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Age-varying Association between Statin Use and Incident Alzheimer's Disease

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Abstract and Introduction

Abstract

Objectives: To determine whether risk reduction of statins for Alzheimer's disease (AD) varies by age or presence of apolipoprotein E (APOE) ε4 allele.

Design: A cohort of cognitively intact elderly participants was assessed biennially for dementia and AD.

Setting: Community based.

Participants: Three thousand three hundred ninety-two members of a health maintenance organization (HMO) aged 65 and older and without dementia.

Measurements: Statin use was identified from the HMO pharmacy database, and proportional hazards models were applied with statin use as a time-dependent covariate to assess the association between statins and AD and the modifying effects of age and the APOE ε4 allele.

Results: Over an average of 6.1 years of follow-up of 3,099 participants, 263 participants developed probable AD. The adjusted hazard ratio (aHR) for statin use was 0.62 (95% confidence interval (CI)=0.40–0.97) for AD in models including demographic characteristics and vascular risk factors as covariates. The strength of the association between statins and AD diminished with age (statin-by–age at entry interaction P=.04); the aHR in those younger than 80 was 0.44 (95% CI=0.25–0.78), versus 1.22 (95% CI=0.61–2.42) for aged 80 and older. The interaction term for statin use–by–APOE ε4 was not significant (P=.65).

Conclusion: This enlarged study confirms earlier findings that statin therapy in early old age, but not in late age, may be associated with a lower risk of AD. The relationship between statin use and AD was consistent across APOE genotypes.

Introduction

The effect of statin therapy in reducing the risk of dementia is still controversial. Alzheimer's disease (AD) may start decades before clinical symptoms of dementia. Epidemiological studies have showed that hypertension and hypercholesterolemia in midlife increase the risk of dementia 20 to 30 years later, but similar effects had been evident in late life.[1] An earlier study[2] and the Canadian Study on Health and Aging,[3] which examined the association between statin exposure and risk of AD in large cohorts, suggested that the association between statin use and AD risk may differ according to age at treatment initiation, with an apparent benefit in individuals younger than 80.[2,3] It was hypothesized that statin therapy initiated in relatively early old age, before profound neuropathological changes of AD occur, may delay dementia onset more than therapy initiated later. The Adult Changes in Thought (ACT) cohort, a large community-based longitudinal study of dementia with computerized pharmacy data, was used to investigate the modifying effect of age on the association between statin use and risk of AD. Statins were not widely used before the mid-1990s, when the ACT study began, and were not available for most of the older subjects in their middle age or early old age. Thus, ACT provides a natural laboratory for a study that would otherwise be difficult to conduct because of ethical concerns.

The apolipoprotein E (APOE) ε4 allele is a well-known genetic risk factor for AD.[4] Statins appear to be more beneficial in reducing mortality for those with the APOE ε4 allele than for those without.[5] An earlier exploratory analysis suggested a trend toward AD risk reduction with statin use in younger participants (age at entry 65–79) who carry the APOE ε4 allele but not in younger participants without the allele or in older participants (age at entry ≥80).[2] The

current study addressed two specific hypotheses related to the APOE ε4 allele: APOE ε4 status modifies the association between statin use and risk of probable AD, and statin use reduces the risk of AD in individuals who carry the ε4 allele and therefore who are more vulnerable to the early development of AD.

Methods

Participants

The ACT study has been described elsewhere.[6] Briefly, this community-based prospective cohort study drew participants from Seattle-area members of the Group Health Cooperative (GHC) health maintenance organization. 2,581 participants aged 65 and older were enrolled from 1994 to 1996 (original cohort), and 811 participants were enrolled from 2000 to 2002 (expansion cohort). The criteria for enrollment were a score of 86 or higher out of 100 on the Cognitive Abilities Screening Instrument (CASI, a brief cognitive screen test)[7] or lack of evidence of dementia after additional examination. Demographic characteristics, medical history, and suspected AD risk factors were obtained at time of entry into the study. Expansion cohort participants tended to be slightly older at ACT study entry (mean±standard deviation 75.2±6.1 vs 76.2±6.7), less likely to be white (13% vs 9%), and more likely to be taking statins (29% vs 21%) at a younger age (73.2±7.3 vs 76.3±5.9) than original cohort participants; they were otherwise similar with respect to sex, education, and baseline CASI score.

Exposure Measurement

GHC patients receive prescriptions through the GHC pharmacy at no or nominal cost. The GHC pharmacy database was established in January 1977. Its data files contain information on drug, dosage, quantity dispensed, prescription date, and instructions. Use of statin medications (simvastatin, lovastatin, pravastatin, and atorvastatin) and other lipid-lowering agents (LLAs), including niacin, cholestyramine, colestipol, gemfibrozil, and clofibrate, was defined as at least three filled prescriptions for statins or LLAs of 15 tablets or more. Subjects who did not use statins consistently with average daily dose (cumulative dose/duration <0.5 and total number of refills <12) were considered nonusers. To quantify statin use, an approximation of one "statin equivalent dose" of 10 mg of simvastatin, 20 mg of lovastatin or pravastatin, or 5 mg of atorvastatin was used. Duration of statin use was defined as the time elapsed from the date of first statin prescription to the date of last prescription. APOE genotype was assessed[8] in 2,755 (89%) participants who had at least one follow-up but was unavailable for 344 participants (11%) for reasons such as refusal or laboratory failure in genotyping.

