

# Do Statins Reduce Risk of Incident Dementia and Alzheimer Disease?

## The Cache County Study

Peter P. Zandi, PhD; D. Larry Sparks, PhD; Ara S. Khachaturian, PhD; JoAnn Tschanz, PhD; Maria Norton, PhD; Martin Steinberg, MD; Kathleen A. Welsh-Bohmer, PhD; John C. S. Breitner, MD; for the Cache County Study Investigators

**Background:** Prior reports suggest reduced occurrence of dementia and Alzheimer disease (AD) in statin users, but, to our knowledge, no prospective studies relate statin use and dementia incidence.

**Objective:** To examine the association of statin use with both prevalence and incidence of dementia and AD.

**Design:** Cross-sectional studies of prevalence and incidence and a prospective study of incidence of dementia and AD among 5092 elderly residents (aged 65 years or older) of a single county. Participants were assessed at home in 1995-1997 and again in 1998-2000. A detailed visual inventory of medicines, including statins and other lipid-lowering agents, was collected at both assessments.

**Main Outcome Measures:** Diagnosis of dementia and of AD.

**Results:** From 4895 participants with data sufficient to determine cognitive status, we identified 355 cases of

prevalent dementia (200 with AD) at initial assessment. Statin use was inversely associated with prevalence of dementia (adjusted odds ratio, 0.44; 95% confidence interval, 0.17-0.94). Three years later, we identified 185 cases of incident dementia (104 with AD) among 3308 survivors at risk. Statin use at baseline did not predict incidence of dementia or AD (adjusted hazard ratio for dementia, 1.19; 95% confidence interval, 0.53-2.34; adjusted hazard ratio for AD, 1.19; 95% confidence interval, 0.35-2.96), nor did statin use at follow-up (adjusted odds ratio for dementia, 1.04; 95% confidence interval, 0.56-1.81; adjusted odds ratio for AD, 0.85; 95% confidence interval, 0.32-1.88).

**Conclusions:** Although statin use might be less frequent in those with prevalent dementia, we found no association between statin use and subsequent onset of dementia or AD. Further research is warranted before costly dementia prevention trials with statins are undertaken.

*Arch Gen Psychiatry.* 2005;62:217-224

**T**HE 3-HYDROXY-3-METHYL-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, are increasingly popular drugs for cardiovascular indications, and they might also have protective effects against dementing illness. Statins are effective treatments for hypercholesterolemia, a possible risk factor for both vascular dementia<sup>1</sup> and Alzheimer disease (AD).<sup>2,3</sup> Hypercholesterolemia is associated with vascular disorders, including atherosclerosis, that might confer increased risk for dementia.<sup>4</sup> High cholesterol levels might also influence the pathogenesis in AD more directly. Experiments both in vivo<sup>5,6</sup> and in vitro<sup>7-11</sup> suggest that cholesterol accelerates the production of Alzheimer amyloid (A $\beta$ ) by shifting amyloid precursor protein (APP) metabolism from alpha to beta cleavage products. Statins might in-

hibit this process by lowering the levels of available cholesterol. Alternatively, statins might prevent atherothrombotic events by action on smooth-muscle function, macrophages, and platelets,<sup>12</sup> or they might reduce inflammatory responses thought to be important in AD pathogenesis<sup>13</sup> by inhibiting nitric oxide synthase.<sup>14</sup>

At least 6 observational studies have examined the association between statin use and the risk of dementing illness. A nested case-control study from the United Kingdom-based General Practice Research Database<sup>15</sup> showed reduced risk of dementia among those with prior use of statins but not other lipid-lowering agents. An analysis of cross-sectional data from 3 hospital databases<sup>16</sup> revealed similar findings relating statin use to the prevalence of AD. Cross-sectional studies of incident cases from the Canadian Study of Health and Aging (CSHA)<sup>17</sup> suggested reduced risks of de-

Author Affiliations are listed at the end of this article.

Group Information: A complete list of the members of the Cache County Study Investigators appears in the box on page 223.

mentia and of AD among users of any lipid-lowering agents who were younger than 80 years. A case-control study in a convenience sample of prevalent cases<sup>18</sup> reported an inverse association of dementia and AD with statin use, as did a cross-sectional population-based study of dementia and lipid-lowering agents in general.<sup>19</sup> Finally, cross-sectional analyses from a randomized trial of estrogen replacement therapies for secondary prevention of cardiovascular outcomes<sup>20</sup> suggested that women who were also taking statins (but not other lipid-lowering agents) performed better on a cognitive test and were less likely to experience cognitive symptoms. These convergent findings have stimulated interest in the potential of statins for the prevention of dementia among the elderly population. Except for the UK report, however, none of the previous studies has examined the association of statin use with subsequent onset of dementia.

