Statins and Cognitive Decline in Older Adults with Normal Cognition or Mild Cognitive Impairment

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OBJECTIVES: To determine the effect of statins on cognitive decline in healthy elderly adults.

DESIGN: Longitudinal.

SETTING: National Institute of Aging network of Alzheimer's Disease Centers.

PARTICIPANTS: Research volunteers with normal cognition at baseline evaluated an average 4.1 times over 3.4 years (1,244 statin users, 2,363 nonusers) and with mild cognitive impairment (MCI) at baseline evaluated an average 3.9 times over 2.8 years (763 users, 917 nonusers).

MEASUREMENTS: Cognitive performance was assessed according to 10 neuropsychological indices and the Clinical Dementia Rating Sum of Boxes (CDR-SOB). Repeated-measures analyses adjusted for age, sex, education, comorbidities, and family history of dementia were conducted.

RESULTS: Of participants with normal cognition at baseline, statin users performed significantly better across all visits in attention (Trails A) and had significantly slower annual worsening in CDR-SOB scores ($P = .006$) and slower worsening in Mini-Mental State Examination scores than nonusers (which was not significant after adjusting for multiple comparisons, $P = .05$). For participants with MCI, statin users performed significantly better across all visits on attention measures (Trail-Making Test Part A), verbal skills (Category Fluency), and executive functioning (Trail-Making Test Part B, Digit Symbol, and Digits Backward), but there were no differences in cognitive decline between users and nonusers.

CONCLUSION: Elderly adults with normal cognition at baseline who used statins had a slower rate of annual worsening in CDR-SOB than nonusers. **J Am Geriatr Soc 61:1449–1455, 2013.**

Key words: cognitive decline; statins

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There is controversy regarding the effects of statins on cognition and cognitive decline in aging. Epidemiological findings have been mixed regarding statin use and cognition.[1–3] Prospective observational studies have mostly found a significantly lower risk of dementia or incident Alzheimer's disease (AD) in statin users;[4–13] some studies have found no association between statins and dementia risk.[14,15] Two previous studies analyzed data according to age and found a strong beneficial effect for subjects younger than 80 at baseline, but not in those aged 80 and older.[8,9]

Two other studies found less cognitive decline in individuals with AD taking statins.[16,17] The potential for a neuroprotective effect of statins has led to two recent multicenter clinical trials for treatment of AD, both of which showed no benefit over time,[18,19] although it may be unlikely that disease-modifying therapies will be successful if initiated at the mild to moderate stages of the disease because there is already extensive AD pathology and irreversible degeneration at those stages.

In support of a possible early benefit of statins, four studies have shown that, in older adults without dementia, statin users have better cognition.[4,13,20,21] One was a secondary analysis of a clinical trial of the effect of ginkgo biloba in 3,069 elderly adults (≥75) in which dementia and cognition were the primary endpoints.[4] A significantly slower rate of decline was found on the Modified Mini-Mental State Examination (3MSE) and the Alzheimer's Disease Assessment Scale—Cognitive Subscale (ADAS-Cog) for current statin users than for nonusers who had normal cognition at baseline, although no effect on rate of decline was found in those who had mild cognitive impairment (MCI) at baseline.

Against this background of many studies showing that statin users have better cognition, other longitudinal studies of cognition (randomized trials and observational studies) in individuals without dementia have yielded negative results.[14,22–25] Cognition was assessed as a secondary endpoint in a population with cardiovascular disease or strong risk factors for cardiovascular disease in two clinical trials

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of statins (pravastatin and simvastatin) (see also[25]). One had an evaluation of cognition only at follow-up and not at baseline,[23] and approximately one-third of the subjects were nonadherent to statin use or nonuse, which was not taken into account in the intention-to-treat analysis. One of the observational studies studied cognitive decline in 6,830 community residents followed for 7 years, 16% of whom were taking statins.[14] No significant protective effects were found on visual memory (Benton Visual Retention Test), attention (Trail-Making Test Part (Trails A)), or set shifting speed (Trails B). A limitation of this study is that trends in cognition over time were not evaluated using continuous scores but instead were dichotomized into decliners and nondecliners. Another study followed 548 community residents aged 65 and older in Spain for a median of 2 years.[25] No differences in cognition were observed between statin users and nonusers at baseline, as measured using a comprehensive battery of cognitive tests at the end of 2 years of follow-up. This study was limited by small numbers of subjects and short follow-up.