Outcome Measurement

After enrollment, participants were re-screened every 2 years using the CASI. Those whose CASI scores were lower than 86 underwent a standardized dementia diagnostic evaluation that included examination by a study physician and neuropsychological tests. Relevant laboratory tests and neuroimaging studies were performed, or results were obtained from GHC records. Diagnoses were assigned at consensus diagnostic conferences using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria for dementia[9] and National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD.[10] Those with new-onset dementia underwent at least one annual follow-up examination for verification of dementia status and subtype. Dementia onset was defined according to convention as halfway between the date of diagnosis and the date of the prior ACT study examination that showed no dementia. The primary outcome was probable AD according to the NINCDS-ADRDA criteria. Participants who developed other types of dementia were censored at the time of estimated onset.

Statistical Analyses

Data from statin users and nonusers were censored at the estimated onset date of dementia or last observation. Bivariate differences in sample characteristics were assessed using two-sample *t*-tests or chi-square tests. Cox proportional hazards regression models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the risk of probable AD associated with statin use.[11] The time axis was participant age. Statin use was modeled as a time-dependent variable in that participants were not considered users until after the initiation of statin use and were

analyzed as exposed to statins thereafter.

To examine the modifying effects of age and APOE genotype on the association between statin use and risk of AD, interaction terms were estimated for age at entry (categorized into 5-year categories) by statin exposure and for APOE ε4 status (unknown status excluded) by statin exposure. A sensitivity analysis was performed in which all of those with missing APOE genotypes were assigned to ε4 present and another in which all of those with missing APOE genotypes were assigned to ε4 absent. Models stratified according to age at entry (65–69, 70–74, 75–79, 80–84, and ≥85) and according to APOE ε4 status were also constructed to examine the association between statin exposure and AD risk within each group.

To control for confounding according to indication and other potential bias, adjusted HRs (aHRs) for the association between statin use and AD were estimated using stratified Cox models with five-category age at onset and APOE ε4 status as the strata over which separate baseline hazard functions were estimated, where appropriate. Additional model covariates included cohort (original vs expansion cohort), sex, self-reported race or ethnicity (white vs nonwhite), years of education, other LLA use (modeled as time dependent, similar to statins), and study entry characteristics, including CASI score (to control for preclinical dementia), body mass index (BMI), cigarette smoking history, and presence of self-reported comorbid vascular diseases (cardiovascular disease, cerebrovascular disease, diabetes mellitus, and hypertension). Sixty-eight participants (2%) who had missing covariates were excluded from the adjusted analyses. For 2,848 participants (92%) who had total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) measurement available through a computerized laboratory database, average TC and HDL-C levels before statin treatment or before entry into study (for nonstatin users) were added as covariates in an additional set of models. Because statin users began treatment an average 1.2 years before study entry, the average time of assessment of untreated cholesterol levels for statin users was close to study entry. Schoenfeld residual plots and statistical tests were used to test the proportional hazards assumption.[12] Results from the Cox models are presented as aHRs and 95% CIs. All statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria).

Results

Of 3,392 enrolled participants, 3,099 (91.4%) had at least one follow-up examination and contributed to the present analyses. Participants who dropped out or died before the first follow-up visit after initial enrollment were slightly older (78 vs 75, $P<.01$), were more likely to be male (46% vs 41%, $P=.05$), and had slightly lower educational attainment (13 vs 14 years of education, $P<.01$) than those remaining in the study. During follow-up, 263 participants developed probable AD. Mean age at onset of AD was 82.9±5.1. The completeness of follow-up rate of 92% was excellent.[13]

Of 3,099 participants, 711 had been exposed to statins, with duration of exposure of 5.4±3.6 years. Statin users were younger, had higher CASI scores at study entry, and were followed longer than nonusers (Table 1). Not surprisingly, statin users had higher rates of self-reported comorbid vascular conditions and history of cigarette smoking, along with higher serum TC, lower HDL-C, and higher BMI; there were no differences in race, education, or presence of APOE ε4 allele between statin users and nonusers.

Table 1. Characteristics of Participants According to Statin Therapy

Characteristic	Statin Users (n=711)	Statin Nonusers (n=2,388)
Age at entry, mean ± SD	74.2 ± 5.5	75.8 ± 6.4*
Age at time of censoring, mean ± SD	80.7 ± 5.4	81.8 ± 6.3*
Duration of follow-up, years, mean ± SD	6.6 ± 3.3	6.0 ± 3.2*
Male, n (%)	355 (50)	901 (38)*
Nonwhite, n (%)	74 (10)	228 (10)

Education, years, mean ± SD	14.1 ± 3.2	14.0 ± 3.1
CASI score at entry, mean ± SD	93.3 ± 4.6	92.8 ± 5.2*
Presence of APOE ε4, n (%)	166 (27)	536 (25)
Comorbid conditions at entry, n (%)		
Cardiovascular disease	315 (44)	293 (12)*
Cerebrovascular disease	92 (13)	221 (9)*
Diabetes mellitus	140 (20)	166 (7)*
Hypertension	357 (50)	845 (36)*
Current cigarette smoking, n (%)	37 (5)	145 (6)
History of cigarette smoking, n (%)	405 (57)	1,211 (51)*
BMI, kg/m^2, mean ± SD	28.5 ± 4.7	27.0 ± 4.8*
TC, mg/dL, mean ± SD	240.3 ± 40.9	227.0 ± 37.0*
HDL-C, mg/dL, mean ± SD	48.9 ± 12.7	56.1 ± 16.0*
Other lipid-lowering agent use, n (%)	211 (30)	133 (6)*

