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Association between different diabetes medication classes and risk of Parkinson's disease in people with diabetes

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Abstract

Purpose: Diabetes has been associated with increased risk of Parkinson's disease (PD). Diabetes medications have been suggested as a possible explanation, but findings have been inconsistent. More information on the role of exposure in different time windows is needed because PD has long onset. We assessed the association between use of different diabetes medication categories and risk of PD in different exposure periods.

Methods: A case–control study restricted to people with diabetes was performed as part of nationwide register-based Finnish study on PD (FINPARK). We included 2017 cases (diagnosed 1999–2015) with PD and 7934 controls without PD. Diabetes medication use was identified from Prescription Register (1995–2015) and categorized to insulins, biguanides, sulfonylureas, thiazolidinediones (TZDs), dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues and glinide. Exposure for each medication class was determined as none, at least 3 years before outcome and only within the three-year lag time before PD outcome.

Results: The use of insulins, biguanides, sulfonylureas, DPP-4 inhibitors, GLP-1 analogues or glinides was not associated with PD. Use of TZDs before lag time compared to non-use of TZDs (adjusted odds ratio (OR) 0.78; 95% Confidence interval (CI) 0.64–0.95) was associated with decreased risk of PD.

Conclusions: Our nationwide case–control study of people with diabetes found no robust evidence on the association between specific diabetes medication classes and risk of PD. Consistent with earlier studies, TZD use was associated with slightly decreased risk of PD. The mechanism for this should be verified in further studies.

KEYWORDS
case–control study, diabetes, diabetes medication, epidemiology, Parkinson's disease, thiazolidinedione

Key points

- In this nationwide nested case–control study in people with diabetes, thiazolidinediones were the only diabetes medication class associated with risk of Parkinson's disease.

- The inverse association between thiazolidinediones and Parkinson's disease was weak, albeit consistent with earlier findings.
- No associations were observed for other diabetes medication categories (insulin, metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 analogues or glinides) when analyses were restricted to exposure that had occurred at least 3 years before the outcome.

1 | BACKGROUND

Parkinson's disease (PD) is the second most common neurodegenerative disorder.[1] Despite active research, its etiology is still unknown and identification of risk factors would aid in understanding the disease development.[2] Diabetes has been linked with increased risk of PD[3,4] and common cellular mechanisms, including mitochondrial dysfunction and increased neuroinflammation,[2,3] have been implied as one possible explanation.

Diabetes medications have been suggested as an alternative explanation, and consequently the association between diabetes medication and risk of PD has been studied in epidemiological studies.[5–12] The findings, but also the comparisons in these studies have been heterogeneous: lower risk of PD has been reported in thiazolidinedione (TZD) users compared to metformin users,[5] sulphonylurea users[9] or TZD nonusers with diabetes,[6,7] although one study did not observe difference in PD risk between TZD users and nonusers with diabetes.[12] Lower risk of PD has also been reported among metformin users compared with nonusers[10] and users of glucagon-like peptide-1 (GLP-1) analogues or dipeptidyl peptidase 4 (DPP-4) inhibitors compared with nonusers.[8] Lastly, a study that compared the risk of PD in users of different oral diabetes medications and those with diabetes without oral diabetes medication, showed an increased risk among sulphonylurea users, and a reduced risk for those who had used both sulphonylureas and metformin.[11]

Timing of exposure in relation to outcome might have biased the results in some of the earlier studies. PD has long onset period and is challenging to diagnose, so exposure close to the diagnosis may less likely reflect an association with disease mechanism but the impact of increased healthcare contact on medication exposure (initiations or discontinuations more likely with increased contact with prescribers). Still, the minimum time difference between the initiation of diabetes medication and outcome assessment has been short, even less than 1 year in some studies.[5,8,9,12] We examined the association between different diabetes medication classes and risk of PD with exposure that had occurred at least 3 years before PD diagnosis.

