RESEARCH ARTICLE

Statin Use and Incidence of Parkinson's Disease in Women from the French E3N Cohort Study

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ABSTRACT: Background: Statins represent candidates for drug repurposing in Parkinson's disease (PD). Few studies examined the role of reverse causation, statin subgroups, and dose–response relations based on time-varying exposures.
Objectives: We examined whether statin use is associated with PD incidence while attempting to overcome the limitations described previously, especially reverse causation.
Method: We used data from the E3N cohort study of French women (follow-up, 2004–2018). Incident PD was ascertained using multiple sources and validated by experts. New statin users were identified through linked drug claims. We set up a nested case-control study to describe trajectories of statin prescriptions and medical consultations before diagnosis. We used time-varying multivariable Cox proportional hazards regression models to examine the statins–PD association. Exposure indexes included ever use, cumulative duration/dose, and mean daily dose and were lagged by 5 years to address reverse causation.
Results: The case-control study (693 cases, 13,784 controls) showed differences in case-control trajectories, with changes in the 5 years before diagnosis in cases. Of 73,925 women (aged 54–79 years), 524 developed PD and 11,552 started using statins in lagged analyses. Ever use of any statin was not associated with PD (hazard ratio [HR] = 0.87, 95% confidence interval [CI] = 0.67–1.11). Alternatively, ever use of lipophilic statins was significantly associated with lower PD incidence (HR = 0.70, 95% CI = 0.51–0.98), with a dose–response relation for the mean daily dose (*P*-linear trend = 0.02). There was no association for hydrophilic statins.
Conclusion: Use of lipophilic statins at least 5 years earlier was associated with reduced PD incidence in women, with a dose–response relation for the mean daily dose. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease; pharmacoepidemiology; drug repurposing; statins; cohort studies

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Relevant conflicts of interest/financial disclosures: T.T.H.N. was supported by postdoctoral grants from The Michael J. Fox Foundation and the France Parkinson Association. E.C. was supported by postdoctoral grants from The Michael J. Fox foundation. F.A., S.E., P.T.-B., I.A., and A.C.M.T. report no disclosures. M.-C.B.-R. received speaker fees in 2020 from Mayoli-Spindler and Gilead outside the field of the present article. I.D. reports no disclosures. E.R. received honorarium for speeches from Orkyn Aguettant and Elivie and for participating in an advisory board from Allergan and has received research support from Merz-Pharma, Orkyn, Aguettant, Elivie, Ipsen, Allergan, Everpharma, Fondation Desmarest, AMADYS, ADCY5.org, French National Research Agency (ANR), Societé Française de Médecine Esthétique, and the Dystonia Medical Research Foundation. M.C. obtained a research grant from the ANR. A.E. has obtained research grants from Plan Ecophyto (French Ministry of Agriculture) and France Parkinson Association. The work reported in this article was performed during A.F.'s term as a visiting scientist at the International Agency for Research on Cancer. The authors declare no other relationships or activities that could appear to have influenced the submitted work.

Funding agencies: This project was funded by the Michael J. Fox Foundation for Parkinson's Research and the France Parkinson Association.

Received: 26 October 2022; **Revised:** 2 January 2023; **Accepted:** 30 January 2023

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29349

Available Parkinson's disease (PD) treatments do not allow slowing its progression. Drug repurposing represents a promising strategy to identify new treatments that could be used to treat or even prevent or delay PD.[1] Statins represent potential candidates that have been investigated in observational studies.[2-7] The latest meta-analysis pooled nine cohort and eight case-control studies and reported a pooled odds ratio (OR) of PD for ever statin use of 0.92 (95% confidence interval [CI] = 0.88–0.97; heterogeneity: $I^2 = 39\%$; $P = 0.05$); the association was present in cohort studies (OR = 0.88, 95% CI = 0.83–0.93), but not in case–control studies (OR = 1.01, 95% CI = 0.94–1.09).[7] Methodological differences likely account for inconsistent findings between cohort and case-control studies. Survival bias may be an issue in case-control studies for exposures associated with survival, in particular in studies with prevalent statin users or prevalent PD cases; in addition, case-control studies are more prone to recall and selection biases.[8]

Nevertheless, cohort studies (Table S1) faced other methodological challenges. The long prodromal PD phase may induce reverse causation because nonmotor and motor symptoms could influence statin use before diagnosis.[9,10] Thus, long follow-ups, allowing lagged analyses while retaining a sufficient number of cases, are necessary to decrease the risk of reverse causation; this issue was rarely addressed in previous studies.[11,12] In addition, several cohort studies considered a fixed exposure at baseline and did not examine changes in exposure over the follow-up.[13-19] Most studies based on electronic databases[11,14,18-20] did not adjust for major confounders (eg, smoking, physical activity).[21] Last, lipophilic statins cross the blood–brain barrier more freely than hydrophilic statins,[22] and only some studies distinguished them.[11,12,14,18,20,23]

We examined whether statins (overall, lipophilic, hydrophilic) are associated with reduced PD incidence in a cohort of French women followed for 15 years, while attempting to overcome the limitations described previously, in particular the incomplete consideration of reverse causation.

Materials and Methods

Participants

E3N is a French cohort study of 98,995 women, born between 1925 and 1950, recruited in 1990, and affiliated with a French national health insurance plan covering mostly teachers (*Mutuelle Générale de l'Education Nationale*).[24]

Participants completed a self-administered questionnaire on lifestyle and medical history at baseline and every 24 to 36 months thereafter. A total of 11 waves of data are available (last, questionnaire Q11-2014; average response rate of 80%).

Since January 1, 2004, drug and medical consultations claims databases were available for 95% of women alive in 2004. Women who stopped responding to questionnaires can be followed in these databases in order to assess statin use. Causes of death for women who died were available.

All participants signed informed consent, in compliance with the rules of The French National Commission for Data Protection and Privacy, which approved the study. Its protocol is registered at clinicaltrials.gov (NCT03285230).