* *P*<.05 using two-sample *t*-test or chi-square between cohorts.
Information missing for Cognitive Abilities Screening Instrument (CASI; range 0–100) (n=1), education (n=3), cardiovascular disease (n=4), cerebrovascular disease (n=3), diabetes mellitus (n=2), hypertension (n=12), body mass index (BMI) (n=49), apolipoprotein E (APOE) ε4 (n=344), total cholesterol (TC) (n=237), and high-density lipoprotein cholesterol (HDL-C) (n=251).
SD=standard deviation.

Table 2 shows participant characteristics according to age and presence of APOE ε4 allele. Older participants were more likely to be female and white; had less education, poorer baseline cognitive performance, and shorter duration of follow-up; and were more likely to develop dementia and AD during the follow-up period than younger participants (<80). Although they were more likely to have comorbid cardiovascular and cerebrovascular disease, older participants had lower BMI and higher serum HDL-C levels and were less likely to smoke and use statins or other LLAs than younger participants. Baseline characteristics were similar in those with and without the APOE ε4 allele except that participants with the APOE ε4 allele were more likely to be female and have higher serum TC levels.

Table 2. Characteristics of Participants According to Age at Study Entry and Apolipoprotein E (APOE) ε4 Status

Characteristic	<80			≥80		
	ε4= (n=553)	ε4– (n=1,526)	Total‡ (n=2,343)	ε4= (n=149)	ε4– (n=527)	Total‡ (n=756)
Age at entry, mean ± SD	72.4 ± 3.8	72.7 ± 3.8	72.6 ± 3.8*	84.0 ± 3.9	84.1 ± 3.5	84.2 ± 3.6
Age at time of censoring, mean ± SD	78.8 ± 4.7†	79.5 ± 4.6	79.2 ± 4.7*	88.3 ± 4.7	88.8 ± 4.1	88.7 ± 4.2
Duration of follow-up, years, mean ± SD	6.4 ± 3.2†	6.8 ± 3.1	6.6 ± 3.2*	4.3 ± 2.7	4.7 ± 2.9	4.5 ± 2.8
Male, n (%)	206 (37.3)†	688 (45.1)	994 (42.4)*	56 (37.6)	184 (34.9)	262 (34.7)

Nonwhite, n (%)	62 (11.2)	151 (9.9)	256 (10.9)*	8 (5.4)	26 (4.9)	46 (6.1)
Education, years, mean ± SD	14.3 ± 3.0	14.2 ± 3.0	14.3 ± 3.0*	13.7 ± 3.0	13.3 ± 3.2	13.3 ± 3.2
CASI score at entry, mean ± SD	93.7 ± 4.5	93.8 ± 4.5	93.6 ± 4.6*	90.3 ± 5.9	91.0 ± 6.0	90.7 ± 5.9
Comorbid conditions at entry, n (%)						
Cardiovascular disease	113 (20.4)	268 (17.6)	433 (18.5)*	37 (25.0)	121 (23.0)	175 (23.2)
Cerebrovascular disease	60 (10.8)	122 (8.0)	215 (9.2)*	20 (13.5)	67 (12.7)	98 (13.0)
Diabetes mellitus	56 (10.1)	168 (11.0)	259 (11.1)*	7 (4.7)	36 (6.8)	47 (6.2)
Hypertension	207(37.4)	574 (37.8)	895 (38.3)	55 (37.2)	215 (41.0)	307 (40.8)
Current cigarette smoking, n (%)	41 (7.4)	101 (6.6)	158 (6.7)*	5 (3.4)	17 (3.2)	24 (3.2)
History of cigarette smoking, n (%)	294 (53.3)	833 (54.6)	1,262 (53.9)*	73 (49.0)	244 (46.3)	354 (46.8)
BMI, kg/m^2, mean ± SD	27.7 ± 5.1	27.6 ± 4.9	27.7 ± 5.0*	26.1 ± 4.2	26.1 ± 4.0	26.1 ± 4.1
Total cholesterol, mg/dL, mean ± SD	235.3 ± 35.6†	229.0 ± 39.7	230.6 ± 38.8	237.1 ± 36.2†	225.9 ± 37.1	229.3 ± 37.3
High-density lipoprotein cholesterol, mg/dL, mean ± SD	53.4 ± 14.7	54.1 ± 15.8	53.9 ± 15.7*	55.3 ± 15.4	55.4 ± 15.1	55.8 ± 15.2
Statin therapy						
Frequency, n (%)	140 (25.3)	379 (24.8)	596 (25.4)*	26 (17.4)	75 (14.2)	115 (15.2)
Daily equivalent dose, mean ± SD	2.1 ± 1.3	2.2 ± 1.4	2.1 ± 2.0	2.0 ± 0.9	2.0 ± 1.0	2.0 ± 0.9
Duration, years, mean ± SD	4.9 ± 3.3	4.8 ± 3.6	4.8 ± 3.5	4.8 ± 3.5	4.4 ± 3.3	4.6 ± 3.4
Other lipid-lowering agent use, n (%)	76 (13.7)	178 (11.7)	292 (12.5)*	9 (6.0)	39 (7.4)	52(6.9)
Dementia, n (%)	105 (19.0)†	141 (9.2)	281 (12.0)*	50 (33.6)†	128 (24.3)	201 (26.6)
Probable Alzheimer's disease, n (%)	65 (11.8)†	72 (4.7)	157 (6.7)*	29 (19.5)†	65 (12.3)	106 (14.0)