In 2012, the Food and Drug Administration required warnings on statin prescriptions indicating that rare instances of memory loss have occurred in association with statin use.[26] These warnings, along with informal communications on the Web, have alarmed some individuals and families regarding the adverse risks of statin use in those concerned with memory loss and cognitive decline. Given the mixed results of studies and public messaging, additional studies of statins and cognition are warranted.

The current investigation further explored the effects of statin use on cognitive functioning and change over time in a sample of more than 5,000 research participants in National Institutes of Health (NIH), National Institute on Aging (NIA)-supported Alzheimer's Disease Centers (ADCs). Whether statins affect cognitive decline in subjects with normal cognition at baseline and subjects with MCI at baseline was investigated separately. These participants had repeated evaluations of cognitive performance and information about statin use at each annual follow-up as part of the Uniform Data Set (UDS), a standardized assessment and data protocol that the National Alzheimer's Coordinating Center maintains. Repeated observations enabled a population taking statins to be characterized consistently throughout follow-up, an advantage over a number of prior studies that queried statin use only at baseline. A standardized battery of neuropsychological measures that examined a wide range of cognitive areas, as opposed to using an index of overall cognitive status such as the 3MSE, was also available. This rich dataset allowed whether certain areas such as executive functioning are more vulnerable to the effects of statins to be determined. The minimum requirement of at least three annual visits, resulting in an average follow-up of 3 years, provided a strong test of whether statins are associated with longitudinal cognitive changes.

METHODS

Data Collection

Variables were collected as part of the UDS, with 31 participating NIH-NIA ADCs nationwide. The UDS consists of longitudinal data obtained in annual comprehensive evaluations of thousands of research volunteers.[27,28] The effects of statins on cognitive performance were ascertained over time in those classified as normal or having MCI at baseline.

Participants

Information from the UDS as of June 2011 was used. Recruitment strategies vary between ADCs, and as such, participants may come from clinics or the community.[27] Inclusion criteria for the current study required that participants have a diagnosis of normal cognition or MCI from the clinicians at each center (N = 6,600). The diagnosis of MCI follows guidelines set forth by an expert panel,[29] including clinical judgment that a person is not cognitively normal and does not meet diagnostic criteria for dementia, has preserved or only minimally impaired functional abilities, and has evidence of cognitive impairment or decline based on self- or informant report and objective cognitive tests. A diagnosis of normal cognition is made when a person does not meet criteria for MCI or dementia. All participants signed consent forms that the institutional review boards at their study sites had approved.

Measures

The outcome measures used in the analyses are listed below.

Clinical Dementia Rating Sum of Boxes

The Clinical Dementia Rating (CDR) was administered using a structured interview format with participant and their informants to assess participants' current cognitive and functional status.[30] Areas involving memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care are each rated for their level of impairment. The CDR Sum of Boxes (SOB) provides a composite of the overall level of impairment.

Neuropsychological Measures

Cognitive test scores were based on the core battery of measures that the ADCs collected.[28] The Mini-Mental State Examination (MMSE) was used to assess overall cognitive status.[31] Attention was assessed according to the maximum number of correct trials for Digits Forward[32] and the number of seconds needed to sequence numbers using a pencil (Trails A).[33] Language was examined using the 30-item version of the Boston Naming Test.[34] The evaluation of memory included verbal episodic memory (immediate and delayed story recall)[32] and semantic memory (timed generation of animal names in 60 seconds; category fluency).[35] Finally, executive functioning was measured using set shifting tasks involving mental manipulation of digits[32] and rapid alternation of numbers or letters and symbols (Trails B and Wechsler Adult Intelligence Scale Digit Symbol).[32,33]

Statin Use

Data on self-reported medication use at each visit were available from the UDS database. The analyses were

restricted to subjects with consistent reporting of statin use at all visits (subjects always using statins (n = 2,029) at all visits or subjects never using statins at any visit (n = 3,309)). These two groups represented 81% of the total population of 6,600; the remainder reported intermittent use of statins. For clarity of presentation, the two groups are referred to as statin users and nonusers. It was felt that this dichotomization provided a cleaner comparison of long-term vs never statin use than including sporadic users and considering statin use as a time-dependent variable.

