Prospective Study of Statin Use and Risk of Parkinson Disease

Xiang Gao, MD, PhD; Kelly C. Simon, ScD; Michael A. Schwarzschild, MD, PhD; Alberto Ascherio, MD, DrPH

Objective: To prospectively examine whether use of statins is associated with altered risk of Parkinson disease (PD).

Design, Setting, and Participants: A prospective study including 38,192 men and 90,874 women participating in 2 ongoing US cohorts, the Health Professional Follow-up Study and the Nurses’ Health Study, was conducted. Information on regular cholesterol-lowering drug use (≥2 times/wk) was collected in 1994 in both cohorts via questionnaire. Relative risks (RRs) and 95% CIs were computed using Cox proportional hazards models adjusting for age, smoking, caffeine intake, duration of hypercholesterolemia, and other covariates.

Main Outcome Measure: Incident PD.

Results: During 12 years of follow-up (1994-2006), we documented 644 incident PD cases (338 women and 306 men). The risk of PD was lower among current statin users (adjusted pooled RR=0.74; 95% CI, 0.54-1.00; P=.049) relative to nonusers. A significant association was observed in participants younger than 60 years at baseline (adjusted pooled RR=0.31; 95% CI, 0.11-0.86; P=.02) but not among those who were older (adjusted pooled RR=0.83; 95% CI, 0.60-1.14; P=.25) (P for interaction=.03).

Conclusions: We found that regular use of statins was associated with a modest reduction in PD risk. The possibility that some statins may reduce PD risk deserves further consideration.

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Statins are one of most prescribed drug classes in the United States. Based on the 2003-2004 National Health and Nutrition Examination Survey, 24 million US adults (11.7%) were taking statins. Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase, the key enzyme that regulates the synthesis of cholesterol from mevalonic acid. Recently, statins have been found to have potent anti-inflammatory and immunomodulating effects, which led to the hypothesis that statins could be neuroprotective agents. However, the beneficial effects of statins could be offset by their unfavorable effects on lowering the level of plasma coenzyme Q10, which may be neuroprotective in individuals with PD. This potential for harm makes it all the more important to assess their effects. Several prospective studies have been conducted to examine the association between statin use and PD risk and have generated mixed results. As shown in a recent review, significant associations between statin use and lower PD risk were observed in 2 of 5 prospective studies. In 2 large registry studies published after that review, statin use was not significantly associated with PD risk overall. However, most of these studies were based on registry data and failed to control for several important confounders such as smoking and caffeine intake. We therefore conducted a prospective study to examine whether use of statins was associated with PD risk in 2 large ongoing US cohorts comprising approximately 140,000 men and women.

METHODS

STUDY POPULATION

The Nurses’ Health Study (NHS) cohort comprises 121,700 female registered nurses aged 30 to 55 years and residing in 1 of 11 US states at the time of enrollment in 1976. The cohort has been followed up by means of biennial mailed questionnaires that inquire about lifestyle practices and other exposures of interest as well as the incidence of disease. The Health Professional Follow-up Study (HPFS) was established in 1986, when 51,529 male US health...
professionals (dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians) aged 40 to 75 years completed a mailed similar questionnaire regarding their medical history and lifestyle. In both cohorts, follow-up questionnaires have been mailed to participants every 2 years to update information on potential risk factors and to ascertain newly diagnosed diseases.

The study was approved by the human research committees at the Harvard School of Public Health and the Brigham and Women’s Hospital, with receipt of each questionnaire accepted as the participant’s consent.

