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Increased Atherogenic Lipoproteins Are Associated with Cognitive Impairment: Effects of Statins and Subclinical Atherosclerosis

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Abstract

Hypercholesterolemia increases the risk for dementia. Some studies suggest that statins may protect cognition, but findings are conflicting. Unmeasured confounders, including high-density lipoprotein (HDL) cholesterol or subclinical atherosclerosis, may have influenced prior study outcomes. In older adults participating in a population-based cohort study (n=1711, aged 65–97 years), we investigated the relationships of total and HDL cholesterol levels, statin use, and carotid intima-media thickness (CIMT) with the prevalence of cognitive impairment. In adjusted models, participants in the highest quartile of non-HDL (total minus HDL) cholesterol had an increased odds of cognitive impairment compared to those in the lowest quartile (OR 2.06, 95% CI 1.07-3.98). Statin use was associated with lower odds of cognitive impairment in unadjusted models (OR 0.57, 95% CI 0.36 to 0.89), but this relationship was not significant after adjusting for vascular and lifestyle factors (OR 0.84, 95% CI 0.47–1.49). In this analysis of older adults, increased atherogenic lipoproteins were associated with impaired cognition. Statin use was related to many factors that both negatively and positively affect cognition, but was not associated with better cognitive function. These results suggest that confounding by indication may explain the contradictory findings in studies assessing the association of statins with cognition. Randomized controlled clinical trials and longitudinal studies are necessary to determine if statins protect against cognitive decline.

Keywords

Hypercholesterolemia; aging; brain; atherosclerosis; epidemiology

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INTRODUCTION

Evidence is rapidly increasing that vascular risk factors in midlife are associated with an increased risk of both Alzheimer's disease and vascular dementia decades later. Chronic cerebrovascular dysregulation may be an early trigger for progressive neurodegeneration,[1] a finding which has led to a growing interest in exploring whether strategies used for cardiovascular prevention could also be utilized to delay the onset of cognitive decline. Midlife hypercholesterolemia increases the risk of developing dementia later in life by up to 3-fold.[2–6] Treatment with lipid-lowering agents (LLAs), specifically statins, is associated with up to a 73% reduction in the prevalence of Alzheimer's disease,[7] suggesting a potentially promising role for statins in the prevention of cognitive decline.[6–11] However, not all studies support this association.[12–15] The discrepant findings may be related to the inability of previous studies to account for the degree to which dyslipidemia[7–9, 13, 15] and vascular dysfunction[6–15] were controlled in the presence of statin use. Statin users who still have poorly controlled dyslipidemia and underlying vascular disease may not demonstrate the improvement in cerebral blood flow necessary to interrupt the cascade of neurodegeneration. Thus, it is critical to evaluate whether unmeasured potential confounding factors, such as atherogenic lipid profiles and significant underlying atherosclerosis, explain the discrepancy in results from studies evaluating statins and cognition.

In older participants from a population-based cohort study, we investigated the relationship between atherogenic lipoproteins, statin use, and cognitive impairment after adjusting for the degree of subclinical atherosclerosis as measured by carotid intima-media thickness (CIMT).

METHODS

Study Population

Data from the population-based Beaver Dam Eye Study (BDES) [16] and the Epidemiology of Hearing Loss Study (EHLS) were used in this analysis.[17] For this cohort, a private census of the population of Beaver Dam, Wisconsin was conducted in 1987–1988 to identify all residents in the city or township of Beaver Dam aged 43 to 84 years. This cohort subsequently was invited to participate in the BDES. Of the 5924 eligible, 4926 participated in the baseline BDES examination between 1988–1990. The 4541 study participants who were alive as of March 1, 1993, were eligible for the baseline examination for the EHLS (1993–1995), 3753 of whom participated. This examination occurred at the same time as the 5-year follow-up visit for the BDES (BDES2). Five years later (1998–2000), a follow-up examination was conducted for both the BDES (BDES3, n=2962) and EHLS (EHLS2, n=2800). The primary reason for attrition between EHLS and EHLS2 was death (n=510; 346 died before March 1998 and 164 died after that date, but before their EHLS2 visit). Of the 3407 EHLS participants that were alive as of March 1998, 2800 (82.2%) participated in the 5-year follow-up study, 436 (12.8%) refused, 164 (4.8%) died before being seen, and 7 (0.2%) were lost to follow-up.[18] Participants (n=2800) were younger than living nonparticipants (64.1 vs. 66.4 years, respectively; $p<0.001$). After adjusting for age, living nonparticipants in the 5-year follow-up (n=443) had fewer years of education and were more likely to smoke than participants ($p<0.001$). The age-adjusted prevalence of cardiovascular disease was similar between participants and living nonparticipants.[18] We used data from adults age 65 years and older (n=1711) at EHLS2 for these cross-sectional analyses. The Institutional Review Board of the University of Wisconsin approved these studies. Subjects provided informed consent prior to their participation.

