Association of statin use with cognitive decline in elderly African Americans

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ABSTRACT

Background: Previously reported associations between statin use and incident dementia or cognitive decline have been inconsistent. We report the results from a 3-year prospective study on the association of statin use on cognitive decline and incident dementia in elderly African Americans.

Methods: A community-based cohort of 1,146 African Americans aged 70 and older living in Indianapolis, Indiana, was evaluated in 2001 and 2004. The instrument used for cognitive assessment was the Community Screening Interview for Dementia (CSI-D). Cognitive decline was defined as CSI-D scores measured at 2001 minus scores at 2004. Measurements of low-density lipoprotein cholesterol (LDL-C) and C-reactive protein (CRP) were obtained from baseline blood samples.

Results: Adjusting for age at baseline, gender, education, and the possession of ApoE $\varepsilon 4$ allele, baseline statin use was associated with less cognitive decline ($p = 0.0177$). There were no significant interactions of statin use when LDL-C and CRP were included. Logistic regression with the four independent variables showed that statin use may be associated with a reduction in incident dementia (OR = 0.32; $p = 0.0673$). Association with cognitive decline was less clear when investigating statin use over time. Significance remained only for those who discontinued prior to follow-up compared to continuous users or users who started after baseline.

Conclusions: The relationship between statin use and cognitive decline is complex and subjected to unknown confounders. This effect may not be associated with the cholesterol lowering or anti-inflammatory action of statins. ***Neurology*® 2007;69:1873–1880**

GLOSSARY

AD = Alzheimer disease; **ANCOVA** = analysis of covariance; **BMI** = body mass index; **CAMDEX** = Cambridge Examination for Mental Disorders of the Elderly informant interview; **CERAD** = Consortium to Establish a Registry for Alzheimer's Disease; **CHIF** = Clinician Home-based Interview to assess Function; **CRP** = C-reactive protein; **CSI-D** = Community Screening Instrument for Dementia; **HDL** = high-density lipoprotein; **HMG-CoA** = 3-hydroxy-3-methylglutaryl-coenzyme A; **LDL-C** = low-density lipoprotein cholesterol; **LLAs** = lipid-lowering agents; **NSAIDs** = nonsteroidal anti-inflammatory drugs.

There is general agreement from both observational and intervention trials that 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also known as statins, protect against cardiovascular-related events.[1] Statin therapy may also reduce the incidence of ischemic strokes.[2] The reported association between statin use and decreased risk of dementia or cognitive decline is less consistent. Results from some studies, observational[3-10] and randomized-controlled,[11] provide evidence of an association while others found no association.[12-14] Statins inhibit cholesterol synthesis, and high serum cholesterol level is a possible risk factor for Alzheimer disease (AD).[15-17] In addition to its lipid-lowering effects in the plasma, studies show that statins lower the level of 24S-hydroxycholesterol, a major product of brain cholesterol metabolism, in patients with AD.[18,19] It is not clear if the health benefits of statins derive solely from their cholesterol-lowering effects. Other biologic mechanisms, commonly termed pleiotropic effects, have

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been reported such as improvement in endothelial function and reduction in oxidative stress,[20,21] that may also reduce cardiovascular events. Statins also reduce the level of the inflammatory marker, C-reactive protein (CRP).[22,23] Because high CRP levels are considered an early marker of cardiovascular disease,[24] studies looking at statin use as preventative therapy have been explored.[25-27] An increased risk for dementia[28,29] or cognitive decline[30] in older persons with high levels of serum CRP have been reported.

In 2001, a community-based cohort of African Americans aged 70 and older living in Indianapolis, IN, was evaluated as part of the Indianapolis-Ibadan Dementia project. This population is particularly interesting because African Americans have a higher overall coronary heart disease mortality rate and a higher prevalence of coronary risk factors than other populations in the United States.[31] In this article we report the results from a 3-year prospective cohort study of the association of statin use on cognitive decline and incident dementia in this elderly African American cohort.