Information missing for Cognitive Abilities Screening Instrument (CASI; score range 0–100) (n=1), education (n=3), cardiovascular disease (n=4), cerebrovascular disease (n=3), diabetes mellitus (n=2), hypertension (n=12), and body mass index (BMI) (n=49).

* *P*<.05 for difference between age groups (<80 vs ≥80) in *t*-test or chi-square test.

† *P*<.05 for difference between those with and without ε4 allele.

‡ Includes participants with missing APOE.

SD=standard deviation.

Table 3 presents frequencies of AD and crude and adjusted HRs for probable AD according to statin use for all subjects and within age and APOE genotype groups. The overall aHR for probable AD with statin use was 0.62 (95% CI=0.40–

0.97). There was no significant association between other LLA use and risk of probable AD (aHR=1.23, 95% CI=0.79–1.91). Further adjustment for average TC and HDL-C levels did not change these findings (data not shown).

Table 3. Statin Use and Risk of Probable Alzheimer's Disease According to Age and Apolipoprotein E (APOE) ε4 Status

Characteristic	Number with Probable AD/Person-Years	Hazard Ratio (95% Confidence Interval)	
		Basic Model	Adjusted Model
All subjects	263/18,933	0.69 (0.46–1.02)	0.62 (0.401–0.97)
Age at entry			
<80	157/15,529	0.52 (0.31–0.88)	0.44 (0.25–0.78)
≥80	106/3,404	1.12 (0.61–2.06)	1.22 (0.61–2.42)
APOE ε4 status			
ε4+	94/4,200	0.61 (0.32–1.18)	0.42 (0.20–0.91)
ε4−	137/12,894	0.73 (0.42–1.27)	0.77 (0.42–1.40)
Unknown	32/1,839	0.59 (0.20–1.70)	0.84 (0.22–3.15)

Basic model adjusted for cohort (original vs expansion) only. Adjusted model based on stratified Cox models adjusted for cohort, sex, race, years of education, Cognitive Abilities Screening Instrument score at baseline (range 0–100), comorbid vascular diseases, body mass index, history of cigarette smoking, and other lipid-lowering agent use, with strata defined according to five-category age group (except for models on individual age groups) and APOE ε4 status (except for models of individual APOE ε4 categories). Adjusted model estimates were based on 68 fewer participants because of participants with missing covariates.

The association between statin use and AD varied according to age at entry (statin × 5-year age interaction *P*=.04) in the fully adjusted model. The aHRs for the association between statin use and risk of probable AD decreased as age increased (Figure 1). Statin exposure was associated with lower risk for probable AD in younger study participants (<80 at study entry; aHR=0.44, 95% CI=0.25–0.78, Table 3). Statin exposure was not associated with risk of probable AD in those aged 80 or older (aHR=1.22, 95% CI=0.61–2.42). By contrast, there was no association between exposure to other LLAs and risk of probable AD in the younger (aHR=1.26, 95% CI=0.75–2.13) or the older (aHR=1.33, 95% CI=0.58–3.06) age group.

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Basic model adjusted for cohort (original vs expansion) only. Adjusted model based on stratified Cox models adjusted for cohort, sex, race, years of education, Cognitive Abilities Screening Instrument score at baseline (range 0–100), comorbid vascular diseases, body mass index, history of cigarette smoking, and other lipid-lowering agent use, with strata defined according to five-category age group (except for models on individual age groups) and APOE ε4 status (except for models of individual APOE ε4 categories). Adjusted model estimates were based on 68 fewer participants because of participants with missing covariates.