Statistical Analysis

Longitudinal linear regression analyses were conducted to determine whether there was a difference in cognitive change over time between statin users and nonusers (PROC MIXED, SAS Institute, Inc., Cary, NC). All participants had at least three observations, spaced approximately 1 year apart. Subjects could have varying number of visits. A repeated-measures analysis with a compound symmetry correlation matrix was used, equivalent to an analysis in which subjects are included as a random effect.

Separate models were first run to evaluate the main effects of time (a continuous variable coded 1, 2, 3, 4, 5, 6, corresponding to visit numbers, which are approximately 1 year apart) and statins on cognitive tests (use of time as a continuous variable because time from first visit yielded virtually identical results). These models assessed whether statin users performed better than nonusers on average on cognitive tests over the course of follow-up. Whether cognition in participants using statins worsened over time more rapidly than those not using statins was then explored. To test this, an interaction term between time as a continuous variable and statin use as a dichotomous variable (always use vs never use during follow-up) was added to the main effects model. Graphical representation of the different slopes for change over time between statin and nonstatin users was based on adding the coefficient of the interaction term to the coefficient for the time variable for nonstatin users in the interaction model; the starting point for the cognitive test in the figures was the value of the cognitive outcome at Visit 1.

There were 11 dependent variables (CDR-SOB, MMSE total score, number of seconds to complete Trails A and B, maximum number of correct trials for Digits Forward and Digits Backward, number of story units recalled immediately after hearing a story and after a delay, number of completed pairings within 90 seconds on the Digit Symbol subtest, number of correct responses on the Boston Naming Test, and number of animal names generated in 60 seconds). For Trails A and B, analyses of the original variable and the log-transformed variable were conducted, because the latter satisfied the normality assumption, and the former did not. Results were concordant, and the untransformed results are reported for ease of interpretation.

The CDR-SOB also did not fulfill normality assumptions, because it is not continuous (0, .5, 1 … up to a maximum of 18 in the data), with most data in the lower part of the distribution. CDR-SOB was therefore modeled as a multinomial (ordinal) variable using a proportional odds logistic regression model (SAS PROC GLIMMIX, assuming a multinomial distribution, and a variance component correlation matrix for correlated multiple observations per subject). To compare the fit for this model with that of a linear regression model, the mean square error was calculated, with error defined as the difference between observed and predicted values. The predicted value was defined as the ordinal CDR-SOB category with the highest probability from the model for each subject, and this predicted value was subtracted from the observed and the result squared. This value was summed across all subjects, and the square root was taken. For an analogous procedure in PROC MIXED, "predicted" was defined as the ordinal CDR value closest to the one that the model predicted, and then the procedure was as described above for the GLIMMIX multinomial model. When graphing the predicted CDR-SOB for statin and nonstatin users, the predicted CDR-SOB for each subject with the highest probability from the logistic regression was used, and then these predicted CDR-SOB scores were averaged across all subjects in each group (users vs nonusers).

Variables that could confound the relationship between statin use and cognitive function were entered a priori in all the statistical models. These covariates were age (continuous); race (white, non-white); sex; education (no high school degree, high school degree, >high school); and presence vs absence of self-reported history of baseline diabetes mellitus, hypertension, heart disease (e.g., myocardial infarction, atrial fibrillation, congestive heart failure), stroke or transient ischemic attack, or depression within the last 2 years. A variable for hypertension was also included and was divided into three levels: no history of hypertension (reference), history of hypertension but not current high blood pressure (>80 diastolic or >120 systolic blood pressure), current high blood pressure.

Because 11 tests were conducted for participants with normal cognition at baseline and 11 tests for those with MCI, the threshold *P*-value for declaring significance using a false discovery rate approximation was adjusted such that the threshold *P*-value for determining statistical significance was $\alpha(m + 1)/2\ m$, where α is the original conventional threshold of 0.05, and m is the number of tests. Thus, a threshold *P*-value of .05[(22 + 1)/(2*22)], or .026 was used.[36]

RESULTS

Table 1 shows the demographic and clinical features of participants stratified according to cognitive status at baseline (normal, MCI) and statin use (nonuser, user). As expected, statin users were significantly more likely to report a history of heart disease, diabetes mellitus, hypertension, and stroke. Of those who were cognitively normal at baseline, statin users had a significantly higher (worse) CDR-SOB.

