

Statins and cognitive function in the elderly

The Cardiovascular Health Study

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Abstract—Objective: To examine the association of statin drug use on cognitive and MRI change in older adults. **Methods:** Participants in the Cardiovascular Health Study, a longitudinal study of people age 65 or older, were classified into three groups determined by whether they were taking statin drugs on a continuous basis, intermittently, or not at all. The untreated group was further divided into categories based on National Cholesterol Education Program recommendations for lipid-lowering treatment. Participants with prevalent or incident clinical TIA or stroke or with baseline Modified Mini-Mental State Examination (3MS) scores at or below 80 were excluded. Outcomes examined included rate of change on the 3MS over an average observational period of 7 years, along with changes in MRI white matter grade and measures of atrophy. **Results:** Three thousand three hundred thirty-four participants had adequate data for analysis. At baseline, the untreated group in which lipid-lowering drug treatment was recommended were slightly older, less likely to be on estrogen replacement, and had higher serum cholesterol and lower 3MS scores than the statin-treated group. The rate of decline on the 3MS was 0.48 point/year less in those taking statins compared with the untreated group for which treatment was recommended ($p = 0.069$) and 0.49 point/year less in statin users compared with the group in which lipid-lowering treatment was not recommended ($p = 0.009$). This effect remained after controlling for serum cholesterol levels. One thousand seven hundred thirty participants with baseline 3MS scores of >80 underwent cranial MRI scans on two occasions separated by 5 years. There was no significant difference in white matter grade change or atrophy measures between groups. **Conclusion:** Statin drug use was associated with a slight reduction in cognitive decline in an elderly population. This relationship could not be completely explained by the effect of statins on lowering of serum cholesterol.

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The influence of serum cholesterol and statin medications on cognitive function has been a topic of recent interest. Most research has focused on the role of these factors in development of Alzheimer disease (AD). Transgenic animal models have implicated hypercholesterolemia in promoting amyloid pathology, whereas several epidemiologic studies suggest that statins may reduce the risk of AD.^{1–7}

Results of some recent studies have cast doubt on the cognitive benefits of statins. A prospective cohort study did not find a significant association between statin use and incident dementia.⁸ Moreover, no favorable cognitive effects were seen in two prospective trials of statins.^{9,10} A number of factors may contribute to the conflicting conclusions on statin cognitive effects, including differences in cohorts studied, duration of follow-up, analytical methods, and endpoints used. Thus, there are still questions as to whether statins may have a pro-cognitive influence and, if so, by what mechanism.

The Cardiovascular Health Study (CHS) is a community-based, prospective, epidemiologic study of risk factors for coronary and cerebrovascular disease in older adults. As part of the study, participants underwent yearly cognitive testing, with 3,660 participants also undergoing cranial MRI scans. We undertook this study with the objective of determining if statin use was associated with a reduction in cognitive change over time in an elderly population free of dementia or overt cerebrovascular disease.

Methods. Members of the CHS cohort were recruited from a random sample of the Health Care Financing Administration Medicare eligibility lists in four US communities: Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh (Allegheny County), PA. Participants had to be age 65 or older, able to give informed consent, and able to respond to questions without the aid of a surrogate respondent. They could not be institutionalized, wheelchair bound in the home, or under treatment for cancer. Of eligible persons recruited for CHS, 58% agreed to participate ($n = 5,888$) and were enrolled. Those who participated were more educated, younger, and more likely to be married

*For a full list of participating Cardiovascular Health Study investigators and institutions, see “About CHS: Principal Investigators and Study Sites” at <http://www.chs-nhlbi.org>

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than those who did not. Details of the CHS design and recruitment have been described elsewhere.¹¹⁻¹³

Data collection. The CHS study protocol consisted of a baseline clinic visit followed by semiannual updates that alternated between phone contacts and clinic visits through June 1999. At study entry in 1989 and 1992, participants underwent an extensive baseline evaluation that included standard questionnaires, physical examination, and laboratory testing as described elsewhere.^{11,12}