METHODS

Study participants. The Indianapolis Ibadan Dementia Project is an ongoing prospective community-based comparative epidemiologic study of rates and risk factors for age-associated dementia and AD in African Americans living in Indianapolis and Yoruba Nigerians. In 1992, a random sample of African Americans age ≥65 years was assembled; the details of the construction of the original sample were previously reported.[32] In 2001, survivors of the original cohort were interviewed (n = 737) and new participants were enrolled. The new enrollees were drawn from Medicare beneficiaries. After completing compliance procedures with Medicare, the study was given names and addresses of African Americans age ≥70 years living in Indianapolis. Of a total of 7,583 eligible participants, interviewers were able to contact by telephone or home visit 4,433, of whom 1,893 (43%) were enrolled, 2,020 (46%) refused, 369 (8%) were too ill, 100 (2%) were deceased, 54 (1%) had moved to a nursing home, and 14 (0.3%) were not African American. Written informed consent was obtained from study participants. The study was approved by the Institutional Review Board of Indiana University.

Research design. A two-stage study design was followed in 2001 and 2004. During the first stage, all study participants were given the Community Screening Interview for Dementia (CSI-D) as part of a home visit. The second stage consisted of a full clinical diagnostic assessment on a subgroup of the larger sample. Selection into the second stage was based upon scores on the CSI-D. Participants were stratified into performance groups (good, intermediate, and poor) using CSI-D cut points. All of the individuals in the poor performance group were invited to have a clinical assessment; a random sample of 75% of the intermediate group and 2.5% of the good performance group were given a clinical assessment. The details of the research design were previously published.[33]

Cognitive assessment. The instrument used for cognitive assessment was the CSI-D, which was developed for comparative epidemiologic studies of age-associated dementias in different communities. The instrument has demonstrated both good 2-week test retest reliability and inter-rater reliability as well as good validity in detecting dementia in various populations.[34,35] The cognitive assessment portion included items to test the following domains: language (naming, definition, fluency, comprehension–motor response), attention and calculation, memory (short term and long term), orientation (time, place), and praxis–copying. Total cognitive scores range from 0 to 34 with higher scores indicating better cognitive function. For this analysis the cognitive score of the 2001 wave of the study was compared to the cognitive score for the 2004 wave.

Other assessments. In addition to the cognitive assessment, the CSI-D screening process included medical history, simple neurologic tests, a risk factor inventory, smoking and alcohol use, social involvement items, and measurement of height, weight, and blood pressure. Blood pressure was taken three times using Omron digital units; the average of the three readings was used. For this analysis, criteria for hypertension included either current blood pressure reading of systolic ≥140, or diastolic ≥90, or taking antihypertension medication.

Medication use. At the time the cognitive assessment was scheduled the participant was told that the interviewer would need to see all of the medications he or she was currently taking. During the home visit the interviewer recorded the name of the medications from the labels on the bottles, or from a printed list of current medications participants obtained from their physicians. Medications were classified into pharmacologic classes, including the lipid-lowering agents (LLAs). This class included statins (simvastatin, atorvastatin, pravastatin, fluvastatin, cerivastatin, and lovastatin) and non-statin LLAs (gemfibrozil, colestipol, and cholestyramine).

Clinical assessment. The clinical assessment was conducted during a home visit by a physician, or specially trained research nurse, and psychometrician. The assessment included the following: 1) a neuropsychological test battery adapted from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)[36]; 2) a standardized neurologic and physical examination and functional status review, The Clinician Home-based Interview to assess Function (CHIF)[37]; 3) a structured interview with a close relative based on an adaptation of the Cambridge Examination for Mental Disorders of the Elderly informant interview (CAMDEX)[38]; 4) a release form to request medical records.

Diagnosis. A consensus diagnostic conference was held in which all clinical assessment data were reviewed by the clinical team for agreement on diagnosis. Normative values for the neuropsychological battery were developed in a separate study.[39]

Diagnostic criteria. The diagnosis of dementia must have met the criteria of both the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, and the International Classification of Diseases, 10th Revision. If a subject was diagnosed with dementia in 2001, he or she was excluded from the study in 2004.

Blood samples. Blood samples were collected from individuals during the 2001 phase and were drawn in 10-mL (EDTA) Vacutainer tubes. Samples were centrifuged and red blood cells, buffy coat, and plasma were separated. Buffy coat samples were used for extraction of DNA and biochemical analyses were carried out on the plasma.