Participants used six different statins: simvastatin (41%), atorvastatin (37%), lovastatin (10%), pravastatin (6%), rosuvastatin (5%), and fluvastatin (1%).

Table 2 shows the coefficients for the main effects for statin use and time (from the main effects model) and their corresponding *P*-values and the coefficient for the interaction between statin use and time (after adding an interaction term to the main effects model) and its corresponding *P*-value. The main effects term for those with

Table 1. Comparison of Baseline Characteristics According to Statin Use

Characteristic	Nonusers	Statin Users	*P*-Value
Normal cognition at baseline, n	2,363	1,224	
Visits, mean ± SD	4.2 ± 1.0	4.0 ± 1.0	<.001
Follow-up time, yrs, mean ± SD	3.4 ± 1.1	3.3 ± 1.1	.004
Baseline values			
Age, mean ± SD	72.6 ± 10.8	72.8 ± 8.17	.64
Education, yrs, mean ± SD	15.5 ± 3.0	15.6 ± 3.03	.33
Male, n (%)	658 (27.8)	547 (44.7)	<.001
White, n (%)	2,001 (84.9)	1,053 (86.0)	.35
Heart disease, n (%)	397 (16.9)	430 (35.4)	<.001
Diabetes mellitus, n (%)	104 (4.41)	212 (17.4)	<.001
Depression, n (%)	377 (16.0)	243 (19.9)	.003
Hypertension, n (%)			
No history of hypertension or current hypertension	1,401 (61.6)	445 (37.6)	<.001
History of hypertension but now controlled	458 (20.1)	425 (35.9)	
With or without history but now uncontrolled	415 (18.2)	314 (26.5)	
First-degree relative with dementia, n (%)	1,126 (55.6)	602 (58.7)	.10
Stroke or transient ischemic attack, n (%)	106 (4.50)	88 (7.22)	<.001
MMSE score, mean ± SD	29.0 ± 1.3	28.9 ± 1.3	.06
Subjects with CDR-SOB score>0, %	10.1	15.0	<.001
MCI at baseline, n		763	
Visits, mean ± SD	3.9 ± 0.9	3.9 ± 0.9	.90
Follow-up time, yrs, mean ± SD	2.9 ± 1.2	2.8 ± 1.1	.15
Baseline values			
Age, mean ± SD	74.3 ± 9.9	73.7 ± 8.3	.15
Education, yrs, mean ± SD	15.0 ± 3.3	15.1 ± 3.3	.52
Male, n (%)	400 (43.6)	417 (54.7)	<.001
White, n (%)	769 (84.0)	614 (80.5)	.06
Heart disease, n (%)	177 (19.5)	303 (40.0)	<.001
Diabetes mellitus, n (%)	58 (6.3)	135 (17.7)	<.001
Depression, n (%)	322 (35.3)	261 (34.3)	.67
Hypertension, n (%)			<.001
No history of hypertension or current hypertension	526 (59.7)	261 (35.7)	
History of hypertension but now controlled	193 (21.9)	255 (34.9)	
With or without history but now uncontrolled	162 (18.4)	215 (29.4)	
First-degree relative with dementia, n (%)	426 (55.4)	357 (57.2)	.50
Stroke or transient ischemic attack, n (%)	62 (6.8)	96 (12.7)	<.001
MMSE score, mean ± SD	27.2 ± 2.4	27.4 ± 2.2	.11
Subjects with CDR-SOB score > 0, %	86.9	87.7	.64

SD = standard deviation; MMSE = Mini-Mental State Examination; CDR-SOB = Clinical Dementia Rating Sum of Boxes; MCI = mild cognitive impairment. Unadjusted for other covariates.

normal cognition at baseline show that, across all visits, statin users had significantly better scores on Trails A and better scores on Digit Symbol ($P = .07$). Of those with MCI at baseline, statin users had significantly better scores across all visits for Trails A, Trails B, Digit Symbol, category fluency, and Digits Backward. The main effects term for time indicate the change over time for each test (statin users and nonusers combined). Most tests, as expected, showed significant deterioration over time. Exceptions were the Boston Naming Test in participants with normal cognition and the Logical Memory test for immediate and delayed recall in participants with normal cognition, which showed significant improvement over time. This probably reflects learning how to take the test. This same phenomenon was not seen for subjects with MCI.

