Featured Articles

Statin use and the risk of Alzheimer's disease: The MIRAGE Study

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Abstract

Background: The aim of this study was to examine the association between statin use before the onset of Alzheimer's disease (AD) symptoms and risk of having AD, and to explore the potential impact of *APOE g*enotype and race on this association.

Methods: Data were collected through standardized, validated questionnaires from 895 subjects with probable or definite AD by research criteria, and 1,483 of their nondemented relatives in this family-based, case-control study of AD patients and their relatives enrolled at 15 research centers from 1996 through 2002. To minimize temporal and prescription biases, exposure to statin use within each family was ignored in the one year before the first appearance of AD symptoms in that family's affected member. Associations were estimated using generalized estimating equations for a logistic model, adjusting for age, sex, race, education, history of heart disease, stroke, diabetes, smoking and *APOE* genotype.

Results: Statin use was associated with lowered odds of having AD (adjusted odds ratio [OR], 0.61; 95% confidence interval [CI], 0.38 to 0.98). Nonstatin cholesterol-lowering medications were not associated significantly with lowered odds of having had AD (adjusted OR, 1.7; 95% CI, 0.61 to 5.0).

Conclusions: Statin medications were associated with lowered risk of AD in this population. Neither African-American race, nor the presence of the *APOE* ε4 allele modified the statin-AD association.
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Keywords: Statin; Alzheimer; Dementia; Cholesterol; Lipids; Risk; Epidemiology

1. Introduction

Prominent risk factors for Alzheimer's disease (AD) include age, family history[1,2], female sex [3], lower education [4], depressive symptoms [5], head trauma [6], and the ε4 allele of the gene coding for Apolipoprotein E (ApoE) [7], while potential protective factors may include Vitamin E [8], estrogen [9,10], and anti-inflammatory medications [11].

Statins inhibit 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the rate-limiting step in cholesterol synthesis, and are highly effective in lowering plasma concentrations of low-density lipoprotein (LDL) and total cholesterol. In randomized trials, statins lowered the risk of coronary heart disease and stroke events [12–15] and are the treatment of choice for most hyperlipidemic patients. Several observational studies [16–20] have reported an inverse association between statin use and the risk of AD or dementia, whereas several studies using incidence data have not found this association [21–23]. In this report, we draw on data obtained in the

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MIRAGE Study (Multi-Institutional Research in Alzheimer's Genetic Epidemiology) to present a family-based, case-control study of the association between statin use and odds of AD development that examines statin use before the start of AD symptoms. This study includes a sufficient number of subjects to adjust not only for age, gender, and education, but also for race, history of heart disease, and *APOE* genotype, and to examine whether there was effect modification of this association by *APOE* genotype and race.

2. Methods

The MIRAGE Study is a National Institutes of Health (NIH)-funded multicenter study of genetic and environmental risk factors for AD that collected information on patients with AD and their first-degree relatives between May 1991 and May 2002 at 15 separate academic research centers. The details of MIRAGE Study data collection procedures, protocols for obtaining family histories, and reports showing the validity studies of the MIRAGE questionnaires have been published elsewhere [1,2,24,25].

2.1. Subjects and data collection

The starting point for recruitment of MIRAGE Study families is the proband: a living individual with probable AD or a recently deceased individual with definite AD verified by brain autopsy and specific neuropathologic criteria. The designation of "probable AD" follows NINCDS-ADRDA criteria, requiring progressive decline in memory and at least one other specific cognitive function, clinical examination, and documentation of mental status testing without systemic or other brain diseases that could account for the dementia [26]. The family's best estimate of the date of the proband's first AD symptoms was carefully solicited through multiple semistructured questions. Probands were recruited at each of the MIRAGE sites through research registries and specialized memory clinics. After obtaining informed consent from nondemented persons and a combination of consent or assent, along with informed consent by proxy on living demented subjects, questions eliciting demographic data and information about presumptive risk factors for AD were obtained using standardized MIRAGE questionnaires. Questions about the use of cholesterol-lowering medication were added to the questionnaire in 1996, and the data presented in this report were collected from May 1996 through May 2002. Questions about the proband were answered by a surrogate source within the family, typically the spouse or adult offspring. Similar information was sought on nondemented first-degree family members of these probands older than 50 years, starting with at least one sibling (required), additional siblings, spouse, parents, or children (if possible).