Statin Use

We used drug claims databases to assess statin use (prescription-only medications) during the follow-up (January 1, 2004 to December 31, 2018). These databases include detailed information on drugs, doses, and dates of purchase. Statins were identified by their Anatomical Therapeutic Chemical (ATC) codes (ATC-C10AA/C10BA/C10BX). To account for differences in recommended daily doses for different statins, doses were converted to defined daily doses (DDD).[25]

We first considered ever use of any statin and then distinguished lipophilic (atorvastatin, fluvastatin, simvastatin) from hydrophilic statins (pravastatin, rosuvastatin).[22]

To assess the role of cumulative duration and dose of treatment, for each statin claim, we extracted information on date of purchase, number of tablets delivered, and dose of each tablet. Under the assumption of one tablet per day,[26-28] we defined the theoretical duration of use (equal to the number of tablets), the theoretical end date, and the daily dose (equal to the dose of tablet).[29] For each claim, the duration of use is the absolute difference between the date of purchase and the minimum of the theoretical end date and date of the next purchase; the total dose of a given claim is obtained by multiplying the duration by the daily dose. Cumulative duration or cumulative dose at any given date was computed by summing up durations or doses up to that date; the mean daily dose was computed by dividing the cumulative dose by the cumulative duration.

Other covariates are described in the Supplementary Methods.

Parkinson's Disease

Our approach to ascertain PD is described in detail elsewhere.[30] Potential PD patients were identified through self-reported doctor diagnoses of PD in questionnaires, antiparkinsonian drug claims (ATC-N04), and death certificates (International Classification of Disease 332.0, G20). When possible, potential PD patients were contacted by mail to confirm the diagnosis. For women who confirmed a PD/parkinsonism

diagnosis and those who could not be contacted, we obtained detailed medical records from their neurologists that were reviewed by an expert panel to adjudicate PD status (definite, probable, possible, no PD).[31] Only definite and probable PD were retained for the analyses.

When no medical records were available, we predicted PD status using a validated algorithm based on antiparkinsonian drug claims and medical visits.[30,32] The proportion of PD diagnoses based on medical records and the algorithm is 62% and 38%, respectively.

Year of PD diagnosis was set as the year of diagnosis (medical records) or, in decreasing order of priority, self-reported year of diagnosis, year of first use of antiparkinsonian drugs, and year of the first questionnaire where PD was self-reported.

We previously showed that PD incidence rates in E3N are in agreement with those observed in women from Western Europe between 1992 and 2018 according to the Global Burden of Disease.[30]

Study Population

Figure 1 illustrates participant selection for survival analyses. We included women who were alive on January 1, 2004. We defined a washout period of 6 months (new user design) to retain only incident statin users (ie, statin users during the first 6 months were excluded); based on the new user design, dose or duration of use are not prone to left truncation, allowing exact values to be used.[33] We also excluded women lost to follow-up during this period. Thus, statin exposure assessment started on July 1, 2004.

To address reverse causation, we included a 5-year exposure lag, during which we assumed that statin exposure would not affect PD risk. This lag was in agreement with the results of our analyses of statin use and medical consultation trajectories (Supplementary Methods). Hence, follow-up for PD incidence started 5 years after statin exposure (ie, July 1, 2009).

We retained for our analyses women who were PD-free on July 1, 2009, with drug reimbursements after that date. End of follow-up was the earliest of date of PD diagnosis, death, end-of-drug reimbursements +5 years, or December 31, 2018.

Statistical Analysis

Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC) and Stata16 (StataCorp, College Station, TX). Two-tailed P values ≤0.05 were considered statistically significant.

Participant characteristics (2004) are described overall and according to statin use and PD status at the end of follow-up.

A nested case-control study was used to describe statin use and medical consultations trajectories prior to PD diagnosis in cases and matched controls and to assess whether trajectories changed in cases compared