Three randomized trials of statins have examined cognitive decline as a secondary end point, finding no evidence of a protective effect. In 431 subjects aged 65 years or older randomized to lovastatin or placebo for 6 months, there were no treatment-related differences in performance over time on cognitive function scales.<sup>21</sup> The Heart Protection Study randomized 20536 high-risk older adults (aged 40-80 years) to simvastatin or placebo for approximately 5 years but found no differences in performance on a telephone assessment of cognitive abilities at the participants' final visits.<sup>22</sup> The PROSPER trial randomized 5804 high-risk elderly adults (aged 70-82 years) to pravastatin or placebo for approximately 3 years but found no effect of treatment on cognitive outcomes.<sup>23</sup>

Here we report new evidence from the Cache County Study suggesting that the cross-sectional association of statin use and dementia reported by other studies is not sustained in prospective analyses of incident illness. These and similar recent findings<sup>24</sup> raise doubts about the previously suggested neuroprotective role of statins.

## METHODS

### STUDY POPULATION AND BASIC DESIGN

The Cache County Study is an ongoing investigation of dementing illnesses and their genetic and environmental antecedents among the elderly population of Cache County, Utah.<sup>25,26</sup> The study began in 1995 with the enrollment of 5092 individuals (90% of county residents aged 65 years or older, "wave 1"). We administered a standardized interview to these participants or, when needed, their collateral informants. The interview included items for dementia screening and inquired into several candidate risk factors for dementing illness. We obtained buccal DNA for the determination of genotype at *APOE* from 4962 participants (97%). Approximately 3 years later, we carried out a second wave of data collection using similar methods, excluding participants who had earlier received diagnoses of dementia ("wave 2").

### ASSESSMENT OF STATIN USE AND OTHER RISK FACTORS

At both waves of the study, we obtained a detailed inventory of all over-the-counter and prescription medications in cur-

rent use, as confirmed by a visual inspection of available medication vials. Information from interviews was supplemented by physician or nursing home records. We then categorized participants by use of statins (lovastatin, simvastatin, cerivastatin, atorvastatin, pravastatin, or fluvastatin) as well as other, nonstatin lipid-lowering agents (fibrates, cholestyramine, or nicotinic acid) to compare the specificity of any observed associations. All of these medications were available in the United States only by prescription. Other variables potentially associated with either the risk of dementia or the use of lipid-lowering agents included educational attainment (years of schooling); history of stroke, hypertension, or diabetes (obtained from a self-report of treatment for these conditions); and general health status (from a self-assessment of overall health in the prior week as excellent, good, fair, or poor). Current smoking was assessed with the question, "Do you smoke cigarettes now?" Finally, the *APOE* genotype was represented by the number of  $\epsilon 4$  alleles.

## OUTCOMES ASSESSMENT

We used a multistage screening and assessment protocol to identify and diagnose prevalent cases of dementia at wave 1 and incident cases at wave 2. Procedures have been described in detail elsewhere.<sup>25,26</sup> Briefly, screening for dementia began with an in-person interview that included an adaptation of the Modified Mini-Mental State examination (3MS)<sup>27</sup> or, for those unable to participate, the Informant Questionnaire on Cognitive Decline in the Elderly<sup>28</sup> administered to a collateral informant. Participants who scored beyond predetermined cut-points on these tests (at wave 1,  $<87$  on the 3MS or  $\geq 3.27$  on the Informant Questionnaire; at wave 2,  $<84$  on the 3MS for those aged 80 years or older, or a decline of  $>3$  points from the wave 1 score on the 3MS) were evaluated further by interviewing collateral informants with the Dementia Questionnaire.<sup>29</sup> Dementia Questionnaire interviews were also administered to a 19% stratified validation subsample of high-risk participants (stratified by age, sex, and number of *APOE*  $\epsilon 4$  alleles, with weighting toward strata with older participants with 1 or, especially, 2  $\epsilon 4$  alleles), regardless of their results on the 3MS or Informant Questionnaire. Participants whose screening results suggested cognitive difficulties, as well as all members of the validation subsample, were then examined by specially trained nurses and psychometric technicians. The examination included a brief physical assessment, a detailed chronological history of medical and cognitive symptoms, a structured neurological examination, and a 1-hour battery of neuropsychological tests. A geriatric psychiatrist and neuropsychologist reviewed these data with the field assessment team and assigned working diagnoses of dementia (*DSM-III-R*) or other cognitive syndromes. Living participants with working diagnoses of dementia were then examined in person by a geriatric psychiatrist or neurologist and referred for laboratory studies, including neuroimaging. To substantiate or refine their diagnoses, we reexamined these individuals 18 months after their initial evaluations. A consensus panel of experts in neurology, geriatric psychiatry, neuropsychology, and cognitive neuroscience then reviewed all available data and assigned final diagnoses. Diagnoses of AD followed the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association.<sup>30</sup> Other dementing illnesses were also diagnosed using current research criteria.<sup>25,26</sup> Onset was defined as the year in which a participant unambiguously met diagnostic criteria for dementia. All evaluations and diagnoses were made without knowledge of the participants' use of statins or other risk factors, including *APOE* genotype.