In a subset of 1,171 of the 1,486 nondemented family members in this analysis who claimed to be cognitively normal, or were reported by family informants to be de-

mentia free, cognitive status was confirmed to be normal in 1,168 (99.7%) through the administration of the modified Telephone Interview of Cognitive Status (mTICS) [27,28]. Those who did not receive cognitive evaluation were older, more likely to be male, less well educated, and more likely to be African American than those who did, but the two groups were not significantly different in having a history of heart disease or diabetes or in their respective use of statins and nonstatins. Information on both patients and first-degree family members was supplemented where available by multiple informants, medical records including autopsy reports, death certificates, and nursing home records.

To elicit information on prior use of cholesterol-lowering medications, the following question was asked: "Did you ever take cholesterol-lowering medication (eg, Mevacor or Pravachol) on a daily basis for more than six months?" For proxy reporting about a relative with AD, the question substituted "your relative" for "you," For any affirmative answer, a follow-up question asked for the dates at which the medications were first used and the names of all cholesterol-lowering medications that had been used. Historical information about the (largely deceased) parents of probands was excluded from the analysis because statins were not available during most of their lifetimes.

To minimize the potential for both temporal bias (owing to increasing use of statin over the last decade) and prescription bias (owing to physicians unwillingness to offer statins to demented persons) subjects from each family (whether AD cases or nondemented family members) were considered to have been exposed to cholesterol-lowering drugs only if the starting date for statin treatment preceded the earliest report of AD symptoms in the probands by at least one year. Age represented the age of cases and of nondemented relatives on the date of first symptom report. History of heart disease, diabetes, stroke, smoking, and hypertension were each treated as a dichotomous variable.

As shown in Figure 1, there were 967 probands and 1,598 relatives over the age of 50 who were queried about cholesterol-lowering drugs. After exclusions for those subjects who had missing or unsure responses for the name of their cholesterol-lowering medication, did not include a medication start date, or had missing data for the variables age, gender, education, or race, there were 892 probands and 1,486 relatives. Of the 1,486 relatives, three were reported to be demented with the onset of their dementia before to the proband exposure period in that family as defined above. The diagnosis in these three participants was verified by review of medical records as having probable or definite AD by research criteria [26,29,30], so these were classified with the probands as having AD. Therefore, this analysis includes 895 subjects with AD and 1,483 nondemented relatives of AD patients. *APOE* genotyping with standard polymerase chain reaction (PCR) procedure was available for a subset of 717 persons with AD and 983 nondemented relatives.
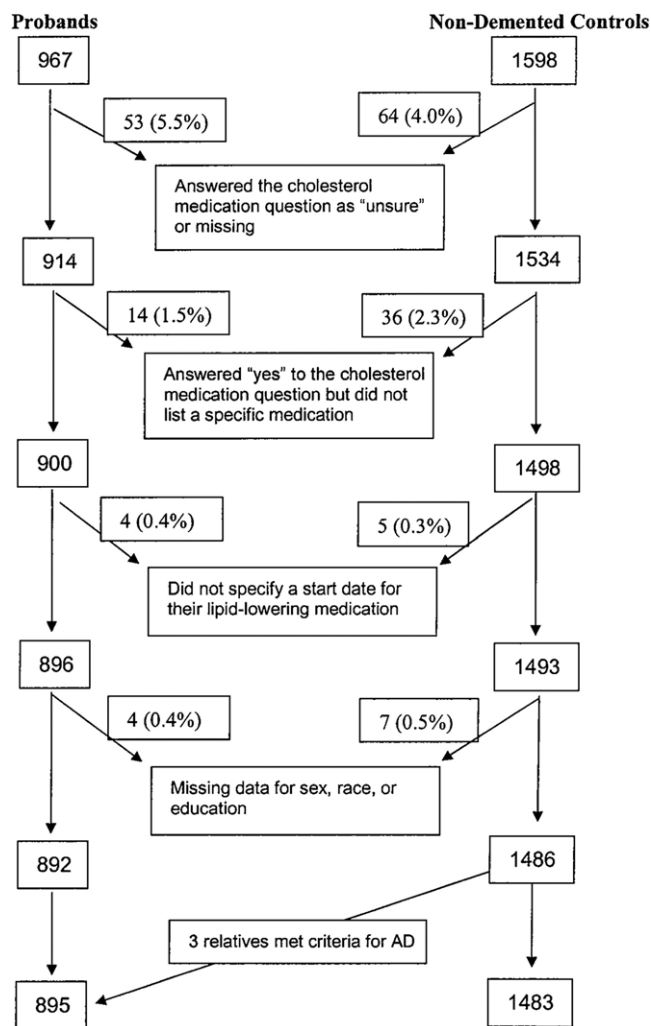
Probands