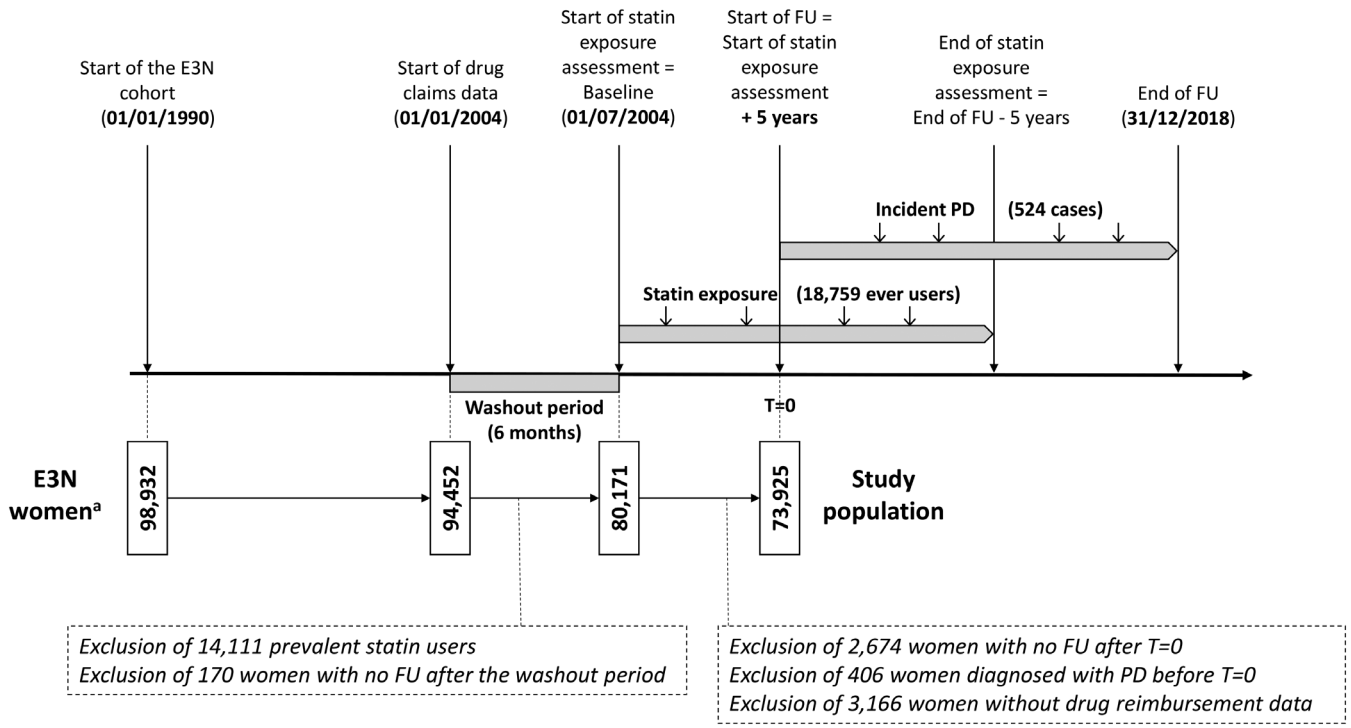

FIG. 1. Study design for the analysis of the relation between time-varying statin exposure and PD with a 5-year lag. FU, follow-up; PD, Parkinson's disease. [a]Of the 98,995 E3N women recruited in 1990, we excluded 50 women with possible PD and 13 women with an unknown date of PD diagnosis.

TABLE 1 *Baseline characteristics of the study population, overall and according to statin exposure*

Characteristics in 2004	All women, N = 73,925	Statin exposure at the end of the FU	
		Ever users, n = 18,759	Never users, n = 55,166
Age, y, mean (SD)	62.5 (6.3)	63.0 (6.2)	62.3 (6.3)
Residence, n (%)			
Rural	10,017 (14.9)	2545 (14.9)	7472 (14.9)
Urban	57,376 (85.1)	14,551 (85.1)	42,825 (85.1)
Missing	6532	1663	4869
Education, n (%)			
<High school	7840 (11.1)	2432 (13.5)	5408 (10.2)
Up to 2 university y	35,756 (50.5)	9360 (52.0)	26,396 (50.0)
>2 university y	27,206 (38.4)	6197 (34.4)	21,009 (39.8)
Missing	3123	770	2353
Parity, n (%)			
Nulliparous	8905 (12.1)	2147 (11.5)	6758 (12.3)
1 child	12,057 (16.4)	2985 (16.1)	9072 (16.6)
2 children	31,894 (43.5)	8140 (43.8)	23,754 (43.4)
≥3 children	20,532 (28.0)	5329 (28.6)	15,203 (27.7)
Missing	537	158	379
Age at menarche, y, n (%)			
<12	15,074 (20.9)	4017 (22.0)	11,057 (20.5)
12–13	18,302 (25.4)	4657 (25.5)	13,645 (25.3)
≥13	38,780 (53.7)	9619 (52.5)	29,161 (54.2)
Missing	1769	466	1303
Caffeine consumption, mg/d, n (%)			
<94	14,144 (25.0)	3367 (24.1)	10,777 (25.2)
94–174	13,974 (24.7)	3405 (24.4)	10,569 (24.8)
174–271	14,123 (24.9)	3541 (25.3)	10,582 (24.8)
≥271	14,412 (25.4)	3658 (26.2)	10,754 (25.2)
Missing	17,272	4788	12,484
Smoking status, n (%)			
Nonsmoker	38,774 (52.6)	9888 (52.9)	28,886 (52.5)
Former smoker	26,526 (36.0)	6485 (34.7)	20,041 (36.4)
Current smoker	8421 (11.4)	2336 (12.5)	6085 (11.1)
Missing	204	50	154
Body mass index, kg/m^2, n (%)			
<18.5	2455 (3.3)	405 (2.2)	2050 (3.7)
18.5–25.0	49,883 (67.6)	11,566 (61.7)	38,317 (69.5)
25.0–30.0	16,708 (22.6)	5062 (27.0)	11,646 (21.1)
≥30.0	4799 (6.5)	1702 (9.1)	3097 (5.6)

(Continues)

TABLE 1 *Continued*

Characteristics in 2004	All women, N = 73,925	Statin exposure at the end of the FU	
		Ever users, n = 18,759	Never users, n = 55,166
Missing	80	24	56
Physical activity, n (%)[a]			
Quartile 1	18,686 (25.3)	5012 (26.8)	13,674 (24.8)
Quartile 2	18,088 (24.5)	4435 (23.7)	13,653 (24.8)
Quartile 3	18,572 (25.2)	4623 (24.7)	13,949 (25.3)
Quartile 4	18,459 (25.0)	4652 (24.8)	13,807 (25.1)
Missing	120	37	83
Menopause, n (%)			
No	1228 (1.7)	278 (1.5)	950 (1.8)
Natural	60,256 (84.9)	15,043 (83.5)	45,213 (85.3)
Artificial	6695 (9.4)	1920 (10.7)	4775 (9.0)
Unknown type	2832 (4.0)	783 (4.3)	2049 (3.9)
Missing	2914	735	2179
Number of consultations, n (%)[b]			
<2	12,348 (16.7)	2445 (13.0)	9903 (18.0)
2–4	20,601 (27.9)	5014 (26.7)	15,587 (28.3)
4–6	16,768 (22.7)	4406 (23.5)	12,362 (22.4)
≥6	24,208 (32.7)	6894 (36.8)	17,314 (31.4)
Comorbidities, n (%)			
Hypercholesterolemia	20,308 (27.5)	8113 (43.2)	12,195 (22.1)
Type 2 diabetes	1813 (2.5)	998 (5.3)	815 (1.5)
Hypertension	19,837 (26.8)	6622 (35.3)	13,215 (24.0)
Cardiovascular disease	1310 (1.8)	563 (3.0)	747 (1.4)
Hyperuricemia	975 (1.3)	335 (1.8)	640 (1.2)
Other lipid-lowering drugs[b]			
Fibrates	6008 (8.1)	2830 (15.1)	3178 (5.8)

Abbreviations: FU, follow-up; SD, standard deviation.
[a]Total physical activity defined based on a latent class mixed model and categorized in quartiles.
[b]Assessed during the first 6 months of 2004.

with controls during the prodromal PD phase (Supplementary Methods).

