Statin Use and Incident Nuclear Cataract

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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.
in this analysis are shown in Figure 1. Comparisons between participants and nonparticipants at baseline and follow-up have been presented elsewhere.\textsuperscript{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.\textsuperscript{39} Grading procedures for the lens photographs were based on detailed codified decision rules.\textsuperscript{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.\textsuperscript{40,41} Whole-blood glycosylated hemoglobin was determined using affinity chromatography (Isolab Inc, Akron, Ohio) from nonfasting blood samples. Smoking and diabetes history 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

![Figure 1](image-url)

*The 598 nonparticipants at the first 2 examinations include 20 who completed interviews at both examinations.
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 cataract were 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 sample size, 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), fluvasatatin (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, fluvasatatin, 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

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (N = 1299)</th>
<th>Incident Nuclear Cataract (n = 210)</th>
<th>No Incident Nuclear Cataract (n = 1089)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SE), y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>697 (53.7)</td>
<td>130 (61.9)</td>
<td>567 (52.1)</td>
<td>.006</td>
</tr>
<tr>
<td>Education, mean (SE), y</td>
<td>13.1 (0.1)</td>
<td>12.5 (0.2)</td>
<td>13.3 (0.1)</td>
<td>.02</td>
</tr>
<tr>
<td><strong>Annual income, $§</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>72 (5.5)</td>
<td>15 (7.1)</td>
<td>57 (5.2)</td>
<td>.002</td>
</tr>
<tr>
<td>&lt;10,000</td>
<td>36 (2.8)</td>
<td>12 (5.7)</td>
<td>24 (2.2)</td>
<td></td>
</tr>
<tr>
<td>10,000-19,000</td>
<td>138 (10.6)</td>
<td>40 (19.0)</td>
<td>98 (9.0)</td>
<td></td>
</tr>
<tr>
<td>20,000-29,000</td>
<td>223 (17.2)</td>
<td>46 (21.9)</td>
<td>177 (16.3)</td>
<td></td>
</tr>
<tr>
<td>30,000-44,000</td>
<td>288 (22.2)</td>
<td>42 (20.0)</td>
<td>246 (22.6)</td>
<td></td>
</tr>
<tr>
<td>&gt;44,000</td>
<td>542 (41.7)</td>
<td>55 (26.2)</td>
<td>487 (44.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Body mass index, mean (SE)§‡§</strong></td>
<td></td>
<td></td>
<td></td>
<td>.59</td>
</tr>
<tr>
<td>Never</td>
<td>30.4 (0.2)</td>
<td>30.0 (0.4)</td>
<td>30.5 (0.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Blood pressure, mean (SE), mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
<td>.19</td>
</tr>
<tr>
<td>Systolic</td>
<td>129.2 (0.5)</td>
<td>132.1 (1.3)</td>
<td>128.6 (0.5)</td>
<td>.99</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76.0 (0.3)</td>
<td>74.5 (0.7)</td>
<td>76.3 (0.3)</td>
<td></td>
</tr>
<tr>
<td><strong>History of cardiovascular disease§</strong></td>
<td></td>
<td></td>
<td></td>
<td>.16</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.1)</td>
<td>0</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1164 (89.1)</td>
<td>188 (89.5)</td>
<td>976 (89.6)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>134 (10.3)</td>
<td>22 (10.5)</td>
<td>112 (10.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes§</strong></td>
<td></td>
<td></td>
<td></td>
<td>.65</td>
</tr>
<tr>
<td>Unknown</td>
<td>12 (0.9)</td>
<td>2 (1.0)</td>
<td>10 (0.9)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1153 (88.8)</td>
<td>186 (88.6)</td>
<td>967 (88.8)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>115 (8.9)</td>
<td>20 (9.5)</td>
<td>95 (8.7)</td>
<td></td>
</tr>
<tr>
<td><strong>History of smoking§</strong></td>
<td></td>
<td></td>
<td></td>
<td>.08</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>614 (47.3)</td>
<td>100 (47.6)</td>
<td>514 (47.2)</td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>546 (42.0)</td>
<td>84 (40.0)</td>
<td>462 (42.4)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>139 (10.7)</td>
<td>26 (12.4)</td>
<td>113 (10.4)</td>
<td></td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Incidence of nuclear cataract, No. (%)</th>
<th>No Statin Use</th>
<th>Statin Use</th>
<th>No Statin Use</th>
<th>Statin Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1029 (17.2)</td>
<td>270 (12.2)</td>
<td>472 (17.0)</td>
<td>88 (9.1)</td>
</tr>
<tr>
<td>Never Smokers With No Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted†</td>
<td>1.00</td>
<td>0.55 (0.36-0.84)</td>
<td>1.00</td>
<td>0.37 (0.16-0.82)</td>
</tr>
<tr>
<td>Fully adjusted†</td>
<td>1.00</td>
<td>0.60 (0.39-0.92)</td>
<td>1.00</td>
<td>0.40 (0.18-0.90)</td>
</tr>
</tbody>
</table>

*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.

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flavum have been shown to be re-
tract.47-50 Thus, it is plausible that pro-
sociated with different types of cata-
evidence of different genetic patterns as-
steroid preparations.45,46 There is also
cataract with hypertension27 and use of
incidence of nuclear cataract but not in-
clude these patients with possible in-
cident 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 in-
idence of cortical or posterior subcap-
sular cataracts. Different relationships
of specific exposures to specific cata-
act types have been previously ob-
erved. For example, nuclear cataract
is associated with cigarette smok-
ing,25,43,44 cortical cataract with UV ex-
posure,26 and posterior subcapsular cata-
lar has been suggested to result from
oxidative stress,7,8 and in-
flammation7,8 and in-
flammation51 may act on physiologic mechanisms
that are not influenced by smoking or
diabetes. Our small sample sizes lim-
ited 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 restrict-
ing the analysis to those who were
nonsmokers and did not have diabe-
tes. These adjustments did not materi-
ally affect the estimate of the relation-
ship of statins to nuclear cataract, sug-
gesting 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, in-
come, and hypertension did not
affect the results. Nevertheless, our
results could be affected by uncon-
trolled 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 dif-
fer between practices, and more mini-
mal 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 vi-
sion complaints that actually arose from
previously undiagnosed or underapp-
preciated conditions unrelated to
nuclear cataract. For these reasons, our
emphasis is placed on using gradings
from photographs for the specific cata-
lar 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 be-
tween 0.5 and 0.9. It is possible that
duration of use may have been some-
what greater in users of simvastatin
than for atorvastatin or other statins
and dose may have had an effect.

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

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

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

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 Cs, 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—particularly, 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.
Financial Disclosures: None reported.

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