Based on data collected from the fully examined 19% subsample, we estimated that the overall sensitivity of the study's screening and examination protocol was 93% for the detection of prevalent dementia<sup>31</sup> and 89% for the detection of incident dementia.<sup>32</sup> A comparison of dementia diagnoses with neuropathological findings in 54 individuals suggested that the accuracy of our (prevalent and incident) AD differential diagnoses was comparable to typical rates reported from university AD clinics (eg, positive predictive value 90%; data not shown).

## STATISTICAL ANALYSES

We compared characteristics of statin users and nonusers using  $\chi^2$  tests for categorical variables and 2-sample *t* tests for continuous variables as aids to interpretation. We then carried out 3 different analyses with the prevalence and incidence data to examine the relationship between statin use and the risk of dementia or AD. In cross-sectional analyses, we investigated the association at wave 1 of prevalent dementia or AD with statin use. We next carried out prospective analyses that compared the subsequent incidence of dementia or AD among users with that of nonusers of statins at wave 1. Finally, we undertook a second cross-sectional analysis using incidence findings and wave 2 exposure data. The 2 cross-sectional analyses used logistic regression to estimate adjusted odds ratios of the association between statin use and dementia or AD. The prospective analyses used discrete-time survival analysis<sup>33</sup> to estimate adjusted hazard ratios of similar associations. The discrete-time approach, used previously for analyses of pharmacologic risk factors in Cache County,<sup>34-36</sup> considers each person-year under observation as a discrete time interval, so participants at risk enter the analytic pool at the age of their initial wave 1 interviews and are then considered year-by-year until they either develop dementia or undergo their wave 2 screenings. Hazard ratios were estimated from these data using logistic regression models. In each analysis, we estimated bivariable associations, as well as age- and sex-adjusted associations and multivariable-adjusted associations. The full multivariable models controlled for all the variables that were shown in previous analyses<sup>25,26</sup> to be associated with dementing illness. These included age, sex, education, the number of  $\epsilon 4$  alleles at the *APOE* locus, and terms for the interaction of age with the presence of 1 (or 2) *APOE*  $\epsilon 4$  alleles. Because of their association with statin use, we also adjusted for a history of treated hypertension or diabetes. All models were fitted using SAS Version 8 (SAS Institute Inc, Cary, NC), and parameter estimates are reported with 95% profile likelihood confidence intervals. Statistical "significance" required an  $\alpha$  level (2-tailed) of  $P < .05$  or, equivalently, a 95% confidence interval that excluded 1.0.

## RESULTS

Among the 5092 wave 1 respondents, 4895 were assessed sufficiently to identify prevalent dementia ( $n=355$ , including 200 with diagnoses of AD and no other dementing illness) or to determine that they were free of dementia ( $n=4540$ ). Among the latter, 719 were members of the fully examined 19% subsample, while the others showed no evidence of dementia on screening and assessment measures and therefore received no further evaluation. A total of 4864 wave 1 respondents (99.4%) provided complete medication data. Of these, only 292 (6.0%) were taking a statin. Approximately 46% of statin users were taking lovastatin, 22% fluvastatin, 19% prava-

**Table 1. Characteristics of the Elderly Population of Cache County (Utah) in the Prevalence Sample ( $n = 4895$ ) by Statin Use at Wave 1\***