Of particular interest is the interaction term between time (or visit number) and statin use, which indicates whether change over time differs in statin users and nonusers. Of those with normal cognition at baseline, there was significantly less deterioration over visits (over time) for statin users on the CDR-SOB and less decline on the MMSE, although the latter fell short of statistical significance after adjusting for multiple comparisons (Figures 1 and 2). There were no significant differences in change over time for those diagnosed with MCI at baseline.

Using an ordinal logistic regression model instead of a linear regression model for the CDR-SOB resulted again in a highly significant interaction term between time and statin use ($P < .001$ vs $P = .006$ for the linear regression model) for those with normal cognition at baseline. This model fit the data better (root mean squared error 0.67) than the linear regression model (root mean squared error 0.82). For participants with MCI at baseline, the ordinal logistic model resulted in a nonsignificant interaction term between time and statin use ($P = .92$).

Supplemental stratified analyses considered the approximately 60% of the population with data on apolipoprotein E (APOE). The data were stratified according to APOE4 status (variant present or absent), and then the interaction term between statins and time was evaluated as

Table 2. Longitudinal Linear Regression Analyses of Cognitive Tests Regressed on Time and Statin Users vs Nonusers[a]

Diagnostic Group and Test	Statin Users vs Nonusers[a]	Change in Outcome Over Time[a]	Interaction Term Between Time and Statin Use
	Regression Coefficient (*P*-Value)		
Normal cognition at baseline			
Trail-Making Test Part A, s	–1.4 (.009)	0.53 (<.001)	–0.12 (.41)
Trail-Making Test Part B, s	–2.6 (.12)	3.05 (<.001)	–0.27 (.53)
Boston Naming, number correct	0.02 (.85)	0.02 (.17)	0.00 (.95)
MMSE score	0.08 (.10)	–0.09 (<.001)	0.04 (.05)
CDR-SOB[b]	–0.03 (.29)	0.08 (<.001)	–0.03 (.006)
Logical Memory immediate recall, number of units	–0.08 (.57)	0.24 (<.001)	–0.04 (.25)
Wechsler Adult Intelligence Scale			
Digit Symbol, number correct	0.79 (.07)	–0.34 (.03)	–0.03 (.67)
Category fluency, number of animals	–0.18 (.35)	–0.19 (<.001)	–0.01 (.82)
Logical Memory delayed recall, number of units	–0.14 (.36)	0.33 (<.001)	–0.03 (.50)
Digits Forward, number of points	–0.02 (.76)	–0.05 (<.001)	0.00 (.92)
Digits Backward, number of points	0.02 (.76)	–0.04 (<.001)	0.01 (.80)
Mild cognitive impairment at baseline			
Trail-Making Test Part A, s	–3.4 (.008)	2.73 (<.001)	–0.23 (.55)
Trail-Making Test Part B, s	–13 (<.001)	9.65 (<.001)	–0.75 (.50)
Boston Naming, number correct	0.24 (.34)	–0.43 (<.001)	0.05 (.43)
MMSE score	0.20 (.22)	–0.62 (<.001)	–0.05 (.73)
CDR-SOB[b]	–0.09 (.44)	0.54 (<.001)	–0.05 (.19)
Logical Memory immediate recall, number of units	0.14 (.55)	–0.26 (<.001)	–0.03 (.60)
WAIS Digit Symbol, number of correct	1.66 (.01)	–1.3 (<.001)	0.14 (.32)
Category fluency, number of animals	0.53 (.04)	–0.53 (<.001)	0.05 (.48)
Logical Memory delayed recall, number of units	–0.07 (.80)	–0.13 (<.001)	–0.04 (.55)
Digit Span Forward, number of points	0.12 (.23)	–0.14 (<.001)	0.02 (.47)
Digit Span Backward, number of points	0.26 (.01)	–0.15 (<.001)	0.02 (.41)

Adjusted for age (continuous), sex, race, education (<high school, high school, >high school), family history (first-degree relative) with dementia, depression in last 2 years (yes/no), and history of heart disease at baseline (yes/no) and diabetes mellitus (yes/no), uncontrolled or controlled hypertension (yes/no), and stroke or transient ischemic attack (yes/no) at baseline. Coefficients for Columns 2 to 3 come from a main effects model; coefficient in Column 4 is from a separate model with an interaction term.

