Statin use and the risk of Parkinson's disease in persons with diabetes: A nested case-control study

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Abstract

Abstract Background: Persons with diabetes may have an elevated risk of Parkinson's disease. Statin use could also modify the progression of Parkinson's disease. Objective: The aim was to study whether there is an association between statin exposure and risk of Parkinson's disease in persons with diabetes Methods: A nationwide nested case-control study of 2,017 Parkinson's disease cases and their 7,934 matched controls with diabetes was performed using data from the Finnish Parkinson's disease study (FINPARK). Persons with Parkinson's disease were diagnosed between 1999–2015 and statin use (1995–2015) was determined from Prescription Register. In the main analysis exposure at least three years before outcome was considered. Cumulative exposure was categorized into tertiles, and associations were analyzed with conditional logistic regression. Results: Prevalence of statin use was similar in Parkinson's disease cases and controls, with 54.2% of cases and 54.4% controls exposed before the lag time (adjusted odds ratio (aOR) = 1.02; 95% CI: 0.91–1.15). Those in the highest cumulative statin exposure tertile had higher risk of Parkinson's disease than statin nonusers (aOR = 1.21; 95% CI: 1.04–1.42), or those in the lowest cumulative statin exposure tertile (aOR = 1.29; 95% CI: 1.07–1.57). Conclusions: Our nationwide study that controlled for diabetes duration and reverse causality does not provide support for the hypothesis that statin use decreases the risk of Parkinson's disease.

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Short title: Statins and risk of PD

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What is already known about this subject: Both diabetes and statins could modify the risk of Parkinson's disease.

What this study adds: After controlling for diabetes duration and reverse causality this study does not provide support for the hypothesis that statin use decreases the risk of Parkinson's disease.

Abstract

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Conclusions: Our nationwide study that controlled for diabetes duration and reverse causality does not provide support for the hypothesis that statin use decreases the risk of Parkinson's disease.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease with significant negative consequences on health and quality-of-life despite of pharmacotherapies [1,2]. While its etiology remains largely unknown, numerous factors have been associated with risk of PD [3]. Statins are indicated for primary and secondary prevention of atherosclerotic coronary and cerebrovascular events, but it has also been suggested that due to their pleiotropic effects they could modify the progression of neurodegenerative diseases [4]. Meta-analyses of observational studies have reported a lower risk of PD among statin users [5,6]. However, confounding by indication and healthy user effect might have affected on findings [7]. Furthermore, the inverse risk has not been unequivocally demonstrated, as four studies have shown an increased risk of PD in statin users [8-11]. Based on these earlier observations, studies in specific populations that can better account for confounding by indication are needed.

Risk of atherosclerotic events is particularly increased in persons with diabetes and the 2019 American College of Cardiology and American Heart Association guidelines recommend at least moderate-intensity statin therapy for all persons with diabetes aged 40–75 years old [12]. Persons with diabetes may also have an elevated risk of PD [13,14]. Therefore, investigation of PD risk factors in this population is needed. Yet, there are only few studies on the association of statin use and risk of PD in persons with diabetes, all three of them reporting lower risk of PD among statin users than nonusers [8-10]. However, in these studies even short-term statin exposure was associated with lower risk [8,10], two of the studies were based on same population [8,10], and one that was published as a short commentary in response to Lin et al. [8] compared risk of PD among users of simvastatin and metformin to metformin only users [9]. We investigated whether

statin use in persons with diabetes is associated with a risk of PD and whether there is a dose-response relationship.

Methods

This case-control study, nested into population of Finland, was based on The Finnish Parkinson's disease study (FINPARK), which includes 22,189 community-dwelling persons who received clinically verified PD diagnosis during 1996–2015. Special Reimbursement Register maintained by the Social Insurance Institution of Finland was used to identify persons with PD diagnosis. PD diagnosis was based on United Kingdom Parkinson's Disease Society Brain Bank's criteria [15]. The FINPARK study and exclusion diagnoses have been described in detail previously [16].

Identification of persons with diabetes within the FINPARK cohort was done using Special Reimbursement Register (code 103, since 1972) and Prescription Register (Anatomical Therapeutic Chemical classification (ATC) [17]; ATC code A10 excluding guar gum, since 1995). Prescription Register contains information on all reimbursed prescription drug dispensing for community-dwelling persons as it does not include drug use during hospital or public nursing home care. Cases who received diabetes diagnosis after PD diagnosis (n=927) or less than three years before PD diagnosis date (index date) (n=639) were excluded (Figure 1). Up to four controls were matched for every PD case by age (+/- 2 years), sex, same or adjacent university hospital district, and time from diabetes diagnosis (+/- 2 years). Controls were persons without PD using the same exclusion criteria that was applied to PD cases. In addition, controls who had dementia in Parkinson's disease (ICD-10 code F02.3) within two years of index date were excluded. Furthermore, 16 PD cases were excluded as no controls could be matched to them.