During the 10 years of follow-up, participants completed annual in-clinic examinations including questions on medication use, smoking status, and hospitalizations. At year 3 of follow-up, examination also included fasting lipid levels. Cognitive function was evaluated annually using the Modified Mini-Mental State Examination (3MS). The 3MS assesses several areas of cognition in greater detail than the original version and has scores ranging from 0 to 100, with higher scores reflecting higher levels of cognitive function.¹⁴ Scores of 80 or below have a high specificity for dementia.¹⁴

Cerebrovascular events (stroke or TIA) were ascertained through regular surveillance every 6 months at the field centers with subsequent review of hospital records, procedures, information from attending physicians, and interviews with the participant or next of kin.¹⁵ Possible cerebrovascular events identified were adjudicated by a stroke subcommittee comprised of neurologists from each site and a neuroradiologist.¹⁶

Consenting CHS participants without contraindication underwent cranial MRI scans in a standard fashion at two time points during the study period separated by an average of 4 years. The scanning protocol included sagittal T1-weighted images and axial T1-weighted, spin density, and T2-weighted images, all with 5-mm thickness and no interslice gaps. Imaging data were sent to a single reading center for interpretation by neuroradiologists with training in the CHS protocol and without knowledge of the subject's clinical information.¹⁷

The white matter signal changes and ventricular and sulcal size of each individual were assessed on a semiquantitative 10-point scale using predefined visual standards. Portions of these atlases have been previously published and the methods described.^{17,18} Cerebral infarcts were classified according to predefined standards described previously.¹⁷ Infarcts were considered silent if the participant had no clinical history of TIA or stroke.

Statistical methods. Because participants may have implemented lifestyle and medical changes soon after entering the study owing to improved risk factor awareness, we used the year 3 visit, when lipid levels were next repeated, as the baseline for analysis. For measurements and characteristics assessed on more than one occasion, such as smoking status or aspirin use, the values obtained at the year 3 exam were used. Of the 5,880 participants in CHS, 2,716 were excluded from analysis for one or more of the following listed in a hierarchical order: 1) had incomplete or no lipid data ($n = 566$), 2) had baseline 3MS score ≤ 80 ($n = 583$), 3) had <2 years of cognitive testing data ($n = 471$), 4) no baseline 3MS score ($n = 161$), 5) had missing information on statin use ($n = 424$), and 6) had an incident stroke or TIA ($n = 349$).

Analysis of cognitive change by years of statin use yielded groups with relatively small numbers. To improve statistical power, we divided the cohort into three categories: 1) an "untreated" group consisting of participants who never received or had <2 years of statin (i.e., atorvastatin, lovastatin, fluvastatin, pravastatin, or simvastatin) treatment, 2) an "intermittent" group composed of those with only 2 to 4 years of continuous treatment or 3, 4, or 5 years of nonconsecutive use, and 3) a "continuous" group, those with greater than 4 years of continuous statin treatment. Participants in the "untreated" group were classified into three mutually exclusive categories based on 1993 National Cholesterol Education Program guidelines for treatment of hyperlipidemia (see Appendix).

For the five categories, we tested univariate associations with continuous variables by analysis of variance (ANOVA) and binary variables by χ^2 tests. Cognitive decline was measured as the rate of change in 3MS scores per year calculated for each participant. The rate was then modeled as the response variable in a linear regression. The regression coefficient represented the change in score per year associated with 1-unit change in the covariate. We used multivariate regression to adjust for factors that could confound the relationship between statins and cognitive decline.

These factors were age, sex, presence of APOE $\epsilon 4$, educational attainment, and cholesterol. We used univariate ANOVA to test the effect of the different treatment categories. This test is based on the linearly independent pairwise comparisons among the estimated marginal means. We tested for trend by handling the treatment categories as a continuous variable. To explore possible effect modification, we repeated adjusted analyses stratified by sex and by the presence or absence of the APOE $\epsilon 4$ alleles. We used SPSS 11.0.1 (Chicago, IL) for all analyses.

