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## Title
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## Permalink
https://escholarship.org/uc/item/5xf666rr

## Journal
The Journals of Gerontology Series A, 77(5)

## ISSN
1079-5006

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## Publication Date
2022-05-05

## DOI
10.1093/gerona/glab220

Peer reviewed

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*Journals of Gerontology: Medical Sciences*
cite as: *J Gerontol A Biol Sci Med Sci*, 2022, Vol. 77, No. 5, 994–1001
https://doi.org/10.1093/gerona/glab220
Advance Access publication July 31, 2021

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Research Article

# Statins and Cognitive Decline in the Cardiovascular Health Study: A Comparison of Different Analytical Approaches

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Received: March 27, 2021; Editorial Decision Date: July 25, 2021

**Decision Editor:** Lewis Lipsitz, MD, FGSA

## Abstract

**Background:** Despite their well-established benefits for the prevention of cardiovascular disease, robust evidence on the effects of statins on cognition is largely inconclusive. We apply various study designs and analytical approaches to mimic randomized controlled trial effects from observational data.

**Methods:** We used observational data from 5 580 participants enrolled in the Cardiovascular Health Study from 1989/1990 to 1999/2000. We conceptualized the cohort as an overlapping sequence of *non*randomized trials. We compared multiple selection (eligible population, prevalent users, new users) and analytic approaches (multivariable adjustment, inverse-probability treatment weights, propensity score matching) to evaluate the association between statin use and 5-year change in global cognitive function, assessed using the Modified Mini-Mental State Examination (3MSE).

**Results:** When comparing prevalent users to nonusers ($N$ = 2 772), statin use was associated with slower cognitive decline over 5 years (adjusted annual change in 3MSE = 0.34 points/year; 95% CI: 0.05–0.63). Compared to prevalent user design, estimates from new user designs (eg, comparing eligible statin initiators to noninitiators) were attenuated showing either null or negative association, though not significant. For example, in a propensity score-matched sample of statin-eligible individuals ($N$ = 454), the annual 3MS change comparing statin initiators to noninitiators was −0.21 points/year (95% CI: −0.81 to 0.39).

**Conclusions:** The association of statin use and cognitive decline is attenuated toward the null when using rigorous analytical approaches that more closely mimic randomized controlled trials. Point estimates, even within the same study, may vary depending on the analytical methods used. Further studies that leverage natural or quasi experiments around statin use are needed to replicate our findings.

In the United States, there are currently more than 5 million people living with dementia, and cognitive decline is frequent among older adults (1). In the absence of curative treatments, identifying factors that may have an impact on dementia risk is of interest. In parallel, a growing body of evidence suggests that cardiovascular health is strongly linked with brain health.

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In fact, Alzheimer's disease and cognitive impairment occur more frequently with certain health behaviors and in presence of modifiable cardiovascular disease (CVD) risk factors (2, 3). Although evidence is mixed, cardiovascular risk factors such as hypercholesterolemia/high blood lipids may be associated with cognitive decline and dementia risk. Antihyperlipidemic agents, including statins, rank as the number 2 most frequently prescribed drugs in the United States (4), with more than 20 million older adults currently taking a lipid-lowering drug (5, 6). As such, it is critical to gain a better understanding of the role of statins in cognitive function and dementia risk.

Physicians have been widely prescribing statins since the 1990s (7), with cited effects ranging from reductions in low-density lipoprotein (LDL) cholesterol to prevention of CVD (8, 9). Despite its well-established cardioprotective benefits, evidence regarding the effect of statins on cognition and dementia risk remains inconsistent (8, 10–18). In 2 large, placebo-controlled randomized controlled trials (RCTs) of statins and cognitive outcomes, the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) and the Heart Protection Study, neither study found a difference in the prevalence of cognitive impairment or the rate of cognitive decline over the short term (nearly 4–5 years) between participants treated with statins and those treated with placebo (8, 10). Similarly, a meta-analysis of RCTs concluded no association between statin use and cognition (19), although individual smaller RCTs have reported mixed results (17). On the other hand, findings from systematic reviews and meta-analyses of observational studies have mostly suggested a beneficial effect, such that statin use is associated with lower cognitive impairment and dementia risk (17, 20–22). Furthermore, while a few observational studies have found a null association between statin use and cognitive function or dementia risk (12, 13, 23), most other studies (15, 18, 24–26) have found statin use to be associated with a reduced risk of a clinical diagnosis of dementia and Alzheimer's disease, including findings from a recent study using Medicare beneficiaries (16) as well as a target trial study of participants in the Rotterdam study (27).