Questionnaire

A questionnaire on medical history, lifestyle factors, and medication use was administered as an interview at the 1998–2000 visit. History of stroke, myocardial infarction (MI), peripheral

vascular disease (PVD) (angioplasty or bypass surgery on legs), or any vascular disease (cardiovascular disease, PVD, transient ischemic attack, angioplasty, endarterectomy) was determined by self-report. The presence of diabetes mellitus was determined by: 1) self-report of physician diagnosis along with use of insulin, oral hypoglycemic agents, or diet to control hyperglycemia, and/ or 2) elevated glycated hemoglobin levels.[19]

Body mass index (BMI) was determined by dividing the weight in kilograms by height in meters squared. Blood pressure was measured with a random zero sphygmomanometer with the average of two measurements used for analysis.[20] Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or the combination of self-reported diagnosis of high blood pressure and use of antihypertensive drugs.[21, 22]

Cognitive Function

Cognitive function was assessed by the Mini-Mental State Examination (MMSE).[23] Data on proxy-reported diagnoses of dementia were also obtained in those adults who were too advanced in their cognitive decline to complete the MMSE. For this analysis, "cognitive impairment" was defined as a MMSE score of <24 or a proxy-reported diagnosis of dementia. Given the large number of cognitively healthy adults in the EHLS cohort, adults scoring ≥15 points (out of 21 possible) on orientation, registration, attention, and delayed recall did not complete the rest of the MMSE. Participants who were administered the abbreviated MMSE were assigned adjusted scores based on percentage correct. Compared to cognitive impairment defined by use of the full MMSE (<24 out of 30 points), this abbreviated method had a sensitivity and specificity for detecting cognitive impairment of 96% and 93%, respectively.[24]

Statin Use

Participants were asked to bring all medications (prescription and over-the-counter) that they were regularly taking to the examination. Medication and vitamin use were recorded and then further assessed using a standardized questionnaire administered by the examiners at each examination.[16, 25] Participants, their physicians, and their pharmacies were called when necessary to verify medication use. Information on duration of use and dose was not obtained.

Laboratory Data

Non-fasting serum total and high-density lipoprotein (HDL) cholesterol levels were measured using enzymatic procedures with standard reagents. Non-HDL cholesterol levels were calculated by subtracting HDL-C from total cholesterol values.[26] Serum glycated hemoglobin was determined using the Abbott IMx glycated hemoglobin test, an ion-capture boronate affinity-binding assay.

B-Mode Ultrasonography

During the examination phase, high-resolution B-mode ultrasound evaluations of atherosclerosis in bilateral segments of the near and far walls of the extracranial carotid arteries were added for participants seen at the field site using a modification of techniques established for the Atherosclerosis Risk in Communities (ARIC) study.[27] A Biosound AU4 ultrasound machine (Biosound Inc., Indianapolis, IN) with a 7.5MHz scanning probe was used to obtain the ultrasound images. Three 1.0-cm segments (the distal portion of the common carotid artery, the carotid bifurcation, and the proximal portion of the internal carotid artery) were scanned bilaterally on both the near and far walls of the vessel for a total of 12 sites. Measurements of CIMT were made by identifying the media-adventitia boundary and the blood-intima boundary over a 1cm length of the artery for the specified site. Readers measured CIMT within the

scanned 1-cm regions. Mean CIMT over these 12 sites was used as a surrogate marker for atherosclerotic burden. CIMT data were available for 1190 of the subjects in this substudy.