967

53 (5.5%) → Answered the cholesterol medication question as "unsure" or missing ← 64 (4.0%)

Non-Demented Controls

1598

914 | 1534

14 (1.5%) → Answered "yes" to the cholesterol medication question but did not list a specific medication ← 36 (2.3%)

900 | 1498

4 (0.4%) → Did not specify a start date for their lipid-lowering medication ← 5 (0.3%)

896 | 1493

4 (0.4%) → Missing data for sex, race, or education ← 7 (0.5%)

892 | 1486

3 relatives met criteria for AD

895 | 1483

Fig. 1. Subjects ≥ 50 years (adjusted for family Index Date) completing MIRAGE questionnaire.

2.2. Methods for evaluating potential bias from asymmetrical data collection

Patients with AD are unable to provide accurate personal histories, so medical information about them was, in each case, provided or supplemented by a surrogate, typically a close family member such as a spouse or adult child. When health information was elicited from the nondemented family members, the information was provided by the subject himself or herself in about two thirds of our nondemented subjects. This presents the potential for bias if family members were more or less likely to recall or report certain conditions pertaining to the relative affected with AD in comparison with self-report.

We addressed this potential bias by interviewing multiple family members, reviewing all available medical records, and performing a reliability study to compare the responses of 81 normal individuals with proxy responses from 159 surrogate informants from their families [25]. In this study, the answers to the question about prior use of cholesterol-lowering medications were 100% reliable (in comparison with self-report) when collected from a spouse, daughter, or son; 80% reliable when collected from a sister; and 64% reliable when collected from a brother. We repeated the analysis reported in this report with and without surrogate information from brothers.

2.3. Statistical analysis

Descriptive statistics were calculated for those with AD and their nondemented relatives. To examine whether the background covariates (Table 1) differed in these two groups, we used generalized estimating equations (GEE) with only the corresponding covariate as an independent measure, thereby accounting for familial correlations that might be reflected in these measures.

Table 1
Characteristics of AD patients and nondemented family members

Characteristic	AD (n = 895)	Nondemented Family Members (n = 1483)	Age-Adjusted Percent AD	Age-Adjusted Percent Non-Demented	p Value*
Mean Age (SD)	70.0 (8.2)	65.2 (8.8)			<0.0001
Sex (% male)	333 (37.2)	586 (39.5)	40.1	38.8	0.327
Greater than HS Ed (%)	665 (74.3)	1196 (80.7)	79.8	76.4	<0.0001
African American (%)	241 (26.9)	306 (20.6)	25.0	20.9	<0.0001
History of Heart disease (%)†	174 (19.7)	310 (21.1)	18.3	22.5	0.362
History of diabetes (%)†	92 (10.4)	161 (11.0)	9.3	11.4	0.543
Use of lipid-lowering med (%)	32 (3.6)	68 (4.6)	3.8	4.8	0.215
Statins‡	23 (2.6)	60 (4.1)	2.6	4.2	0.047
Non-statins‡	9 (1.0)	8 (0.54)	1.2	0.6	0.210
APOE Genotyping					
Blood drawn (%)	717 (80.1)	983 (66.3)	79.7	66.0	<0.0001
Persons with 1 to 2 ε4 alleles (%)§	463 (64.6)	370 (37.6)	64.6	37.6	<0.0001

* Reported p values use General Estimating Equations to account for correlation among observations.