There may be several reasons for such inconsistent findings. In observational studies, differences in study populations, selection bias toward health-conscious individuals selectively using statins or toward less-healthy individuals with CVD, or differential methodological techniques such as handling of confounders and/or mediators could lead to biased estimates as well as to varied estimates across observational studies. Ideally, to answer the question of statin use and cognition, we would need to have a large randomized trial over enough follow-up time to observe clinically meaningful changes in cognition. However, long-term RCTs in a representative population of statin users can be both time-consuming and expensive.

The goal of this study is to highlight the methodological complexities in pharmacoepidemiologic studies that examine the relationship between drug use and health outcomes. And we use the inconclusive relationship between statins and cognition as an example to demonstrate the analytical challenges in analyzing and interpreting such data. To do so, we used observational data from the Cardiovascular Health Study (CHS) and compared the relationship between statin use and global cognitive decline using multiple study designs and analytic approaches (28), including a target trial new user design. The CHS, which was initiated shortly after statins were approved and released into the US market, is well-positioned to address such a research question.

## Method

### Study Population

The CHS is a community-based longitudinal observational cohort study of 5 888 older adults. Enrollment began in 1989–1990 with 5 201 participants recruited from Medicare eligibility lists in 4 locations (Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Allegheny County, PA). An additional 687 predominantly African American participants were later enrolled in 1992–1993. Exclusion criteria included institutionalization, active cancer treatment, or expectation of moving from the area within 3 years. In addition to the baseline interview in 1989–1990, participants underwent semiannual interviews, alternating between telephone and annual clinic examination until 1998–1999, with continuing telephone interviews afterward. Additional information was collected from medical records and interviews with surviving participants or proxies. Details of the CHS study design have been previously published (29).

### Study Design: A Sequence of *Non*randomized Trials

Our study design intended to emulate an intention-to-treat (ITT) approach of a 5-year randomized trial. For this purpose, each CHS exam/study visit was considered as the baseline of a "trial," and cognitive change in the subsequent 5 years was evaluated in relation to statin status at the beginning of that trial/study visit. In total, 6, overlapping, *non*randomized trials, each of 5-year duration, were created (Figure 1). The sequence of trials helped to increase sample size and statistical power. Results from all 6 trials were then pooled, and we used cluster standard errors to appropriately account for the fact that participants could contribute to more than one trial. This approach has been validated and described previously (30, 31). In Table 1, we describe the various components of our nonrandomized trial design, using a protocol outlined by Hernán and Robins (32).

### Ascertainment of statin eligibility and statin use

At each visit, medication use during the past 2 weeks was determined by inspection of prescription bottles that participants brought to the study site. Data on medication use were collected by study examiners (33).

*Statin eligibility.* We defined eligibility for statins as the following: (a) having total cholesterol >240 mg/dL or LDL cholesterol >190 mg/dL, or (b) having LDL cholesterol >130 mg/dL with prevalent coronary heart disease (CHD), or (c) having LDL cholesterol >130 mg/dL and one or more of the following risk factors (current smoker, diabetic, hypertensive, high-density lipoprotein [HDL] cholesterol <35 mg/dL, history of transient ischemic attack, history of stroke or sibling history of early MI, with HDL cholesterol >60 mg/

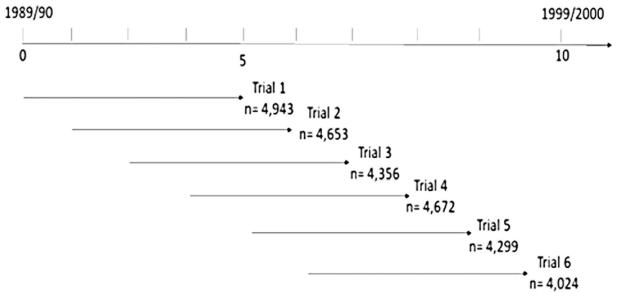


**Figure 1.** Study design pooling 6 "nonrandomized" trials each with a 5-year follow-up for a total of 26 947 observations, Cardiovascular Health Study.