Only 3,660 of the 5,888 CHS participants underwent an MRI. Cross-sectioning those who underwent MRI at year 5 and year 10 visits with the statin data, we were left with 1,823 subjects with an average interval between scans of 5.1 years for analyses of change in MRI. Of these, 1,730 had a baseline 3MS score of >80 , and these were used in the MRI analysis. For the MRI analysis, white matter, ventricular, and sulcal grade were treated as continuous variables. Our primary analyses used linear regression to examine the association of statin use with the difference between first and second MRI after adjusting for covariates, with those not treated with statins and classified as normal as a reference group. For each group, the difference in adjusted means was compared with the reference group, and the 95% CI for the difference in means was obtained. Covariates that were associated with cognitive decline and type of treatment group were examined in general linear models. Covariates that changed the adjusted mean white matter grade, ventricular size, and sulcal size for any treatment group by $\geq 5\%$ were retained in the final models.

Results. Baseline characteristics of the 3,334 participants included in analysis are shown in table 1. Total cholesterol, low-density lipoprotein (LDL), and age were highest among the untreated group for whom drug therapy was recommended, whereas the proportion of woman on estrogen replacement was highest in the group treated with statins continuously and the no therapy recommended group. Baseline 3MS score and other characteristics were similar among the five groups.

Table 2 lists the unadjusted and adjusted mean change in cognitive decline. The adjusted model uses the covariates that were associated with cognitive decline and displays the rate of change per year in the various treatment categories. The unadjusted difference in mean rate of 3MS change between those in the continuous statin group compared with the drug therapy-recommended group was 0.48 point/year (95% CI 0.06, 0.89; p value = 0.024). After adjusting for age, APOE $\epsilon 4$, sex, race, cholesterol, and education, the difference in 3MS rate was 0.40 point/year (95% CI -0.03, 0.87; p value = 0.069). The unadjusted difference in 3MS between the continuous statin group compared with the not recommended treatment group was 0.49 (95% CI 0.12, 0.85; p value = 0.009), which remained significant even after adjustments (0.49; 95% CI 0.04, 0.95; p value = 0.026).

Baseline characteristics of those participants with 3MS score of >80 and who underwent two MRI scans are seen in tables 3 and 4. There was no significant difference in white matter, ventricular, or sulcal grade change between continuous statin users and the untreated groups, as displayed in table 5. There was, however, a fourfold increase in individuals with silent infarcts seen in the treatment-recommended group compared with the statin-treated group.

Cholesterol, LDL, HDL, and triglycerides were not identified as significant covariates as the classification of the untreated groups was based on LDL levels and other risk factors such as HDL level. To determine if high levels of cholesterol contributed to the cognitive decline seen, adjustments for cholesterol level at baseline were added in