To estimate the association between statin use and PD incidence, we used the Cox proportional hazards regression model for time-varying covariates with age as the time scale.[34] The strength of the associations is quantified through hazard ratios (HRs; 95% CIs). Given the 5-year lag, the hazard of PD at time t is a function of exposure up to 5 years earlier.

Exposures included ever use of statins (any type, lipophilic, hydrophilic), cumulative dose and duration of use, and mean daily dose. We fitted exposures in a time-varying manner based on the exact dates of statin purchases, allowing participants to move from non-exposure to exposure and to update during the follow-up cumulative duration/dose and daily dose. Continuous exposures were categorized in the following four groups: never use and three groups based on tertiles of their distribution in ever users; a four-level ordinal variable corresponding to the medians of each group was used to test for linear trend. For analyses of lipophilic and hydrophilic statins, both types were included in the same model; interactions between the two were not statistically significant and were not retained in the models.

Potential confounders were considered as fixed or time-varying (Supplementary Methods) and lagged in

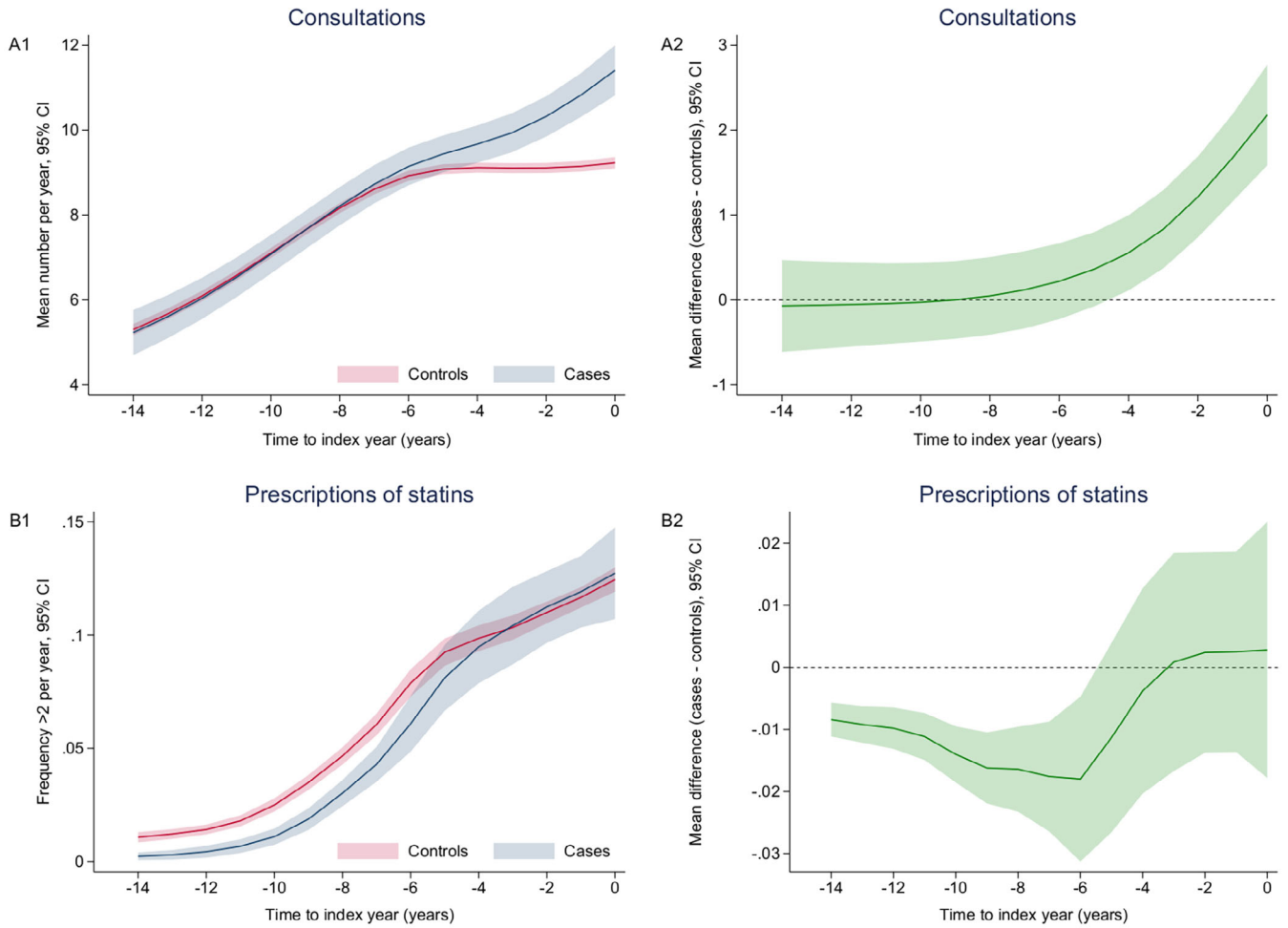

FIG. 2. Trajectories of statin prescriptions and medical consultations in cases and controls before the index date. The figures show estimates (95% confidence intervals [CIs]) of (**A1**) the mean annual number of prescriptions of medical consultations and (**B1**) the frequency of >2 annual prescriptions of statins in cases and controls aged 75 years old at the index date (index year = 0) based on marginal predictions of a mixed Poisson (consultations) or logistic (statins) regression model with time in years (backward scale) coded as restricted cubic splines. (**A2**, **B2**) Corresponding average differences between cases and controls; differences whose CIs do not include 0 are statistically significant ($P \leq 0.05$). [Color figure can be viewed at wileyonlinelibrary.com]

the same way as statins. A missing category was created for covariates with missing values.