**Table 1.** Number of Participants, Prevalent Users, Eligible Prevalent Users, Eligible Initiators (New Users) by Nonrandomized Trial, Cardiovascular Health Study

| Trial | Questionnaire/Visit Year | Participants | Prevalent Users | Eligible | Eligible Prevalent Users | Eligible Initiators |
|---|---|---|---|---|---|---|
| 1 | 1990 | 4 943 | 93 | 2 125 | 0 | — |
| 2 | 1991 | 4 653 | 113 | 2 031 | 36 | 36 |
| 3 | 1992 | 4 356 | 151 | 1 916 | 69 | 41 |
| 4 | 1993 | 4 672 | 221 | 1 785 | 85 | 27 |
| 5 | 1994 | 4 299 | 255 | 1 738 | 132 | 60 |
| 6 | 1995 | 4 024 | 273 | 1 616 | 151 | 42 |
| Overall | | 26 947 | 1 106 | 11 211 | 473 | 206 |

dL negating one risk factor). The eligibility criteria were informed by the National Cholesterol Education Program's 1993 Adult Treatment Panel (ATP) II guidelines (34) and common practices in the early 1990s, the time when the CHS began. At the beginning of every trial, eligibility was calculated based on covariate values from the previous visit (ie, pretreatment), and eligibility was carried forward for the duration of the trial (ie, subsequent 5 years).

*Statin use definitions*. *Prevalent statin use* was defined as anyone who was identified as a statin user at the beginning of each trial. To determine those participants who were statin users, medication use during the prior 2 weeks was determined by inspection of prescription bottles at each study visit. Meanwhile, for *new statin users*, statin initiation was defined at the first study visit where statins were used, if statins were not used at the previous visit (to approximate a 1-year washout period, though the precise time of initiation is unknown). Statin users whose statin status at the previous visit was missing were classified as prevalent statin users but not statin initiators. Given the statin eligibility and statin use, it would be possible for one participant to simultaneously fall into the prevalent user, eligible prevalent user, new user, and eligible new user categories at a given time. These categorizations, based on statin eligibility and use, were then used to define each of our predictors of interest (treatment and relevant comparison group) as detailed in the Statistical Analysis section.

## Ascertainment of Global Cognitive Function and Decline

To examine global cognitive function, we used the Modified Mini-Mental State (3MS) Examination, ranging from 0 to 100 with higher scores representing better cognitive function (35). The 3MS was administered in person unless a participant could not attend an in-person visit in which case the Telephone Interview for Cognitive Status (TICS) was administered. If the participant required a proxy, for example, in cases of problems with vision or hearing, then the IQCODE was administered. Study-specific calibration equations (36) were derived to convert TICS and IQCODE into 3MS scores. In the present analysis, cognitive decline was evaluated in the 5 years following the beginning of each trial (ie, baseline; as depicted in Figure 1), and annual change was reported.

## Ascertainment of Additional Covariates

Participants reported their race (White vs non-White) at baseline and their age at every study visit. Education was measured at baseline and dichotomized as completion of 4+ years of college. Private insurance status was collected in 1993, 1994, 1996, 1997, and 1998. Living arrangement was dichotomized to living with spouse or other and was available in 1989/1990, 1992, and 1998. General health status (coded excellent, very good, good, fair, or poor) was assessed every year except 1991. CHD status (defined as myocardial infarction, angina, coronary bypass, or angioplasty) was determined at each visit, by comparing the date of the visit with incidence dates of CHD as established by the cardiovascular event review committee. Total cholesterol was collected every year through 1999 except for 1990, 1991, and 1995; LDL cholesterol and HDL cholesterol were only available in 1989/1990 and 1992. Hypertension status (as normal, borderline [SBP 130–139 mmHg or DBP 80–90 mmHg], or hypertensive [systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or use of antihypertensive medication as determined by medication inventory interview and a self-report of a history of high blood pressure]) was assessed every year except 1995. Body mass index and smoking status (current, former, or never) were available every year. Diabetes (use of insulin or oral hypoglycemic agents, or fasting glucose ≥126 mg/dL) was available in 1989, 1992, and 1996.