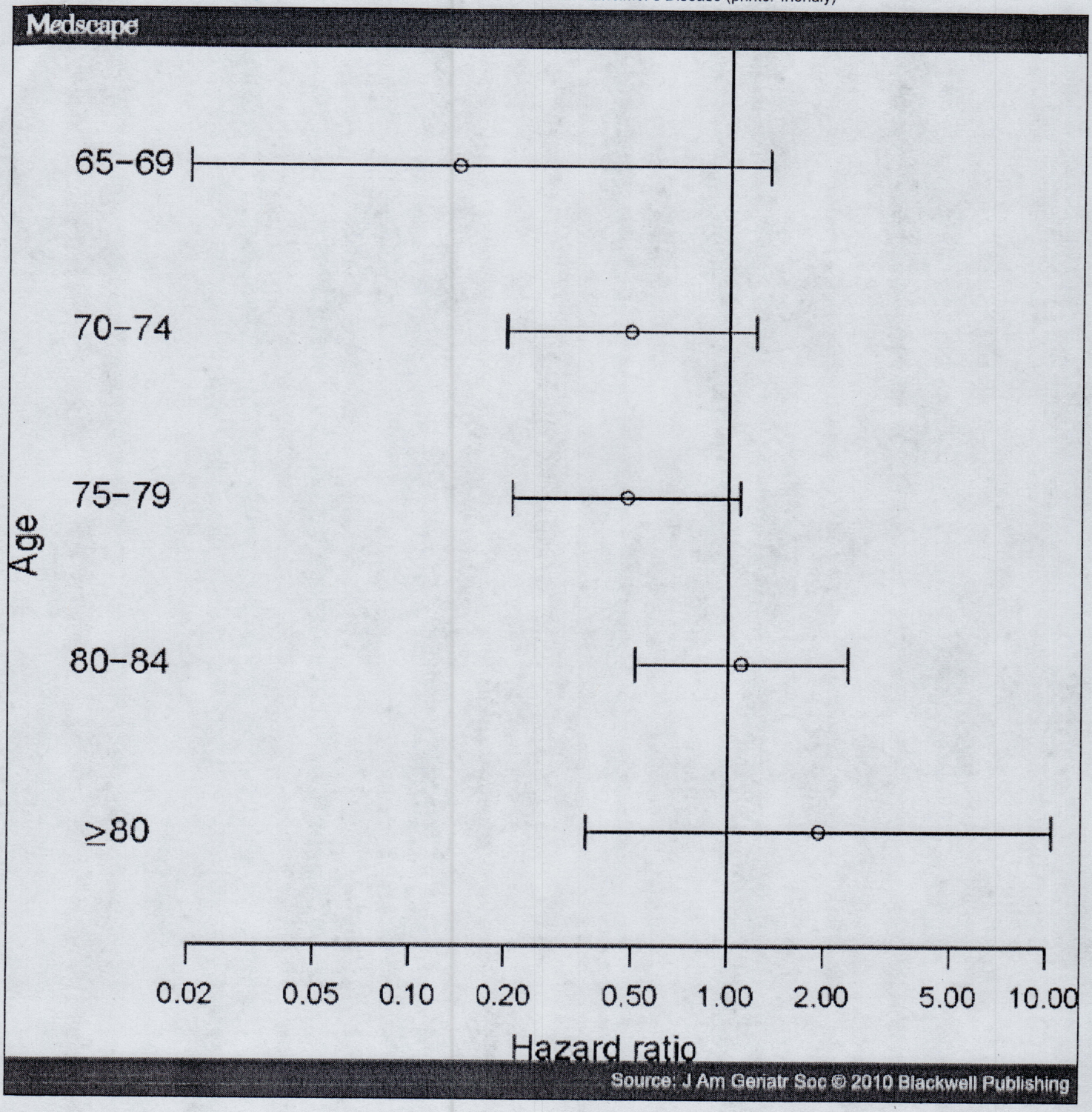

Figure 1. Adjusted hazard ratio and 95% confidence interval of statin therapy for Alzheimer's disease according to age at entry based on Cox models adjusted for cohort, sex, race, years of education, Cognitive Abilities Screening Instrument score at baseline (score range 0–100), comorbid vascular diseases, body mass index, history of cigarette smoking, and other lipid-lowering agent use

Figure 2 presents a HRs according to APOE genotype. The interaction between statin use and APOE ε4 status was not significant (P=.65) in the adjusted stratified Cox model with five-category age at entry defining the strata. This result was consistent whether assigning all of those with missing APOE ε4 status to absent or present as well as in those younger than 80 and aged 80 and older (P>.67). Statin use was associated with a significantly lower risk of AD in those with an ε4 allele (aHR=0.42, 95% CI=0.20–0.91; including those with missing APOE ε4 genotype, aHR=0.43, 95% CI=0.22–0.84) but not in those without (aHR=0.77, 95% CI=0.42–1.40; including missing APOE ε4, aHR=0.82, 95%

CI=0.48–1.41). This pattern was seen in the younger participants but not in older participants, in whom statin use showed no association with AD risk regardless of APOE ε4 status (Figure 2). All of the main findings reported remained unchanged with the addition of the baseline cholesterol measures TC and HDL-C to the model (data not shown).

