Statins, Risk of Dementia, and Cognitive Function: Secondary Analysis of the Ginkgo Evaluation of Memory Study

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Background: Lipid-lowering medications (LLMs) and especially statin drugs can delay cognitive decline and dementia onset in individuals with and without mild cognitive impairment (MCI) at baseline. *Methods:* A longitudinal, observational study was conducted of 3069 cognitively healthy elderly patients (≥75 years of age) who were enrolled in the Ginkgo Evaluation of Memory Study. The primary outcome measure was the time to adjudicated all-cause dementia and Alzheimer dementia (AD). The secondary outcome measure was the change in global cognitive function over time measured by scores from the Modified Mini-Mental State Exam (3MSE) and the cognitive subscale of the AD Assessment Scale (ADAS-Cog). *Results:* Among participants without MCI at baseline, the current use of statins was consistently associated with a reduced risk of all-cause dementia (hazard ratio [HR], 0.79; 95% confidence interval [95% CI], 0.65-0.96; $P = .021$) and AD (HR, 0.57; 95% CI, 0.39-0.85; $P = .005$). In participants who initiated statin therapy, lipophilic statins tended to reduce dementia risk more than nonlipophilic agents. In contrast, there was no significant association between LLM use (including statins), dementia onset, or cognitive decline in individuals with baseline MCI. However, in individuals without MCI at baseline, there was a trend for a neuroprotective effect of statins on cognitive decline. *Conclusions:* Statins may slow the rate of cognitive decline and delay the onset of AD and all-cause dementia in cognitively healthy elderly individuals, whereas individuals with MCI may not have comparable cognitive protection from these agents. However, the results from this observational study need to be interpreted with caution and will require confirmation by randomized clinical trials stratifying treatment groups based on MCI status at baseline. **Key Words:** 3HMG-ACoA reductase inhibitors—cognitive function—dementia—mild cognitive impairment.

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If present trends continue, developed countries are likely to experience a global dementia epidemic. The most common etiologies for dementia are presently attributed to progressive neurodegenerative and vascular diseases, either alone or in combination. Because there is no curative therapy, strategies to prevent or delay dementia are emphasized.

Early treatment by modification of vascular risk factors may play an essential role, because they are strongly associated with the development of Alzheimer dementia (AD), vascular, and mixed dementia.[1-4] The successful treatment of hyperlipidemia, a major risk factor for coronary artery disease and ischemic stroke, with HMG-CoA reductase inhibitors (statin drugs) and their pleiotropic therapeutic effects have spurred an interest in these drugs as a potential aid for dementia prevention. Many experimental studies indicate a link between cholesterol, amyloid metabolism, cellular membrane integrity, and cerebral vascular function, although the clinical relevance of these data remains unclear.[5] Controversy continues whether increased cholesterol levels are associated with an increased risk of AD and other dementias.[6-9]

Some observational studies have suggested a lower rate of dementia in individuals receiving statins, but other studies yielded negative results.[10-18] Prospective clinical trials did not show a protective effect of statins on cognition, but these studies were either not primarily designed to examine the effects of statin on cognitive function and enrolled predominantly participants with advanced vascular disease, including cerebrovascular disease,[19,20] or studied patients with already established AD.[21] The results of these randomized controlled studies seem to conflict with the finding that statins significantly reduce ischemic stroke risk.[19,20,22-26] Because randomized controlled trials of statins reduced the incidence of cerebral ischemic events by about 10% to 30%,[19,20,27] it is surprising that the same intervention does not lead to a decreased incidence of vascular and mixed dementia.

Statins have multiple potential effects that may impact the development of dementia, such as lowering amyloid levels.[28-30] However, the clinical relevance of lowering APP and Aβ remains unknown, because cognitive function may not be dependent on Aβ levels.[31] Observational studies have suggested a reduced risk of AD in those treated with statins during midlife,[32] and analysis of data from the Cardiovascular Health Study (CHS) suggested a potential positive effect of statin drugs on cognitive function in the elderly.[33] These findings may indicate that the timing of statin therapy is essential. Statins may exert a protective effect only if started early in cognitively healthy individuals.