ASSESSMENT OF STATIN USE

In the NHS, women were asked to report regular use of cholesterol-lowering drugs (≥2 times/wk) in 1988, 1994, 1996, and 1998. In the HPFS, information on regular use of cholesterol-lowering drugs was assessed every 2 years from 1986 to 1998. Starting in the 2000 HPFS and NHS questionnaires and then every 2 years thereafter, participants were asked to report separately use of statins and other classes of cholesterol-lowering drugs. Because previous studies based on national data have shown that statins constituted the majority of the cholesterol-lowering drugs. Because previous studies based on national data have shown that statins constituted the majority of the cholesterol-lowering drugs since 1994,10 we used this year as the baseline for our primary analysis and considered use of any cholesterol-lowering drugs as statin use. This assumption is also supported by the fact that approximately 92% of participants who reported use of cholesterol-lowering drugs were statin users based on the 2000 questionnaire. In the current analysis, we excluded participants with PD onset in or prior to 1994 and those missing information on statin use at baseline, leaving 38,192 men and 90,874 women for analyses.

ASSESSMENT OF POTENTIAL COVARIATES

Dietary intakes were assessed every 4 years with validated semi-quantitative food frequency questionnaires in both cohorts.11 Information on age, weight, height, smoking status, elevated cholesterol level, hypertension, diabetes, coronary heart disease, and use of ibuprofen was collected through biennial questionnaires. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Duration of hypercholesterolemia was estimated by summing use across the 2-year periods encompassed by the biennial questionnaires.

ASCERTAINMENT OF PD

We identified new PD cases by biennial self-reported questionnaires.12,13 We then asked the treating neurologists to complete a questionnaire to confirm the diagnosis of PD or to send a copy of the medical record. A case was confirmed if a diagnosis of PD was considered definite or probable by the treating neurologist or internist, or if the medical record included a final diagnosis of PD made by a neurologist or evidence of at least 2 of the 3 cardinal signs (rest tremor, rigidity, bradykinesia) in the absence of features suggesting other diagnoses. The review of medical records was conducted by investigators blinded to the exposure status. Overall, the diagnosis was confirmed by the treating neurologist in more than 90% of the cases.

STATISTICAL ANALYSIS

We computed the person-time of follow-up for each participant from the return date of the baseline questionnaire (1994) to the date of the occurrence of the first symptoms of PD, the date of death, or the end of follow-up (2006), whichever came first. We categorized participants into regular users vs nonusers of statins at baseline and calculated relative risks (RRs) and 95% CIs using a Cox proportional hazards model controlling for age (in months), smoking status (never smoker, past smoker, current smoker of 1-14 cigarettes/d, or current smoker of ≥15 cigarettes/d), BMI (<23.0, 23.0-24.9, 25.0-26.9, 27.0-29.9, or ≥30.0), use of ibuprofen (yes or no), duration of hypercholesterolemia (in years), presence of coronary heart disease, hypertension, and diabetes (yes or no for each), and intake of alcohol (0, 1.0-4.9, 5.0-9.9, 10.0-14.9, or ≥15.0 g/d for women; 0, 1.0-9.9, 10.0-19.9, 20.0-29.9, or ≥30.0 g/d for men), caffeine (quantiles), and lactose (quantiles). Log RRs from the 2 cohorts were pooled by a random-effects model weighted by the inverse of their variances.

We also examined potential interactions between use of statins and age (continuous), smoking status (never vs ever), caffeine intake (based on median intake), BMI (<25.0 vs ≥25.0), and use of postmenopausal hormones (never vs ever) by adding multiplicative terms in the Cox models and adjusting for other potential confounders.

To take advantage of repeatedly collected information on statin use, in the secondary analysis we considered updated statin use to predict the subsequent incidence of PD. This is practically important because statin use has become increasingly more common during the period of follow-up of our cohorts. To test the robustness of our results, we conducted a sensitivity analysis by restricting to PD cases diagnosed by neurologists. An additional sensitivity analysis was conducted by imputing statin use in 1994 based on the duration of statin use reported in the 2000 HPFS and NHS questionnaires; in this analysis, participants were assumed to be statin users in 1994 if they reported a 6-year or longer duration of use in 2000 and were assumed to be nonusers otherwise.

