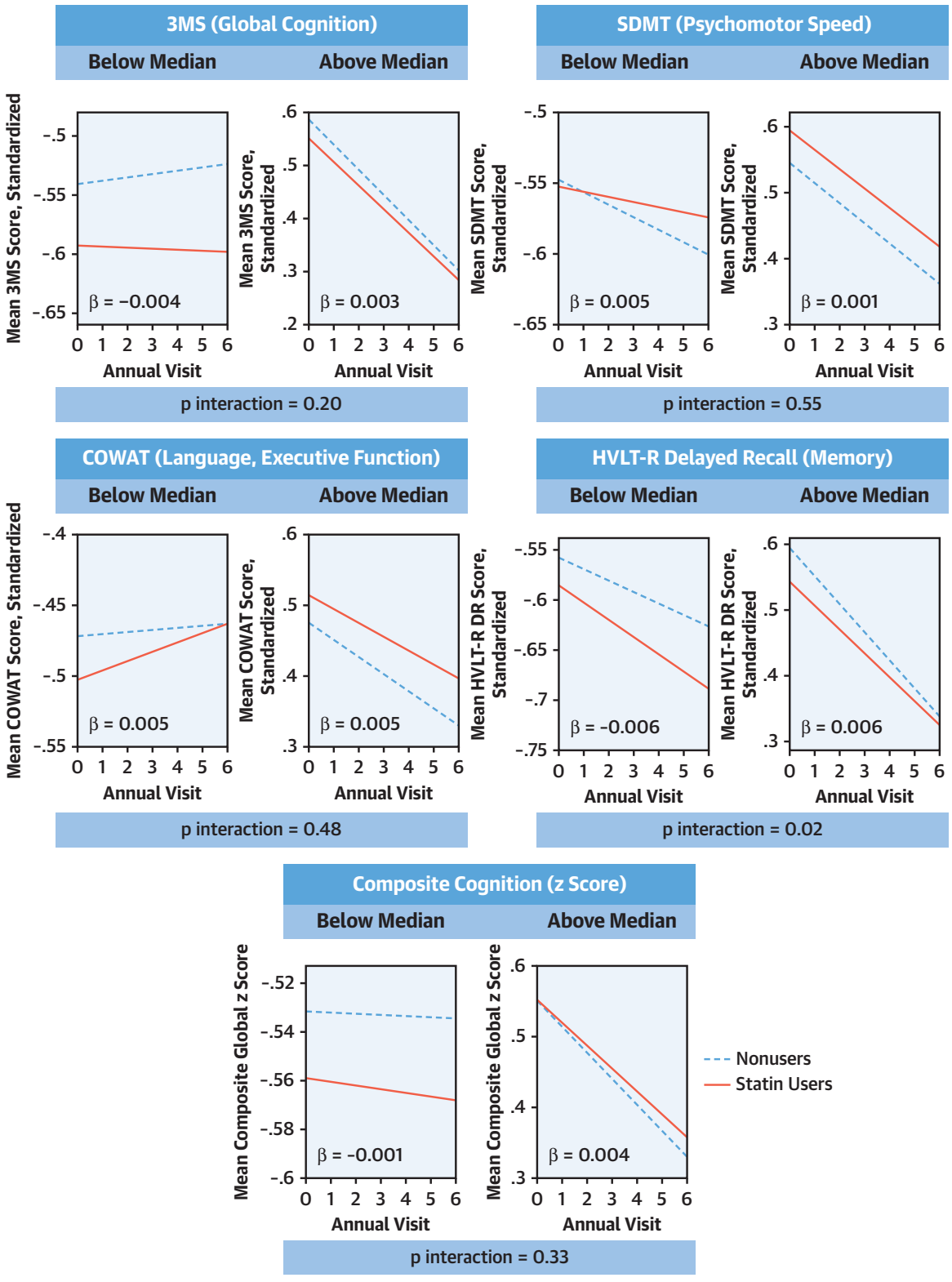
The table and figures show the associations of baseline statin use with dementia and its subclassifications, stratified according to quartiles of baseline composite cognitive *z* scores. *Adjustment was made for all baseline covariates listed in Table 1, 4 individual cognitive test scores, and ASPREE (Aspirin in Reducing Events in the Elderly) randomized treatment (aspirin or placebo). AD = Alzheimer's disease; CI = confidence interval; HR = hazard ratio.

