

Statin Use and Incident Nuclear Cataract

Barbara E. K. Klein, MD, MPH

Ronald Klein, MD, MPH

Kristine E. Lee, MS

Lisa M. Grady, BS

STATINS ARE WIDELY USED TO reduce serum cholesterol for cardiovascular disease prevention.¹ Associations have been claimed between statin use and a variety of diseases, including Alzheimer disease² and multiple sclerosis.³ An inverse association between age-related macular degeneration and statin use has been reported,^{4,5} although a similar relationship was not found in a large, population-based study.⁶ Statins have been shown to have antioxidant activity,^{7,8} especially in the context of cardiovascular disease, where nitric oxide-derived oxidant species that are active in atherogenesis have been shown to be suppressed by statins.^{9,10} In addition, statins have been found in the lens.^{7,8}

Oxidative stress has been postulated as a risk factor for age-related cataract.¹¹⁻¹⁵ Although there is much speculation about the mechanism of increased oxidation in lenses that develop cataract, some evidence,^{16,17} but not all,^{18,19} suggests an association between nutritional intake of antioxidants and age-related cataract. Protective effects on the lens of specific antioxidant nutrients have been addressed by many studies.^{16,17,20-24} Furthermore, risk factors^{17,25-27} as well as protective factors appear to differ between the types of cataract. Oxidative stress is thought to be related in particular to nuclear cataract.^{20,24,28,29} We

Context Statins are widely prescribed for their lipid-lowering effects but also have putative antioxidant properties. Oxidative stress is believed to play a role in the development of nuclear cataract, but little is known regarding the relationship of statin use and cataract incidence.

Objective To evaluate the relationship of use of statins and incident cataract in adults in a midwestern community in the United States.

Design, Setting, and Participants The Beaver Dam Eye Study, an observational, longitudinal, population-based study of age-related eye disease in Beaver Dam, Wis. There were 1299 persons who were seen at the third examination in 1998-2000, had gradable photographs in both eyes, and were deemed to be at risk of developing nuclear cataract within 5 years.

Main Outcome Measure Five-year incidence of cataract with respect to statin use. Cataracts were graded from photographs taken through the participant's dilated pupil.

Results A total of 210 persons developed incident nuclear cataract in the interval from 1998-2000 to 2003-2005. Five-year incidence of nuclear cataract was 12.2% in statin users compared with 17.2% in nonusers (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.36-0.84), controlling for age. When only never smokers without diabetes were assessed, the age-, lipid level-, and sex-adjusted OR was 0.40 (95% CI, 0.18-0.90). Five-year incidence of cortical cataract was 9.9% in statin users and 7.5% in nonusers (OR, 1.28; 95% CI, 0.79-2.08); posterior subcapsular cataract occurred in 3.0% of statin users and 3.4% of nonusers (OR, 0.82; 95% CI, 0.39-1.71).

Conclusion Statin use in a general population appears to be associated with lower risk of nuclear cataract, the most common type of age-related cataract.

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sought to determine if statin use is associated with reduced risk of age-related cataract, and nuclear cataract specifically.

METHODS

The population and recruitment methods for the full cohort of the Beaver Dam Eye Study have been described in previous reports.³⁰⁻³⁸ In brief, at baseline, a private census of the population of Beaver Dam, Wis, was performed from September 15, 1987, to May 4, 1988, to identify all residents in the city or township of Beaver Dam who were 43 to 84 years of age. The tenets of the Declaration of Helsinki were followed, the Health Sciences Institutional Review

Board approved the study, and written informed consent was obtained from each participant. Ninety-nine percent of the population was non-Hispanic white as classified by the examiner, who questioned participants when uncertain. A total of 5924 eligible individuals were identified and invited for a baseline examination between March 1, 1988, and September 14, 1990.³⁰ The participants included

Author Affiliations: Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, Madison.

Corresponding Author: Barbara E. K. Klein, MD, MPH, Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison, 610 N Walnut St, Fourth Floor WARF, Madison, WI 53726 (kleinb@epiophth.wisc.edu).

in this analysis are shown in FIGURE 1. Comparisons between participants and nonparticipants at baseline and follow-up have been presented elsewhere.³⁰⁻³² In brief, nonparticipants (dead or alive) at previous examinations were older, had fewer years of education, were less likely to be currently employed, had poorer visual acuity, were more likely to have had cardiovascular disease and diabetes, smoked more, and had higher systolic blood pressure. The most common reason for nonparticipation was death.