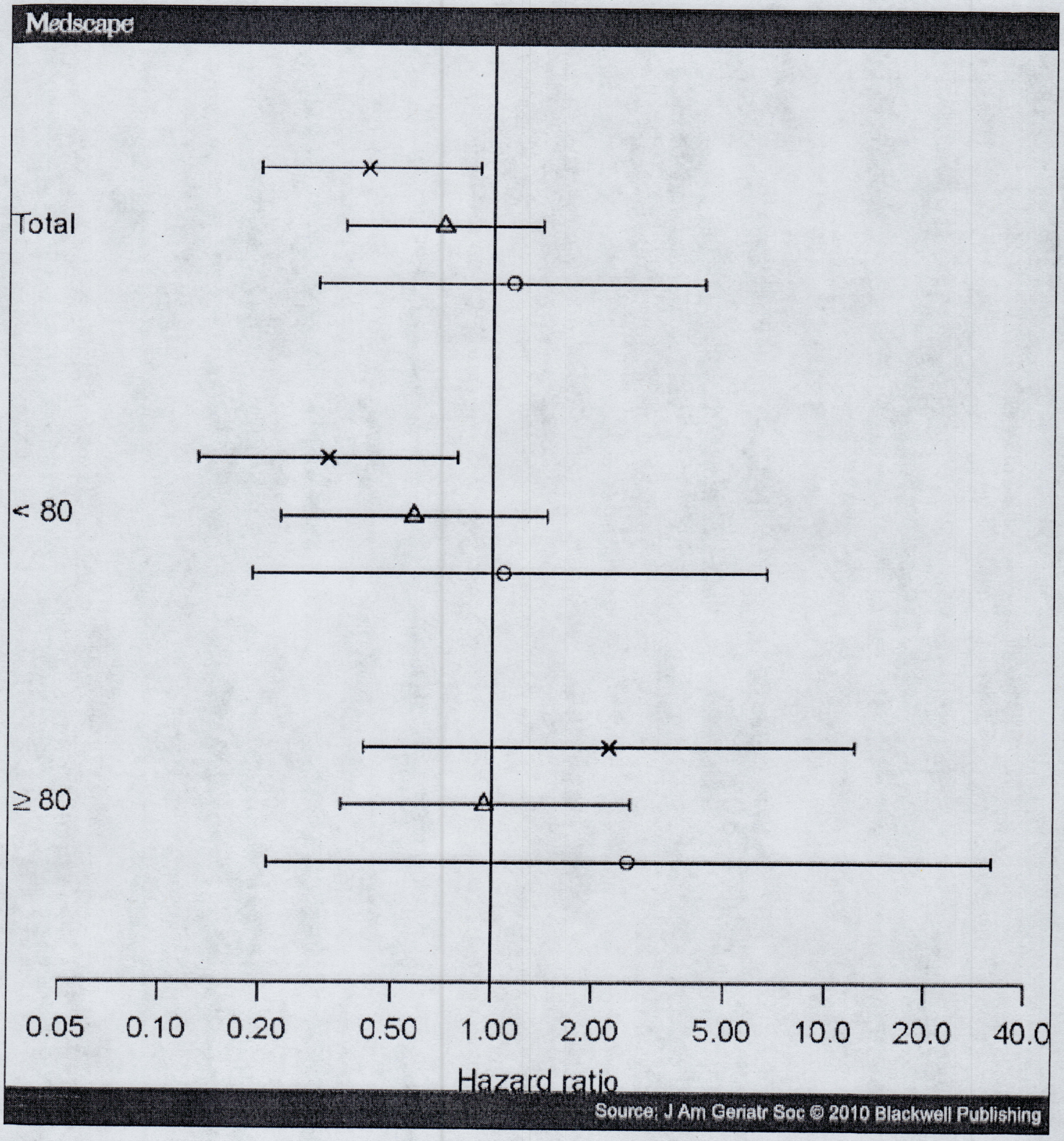

Figure 2. Adjusted hazard ratio and 95% confidence interval of statin therapy for Alzheimer's disease according to age at entry and apolipoprotein E allele ε2/ε2 or ε2/ε3 (circle); ε3/ε3 (triangle); and ε2/ε4, ε3/ε4, or ε4/ε4 ('x') based on stratified Cox models adjusted for cohort, sex, race, years of education, Cognitive Abilities Screening Instrument score at baseline (range 0–100), comorbid vascular diseases, body mass index, history of cigarette smoking, and other lipid-lowering agent use, with strata defined according to five-category age.

Discussion

This study, with an additional 3 years of follow-up of the original cohort and 2,006 person-years from a new cohort enrolled from 2000 to 2002, confirmed earlier findings that the potential protective effect of statins for AD appears to diminish with advancing age. This result is also consistent with the results of the Canadian Study of Health and Aging, which found a lower risk of AD in statin users younger than 80 years but no lower risk in older individuals.[3] Survival bias may explain in part the lack of association between statin use and AD in very old participants. Participants who survived to old age without dying or getting dementia may have biological characteristics that those who did not survive to a similar age without dementia do not have. For example, those with the most-severe cardiovascular disease, diabetes mellitus, or cerebrovascular disease, who were likely to have been at highest risk for dementia, were also more likely to have died from vascular diseases or to have developed dementia at earlier ages and, thus, to have been unavailable or ineligible to be enrolled in the ACT study. If statins protect against AD by lowering the risk of vascular disease, then the association between statins and AD could be weakened in the surviving older participants. Another potential bias may be due to older participants having different indications for statin therapy and receiving a combination of slightly lower dosages with relatively shorter durations of exposure than younger participants, although the difference in duration or average daily dose of statin therapy between the older and younger groups was not statistically significant (Table 2). Alternatively, an age-dependent association between statins and risk of AD might suggest the existence of a critical time window for the use of statins to protect against AD. The neurodegenerative processes of AD begin years, probably decades, before the onset of dementia.[14,15] Although animal and epidemiological studies provide fairly strong evidence of a potential protective effect of statins against AD, randomized controlled clinical trials of statins for treatment of AD and vascular care in patients with AD with cerebrovascular lesions have been largely negative.[16–18] Together, these findings suggest that statin use might prevent or delay pathogenic neurodegenerative process(es) early in the course of AD but may not reverse profound neuronal damage seen later.