Given our study design that includes a sequence of nonrandomized trials, all covariates listed above, except for race, sex, and education, are time-varying and are thus updated at the beginning of each trial and are incorporated either as adjustment covariates or in the form of a propensity score (details in the Statistical Analysis section). Some covariates were structurally missing at certain visits: For example, as described above, diabetes was only reported at 3 visits. In the case of structural missingness of any of the covariate values, we carried forward the values from the previous visit.

## Statistical Analysis

Our outcome of interest is the annual change (ie, slope) in 3MS in a 5-year *non*randomized trial. As such, for each participant, using a long data format, we first modeled 3MS as a function of time (spanning from baseline and across the 5 subsequent years/visits). The coefficient of "time" from that regression model is the annual change in 3MS (ie, slope) which is our outcome of interest. Next, we modeled the relationship between statin use (eg, prevalent statin user, new statin user) and the annual change in 3MS using linear regression models. We tested 7 different analytic approaches/models, as shown below as well as in Supplementary Table 2. Supplementary Table 1 provides further details, including a list of adjustment covariates. Our statistical analysis was approved by the CHS Publications & Presentations Committee, and all analyses were conducted in Stata 10.

- Model 1 "Prevalent users, unadjusted" compares all prevalent statin users to all nonusers in this nonrandomized trial framework.
- Model 2 "Eligible prevalent users, unadjusted" and Model 3 "Eligible prevalent users, adjusted" were restricted to only participants meeting eligibility criteria as described above and thus compared eligible prevalent statin users to eligible nonusers. Model 3 was

adjusted for age at baseline, visit year, sex, race, education, living arrangement, cardiovascular risk points, CHD status, LDL, HDL, total cholesterol, hypertension, antihypertensive medication, diabetes, oral hypoglycemic agents, smoking status, insurance status, general health status, nonsteroidal inflammatory drugs, and LDL squared. Adjustment covariates were chosen a priori based on prior literature and their relationship with statin use.

- Model 4 "Eligible new users, unadjusted" and Model 5 "Eligible new users, adjusted" were further restricted to new users (initiators), that is, those who were not taking statins at the previous visit (1-year washout period). These models estimate the ITT annual cognitive change in 3MS among a statin-eligible population comparing statin initiators to noninitiators. Model 5 was adjusted for the same covariates as in Model 3.
- Model 6 "Eligible new users, IPTW" estimates the ITT annual cognitive change in 3MS among a statin-eligible population comparing statin initiators to noninitiators, had the whole population been treated versus untreated. Model 6 applies inverse probability of treatment weights (IPTW), derived from a propensity score model that accounts for potential confounding due to time-variant covariates. We estimated this propensity score model using statin initiation as the outcome and preinitiating statin characteristics as the predictors (these included the same variables we adjusted for in Models 3 and 5; Supplementary Table 1). This process yielded an "initiating statin" propensity score which was then used in stabilized inverse-probability weighting when estimating the effect of initiating statin on annual cognitive change in 3MS. The numerator for the stabilized weights was the marginal probability of statin initiation. Supplementary Figure 1 depicts the distribution of this propensity score for statin initiators and noninitiators, indicating good common support.
- Model 7 "Eligible new users, propensity score matched": This model estimates the ITT annual cognitive change among a statin-eligible population comparing statin initiators to noninitiators within a population matched on the predicted probability of treatment. To accomplish this, we matched individuals on their propensity for initiating statins. Matching was done by identifying the 3 noninitiators with propensity scores closest to the propensity score for each statin initiator, within a caliper of 0.001 (nearest neighbor matching with replacement). The propensity score used for this model was based on the same variables we adjusted for in Model 3, as well as a cohort, stroke, and baseline MSE score (Supplementary Table 1).

In addition, we replicated all 7 models above by applying inverse probability of attrition weights to account for selective attrition. Attrition weights modeled the probability of loss to follow-up that is not due to death. To establish the probability of attrition, the model included the same covariates used in the multivariable-adjusted models (described in Supplementary Table 1), in addition to the following: cohort, stroke, and baseline 3MS score. Attrition weights were updated at the beginning of each trial using covariates from the previous visit.