2 | METHODS

We performed a nested case–control study using Finnish community-dwellers with diabetes as the source population. This study used data from the nationwide register-based Finnish study on Parkinson's disease (FINPARK), which includes 22 189 people with clinically confirmed PD diagnosis and their matched comparison persons (N = 148 009). Data were retrieved from Prescription Register

(1995–2016), Special Reimbursement Register (1972–2016) and Care Register for Health Care (1972–2016).

2.1 | Identification of PD cases and controls

Special Reimbursement Register of Finland was used to identify persons with PD. For the reimbursement of PD, SII requires medical certificate from a neurologist and the diagnosis criteria was based on the
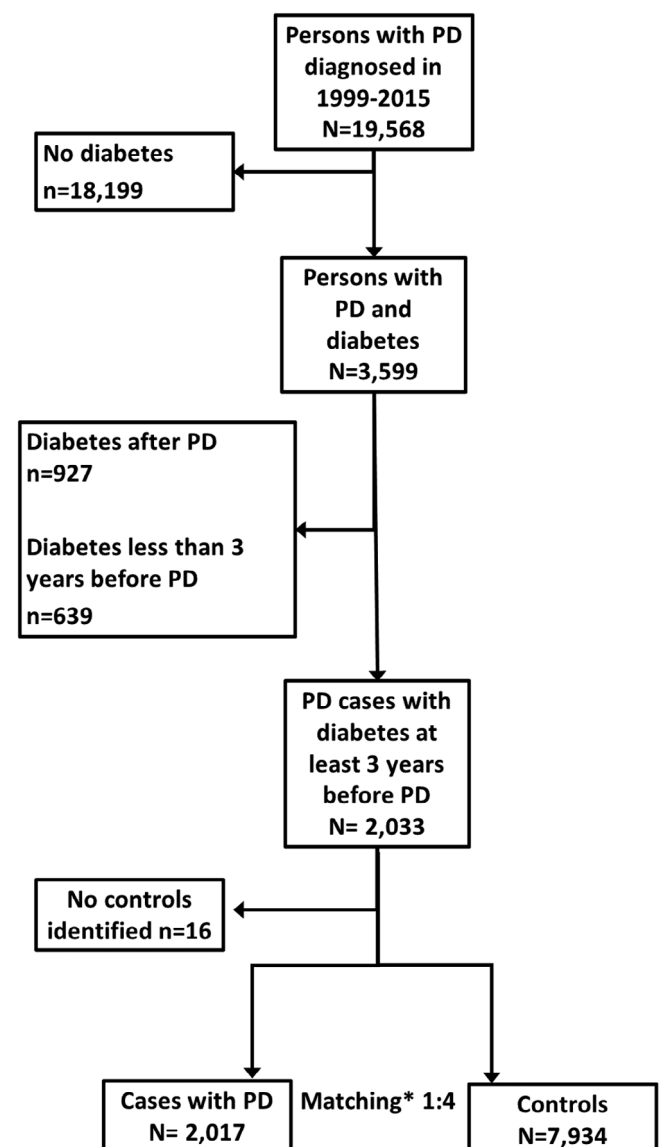

FIGURE 1 Formation of the study population

United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) criteria. Originally, there were 29 942 persons who were eligible for reimbursement of PD medications. Because some of the medications can also be used to other conditions than PD, persons without International Statistical Classification of Diseases and Related Health Problems diagnostic code for PD (ICD-10 code G20) in the Special Reimbursement register were excluded (N = 1244). In addition, we excluded persons who had diagnosis with similar symptoms to PD, such as secondary parkinsonism, multiple sclerosis and dementia (N = 6456) within 2 years of PD diagnosis. The FINPARK cohort formation and exclusion diagnoses have been described in detail previously.[13] We also excluded persons who were <35 years old at the time of PD diagnosis (N = 53), because primary PD is rare among young people.