The present study analyzes the effects of lipid-lowering medications (LLMs), predominately statins, on incident dementia and cognitive function in participants with and without mild cognitive impairment (MCI) at baseline who participated in the Ginkgo Evaluation of Memory Study (GEMS), a clinical trial testing the ability of *Ginkgo biloba* to prevent or delay development of dementia.[34]

Methods

Study Population and Study Design

The GEMS study design has been described previously.[34] Briefly, 3069 cognitively healthy individuals and those with MCI 75 years of age and older were enrolled at 4 academic medical centers (University of Pittsburgh, University of California-Davis, Johns Hopkins School of Medicine, and Wake Forest University) with a mean follow-up of 6 years. Similar to the primary analysis, data from 3069 of 3072 participants who were initially randomized into GEMS were included in this time-adjusted analysis.[34] Participants had to be able to sign informed consent and were required to have a proxy who provided an independent assessment of the participant's functional and cognitive abilities. All participants underwent a detailed physical, neurologic, and neuropsychiatric examination. At baseline and at regularly scheduled 6-month visits, medical history and current medication use were reviewed, with participants bringing to the clinic medicine bottles for currently used medications in order to record the exact name and dose of each. Fasting lipid profiles were not measured.

Cognitive Assessments

The baseline neuropsychological battery measured language, mood, executive and visuospatial function, memory, psychomotor speed, and global cognitive function using previously validated cut-off scores in subjects of similar age.[34] At each follow-up visit, participants were reevaluated with an abbreviated cognitive test battery including the Modified Mini-Mental State Exam (3MSE), the Clinical Dementia Rating Scale, and the cognitive subscale of the AD Assessment Scale (ADAS-Cog).[34] If scores on 2 of the 3 assessments were below preset cutpoints, or when dementia was suspected by the proxy, family, or a treating physician, the complete baseline neuropsychological test battery was repeated, followed by an additional neurologic and medical examination and brain magnetic resonance imaging. Final diagnosis classification was made by an expert consensus panel.[34]

If a participant was unable to come to the clinic, the Telephone Instrument of Cognitive Status (TICS) was administered, and these scores were used to estimate the 3MSE score.[35] Individuals who reached dementia endpoint were excluded from further assessments.

Exposures and Adjustment Variables

The focus of our analysis was the use of LLMs as assessed every 6 months. Exposure was defined and updated at each visit as never use of LLMs, ever use of statins, or ever use of an alternative (nonstatin) LLM. Additional analyses assessed associations with former/current use of statins,

and ever use of lipophilic versus nonlipophilic statins. Adjustment variables included age, sex, race, education, clinic, treatment group, MCI at baseline, APOe4 genotype, and history of coronary heart disease (CHD), defined as definite/probable myocardial infarction, definite/probable angina pectoris, definite/probable resuscitated cardiac arrest, status post–coronary artery bypass graft or coronary angioplasty/stent placement and stroke (both groups together are summarized as cardiovascular disease [CVD]). The latter were determined by self-report at baseline and by review of medical records if any vascular events occurred during follow-up, as previously described.[36] In the longitudinal analyses, CHD, stroke, and LLM use were updated at each visit.

Statistical Analysis

Participant characteristics by LLM use at baseline were compared using Chi-square tests for categorical measures and analysis of variance (ANOVA) for continuous measures. Cox regression models were used to compute hazard ratios (HRs) as estimates of relative risk of all-cause dementia, AD, and mixed vascular dementia associated with ever use of statins or other LLMs compared to no use, updating LLM use over time. There were too few participants on other LLMs to allow that group to serve as the comparison group for the statin users. We also developed models excluding participants who were taking LLMs at baseline in order to consider an inception cohort, because duration of use at baseline was unknown. In the absence of lipid levels, CVD status at baseline represents a possible indication for use of LLMs. In order to address indication bias, analyses were repeated restricting to participants without CVD at baseline. Significant results were further explored by examining former versus current use of statins and lipophilic class of statins. The assumption of proportional hazards was not met for the variable MCI at baseline, leading us to stratify analyses by MCI at baseline.

Mixed effects regression models were used to estimate the association of LLM use with change in cognitive function scores over time for participants without MCI at baseline. Change was modeled with a linear and quadratic term for year, but only interactions with the linear term were assessed. Year was centered at year 3 to reduce the collinearity between year and year squared, with the result that the coefficient for LLM use by year assesses the difference in the instantaneous rate of change at year 3 attributable to LLM use compared to no use.