Study visits have occurred at 5-year intervals since the baseline examination for 3 follow-up evaluations. All eligible individuals were invited for follow-up examinations, regardless of previous participation or disease status.

The analyses pertinent to this report are based on exposures measured in the 2962 persons seen at the third examination. Analyses are based on cataract present in the worse eye. Persons without gradable photographs in both eyes were excluded, as well as persons with prevalent cataract in either eye. Numbers for each cataract type are similar to those for nuclear cataract (FIGURE 2).

The same protocols, with few additions or deletions, were used at each examination phase. Photographs of

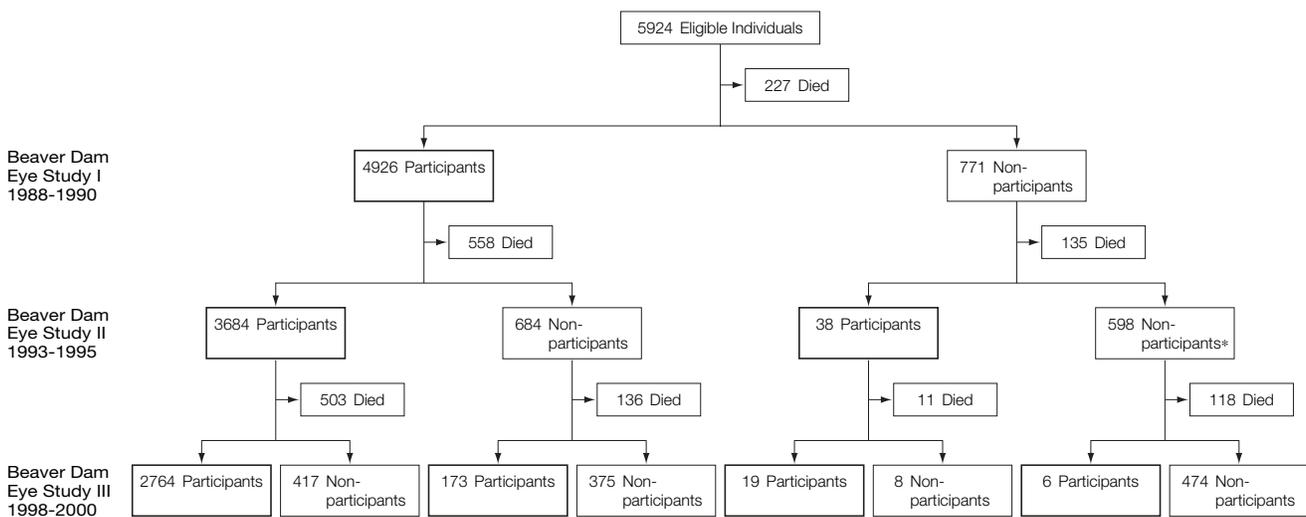
the lens were taken after pharmacologic dilation. Slit-lamp photographs were taken to grade the degree of nuclear sclerosis. Retroillumination photographs were taken to grade presence and severity of cortical and posterior subcapsular cataracts. The protocols for photography and for the grading procedures have been previously described.³⁹ Grading procedures for the lens photographs were based on detailed codified decision rules.³⁹ Graders were masked to participant identity. Scores for nuclear sclerosis were based on comparisons with standard photographs, which resulted in a 5-step scale of severity based on opacity of the nucleus. Severities greater than standard 3 were considered nuclear cataract. Scores for cortical and posterior subcapsular cataracts were based on estimated amount of involvement.

Nonfasting blood specimens were obtained at the time of examination. An aliquot of serum was used immediately for determination of serum total and high-density lipoprotein cholesterol levels.^{40,41} Whole-blood glycosylated hemoglobin was determined using affinity chromatography (Isolab Inc, Akron, Ohio) from nonfasting blood samples. Smoking and diabetes his-

tory were obtained as part of a medical questionnaire. Participants were asked to bring to the examination all medications (prescription and over-the-counter) that they were currently taking. The examiner listed all the medications that were brought to the examination and asked if the participant was taking any others. When medications were not brought to the examination, a follow-up telephone call was made to obtain the missing information. Use of medications as risk factors for eye disease was not a primary aim of our study and we did not collect information on dose or duration of use. Statins included medications in which the active ingredient was a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor and that were being used on a regular basis by those who reported taking them. Other reported lipid-lowering preparations were primarily niacin, gemfibrozil, and cholestyramine.