Statistical Analyses

The primary endpoints were the impact of cholesterol levels or statin use on odds of cognitive impairment (present or absent), as defined above. Non-HDL-C values (total minus HDL cholesterol levels)[28] were evaluated both as continuous variables and quartiles. Total and HDL cholesterol levels were evaluated as both continuous and categorical variables using the following clinical cut points: total cholesterol >200 vs. ≤200 mg/dL and HDL-C ≥45 vs. <45 mg/dL.[28] Unadjusted associations between cognitive impairment and categorical variables that were potential confounders were also evaluated with the chi-square test for independence, or when appropriate, with the Mantel-Haenszel chi-square test for trend. For continuous covariates, *t*-tests were used to identify potential confounders of the relation between serum cholesterol levels and cognitive impairment.

The preliminary association between cognitive impairment and use of cholesterol-lowering medications was assessed with the chi-square test. As statins are the most commonly prescribed and studied group of LLAs, the analysis was focused on statin vs. non-statin LLAs. Multiple logistic regression models were utilized with a manual backward elimination selection criterion. Statin use was included in the models as: 1) a dichotomous variable (user versus non-user), 2) part of a variable indicating the use of any LLA, or 3) one of three indicator variables (statins that cross the blood-brain barrier [BBB], statins that do not cross the BBB, and non-statin cholesterol-lowering agents, with the reference group being those not taking LLAs). History of cardiovascular disease was modeled as: 1) a composite vascular disease variable (defined above), 2) history of MI, 3) history of stroke, or 4) history of PVD. The Hosmer and Lemeshow Goodness-of-Fit test was used to assess model fit.[29]

Cognitive status was modeled with continuous MMSE scores as the outcome using similar procedures. Least squares regression models were utilized to assess the association between the use of statins (or classes of LLAs) and MMSE score, adjusting for other covariates in the manner described above. All analyses were performed using the SAS System (SAS Institute Inc, Cary, NC). Using a two group t-test with a 0.05 two-sided significance level, this study had at least 80% power to detect a mean difference in total cholesterol levels of 11.5 mg/dL or greater and in HDL-C of 5.0 mg/dL or greater between those who were cognitively impaired and those who were not. In addition, this study had at least 80% power (0.05 two-sided significance level) to detect an odds ratio for cognitive impairment of 0.441 or smaller when the sample sizes are 901 and 251 for non-statin users and statin users, respectively.

RESULTS

Baseline participant characteristics are summarized in Table 1. Univariate analyses showed that current statin use was related to younger mean age, male sex, higher mean years of education, lower mean serum total, HDL, and non-HDL-C levels, presence of diabetes mellitus, higher BMI, regular exercise, history of any vascular disease, and higher mean CIMT level (Table 2). Cognitive impairment was associated with older mean age, male sex, lower mean years of education, lower mean HDL-C, less use of statin drugs, less physical activity, increased history of stroke or any vascular disease, and higher mean CIMT level (Table 2).

Serum Cholesterol Levels and Cognition

When non-HDL-C levels were divided into quartiles, unadjusted analyses showed that those persons in the highest non-HDL-C quartile did not have a statistically significant increase in the odds of cognitive impairment compared to those in the lowest quartile (Table 3). However,

after adjusting for age, sex, education, and mean CIMT, participants in the highest non-HDL-C quartile had a 2-fold increase in the odds of impaired cognition compared to those in the lowest quartile (Table 3). This relationship was maintained after further adjustment for statin use (Table 3). Since participants who were able to come in to the field site for CIMT measurements tended to be healthier than those who did not have CIMT measured, we evaluated whether selection bias accounted for the findings. When the model adjusted for age, sex, and education (Model 2, Table 3) was limited to the 1144 persons with CIMT data included in Model 3 (Table 3), the odds of cognitive impairment (OR 1.97, 95% CI 1.06–3.67) were similar to those noted after adjustment for CIMT (Model 3, Table 3). These findings suggest that the association of high non-HDL cholesterol with cognitive impairment was significant in this healthier subset of older individuals, independent of adjustment for CIMT measures.