	Nonusers	Users	Missing
Total	4572	292	31
Mean age, y (SD)	75.7 (7.2)	73.0 (5.4)†	80.2 (9.0)†
Mean education, y (SD)	13.2 (2.9)	13.6 (2.9)†	12.5 (3.5)
Mean baseline 3MS score (SD)	89.3 (9.6)	91.3 (6.8)†	81.3 (16.2)†
Women	2624/4572 (57.4)	154/292 (52.7)	19/31 (61.3)
History of stroke	242/4510 (5.4)	15/287 (5.2)	2/30 (6.7)
History of hypertension	1822/4551 (40.0)	165/291 (56.7)†	5/28 (17.9)†
History of diabetes	562/4563 (12.3)	53/292 (18.2)†	3/31 (9.7)
Poor or fair health	1154/4570 (25.3)	68/292 (23.3)	13/31 (41.9)†
Current smoker	108/4561 (2.4)	4/290 (1.4)	0/31 (0.0)
No. of $\epsilon 4$ alleles			
0	3038/4485 (67.7)	191/286 (66.8)	20/29 (69.0)
1	1319/4485 (29.4)	86/286 (30.1)	9/29 (31.0)
2	128/4485 (2.9)	9/286 (3.1)	0

Abbreviation: 3MS, Modified Mini-Mental State examination.

\*Data are reported as number/total (percentage) unless otherwise indicated.

†Difference compared with the group of nonusers is significant at  $P < .05$ ; comparisons made using the *t* test for continuous data and  $\chi^2$  test for categorical data.

statin, and 13% simvastatin. **Table 1** shows demographic and dementia risk factor attributes for the statin users and nonusers at wave 1. Predictably, statin users had a higher prevalence of hypertension and diabetes.

Three years later, as we attempted to follow up the 4540 initially nondemented respondents, 508 had died, and another 724 had moved out of the area, could not be located, or refused participation. Excluding decedents, those lost to follow-up were predictably older (76.2 vs 74.1 mean years of age;  $t=7.81$ ;  $P < .01$ ), less well educated (12.8 vs 13.4 mean years of education;  $t=-5.07$ ;  $P < .01$ ), and had performed less well on their wave 1 3MS (mean score 88.8 vs 91.6;  $t=-10.03$ ;  $P < .01$ ). However, there was no notable association of statin use at baseline and loss to follow-up (7.0% for those lost vs 6.3% for others;  $\chi^2=0.47$ ;  $P=.49$ ).

Among the 3308 remaining respondents, 185 had developed incident dementia, 104 with a diagnosis of AD and no other dementing illness. The other 3123 participants included 394 who were members of the 19% subsample and were thus examined directly and another 2729 who showed no evidence of dementia on screening measures. We obtained complete exposure data from 3274 wave 2 participants (99.0%). The number of statin users at wave 2 had grown to 481 (14.7%) as follows: simvastatin, 35%; atorvastatin, 26%; fluvastatin, 17%; pravastatin, 14%; lovastatin, 7%; and cerivastatin, 1%. More than half (298) had initiated statin use between the 2 waves. The statin users at the 2 waves were similar in their baseline risk factors for dementia.

There was significant inverse association of statin use at wave 1 with prevalent dementia and AD (**Table 2**). After adjustment for age and sex, the odds ratios shifted toward the null but remained significant for dementia (odds ratio, 0.45; 95% confidence interval, 0.18-0.95). Further adjustment for education, the number of *APOE*

**Table 2. Cross-sectional Association of Medication Use at Wave 1 and Prevalent Illness Estimated With Logistic Regression Models of Data From the Wave 1 Sample (n = 4895)\***

	No. With Dementia (AD)/Nondemented	Dementia			Alzheimer Disease		
		Bivariable OR (95% CI)	Age- and Sex-Adjusted OR (95% CI)	Multivariable-Adjusted OR† (95% CI)	Bivariable OR (95% CI)	Age- and Sex-Adjusted OR (95% CI)	Multivariable-Adjusted OR† (95% CI)
Statins							
No	342 (190)/4230	1.0	1.0	1.0	1.0	1.0	1.0
Yes	6 (5)/286	0.26 (0.10-0.54)	0.45 (0.18-0.95)	0.44 (0.17-0.94)	0.39 (0.14-0.86)	0.69 (0.24-1.56)	0.71 (0.24-1.69)
Other LLAs							
No	345 (193)/4417	1.0	1.0	1.0	1.0	1.0	1.0
Yes	3 (2)/99	0.39 (0.10-1.04)	0.72 (0.17-1.99)	0.78 (0.19-2.22)	0.46 (0.08-1.47)	0.92 (0.15-3.05)	1.24 (0.20-4.35)

Abbreviations: AD, Alzheimer disease; CI, confidence interval; LLAs, lipid-lowering agents (other than statins); OR, odds ratio.