## Results

Components of the nonrandomized trials are described in Table 1, using the protocol outlined by Hernán and Robins (32). This analysis included a total of 6 nonrandomized trials, totaling 26 947 observations (Table 2). In the 6 pooled trials, there was a total of 1 106 prevalent statin users, and the number of users increased over time. As expected, the number of participants eligible for statins at each trial decreased every year. Among those eligible, the number of statin users also increased gradually with every trial, totaling 473 eligible prevalent users across the 6 pooled trials. Among those eligible, participants who were new users (ie, initiators) totaled 206 participants across the 6 trials.

In our study population, compared to nonusers, statin initiators were more likely to be female, current smokers, have private insurance, higher prevalence of CHD, and higher mean LDL cholesterol (Table 3). Of the statin initiators, only 68.9% were eligible for statins based on the ATP II guidelines (which uses the previous year's covariates).

For the association between statin use and annual cognitive slope in a 5-year nonrandomized trial, we examined the estimates using various study designs and analytical models (Figure 2A; Table 3). When comparing *prevalent users to nonusers* (Model 1), statin use was associated with slower cognitive decline over 5 years, as evident in the positive average annual slope of 3MS comparing prevalent users versus nonusers (β slope = 0.34; 95% CI: 0.05–0.63). When further restricting the population to those eligible for statin according to the ATP II guidelines, the point estimates were almost unchanged though became nonsignificant, in unadjusted (Model 2) and adjusted (Model 3) models comparing *eligible prevalent users to eligible nonusers*. When further restricting the eligible population to *new users* (Models 4–7), the point estimates were gradually attenuated toward the harmful direction (ie, negative average annual slope of 3MS), in models that are unadjusted, adjusted, using IPTW, and PS matched. For example, within a population matched on the predicted probability of treatment (ie, statin initiation), the annual cognitive change among a statin-eligible population comparing statin initiators to noninitiators was −0.21 (95% CI: −0.81 to 0.39)—meaning that statin initiators had a faster 5-year cognitive decline than noninitiators. Accounting for selective attrition (Figure 2B; Table 3) slightly influenced the point estimates but conclusions were unchanged. Point estimates and 95% CIs from the various study

**Table 2.** Characteristics of Participants by Statin Status, Cardiovascular Health Study

| | Nonusers | Users | Initiators |
|---|---|---|---|
| Number of observations | 25 841 | 1 106 | 299 |
| Number of individuals | 5 506 | 401 | 285 |
| *From all pooled observations:* | | | |
| Age | 74.6 (5.5) | 73.5 (4.2) | 73.6 (4.1) |
| Female | 58.1% | 71.3% | 70.2% |
| Non-White | 10.8% | 10.8% | 9.7% |
| LDL cholesterol | 128.7 (34.3) | 138.3 (40.1) | 155.3 (38.9) |
| BMI | 26.7 (4.6) | 26.9 (4.4) | 27.0 (4.1) |
| Current smoker | 9.8% | 9.7% | 12.0% |
| Prevalent CHD | 20.2% | 38.8% | 39.1% |
| Diabetic | 14.7% | 13.7% | 11.0% |
| Taking OHGA | 6.3% | 7.3% | 6.4% |
| Private insurance | 67.0% | 73.1% | 77.6% |
| 4+ years of college | 21.9% | 22.4% | 20.1% |
| Income ≥$35 000 | 23.6% | 28.6% | 25.1% |
| Eligible for statins | 41.0% | 42.8% | 68.9% |
| Baseline 3MS score | 90.6 (9.0) | 91.8 (8.0) | 91.6 (8.7) |

*Note:* BMI = body mass index; CHD = coronary heart disease; OHGA = oral hypoglycemic agents; 3MS = Modified Mini-Mental State; LDL = low-density lipoprotein.

