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Statin use and Parkinson's disease in Denmark

Beate Ritz, MD PhD^{1,*}, Angelika D. Manthripragada, PhD¹, Lei Qian, MS², Eva Schernhammer, MD DrPH³, Lene Wermuth, MD⁴, Jorgen Olsen, MD⁵, and Soren Friis, MD⁵

Angelika D. Manthripragada: Angelika.Manthripragada@fda.hhs.gov; Lei Qian: leiqian@ucla.edu; Eva Schernhammer: eva.schernhammer@channing.harvard.edu; Lene Wermuth: l_wermuth@dadlnet.dk; Jorgen Olsen: jorgen@cancer.dk; Soren Friis: friis@cancer.dk

¹Department of Epidemiology, UCLA School of Public Health, Los Angeles, California, USA

²Department of Biostatistics, UCLA School of Public Health, Los Angeles, California, USA

³Channing Laboratory, Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA

⁴Department of Neurology, Odense University Hospital, Denmark

⁵Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark

Abstract

Objective—To investigate whether statin (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor) use is associated with risk of Parkinson's disease (PD) in Denmark.

Methods—We identified 1,931 patients with a first time diagnosis of PD reported in hospital or outpatient clinic records between 2001–2006. We density matched to these patients 9,651 population controls by birth year and sex relying on the Danish population register. For every participant, we identified pharmacy records of statin and anti-Parkinson drug prescriptions since 1995 and prior to index date from a prescription medication use database for all Danish residents. Whenever applicable, the index dates for cases and their corresponding controls were advanced to the date of first recorded prescription for anti-Parkinson drugs. In our primary analyses, we excluded all statin prescriptions 2-years before PD diagnosis.

Results—In unconditional logistic regression analyses adjusting for matching factors and co-morbidities, we observed none to slightly inverse associations between PD diagnosis and statin prescription drug use. Inverse associations with statin use were only observed for short-term (≤ 1 yrs) statin users (2-year lag OR 0.57; 95% CI 0.36 to 0.89); and suggested at higher intensity statin use (2-year lag OR 0.69; 95% CI 0.45–1.04). No associations were seen among longer-term users and no difference by sex, age, or type of statins used (lipophilic/hydrophilic).

*Correspondence to: Beate Ritz, UCLA School of Public Health, Box 951772, 650 Charles E. Young Drive, Los Angeles, CA 90095-1772. britz@ucla.edu. Phone: 310-206 7458. Fax: 310-206-6039.

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Author's role on manuscript:

Beate Ritz: study design, data analysis, writing of manuscript

Angelika D. Manthripragada: data analysis concept and manuscript preparation

Lei Qian: data analysis and data management

Eva Schernhammer: concept and writing of manuscript

Lene Wermuth: PD clinical concepts (case identification from records) and writing

Jorgen Olsen: conceptualizing of analysis, data linkage, and writing of manuscript Soren

Friis: conceptualizing of analysis, data linkage, and writing of manuscript

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Conclusion—We found little evidence for a neuroprotective role of statins in PD except for short-term or high intensity users. Yet, further investigations into the contributions of intensity, duration, and lag periods of statin use may still be warranted.

Introduction

Parkinson's disease (PD) is a neurologic movement disorder characterized by a progressive loss of substantia nigra cells that produce dopamine and a broad spectrum of non-motor features including sensory dysfunction, behavioral abnormalities, autonomic impairment, and sleep disturbances.¹ It is one of the most common neurodegenerative diseases with a large impact on quality of life in the elderly. Recently it has been suggested that cholesterol-lowering drugs known as statins, widely used in the Western world, may be neuroprotective for several diseases including PD.² Oxidative stress and neuroinflammation are thought to be pathways involved in PD pathology,^{3–5} and statins have anti-oxidants properties and attenuate neuroinflammation.^{6,7} Furthermore, *in-vitro* studies recently showed that statins reduce alpha-synuclein oxidation and accumulation, both key events in the formation of hallmark Lewy-bodies in PD.⁸