ApoE status was available for 80% of participants. We performed sensitivity analyses classifying all those missing ApoE genotype in turn as absent or present, then used a separate code for missing; results were consistent across all 3 approaches. The results presented used an indicator for missing ApoE. Statistical analysis was performed using STATA statistical software (v. 10; StataCorp, College Station, TX).

Results

The cohort was predominantly white and highly educated (average years of education, 14.4). Participant characteristics by type of LLM used at baseline are summarized in Table 1. About 16% of the total cohort was classified as having MCI at baseline; the prevalence of MCI did not differ by LLM use.[37] LLM use was more common in men and in participants with a history of stroke or CHD.

At baseline, 25.3% of participants were taking statins and 2.4% were taking other LLMs, including bile acid sequestrants, fibrates, niacin, or nicotinic acid. The percentage of statin users increased to more than 40% over

Table 1. *Participant characteristics by lipid-lowering medication use at baseline**

Characteristic	No LLM (n = 2218)	Statins (n = 778)	Other LLM (n = 73)	Total (N = 3069)	*P* value†
Male	1147 (51.7)	457 (58.7)	46 (63.0)	1650 (53.8)	.001
Black	71 (3.2)	19 (2.4)	0 (0)	90 (2.9)	.18
MCI	346 (15.6)	123 (15.8)	13 (17.8)	482 (15.7)	.87
Cerebrovascular disease	147 (6.6)	105 (13.5)	5 (6.8)	257 (8.4)	<.001
Coronary heart disease	219 (9.9)	370 (47.6)	25 (34.2)	614 (20.0)	<.001
Age, yrs, mean (SD)	78.7 (3.4)	78.4 (3.0)	77.8 (2.9)	78.6 (3.3)	.007
Education, yrs, mean (SD)	14.3 (3.2)	14.5 (3.1)	14.8 (3.2)	14.4 (3.2)	.26
Apoe4					
Yes	393 (17.7)	175 (22.5)	10 (13.7)	578 (18.8)	.008
Missing	471 (21.2)	132 (17.0)	14 (19.2)	617 (20.1)	
3MSE	93.4 (4.7)	93.2 (4.6)	93.7 (4.7)	93.4 (4.7)	.34
ADAS-cog	6.5 (2.7)	6.5 (2.7)	6.3 (2.4)	6.5 (2.7)	.86

Abbreviations: 3MSE, Modified Mini-Mental State Examination; ADAS-Cog, cognitive subscale of the Alzheimer Disease Assessment; LLM, lipid-lowering medication; MCI, mild cognitive impairment; SD, standard deviation.

*Entries in table are n (%) unless otherwise noted.

†Comparison across all 3 groups.

time, but the percent taking other LLMs did not change (Figure 1).

Cross-sectional Analysis of LLM Use with Cognitive Function Scores at Baseline

Cross sectional analysis showed no association of LLM use with either 3MSE ($P = .71$) or ADAS-Cog scores ($P = .81$). This was consistent with a lack of association with MCI at baseline, indicating that at entry participants with MCI were not less likely to receive a LLM than those without MCI.

Survival Analysis of Time to Dementia

A total of 523 GEMS participants reached the dementia endpoint during the trial, including 353 classified as having AD without vascular disease, and 24 with pure vascular dementia (Figure 2).[34] For analysis, those with vascular dementia were combined with the mixed dementia cases to form a group with a vascular component. Among participants without MCI at baseline, there was some evidence for a reduced risk of all-cause dementia among ever users of statins, and although HRs were often similar for users of other LLM, our data were insufficient to confirm a statistically significant effect in this group (Table 2). The strongest results were a reduction in risk of AD and all-cause dementia among those who initiated statin use during the study (HR, 0.46; 95% confidence interval [CI], 0.29-0.74; $P <$ .001; and HR, 0.53; 95% CI, 0.37-0.75; $P <$ .001, respectively). HRs for ever use of statins and dementia with a vascular component were consistently less than 1.0, but did not reach statistical significance. There were no significant associations of LLM use and dementia in the group with MCI at baseline.