APOE genotyping. Standard protocols were used for extracting DNA from the buffy coat. Hhal digestion of amplified products was used to determine genotype.[40]

Biomarkers. Cholesterol, triglycerides, and high-density lipoprotein (HDL) levels were determined using commercial kits from Roche Diagnostics (Indianapolis, IN). Low-density lipoprotein cholesterol (LDL-C) levels were calculated from the Friedewald equation. CRP was measured by ELISA using a commercial kit from Diasorin (Stillwater, MN).

Statistical analysis. Cognitive decline was defined as CSI-D scores at 2001 minus CSI-D scores at 2004. *t* Tests and χ^2 tests were used to compare the demographics and baseline characteristics between the statin users and nonusers. Univariate analysis of covariance (ANCOVA) models were used to first identify demographic and baseline characteristics associated with 3-year cognitive decline. For the models, the cognitive decline values were standardized by subtracting the mean and then dividing by the SD of the entire cohort. All variables that met an alpha cut-off level = 0.15 were included in an overall ANCOVA model. Model fitting using backwards selection was then used to identify a final model keeping only those variables that were significant at the alpha = 0.05 level. Using the final model, LDL-C and CRP were each included in separate models as dichotomous independent variables in addition to the interaction with statins. All ANCOVA models were adjusted for age at baseline, education, and gender. To examine statin's effect on incident dementia, a logistic regression model was used with incident dementia as the outcome variable and the variables identified for the cognitive decline model as independent variables. Since the analysis included only those participants who consented to blood samples for DNA, to ensure unbiased results, *t* tests and χ^2 tests were also used to compare participants with and without blood samples on cognitive decline and statin use. Statin use at the 2001 and 2004 waves were combined in a single variable to describe statin use over time. The final ANCOVA model was reanalyzed with statin use over time replacing statin use at 2001.

RESULTS There were 2,519 nondemented individuals evaluated in 2001 with the CSI-D of which 1,808 were re-evaluated in 2004. The 711 participants not re-evaluated were deceased (33.6%), refused (34.2%), too sick (9.4%), or lost for other reasons (22.8%). This analysis was also restricted to the 1,146 participants who provided blood samples for ApoE genotyping. Of the 1,146 participants, 292 (25.5%) were on LLAs at baseline. Breaking down the types of LLAs used, 284 (97.3%) were only on statins, 3 (1.0%) were on both statin and another LLA, and 5 (1.7%) were solely on another LLA. For the analysis, we excluded the five participants who were only on a non-statin LLA. Approximately 41% of statin users were taking simvastatin, 41% atorvastatin, 8% pravastatin, 6% fluvastatin, 2% cerivastatin, and 2% lovastatin. Table 1 shows demographic and baseline characteristics for both statin users and those participants not taking statins (statin nonusers). Level of education, presence of ApoE ε4 allele, and history of smoking were similar in both groups ($p > 0.05$). Baseline statin use was significantly associated with younger age, male sex, hypertension, higher body mass index (BMI), and prevalence of alcohol use, nonsteroidal anti-inflammatory drug use, stroke, diabetes, and heart disease ($p < 0.05$). Baseline statin nonusers were significantly associated with elevated total cholesterol, LDL-C, and CRP levels ($p < 0.05$).

On the standardized cognitive change scores, statin users at baseline had a mean change of −0.14 SD while non-statin users had a mean change of 0.05 SD, a difference of 0.19 SD with statin users showing less cognitive decline than the nonusers ($p = 0.0020$).

Univariate analyses showed that only statin use, possession of an ApoE 4 allele, and hypertension were associated with cognitive decline after adjusting for age, sex, and education ($p < 0.10$). When these variables were included together in an ANCOVA model, hypertension was no longer significant. An interaction between baseline statin use and possession of ApoE ε4 allele was investigated but found not significant and not included in the final model. Results from the final model are shown in table 2. After adjusting for age, gender, education, and the possession of ApoE ε4 allele, baseline statin use was associated with less cognitive decline ($p = 0.0177$). When adjusting for baseline cognitive score, an inverse association between statins and cognitive decline remains ($p = 0.0046$).