In all multivariable models, serum total cholesterol levels were not associated with cognitive impairment or MMSE score even after controlling for factors associated with vascular disease and cognition, including CIMT (all $p > 0.05$, data not shown). Although lower mean serum HDL-C levels were associated with cognitive impairment in unadjusted models, adjusted models did not show an association between HDL-C and cognitive status when evaluated as either a dichotomous or continuous variable (all $p > 4\ 0.05$, data not shown).

Statin Use and Cognition

In unadjusted analyses, use of any LLA or use of statins alone was associated with a lower odds of cognitive impairment (Table 4). Use of non-statin LLAs was not associated with better cognitive function (Table 4). After adjusting for age, the relationship between cognition and use of all LLAs or statins alone was no longer significant (Table 4). Following further adjustment for age, sex, education, and mean CIMT values, cognitive function was not associated with the use of statins, non-statins, or any LLA (Table 4). For the statin and non-statin LLA analyses, results were similar in unadjusted and adjusted analyses using those not taking any LLAs as the comparison group.

Since the effects of statins on cognition may vary by the ability of the medication to cross the BBB, we then performed a subgroup analysis comparing persons taking lipophilic statins (cerivastatin, lovastatin, and simvastatin) that cross the BBB to those taking hydrophilic statins (atorvastatin, fluvastatin, and pravastatin), which do not cross the BBB well. Unadjusted analyses showed that persons using lipophilic statins had lower odds of cognitive impairment compared to non-users (Table 4). Participants using hydrophilic statins, however, had an odds ratio of cognitive impairment that was similar to that of non-users (Table 4). After adjusting for age, sex, and other variables associated with cognition and vascular disease these relationships were no longer statistically significant (Table 4). Similar results were seen in unadjusted and adjusted analyses comparing the two BBB groups of statins to those not using any LLAs.

DISCUSSION

In this population-based cohort of older adults, we found that older individuals with elevated non-HDL-C levels had an increased odds of cognitive impairment compared to those with lower levels. These findings suggest that non-HDL-C levels, a surrogate for apolipoprotein B-containing atherogenic lipoproteins, may be a better indicator of cognitive risk than total cholesterol or HDL-C levels alone. In our analysis, the impact of high non-HDL-C levels on impaired cognition became even greater after adjusting for factors related to survivor bias (age and sex) and subclinical atherosclerosis (CIMT). Since persons having CIMT measured tended to be healthier, however, selection bias limited our ability to comment on the impact of subclinical atherosclerosis on the relationship of non-HDL cholesterol with cognition. Given the widespread use of non-HDL cholesterol levels in risk assessment for cardiovascular disease

prevention, use of this marker in assessing cognitive risk can be readily implemented by clinicians.[28] Since non-HDL-C levels can be measured fairly accurately in a non-fasting state, these findings also may have important implications for the design and analysis of future epidemiological studies.[28]

In unadjusted analyses, we found suggestive evidence that use of statins was associated with better cognition. However, statin use also was associated with numerous conditions that both positively and negatively affect cognition, and after adjusting for these factors, statins were not related to better cognitive function. Confounding by indication may arise when use of a drug (such as a statin) serves as a marker for a clinical characteristic (younger age, higher education, regular exercise) or medical condition (diabetes mellitus, higher BMI, vascular disease, higher mean CIMT level) that triggers the use of the treatment and also increases the risk of the outcome under study (cognitive impairment).[30] The association of statin use with numerous potential confounding conditions in our study suggests that indication bias could have affected prior study results by leading to incomplete adjustment of vascular risk factor burden on cognitive function in statin users vs. non-users. For example, if in one study the most common indication for statin use is established cardiovascular disease and in another study it is treatment of hypercholesterolemia for primary prevention, then participants in these two study cohorts may have significantly different levels of diffuse underlying cerebrovascular dysfunction leading to chronic cerebral hypoperfusion and cognitive decline. Due to confounding by indication and inadequate adjustment for underlying subclinical atherosclerosis, the potential protective effects of statins in these two study cohorts could look vastly different. In support of the idea that prior studies may have inadequately adjusted for underlying vascular risk burden, we found that 62% of persons in the highest quartile of CIMT measures had no self reported vascular disease, suggesting that prior studies relying on self report may not capture the full atherosclerotic burden of participants, and, thus, may have inadequately adjusted for this critical confounding factor. Although we were able to control for degree of underlying atherosclerosis and serum cholesterol levels in our analysis, we did not have data on more dynamic assessments of vascular function, such as endothelial function, which could potentially significantly affect cerebral perfusion and risk of cognitive decline.