Analyses included all persons with gradable photographs for both eyes at both the third and fourth examinations. Logistic regression was used to examine the incidence of cataract with regard to statin use adjusting for age and other confounders. Models were derived based on our hypotheses

Figure 1. Beaver Dam Eye Study: Overall Participant Flow



*The 598 nonparticipants at the first 2 examinations include 20 who completed interviews at both examinations.

Figure 2. Beaver Dam Eye Study: Flow of Participants From the Third Examination Who Were Eligible for Nuclear Cataract Analyses

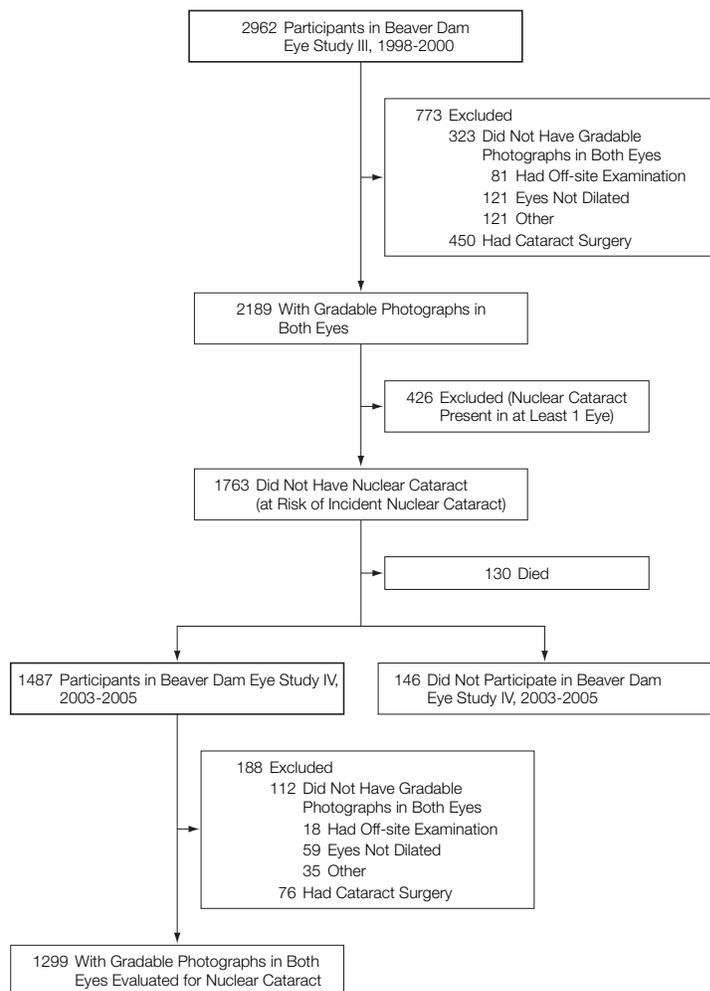


Table 1. Distribution and Age-Adjusted ORs for Each Cataract Type Based on Statin Use

	No. in Each Group*	Incidence, No. (%)	Age-Adjusted OR (95% CI)
Any cataract			
No statin use	834	185 (22.2)	1.00
Statin use	214	42 (19.6)	0.74 (0.50-1.10)
Nuclear cataract			
No statin use	1029	177 (17.2)	1.00
Statin use	270	33 (12.2)	0.55 (0.36-0.84)
Cortical cataract			
No statin use	1006	75 (7.5)	1.00
Statin use	253	25 (9.9)	1.28 (0.79-2.08)
Posterior subcapsular cataract			
No statin use	1209	41 (3.4)	1.00
Statin use	304	9 (3.0)	0.82 (0.39-1.71)

Abbreviations: CI, confidence interval; OR, odds ratio.

*Numbers are those in each exposure category at risk of the outcome (ie, without prevalent specific type of cataract).

and biologic rationale. Because of the limited sample size, we did not assess interactions and we limited confounders for adjustment. The SAS software program was used for all analyses.⁴²

RESULTS

Among the 2962 persons participating in the third examination, 1340 were free of all types of cataract and were at risk of incidence of any type of cataract. Photographs were available for both eyes at the fourth examination for 1048 of these eligible individuals. Two hundred fourteen persons were using statins at the third examination. Incidence of any cataract was not significantly lower among the statin users after adjusting for age (TABLE 1). If the 19 persons free of cataract at the third examination who had cataract surgery by the fourth examination are included in the analysis as having developed incident cataract, the age-adjusted odds ratio (OR) is 0.74 (95% confidence interval [CI], 0.50-1.09).