Table 1 Characteristics at baseline for patients with 3MS score of >80*

| Characteristics | Treated at baseline | | Untreated at baseline | | | <i>p</i> † |
|------------------------------|------------------------|--------------------------|----------------------------|---|---|------------|
| | Continuous, n = 293 | Intermittent, n = 158 | No treatment, n = 2,031 | Diet therapy recommended, n = 501 | Drug therapy recommended, n = 351 | |
| Mean (SD) age, y | 72.9 (3.6) | 73.4 (4.2) | 74.6 (5.3) | 74.7 (5.0) | 75.9 (5.8) | <0.0001 |
| Older than 75 y | 27.3 | 31.6 | 42.2 | 45.9 | 54.7 | <0.0001 |
| Female, % | 65.5 | 59.5 | 58.3 | 61.9 | 66.7 | 0.279 |
| Nonblack, % | 91.8 | 86.1 | 83.8 | 79.4 | 77.2 | <0.0001 |
| High school graduate, | 77.1 | 77.8 | 78.0 | 68.2 | 67.4 | 0.608 |
| Aspirin use, % | 6.1 | 6.3 | 2.4 | 2.6 | 5.1 | 0.998 |
| Estrogen use, % of women | 15.1 | 9.6 | 17.2 | 6.8 | 3.8 | <0.0001 |
| Current or past smoker, % | 52.6 | 56.3 | 52.8 | 54.1 | 51.6 | 0.140 |
| Systolic BP, mm Hg | 134 (21.1) | 133.3 (19.6) | 136.1 (21.1) | 133.8 (21.1) | 135.1 (20.9) | 0.509 |
| Diastolic BP, mm Hg | 69.2 (9.7) | 69.7 (10.1) | 71.4 (11.5) | 71.1 (10.6) | 71.7 (11.2) | 0.003 |
| Hypertension, % | 47.4 | 46.8 | 35.0 | 47.0 | 49.3 | 0.054 |
| Cholesterol, mg/dL | 221.5 (34.5) | 233.1 (58.5) | 193.9 (29.9) | 222.0 (31.7) | 249.1 (32.5) | <0.0001 |
| LDL, mg/dL | 135.5 (33.0) | 146.7 (50.9) | 112.5 (25.9) | 141.8 (25.3) | 166.7 (27.1) | <0.0001 |
| HDL, mg/dL | 51.4 (13.5) | 50.7 (14.8) | 55.2 (15.0) | 52.4 (12.8) | 52.1 (12.8) | 0.504 |
| Triglycerides, mg/dL | 175.7 (115.6) | 181.8 (115.0) | 138.9 (77.3) | 130.4 (68.9) | 133.1 (68.3) | <0.0001 |
| Alcohol, drinks/wk | 1.7 (4.5) | 1.4 (3.7) | 2.4 (5.8) | 1.8 (4.8) | 1.7 (4.9) | 0.960 |
| 3MS score | 93.7 (4.5) | 92.9 (4.6) | 92.9 (4.9) | 92.9 (5.1) | 93.1 (4.9) | 0.115 |
| APOE ε4 allele prevalence, % | 29.6 | 25.2 | 22.6 | 29.6 | 29.4 | 0.149 |

* Values for variables are means (SD) for continuous variables and percentages for discrete variables.

† *p* Values are two tailed and based on analysis of variance for continuous variables and χ^2 for discrete variables. They represent the differences between the drug therapy–recommended group and continuous statin users.

3MS = Modified Mini-Mental State Examination; BP = blood pressure; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

the final model. This adjustment did not make any change in the rate of cognitive decline between groups.

Discussion. In the elderly cohort that comprises the CHS, the use of statin drugs was associated with a very slight reduction in rate of cognitive decline compared with individuals in whom statin medications were not indicated. Moreover, the attenuation in cognitive decline in statin users was not related to

baseline serum lipid levels. In a subset of participants who underwent serial MRI scans separated by 5 years, there were no notable differences in the evolution of white matter or atrophy measures between treatment groups. However, those in the treatment-recommended group had a greater accumulation of silent infarcts than the statin-treated group.

Prior work has implied that hypercholesterolemia

Table 2 Unadjusted/adjusted* mean change in 3MS total (3MS score of >80)

| | Treated | | Untreated | | |
|---------------------------------|------------------------|--------------------------|----------------------------|---|---|
| | Continuous, n = 293 | Intermittent, n = 158 | No treatment, n = 2,031 | Diet therapy recommended, n = 501 | Drug therapy recommended, n = 351 |
| Unadjusted, mean (95% CI) | −0.26 (−0.56 to 0.05) | −0.50 (−0.92 to −0.09) | −0.75 (−0.86 to −0.63) | −0.61 (−0.85 to −0.38) | −0.73 (−1.01 to −0.45) |
| Adjusted,* mean (95% CI) | −0.27 (−0.61 to 0.06) | −0.45 (−0.89 to −0.01) | −0.76 (−0.89 to −0.63) | −0.61 (0.87 to −0.36) | −0.70 (−1.02 to −0.38) |

* Mean adjusted for age, gender, race, APOE, education level, and cholesterol.

3MS = Modified Mini-Mental State Examination.