Sensitivity analyses are described in the Supplementary Methods.

Results

Characteristics of the Study Population

The study population consisted of 73,925 women aged 62.5 years (standard deviation [SD], 6.3) at baseline (July 1, 2004) (Fig. 1). Table 1 shows participant characteristics. During the study period, 18,759 (25.4%) women started using statins. In comparison with never users, statin users tended to be older at baseline and have lower education and physical activity level, earlier age at menarche, more children, higher body mass index [BMI], and more frequent medical contacts and comorbidities. They consumed more caffeine and were more often current smokers, postmenopausal, and fibrates users.

Between July 1, 2004 to December 31, 2018, 693 women developed PD. After excluding those who developed PD within the first 5 years, 524 participants developed PD between July 1, 2009 and December 31, 2018 (669,836 person-years; mean follow-up = 9.1 years, SD = 1.5; incidence rate/1000 person-years = 0.78, 95% CI = 0.72–0.85). Compared with those who did not, women who developed PD were older, less often obese, more frequently postmenopausal, and had more children and a more frequent history of hypercholesterolemia; they consumed less caffeine and were less frequently smokers (Table S2).

Trajectories of Statin Use and Medical Consultations Prior to Disease Diagnosis

The case-control sample included 693 incident PD cases and 13,784 controls; 680 cases were matched to

TABLE 2 *Association of statin use with incidence of Parkinson's disease: analyses lagged by 5 years*

Statin use	No. of cases, N = 524	Age-adjusted HR (95% CI)	*P* value	Fully adjusted HR (95% CI)	*P* value
Never use	444	1.00 (Reference)	0.23	1.00 (Reference)	0.26
Ever use	80	0.87 (0.68–1.10)		0.87 (0.67–1.11)	
Cumulative duration,d					
Never	444	1.00 (Reference)	0.57[a]	1.00 (Reference)	0.66[a]
<171	26	0.89 (0.60–1.32)		0.89 (0.60–1.34)	
171–729	23	0.75 (0.49–1.14)		0.75 (0.49–1.16)	
≥729	31	0.95 (0.66–1.37)		0.96 (0.65–1.40)	
Cumulative dose (DDDs)					
Never	444	1.00 (Reference)	0.50[a]	1.00 (Reference)	0.57[a]
<108	26	0.89 (0.60–1.33)		0.89 (0.60–1.33)	
108–454	24	0.78 (0.52–1.18)		0.78 (0.51–1.18)	
≥454	30	0.92 (0.63–1.33)		0.92 (0.63–1.36)	
Average daily dose (DDDs)					
Never	444	1.00 (Reference)	0.20[a]	1.00 (Reference)	0.27[a]
<0.5	6	0.96 (0.43–2.15)		0.94 (0.42–2.10)	
0.5–0.67	42	0.90 (0.66–1.24)		0.91 (0.66–1.26)	
≥0.67	32	0.80 (0.56–1.15)		0.83 (0.57–1.20)	

Abbreviations: HR, hazard ratio; CI, confidence interval; DDD, defined daily dose.
Note; HRs, 95% CIs, and *P* values were computed using Cox proportional hazards regression for time-varying variables with age as the timescale. HRs were adjusted for baseline type of residence, education level, parity, age at menarche, and caffeine consumption and for time-varying smoking status, body mass index, physical activity level, menopausal status, number of consultations in the previous 6 months, comorbidities, and use of fibrates.
[a]*P* values for linear trend.

20 controls, 11 cases were matched to 10 to 19 controls, and two cases were matched to <10 controls. Trajectories of medical consultations and statin prescriptions were different in cases and controls (both $P < 0.001$; Fig. 2). The average annual number of consultations increased during the follow-up in cases and controls, and there was no difference between the two groups until approximately 5 years prior to diagnosis (Fig. 2A1, 2A2); it then continued to increase in cases while it plateaued in controls at approximately 9/year, with an average difference at index year (Y0) of 2.2 (95% CI = 1.6–2.8; $P < 0.001$).

The frequency of >2 annual statin prescriptions increased over time; it was significantly lower in cases compared with controls until approximately 5 years prior to diagnosis, when it became similar (difference at Y0 = 0.0, 95% CI = −0.02 to 0.02; $P = 0.79$) (Fig. 2B1, 2B2).

Association of Statins with PD Incidence

Table 2 summarizes our analyses of the relation between incident statin use (overall) and PD incidence. Compared with never users, ever users had a nonsignificantly decreased PD incidence (HR = 0.87, 95% CI = 0.67–1.11). There was no evidence of a dose–response relation for any exposure index.

During the follow-up, 11,552 (15.6%) women used lipophilic and 11,198 (15.1%) hydrophilic statins; of these, 3991 (5.4%) used both types. Lipophilic statin users were older at baseline and more often diabetic and hypertensive than hydrophilic statin users; there were no major differences for other covariates, including hypercholesterolemia and cardiovascular disease (Table S3). In the fully adjusted model (Table 3), PD incidence was 30% significantly lower in ever users of lipophilic statins (HR = 0.70, 95% CI = 0.51–0.98) compared with never users, whereas there was no association for hydrophilic statins (HR = 1.03, 95% CI = 0.75–1.40). For lipophilic statins, HRs decreased with increasing doses (P trend = 0.02), with a statistically significant inverse association for the highest tertile (HR = 0.52, 95% CI = 0.30–0.91); this trend was present in analyses restricted to lipophilic statin users (P trend = 0.04). There were no dose–response relations for other exposure indexes for lipophilic statins or

TABLE 3 *Association of lipophilic and hydrophilic statin use with incidence of Parkinson's disease: analyses lagged by 5 years*