Table 2. Characteristics of Participants According to Age at Study Entry and Apolipoprotein E (APOE) ε4 Status

Characteristic	<80			≥80		
	ε4= (n=553)	ε4– (n=1,526)	Total‡ (n=2,343)	ε4= (n=149)	ε4– (n=527)	Total‡ (n=756)
Age at entry, mean ± SD	72.4 ± 3.8	72.7 ± 3.8	72.6 ± 3.8*	84.0 ± 3.9	84.1 ± 3.5	84.2 ± 3.6
Age at time of censoring, mean ± SD	78.8 ± 4.7†	79.5 ± 4.6	79.2 ± 4.7*	88.3 ± 4.7	88.8 ± 4.1	88.7 ± 4.2
Duration of follow-up, years, mean ± SD	6.4 ± 3.2†	6.8 ± 3.1	6.6 ± 3.2*	4.3 ± 2.7	4.7 ± 2.9	4.5 ± 2.8
Male, n (%)	206 (37.3)†	688 (45.1)	994 (42.4)*	56 (37.6)	184 (34.9)	262 (34.7)
Nonwhite, n (%)	62 (11.2)	151 (9.9)	256 (10.9)*	8 (5.4)	26 (4.9)	46 (6.1)
Education, years, mean ± SD	14.3 ± 3.0	14.2 ± 3.0	14.3 ± 3.0*	13.7 ± 3.0	13.3 ± 3.2	13.3 ± 3.2
CASI score at entry, mean ± SD	93.7 ± 4.5	93.8 ± 4.5	93.6 ± 4.6*	90.3 ± 5.9	91.0 ± 6.0	90.7 ± 5.9
Comorbid conditions at entry, n (%)						
Cardiovascular disease	113 (20.4)	268 (17.6)	433 (18.5)*	37 (25.0)	121 (23.0)	175 (23.2)
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History of cigarette smoking, n (%)	294 (53.3)	833 (54.6)	1,262 (53.9)*	73 (49.0)	244 (46.3)	354 (46.8)
BMI, kg/m^2, mean ± SD	27.7 ± 5.1	27.6 ± 4.9	27.7 ± 5.0*	26.1 ± 4.2	26.1 ± 4.0	26.1 ± 4.1
Total cholesterol, mg/dL, mean ± SD	235.3 ± 35.6†	229.0 ± 39.7	230.6 ± 38.8	237.1 ± 36.2†	225.9 ± 37.1	229.3 ± 37.3
High-density lipoprotein cholesterol, mg/dL, mean ± SD	53.4 ± 14.7	54.1 ± 15.8	53.9 ± 15.7*	55.3 ± 15.4	55.4 ± 15.1	55.8 ± 15.2
Statin therapy						
Frequency, n (%)	140 (25.3)	379 (24.8)	596 (25.4)*	26 (17.4)	75 (14.2)	115 (15.2)
Daily equivalent dose, mean ± SD	2.1 ± 1.3	2.2 ± 1.4	2.1 ± 2.0	2.0 ± 0.9	2.0 ± 1.0	2.0 ± 0.9
Duration, years, mean ± SD	4.9 ± 3.3	4.8 ± 3.6	4.8 ± 3.5	4.8 ± 3.5	4.4 ± 3.3	4.6 ± 3.4
Other lipid-lowering agent use, n (%)	76 (13.7)	178 (11.7)	292 (12.5)*	9 (6.0)	39 (7.4)	52(6.9)
Dementia, n (%)	105 (19.0)†	141 (9.2)	281 (12.0)*	50 (33.6)†	128 (24.3)	201 (26.6)
Probable Alzheimer's disease, n (%)	65 (11.8)†	72 (4.7)	157 (6.7)*	29 (19.5)†	65 (12.3)	106 (14.0)

Information missing for Cognitive Abilities Screening Instrument (CASI; score range 0–100) (n=1), education (n=3), cardiovascular disease (n=4), cerebrovascular disease (n=3), diabetes mellitus (n=2), hypertension (n=12), and body mass index (BMI) (n=49).

* *P*<.05 for difference between age groups (<80 vs ≥80) in *t*-test or chi-square test.

† *P*<.05 for difference between those with and without ε4 allele.

‡ Includes participants with missing APOE.

SD=standard deviation.

Whereas previous analyses failed to demonstrate a significant relationship between statin use and incident AD (aHR=0.82, 95% CI=0.46–1.46),[2] analyses in this enlarged cohort that included younger statin users showed that statin exposure was associated with a lower risk of AD (aHR=0.58). The magnitude of this risk reduction is comparable to the recently reported HR of 0.52 (95% CI=0.34–0.80) for dementia and cognitive impairment in the Sacramento Area Latino Study on Aging Study[19] and to the HR of 0.57 (95% CI=0.37–0.90) for AD from the Rotterdam Study,[20] with both of these studies enrolling relatively younger participants. The current positive findings may reflect the addition of the expansion cohort in which participants had a greater opportunity to be treated with statins earlier in life than those in the original ACT cohort because these individuals were younger when statins came on the market.