When use of statins was separated into former and current use, there was a consistent association of current use with reduced risk of all-cause dementia and AD among

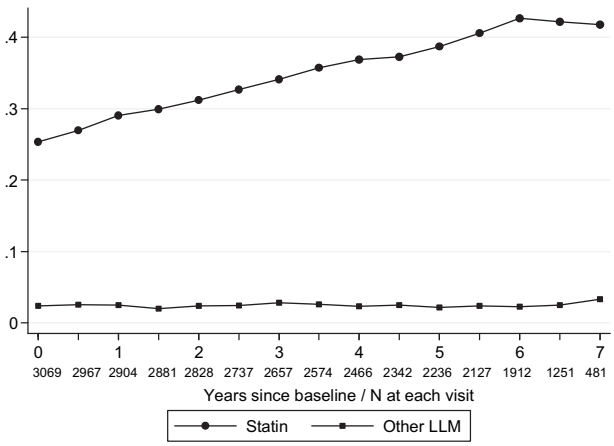

Figure 1. *Proportion of participants taking statins and other lipid lowering medications by year. Circles indicate statins; squares indicate other lipid-lowering medications.*

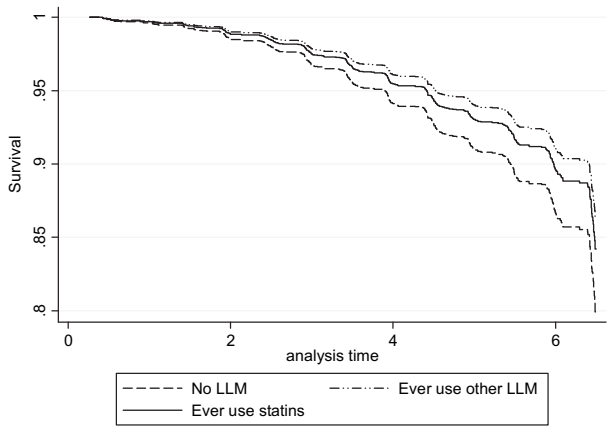

Figure 2. *Estimated survival curves for time to dementia in all participants. Dashed line, no lipid-lowering medications (LLMs); solid line, statins; dash-dot line, other LLM.*

participants without MCI at baseline (Table 3). Duration of use could only be determined in participants who initiated statins during the study, and there was a linear trend of reduced risk with longer duration of use. This result needs to be interpreted with caution, because duration of use is correlated with length of dementia-free follow-up time. Lipophilic statins tended to reduce risk of dementia more than nonlipophilic statins, especially among initiators of statin therapy.

Longitudinal Analysis of Cognitive Decline: 3MSE and ADAS-Cog

Trajectories of cognitive function over time showed a significant quadratic trend, with scores initially improving after baseline, probably because of a practice effect, and then gradually declining. The amount of cognitive decline as assessed by these measures was minimal in this cohort. Among participants without MCI at baseline, the mean linear rate of change at the third year of follow-up was –0.09 (95% CI, –0.13 to –0.06) points per year for the 3MSE and 0.03 (95% CI, 0.01-0.05) for the ADAS-Cog. The subscore of the 3MSE associated with memory showed no linear rate of change at year 3, with an estimated slope of 0.00 (95% CI, –0.02 to 0.02). Participants with MCI at baseline had a greater change of –0.45 (95% CI, –0.58 to –0.32) points per year for the 3MSE, and 0.18 (95% CI, 0.12-0.24) for the ADAS-Cog. The subscore of the 3MSE associated with memory showed a modest linear rate of change at year 3, with an estimated slope of –0.08 (95% CI, –0.14 to –0.02) points per year.

Similar to the results for dementia, there was no association of statin use with rate of cognitive decline among participants with MCI at baseline. Table 4 summarizes the results for participants free of MCI at baseline. For the 3MSE, statin users tended to have a slower rate of decline compared to nonusers of the medication, with current users having half the rate of change of nonusers