To account for confounding by indication, this study was restricted to people with diabetes. People with diabetes were identified using Special Reimbursement Register and Prescription Register (Anatomical Therapeutic Chemical classification[14,15]; ATC-code A10 excluding guar gum, since 1995). We excluded cases who had diabetes after PD (n = 927) and cases who had diabetes less than 3 years before diagnosing of PD (n = 639) (Figure 1). Each PD case was matched with up to four controls by age (±2 years), sex, same university hospital district or adjacent district, and time from diabetes diagnosis (± 2 years) on the index date (date of PD diagnosis of the index case which was the matching date). Controls were persons without PD and the same exclusion criteria were applied as for PD cases. In addition, controls were not allowed to have dementia in Parkinson's disease (ICD-10 code F02.3) within 2 years of the index date. Altogether 16 cases with PD could not be matched with controls and they were excluded, leading to final study population of 2017 cases and 7934 controls.

2.2 | Exposure identification

The use of diabetes medication was determined from 1995 to index date from Prescription Register, which contains information of the reimbursed prescription medicine purchases with ATC codes and date of dispensing. The following medication classes were investigated: insulins, biguanides, sulfonylureas, TZDs, DPP-4 inhibitors, GLP-1 analogues and glinides (Tables S1 and S2). Combination products were recoded to use of each active ingredient, for example users of metformin and rosiglitazone combinations were counted as users of metformin and users of rosiglitazone.

In the main analyses, we considered exposure that had occurred at least 3 years before outcome assessment to control for reverse causality. The choice of this three-year lag time was based on our earlier study showing increased incidence of muscle relaxant use in this time window.[16] Therefore, exposure to diabetes medications was classified as no use, use only during 3-year lag time or use before lag time. People who were exposed during the main exposure assessment period (before lag time) and during lag time are categorized as being exposed before lag time.

2.3 | Comorbidities

Identification of comorbidities (cardiovascular disease, asthma or chronic obstructive pulmonary disease [COPD], rheumatoid arthritis and connective tissue diseases, cancer, mood disorder or schizophrenia, and history of head injury) including data sources and coding systems is described in detail in Table S2. Comorbidities were defined prior to exposure assessment period.

TABLE 1 Comparison of cases with Parkinson's disease and controls

	Parkinson's disease cases, n = 2017	Control (no Parkinson's disease) n = 7934	p
Sex (men) (n, %)	1201 (59.5)	4749 (59.9)	0.80
Age at Parkinson's disease diagnosis (mean) (95% CI)	73.5 (73.2–73.9)	73.6 (73.4–73.8)	0.75
Age at diabetes diagnosis (mean)	62.7 (62.2–63.1)	63.1 (62.8–63.3)	0.11
Duration of diabetes in years	10.8 (10.5–11.1)	10.5 (10.3–10.7)	0.08
Comorbidities (n, %)			
Cardiovascular disease	867 (43.0)	3348 (42.2)	0.52
Asthma/COPD	92 (4.6)	363 (4.6)	0.98
Rheumatoid arthritis	49 (2.4)	166 (2.1)	0.35
Cancer	50 (2.5)	234 (3.0)	0.26
Mood disorder or schizophrenia	67 (3.3)	133 (1.7)	<0.001
History of head injury	19 (0.9)	107 (1.4)	0.15
University hospital district			0.99
Helsinki	533 (26.5)	2105 (26.5)	
Kuopio	382 (18.9)	1518 (19.1)	
Oulu	317 (15.7)	1248 (15.7)	
Tampere	527 (26.1)	2085 (26.3)	
Turku	258 (12.8)	978 (12.3)	

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease.

TABLE 2 Associations between use of diabetes medication and Parkinson's disease (PD), compared with non-use