The lack of a modifying effect of APOE ε4 is consistent with findings in other reports.[21–24] Adjusted HRs and 95% CIs reported from the Multi-Institutional Research in Alzheimer Genetic Epidemiology Study (with ε4: HR=0.55, 95% CI=0.28–1.1; without ε4: HR=0.56, 95% CI=0.19–1.7)[24] and those reported from the Rotterdam Study (with ε4: HR=0.50, 95% CI=0.26–0.94; without ε4: HR=0.61, 95% CI=0.32–1.18)[20] also demonstrated no differences in the association between statin use and risk of AD according to presence of the APOE ε4 allele. Although the association between statins and AD did not differ significantly according to the presence of APOE ε4, a significant association was found between statins and AD in those with an ε4 allele (aHR=0.37, 95% CI=0.17–0.81) but not in those without

(aHR=0.71, 95% CI=0.39–1.29), similar to the Rotterdam results.[20] The absence of a significant association for those without an APOE ε4 allele may reflect the heterogeneous nature of these individuals as a group with respect to the pathogenesis of AD. The aHR of 0.71 (95% CI=0.39–1.29) leaves open the possibility of a weaker association between statins and AD risk that might be demonstrable with a larger sample. For now, it can be concluded that statin use by APOE ε4 carriers, who are particularly vulnerable to AD, may be associated with lower risk of AD. Whether the potential protective effect of statins on the risk of AD occurs in those without ε4 requires further study.

Because the present study was observational in nature, and statin therapy was not randomly assigned, the results are subject to the potential for confounding by indication and other potential sources of bias. For example, participants who used statins were more likely to have multiple cardiovascular risk factors in addition to high cholesterol. Because these vascular risk factors are probably associated with greater risk of AD, the estimates of the association between statin exposure and risk of AD may have been biased toward the null (i.e., with diminished ability to detect a potential protective effect). After adjusting for baseline comorbid vascular disease, the inverse association between statin use and risk of AD appeared to be stronger (Table 3). A similar finding was demonstrated in an earlier study of the relationship between statin use and AD-related neuropathological changes.[25] In that study, the association between statin therapy and less neurofibrillary tangles burden became stronger after adjustment for brain microvascular lesions,[25] but the model adjustments in the current study may not accomplish full control of confounding due to indication. Frailty, variation in the type of statin or dosage, adherence to medication, and other unmeasured factors (such as serum low-density lipoprotein cholesterol) could affect the relationship between statin exposure and risk of AD. Given these considerations, these findings should be interpreted cautiously, especially in their application to clinical practice. Risks and benefits need to be weighed carefully in light of these limitations of observational data.

Table 3. Statin Use and Risk of Probable Alzheimer's Disease According to Age and Apolipoprotein E (APOE) ε4 Status

Characteristic	Number with Probable AD/Person-Years	Hazard Ratio (95% Confidence Interval)	
		Basic Model	Adjusted Model
All subjects	263/18,933	0.69 (0.46–1.02)	0.62 (0.401–0.97)
Age at entry			
<80	157/15,529	0.52 (0.31–0.88)	0.44 (0.25–0.78)
≥80	106/3,404	1.12 (0.61–2.06)	1.22 (0.61–2.42)
APOE ε4 status			
ε4+	94/4,200	0.61 (0.32–1.18)	0.42 (0.20–0.91)
ε4–	137/12,894	0.73 (0.42–1.27)	0.77 (0.42–1.40)
Unknown	32/1,839	0.59 (0.20–1.70)	0.84 (0.22–3.15)

Basic model adjusted for cohort (original vs expansion) only. Adjusted model based on stratified Cox models adjusted for cohort, sex, race, years of education, Cognitive Abilities Screening Instrument score at baseline (range 0–100), comorbid vascular diseases, body mass index, history of cigarette smoking, and other lipid-lowering agent use, with strata defined according to five-category age group (except for models on individual age groups) and APOE ε4 status (except for models of individual APOE ε4 categories). Adjusted model estimates were based on 68 fewer participants because of participants with missing covariates.

Ideally, a randomized controlled trial will eliminate indication bias and provide a more-definitive finding concerning the effect of statins for protection against AD, but such a primary prevention trial faces great challenges because of the current lack of tools to assess disease-modifying effects in the absence of clinical signs of dementia and requires the

recruitment and retention of a large cohort of subjects over a prolonged follow-up period. The present observational study capitalized on pharmacy dispensing exposure data, longer duration of follow-up, and the recent addition of the expansion cohort that includes participants who were exposed to statins at earlier ages. The findings now suggest that statin treatment in early old age may prevent or delay the neurodegenerative process in AD, especially in those who carry the APOE ε4 allele. At what age statin therapy ceases to be beneficial and whether those without the APOE ε4 allele benefit from statin therapy are open and important questions that need to be further investigated. As obstacles to conducting a randomized controlled trial are resolved, future clinical trials should target preclinical stages of disease in middle-aged or early-old-age populations, especially those with the APOE ε4 allele because these individuals may especially benefit from statin therapy.

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Conflict of Interest
The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

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Study concept and design: Li, Kukull, Peskind, and Larson. Acquisition of study participants and data: Bowen, McCormick, Larson, and Schellenberg. Analysis and interpretation of data: Shofer, Rhew, Breitner, and Crane. Preparation of manuscript: Li. Critical review of the manuscript: Breitner, Crane, Kukull, Peskind, Larson, Shofer, Rhew, McCormick, Bowen, and Schellenberg.

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