Table 2. *Results by dementia type*

		All-cause dementia (n = 523)		AD only (n = 353)		Vascular component (n = 148)	
Risk group	Exposure	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
No MCI at baseline, N = 2587	Statin ever	0.77 (0.60-0.98)	.034	0.83 (0.61-1.12)	.21	0.72 (0.46-1.13)	.15
	Other LLM ever	0.65 (0.37-1.14), n = 324	.135	0.48 (0.21-1.08), n = 212	.076	0.98 (0.42-2.28), n = 97	.96
No CVD at baseline, N = 1941	Statin ever	0.75 (0.56-1.01)	.060	0.78 (0.55-1.12)	.18	0.79 (0.44-1.43)	.44
	Other LLM ever	0.89 (0.46-1.75), n = 223	.74	0.55 (0.20-1.49), n = 155	.24	2.26 (0.88-5.80), n = 58	.09
Initiators only, N = 1872	Statin ever	0.53 (0.37-0.75)	<.001	0.46 (0.29-0.74)	<.001	0.67 (0.36-1.22)	.19
	Other LLM ever	0.43 (0.13-1.33), n = 220	.14	0.21 (0.03-1.49), n = 142	.12	0.97 (0.23-4.03), n = 68	.96
MCI at baseline, N = 482							
	Statin ever	0.88 (0.64-1.21)	.43	0.70 (0.47-1.04)	.075	1.34 (0.72-2.50)	.36
	Other LLM ever	0.78 (0.36-1.68), n = 199	.52	0.83 (0.33-2.07), n = 141	.69	0.73 (0.17-3.17), n = 51	.68
Initiators only, N = 346	Statin ever	0.73 (0.45-1.20)	.22	0.64 (0.35-1.15)	.13	1.15 (0.45-2.92) N/A, n = 32	.77
	Other LLM ever	0.47 (0.11-1.97), n = 143	.30	0.63 (0.15-2.70), n = 109	.54		

Abbreviations: AD, Alzheimer disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; LLM, lipid-lowering medication; MCI, mild cognitive impairment.
All models were adjusted for age, sex, race, field center, years of education, *Ginkgo biloba* randomization group, Apoe(4), and time-varying stroke and coronary heart disease.

at the midpoint of follow-up. The scale of the ADAS-Cog is reversed, such that a higher score indicates worse cognitive function, and therefore a larger slope coefficient indicates a faster rate of cognitive decline. As with the 3MSE, there was a trend toward slower decline among statin users. These results are not striking by themselves, but they are consistent with the results of our time to dementia analysis showing a trend towards neuroprotection with statin use. Results were similar when restricted to participants without CVD at baseline.

Discussion

The present analysis focuses mainly on the effects of statins on cognitive function, because the number of participants on alternative lipid-lowering agents was relatively low. Among participants without MCI at baseline, current use of statins was associated with a reduced risk of all cause dementia (HR, 0.79; 95% CI, 0.65-0.96; $P = .021$) and AD (HR, 0.57; 95% CI, 0.39-0.85; $P = .005$). Results were strongest when restricted to initiators of statins during the study, and in this group, there was a significant association of lipophilic statins with reduced risk of dementia which was not seen for nonlipophilic statins. In contrast, there was no significant association of LLM use (including statins) and dementia onset in individuals with baseline MCI. Consistent with these results, there was no association of statin use with rate of cognitive decline among participants with MCI at baseline as measured by 3MSE and ADAS-Cog. However, in individuals without MCI at baseline there was a trend for a neuroprotective effect of statins on cognitive decline.

Previous observational studies have shown mixed results. While some studies have been negative, others have shown a lower rate of dementia in individuals receiving statins.[10-18] Similar to our results, a Canadian study found that the use of LLMs was associated with a lower risk of dementia, specifically AD,[11] and in the recently published Rotterdam study, statin use was associated with lower risk of AD in the general population.[16]

However, data from 2 prospective randomized trials comparing statin users with nonusers showed no significant effects of statins on cognition.[19,20] Both studies used cognitive function only as a tertiary outcome measure, and in contrast to GEMS, enrolled individuals with advanced vascular disease who were at increased risk for stroke and other vascular events potentially compromising cerebral blood supply. In the Heart Protection Study, 33% of all participants had cerebrovascular disease and 51% had vascular disease,[38] and PROSPER enrolled 11% of individuals with stroke and 50% with vascular disease.[39] The Heart Protection Study used one phone interview during the final follow-up to assess risk of cognitive decline but did not include routine detailed neuropsychological evaluations. The PROSPER study used a comprehensive neuropsychological testing battery consisting of 3MSE, the

Table 3. *Further classification of statin use for significant results in Table 2*