RESULTS

Individuals who reported statin use had higher BMI, exercised less, were more likely to be a past smoker and to use ibuprofen, consumed less caffeine and more lactose, and had a higher prevalence of coronary heart disease, diabetes, and hypertension and a longer history of hypercholesterolemia relative to nonusers (Table 1). During 12 years of follow-up, we documented 644 incident PD cases (338 women and 306 men). The incidence of PD was lower among statin users relative to nonusers. The pooled RR of PD was 0.74 (95% CI, 0.54-

1.00; P = .049) comparing statin users with nonusers after adjusting for age, smoking, consumption of caffeine and lactose, use of ibuprofen, duration of hypercholesterolemia, history of major chronic diseases, and other potential confounders (Table 2). Results were similar after restricting the analyses to PD cases confirmed by a neurologist (pooled RR = 0.69; 95% CI, 0.48-0.99) or in analyses in which statin use in 1994 was imputed from the duration of statin use reported on the 2000 questionnaire (pooled RR = 0.76; 95% CI, 0.38-1.54). When we used updated statin use to predict incidence of PD, a significant association was seen for PD onset 6 or more years after statin use (pooled RR = 0.70; 95% CI, 0.53-0.93; P = .02) but not for short-term use (P > .20 for all) (Figure 1). These observations are consistent with the notion that PD has a long preclinical stage.15

We observed a significant interaction between statin use and age in relation to PD risk (P for interaction = .03). The significant association was observed in
participants younger than 60 years at the beginning of follow-up (adjusted pooled RR = 0.31; 95% CI, 0.11-0.86; \(P = .02\)) but not among those who were older (adjusted pooled RR = 0.83; 95% CI, 0.60-1.14; \(P = .25\)) (Figure 2). The interactions between smoking status, caffeine intake, or BMI and statin use on PD risk were not significant (\(P\) for interaction \(> .20\) for all).

In this prospective study, self-reported statin use was associated with a lower PD risk. Adjustment for smoking, caffeine intake, history of heart disease and hypercholesterolemia, and other potential confounders did not materially change the results.

The observed association between regular use of statins and lower PD risk is consistent with the results of in vivo and in vitro experimental studies in models of PD, which suggest that statins could reduce \(\alpha\)-synuclein accumulation and oxidative stress, suppress cyclooxygenase 2 expression, reduce release of tumor necrosis factor \(\alpha\) and nuclear factor \(\kappa\)B activation, activate peroxisome proliferator-activated receptor \(\gamma\), and up-regulate dopamine D1 and D2 receptors in the brain.\(^2,4,10,17\) These effects would be expected to alleviate neuroinflammation and reduce PD risk.

Epidemiologic studies have generated mixed results regarding statin use and PD risk. Significant protective effects of statins were observed in 2 retrospective case-control studies.\(^18,19\) However, recall and selection biases cannot be ruled out in these studies. In a prospective study based on the Rotterdam cohort (87 incident PD cases), use of any statins was associated with a nonsignificant 67% lower risk of PD (RR = 0.33; 95% CI, 0.08-1.35) after adjustment for age (in months), smoking status (never smoker, past smoker, current smoker of 1-14 cigarettes/d, or current smoker of \(\geq 15\) cigarettes/d), body mass index (calculated as weight in kilograms divided by height in meters squared; \(< 23.0, 23.0-24.9, 25.0-26.9, 27.0-29.9, \text{or } \geq 30.0\)), intake of caffeine (quintiles), lactose (quintiles), and alcohol (0, 1.0-4.9, 5.0-9.9, 10.0-14.9, or \(\geq 15.0\) g/d for women; 0, 1.0-9.9, 10.0-19.9, 20.0-29.9, or \(\geq 30.0\) g/d for men), physical activity (quintiles), use of ibuprofen (yes or no), duration of hypercholesterolemia (in years), and presence of coronary heart disease, hypertension, and diabetes (yes or no for each).