A logistic regression model on incident dementia, in 2004 as the outcome using the same independent variables as in the model above, showed that statins may be associated with a reduction in incident dementia (OR = 0.32; $p = 0.0673$). The number of incident dementia cases was 3 (1.2%) for statin users and 29 (3.9%) for participants not taking statins. For this analysis, 32 (2.8%) participants were diagnosed with dementia and 960 (84.1%) participants were either diagnosed nor-

Table 1 Demographics and baseline characteristics both overall and by baseline statin use

	Overall (n = 1,141)	Statin users (n = 287)	Statin nonusers (n = 854)	*p* Value
Age at baseline, y	77.3 ± 5.3	76.4 ± 4.7	77.6 ± 5.5	0.0003
Years of education	11.3 ± 2.6	11.2 ± 2.7	11.3 ± 2.6	0.7536
Female	791 (69.3)	185 (64.5)	606 (71.0)	0.0388
Any ApoE ε4 alleles	390 (34.2)	108 (37.6)	282 (33.0)	0.1543
Baseline cognitive score	31.1 ± 1.7	31.3 ± 1.6	31.0 ± 1.7	0.0564
BMI at baseline	30.9 ± 6.6	32.0 ± 6.6	30.6 ± 6.6	0.0013
Hypertension	1037 (90.9)	278 (96.9)	759 (88.9)	<0.0001
History of smoking	619 (54.5)	160 (55.9)	459 (54.1)	0.5807
History of alcohol use	403 (35.9)	118 (41.8)	285 (33.9)	0.0165
History of stroke	169 (14.9)	58 (20.4)	111 (13.0)	0.0027
History of diabetes	328 (28.9)	126 (44.2)	202 (23.8)	<0.0001
History of heart disease	195 (17.1)	83 (28.9)	112 (13.2)	<0.0001
History of depression	112 (9.9)	27 (9.4)	85 (10.1)	0.7621
Cholesterol >200 mg/dL	387 (34.6)	54 (18.9)	333 (39.9)	<0.0001
LDL-C >130	314 (28.1)	41 (14.4)	273 (32.7)	<0.0001
Human C-reactive protein (>2 mg/L)	813 (76.3)	195 (72.0)	618 (77.8)	0.0493
Use of estrogen (women only)	82 (10.4)	23 (12.4)	59 (9.7)	0.2923
Use of NSAIDs	518 (45.4)	166 (57.8)	352 (41.2)	<0.0001
Use of antiplatelet medication/aspirin	385 (33.7)	143 (49.8)	242 (28.3)	<0.0001

Values are mean ± SD or n (%).
BMI = body mass index; LDL-C = low-density lipoprotein cholesterol; NSAIDs = nonsteroidal anti-inflammatory drugs.

mal by clinical examination or in the good performance group based upon their CSI-D score. The remaining 149 (13.1%) participants, who were in the poor performance category in 2004, were excluded.

When LDL-C and CRP were included in the final model on cognitive decline (tables 3 and 4), there were no interactions with statin use with either variable ($p = 0.7605$ for LDL-C and $p = 0.3216$ for CRP). In both models, however, the main effects for statin use were significant.

Of the 1,808 participants with 3-year follow-up, we compared the 1,146 participants included in the analyses to the 662 participants who were excluded from the analyses due to lack of blood samples. The rates of statin use at 2001 and the magnitude of cognitive decline between the two groups were similar.

We also investigated statin use over time. Of the 287 participants who were statin users in 2001, 212 (73.9%) were still statin users while 72 (25.1%) discontinued using statins during the follow-up wave in 2004. Of the 859 participants who were not using statins in 2001, 120 (14.1%) began using statins by 2004 while 730 (85.5%) still reported no use. The remaining subjects did not provide their medications at 2004. When the final model for cognitive decline used statin use over time instead of statin use at 2001, while both groups of 2001 statin users demonstrated less cognitive decline than statin nonusers, this difference was significant only for the statin users who had discontinued prior to the 2004 wave (table 5). A comparison of the demographic, clinical, biochemical characteristics and statin use of the four types of statin use from 2001 to 2004 found no significant differences between the 72 participants who discontinued use and the 212 participants who continued use, which was the main comparison of interest.