Risk group	Exposure	All-cause dementia		AD only	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
No MCI at baseline	Statin use				
	Former	0.98 (0.66-1.46)	.92	1.39 (0.89-2.15)	.14
	Current	0.71 (0.55-0.93)	.012	0.69 (0.49-0.97)	.03
	Type of statin (ever use)				
	Lipophilic	0.76 (0.60-0.98)	.033	0.79 (0.58-1.08)	.14
	Nonlipophilic	0.89 (0.61-1.29)	.54	1.01 (0.65-1.58)	.96
No CVD at baseline	Statin use				
	Former	1.01 (0.62-1.64)	.97	1.35 (0.80-2.27)	.26
	Current	0.69 (0.49-0.96)	.026	0.64 (0.42-0.96)	.032
	Type of statin (ever use)				
	Lipophilic	0.82 (0.60-1.11)	.19	0.85 (0.59-1.22)	.37
	Nonlipophilic	0.70 (0.41-1.20)	.19	0.70 (0.36-1.34)	.28
Initiators only	Statin use				
	Former	0.47 (0.23-0.95)	.035	0.48 (0.20-1.13)	.091
	Current	0.53 (0.36-0.79)	.002	0.45 (0.27-0.76)	.003
	Duration				
	<1 yr	0.69 (0.41-1.14)	<.001*	0.31 (0.12-0.76)	.003*
	1-3 yrs	0.56 (0.34-0.91)		0.71 (0.41-1.22)	
	>3 yrs	0.26 (0.11-0.60)		0.22 (0.07-0.70)	
	Type of statin (ever use)				
	Lipophilic	0.53 (0.36-0.77)	.001	0.47 (0.29-0.77)	.003
	Nonlipophilic	0.89 (0.46-1.69)	.71	0.78 (0.34-1.80)	.56

Abbreviations: AD, Alzheimer disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MCI, mild cognitive impairment.
All models were adjusted for age, sex, race, field center, years of education, *Ginkgo biloba* randomization group, Apoe(4), and time-varying stroke, coronary heart disease, and ever use of other lipid-lowering medications.
*Test for linear trend.

Picture-Word Learning Test, the Stroop Color Word Test, and the Letter Digit Coding Test at baseline and during follow-ups. Detailed neuropsychological testing with screening for MCI at baseline or brain MRIs were not performed in these high-risk populations so that a relatively high proportion of individuals with cognitive impairment caused by significant vascular disease at baseline may have been enrolled in both studies. Conflicting results from our analysis and those studies may therefore be related to the fact that study populations are not comparable, and

Table 4. *Results of longitudinal models of cognitive function among participants free of mild cognitive impairment at baseline*

Exposure	3MSE		ADAS-cog	
	Slope* (95% CI)	*P* value†	Slope* (95% CI)	*P* value†
No LLM	−0.11 (−0.15 to −0.07)	—	0.05 (0.02-0.07)	—
Statin ever	−0.06 (−0.10 to −0.01)	.066	0.015 (−0.01-0.04)	.058
Other LLM ever	−0.16 (−0.29 to −0.04)	.43	−0.03 (−0.11 to −0.04)	.041
Statin use				
None	−0.14 (−0.18 to −0.10)	—	0.04 (0.02-0.07)	—
Former	−0.06 (−0.18-0.07)	.19	0.03 (−0.05-0.11)	.73
Current	−0.07 (−0.12 to −0.02)	.014	0.01 (−0.02-0.04)	.045
Type of statin (ever use)				
None	−0.10 (−0.14 to −0.06)	—	0.04 (0.02-0.06)	—
Lipophilic	−0.06 (−0.11 to −0.01)	.13	0.01 (−0.02-0.03)	.044
Nonlipophilic	−0.16 (−0.26 to −0.06)	.26	0.05 (−0.00-0.11)	.66

Abbreviations: 3MSE, Modified Mini-Mental State Examination; ADAS-Cog, cognitive subscale of the Alzheimer Disease Assessment; CI, confidence interval; LLM, lipid-lowering medication.
*Estimate of rate of change at midpoint of follow-up time.
†Test for difference in slope compared to nonusers.

may be consistent with our finding that statins may not exert a protective cognitive effect when treatment is initiated after MCI and cerebrovascular disease have developed.