The final study population for our main analysis included 2,017 cases and 7,934 matched controls. To address healthy user bias and confounding by indication, we performed a secondary analysis restricted to statin users only (1,045 cases and 2,817 controls after excluding cases and controls who were unmatched after the exclusion of nonusers).

The first purchases of statins among PD cases and controls since 1995 were collected from the Prescription Register. Statin use was defined using ATC codes and included simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, and rosuvastatin (supplementary table 1). While pitavastatin is authorized for sale in Finland, no purchases were present in the study data. A three-year lag time was used to exclude statin purchases that were made within a three-year period before PD diagnosis. Statin use was categorized as non-use, statin use initiated during lag time and use before three-year lag. Cumulative statin exposure was defined as a continuous variable by defined daily dose (DDD) [17] which was then divided into tertiles.

Identification of comorbidities (any cardiovascular disease, coronary artery disease, history of cancer, asthma or chronic obstructive pulmonary disease (COPD), stroke, history of traumatic brain injury, and rheumatoid arthritis and connective tissue diseases) is described in detail in Supplementary Table 2. Care Register for Health Care (International Classification of Diseases 8^{th}, $9^{th,}$ and 10^{th} revision), Special Reimbursement Register (reimbursement codes) and Cancer Register (International Association of Cancer Registries Tools coding) were used to identify these conditions before the three-year lag.

T-test and Mann-Whitney U test were used to compare the distribution of continuous variables and chi square test to compare the distribution of categorical variables between cases and controls. Conditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) for the risk of PD. Results were adjusted for comorbidities. Persons with no statin purchases before the three-year lag were the reference group in the main analysis, and the lowest statin exposure tertile in the secondary analysis. All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

Collected data was de-identified thus no ethics committee approval was required according to Finnish legislation.

Results

The mean age of persons with PD and their controls were 73.5 years and 73.6 years, respectively (range 44.4–95.8), and majority of them were men (table 1). Median duration of diabetes on index date was 8.8 years in persons with PD and 8.5 years in persons without PD. There were no differences in comorbidities, except for history of traumatic brain injury which was more prevalent among PD cases compared to controls.

Statin users were more likely to be men (61.9% of users and 38.1% of nonusers) (table 2). All comorbidities, except cancer and rheumatoid arthritis, were more common among statin users, with largest difference observed in cardiovascular diseases (71.9% of users and 59.7% of nonusers).

Prevalence of any statin exposure before or only during the three-year lag was similar among persons with PD and without PD (54.2% vs. 54.4% and 10.9% vs. 10.6%) (table 3). Simvastatin was the most commonly used statin, with 38.8% of cases and 40.1% controls exposed before the three-year lag. There was no difference in use of specific statins between PD cases and controls (table 3). Use of hydrophilic statins was not common before the three-year lag (n=901), and majority of their users had also purchased lipophilic statins (78.0%, n=703). There was no difference in prevalence of lipophilic or hydrophilic statin use between cases and controls.

Any statin use before the three-year lag was not associated with the risk of PD (adjusted odds ratio (aOR) = 1.02; 95% CI: 0.91–1.15) (table 4). In the dose-response analyses, an increased risk of PD was observed in the highest statin exposure tertile compared to statin non-use (aOR = 1.21; 95% CI: 1.04–1.42). Similarly, in the secondary analysis restricted to statin users only, an increased risk of PD was observed in the highest exposure tertile compared to the lowest exposure tertile (aOR = 1.29; 95% CI: 1.07–1.57).

Discussion

Taken together, the findings of our nationwide case-control study of persons with diabetes do not support the suggestion of lower risk of PD among statin users based on earlier studies on the general population [5,6] or persons with diabetes [8-10]. On the contrary, higher risk of PD in those with highest cumulative statin exposure was observed, regardless of whether nonusers or those with lowest cumulative exposure were used as the reference group. No association was observed when medium or low cumulative exposure tertile was compared to statin no-use, nor when medium tertile was compared to low cumulative exposure tertile. Considering the high DDDs of highest cumulative statin exposure tertiles (mean 2500+ DDDs) in both analyses, statin exposure within these groups can be considered long-term.