† Based on a subset of subjects for whom these data were available.

‡ Exposure to statins and nonstatins had to precede AD symptom onset by one year or more.

§ Percentages are expressed as a percentage of the group who had blood drawn.

Table 2
Adjusted ORs for exposure to statin and nonstatin lipid-lowering medications with those who reported no use of a cholesterol-lowering medication

Exposure	AD	Nondemented Family Members	Crude OR (95% CI)	Age-Adjusted OR (95% CI)	Adjusted OR* (95% CI)
No lipid medications	863	1,415	1.0	1.0	1.0
Use of statins	23	60	0.63 (0.40 to 0.99)	0.60 (0.37 to 0.97)	0.61 (0.38 to 0.98)
Use of non-statins	9	8	1.8 (0.71 to 4.8)	1.7 (0.60 to 5.0)	1.7 (0.61 to 5.0)

* Adjusted for age, sex, race, and education.

Adjusted associations were also estimated using GEE with the presence or absence of AD as the dependent variable and statin use as the primary independent variable. Confounding was evaluated by creating models with different combinations of covariables and examining the association between statin use and AD for change. Key variables, such as age, sex, race, and education, were retained in the model even though they did not appear to be confounding.

Initially, we used stratification methods to evaluate whether the association between statin use and AD was comparable across all subgroups. We specifically evaluated whether the association between statin use and AD was similar for those with an APOE $\epsilon 4$ allele and those without in the subset of subjects in whom genotype information was available. In addition to stratification by APOE $\epsilon 4$ status, we formally evaluated these associations in a GEE model (Table 3). To do so, we added an interaction term ($\epsilon 4$ * statin use) to the model. Our analyses also considered the effect of nonstatin cholesterol-lowering medications ($\epsilon 4$ * nonstatin use). Finally, we evaluated whether the association was the same for statins and for nonstatins with a Z statistic that compared the difference between the estimated regression coefficients, weighted by the variance of this difference. We examined the associations among African Americans and European Americans in the same manner. All analyses were performed using SAS version 8.2.

3. Results

Characteristics of the 2,378 subjects are listed in Table 1. AD patients were older than nondemented relatives. AD patients were also less well educated, but history of heart disease and diabetes were not significantly different between groups. Subjects with one or two $\epsilon 4$ alleles were significantly more likely to have AD.

Of the 1,483 nondemented relatives, 60 (4.1%) reported ever using statins compared with 23 (2.6%) of cases (age adjusted $p = 0.047$). Use of nonstatin cholesterol-lowering medications was not significantly different between AD cases (1.0%) and nondemented relatives (0.54%), (age adjusted $p = 0.21$).

The relative risk of AD with prior use of statins and nonstatin cholesterol-lowering medications was estimated by calculating crude, age-adjusted, and multivariate adjusted odds ratios as shown in Table 2. In our planned analysis, after adjustment for age, gender, educational level, and race, subjects who reported prior use of statins had a reduced odds of having had AD with an odds ratio (OR) of 0.61 (95% confidence interval [CI], 0.38 to 0.98). In contrast, there was no significant reduction in odds of having had AD among those with prior use of nonstatin cholesterol-lowering medications (OR, 1.7; 95% CI, 0.61 to 5.0). The association (adjusted for covariates as in Table 2) among European Americans (OR, 0.62; 95% CI, 0.37 to 1.1) was similar to that among African Americans (OR, 0.55; 95% CI, 0.20 to 1.5), and these were not significantly different from each other ($p = 0.83$). Adjustment for history of heart disease, diabetes, stroke, smoking, or hypertension did not change the association between statin use and AD. We did not have information on cholesterol levels of the subjects in our study and could not adjust for this potential confounder.