FIGURE 1 Statin Use and Changes in Composite and Domain-Specific Cognitive Scores



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time-to-event data yielded results consistent with our main analyses (Supplemental Tables 9 and 10). There were 13.2% of baseline nonusers (1,708 of 12,948) who initiated statins during follow-up. Excluding these participants from the study cohort yielded similar results to our main findings (Supplemental Tables 11 to 13).

DISCUSSION

This post hoc observational study included data from 18,446 ASPREE participants ≥65 years of age who had no prior CVD events, dementia, or major physical disability and were followed for a median of 4.7 years. Compared with no statin use, baseline statin use was not associated with incident dementia or MCI and their subclassifications; nor was statin use associated with changes over time in composite cognition and its components, including global cognition, episodic memory, language and executive function, and psychomotor speed. These results did not differ by statin lipophilicity. However, the associations of statin use with dementia outcomes and memory change differed among participants with different composite cognitive levels at baseline, with the outcome risks for statin use increasing as baseline cognitive levels decreased. No effect modification was found for age, sex, diabetes, hypertension, smoking, and ASPREE randomized treatment assignment to aspirin or placebo.

With statins being increasingly prescribed to older adults, their long-term effects on cognitive decline and dementia risk have attracted growing interest. Any neurocognitive effect of statins may change the drug's net benefit in older people, particularly those with low cognitive function initially. Previous studies investigating the statin-associated neurocognitive outcomes have yielded inconsistent findings (9,10,35-37). Major limitations of these studies include their cross-sectional study design, the one-off measurement of cognition and the measurement of a single cognitive domain, the lack of adjudication of major neurocognitive disorder outcomes, and short duration of follow-up that was insufficient to capture the events over the long term. Moreover, many studies draw conclusions from the general population, which may not be extrapolated to the older population, in whom the risk for incident dementia doubles every 10 years starting at 65 years (38). It is very likely that younger adults are far less susceptible to possible neurotoxic effects of medications such as statins. Using cognition data systematically collected at a number of time points from all participants in a large, contemporary, community-based, and well-characterized cohort, the present study adds to previous research by suggesting that statin use at baseline was not associated with subsequent dementia incidence and long-term cognitive decline in older adults. The reliability of the study outcomes was ensured by the repeated comprehensive cognitive assessments over time, adjudication of incident dementia cases by endpoint committees, and findings obtained from sensitivity analyses that were consistent with the main results.

Our main results regarding the overall statin-related neurocognitive effects are in line with many previous studies (8-10,17,39-42). A meta-analysis of 25 randomized trials including 46,836 patients 20 to 86 years of age reported no effect of statins on any cognitive domains (global, attention, executive, memory, processing speed, and working memory) in initially cognitively normal subjects (10). A Cochrane analysis pooling data from 2 randomized trials (PROSPER [Prospective Study of Pravastatin in the Elderly at Risk] and HPS [Heart Protection Study]) comprising 26,340 participants reported that statins did not reduce the risk for incident dementia compared with placebo (9). A recent community-based cohort study of older adults found that statin use was not associated with changes in memory, global cognition, and brain structure over 6 years (17).

In ancillary analyses, our data further showed similar risk associations between statins and the study outcomes across subgroups stratified by quartile of baseline LDL-C, and similar effects of LDL-C across baseline LDL-C quartiles, for both statin and nonstatin users. These data were consistent with the results of the EBBINGHAUS (Evaluating PCSK9

FIGURE 1 Continued

The figures show the fitted trajectory of changes in composite and domain-specific cognitive scores in statin users **(solid red line)** versus nonusers **(dashed blue line)**, stratified according to the median of baseline composite cognitive *z* score. To allow direct comparisons to be made across cognitive tests, we standardized the raw cognitive test scores to *z* scores. β is the coefficient of the statin by year interaction, representing the average difference between statin users and nonusers in the change of scores of specific cognitive domains, in the below-median and above-median groups, separately. The p value for interaction represents the interaction effect of baseline statin use and baseline composite cognitive *z* score (treated as continuous variable) on the change in a certain cognitive domain. 3MS = Modified Mini-Mental State Examination; COWAT = Controlled Oral Word Association Test; HVLT-1R = Hopkins Verbal Learning Test-Revised; SDMT = Symbol Digit Modalities Test.

Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects) trial (34). Over 19 months, cognitive change across participant subgroups stratified by the lowest attained LDL-C was similar for both statin plus evolocumab and statin monotherapy intervention groups.

Noting that the neurocognitive effects of statins may be mediated by the drug lipophilicity and vary across participants with different characteristics (12,14–17,43), we have undertaken several secondary analyses. By comparing the event incidence between hydrophilic and lipophilic statin users, we found that statin lipophilicity plays no role in its association with any of the cognition outcomes. This finding is in line with the results of some other studies (7,12). Given the statin dose was not recorded in this study, this result may require further validation in future research.

We also found that participants' baseline cognitive performance modified the statin-dementia association, with the direction of the association changing from positive to null from the lowest to highest quartiles of cognition. Results of the dementia subclassifications further suggest that the increased dementia risk with statin use at lower baseline cognition was attributable mainly to the increased risk for AD. Consistent with this, this effect modification was also observed for the association between statin use and change in episodic memory that is traditionally considered a core feature of AD. It is possible that the increased dementia risk with statin use seen in the lowest cognition quartile reflected reverse causality or an indication bias whereby participants with lower cognition have been prescribed statins in the hope of preventing deterioration in the vascular component of dementia. It is also possible that participants with lower cognitive function might have their statin treatment initiated too late to produce any measurable functional improvement, and indeed if disease is already present, the statin may exacerbate it further. In contrast, among subgroups of the higher cognition quartiles whose cognition was less likely to be affected, the observed null statin effect could be a result of the beneficial effects of statins on cerebrovascular infarcts and microvascular disease, outweighing or neutralizing their neurotoxic effects. These results suggest that a blanket conclusion on statin-related neurocognitive effects in older populations may not generalize to certain patient groups.

STUDY LIMITATIONS. Like all observational studies, this study may be biased by residual confounding, in addition to the possible indication bias previously described. We did not collect data on the length of prior use of statins. The dose of statins was not recorded in ASPREE, thus their effects could not be fully explored. The analyses did not adjust for apolipoprotein E genotypes, as a significant proportion (approximately 35%) of participants were missing this information. Subgroup analyses may have modest power to detect associations and the interactions between statin use and stratification variables. As all ASPREE participants were without dementia at trial entry, our data do not allow conclusions as to whether statins worsen cognitive function or dementia symptoms in such patients. Finally, as ASPREE participants were highly selected, with few morbidities, drug intolerances, and with less frailty and taking fewer concomitant drugs than older people in the general populations, our study findings may not be generalizable to broader, unselected older populations.

Given these limitations, future clinical trials are needed to provide more robust evidence. Two ongoing randomized statin trials of primary prevention in older populations, which include dementia as a study endpoint, are powered to enable firm conclusions concerning any statin effects: the Australian STAREE (Statin Therapy for Reducing Events in the Elderly) (44) trial and the U.S. PREVENTABLE (Pragmatic Evaluation of Events and Benefits of Lipid-Lowering in Older Adults) trial (45).

CONCLUSIONS

In adults ≥65 years of age, statin use was not associated with incident dementia, MCI, or declines in individual cognitive domains or their composite. These findings did not differ by statin lipophilicity, while baseline cognitive function appeared to modify the associations of statins with dementia outcomes and memory change. The study results must be interpreted with caution because of the study's observational nature and will require confirmation by randomized clinical trials designed to explore the neurocognitive effects of statins in older populations.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

In adults >65 years of age, statin therapy was not associated with incident dementia, MCI, or functional declines in individual cognition domains.

TRANSLATIONAL OUTLOOK:

Randomized trials are needed to clarify the neurological effects of statin therapy in elderly populations.

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APPENDIX For supplemental tables, please see the online version of this paper.