Statin use	No. of cases, N = 524	Age-adjusted HR (95% CI)	*P* value	Fully adjusted HR (95% CI)	*P* value
Lipophilic statins					
Never use	483	1.00 (Reference)	0.03	1.00 (Reference)	0.04
Ever use	41	0.70 (0.51–0.97)		0.70 (0.51–0.98)	
Cumulative duration, d					
Never	483	1.00 (Reference)	0.43[a]	1.00 (Reference)	0.48[a]
<113	14	0.75 (0.44–1.28)		0.76 (0.44–1.31)	
113–595	8	0.41 (0.20–0.83)		0.41 (0.20–0.84)	
≥595	19	0.92 (0.58–1.47)		0.93 (0.58–1.48)	
Cumulative dose (DDDs)					
Never	483	1.00 (Reference)	0.33[a]	1.00 (Reference)	0.38[a]
<75	14	0.76 (0.44–1.30)		0.76 (0.44–1.30)	
75–378	9	0.47 (0.24–0.91)		0.47 (0.24–0.91)	
≥378	18	0.88 (0.55–1.41)		0.88 (0.54–1.42)	
Average daily dose (DDDs)					
Never	483	1.00 (Reference)	0.02[a]	1.00 (Reference)	0.02[a]
<0.5	5	1.00 (0.41–2.41)		0.98 (0.40–2.37)	
0.5–0.67	23	0.84 (0.55–1.28)		0.83 (0.54–1.27)	
≥0.67	13	0.50 (0.29–0.87)		0.52 (0.30–0.91)	
Hydrophilic statins					
Never use	476	1.00 (Reference)	0.84	1.00 (Reference)	0.87
Ever use	48	1.03 (0.76–1.40)		1.03 (0.75–1.40)	
Cumulative duration, d					
Never	476	1.00 (Reference)	0.70[a]	1.00 (Reference)	0.74[a]
<134	15	1.01 (0.60–1.70)		1.01 (0.60–1.70)	
134–589	18	1.20 (0.74–1.93)		1.19 (0.74–1.93)	
≥589	15	0.93 (0.56–1.56)		0.93 (0.55–1.57)	
Cumulative dose (DDDs)					
Never	476	1.00 (Reference)	0.99[a]	1.00 (Reference)	0.98[a]
<82.5	15	1.01 (0.60–1.69)		1.01 (0.60–1.69)	
82.5–363	16	1.05 (0.63–1.73)		1.04 (0.63–1.72)	
≥363	17	1.06 (0.65–1.72)		1.05 (0.64–1.72)	
Average daily dose (DDDs)					
Never	476	1.00 (Reference)	0.73[a]	1.00 (Reference)	0.70[a]
<0.5	2	1.10 (0.27–4.40)		1.05 (0.26–4.20)	
0.5–0.67	23	0.95 (0.62–1.45)		0.96 (0.63–1.47)	
≥0.67	23	1.14 (0.75–1.74)		1.15 (0.75–1.76)	

Abbreviations: HR, hazard ratio; CI, confidence interval; DDD, defined daily dose.

Note: HRs, 95% CIs, and *P* values were computed using Cox proportional hazards regression for time-varying variables with age as the timescale. Lipophilic (atorvastatin, fluvastatin, simvastatin) and hydrophilic (pravastatin, rosuvastatin) statins were included in the same model. HRs were adjusted for baseline type of residence, education level, parity, age at menarche, and caffeine consumption and for time-varying smoking status, body mass index, physical activity level, menopausal status, number of consultations in the previous 6 months, comorbidities, and use of fibrates.

[a]*P* values for linear trend.

for any exposure index for hydrophilic statins. HRs for the highest tertile of dose were different between lipophilic and hydrophilic statins ($P = 0.03$).

To better understand differences in dose–response relations for exposure indexes to lipophilic statins, we included in a model both continuous cumulative dose and duration of use of lipophilic statins and their interaction ($P = 0.02$). We then estimated the association between an increase of 365 DDDs in cumulative dose and PD for different cumulative durations (Fig. S1). Cumulative dose was inversely associated with PD for shorter durations, whereas there was no association for longer durations, a pattern consistent with our findings for the daily dose. For instance, the HR for an increase of 365 DDD in cumulative dose for 1 year (one daily DDD) was 0.52, whereas it was 0.63 for 3 years (0.3 daily DDD).

Sensitivity Analyses

Among lipophilic statins, atorvastatin was the most frequent (n = 6850, 9.3%), followed by simvastatin (n = 4839, 6.5%), and fluvastatin (n = 1315, 1.8%). The strongest inverse associations were seen for simvastatin (HR = 0.59, $P = 0.07$) and atorvastatin (HR = 0.73, $P = 0.14$), whereas the HR was >1 for fluvastatin (Fig. S2).

Results for lipophilic statins were unchanged after excluding participants who used statins less than 5 times (HR = 0.67, 95% CI = 0.46–0.98, $P = 0.04$).

Ever use of lipophilic statins was inversely associated with PD ≤75 years, thus suggesting that the association seen overall is not explained by survival bias (Fig. S3).

There was no interaction of ever use of lipophilic statins with smoking ($P = 0.69$), hypercholesterolemia ($P = 0.75$), cardiovascular disease ($P = 0.95$), diabetes ($P = 0.13$), or hypertension ($P = 0.88$).

Discussion

Lipophilic statin use was associated with decreased PD incidence in 73,925 French women followed for 15 years, with a dose–response relation for the mean daily dose. To account for reverse causation, our analyses included a 5-year lag between exposures and PD incidence, consistent with changes in statin use and medical consultation trajectories prior to diagnosis.

A total of 12 cohort studies examined the association between statins and PD; six[14-16,18-20] reported an inverse association, four[11,13,23,35] did not find an association, and two[12,17] reported a positive association (Table S1). Methodological differences likely account for inconsistent findings. In contrast to ours, no single study combined a follow-up >10 years, new user design, use of drug claims, time-varying exposures, validation of PD diagnoses by neurologists, analyses of statin subgroups and dose–response relations, and adjustment for major confounders (ie, smoking, physical activity).