\*A total of 31 participants (7 with dementia, of which 5 had AD, and 24 without dementia) did not provide data on medication use.

†Multivariable models included terms for age, sex, education, the number of  $\epsilon 4$  alleles at *APOE*, age  $\times$   $\epsilon 4$  interaction, a history of hypertension, and a history of diabetes.

**Table 3. Prospective Association of Drug Use at Wave 1 and Incident Illness Estimated With Discrete-Time Survival Models of Data From the Wave 2 Sample (n = 3308)\***

	No. With Dementia/ Total PYRS	Dementia			Alzheimer Disease			
		Bivariable HR (95% CI)	Age- and Sex-Adjusted HR (95% CI)	Multivariable-Adjusted HR† (95% CI)	No. With AD/ Total PYRS	Bivariable HR (95% CI)	Age- and Sex-Adjusted HR (95% CI)	Multivariable-Adjusted HR† (95% CI)
Statins								
No	174/9683	1.0	1.0	1.0	98/9522	1.0	1.0	1.0
Yes	8/641	0.70 (0.31-1.33)	1.22 (0.54-2.37)	1.19 (0.53-2.34)	4/630	0.62 (0.19-1.48)	1.15 (0.35-2.81)	1.19 (0.35-2.96)
Statins								
No	174/9683	1.0	1.0	1.0	98/9522	1.0	1.0	1.0
$\leq 3$ y	5/409	0.68 (0.24-1.50)	1.42 (0.50-3.20)	1.40 (0.49-3.21)	2/399	0.49 (0.08-1.54)	1.17 (0.19-2.77)	1.41 (0.23-4.70)
$> 3$ y	2/225	0.50 (0.08-1.56)	0.69 (0.11-2.23)	0.71 (0.12-2.32)	1/224	0.43 (0.03-1.96)	0.60 (0.03-2.77)	0.62 (0.03-2.92)
Other LLAs								
No	178/10100	1.0	1.0	1.0	102/9934	1.0	1.0	1.0
Yes	4/224	1.01 (0.31-2.42)	1.66 (0.50-4.04)	1.71 (0.51-4.20)	0/218	NE	NE	NE

Abbreviations: AD, Alzheimer disease; CI, confidence interval; HR, hazard ratio; LLAs, lipid-lowering agents (other than statins); NE, not estimated; PYRS, person-years.

\*A total of 11 participants (3 with dementia, of which 2 had AD, and 8 without dementia) contributing 32 person-years did not provide data on medication use; an additional 3 participants contributing 7 person-years provided data on medication use but did not provide enough information to classify their duration of use.

†Multivariable models included terms for age, sex, education, the number of  $\epsilon 4$  alleles at *APOE*, age  $\times$   $\epsilon 4$  interaction, a history of hypertension, and a history of diabetes.

$\epsilon 4$  alleles, age  $\times$  *APOE* genotype, and a history of hypertension or diabetes did not appreciably alter these results.

Crude prospective analyses also suggested a modest inverse association of statin use at wave 1 with subsequent incidence of dementia and AD (Table 3). In adjusted analyses, however, the hazard ratios were above the null value of 1.0 for both dementia (adjusted hazard ratio, 1.19; 95% confidence interval 0.53-2.34) and AD (adjusted hazard ratio, 1.19; 95% confidence interval, 0.35-2.96). To investigate this result, we dichotomized statin use post hoc by duration of use ( $\leq 3$  years vs  $> 3$  years) and observed some reduction in risk of dementia and AD with longer use, but the trends were unimpressive ( $P > .40$ , from a likelihood ratio  $\chi^2$  test that examined improvement of fit after the dichotomization of duration as earlier). We also examined other cutoffs for duration of use, but none of them provided stronger evi-

dence for a duration-response relationship. The sample sizes for these analyses of the duration of statin use were small, thus limiting definitive conclusions.

We tried to reproduce the results reported from the CSHA<sup>17</sup> using cross-sectional analyses of the data at wave 2 (Table 4). Unadjusted analyses showed an inverse association of statin use with incident dementia and AD, but this finding again “disappeared” after an adjustment for covariates, particularly age and sex. In multivariable-adjusted analyses, dichotomization at age 80 years, as suggested in the CSHA report, produced no suggestion of inverse association of statin use and dementia or AD in either age group.