Table 3
Risk of AD with and without prior use of lipid-lowering medications, stratified by *APOE* genotype

Exposure	AD	Nondemented Family Members	Crude OR (95% CI)	Age-Adjusted OR (95% CI)	Adjusted OR* (95% CI)
Having no $\epsilon 4$ alleles					
No lipid medications	246	589	1.0	1.0	1.0
Use of statins	5	19	0.63 (0.23 to 1.7)	0.55 (0.19 to 1.6)	0.56 (0.19 to 1.7)
Use of nonstatins	3	5	1.4 (0.23 to 3.3)	1.4 (0.28 to 7.5)	1.5 (0.28 to 7.5)
Having at least one $\epsilon 4$ allele					
No lipid medications	444	349	1.0	1.0	1.0
Use of statins	14	19	0.58 (0.30 to 1.1)	0.54 (0.27 to 1.1)	0.55 (0.28 to 1.1)
Use of nonstatins	5	2	2.0 (0.38 to 10.1)	2.1 (0.38 to 11.4)	2.0 (0.39 to 9.9)

* Adjusted for age, sex, ethnicity, and education.

Table 4
Specific statins used by study subjects

	AD (N = 895)	Nondemented (N = 1,483)
Natural statins		
Lovastatin	12	23
Pravastatin	6	8
Simvastatin	1	14
Synthetic statins		
Fluvastatin	0	4
Cerivastatin	1	0
Atorvastatin	3	11

Several post-hoc analyses were conducted because of the possibility of heterogeneity. When surrogate information provided by brothers of probands was excluded from the analysis, the odds ratio was unchanged (OR, 0.61; 95% CI, 0.38 to 0.99). In the subset of 717 AD patients and 983 nondemented relatives for whom *APOE* genotype was available, the results were similar for statins, adjusted for the presence of the ϵ4 allele (adjusted OR, 0.56; 95% CI, 0.31 to 0.99) and nonstatins (adjusted OR, 1.7; 95% CI, 0.54 to 5.1). Evaluation of the potential interaction between statin use and the presence or absence of at least one ϵ4 allele was not significant ($p = 0.98$), and there was no apparent trend toward interaction when the data were stratified by *APOE* genotype (Table 3).

Among those who used statins, the distribution of type of statin used is summarized in Table 4. Of the 83 subjects who reported statin use, 13 (15.7%) reported using more than one statin, and, in these cases, the first-marketed of the statins listed was recorded in Table 4.

4. Discussion

These findings suggests that use of statin medications for at least six months is associated with significantly lowered odds of AD development, adjusting for age, gender, education, and race. Further adjustment for history of heart disease, diabetes, smoking, hypertension, and stroke did not alter the results. No effect modification was observed by *APOE* genotype. This study examined a large number of persons evaluated at AD research centers whose diagnosis was obtained using standardized and validated research criteria. To minimize temporal and prescription biases that could occur in patients with prevalent AD and with conventional censoring of controls, the date of earliest symptom onset was carefully determined by examination of the proband or chart review by an expert clinician. Exposure to statins was not counted in either probands or family members within any given family unless it preceded that date by at least one year. The subjects without dementia were first-degree family members of those subjects with AD, providing some degree of informal matching on age, socioeconomic status, health-seeking behavior, and physician prescribing practices. Most nondemented relatives were

verified to be cognitively intact by administration of a validated telephone cognitive screening measure.

Our subject selection was not representative of AD patients at large because our subjects began as patients at academic medical centers and were then recruited as volunteers in the MIRAGE Study. Statin use will be influenced by other medical concerns such as elevated cholesterol levels and heart disease. Medication use was reported historically and may not be entirely accurate, and "heart disease" was not specified as to type in our questions. Also, our study did not have access to information about cholesterol levels or duration of medication use in our subjects; however, probands and relatives were well balanced with respect to having a history of heart disease and diabetes (Table 1), and adjustment for these did not alter the point estimate of the association between statin use and risk of AD. Although our study has the largest numbers for any case-control study of this association, there were only 547 African Americans, so we cannot exclude the possibility that there was insufficient power to find differences in the statin–AD association by race.