	PD cases N = 2017	Controls N = 7934	p Value	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)	Adjusted[b] OR (95% CI)
Insulin			0.011			
No use	1280 (63.4)	4899 (61.8)				
Use only during lag time	138 (6.8)	707 (8.9)		0.73 (0.60–0.89)	0.74 (0.61–0.90)	0.73 (0.60–0.89)
Use before lag time	599 (29.7)	2328 (29.3)		0.93 (0.81–1.06)	0.93 (0.81–1.06)	0.90 (0.78–1.03)
Metformin			0.88			
No use	361 (17.9)	1382 (17.4)				
Use only during lag time	136 (6.7)	534 (6.7)		1.01 (0.81–1.27)	1.02 (0.82–1.28)	1.04 (0.83–1.30)
Use before lag time	1520 (75.3)	6018 (75.9)		1.02 (0.88–1.18)	1.02 (0.88–1.18)	1.03 (0.88–1.19)
Sulfonylureas			0.92			
No use	764 (37.9)	2981 (37.6)				
Use only during lag time	58 (2.9)	240 (3.0)		0.95 (0.70–1.29)	0.96 (0.71–1.31)	0.97 (0.71–1.32)
Use before lag time	1195 (59.2)	4713 (59.4)		1.00 (0.87–1.14)	1.00 (0.88–1.14)	0.98 (0.86–1.12)
Thiazolidinediones			0.028			
No use	1825 (90.9)	7012 (88.4)				
Use only during lag time	51 (2.3)	241 (3.0)		0.82 (0.60–1.12)	0.81 (0.59–1.11)	0.80 (0.59–1.10)
Use before lag time	141 (7.0)	681 (8.6)		0.79 (0.65–0.96)	0.79 (0.65–0.97)	0.78 (0.64–0.95)
Dipeptidyl peptidase 4 inhibitors			0.35			
No use	1688 (83.7)	6537 (82.4)				
Use only during lag time	214 (10.6)	888 (11.2)		0.92 (0.77–1.10)	0.93 (0.78–1.10)	0.92 (0.77–1.09)
Use before lag time	115 (5.7)	509 (6.4)		0.85 (0.67–1.07)	0.84 (0.67–1.07)	0.83 (0.65–1.05)
Glucagon-like peptide-1 analogues			0.77			
No use	2004 (99.4)	7880 (99.3)				
Use only during lag time	10 (0.5)	46 (0.6)		0.87 (0.43–1.74)	0.90 (0.45–1.80)	0.90 (0.45–1.80)
Use before lag time	3 (0.2)	8 (0.1)		1.50 (0.40–5.64)	1.51 (0.40–5.69)	1.48 (0.39–5.58)
Glinides			0.37			
No use	1978 (98.1)	7776 (98.0)				
Use only during lag time	17 (0.8)	50 (0.6)		1.36 (0.78–2.35)	1.40 (0.80–2.43)	1.38 (0.79–2.41)
Use before lag time	22 (1.1)	108 (1.4)		0.78 (0.49–1.26)	0.78 (0.49–1.25)	0.77 (0.48–1.24)

Note: People with exposure during the main exposure assessment period (before lag time) and during lag time are categorized as being exposed before lag time.

Abbreviations: CI, confidence interval; OR, odds ratio; PD, Parkinson's disease.

[a]Adjusted for cardiovascular disease, asthma or chronic obstructive pulmonary disease (COPD), rheumatoid arthritis and connective tissue diseases, cancer, mood disorder or schizophrenia, and history of head injury.

[b]Adjusted as previous and duration of diabetes.

2.4 | Ethics

Persons were not contacted, and the data were pseudonymised. Therefore, approval from ethics committee or informed consent was not required. Data were used with permission from the register maintainers.

2.5 | Statistical analyses

The analyses were performed using Stata MP 14.2. *T*-test was used to compare continuous variables and chi square test to compare categorial variables. Conditional logistic regression was used to calculate odds ratios (OR) and 95% confidence interval (CI) for different exposure groups. The results were adjusted for comorbidities. In addition, due to small difference in diabetes duration between cases and controls, additional adjustment for diabetes duration was performed. Age, sex and region were controlled by matching only.

To evaluate the association of specific medication class (Table S2), those exposed to specific diabetes medication class were compared to unexposed (e.g., metformin users were compared to those who did not use metformin). Similar approach was used in earlier studies.[6–8,10,12]

To account for use of multiple diabetes medications during the main exposure assessment time, the participants were grouped based on which medication classes they had used before the lag time and risk of PD in different diabetes treatment histories were compared to those who had used only metformin during this period. As there were multiple small categories, the following grouping, based on frequency and similarity of associations, was used: 'metformin only', 'metformin + ≥1 other oral medication', 'sulphonylureas only', 'insulin +oral medication', 'insulin only' and 'oral mono-/polytherapy without metformin and sulphonylureas'.