There was little association between the use of non-statin lipid-lowering agents and risk of prevalent or incident dementia or AD. Furthermore, none of our analyses showed any suggestion of variation in the association (or lack thereof) of statins with dementia or AD in groups

**Table 4. Cross-sectional Association Between Statin Use at Wave 2 and Incident Illness Estimated With Logistic Regression Models of Data From the Wave 2 Sample (n = 3308)\***

	No. With Dementia (AD)/Nondemented	Dementia			Alzheimer Disease		
		Bivariable OR (95% CI)	Age- and Sex-Adjusted OR (95% CI)	Multivariable-Adjusted OR† (95% CI)	Bivariable OR (95% CI)	Age- and Sex-Adjusted OR (95% CI)	Multivariable-Adjusted OR† (95% CI)
Statins							
No	136 (78)/2657	1.0	1.0	1.0	1.0	1.0	1.0
Yes	15 (6)/466	0.63 (0.35-1.05)	1.04 (0.57-1.77)	1.04 (0.56-1.81)	0.44 (0.17-0.93)	0.78 (0.30-1.70)	0.85 (0.32-1.88)
Other LLAs							
No	148 (84)/3060	1.0	1.0	1.0	1.0	1.0	1.0
Yes	3 (0)/63	0.99 (0.24-2.69)	1.31 (0.31-3.73)	1.37 (0.32-3.99)	NE	NE	NE

Abbreviations: AD, Alzheimer disease; CI, confidence interval; LLAs, lipid-lowering agents (other than statins); NE, not estimated; OR, odds ratio.

\*A total of 34 participants with dementia (of which 20 had AD) did not provide data on medication use.

†Multivariable models included terms for age, sex, education, the number of ε4 alleles at *APOE*, age × ε4 interaction, a history of hypertension, and a history of diabetes.

defined by age, sex, or number of ε4 alleles at *APOE* (data not shown).

### COMMENT

Using data from the large Cache County Study, we examined the association of statin use with prevalent and incident dementia and AD. As had been suggested by previous studies, cross-sectional analyses showed an inverse relationship of statin use with prevalent dementia. Notably, however, no association was evident with incident dementia in either cross-sectional or prospective analyses. Overall, these findings do not suggest that statins reduce the risk of dementia.

Although they are consistent with incidental findings on cognition (not dementia incidence) from 3 randomized trials, our findings conflict with at least 6 previous observational studies<sup>15-20</sup> that have suggested that statins reduce the occurrence of dementia. All but 1 of these studies<sup>15</sup> was cross-sectional, and our own cross-sectional findings with prevalent illness also suggested a neuroprotective effect. The distinction in results of cross-sectional and prospective analyses might reflect the vulnerability of the former to an artifact wherein the outcome (AD) might be responsible for reduced prevalence of exposure instead of vice versa. This concern is logical for statins (but not necessarily for older lipid-lowering agents) because statins are indicated specifically for the prevention of future cardiovascular outcomes.<sup>37</sup> Physicians might be less motivated to prescribe long-term preventive agents to those who are cognitively impaired because such patients have a reduced ability to adhere to prescribed treatment, are at a greater risk of treatment-related complications, and might not derive benefit because of their diminished life expectancy.<sup>38</sup> Indeed, 1 study has shown that dementia status is a predictor of underutilization of other medicines for the prevention of vascular disease.<sup>39</sup> By contrast, a study of 3 hospital databases<sup>16</sup> found no evidence that physicians were less likely to prescribe statins to those with dementia. We note, however, that hospital-based samples might not be representative of the general population, particularly as regards this issue.

One previous cross-sectional study, from the CSHA,<sup>17</sup> used incident rather than prevalent case data. We conducted a similar analysis. Our unadjusted results were similar to the CSHA findings, but the association disappeared in multivariable models even though our analysis had 80% statistical power to detect a relative risk of 0.55 or lower. Although adjusted for some covariates, the CSHA analyses were not adjusted for age. Instead, the CSHA used data dichotomized into broad categories from participants younger or older than 80 years. Dementia is strongly associated with age, and statin use is likely also to be so. The CSHA design might therefore be vulnerable to residual confounding with age (ie, statin use might still appear to be inversely associated with dementia because both are strongly associated with age even within the age ranges of the 2 age strata). Consistent with this view, among the covariates in our models, age had by far the greatest influence in shifting risk estimates toward the null.