Differential reporting is a potential source of bias in a study that uses self-report on most of the nondemented subjects, yet relies on surrogate respondents for all of the subjects with AD. Asymmetric data collection is difficult to avoid when cases are cognitively impaired but may be more accurate than expected in AD patients where the surrogate historian has a long association with the subject. Nonetheless, we addressed this potential bias by performing an independent reliability study to determine the accuracy of surrogate information on a number of questions, including the same questions used in this report about the use of cholesterol-lowering medications [25]. A study comparing proxy historians for nondemented persons does not perfectly mirror the situation in which proxy historians report on demented individuals. However, our reliability study found excellent concordance for surrogate responses from all categories of relatives except brothers of index cases, and repeating the analyses reported in this report without including AD patients whose information was provided by brothers did not change the results.

These data confirm and extend the results of several other observational studies that found similar associations in smaller numbers of participants [16,17,19]. In one of these, the Canadian Study of Health and Aging, the use of lipid-lowering drugs was associated with lowered risk of AD in subjects younger than 80 years, but not in those 80 or older [19]. However, several community-based prospective studies have been unable to show a clear association between statin use and reduced risk of AD [21–23]. In the Cache County Study, examination of 185 cases of incident dementia (104 with AD), failed to show a protective association; however, the number of outcome events may have been too small to provide adequate statistical power [22]. In another prospective study with 312 incident cases of dementia (216

with probable or possible AD), no association was seen between the use of statins and risk of dementia or AD. However, post-hoc analyses in this study did show statistically insignificant point estimates suggestive of a protective effect of statin use among those whose age at entry to the study was lower than 80 years, and most of the AD patients in our study were younger than age 80 [21].

Randomized controlled trials will be the definitive way to answer this question. Simple cognitive measures administered as part of the MRC/BHF Heart Protection study [31] and the PROSPER trial [32] found no aggregate cognitive benefit at the end of three to five years. A recent randomized controlled trial of 63 evaluable subjects treated with atorvostatin or placebo found trends in the direction of efficacy [33].

Several lines of evidence offer possible biological mechanisms by which statins may confer protection. First, elevations of cholesterol inhibit the release of soluble APP [34,35] and cause overproduction of Aβ by shifting the metabolism of APP from α to β cleavage [36,37], while reduction of cholesterol with statins attenuates β-secretase cleavage of newly synthesized APP27 and inhibits the generation or level of Aβ in hippocampal neurons, cerebrospinal fluid, brain homogenate, and human serum [38–41]. Second, in vivo models of cholesterol-fed rabbits accumulate excess Aβ and ApoE immunoreactivity in their brains, which is cleared by microglia when they are returned to normal diets [42–44], and transgenic mouse models of AD fed high cholesterol diets show increased Aβ concentrations [45,46]. Third, the protein coded by the *APOE* gene is a ligand for lipoprotein receptor binding [47,48], and the ϵ4 allele is associated with higher plasma cholesterol levels, atherosclerosis, and heart disease[49–58]. Fourth, elevated cholesterol has been associated with increased risk of AD or AD pathology in some epidemiologic studies of humans [59–62] but not in others [63,64]. Fifth, nondemented individuals with severe coronary artery disease (CAD) who come to brain autopsy have more senile plaques and neurofibrillary tangles than those without CAD, and a connection to elevated cholesterol has been inferred from these data by some investigators [65–68]. Sixth, in addition to lowering cholesterol, statins have antioxidant, anti-inflammatory, and anti-atherosclerotic effects [69–73] that might positively affect the pathophysiology or clinical symptomatology of AD. Associations have also been reported between increasing late-life HDL cholesterol levels and neuropathologic markers of AD [74] and between altered cerebrospinal fluid high-density lipoproteins and AD [75].

Our data provide additional evidence that statin use may be associated with lowered risk of AD, and new evidence that this protective effect is not altered by *APOE* genotype or African-American race. Randomized trials of statin medications in patients with AD are underway, and primary prevention trials are under consideration to prospectively explore this association.

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