While there is a growing literature examining whether and how statins and/or cholesterol levels play a role in the development of PD, to date findings have generally been equivocal if not outright contradictory. Two U.S. studies reported that statin use reduce PD risk,^{9,10} while two larger UK and Canadian pharmacy record based studies found no associations.^{11,12} A third U.S study did not find associations with statin use, but suggested that higher levels of cholesterol may reduce PD risk.¹³ This however was contradicted by a recent Finnish study reporting that higher baseline levels of serum cholesterol increased risk of PD among younger cohort members.¹⁴

Here, we report new results for PD and statin use examined in a large population-based case control study conducted in Denmark. Our investigation was based on a nationwide prescription database that documents statin and anti-Parkinson's prescriptions and the National Danish Hospital Register.

Subjects and Methods

The study protocol was approved by the Danish Data Protection Agency (No 2002-41-2112) and the UCLA human subject review board.

Study Population

Denmark's National Health Service provides free equal access to healthcare for the entire population. Each health services related event is recorded in national databases, including the Danish Hospital Register¹⁵ and the Danish Registry of Medical Products Statistic (the national prescription database¹⁶), and both can be linked to each other and the Danish Central Population Registry using a unique personal identification number assigned to all Danish citizens at birth or when awarded citizenship.

We conducted a population-based case control study using a record linkage approach within this registry system. PD cases were ascertained from the Danish Hospital Register that has registered all hospitalizations with a PD diagnosis since 1977 and all clinic visits - including outpatient clinics - since 1995. Roughly five controls were selected per case, matched on sex and year of birth from the Danish Central Population Registry using density sampling. Based on having received a primary PD diagnosis in the Danish Hospital Register in the period 1986 – 2006, we identified 82,140 subjects (13,695 cases and 68,445 controls) who (1) had a valid personal identification number (2) were over 35 years of age at the time of

diagnosis or (3) had not emigrated from Denmark. We further restricted the participants to all cases (and their matched controls) registered for the first time with a primary diagnosis of Parkinson's disease (*International Classification of Diseases, 10th revision*, code G20) between Jan 2001 and Dec 2006. To identify the earliest possible date of a PD diagnosis, we further dated the primary PD diagnoses back to the first hospital or outpatient record that ever mentioned PD or the first prescription of PD medications (anatomical therapeutic chemical (ATC) code N04B)¹⁷ since inception of the national prescription database (1995), whichever was earlier. If the backdated diagnosis (index) date fell into the period before 2001, the case and the case's matched (5 or less) controls were excluded. This resulted in 13,123 total subjects (2,188 cases and 10,935 controls). We furthermore excluded PD patients who had never received a PD drug prescription (ATC N04 AA01-04, BA02-03, BB01, BC01-06, BD01-02, BX01-02), i.e. 257 cases and their respective 1,284 matched controls (1,541 total subjects), leaving us with 1,931 PD cases and 9,651 controls. In sensitivity analyses, we further excluded PD cases (and these cases' matched controls) and controls diagnosed with any type of dementia (both Alzheimer type and unspecified) or cerebrovascular disease before the index date (305 cases, 2282 controls) or patients having taken neuroleptic medications (ATC N05A) within half a year of diagnosis (194 cases).

Assessment of statin use

Since Jan 1995, the national prescription database has received data on dispensed prescriptions from all pharmacies in Denmark. Available data include the individual's personal identification number, drug type by ATC code and prescription dispensing date. For each study subject we identified any recording of statin prescriptions (ATC codes group: C10AA including atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin) prior to the index date. We defined statin use as filling 2 or more prescriptions during the relevant period prior to the index date; nonusers filled <2 prescriptions. For statin users, we defined duration of use (starting with the subject's second prescription) and intensity of use according to the World Health Organizations (WHO) defined daily doses (DDDs) per package,¹⁷ i.e. our measure of 'average intensity per day' sums over all package DDDs from the date of the second to the last prescription plus 60 days and divides this by the number of days in this period. For example, an intensity of '2 per day' means that the subject had on average been prescribed double the WHO defined daily dose.