[a]Higher scores are better for Boston Naming, Mini-Mental State Examination (MMSE), Logical Memory, Wechsler Adult Intelligence Scale (WAIS) Digit Symbol, Category Fluency, and Digit Span tests and worse for Trails A and B and Clinical Dementia Rating Sum of Boxes (CDR-SOB).

[b]Statin users with normal cognition at baseline had significantly less deterioration over time in CDR-SOB (higher scores worse) than nonusers, adjusted for multiple comparisons (significance judged with $P < .026$). They also showed less decline in MMSE scores ($P = .05$), which did not reach statistical significance using the criterion $P < .026$. Use of an ordinal logistic regression model as an alternative to linear regression for CDR-SOB resulted in a stronger interaction term ($P < .001$).

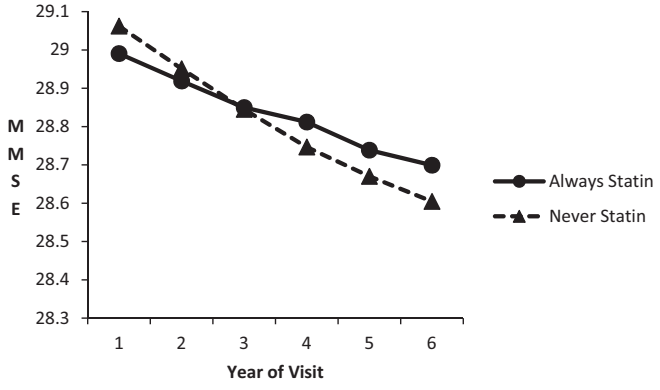

Figure 1. Decline in Mini-Mental State Examination (MMSE) score over annual visits for participants with normal cognition at baseline for statin users and nonusers, from linear regression model.

before. A stronger protective effect of statins against MMSE decline was found in participants with normal cognition at baseline in those without the APOE4 variant, although this protective effect was not significant ($P = .08$ for interaction term between statin use and visit); no suggestion of a protective effect was found for those with the variant ($P = .95$). In participants with MCI, a significant protective effect for MMSE was seen for those who were APOE4 negative ($P = .03$ for the interaction term); for APOE4-positive participants with MCI, the interaction term was in the wrong direction and not significant ($P = .10$). For the CDR-SOB, in individuals with normal cognition, a protective effect of statins against decline was seen for APOE4-positive ($P = .01$) subjects for the interaction term between statin use and visit and APOE4-negative ($P = .01$ for the interaction term) subjects using the ordinal logistic regression model. In individuals with MCI, statins did not affect decline over time regardless of

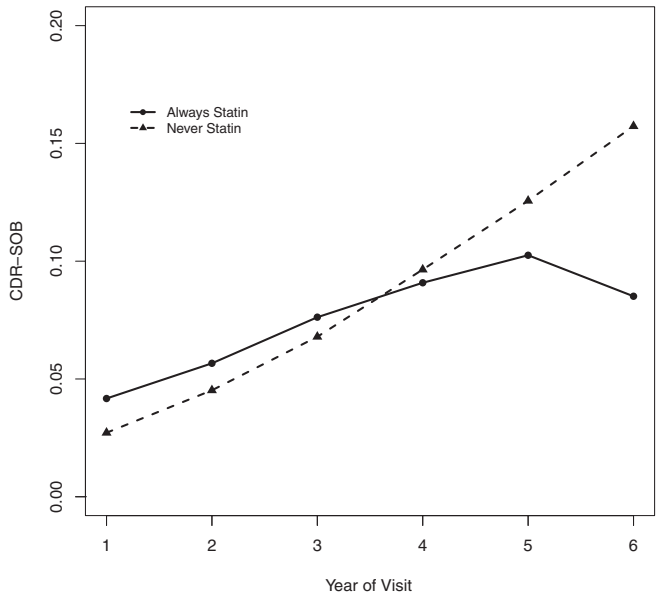

Figure 2. Increase in mean predicted Clinical Dementia Rating Sum of Boxes (CDR-SOB) over annual visits for participants with normal cognition at baseline, statin users vs nonusers, using predicted CDR category from the logistic regression model.

APOE genotype. No multiple comparison adjustments were used in these targeted analyses.

DISCUSSION

These data show that statin users had better function during follow-up than nonusers on cognitive tests evaluating attention (Trails A) and executive function (Trails B, Digit Symbol) after adjustment for other covariates. Furthermore, in those with normal cognition at baseline, overall cognitive deterioration over time (measured using the MMSE and CDR-SOB) was significantly less pronounced in statin users than nonusers. No such protective effect was seen in those who were diagnosed with MCI at baseline, perhaps reflecting that statins exert an effect only before significant deterioration is observed.