While our sample size may have limited our ability to comment on the differential effects of lipophilic vs. hydrophilic statins on cognition, neurobiological evidence supports the idea that the ability of these medications to cross the BBB may impact their cognitive effects.[31, 32] However, use of newer hydrophilic vs. older lipophilic statins may be confounded with other dementia risk factors, most notably age. [33] Thus, future longitudinal analyses evaluating statins and cognition will need to include not only objective measures of vascular dysfunction, but also further investigate the effects of lipophilic vs. hydrophilic statins on cognitive outcomes.

Despite conflicting data from epidemiological studies, animal and clinical data support that statins may have a role in the prevention and/or treatment of dementia.[31] In addition to their role in the prevention of stroke[34] and subsequent vascular dementia, statins reduce β-amyloid levels, the pathologic hallmark of Alzheimer's disease, in the CSF and brains of animals.[31] Statins also reduce inflammation and improve endothelial function – two additional processes that may be closely related to the development of dementia.[35–37] In addition, some clinical trials have shown some mild cognitive benefits from statins in persons with AD[38] and at risk for the disease.[39] While statins may potentially have a role in delaying the progression of dementia once it develops, the high level of underlying neurodegeneration that is present by the time clinical symptoms develop may limit the utility of statins in treating established disease. Many suspect that, if statins are effective, they may be most useful for the primary prevention of dementia. Further prospective clinical trials are needed to clarify the role of statins in the prevention and treatment of cognitive impairment.

Some of the strengths of this analysis include the availability of data on HDL cholesterol, measures of subclinical atherosclerosis, and other vascular and lifestyle factors related to cognition. In addition, we anticipate that the findings presented in this analysis are generalizable to other older adults, since this large subset of older participants from this population-based cohort has mean values of vascular risk factors that are similar to older persons throughout the United States.[22, 40]

There are some limitations to this study. Our study is limited by its cross-sectional design which precludes making a temporal association between elevated serum cholesterol levels and the development of cognitive impairment.[41] Given the relatively few older adults who were prescribed statins at the BDES2/ EHLS visit in 1993–1995, we were not able to comment on the longitudinal effects of statins on incidence of cognitive impairment at the 1998–2000 follow up visit. We also did not have data on dose and duration of statin therapy which could influence cognitive effects. Although the MMSE is a widely-used cognitive screen, its sensitivity to detect cognitive impairment in a general community-based population is limited.[42, 43] To account for this, we analyzed MMSE score as a continuous variable and found similar results to using cognitive impairment as a categorical variable. Full medical, neurological, and neuropsychological evaluations were not available on participants, limiting our ability to diagnose clinical dementia. We also did not have information on apolipoprotein E ε4 (*APOE4*) genotype, a genetic risk factor for late-onset Alzheimer's disease and cardiovascular disease.[44] These issues are all being addressed in an ongoing, prospective longitudinal study of middle-aged adults at increased risk for Alzheimer's disease.[45]

CONCLUSIONS

In summary, high non-HDL cholesterol, a measure of atherogenic lipoproteins, may be a better indicator of cognitive risk in healthy older adults than total cholesterol alone. Statin use was associated with numerous factors that positively and negatively influence cognition, suggesting a high risk for confounding by indication. This indication bias could possibly explain the discrepancy in prior study results evaluating statins and cognition[6–10, 12–14, 46] and the lack of an association with better cognitive function in the present study. Randomized controlled clinical trials and longitudinal studies including more dynamic measures of vascular function and detailed cognitive assessments are needed to clarify if statins protect against neurobiological processes leading to cognitive decline.