Although it was conducted retrospectively, 1 previous study in the UK General Practice Research Database specifically examined the prior use of statins, noting an inverse association with dementia.<sup>15</sup> Other than their reliance on a clinic-based sample, we can find no direct explanation of why the UK findings should have differed from our own. Like all observational studies, however, the UK study was vulnerable to confounding with factors that were not suspected or not measurable. We speculate that, particularly in the middle 1990s, its statin users might have been more “health conscious” than nonusers, or have enjoyed better access to health care. Those who received the newest treatments (ie, statins) might have been more proactive in general about their health.<sup>40</sup> (The CSHA<sup>17</sup> found no evidence that initiating the use of statins was associated with health-related characteristics, but the particular characteristics examined—age, education, self-reported health, community residence, hypertension, and smoking status—might not be perfect measures for “health consciousness.”) Difficulty in measuring and controlling such forms of confounding has, in fact, prompted our strategy elsewhere of examining the Cache County cohort for the association of

incident dementia with prior use of other classes of drugs (eg, multivitamins, calcium supplements) likely to be used by “health-conscious” individuals but with different pharmacological effects.<sup>34,35,41</sup> Although we examined the association of lipid-lowering agents with dementia risk for other reasons, it is not clear that these agents form a satisfactory “control” exposure for this purpose.

Our study has several limitations that warrant note. Although based on one of the largest population-based studies to examine statins and risk of dementia, our null results in prospective analyses might still reflect inadequate statistical power. Statin use in this cohort was relatively rare, especially at wave 1. Among the 6.3% of participants who endorsed statin use, only 3.8% subsequently developed dementia. Given the number of outcome events, our prospective analyses had only a 66% probability of producing a “statistically significant” finding when the risk of dementia among statin users was reduced by half or more. Yet, even a more moderate reduction in risk might typically have been evidenced by some (perhaps modest) statistical trend. Instead, the adjusted hazard ratios for both dementia and AD were higher than 1.0. Reflecting this fact, the adjusted hazard ratio lower bound confidence limit for dementia was 0.53. This result suggests that statins do not reduce the risk of dementia by as much as half. Furthermore, 2 other longitudinal studies of statin use and AD<sup>42,43</sup> find results that closely approximate ours—ie, a null result in prospective analyses but an apparent “protective” effect in cross-sectional or simulated case-control analyses. In all, the prospective analyses in this and the other 2 studies fail to find evidence of protection with statins in more than 33 000 person-years of observation.

Our study also assessed the use of statins via self-report, leaving some possibility of the misclassification of exposure status, which could bias our results. In the prevalence analyses, reliance on self-report could expose the study to recall bias resulting from failure of demented participants to provide complete data on medication use. Although such bias could create a spurious inverse association between statin use and dementia, the threat of its occurrence was probably mitigated by the collection of data from collateral respondents and nursing homes. Collateral respondents (typically caregivers) were generally knowledgeable about participants’ prescription medications. Their recall (as well as that of the participants themselves) was also corroborated by a rigorous visual “medicine cabinet” review. (Note, however, that this review was not helpful in validating recall of the duration of statin use.) Nursing home medication dispensing records can be regarded as authoritative. We also discount recall bias as a likely explanation of our prospective analytic results for 2 reasons. First, the wave 2 participants were cognitively intact at their wave 1 interviews, and self-report from such individuals has been shown to be a valid method for ascertaining drug use.<sup>44</sup> If some participants who subsequently developed AD had suffered prodromal cognitive difficulties at baseline, they would presumably have underreported statin use. Such underreporting would tend to bias the results toward an inverse association of dementia with prior statin use, which is the opposite of what we found. Second, the methods used here are indistinguish-

able from those that have revealed strong associations in Cache County with other pharmacologic treatments, including nonsteroidal anti-inflammatory drugs,<sup>34,41</sup> remote past use of postmenopausal hormone replacement therapy,<sup>35</sup> and antioxidant vitamin supplements.<sup>36</sup>

As might be expected with any longitudinal (randomized or observational) study, some of our participants were lost to follow-up over time. These participants tended to be older, less educated, and poorer performers on the baseline 3MS. Conceivably, they might therefore have been more likely subsequently to develop dementia. Because they did not differ substantially from others with respect to their use of statins, however, their failure to complete the study is unlikely to explain the null findings of our prospective analyses. If anything, those lost to follow-up reported slightly more statin use, so their non-response might have biased our observed results toward an inverse association.