Similar to results from those randomized trials, there was no benefit of statins on cognitive function in individuals with mild to moderate AD in the LEADe trial.[21] The investigators raised the interesting question as to whether a different timing of statin therapy could have yielded different results. Findings from the Rotterdam study suggest that statins are associated with a reduced AD risk in the general population, a sample that consists of a greater group of cognitively healthy individuals at baseline compared to the discussed studies, which again could indicate that timing of statin therapy is crucial.

Our analysis has several limitations. The data were derived from the observational component of a clinical trial in which LLM use was not the primary exposure of interest and cholesterol levels were not measured, so we were unable to restrict our analysis to those with an indication for LLMs. To address this limitation, we repeated our complete statistical analysis in participants without CVD, which produced similar estimates of reduced risk. We recognize, however, that there remains a substantial potential for confounding by indication.

Whereas our results do not point to any specific advantage for statin over alternative LLM use, the group comparison is limited by statistical power. Given that participants on LLMs might differ from those not on LLMs in ways for which we are unable to adjust, the ideal analysis to identify a particular benefit of statin use would have been a comparison of statin users with users of other LLMs. Unfortunately, the number of alternative LLM users was too small to allow for this comparison.

Our results were stronger for current statin users, which could suggest treatment bias. As participants loose cognitive function, treating physicians may reduce the number of medications, with the result that current statin use appears protective. Although cross sectional analysis showed no association of LLM use with cognitive scores or MCI at baseline, we cannot rule out that physicians are less likely to prescribe new medications to patients experiencing cognitive difficulty during study follow-up. Our results for duration of treatment show an increasing protective effect with longer treatment, but again, we cannot rule out treatment bias. In addition, there is theoretical concern of confounding by selection bias. Participants with low socioeconomic status may be less likely to receive a statin drug. However, we found no association between race, education, or income status and LLM use, and adding those covariates to the model did not change the results.

We have examined the effects of different statin types in a secondary analysis dividing lipophilic and hydrophilic statins (Tables 3 and 4). Initiators of lipophilic statins seemed to experience the greatest risk reduction of dementia and AD onset. Lipophilic statins may be more beneficial because they cross the blood–brain barrier much more easily than their hydrophilic counterparts. The mechanism by which LLMs may exert their effect on cognition remains unclear, but could be related to direct effects within the nervous system. It has been hypothesized that statins not only lower lipid levels and reduce atherosclerosis-related vascular disease, but that they also have multiple pleiotropic effects.[28-30,40] However, because of study limitations, these results need to be interpreted with caution.

The observed rate of cognitive decline was relatively low, in part because of the relative insensitivity of the 3MSE and ADAS among highly educated people who exhibit more cognitive reserve, and in part because subjects who showed decline were excluded when they reached the dementia endpoint. Follow-up data from these individuals are not available to comment on the effect of LLMs on cognitive function in demented participants over time, which may differ from the effects observed in cognitively healthy individuals.

The strengths of this study include that it followed a population of highly functional and cognitively healthy individuals with regular cognitive assessments over a relatively long observation period. Medication intake was verified by inspection of pill bottles and medication lists at each study visit. The primary outcome measure of adjudicated dementia was based on a detailed testing battery, neurologic examination and review by a neuropsychologist, and was well defined, yielding robust data of dementia onset and dementia subtype. The effects of different statin types and alternative LLMs were analyzed and data analysis was stratified by cognitive status at baseline and included participants with and without MCI, allowing us to monitor the effects on statins on early disease stages. The current analysis adds novel information to the existing literature because it raises the intriguing question whether statins may be protective for cognitive function in the elderly if treatment is initiated before cognitive impairment caused by vascular or neurodegenerative disease has developed.

Overall, the effects of LLMs on cognitive scores over time were modest, and these findings may not translate into a clinically meaningful functional improvement. However, the effect size may become more significant when treatment is initiated in midlife or if the observational period is extended. It is unclear when to expect an effect of statins on cognition. If there is any benefit, it may depend on exposure time and also on LLM type and dose.

In summary, we found that statins reduce the risk of incident AD and all-cause dementia in elderly individuals without MCI at baseline. However, confirmation of these results by randomized trials stratifying participants by MCI status would be required.

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Appendix

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