Statistical Analysis

We used unconditional logistic regression to calculate odds ratios and 95% confidence intervals for statin use while adjusting for age (continuous), sex, co-morbidities registered before the index date (using the Charlson index) and chronic obstructive pulmonary disease (COPD) diagnosis (ICD code = J42, J43, J44 and 490.00, 491.00, 491.01, 491.03) identified in the Danish Hospital Register. The Charlson index was based on ICD codes for 19 chronic disease categories recorded in the hospital records.¹⁸ Diagnosis of COPD served as a proxy for heavy smoking. The Danish population is primarily Caucasian so we did not adjust for race/ethnicity.

For our primary analyses, we advanced (lagged) the index date for statin prescriptions by 2 years. In addition, we performed non-lagged and 5-year lagged analyses, but the 5-year lagged data were too sparse. Despite careful assessment of the index date, our case identification methods may have ascertained some prevalent cases due to the presumed long preclinical period of PD, thus lagged analyses are preferable. We also lagged both the Charlson index and COPD by 5 years to capture the general health status of subjects prior to the index date. Analyses for duration and intensity of statin use were based on tertile categories defined by the control population distribution. Due to small numbers per stratum, intensity of statin use stratified by duration was analyzed in unlagged data. We also stratified

by age at first diagnosis (≤ 60 , >60 years) and sex. In sensitivity analyses, we adjusted for the use of many cardiovascular disease drugs (ATC codes: B01AA03, B01AA04, C01A-D, C07, C08, C09A-D) recorded in the prescription database and excluded cases (and their matched controls) and all controls diagnosed with dementia or cerebrovascular disease prior to their PD diagnosis.

Results

Cases and their matched controls were on average 72.2 years of age ($SD=10.2$) at the index date. We identified more males than females with a diagnosis of PD. Five years prior to the index date, the Charlson index suggested that cases and controls suffered equivalently from chronic diseases and COPD was rare. COPD was rare and slightly more common in controls (Table 1). At the index date, 9.5% of our study population had ever received 2 or more prescriptions for any type of statin; among all statins the specific prescriptions included simvastatin (58.1%), atorvastatin (20.5%), pravastatin (11.0%), lovastatin (4.1%), fluvastatin (4.1%), rosuvastatin (1.1%), and cerivastatin (1.1%) and 18% of subjects had received more than one type of statin prescription. The median length of time receiving prescriptions for statins since 1995 was 2.5 years (0.2–11.4 yrs for PD cases and 2.3 years (0.2–11.1 yrs) for controls).

At the index date slightly more controls (9.6%) than cases (8.8%) had ever received 2 or more statin prescriptions, but when lagging statin use by 5-years few cases (2.5%) or controls (2.3%) remained who had ever received these medications; thus, we did not estimate risks except for ever/never use with a 5-year lag for statin use in logistic models (adjusted OR 0.97; 95% CI 0.70–1.34). Our main logistic regression analyses using a 2-year lag for statins suggested if anything a slightly inverse association for ever use of statins (8–10% less use in PD patients) depending on the model used and all 95% confidence intervals included the null value (Table 2).

In the 2-year lagged analysis, we did not observe a duration-response with increasing length of use; on the contrary, we found the strongest inverse association with PD (43% less use in PD patients) for short term users of statins (1 year or less) while longer term use was not associated with PD (Table 2); higher intensity of use as measured by average DDD seemed inversely associated with PD (29–31% less use in PD patients). We estimated odds ratios of less than 1 for medium and high intensity shorter term users of statins when taken within a 5 year period prior to index date (Table 3), but these unlagged results did not approach statistical significance.