3 | RESULTS

The mean age of cases and controls at the time of diabetes diagnosis were 62.7 and 63.1 years, respectively. The average age on matching date (PD diagnosis) was 73.5 years for cases and 73.6 years for controls (Table 1). Nearly 60% of cases and controls were men. The mean of duration of diabetes at the end of exposure period was 10.8 years for cases and 10.5 years for controls. Metformin was the most commonly used diabetes medication in both cases and controls (with three quarters exposed before lag time), followed by sulfonylureas and insulin (Table 2).

TZDs were the only group associated with PD in the main analyses restricted to exposure before lag time (adjusted OR 0.78; 95% CI 0.64–0.95 in comparison to nonusers of TZDs) (Table 2). Use of insulin before lag time was not related to PD (adjusted OR 0.90; 95% CI 0.78–1.03) but insulin use the during lag time was associated with lower risk of PD (adjusted OR 0.73; 95% CI 0.60–0.89).

Nearly all (96.7%) of those who had used TZDs before lag time had also been exposed to other diabetes drugs (Table S3), with 73.7% having diabetes drugs from two or more of the other diabetes drug categories in addition to TZDs.

Nearly half of all cases and controls had used only one diabetes medication class (47.6% of cases and 46.0% of controls, Table 3) and 44 people were not exposed to any diabetes medications before the lag time. There was no difference in the distribution of these nonusers between cases and controls and all of them initiated diabetes medications during the lag time. Excluding these people had no effect on results (data not shown). There was no difference in risk of PD between those who had used diabetes medications from multiple classes or had not initiated diabetes medication prior to the lag time in comparison to those who had used only one type of diabetes medication. After adjusting for the duration of diabetes, there was a suggestion of decreased risk of PD among those who had been exposed to four or more different classes compared to users of just one diabetes medication class (OR, 95% CI 0.74, 0.55–1.00).

In the analyses that accounted for exposure to different types of diabetes medication, there was no difference in the risk of PD in comparison to those who had used only metformin in confounder-adjusted analyses (Table 3). After additional adjustment for diabetes duration, a slightly lower risk was observed among those who used another oral diabetes medication in addition to metformin (OR, 95% CI 0.85, 0.73–0.99) or insulin only (OR, 95% CI 0.74, 0.55, 1.00). The average duration of diabetes was shortest in the metformin only group, and longest in the insulin only group (6.1 and 22.3 years, respectively, Table S4). All different exposure combinations and their distribution in cases and controls are listed in Table S5.

4 | DISCUSSION

In our indication-restricted nationwide study, we observed no association between use of insulin, metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 analogues or glinides and PD with exposure preceding the

TABLE 3 Associations between number of diabetes medications, and different combinations of diabetes medication history used during exposure assessment period and Parkinson's disease (PD)

	PD cases N = 2017	Controls N = 7934	p Value	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)	Adjusted[b] OR (95% CI)
Number of different drugs prior to lag time			0.394			
None	7 (0.4)	37 (0.5)		0.67 (0.30–1.53)	0.67 (0.30–1.52)	0.66 (0.29–1.50)
1	959 (47.6)	3646 (46.0)		1.00 (reference)	1.00 (reference)	1.00 (reference)
2	596 (29.6)	2423 (30.5)		0.93(0.82–1.05)	0.93(0.82–1.06)	0.91 (0.81–1.04)
3	386 (19.1)	1499 (18.9)		0.96(0.82–1.12)	0.96(0.82–1.12)	0.93 (0.79–1.08)
4 or more	69 (3.4)	329 (4.2)		0.77(0.57–1.03)	0.77(0.57–1.03)	0.73 (0.55–0.99)
Exposure history prior to lag time			0.553			
Metformin only	539 (26.7)	2.072 (26.1)		1.00 (reference)	1.00 (reference)	1.00 (reference)
Metformin + ≥1 other oral medication	571 (28.3)	2392 (30.2)		0.88 (0.76–1.03)	0.89 (0.76–1.03)	0.85 (0.73–0.99)
Sulphonylureas only	284 (14.1)	1052 (13.3)		1.01 (0.83–1.23)	1.01 (0.83–1.22)	0.98 (0.81–1.19)
Oral mono−/polytherapy (exc. Methormin/ sulphonylureas)	17 (0.8)	53 (0.7)		1.23 (0.71–2.14)	1.27 (0.71–2.21)	1.25 (0.72–2.18)
Insulin + oral medication	472 (23.4)	1840 (23.2)		0.92 (0.77–1.10)	0.92 (0.77–1.10)	0.87 (0.72–1.04)
Insulin only	127 (6.3)	488 (6.2)		0.80 (0.60–1.07)	0.81 (0.61–1.08)	0.75 (0.56–1.00)