Table 3 Characteristics at baseline of those undergoing MRI scanning

| Characteristics | Treated at baseline | | Untreated at baseline | | | <i>p</i> |
|---------------------------|------------------------|-------------------------|----------------------------|---|---|----------|
| | Continuous, n = 173 | Intermittent, n = 84 | No treatment, n = 1,021 | Diet therapy recommended, n = 274 | Drug therapy recommended, n = 178 | |
| Age, y | 72.8 (3.5) | 73.4 (4.5) | 74.6 (5.2) | 74.1 (4.9) | 76.5 (5.7) | <0.0001 |
| Older than 75 y | 29.5 | 29.8 | 41.0 | 40.1 | 61.8 | <0.0001 |
| Female, % | 65.3 | 54.8 | 57.8 | 65.0 | 68.0 | 0.782 |
| Non black, % | 91.9 | 85.7 | 84.9 | 80.7 | 75.8 | 0.162 |
| High school graduate, % | 81.5 | 81.0 | 77.3 | 68.9 | 68.4 | 0.217 |
| Aspirin use, % | 5.8 | 6.0 | 1.6 | 2.2 | 3.4 | 0.317 |
| Estrogen use, % of women | 15.9 | 13.0 | 18.5 | 6.7 | 4.1 | 0.007 |
| Current or past smoker, % | 53.8 | 58.3 | 54.6 | 56.6 | 57.3 | 0.519 |
| Hypertension, % | 48.6 | 34.5 | 36.0 | 46.9 | 50.6 | 0.649 |
| Systolic BP, mm Hg | 134.5 (20.8) | 130.4 (18.5) | 133.9 (19.9) | 133.0 (18.9) | 132.3 (18.7) | 0.295 |
| Diastolic BP, mm Hg | 69.2 (9.3) | 69.0 (10.0) | 71.0 (11.4) | 71.1 (10.3) | 71.6 (10.3) | 0.026 |
| Cholesterol, mg/dL | 221.9 (32.3) | 233.7 (65.9) | 193.3 (30.1) | 222.9 (31.6) | 250.0 (33.4) | <0.0001 |
| LDL, mg/dL | 136.4 (30.5) | 147.7 (53.2) | 112.0 (25.6) | 142.0 (25.5) | 167.8 (28.1) | <0.0001 |
| HDL, mg/dL | 52.2 (13.6) | 49.3 (15.0) | 54.9 (14.8) | 52.4 (12.6) | 52.8 (13.8) | 0.671 |
| Triglycerides, mg/dL | 172.7 (118.4) | 183.3 (136.1) | 135.7 (76.9) | 124.1 (63.9) | 129.3 (69.0) | <0.0001 |
| Alcohol, drinks/wk | 1.8 (4.0) | 1.3 (3.4) | 2.5 (6.3) | 1.8 (4.8) | 1.8 (5.1) | 0.888 |
| 3MS score | 94.2 (4.4) | 93.5 (4.5) | 93.4 (4.6) | 93.3 (5.0) | 93.7 (4.8) | 0.291 |
| APOE ε4 allele, % | 31.4 | 25.0 | 21.7 | 32.1 | 29.3 | 0.919 |

p values are two tailed and based on analysis of variance for continuous variables and χ^2 for discrete variables; they represent the differences between the drug therapy–recommended group and continuous users.

BP = blood pressure; LDL = low-density lipoprotein; HDL = high-density lipoprotein; 3MS = Modified Mini-Mental State Examination.

promotes, and statins protect against, AD pathology. Animal and cell models have shown that serum cholesterol levels and statin drugs modulate β -amyloid deposition and metabolism in the brain.^{19–27} In addition,

several epidemiologic studies have reported a reduced risk of AD in those taking statins.^{5,6}

Though we attempted to segregate out cognitively impaired individuals at baseline by using a 3MS