In additional stratified analyses (with a 2-year lag) risk estimates were not different for men and women or for those of younger (≤ 60) or older age at diagnosis/index date, or for lipophilic vs. hydrophilic statins (results not shown). There was also no difference when we adjusted models for CVD drugs or for aspirin or non-aspirin NSAID use. Other cholesterol lowering drugs (ATC codes C10AC, C10AD) were prescribed very rarely ($N=31$ subjects) and not associated with PD (OR 1.14; 95% CI 0.45–2.79 for ever/never use with zero lag). Finally, excluding PD patients and controls diagnosed with dementia or cerebrovascular diseases prior to the index date changed risk estimates no more than minimally (ever/never use 2 year lagged OR 0.87; 95% CI 0.69–1.09).

Discussion

We identified all cases with a primary diagnosis of PD in Denmark from hospital and outpatient clinic records between 2001–2006. We relied on an ongoing national prescription database created in 1995 to adjust the date of first diagnosis to the time of first prescription

drug use for PD and to determine statin use among cases and matched population controls. Statin use was not or no more than weakly inversely associated with PD, and only among those with prescriptions on a short but not long term basis, no matter whether we employed lags of zero, 2 or 5 years prior to diagnosis or excluded study subjects with dementia or cerebrovascular diseases prior to the index date. Higher intensity of use according to average DDD seemed to confer a somewhat stronger inverse association, but only a small percentage of subjects were prescribed statins at this level. Adjustment for potential confounders made little difference for our results. We saw no difference in PD risk by type of statins (hydrophilic: pravastatin, rosuvastatin; or lipophilic: simvastatin, lovastatin, fluvastatin, atorvastatin, cerivastatin) - although lipophilic statins are able to cross the blood brain barrier more easily.¹⁹

Two studies previously suggested inverse associations between statins and PD. We previously reported a large (50–60%) decrease in risk among long-term (more than 5 years) statin users in a population-based case-control study.¹⁰ Our California study relied solely on self-reported use and may have suffered from recall bias. A study of US Veterans 65 years and older reported that those receiving prescriptions for simvastatin had halve the risk of PD compared to Veterans prescribed any other cardiovascular disease drugs except for statins during a 3 years follow-up.⁹ Yet the very select group of Veterans used as controls raised concerns about selection bias. A study conducted in the UK primary care setting found no association between PD with current as well as longer term (5 years and more) statin prescriptions.¹¹ Similarly, a study based on the British Columbia Linked Health Databases following a cohort of older adults from 1997 to 2003 found no association with statin use currently or anytime during follow-up.¹²

Statins may act as neuroprotectors or alternatively as neurotoxins. Concerning neuroprotection, statins may reduce oxidative stress or neuroinflammation, pathways hypothesized to contribute to PD pathology.^{3,7} For example, simvastatin inhibits the formation of the inflammatory cytokine TNF α and the reactive oxygen species nitric oxide (NO) and superoxide (O₂⁻) in microglia and attenuates dopamine depletion in MPTP-treated mice, a model of Parkinsonism.²⁰ Furthermore, lovastatin reduces cytokine-mediated induction (upregulation) of inducible nitric oxide synthase (iNOS) and subsequent NO production in rat astrocytes, microglia, and macrophages.²¹ While animal models suggested etiologic roles for both NO and NOS in PD,²² human studies focused on nitric oxide synthase genes produced equivocal results.^{23–25}

With regard to neurotoxicity, statins inhibit the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA) enzyme that participates in both cholesterol and co-enzyme Q10 synthesis pathways, thereby decreasing levels of both synthesis products. Since co-enzyme Q10 participates in mitochondrial respiration and protects against dopaminergic cell death, this raises the possibility that statins might in fact be harmful to the dopaminergic system^{26–28}. Thus, when two studies reported lower levels of cholesterol in patients with PD or in those later developing PD, it was proposed that either low cholesterol or low co-enzyme Q10 may increase PD risk;^{29–31} surprisingly however, statin users in these studies seemed to be protected against PD.