Each specific type of cataract has been found to be associated with different risk factors except age. Therefore, each cataract type was examined separately (Table 1). Among those at risk of incidence of a given cataract type, 210 developed nuclear cataract, 100 developed cortical cataract, and 50 developed posterior subcapsular cataract (not mutually exclusive). The respective ORs, adjusted for age, for incident nuclear, cortical, and posterior subcapsular cataracts 5 years after the third examination in statin users were 0.55 (95% CI, 0.36-0.84; *P* = .006), 1.28 (95% CI, 0.79-2.08; *P* = .31), and 0.82 (95% CI, 0.39-1.71; *P* = .59) (Table 1). The small number of cases of cortical and posterior subcapsular cataracts limited our ability to conduct further analyses, but we reanalyzed nuclear cataract to adjust for other possible confounders (factors shown in TABLE 2). Those developing nuclear cataract were more likely to be older, to be female, to have had less education, and to have lower income than those free of incident cataract. TABLE 3 shows analyses adjusting for all signifi-

cant confounders; education, income, lipid levels, and hypertension did not alter the models. Although smoking and diabetes were not strongly related, because of the possibility that these characteristics might confound analyses with statins, we recalculated the models limiting the analyses to those who had never smoked and did not have diabetes. The relationship persisted, with an OR of 0.37 (95% CI, 0.16-0.82; P = .01).

Because we did not collect information on total duration of statin use, we evaluated current use at the second and fourth examinations in addition to use at the third examination in association with incident nuclear cataract at the fourth examination. Most people continued to take statins once they began. The OR for incident nuclear cataract among the 45 individuals who used statins at 3 consecutive examinations was 0.29 (95% CI, 0.09-0.96), while the OR for those taking statins at 2 visits was 0.61 (95% CI, 0.38-0.98), and the OR for those starting statins between the third and fourth visit was 0.98 (95% CI, 0.66-1.46) (TABLE 4). Because of the small sample sizes, we were able to adjust only for age in this analysis.

Simvastatin (n=95) and atorvastatin (n=98) were the most commonly used statin preparations at the third examination, followed by pravastatin (n=36), fluvastatin (n=35), and lovastatin (n=6). We recalculated analyses (controlling only for age) of incidence of nuclear cataract by statin type. Six percent of the simvastatin users developed nuclear cataract, while 16% of the atorvastatin users and 14% of users of all other statins (combined pravastatin, fluvastatin, and lovastatin) developed nuclear cataract. Compared with nonusers, the age-adjusted ORs were 0.28 (95% CI, 0.12-0.65) for simvastatin, 0.73 (95% CI, 0.41-1.33) for atorvastatin, and 0.67 (95% CI, 0.34-1.33) for all other statins.

Finally, a total of 76 individuals at risk of incident nuclear cataract had cataract surgery between the third and fourth examinations, of whom 51 had

Table 2. Characteristics at the Third Examination (1998-2000) of Participants Who Developed Nuclear Cataract Compared With Those Who Did Not*

Characteristics	Total (N = 1299)	Incident Nuclear Cataract (n = 210)	No Incident Nuclear Cataract (n = 1089)	P Value†
Age, mean (SE), y	63.2 (0.2)	68.1 (0.5)	62.3 (0.2)	.008
Female	697 (53.7)	130 (61.9)	567 (52.1)	.006
Education, mean (SE), y	13.1 (0.1)	12.5 (0.2)	13.3 (0.1)	.02
Annual income, \$\$.002
Unknown	72 (5.5)	15 (7.1)	57 (5.2)	
<10 000	36 (2.8)	12 (5.7)	24 (2.2)	
10 000-19 000	138 (10.6)	40 (19.0)	98 (9.0)	
20 000-29 000	223 (17.2)	46 (21.9)	177 (16.3)	
30 000-44 000	288 (22.2)	42 (20.0)	246 (22.6)	
>44 000	542 (41.7)	55 (26.2)	487 (44.7)	
Body mass index, mean (SE)‡§	30.4 (0.2)	30.0 (0.4)	30.5 (0.2)	.59
Blood pressure, mean (SE), mm Hg§				
Systolic	129.2 (0.5)	132.1 (1.3)	128.6 (0.5)	.19
Diastolic	76.0 (0.3)	74.5 (0.7)	76.3 (0.3)	.99
High blood pressure (>140/90 mm Hg)§				
Unknown	0	0	0	.47
No	636 (49.0)	86 (41.0)	550 (50.5)	
Yes	663 (51.0)	124 (59.0)	539 (49.5)	
History of cardiovascular disease§				.16
Unknown	1 (0.1)	0	1 (0.1)	
No	1164 (89.6)	188 (89.5)	976 (89.6)	
Yes	134 (10.3)	22 (10.5)	112 (10.3)	
Diabetes§				.65
Unknown	12 (0.9)	2 (1.0)	10 (0.9)	
No	1153 (88.8)	186 (88.6)	967 (88.8)	
Possible	19 (1.5)	2 (1.0)	17 (1.6)	
Definite	115 (8.9)	20 (9.5)	95 (8.7)	
History of smoking§				.08
Unknown	0	0	0	
Never	614 (47.3)	100 (47.6)	514 (47.2)	
Past	546 (42.0)	84 (40.0)	462 (42.4)	
Current	139 (10.7)	26 (12.4)	113 (10.4)	