Table 2 Results from final model showing the association of statin use at baseline with 3-year cognitive decline

	Parameter estimate	Standard error	*p* Value
Age at baseline	0.02	0.01	<0.0001
Female	0.02	0.06	0.7489
Years of education	−0.02	0.01	0.1668
Any ApoE ε4 allele	0.15	0.06	0.0149
Use of statins at baseline	−0.16	0.07	0.0177

DISCUSSION The results from our study suggest that the relationship between statin use and cog-

Table 3 Results from final model including the interaction between baseline statin use and LDL-C on 3-year cognitive decline

	Parameter estimate	Standard error	*p* Value*
Age at baseline	0.02	0.01	0.0003
Female	0.01	0.06	0.8269
Years of education	−0.02	0.01	0.1543
Any ApoE ε4 allele	0.16	0.06	0.0110
LDL-C >130 mg/dL	−0.05	0.16	0.7874
Use of statins at baseline	−0.16	0.08	0.0415
Use of statins at baseline and LDL-C interaction	−0.05	0.18	0.7605

*p Values are from the Type III tests from the analysis of covariance model including the interaction of statin use and low-density lipoprotein cholesterol (LDL-C).

nitive decline is complex. In our analysis, baseline statin use was associated with a lower risk of cognitive decline ($p = 0.0177$) in this elderly community-dwelling African American cohort. The strength of the association between baseline statin use and cognitive decline, although small in magnitude, was similar to the strength of the association between the possession of the ApoE ε4 allele and cognitive decline as indicated by the parameter estimates (0.15 for possession of ApoE ε4 allele and −0.16 for baseline statin use) although in the opposite direction. Statin users also had fewer cases of incident dementia than did non-statin users (3 cases [1.2%] in statin users and 29 [3.9%] cases in non-statin users,) but these differences did not quite reach significance. It is noteworthy that 25% of elderly African Americans in this cohort of the study were using statins in 2001 as compared to 5% of statin use in 1997 in our original cohort.

However, when we incorporated statin use over time into our model, the association between cognitive decline and statin use became less certain. Now the significance of the overall association between any statin use and cognitive decline compared to nonusers is nonsignificant. This is perhaps not surprising because now statin users include three groups: statin use at both baseline and follow-up (n = 212), statin use only at baseline (n = 72), and statin use only at follow-up (n = 120). What is surprising and puzzling is that when the three groups of statin users are compared separately to the non-statin users at either wave, a significant inverse association for cognitive decline was seen only in the group that was using statins at baseline but had discontinued use at follow-up. If statin use was clearly associated with a reduction in cognitive decline it might have been anticipated that continuous statin use would produce the greatest effect.

Results from other observational studies exploring the association of statins with cognitive decline have been inconsistent. Previous articles have reported a significant association with baseline statin use and cognitive decline[10] or dementia[3-9] similar to ours. However, there are at least three major studies that have reported no association between baseline statin use and incident dementia.[12-14] The reason for these discrepant results is not clear, but could be related to the differences between the population characteristics of these studies and our study. Our cohort was exclusively African Americans and we reported 25% of statin use. Statin use was 6.3% in the Cache County Study,[14] 16.6% in the Adult Changes in Thought Study,[12] and approximately 9% (calculated in patient-years) in the Cardiovascular Health Study,[13] perhaps making it more likely that statin effects could be detected in our cohort. In addition, our African American cohort had higher rates of comorbid illnesses such as hypertension and diabetes than were reported in the other studies.

Several studies have explored possible explanations for the discrepancies in reported results. The Cache County investigators for example found a significant association between statin use and dementia in cross-sectional analysis but not in their longitudinal, prospective analysis. They concluded, as have other investigators, that it is likely that the apparent beneficial effects of statins can be explained by lifestyle or socioeconomic confounders. That is, statin use is more likely in better educated and more health conscious individuals.[13,14] In our study, however, there were no differences in education levels between statin users and nonusers and the statin users had higher levels of comorbid illnesses than statin nonusers. These results are similar to those reported from the Canadian Study of Health and

Table 4 Results from final model including the interaction between baseline statin use and C-reactive protein (CRP) on 3-year cognitive decline

	Parameter estimate	Standard error	*p* Value*
Age at baseline	0.02	0.01	0.0005
Female	0.02	0.07	0.7919
Years of education	−0.02	0.01	0.1759
Any ApoE ε4 allele	0.16	0.06	0.0150
CRP >2 mg/L	0.09	0.13	0.8733
Use of statins at baseline	−0.14	0.08	0.0056
Use of statins at baseline and CRP interaction	0.16	0.16	0.3216

*p Values are from the Type III tests from the analysis of covariance model including the interaction of baseline statin use and CRP.