A recently published *in-vitro* cell study⁸ suggested a link between both cholesterol and statins and PD by way of alpha-synuclein oxidation and accumulation - reduced by statins and increased by cholesterol. This supports a Finnish cohort study¹⁴ that reported an increase in the risk of PD with higher total serum cholesterol in subjects aged 25–54 but not in those older, raising questions about the importance of considering the age at which the cholesterol increase occurs. A study conducted in a much smaller cohort of Rotterdam

residents 55 years or older reported no association in males and an inverse association between total cholesterol and PD incidence in females.³⁰

Two U.S. cohort studies have published data on cholesterol levels and PD, the Nurses' Health Study and the Health Professional Follow-up Study¹³ and the Hawaiian Aging Study.³² PD risk among health professionals (age 44–79 at baseline in 1990; 314 PD cases) decreased modestly with increasing levels of baseline self-reported total cholesterol, again primarily in women; but use of cholesterol-lowering drugs was unrelated to PD risk (RR 0.85, 95% CI 0.59–1.23 for ever/never use). The Hawaiian (male only) study³² measured fasting lipids in 1991–1993 when the youngest men alive were already in their early 60s. All of these findings, except for the younger Finns, are contrary to expectations based on cell and animal models that suggest that cholesterol increases alpha-synuclein oxidation and accumulation, raising questions about possible changes in meaning for this biomarker depending on age and sex.

Our study may have suffered from some disease misclassification since primary PD diagnoses were identified from hospital and clinic records and may have included some cases of non-idiopathic Parkinsonism. Sensitivity analyses in which we excluded PD cases with prior diagnoses of dementia and cerebrovascular diseases in the 2 years before PD diagnosis or patients having taken any neuroleptic medication (ATC codes N05A) within half a year of diagnosis suggested the bias to be minimal. Controls were selected at random from a population registry and did not have to volunteer information for our study, thus, avoiding bias due to selective non-participation. We required that all PD cases had been admitted at least once with a primary diagnosis of PD and whenever possible we dated diagnoses back to the likely earliest diagnosis (e.g. a first prescription of PD medications). We might have selected less healthy PD cases more likely to be hospitalized than Danish PD patients seen exclusively by private practitioners without ever attending a specialty clinic before 2007. The higher Charlson index and greater number of CVD drug prescriptions among our study's PD patients compared to controls 2 years prior to and at the index date (data not shown) might support the possibility for such a selection bias. Interestingly, differences in general health status were not evident 5 years prior to PD diagnosis/index date. Less healthy subjects are more likely to be in contact with the medical system and would have had a greater likelihood of being treated with medications including statins. We would therefore expect that a poorer health status in cases compared to controls would increase the number of statin prescriptions for cases within 5 years of PD diagnosis, opposite of what we observed.

Our data were too sparse to explore longer lag times or duration of use with sufficient statistical precision. Statins were first introduced in Denmark in 1989 and are prescription-only drugs not widely prescribed until the late 1990s; only 2.3% of our controls used statins in 1995 compared to more than 10% after 1999. Due to the relative novelty of statins, we could only examine relatively short-term use with adequate statistical power. Nevertheless, the nationwide prescription database likely captured practically all regular and continuing users in Denmark; also, it is reasonable to assume that individuals with multiple prescriptions were likely compliant statin drug users.

The universal coverage of most health care expenses in Denmark, including partial reimbursement of costs for prescribed drugs, makes it less likely that statin prescriptions or PD diagnoses were influenced by factors determining access to care. We were unable to control for smoking, known for its strong negative association with PD. We adjusted for COPD since it may serve as proxy for heavy smoking but we most likely controlled for smoking insufficiently.