The major difference between previous studies and our own is the consideration of an exposure lag to account for reverse causation. Only two previous studies included lag times: one study that used a 1-year lag and 5-year lag found no association between annual statin adherence and PD[11]; another study reported no benefit of statins for PD in the main analyses and reported similar findings using 2-year and 4-year lags in sensitivity analyses.[12] Our analyses of statin use and medical consultation trajectories suggest that failure to include an exposure lag may bias associations toward the null.

Some previous cohort studies distinguished lipophilic from hydrophilic statins or individual statins.[11,12,14,18,20,23] Our finding of a significant risk reduction for lipophilic statins is in line with a study that showed reduced PD risk for continuous lipophilic statin use compared with discontinuation in men and women, but not for hydrophilic statins.[20] Among individual lipophilic statins, simvastatin showed the strongest association in our study and others.[14,18,20,23] Two studies also showed significant inverse associations for atorvastatin.[18,20] The latest meta-analysis reported pooled ORs of 0.79 (95% CI = 0.75–0.82) for simvastatin and 0.92 (95% CI = 0.84–1.00) for atorvastatin.[7]

We found a significant dose–response relation for the mean daily dose of lipophilic statins. Few studies examined dose–response relations, and none examined the role of mean daily dose or the combined effect of cumulative dose and duration.

Our findings are unlikely to be explained by indication bias because analyses were adjusted for the main indications of statins. In particular, two pieces of evidence argue against confounding by hypercholesterolemia. First, studies on the relation between cholesterol level and PD are inconsistent. A meta-analysis of eight cohort studies showed no significant association between total cholesterol and PD[36]; alternatively, there was an inverse association for high low-density lipoprotein (LDL) cholesterol (five studies, HR = 0.73, 95% CI = 0.57–0.93; $I^2 = 52.2\%$, P heterogeneity = 0.079), but no study used an exposure lag >1 year.[36] Mendelian randomization (MR) studies are less likely to be biased by unmeasured confounding and reverse causation. One study did not find an association of PD with genetically predicted LDL cholesterol, triglycerides, and apolipoprotein B.[37] Another study performed sex-stratified analyses and reported no association for genetically predicted LDL cholesterol both in women and men.[38] Hence, MR studies are not in favor of a causal association between LDL cholesterol and PD. Second, the observation of a differential association for lipophilic and hydrophilic statins argues against

indication bias. Hence, a potential beneficial effect of statins is likely to be independent of their effect on cholesterol.

One MR study (37,688 cases, 981,372 controls) examined whether statins were associated with PD by using genetic variants in their drug target (hydroxymethylglutaryl-coenzyme A [HMG-CoA] reductase) and reported an inverse association (OR = 0.83, 95% CI = 0.65–1.07); although it was not statistically significant, the authors concluded that it did not rule out possible benefits of statins for PD prevention and that larger MR studies were needed.[37] Another MR analysis of two smaller data sets (553 + 538 cases) did not show significant associations.[39]

The inverse association between statin use and PD raises the question of potential benefits in terms of disease modification in PD patients. In a 4-year retrospective study (N = 104), statin users had slower progression in Movement Disorder Society–Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score and rigidity subscore than nonusers; this finding was driven by lipophilic statins, but the number of PD patients on hydrophilic statins was small.[40] Another study (N = 125) showed faster PD progression (MDS-UPDRS Part I, imaging markers) for 18 months in hydrophilic statin users compared with nonusers, but not for lipophilic statins.[41] Two clinical trials are also available. One double-blind, randomized, placebo-controlled trial enrolled 77 early-stage PD patients, in whom a lipophilic statin (lovastatin 80 mg/d, 48 weeks) and placebo were administered. Lovastatin had a beneficial, but not statistically significant, effect on MDS-UPDRS Part III score change; alternatively, the mean percentage change in the striatal F-fluoro-dihydroxyphenylalanine uptake ratio deteriorated significantly less in the lovastatin than in the placebo group.[42] The other double-blind, randomized, placebo-controlled trial compared simvastatin (1-month 40 mg, 23-month 80 mg) to placebo in 235 PD patients. Simvastatin was futile for slowing motor progression in PD patients of moderate severity.[43] Investigations in particular subgroups or early PD, even at prodromal stages, may be more fruitful in terms of detecting a protective effect.[1,43] Given the progressive nature of PD, very early treatment would be needed. Our finding of a significant dose–response relation for the mean daily dose of lipophilic statins suggests that higher daily doses may be more beneficial. Additional larger clinical trials are needed to examine issues related to the timing and duration of treatment and risk stratification.

Inflammation and oxidative stress are considered key mechanisms in PD. Statins act as lipid-lowering agents by inhibiting the HMG-CoA reductase that catalyzes the conversion of HMG-CoA to mevalonate (MVA), the key step of the mammalian MVA cascade in the biosynthesis of hepatocyte cholesterol.[22] Cholesterol accelerates α-synuclein aggregation; by reducing cholesterol levels, statins may attenuate the deposition of Lewy bodies in the substantia nigra.[44] The MVA pathway generates a range of other end products particularly abundant in the brain, such as proinflammatory cytokines and reactive oxygen species; by regulating their synthesis, statins display pleiotropic anti-inflammatory and antioxidant properties in the brain that may partially account for cholesterol-independent neuroprotection.[45] Statin-induced MVA inhibition has other potentially beneficial effects (eg, enhanced expression of neurotropic factors, increased endothelial nitric oxide synthase production).[44] The specific association of lipophilic statins with PD may be explained by easier brain penetration through the blood–brain barrier.[22,45]

In addition to the large sample size and long follow-up, lagged analyses represent another strength. Prodromal PD symptoms could influence medical contacts and, therefore, statin prescriptions for cardio-metabolic risk prevention.[9,10] Changing trajectories in cases compared with controls within 5 years before diagnosis confirmed this hypothesis. The new-user design and assessment of time-varying exposures based on drug claims represent additional strengths, allowing to perform dose–response analyses and to minimize the risk of immortal time bias.[46] PD incidence rates in E3N are consistent with those in Western European women, and the well-established association with smoking was replicated,[30] in favor of the validity of our approach.[30] Finally, we adjusted our analyses for numerous characteristics to rule out confounding and indication bias.