**Table 3.** Beta Coefficient for the 3MS Slope (average annual change) With and Without Adjustment for Selective Attrition Via Inverse Probability of Attrition Weights, Cardiovascular Health Study

| | Annual Slope Among Nonusers | Annual Slope Among Statin Users | Unweighted Linear Regression Model β (95% CI) | Weighted Linear Regression Model β (95% CI) |
|---|---|---|---|---|
| Model 1: prevalent users, unadjusted | −0.74 | −0.41 | 0.34 (0.05, 0.63) | 0.31 (−0.01, 0.63) |
| Model 2: eligible prevalent users, unadjusted | −0.70 | −0.45 | 0.25 (−0.05, 0.56) | 0.29 (−0.02, 0.60) |
| Model 3: eligible prevalent users, adjusted | −0.77 | −0.50 | 0.28 (−0.05, 0.61) | 0.32 (−0.02, 0.66) |
| Model 4: eligible new users, unadjusted | −0.79 | −0.66 | 0.13 (−0.25, 0.52) | 0.02 (−0.44, 0.48) |
| Model 5: eligible new users, adjusted | −0.89 | −0.77 | 0.06 (−0.34, 0.47) | 0.01 (−0.45, 0.47) |
| Model 6: eligible new users, IPTW | −0.81 | −0.83 | −0.02 (−0.51, 0.47) | −0.10 (−0.64, 0.44) |
| Model 7: PS-matched new users | −0.67 | −0.88 | −0.21 (−0.81, 0.39) | −0.38 (−1.08, 0.31) |

*Notes:* 3MS = Modified Mini-Mental State; IPTW = inverse probability of treatment weights. The β coefficients represent the effect estimate for the association comparing users to nonusers.

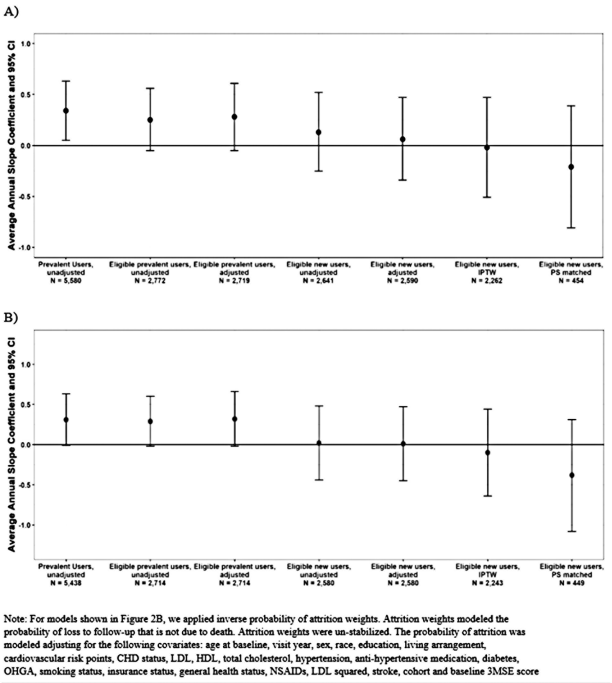


**Figure 2.** Comparing approaches to estimate the association between statin use and annual cognitive trajectory in a 5-year trial, the Cardiovascular Health Study: (A) without adjustment for selective attrition and (B) with adjustment for selective attrition.

designs and analytical models, unadjusted and adjusted for selective attrition, are presented in Table 3.

## Discussion

Leveraging data from the CHS, which is a well-characterized cohort enrolled shortly after the introduction of statins into the market, we examined the relationship between statin use and global cognitive function using a *non*randomized trial framework. We compared several study designs and analytical approaches that address confounding in observational data, while mimicking randomized trial design. In models comparing prevalent users to nonusers, statins were beneficial and associated with a slower annual change in 3MS. Compared to *prevalent user design*, estimates from models using *eligible new user design* were in the harmful direction showing either null or faster average annual change in 3MS, although the estimates are imprecise and compatible with both protective and deleterious associations. In addition, in *new user design models*, the point estimate from the *PS-matched* model was more strongly in the negative (harmful) direction than the IPTW model. Overall, as our study design uses a causal contrast that mimicked an RCT (Models 4–7), we find that the relationship between statin use and cognitive function was null. Our findings also provide evidence that point estimates for the same relationship, even within the same study, may vary depending on the study design used and the causal contrast that it provides.