Our findings are not in line with previous studies reporting lower risk of PD among statin users with diabetes [8-10]. However, methodological differences may partly explain the differences. In our case-control study, we matched cases and controls according to diabetes duration, whereas only one of the earlier cohort studies propensity score-matched for diabetes duration [10]. In addition, all persons in our study had used diabetes medications during the exposure assessment time, and those 44 (<0.5% of the study population) who had not yet initiated their diabetes medications during the exposure assessment time did so during the lag time [18]. In contrast, two of the prior studies apparently also included those with who managed with lifestyle modifications [8,10]. Furthermore, one study was restricted to metformin users, leaving out persons with diabetes who were treated with other diabetes medications [9]. Further, to account for reverse causality, i.e., impact of prodromal PD symptoms on contact with prescribers increasing the likelihood of changes in drug exposure among cases, we did not consider exposure during the three-year lag before the outcome, while all prior studies considered all statin exposure until the diagnosis of PD. In addition, the exposure levels in our study differ from the earlier studies: The highest cumulative statin exposure tertiles started from 616 [8] and 675 [10] DDDs, which would correspond to less than two years of statin treatment (atorvastatin 20 mg) [17] which is less than the length of lag time used in our study. It should also be noted that two of these earlier studies were based on the same data source, National Health Insurance reimbursement database of Taiwan, although with different population sample, follow-up period and definition of statin use [8,10].

Of the two previous nested case-control studies that were not restricted to persons with diabetes, one found no association between users and nonusers [19] whereas the other reported that statin use of 12 months or more was associated with increased risk of PD compared to statin use of less than six months [20].

These nested case–control studies differed from ours as they included people without diabetes, did not assess cumulative statin exposure, nor did they utilize lag time. Interestingly, a case-control study by Liu et al. reported a higher risk of PD among users of lipophilic statins compared to nonusers, although the study was limited to persons aged less than 65 years which may limit the generalizability of results [21].

We applied a three-year lag period to decrease the effect of possible protopathic bias [22]. The lag duration was based on an earlier FINPARK study that showed an increase in muscle relaxant use already three years before PD diagnosis indicating prodromal motor symptoms [23]. The lag time might be important also due to the observation that cholesterol levels have been reported to begin declining already 4 years before diagnosis [24]. On the other hand, reverse causality may partially explain the inverse association in earlier studies with shorter follow-up time, because initiation of statin therapy or increasing intensity may be less likely during the prodromal phase of PD if there is a decline in cholesterol levels [24].

Prescription register accurately represents statin use in Finnish population as this register includes all reimbursed medication purchases to which all Finnish citizens are eligible. However, data on drugs used in hospitals or public nursing homes was not available. Registry-based study approach effectively controls for selection bias and recall bias. A common limitation of register-based studies is the accuracy of PD diagnosis. In our study, we applied data from multiple sources to ascertain PD cases. Due to reimbursement criteria and additional exclusions performed by us described earlier [16], it is likely that these persons had clinically verified PD. In addition, the proportion of excluded cases in the FINPARK study (25.9%) is in line with the estimated proportion of false diagnoses [15,25,26]. Weaknesses of our study include the possibility of residual confounding explaining our findings.

Duration of diabetes was controlled by matching, but severity of diabetes was unknown. However, if diabetes severity is an intermediate variable between statin use and PD, adjusting for it would not be feasible as it would introduce overadjustment bias [27]. We could not adjust for low-density lipoprotein cholesterol levels as they are not recorded in the registers. However, as higher low-density lipoprotein cholesterol levels have been suggested to be a significant confounder for the association between statin use and lower risk of PD in earlier studies [7], and we observed a slightly higher risk of PD among those with higher statin exposure and no association in the use-nonuse analyses, it seems unlikely that adjustment for low-density lipoprotein cholesterol levels would have led towards an inverse among statin users.

To decrease the influence of confounding by indication we restricted our study to persons with diabetes, a population at increased risk of PD [13,14]. Due to the resulting limitation in sample size, we were unable to assess whether the association of increased risk of PD with high cumulative statin exposure was driven by specific statins, statin therapy intensity or the length of exposure, or any combination thereof. In addition, our study included persons who had used multiple statins and therefore we did not perform more detailed statin -specific analyses. It has been suggested that the association between statins and PD is different for lipophilic and hydrophilic statins [21]. However, all statins regardless of their lipophilicity can cross the blood-brain barrier, although lipophilic statin may impair brain cholesterol synthesis slightly more [28]. In our study the number of hydrophilic statin users was small due to major overlap with lipophilic statin use. Therefore, we did not perform dose-response analyses based on different categories. It has been suggested that initiation of statin therapy may rapidly "unmask" PD in those with preclinical symptoms [11,29]. We did not explore the unmasking theory as any association near PD diagnosis would be indistinguishable from protopathic bias; Incidence of preclinical PD symptoms may increase healthcare contacts which can increase the likelihood of initiation of statin therapy. However, since the prevalence of statin users only during the lag time was indifferent between PD cases and controls, our results do not support this theory. Our nationwide study that controlled for diabetes duration and reverse causality does not provide support for the hypothesis that statin use decreases the risk of PD.

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Figure captions:

Figure 1. Formation of the study populations

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