Our study has limitations. First, participants are mostly health-conscious women not representative of the general population. However, because PD incidence rates were similar to the expected rates,[30] the selected nature of the cohort does not appear to have led to lower PD rates. E3N participants are educated and motivated women who provide high-quality information in questionnaires with high response rates.[24] It is also generally considered that representativeness is not essential for estimating associations.[47,48] We acknowledge that we included only women, which hampers generalizability to men; however, women represent an understudied population in PD research, in whom additional studies are needed.[49] In addition, there are no major sex differences in statin use after 60 years,[50] and statins display similar benefits in both sexes.[51-53] Second, our analyses with a 5-year lag are based on 524 incident PD cases (80 ever used statins); ours is the largest prospective study in women to date, as larger studies were retrospective and based on healthcare databases. However, results of subgroup and dose-effect analyses need to be interpreted cautiously due to the small number of exposed PD patients; we were not able to perform sensitivity analyses using lags >5 years

or to examine dose–response relations for individual molecules. Third, some participants may not have consumed the drugs they purchased. This is unlikely to be differential with respect to disease status, especially several years before disease onset; sensitivity analysis excluding participants with few purchases yielded consistent results. Fourth, because analyses were adjusted on history of hypercholesterolemia rather than cholesterol level, residual confounding by cholesterol would be an issue if cholesterol level was associated with PD, but MR studies are not in favor.[37,38] Fifth, patients initiating or adhering to statins are more likely to engage in health-promoting behaviors (healthy user bias).[54] However, this is unlikely to account for the inverse association between lipophilic statins and PD for several reasons. Statin initiators had a worse health profile (more frequent history of comorbidities, higher BMI, lower physical activity) than never users, and we adjusted for these variables. Medical service use should be considered when evaluating associations of exposures with PD to ensure that they are not attributable to bias[55]; our analyses are adjusted for the number of medical contacts. The new user design allowed the exclusion of prevalent users who may be more health conscious or survivors in better health. A healthy user bias would not explain a specific association with lipophilic statins. Sixth, although most studies consider atorvastatin as lipophilic, it remains unclear whether it is able to passively cross the blood–brain barrier given its large size; other mechanisms (eg, lactonization, active transportation) may be involved.[56]

We showed an inverse association between lipophilic statins and PD incidence while addressing reverse causation. Statins are widely prescribed, relatively safe, and readily available. Given the need for neuroprotective agents in PD, further clinical trials are needed to examine their benefit in PD, with special reference to the timing of treatment, molecule, and dose. ●

Acknowledgments: This work was realized with data of the E3N cohort (INSERM) and supported by the Mutuelle Générale de l'Education Nationale (MGEN), Gustave Roussy Institute, and French League against Cancer for the constitution and maintenance of the cohort. This work has benefited from State aid managed by the National Research Agency (ANR) under the program "Investment in the future" bearing the reference ANR-10-COHO-0006 and under the program "Young researcher" bearing the reference ANR-18-CE36-0006-01, as well as a subsidy from the Ministry of Higher Education, Research and Innovation for public service charges bearing the reference N°2102918823, 2103236497, and 2103586016, and from IRESP (Institut de Recherche En Santé Publique). The authors acknowledge all women enrolled in the E3N cohort for their continued participation. They are also grateful to all members of the E3N study group.

Data Availability Statement

E3N data are available to bona fide researchers for all type of health-related research, which is in the public interest. Data are made available under managed access owing to governance constraints and need to protect the privacy of participants. Raw data requests should be submitted through the E3N website (www.e3n.fr) or sent to contact@e3n.fr and will be reviewed by the E3N Access Committee (https://www.e3n.fr/node/78).

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

T.T.H.N.: 1A, 1C, 2A, 2B, 2C, 3A, 3B
A.F.: 1A, 1C, 2C, 3B
E.C.: 1C, 2C, 3B
F.A.: 2C, 3B
S.E.: 1C, 2C, 3B
P.T.-B.: 2C, 3B
M.-C.B.-R.: 1B, 2C, 3B
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E.R.: 2C, 3B
M.C.: 2C, 3B
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A.C.M.T.: 1A, 1C, 2C, 3B
A.E.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B

Financial Disclosures

T.T.H.N. was supported by post-doctoral grants from the Michael J Fox foundation and the France Parkinson association. E.C. was supported by post-doctoral grants from the Michael J Fox foundation. F.A. reports no disclosures. S.E. reports no disclosures. P.T.-B. reports no disclosures. M.-C.B.-R. received speaker fees in 2020 from MAYOLI-SPINDLER and GILEAD outside the field of the present paper. I.D. reports no disclosures. E.R. received honorarium for speech from Orkyn Aguettant, Elivie and for participating in an advisory board from Allergan and has received research support from Merz-Pharma, Orkyn, Aguettant, Elivie, Ipsen, Allergan, Everpharma, Fondation Desmarest, AMADYS, ADCY5.org, ANR, Societé Française de Médecine Esthétique, and Dystonia Medical Research Foundation. M.C. has obtained research grant from French National Research Agency (ANR). I.A. reports no disclosures. A.C.M.T. reports no disclosures. A.E. has obtained research grants from Plan Ecophyto (French ministry of agriculture) and France Parkinson.

The work reported in this paper was performed during A.F.'s term as a Visiting Scientist at the International Agency for Research on Cancer.

The authors declare no other relationships or activities that could appear to have influenced the submitted work.