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TABLE 1

Baseline Participant Characteristics in 1998–2000 (Adults ≥65 Years, n=1711)

Characteristic	Value
Age, mean (SD), y	76 ± 7 (range 65–97 years)
Women, No. (%)	1043 (61)
Non-Hispanic White, No. (%)	1701 (99)
Education, mean (SD), y	12 ± 3
MMSE score, mean (SD) points out of 30	27 ± 3
Cognitive impairment,* No. (%)	202 (13)
Poor or fair health, No. (%)	310 (20)
Vascular risk factors	
Total cholesterol, mean (SD) mg/dL†	212 ± 42
HDL cholesterol, mean (SD) mg/dL	50 ± 17
Non-HDL cholesterol, mean (SD) mg/dL	161 ± 41
Systolic blood pressure, mean (SD) mm Hg	136 ± 21
Diabetes mellitus, No. (%)	233 (15)
Body mass index, mean (SD) kg/m^2	29 ± 5
Exercise ≥ 3 times / wk, No. (%)	379 (23)
Tobacco use, mean (SD) pack-years	15 ± 26
Mean carotid intima-media thickness, mean (SD) mm‡	0.95 ± 0.24
Medication Use	
Lipid-lowering agents, No. (%)	442 (27)
Statins, No. (%)	319 (20)
Atorvastatin, No. (%)	113 (7)
Simvastatin, No. (%)	110 (7)
Fluvastatin, No. (%)	45 (3)
Pravastatin, No. (%)	40 (2)
Lovastatin, No. (%)	10 (1)
Cerivastatin, No. (%)	1 (<1)
Non-statin lipid-lowering agents, No. (%)	123 (8)

MMSE=Mini-Mental State Exam; HDL=high-density lipoprotein.

*Cognitive impairment = MMSE <24 or proxy-reported dementia.

†To convert to mmol/L multiply by 0.0259.

‡Number of participants with CIMT measures = 1190.

TABLE 2

Participant Characteristics by Statin Use and Cognitive Status

Characteristic	Statin Use			Cognitive Status		
	Statin Users (n=319)	Non-Users (n=1299)	*P*-value (difference between Statin Users and Non-Users)	Cognitive Impairment* (n=202)	No Cognitive Impairment* (n=1404)	*P*-value (difference between those with and without Cognitive Impairment)
Age, mean ± SD, y	73.5 ± 5.5	75.9 ± 7.2	<0.001	80.0 ± 7.1	74.8 ± 6.6	<0.001
Women, No. (%)	167 (52)	811 (62)	0.001	110 (54)	867 (62)	0.047
Education, mean ± SD, y	12.6 ± 2.8	12.0 ± 2.8	<0.001	10.4 ± 2.7	12.3 ± 2.7	<0.001
Non-Hispanic White, No. (%)	317 (99.4)	1291 (99.4)	1.000	202 (100)	1396 (99)	0.285
MMSE score, mean ± SD points out of 30	27.1 ± 2.5	26.8 ± 2.8	0.069	21.1 ± 2.9	27.6 ± 1.7	<0.001
Poor or fair health, No. (%)	57 (18)	253 (20)	0.439	35 (22)	259 (19)	0.379
Total cholesterol, mean ± SD mg/dL†	195 ± 35	216 ± 43	<0.001	210 ± 47	212 ± 41	0.700
HDL cholesterol, mean ± SD mg/dL†	47 ± 14	51 ± 18	<0.001	47 ± 15	51 ± 17	<0.001
Non-HDL cholesterol, mean ± SD mg/dL†	148 ± 33	165 ± 42	<0.001	164 ± 47	161 ± 41	0.412
Current use of statin drug, No. (%)	---	---	---	24 (13)	287 (21)	0.012
Systolic blood pressure, mean ± SD mm Hg	136.0 ± 20.4	135.9 ± 21.7	0.933	137.3 ± 24.5	135.8 ± 20.9	0.408
Diabetes mellitus, No. (%)	64 (21)	169 (13)	0.002	28 (16)	192 (14)	0.536
Body mass index, mean ± SD kg/m^2	30.5 ± 5.4	28.9 ± 5.4	<0.001	28.5 ± 5.1	29.4 ± 5.4	0.060
Exercise ≥ 3 times/ wk, No. (%)	102 (32)	277 (21)	<0.001	18 (10)	351 (26)	<0.001
Tobacco use, mean ± SD pack-years	17.1 ± 26.1	14.2 ± 25.9	0.071	11.7 ± 24.9	15.3 ± 26.3	0.086
History of stroke, No. (%)	14 (4)	67 (5)	0.562	22 (12)	46 (3)	<0.001