outcome by at least 3 years. TZD use was associated with modestly lower risk of PD compared to no use of TZDs. Our findings are in line with a meta-analysis of retrospective studies comparing TZD users to persons with diabetes using other diabetes medications, in which TZD users had lower risk of PD.[17] That meta-analysis stratified studies based on whether the average follow-up was ≤5 years[9,12] or >5 years[5,7] and reported that associations were stronger in studies with the longer follow-up period.[17] It should be noted that the design of those studies with longer follow-up also included the assessment of recent or short-term exposure. For example, current use (prescription for TZD during last 180 days) of TZD was associated with lower risk of PD, compared to other diabetes medication in one of the studies[7] that was categorized as having longer average follow-up in the meta-analysis.[17] Similarly, in the other study categorized as having long-term follow-up, the time on medication had to be at least 6 months.[5] That study showed a 28% decreased relative risk of PD among current TZD users compared to metformin users, but no association was observed with previous use of TZDs.[5]

A Taiwanese study of persons with newly diagnosed diabetes, which was not included in the meta-analysis also reported that TZD users had lower risk of PD compared to those without TZD medication and the association was dose-dependent.[6] It should be noted that PD has long onset period and the observation of risk difference after relatively short course of drug exposure may be due to bias. Three retrospective cohort studies in persons with diabetes did not observe decreased risk of PD among TZD users.[8,9,12] One of these studies compared the risk of PD between pioglitazone users and nonusers and considered any exposure before PD.[12] Another study compared TZD users to sulfonylurea users with exposure occurring at least 10 months before the outcome.[9] A study from United Kingdom observed no difference in PD risk between TZD users compared to users of other diabetes medications or when the use of TZDs was assessed as ever exposed and never exposed.[8] The comparison group in these studies varied from non-use to different diabetes medication groups, which complicates the direct comparison between studies. They also had relatively short exposure periods or did not use any lag time between the exposure and outcome.

In our main analysis, no associations between other diabetes medication classes and risk of PD were observed, although an earlier study restricted to people with diabetes showed a lower risk of PD among those who had used metformin for over 4 years compared with metformin nonusers.[10] Another cohort study of people with diabetes reported lower risk of PD in those who used metformin and sulphonylureas and had initiated metformin before sulphonylureas compared to those who did not use oral diabetes medications.[11] In addition, a lower risk of PD among those people with oral diabetes medication in comparison to those with type 2 diabetes but who did not use any oral diabetes medication was reported.[6]

We performed additional analyses for exposure that had occurred in the three-year lag, and the point estimates of nearly all medication classes were similar as for the exposure that had occurred before the lag which implies that risk of reverse causality in our study would have been small, possibly because the study was restricted to persons with diabetes diagnosed prior to lag. However, a lower risk of PD was observed among those who initiated insulin in the lag time, and the point estimate was also supportive of lower risk in the main analyses. In addition, the analyses that accounted for exposure to multiple classes showed a lower risk among those who were exposed to insulin only in comparison to metformin users. These findings may be due to unmeasured confounding by severity of diabetes as they were partially masked by diabetes duration. It is also possible albeit unlikely that they reflect slower progression towards PD by improved glycemic control among insulin users, or they may be chance findings. As similar findings have not been reported in earlier studies, our findings with insulin should be interpreted cautiously until they are replicated with a robust design.