Our findings from Models 1–3 showing a protective/beneficial relationship between statin use and cognitive change in models using *prevalent user design* are consistent with many other population-based studies that have used similar approaches. For example, in a study using CHS data, researchers reported a slight reduction in the

decline of the 3MS scores in prevalent statin users versus nonusers (37). Another CHS showed current statin use was associated with a trend toward lower dementia risk (hazard ratio = 0.69, 95% CI = 0.46–1.02) in a case–control approach, although no associations were found when using a standard Cox model (12). Results from the Rotterdam study and the Sacramento Area Latino Study on Aging evidenced a lower risk of dementia among prevalent statin users at any time during the follow-up, compared to nonusers (25, 38). Furthermore, 2 more recent studies, one using data from Medicare beneficiaries and the other using cross-sectional data from the Multi-Ethnic Study of Atherosclerosis, respectively, showed a reduction of Alzheimer's disease risk for high-exposure prevalent users compared to low-exposure users (exposure defined according to percentile of days of filled prescriptions in a given year) and higher cognitive scores for statin users compared to nonusers, respectively (16, 18). However, there have been some observational studies that have *not* found any protective effects of statins on cognition or dementia under prevalent user design. For instance, cross-sectional findings from the REasons for Geographic and Racial Differences in Stroke study showed no association between prevalent statins use and cognition, using the 6-item screener, after adjustment for potential confounders (13). Moreover, baseline statin use was not associated with the risk of cognitive decline or dementia over a 7-year period in a French cohort (14).

When instead we used study designs that included causal contrasts that better mimic an RCT by examining new users/initiators (Models 4–7), our findings were either null or in the negative direction. These findings are consistent with evidence from a recent target trial study which found no significant difference in the 10-year risk of dementia between statin initiators and noninitiators, after using inverse-probability weighting (27). Our findings are also consistent with recent findings from the Sydney Memory and Ageing Study in which researchers came to the conclusion of no significant difference in global cognition by statin use over a 6-year period, using a new user design (though they did not incorporate IPTW nor PS matching) (39). Furthermore, our findings are also consistent with conclusions from the 2 largest clinical trials. In participants aged 40–80 years, the Heart Protection Study reported a similar proportion of cognitively impaired (23.7% vs 24.2%) and dementia cases comparing the statin group to the placebo group, after 4–7 years of follow-up (8). Similarly, the PROSPER trial among participants aged 70–82 years did not find differences in cognitive decline, at any of the cognitive domains, between the statin and the placebo groups over an average of 4 years of follow-up (10).

Over the past few years, research has suggested several mechanisms through which statins may be beneficial for cognitive function and reduce dementia risk. For example, dyslipidemia, especially in midlife, is a major contributor to vascular brain health (40, 41) and has been associated with an increased risk of dementia (42–44). As such, treatment of dyslipidemia is suggested to reduce dementia risk. Statins may also protect cerebrovascular health through antioxidant and anti-inflammatory effects, as well as improved endothelial function (45, 46). Despite these proposed protective mechanisms, other evidence suggests that regulating brain cholesterol could lead to harm. Brain cholesterol is involved in synaptic plasticity and neurotransmission, and specific levels may be necessary for normal neuronal functioning (47, 48), especially among older adults with poor health and with multiple chronic conditions (49).

Our study has some limitations and implications for future work that are worth noting. First, our sample was predominantly Caucasian, likely limiting the external validity of our findings. Second, despite the large sample size of the CHS with more than 5 000 participants, the number of *eligible initiators* (new statin users) across all 6 nonrandomized trials was only 206. As such, our analyses may have suffered from a lack of statistical power (evident in the large confidence intervals) and which may have prevented us from observing the true impact of such study design and analytical methods (eg, new user design adjusted, with IPTW, PS matched). We also acknowledge that the lack of statistical power inhibited us from examining treatment effects across statin type or dosage, both of which could have affected the magnitude of the relationship between statin use and global cognition. We also lacked statistical power to examine the relationship across relevant subgroups defined by age, sex, frailty, and chronic health conditions. In the present analysis, we only examined global cognition, and as such our findings may not be generalizable to studies using other cognitive measures. Furthermore, the fact that studies often use different cognitive measures adds to the complexity of this research (50). Given that the CHS began in 1990, we used the ATP II guidelines. We acknowledge that these are not the most recent guidelines; however, this does not affect the robustness of our results because we used the guidelines appropriate to the data at the time it was collected, thus ensuring we are making appropriate inferences. In addition, only 68.9% of the statin initiators in our sample were eligible for statins according to the ATP II guidelines (which suggests prescription practices may not have been completely following guidelines), and overall adherence to statins in CHS was only around 50% (data not shown), which prevents us from having statistical power to conduct a per-protocol analysis. Given the low adherence rates, we would expect the statins to be less effective in this study than in other studies. Furthermore, our ability to measure eligibility to statins was limited by infrequently measured LDL cholesterol, and this limited our ability to appropriately evaluate statin compliance.