Table 4 Analysis with first and second MRI data: Characteristics of first and second MRI variables and characteristics at baseline (only for 3MS score of >80)

| Characteristics | Treated at baseline | | Untreated at baseline | | | <i>p</i> |
|--------------------|------------------------|-------------------------|---------------------------|---|---|----------|
| | Continuous, n = 173 | Intermittent, n = 84 | No treatment, n = 1021 | Diet therapy recommended, n = 274 | Drug therapy recommended, n = 178 | |
| 1st MRI | | | | | | |
| Ventricular grade | 3.17 | 3.61 | 3.39 | 3.43 | 3.43 | 0.037 |
| Sulcal grade | 3.14 | 3.54 | 3.29 | 3.25 | 3.24 | 0.426 |
| White matter grade | 1.99 | 2.25 | 2.02 | 1.96 | 1.98 | 0.936 |
| Infarcts, % | 33.1 | 32.9 | 22.7 | 23.2 | 21.6 | 0.051 |
| 2nd MRI | | | | | | |
| Ventricular grade | 3.43 | 3.85 | 3.70 | 3.76 | 3.80 | 0.012 |
| Sulcal grade | 3.62 | 4.25 | 3.82 | 3.76 | 3.81 | 0.226 |
| White matter grade | 2.42 | 2.92 | 2.54 | 2.60 | 2.55 | 0.446 |
| Infarcts, % | 35.6 | 37.0 | 28.3 | 30.7 | 31.3 | 0.850 |

3MS = Modified Mini-Mental State Examination.

Table 5 Unadjusted/adjusted* mean difference per annum between first and second MRI, mean of 5.1 years between MRI scans

| | Treated | | Untreated | | |
|--------------------|------------------------|-------------------------|----------------------------|---|---|
| | Continuous, n = 173 | Intermittent, n = 84 | No treatment, n = 1,021 | Diet therapy recommended, n = 274 | Drug therapy recommended, n = 178 |
| White matter grade | | | | | |
| Unadjusted, mean | 0.09 | 0.13 | 0.11 | 0.13 | 0.12 |
| (95% CI) | (0.05, 0.12) | (0.08, 0.18) | (0.10, 0.12) | (0.10, 0.16) | (0.08, 0.15) |
| Adjusted,* mean | 0.09 | 0.13 | 0.11 | 0.13 | 0.10 |
| (95% CI) | (0.05, 0.13) | (0.08, 0.18) | (0.10, 0.13) | (0.11, 0.16) | (0.06, 0.14) |
| Ventricular grade | | | | | |
| Unadjusted, mean | 0.05 | 0.05 | 0.07 | 0.07 | 0.07 |
| (95% CI) | (0.02, 0.08) | (0.02, 0.09) | (0.05, 0.08) | (0.04, 0.09) | (0.04, 0.11) |
| Adjusted,* mean | 0.05 | 0.05 | 0.06 | 0.07 | 0.08 |
| (95% CI) | (0.02, 0.09) | (0.003, 0.09) | (0.05, 0.08) | (0.05, 0.10) | (0.05, 0.11) |
| Sulcal grade | | | | | |
| Unadjusted, mean | 0.10 | 0.15 | 0.11 | 0.11 | 0.13 |
| (95% CI) | (0.05, 0.15) | (0.08, 0.22) | (0.09, 0.13) | (0.07, 0.15) | (0.08, 0.18) |
| Adjusted,* mean | 0.10 | 0.15 | 0.12 | 0.11 | 0.12 |
| (95% CI) | (0.05, 0.16) | (0.08, 0.22) | (0.10, 0.14) | (0.07, 0.16) | (0.07, 0.18) |

* Mean adjusted for age, gender, race, *APOE*, education level, and cholesterol.

p values are two tailed and based on a comparison between the drug therapy–recommended group and continuous users.

score generally considered relatively specific for dementia,¹⁴ undoubtedly patients with mild AD were included in the group with 3MS score of >80. Thus, it is possible that the slowing in cognitive decline seen in CHS statin users may reflect the drugs' effect on AD patients in the cohort.