Diabetes itself has been suggested to be a risk factor for PD,[4] possibly because of shared cellular mechanisms.[2] Other hypotheses include decreased number of dopaminergic neurons in persons with diabetes[17] and under-expression of peroxisome proliferator-activated receptor γ (PPARγ). These receptors have been suggested as possible explanation for the association between TZDs and PD, as activation of PPARγ by TZDs increases insulin sensitivity.[2,6] TZDs' anti-inflammatory properties have also been suggested as an explanation.[5] However, it is important to acknowledge that the actual number behind the relative risk differences are quite small (cf. 1.6% difference in TZD exposure in our study) when evaluating the clinical significance.

TZDs are usually used in second- or third-line treatment with other diabetes medications,[18] and in fact, only 3.3% of TZD-exposed persons had not used other diabetes medications during the exposure assessment period. Due to small number of persons with different diabetes drug combinations with TZDs we did not perform specific analyses to TZD in combination to other diabetes medications. The analyses accounting for overall exposure combinations did not provide support for a protective combination, although there was a small masking effect of diabetes duration for insulin only and metformin plus other oral diabetes medication. However, the confidence intervals for these groups were very close to, or equal to one after adjusting for diabetes duration and the difference in exposure prevalence between cases and controls was very small (0.1% for insulin and 1.9% for metformin plus other oral diabetes medication.

Strengths of our study include the nationwide study with community-dwelling persons. Diagnosis of PD was verified by neurologist, and it is consistent with the United Kingdom Parkinson's Disease Society Brain Bank criterion. By excluding those with diagnoses indicating high possibility of false diagnosis of PD, we could further increase the reliability of the outcome. The proportion of excluded participants is in line with proportion of assumed false diagnosis.[19,20] By focusing on the exposure which preceded the outcome by at least 3 years we were more likely to capture a risk factor than reflection of reverse causality. We acknowledge that the onset of PD is longer and future studies should preferably assess exposure that had occurred even further away from the PD diagnosis. The choice of lag time in this study was based on our earlier study in this study population

which an increase in muscle relaxant use, indicating the occurrence of prodromal symptoms in this time window.[16]

Although Special Reimbursement Register enables the identification of diabetes since 1972, we acknowledge that identification of newly diagnosed diabetes is hampered by Prescription Register which starts from 1995. Therefore, we could not identify persons who had used diabetes medication before 1995. In addition, we could not adjust the results for lifestyle factors or diabetes severity, and it is possible that the association between TZDs and PD is biased by unmeasured confounding by these or other unmeasured factors. It should be noted that the number of users, and consequently the statistical power to detect association was limited for some newer diabetes medications such as glinides. Similarly, dose–response analyses would have been underpowered and were therefore not conducted.

To conclude, our findings support the earlier observations on lower risk of PD among thiazolidinedione users in comparison to nonusers when the exposure had occurred at least 3 years before Parkinson disease diagnosis, regardless of concomitant or earlier exposure to other diabetes drugs. Although the difference in the proportion of exposed cases and controls was small, the finding is supportive of the earlier suggestions on shared mechanisms between diabetes and PD.

AUTHOR CONTRIBUTIONS

Katriina Sunnarborg: Participated in designing and conceptualization of the study, interpreted the results, wrote the first draft of the manuscript, revised the draft with input from all authors. Miia Tiihonen: Designed and conceptualized the study, interpreted the results, revised the manuscript for important intellectual content. Marjo Huovinen: Interpreted the results, revised the manuscript for important intellectual content. Marjaana Koponen: Interpreted the results, revised the manuscript for important intellectual content. Sirpa Hartikainen: Designed and conceptualized the study, interpreted the results, revised the manuscript for important intellectual content. Anna-Maija Tolppanen: Designed and conceptualized the study, performed the statistical analyses, interpreted the results, revised the manuscript for important intellectual content.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

According to the Finnish legislation no formal ethical approval was required for this register-based study. The data were de-identified and the study participants were not contacted nor interfered for any treatment. The data were used with the permission of the register maintainers.

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SUPPORTING INFORMATION

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