Characteristic	Statin Use			Cognitive Status		
	Statin Users (n=319)	Non-Users (n=1299)	*P*-value (difference between Statin Users and Non-Users)	Cognitive Impairment* (n=202)	No Cognitive Impairment* (n=1404)	*P*-value (difference between those with and without Cognitive Impairment)
History of any vascular disease,‡ No. (%)	147 (46)	286 (22)	<0.001	72 (38)	345 (25)	<0.001
Mean carotid intima-media thickness, mean ± SD mm	1.02 ± 0.25	0.93 ± 0.23	<0.001	1.00 ± 0.25	0.950.23	0.019

MMSE = Mini-Mental State Exam; HDL = high-density lipoprotein

*Cognitive impairment = MMSE <24 or proxy-reported dementia.

†To convert to mmol/L multiply by 0.0259.

‡History of any vascular disease includes cardiovascular disease, peripheral vascular disease, transient ischemic attack, angioplasty, or endarterectomy.

TABLE 3

Odds Ratios for Cognitive Impairment by Non-HDL Cholesterol Quartiles

	Unadjusted OR (95% CI) (N=1532)	Model 1* Adjusted OR (95% CI) (N=1532)	Model 2* Adjusted OR (95% CI) (N=1532)	Model 3* Adjusted OR (95% CI) (N=1144)	Model 4* Adjusted OR (95% CI) (N=1124)
Highest Non-HDL Cholesterol Quartile (vs. Lowest)†	1.32 (0.86–2.02)	1.80 (1.14–2.82)	1.49 (0.94–2.39)	2.02 (1.08–3.78)	2.06 (1.07–3.98)

OR=odds ratio; CI=confidence interval; HDL = high-density lipoprotein; CIMT=carotid intima-media thickness.

*Model 1: Adjusted for age and sex. Model 2: Adjusted for age, sex, and education. Model 3: Adjusted for age, sex, education, and mean CIMT. Model 4: Adjusted for age, sex, education, mean CIMT, and statin use.

†Non-HDL-C quartiles were: 1) 44 to 133 mg/dL, 2) 134 to 157 mg/dL, 3) 158 to 186 mg/dL, 4) 187 to 419 mg/dL.

TABLE 4

Odds Ratios for Cognitive Impairment by Lipid-Lowering Agent Use

	Unadjusted OR (95% CI) (N=1552)	Age-Adjusted OR (95% CI) (N=1552)	Age- and Sex-Adjusted OR (95% CI) (N=1552)	Multivariable-Adjusted OR* (95% CI) (N=1150)
All Lipid-Lowering Agents (n=442)				
Yes (vs. No)	0.62 (0.42, 0.90)	0.76 (0.52, 1.13)	0.74 (0.50, 1.09)	0.84 (0.51, 1.38)
All Statins (n=319)				
Yes (vs. No)	0.57 (0.36, 0.89)	0.76 (0.48, 1.21)	0.73 (0.46, 1.16)	0.84 (0.47, 1.49)
Lipophilic Statins (Cross BBB Well, n=121)				
Cerivastatin, Lovastatin, Simvastatin				
Yes (vs. No)	0.45 (0.21, 0.99)	0.58 (0.26, 1.29)	0.55 (0.25, 1.23)	0.56 (0.22, 1.46)
Hydrophilic Statins (Do Not Cross BBB Well, n=198)				
Atorvastatin, Fluvastatin, Pravastatin				
Yes (vs. No)	0.69 (0.41, 1.16)	0.91 (0.53, 1.56)	0.88 (0.51, 1.52)	1.10 (0.56, 2.15)
Non-Statin Lipid-Lowering Agents (n=123)				
Yes (vs. No)	0.88 (0.48, 1.60)	0.85 (0.46, 1.56)	0.83 (0.45, 1.55)	0.91 (0.41, 1.99)

OR=odds ratio; CI=confidence interval; BBB=blood-brain barrier; CIMT=carotid intima-media thickness.

* Adjusting for age, sex, education, and mean CIMT.