*Data are expressed as No. (%) unless otherwise noted.
 †All P values are for incident vs no incident nuclear cataract, adjusted for age (except for age comparison); data classified as unknown were not included in P value calculations.
 ‡Calculated as weight in kilograms divided by height in meters squared.
 §At third examination.

Table 3. Five-Year Incidence of Nuclear Cataract Identified at Fourth Examination, Classified by Use of Statins at Third Examination, 1998-2000

	All		Never Smokers With No Diabetes	
	No Statin Use	Statin Use	No Statin Use	Statin Use
Incidence of nuclear cataract, No. (%)	1029 (17.2)	270 (12.2)	472 (17.0)	88 (9.1)
OR (95% CI)				
Age-adjusted	1.00	0.55 (0.36-0.84)	1.00	0.37 (0.16-0.82)
Adjusted*	1.00	0.60 (0.39-0.92)	1.00	0.40 (0.18-0.90)
Fully adjusted†	1.00	0.60 (0.39-0.93)		

Abbreviations: CI, confidence interval; OR, odds ratio.
 *Adjusted for age, sex, total cholesterol, and high-density lipoprotein cholesterol.
 †Fully adjusted for age, sex, total cholesterol, high-density lipoprotein cholesterol, smoking, and diabetes.

Table 4. Incident Nuclear Cataract by Duration of Statin Use*

Statin Exposure	No. of Participants	Incidence, No. (%)	Age-Adjusted OR (95% CI)
No statin exposure	779	133 (17.1)	1.00
Statin use started between third and fourth examinations	250	44 (17.6)	0.98 (0.66-1.46)
Statin use during third examination only, then stopped	26	3 (11.5)	0.51 (0.14-1.79)
Statin use during third and fourth examinations	196	26 (13.3)	0.61 (0.38-0.98)
Statin use during second and third examinations, then stopped	3	1 (33.3)	1.26 (0.09-17.23)
Statin use during second, third, and fourth examinations	45	3 (6.7)	0.29 (0.09-0.96)

Abbreviations: CI, confidence interval; OR, odds ratio.

*As assessed by combining 3 examination phases: the second (1993-1995), third (1998-2000), and fourth (2003-2005).

cortical or posterior subcapsular cataract, 4 had missing information, and 21 were free from all types of cataract. Including these patients with possible incident nuclear cataract in the analyses as having incident nuclear cataract did not change the results.

COMMENT

These data demonstrate an inverse association between use of statins and incidence of nuclear cataract but not incidence of cortical or posterior subcapsular cataracts. Different relationships of specific exposures to specific cataract types have been previously observed. For example, nuclear cataract is associated with cigarette smoking,^{25,43,44} cortical cataract with UV exposure,²⁶ and posterior subcapsular cataract with hypertension²⁷ and use of steroid preparations.^{45,46} There is also evidence of different genetic patterns associated with different types of cataract.⁴⁷⁻⁵⁰ Thus, it is plausible that protective factors may differ. As previously noted, a protective effect of statins on nuclear cataract is biologically plausible because oxidative stress^{7,8} and inflammation⁵¹ have been shown to be related to nuclear cataract, and statins have been reported to counter such effects.⁵²⁻⁵⁵