It seems premature to draw conclusions about the role of statin use for PD since human studies are sparse and the data inconclusive. It cannot be ruled out that statin use later in life might be a proxy for detrimental high cholesterol and/or for protective higher serum co-enzyme Q10 levels earlier in life. But, since mechanistic studies suggest that statins may act neuroprotectively as antioxidants, reduce pro-inflammatory mediators, or prevent alpha-synuclein accumulation, further investigations of the possible role of statins and cholesterol in PD etiology seem warranted. Future studies would be most informative if they employed a longitudinal design with long follow-up periods, enrolled long-term and midlife statin users or measured cholesterol levels earlier in life (before age 40), and included large numbers of women as well as men.

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Table 1

Characteristics of Danish Study Population, 2001–2006

	Cases (n=1,931) n (%)	Controls (n=9,651) n (%)
Age, mean (std)	72.2 (10.5)	72.2 (10.5)
Sex		
female	810 (41.9)	4,048 (41.9)
Male	1,121 (58.1)	5,603 (58.1)
Years of age		
>30–40	15 (0.8)	68(0.7)
>40–50	59 (3.0)	298 (3.1)
>50–60	183 (9.5)	921 (9.5)
>60–70	438 (22.7)	2,190 (22.7)
>70–80	753 (39.0)	3,769(39.1)
>80–90	455 (23.6)	2,279 (23.6)
>90	28 (1.4)	126 (1.3)
Charlson index (5-year lag)		
0	1,454 (75.4)	7,365 (76.3)
1	251 (13.0)	1,245 (12.9)
>=2	226 (11.7)	1,041 (10.8)
COPD (5-year lag)		
No	1,910 (98.9)	9,448 (97.9)
Yes	21 (1.1)	203 (2.1)

Table 2

Association between statin prescriptions (2-year lag) and Parkinson's disease

	Cases (n=1,931)	Controls (n=9,651)	Adjusted model <i>1</i>	Adjusted Model <i>2</i>
	N (%)	N (%)	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Ever prescribed (2 prescriptions or more)				
No	1,830 (94.8)	9,103 (94.3)	Ref	Ref
Yes	101 (5.2)	548 (5.7)	0.92 (0.74–1.14)	0.89 (0.72–1.11)
Length of statin prescription use (years)				
None	1,830 (94.8)	9,103 (94.3)	ref	ref
<=1.0	21 (1.1)	183 (1.9)	0.57 (0.36–0.90)	0.57 (0.36–0.89)
1.0–3.4	39 (2.0)	183 (1.9)	1.06 (0.75–1.50)	1.03 (0.72–1.46)
>= 3.4	41 (2.1)	182 (1.9)	1.12 (0.80–1.58)	1.08 (0.76–1.52)
Intensity of statin prescription (defined daily doses)				
none	1,830 (94.8)	9,103 (94.3)	ref	ref
<=0.9	32 (1.7)	183 (1.9)	0.90 (0.62–1.30)	0.87 (0.59–1.26)
>0.9–1.3	43(2.2)	183 (1.9)	1.14 (0.81–1.60)	1.12 (0.80–1.58)
>1.3	26 (1.4)	182 (1.9)	0.71 (0.47–1.08)	0.69 (0.45–1.04)

¹ adjusting for age, sex² adjusting for age, sex, COPD (lagged 5 years), Charlson index (lagged 5 years)

Table 3Associations between short and long term statin prescription use (unlagged) and Parkinson's disease¹

	Cases N	Controls N	Odds Ratio (95% CI)
Intensity 0 (no or < 2 prescriptions)	1,761	8,723	Ref
Short term prescriptions (<=5 years) (n= 848)			
Low intensity	43	220	0.98 (0.71–1.37)
Medium intensity	37	234	0.75 (0.53–1.07)
High intensity	45	269	0.82 (0.60–1.13)
Long term prescriptions (>5 years) (n= 250)			
Low intensity	18	90	0.95 (0.57–1.58)
Medium intensity	21	75	1.36 (0.83–2.21)
High intensity	6	40	0.71 (0.30–1.68)

¹ Adjusting for age, sex, COPD (5-year lag), Charlson index (5-year lag)