Whether statin drugs influence the maintenance of cognitive function with aging in non-AD individuals is unclear. Multiyear treatment trials of pravastatin and simvastatin failed to show any beneficial cognitive effect of those statins.^{9,10} On the other hand, in the Heart Estrogen/Progestin Replacement Study, the authors reported an association between statin use and better cognitive function in older women without dementia.²⁸ Hypothetically, there may be several ways by which statins exert a pro-cognitive effect. Some statins cross the blood–brain barrier and may modulate brain cholesterol metabolism.^{29–32} It has been proposed that alterations in brain cholesterol homeostasis can directly alter neurotransmission and synaptic plasticity.^{33,34} In addition, statins have been shown to reduce oxidative stress and inflammation, increase endothelial nitric oxide synthase, and improve endothelial function and blood flow.^{35–37}

The latter mechanism might play a role in reducing subclinical cerebrovascular disease. After removing participants who sustained a clinically recognized TIA or stroke from analysis, there was no noticeable difference in evolution of white matter disease or atrophy measures between groups over a 5-year period. However, there was a fourfold in-

crease in those with silent infarcts in the untreated group where treatment was recommended compared with the statin users. This finding raises the possibility that the more rapid rate of cognitive decline in our statin-untreated participants for whom treatment would be recommended was due to subclinical vascular disease. Previously published results from CHS indicate that increasing white matter disease or the presence of silent infarcts is linked with worsening cognitive function.³⁸ Most of these silent infarcts were located subcortically.

We might have expected that white matter grade would also have had a higher rate of worsening in the statin-untreated group. Yet, whereas we were able to evaluate sequential MRI data in a substantial number of participants, the grading system used to measure white matter disease or atrophy change may not have adequate sensitivity or interreader reliability to detect significant changes within a relatively short interval. Also, the number of participants in some of the groups does limit the conclusions that can be drawn on the MRI data.

In designing our analysis, we attempted to address several issues that could confound result interpretation. Nevertheless, certain study limitations need to be acknowledged. This is the first study to longitudinally compare, and provide a value of, rate of change in statin-treated and -untreated individuals in a community cohort. Although the rate of cognitive decline in statin users in the general cohort was over half that of untreated participants for whom lipid-lowering drug treatment was recom-

mended, the absolute difference on a yearly basis was quite small. Moreover, CIs were rather large, casting doubt on the significance of the differences between groups. If, indeed, statins provide a small degree of cognitive protection, it may take large numbers of subjects with long periods of observation to recognize a benefit if an endpoint such as conversion to dementia is used.

The relationship of statins to lesser decline in cognitive performance may, of course, not be an effect of the drugs at all. Observational studies assessing drug effect can be confounded by indication bias. In clinical practice, physicians may selectively choose not to treat patients who have declining health or early features of dementia. We attempted to reduce this bias by comparing the statin-treated group with an untreated group where both lipid-lowering medications would and would not be recommended. In addition, whereas we controlled for many factors that have been related to cognitive impairment, there may have been other unrecognized characteristics of the various groups that themselves account for the results seen. For our analysis, we divided the groups based on lipid levels measured at one point in time; we do not have information on whether there was significant change in these levels over the years of the study.

Despite the limitations, the findings from this large, community-based, prospective study support the idea that statin drugs may have a slight beneficial influence on cognitive function in an elderly population apart from their serum lipid-lowering effect. Whether the effect is solely through a modifying influence on AD progression, reduction in cerebrovascular disease or some other mechanism is unclear. Findings from randomized clinical trials of statins in AD currently under way may help clarify this issue in the future.

Appendix

1993 National Cholesterol Education Program Guidelines

| Dietary therapy recommended | LDL, mg/dL |
|-------------------------------|------------|
| Without CHD, <2 risk factors* | ≥160 |
| Without CHD, ≥2 risk factors* | ≥130 |
| With CHD | >100 |
| Drug therapy recommended | LDL, mg/dL |
| Without CHD, <2 risk factors* | ≥190 |
| Without CHD, ≥2 risk factors* | ≥160 |
| With CHD | ≥130 |

* Risk factors: men age ≥45, women age ≥55, family history of premature coronary heart disease (CHD), smoking, hypertension, low levels of high-density lipoprotein (<35 ng/dL), and diabetes. LDL = low-density lipoprotein.

From Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* 1993; 269:3015–3023.

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