### Table 1. Basic Characteristics According to Use of Statins at Baseline in the Health Professionals Follow-up Study and the Nurses’ Health Study in 1994

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Use of Statins by Men</th>
<th>Use of Statins by Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 34 886)</td>
<td>Yes (n = 33 066)</td>
</tr>
<tr>
<td>Age, mean, y</td>
<td>62.0</td>
<td>61.9</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>6.1</td>
<td>5.2</td>
</tr>
<tr>
<td>Current</td>
<td>49.8</td>
<td>55.5</td>
</tr>
<tr>
<td>Past</td>
<td>25.9</td>
<td>26.3</td>
</tr>
<tr>
<td>BMI, mean</td>
<td>14.1</td>
<td>13.4</td>
</tr>
<tr>
<td>Intake, mean</td>
<td>232</td>
<td>216</td>
</tr>
<tr>
<td>Alcohol, g/d</td>
<td>36.4</td>
<td>33.2</td>
</tr>
<tr>
<td>Caffeine, mg/d</td>
<td>12.9</td>
<td>15.4</td>
</tr>
<tr>
<td>Lactose, g/d</td>
<td>2.1</td>
<td>6.5</td>
</tr>
<tr>
<td>Physical activity, mean, MET/wk</td>
<td>3.14</td>
<td>49.7</td>
</tr>
<tr>
<td>Use of ibuprofen, %</td>
<td>5.3</td>
<td>9.4</td>
</tr>
<tr>
<td>Duration of hypercholesterolemia, mean, y</td>
<td>3.14</td>
<td>9.4</td>
</tr>
<tr>
<td>Coronary heart disease, %</td>
<td>3.14</td>
<td>9.4</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>3.14</td>
<td>9.4</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>3.14</td>
<td>9.4</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MET, metabolic equivalents.

### Table 2. Use of Statins and Parkinson Disease Risk in the Health Professionals Follow-up Study and the Nurses’ Health Study From 1994 to 2006

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Use of Statins</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age- and smoking-adjusted RR (95% CI)</td>
<td>1 [Reference]</td>
<td>0.79 (0.52-1.20)</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)(^a)</td>
<td>1 [Reference]</td>
<td>0.78 (0.50-1.22)</td>
</tr>
<tr>
<td>NHS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age- and smoking-adjusted RR (95% CI)</td>
<td>1 [Reference]</td>
<td>0.74 (0.50-1.11)</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)(^a)</td>
<td>1 [Reference]</td>
<td>0.70 (0.46-1.07)</td>
</tr>
<tr>
<td>Pooled RR (95% CI)</td>
<td>1 [Reference]</td>
<td>0.74 (0.54-1.00)</td>
</tr>
</tbody>
</table>

Abbreviations: HPFS, Health Professionals Follow-up Study; NHS, Nurses’ Health Study; RR, relative risk.

\(^a\) Adjusted for age (in months), smoking status (never smoker, past smoker, current smoker of 1-14 cigarettes/d, or current smoker of \(\geq 15\) cigarettes/d), body mass index (calculated as weight in kilograms divided by height in meters squared; \(< 23.0, 23.0-24.9, 25.0-26.9, 27.0-29.9, \text{or } \geq 30.0\)), intake of caffeine (quintiles), lactose (quintiles), and alcohol (0, 1.0-4.9, 5.0-9.9, 10.0-14.9, or \(\geq 15.0\) g/d for women; 0, 1.0-9.9, 10.0-19.9, 20.0-29.9, or \(\geq 30.0\) g/d for men), physical activity (quintiles), use of ibuprofen (yes or no), duration of hypercholesterolemia (in years), and presence of coronary heart disease, hypertension, and diabetes (yes or no for each).
Women differ in blood-brain barrier penetrability. For example, it was not observed in another Denmark-based prospective study, but not all prospective studies using registry data. However, these studies were limited by residual confounding and potential misclassification of PD diagnosis.

We observed that the association between statin use and PD was modified by age—the protective effects of statins appeared only among adults younger than 60 years. In a previous case-control study, a slightly stronger association was also seen in younger participants (aged <60 years) relative to older participants. However, such difference was not observed in another Denmark-based prospective study. Because we used cholesterol-lowering drug use as a surrogate of statin use in our study, we cannot exclude the possibility that the significant statin × age interaction is confounded by the indications that younger participants were more likely to receive the newer and more expensive cholesterol-lowering drugs such as statins relative to older participants.