Table 5 Results from analysis of covariance model on cognitive decline by statin use over time after adjusting for age, sex, education, and ApoE ε4

	Parameter estimate	Standard error	*p* Value
Age at baseline	0.02	0.01	<0.0001
Female	0.03	0.06	0.6076
Years of education	−0.02	0.01	0.1708
Any ApoE ε4 allele	0.16	0.06	0.0115
Statin use from 2001 and 2004 waves			
Used at both waves	−0.12	0.08	0.1258
Used only in 2001	−0.28	0.12	0.0217
Used only in 2004	0.04	0.10	0.6765
Not used at either wave	ref	ref	ref

Aging,[7] where statin users reported poorer health (higher BMI, blood pressure, alcohol use, stroke, diabetes, and heart disease) than statin nonusers. Other confounders relating to lifestyle, which were not measured by our study, may be present.

In a few studies the criteria of statin administration have been reported to have influenced its effects on dementia. In contrast to our findings, statin users who discontinued therapy in the Cardiovascular Health Study[13] had an elevated risk for dementia. An explanation for this finding suggested by the authors was that discontinuation of therapy may be a surrogate marker for declining health. In our study individuals who had discontinued statin use on follow-up did not differ from the other statin user groups in any health, demographic, clinical, or biochemical characteristics.

Although the Cache County Study[14] did not show a significant association with statin use and risk of dementia/AD, they did report that there was some reduction in risk with longer statin use. Our study did not collect information on the compliance, duration, or dosage of statin use, thus we could not determine the length of exposure to statins. Therefore it is possible, if perhaps unlikely, that the statin users who had discontinued use at follow-up had in fact longer exposure to statins than the other statin user groups.

Other studies[41-43] have shown an association with chronic statin use and minimal cognitive deterioration and this effect could be reversible with discontinuation of statins. In our study this might explain the cognitive improvement seen in the statin users that discontinued prior to follow-up.

We attempted to explore putative biologic mechanisms for the statin effect on cognition. Previous reports have indicated that reducing lipids[15,16] and controlling inflammation[28,29] may be important pathways in reducing the risk of dementia. We included in our predictive models measurements of lipids (LDL-C) and indicators of inflammation (CRP). However, there were no interactions between LDL-C or CRP and statin use in our model using baseline measurements for cognitive decline. In this model, statin use remained significantly associated with cognitive decline. These results suggest that neither the lipid-lowering nor the anti-inflammatory actions of statins explain the effect on cognitive decline observed in this analysis. The Cardiovascular Health Study[10] also came to this same conclusion that the effects of statins on cognitive decline could not be explained by their lipid-lowering effects. It may be that some of the other mechanisms of statins, e.g., its antioxidant effects[21] or its protective effect on endothelial dysfunction,[20] may be implicated. We intend to explore these possibilities in future studies.

This study has a number of additional limitations. Unlike the Cardiovascular Health Study,[10] our study design used only two points (baseline and 3-year follow-up) to estimate cognitive decline.[44] We did not measure overall blood glucose (HbA1C) or blood pressure control, which are markers to assess vascular disease that could contribute to cognitive decline. Blood samples were not obtained on 662 participants. However, statin use and cognitive decline were similar between the 1,146 participants included in these analyses and those 662 participants. Our cohort was entirely African American with a high prevalence of vascular risk factors making their generalizability to other populations with lower vascular risk uncertain.

Statin use plays an important role in the prevention of cardiovascular disease. In view of the apparent link between cardiovascular risk factors and risk factors for cognitive decline it is possible that they could play a major role also in prevention of dementia. However, given the inconsistency of the results of statin use on cognitive function from observational studies and the complexities involved in interpreting the results of these studies, it is likely that only carefully designed randomized clinical trials of statins will provide definitive answers to their potential role in dementia prevention.

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