In an experimental model, statins were differentially distributed in the lens.⁵⁶ Over a short duration of administration in beagles, concentration of statin was higher in the cortex than in the nucleus of the lens. Over longer durations, a greater proportional in-

crease of the drug was found in the nucleus. Nuclear cataract in particular has been suggested to result from oxidative stress, presumably the mechanism behind the association of smoking and nuclear cataract. Although other studies⁵⁷⁻⁶¹ did not report a protective effect of statins for nuclear cataract, a relationship is still plausible.⁵⁸⁻⁶¹ Most of the other studies in humans did not objectively record the degree of nuclear sclerosis (or other cataract type); investigators usually relied on clinical examinations, which are difficult to standardize between examiners even at the same clinical centers, let alone in multicenter studies. Also, in some studies it is not clear that the assessment was unbiased with regard to treatment. That, coupled with the anticipation of a deleterious effect on the lens, suggests that the lack of a previous protective finding does not mean that one does not exist.

Because smoking has been found in many studies (including ours) to increase the risk of nuclear cataract^{17,25,43} and diabetes less consistently so,^{44,62-65} we evaluated the association of statins in nonsmokers without diabetes. There was no meaningful difference in this association compared with the estimates derived from the entire population. This suggests that statins may act on physiologic mechanisms that are not influenced by smoking or diabetes. Our small sample sizes limited our ability to further adjust for other potential risk factors. In another analysis, we controlled for level of

serum total cholesterol in the event that the statin effect might reflect a beneficial effect on that lipid. This had no effect either when compared with the entire population or when restricting the analysis to those who were nonsmokers and did not have diabetes. These adjustments did not materially affect the estimate of the relationship of statins to nuclear cataract, suggesting that the mechanism is not entirely (or at all) due to decreased serum total cholesterol. Additional models adjusting for other potential confounders such as education, income, and hypertension did not affect the results. Nevertheless, our results could be affected by uncontrolled confounding.

Cataract surgery may be performed for any number of reasons that may be unrelated or only partly related to the presence of nuclear cataract as we have defined it. Cataract surgery criteria differ between practices, and more minimal levels of nuclear opacity may be considered a surgical indication in some practices. Also, persons with cortical or posterior subcapsular cataracts with minimal or no nuclear opacity may have had surgery. In addition, surgery may have been performed because of vision complaints that actually arose from previously undiagnosed or underappreciated conditions unrelated to nuclear cataract. For these reasons, our emphasis is placed on using gradings from photographs for the specific cataract types.

In examining whether a specific type of statin has differential effects, we found that simvastatin users had significantly less nuclear cataract development compared with nonusers of statins. The smaller reductions among atorvastatin and other statin users were not significant, but we did not have adequate power to identify significant relationships for ORs between 0.5 and 0.9. It is possible that duration of use may have been somewhat greater in users of simvastatin than for atorvastatin or other statins and dose may have had an effect. Although drug exposure was an inter-

est when the study was developed, it was not a primary aim. For pragmatic reasons, we opted not to obtain dose and duration information for many hundreds of drugs that were being assessed. Although information on dose and duration were not available, we were able to categorize statin users at each examination and consider the number of consecutive examinations with statin use as a surrogate for generally longer vs shorter duration of use. Those taking statins for more consecutive examinations had a lower rate of developing nuclear cataract despite overlapping CIs, which is compatible with the possibility that duration may be important.

Despite the small sample size, which limited the factors we could control for, we observed an association between statin use—in particular, simvastatin—and incident nuclear cataract. We did not find such a relationship for cortical or posterior subcapsular cataracts. Further study of the relationship of cataract and statin use is needed in which each type of cataract is considered individually. Further follow-up of our cohort, with anticipated increase in number of persons with cataract and wider use of statins, will permit us to evaluate whether our finding persists. In addition, evaluating the lens for the possibility of nuclear cataract could be incorporated into clinical trials that are currently ongoing or planned for purposes of evaluating these drugs in systemic diseases. This would provide important information concerning the association we have observed. The potential health care implications of the relationship between statin use and cataract incidence are great because nuclear cataract is the most common type of age-related cataract.

Author Contributions: Dr B. Klein had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: B. Klein, Lee.

Acquisition of data: R. Klein, Lee.

Analysis and interpretation of data: R. Klein, Lee, Grady.

Drafting of the manuscript: B. Klein, Lee.

Critical revision of the manuscript for important intellectual content: R. Klein, Lee, Grady.

Statistical analysis: Lee.

Obtained funding: B. Klein, R. Klein.

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Study supervision: B. Klein.

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