A neuroprotective effect in participants with normal cognition was confined to two measures and must therefore be interpreted cautiously, although the findings concur with those of a previous study[4] that also found a protective effect against cognitive decline only in subjects with normal cognition at baseline but not in those with MCI using the 3MSE and the ADAS-Cog. Other statin studies have not separated subjects with normal cognition from those who were mildly impaired at baseline, which may account for differences in findings.

There are a number of hypotheses regarding the way that statins may affect cognitive function. Several statins cross the blood–brain barrier, and animal and cell studies have shown that statins can decrease amyloid-beta production, thereby being neuroprotective.[37,38] Reduction of plasma cholesterol using statins lowers risk of cardiovascular disease and may lead to less cognitive decline, although this is debated. Nevertheless, statins could mediate neuroprotection through a wide variety of other mechanisms, including anti-inflammatory, antioxidant, and antithrombotic actions, in addition to pleiotropic cell biological effects on regulation of gene expression, cytoskeletal function, and membrane traffic.[39]

Strengths of the current study include its large sample size, standardized cognitive testing, reasonably long follow-up, and clinical diagnoses enabling those diagnosed with normal cognition to be differentiated from those with MCI at baseline.

Limitations of the study include the use of multiple outcomes (with the potential of false positives). To this end, the data are reported with and without adjustment for multiple comparisons. A second limitation is the use of observational data rather than randomized assignment of statin use, as in clinical trials. Observational data are subject to confounding, unlike clinical trials, although the major likely confounders were controlled for in the analyses. Furthermore, clinical trial data thus far on cognitive decline have their own limitations, given that they have been restricted to individuals with cardiovascular disease or risk factors for cardiovascular disease or persons with AD. In contrast, the observational data included participants with and without a history of cardiovascular disease and those who had normal cognition at baseline. In this sense, the results may be more generalizable. Furthermore, the available clinical trial data from cardiovascular cohorts consider cognition as a secondary endpoint and use only screening instruments to measure cognition, rather than a comprehensive evaluation of domains such as attention, memory, language, and executive functioning, as in the present study.

The data are also subject to possible selection biases. One type of selection bias is indication bias, which other authors have discussed in the present context.[8] Indication bias could occur if those who were less susceptible to cognitive decline were more likely to be prescribed statins, which might occur for example if statin users were perhaps more health conscious and healthier than other subjects, although information was available on health status, and it was possible to control for differential health status between those taking and not taking statins. Furthermore, those taking statins at baseline were in worse health at baseline (Table 1), with significantly greater prevalence of hypertension, diabetes mellitus, and heart disease. Thus, even if it had not been possible to adjust for differential health status, such worse health would be expected to cause statin uses to show more, not less, cognitive decline.

Another related type of selection bias could occur if different types of subjects were more likely to volunteer for research. For example, those with high levels of comorbidities, and possibly worse cognition, might be less likely to serve as research volunteers and more likely to take statins, although the reverse situation is also possible, in that subjects with comorbidities, more statins, and worse cognition might be more likely to volunteer as research participants. In either case, although such possible biases might affect comparison of cognition between statin users and nonusers across a longitudinal series of tests, they would not be likely to affect a comparison of the longitudinal rate of decline over time between the two groups.

In sum, this study confirms and extends the results that others[4] have observed, demonstrating a modest but positive effect of statin use for those with normal cognition

but not for those with MCI. To confirm these results directly with clinical trials, the study designs would necessarily randomize statin and placebo treatment in individuals with normal cognition and monitor cognitive decline as the primary outcome. Such studies have not been performed but warrant further consideration given the urgent need for treatments to reduce the prevalence of MCI and dementia. Moreover, additional evidence suggesting that statins may protect against cognitive decline should mitigate concerns about widespread use of statins in elderly adults because of possible cognitive side effects of statins that have been reported in rare cases.

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Author Contributions: Steenland: study concept and design, data analysis, writing, interpretation, study supervision. Zhao: data analysis. Goldstein, Levey: writing, interpretation.

Sponsor's Role: NACC provided the data used in this study under cooperative agreement number U01 AG016976.

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