Our results should be interpreted in the context of several limitations. Because we classified use of any cholesterol-lowering drugs before 2000 as statin use, misclassification was inevitably introduced. However, based on the US retail prescription data, statins accounted for 72% of total cholesterol-lowering drug use in 1994 and 80% in 1996. In the HPFS and NHS, statins accounted for more than 90% of all cholesterol-lowering drugs used in 2000.

Further, the sensitivity analysis based on the information on duration of statin use on the 2000 questionnaire generated similar results.

We did not collect information on use of specific statins, which could have different effects on the central nervous system owing to differences in synthetic origins and structure (eg, lipophilicity vs hydrophilicity) and thus differ in blood-brain barrier penetrability. For example, lovastatin and simvastatin have been shown to have more potency to cross the blood-brain barrier relative to atorvastatin calcium. Further, hypouricemic effects differ among various statins. Previous studies have reported that atorvastatin, but not simvastatin, can lower the level of serum urate, a powerful antioxidant associated with lower PD risk or slower disease progression among individuals with PD. However, based on the national retail data, lovastatin and simvastatin were the 2 most commonly used statins from 1994 to 1996, composing approximately 60% to 70% of total statins. Our results therefore could be largely driven by these 2 subclasses. Interestingly, simvastatin use was associated with a lower PD risk in 2 previous prospective studies. Although this has been shown to reduce α-synuclein accumulation and nitric oxide production in animal studies, human studies regarding lovastatin and PD risk generated inconsistent results.

Another limitation is that we cannot exclude a possibility of residual confounding because of the observational study design. Among participants in these cohorts, we have previously reported a significant association between ibuprofen use and lower PD risk. Further, indication bias cannot be excluded because an elevated level of cholesterol has been found to be associated with lower PD risk in some but not all previous prospective studies, as reviewed elsewhere.

It is important to note that statins may have unfavorable effects on the central nervous system. Because 3-hydroxy-3-methylglutaryl coenzyme A involves the synthesis of coenzyme Q10, inhibition of this enzyme by statins leads to reduction of concentrations of serum coenzyme Q10, which is an essential carrier in the mitochondrial respiratory chain and is under clinical investigation for the treatment of PD. Further, as discussed earlier, certain statins could lower plasma urate concentrations. A case report found that use of lovastatin was associated with onset of PD symptoms. However, this has not been confirmed by large-scale prospective studies.

In summary, we observed an association between regular use of statins and lower risk of developing PD, par-
particularly among younger participants. However, our results should be interpreted with caution because only approximately 70% of users of cholesterol-lowering drugs at baseline were actual statin users. Further, the results were only marginally significant and could be due to chance. In contrast with use of ibuprofen, which has been consistently found to be inversely associated with PD risk in these cohorts (pooled RR = 0.62; 95% CI, 0.42-0.93) as well as in other longitudinal studies, the overall epidemiological evidence relating statin use to PD risk remains unconvincing. Given the potential adverse effects of statins, further prospective observational studies are needed to explore the potential effects of different subtypes of statins on risk of PD and other neurodegenerative diseases.

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Correspondence: Xiang Gao, MD, PhD, Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, 181 Longwood Ave, Boston, MA 02115 (xiang.gao@channing.harvard.edu).

Author Contributions: Study concept and design: Gao and Ascherio. Acquisition of data: Gao, Schwartz, and Ascherio. Analysis and interpretation of data: Gao, Simon, Schwartz, and Ascherio. Drafting of the manuscript: Gao. Critical revision of the manuscript for important intellectual content: Simon, Schwartz, and Ascherio. Statistical analysis: Gao, Simon, and Ascherio. Obtained funding: Ascherio. Administrative, technical, and material support: Schwartz, and Ascherio.

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