Despite those limitations, notable strengths of this study include leveraging data from a well-characterized cohort of older adults who were observed and followed shortly after the launch of statins into the US market. The latter enabled us to address the relationship of statin and cognition within a *non*randomized trial framework and to compare various study designs and causal contrasts, some of which more closely mimic randomized trial designs than others. Examples of these include restriction to those eligible for statin use, further restriction to new users, and adjustment for pretreatment covariates—all of which help achieve a more appropriate alignment between treatment assignment (at time zero) and outcome follow-up, as is usually the case in randomized trials. Overall, although the estimates from our *new user design models* (Models 4–7) were imprecise, the latter is likely due to the lack of statistical power given the small number of eligible new users, especially in the matched sample (PS-matched model). This suggests that the apparent protective effect of statins may be due to the selection of prevalent users and confounding by healthy user bias (as opposed to confounding by indication).

In conclusion, while our sample is confined to a predominantly White population, our results using a target trial design provide useful information for future pharmacoepidemiologic studies and for clinical practice. These results are particularly important given the scarcity of trials addressing the relationship of statin and cognition, as well the largely mixed evidence from prior literature. Our study illustrates that point estimates from observational data, addressing the same research question of statin use and cognitive function using the same data set, may vary depending on the study design and the relevant causal contrast. Overall, our

findings using a new user design that includes a causal contrast that mimics an RCT suggest no relationship between statins and global cognitive function. Future studies that leverage natural or quasi experiments around statin use are needed to better understand their relationship with cognition and dementia risk. Finally, our findings suggest that investigators should take caution when analyzing and interpreting observational data on drug use and health outcomes.

## Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

## Funding

This work was supported by grants from the National Institutes of Health, National Institute on Aging (R56AG061177, K01AG047273, R21-HL135195). The *Cardiovascular Health Study (CHS)* is supported by contracts HHSN268201200036C, HHSN268200800007C, HHSN268201800001C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grants U01HL080295 and U01HL130114 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke. Additional support was provided by R01AG023629 from the National Institute on Aging. A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org.

## Conflict of Interest

The authors have no conflicts of interest to declare or relevant disclosures. This study is not industry-sponsored.

*Standard protocols approval, registrations, and patient consent*: For every year of the study period, spanning from 1989–1990 till 1998–1999, participants provided informed consent, and institutional review boards at each site approved the study.

## Author Contributions

A.Z.A.H. contributed to the conception of the research question, statistical analysis, interpretation of the results, drafting of the manuscript, and review of the manuscript for the scientific content. N.J. contributed to the interpretation of the results, drafting of the manuscript, and review of the manuscript for the scientific content. L.G. contributed to the interpretation of the results, drafting of the manuscript, and review of the manuscript for the scientific content. P.K. contributed to the interpretation of the results and review of the manuscript for the scientific content. K.K. contributed to the interpretation of the results, drafting of the manuscript, and review of the manuscript for the scientific content. S.C. contributed to the interpretation of the results and review of the manuscript for the scientific content. M.G. contributed to the interpretation of the results and review of the manuscript for the scientific content. C.H. contributed to the interpretation of the results and review of the manuscript for the scientific content. A.M.A. contributed to the interpretation of the results and review of the manuscript for the scientific content. R.V. contributed to the interpretation of the results and review of the manuscript for the scientific content. M.C.O. contributed to the conception of the research question, statistical analysis, interpretation of the results, drafting of the manuscript, and review of the manuscript for the scientific content.

## Data Availability

Cardiovascular Health Study (CHS) facilitates data sharing through formal data use agreements. Any investigator is welcome to access the CHS data through this process.

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