Finally, our follow-up period of approximately 3 years might have been inadequate to reveal a protective effect of statins. Several years of statin use might be required for any reduction in the risk of dementia, or statin use might be effective only when treatments are taken several years before the onset of dementia symptoms. We could not test for such a lag effect, but we saw little suggestion (albeit with less rigorous methods of exposure classification and with limited statistical power) that the longer use of statins produced more notable reduction in dementia risk.

The definitive test for any claimed protective effect of statins against dementia would be one or more randomized controlled prevention trials. Recently, considerable interest has been expressed in such trials. However, the present prospective analyses do not support the hypothesis that statins reduce the risk of dementia or AD. Instead, they suggest that further observational studies are needed. The new studies should use a prospective design, should possess sufficient statistical power to detect reasonable effect sizes, and should afford the opportunity to examine potential lag effects or variability among individual statin drugs, relating perhaps to the varying lipophilicity and hence blood-brain barrier permeability of different agents.<sup>45</sup> The current study could not examine these issues because of inadequate numbers of statin users. However, with the dramatic recent increase in statin use, such studies are becoming more feasible. Finally, additional animal studies and basic science research might further help clarify the relationship between statin use and risk of dementia. Until such research is able to demonstrate more promising results, however, we suggest that costly randomized prevention trials of statins are premature.

**Submitted for Publication:** March 23, 2004; final revision received May 24, 2004; accepted July 2, 2004.

**Author Affiliations:** Department of Mental Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Md (Drs Zandi and Khachaturian); Sun-Health Research Institute, Sun City, Ariz (Dr Sparks); Department of Psychology and the Center for Epidemiologic Studies (Drs Tschanz and Norton), Department of Family and Human Development (Dr Norton), Utah State Uni-

## Cache County Study Investigators

Cache County Study Investigators involved in the project in addition to the authors are James C. Anthony, PhD; James Burke, MD; Tony Calvert, RN; Chris Corcoran, PhD; Deborah Gustafson, PhD; Andrea Hart, PhD; Michael Helms, MS; Carole Leslie, MS; Constantine Lyketsos, MD, MHS; Larry Mayer, MD; Ronald Munger, PhD; Brenda Plassman, PhD; Ingmar Skoog, MD, PhD; David C. Steffens, MD; Joslin Werstak, BS; Nancy West, MS; and Bonita Wyse, PhD.

For more information about the Cache County Study Investigators, refer to *Arch Gen Psychiatry*. 2004;61:524.

versity, Logan; Department of Psychiatry, School of Medicine, Johns Hopkins University, Baltimore (Dr Steinberg); Department of Psychiatry and Behavioral Sciences and the Joseph and Kathleen Bryan Alzheimer's Disease Research Center, Duke University Medical Center, Durham, NC (Dr Welsh-Bohmer); VA Puget Sound Health Care System and the Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle (Dr Breitner).

**Correspondence:** John C. S. Breitner, MD, GRECC (S-182), VA Puget Sound Health Care System, 1660 South Columbian Way, Seattle, WA 98108 (jcsb@u.washington.edu).

**Funding/Support:** This work was supported by the National Institutes of Health grant R01-AG-11380.

**Acknowledgment:** We are grateful to the neurogenetics laboratory of the Bryan Alzheimer's Disease Center at Duke University for doing the *APOE* genotyping. We thank Drs Bruce Psaty and Eric Larson for their valuable comments on earlier versions of this manuscript.

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### Correction

**Errors in Byline and Affiliations.** In the Original Article titled "Pharmacotherapy Plus Psychotherapy for Treatment of Depression in Active Injection Drug Users," published in the February issue of the ARCHIVES (2004;61:152-159), an author's name was inadvertently omitted from the byline on page 152. The byline should have appeared as follows: "Michael D. Stein, MD; David A. Solomon, MD; Debra S. Herman, PhD; Jennifer L. Anthony, PhD; Susan E. Ramsey, PhD; Bradley J. Anderson, PhD; Richard Brown, PhD; Ivan W. Miller, PhD." Also on that page, the affiliations paragraph should have appeared as follows: "From the Departments of Medicine (Drs Stein, Herman, Ramsey, and Anderson) and Psychiatry (Drs Solomon, Anthony, Brown, and Miller), Brown University School of Medicine, Providence, RI."