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ORIGINAL ARTICLE

Risk of fracture in patients with Parkinson's disease

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Abstract
Summary The aim of the study was to determine fracture risk in incident Parkinson's disease (PD) patients. This study showed that fracture risk assessment may be indicated among patients with PD, in particular when they have recently used selective serotonin re-uptake inhibitors or high-dose antipsychotics, or have a history of fracture, falling, low body mass index (BMI) or renal disease.
Introduction PD is a movement disorder associated with falling and detrimental effects on bone. Both are recognized risk factors for fracture. Therefore, the aim was to determine fracture risk in incident PD patients stratified by treatment, severity, duration of disease and related comorbidities.
Methods We conducted a retrospective cohort study using the UK General Practice Research Database (1987–2011). Each PD patient was matched by age, sex, calendar time and practice to a control patient without history of PD.
Results We identified 4,687 incident PD patients. Compared to controls, a statistically significant increased risk was observed for any fracture (adjusted hazard ratio [AHR], 1.89; 95 % confidence interval [CI], 1.67–2.14), osteoporotic fracture (AHR, 1.99; 95 % CI, 1.72–2.30) and hip fracture (AHR 3.08; 95 % CI, 2.43–3.89). Fracture risk further increased with history of fracture, falling, low BMI, renal disease, antidepressant use and use of high-dose antipsychotics.
Conclusion This study showed that incident PD patients have a statistically significant increased risk of fracture. Therefore, fracture risk assessment may be indicated among PD patients, who, besides the general risk factors for fracture, like increasing age and female gender, have recently used selective serotonin re-uptake inhibitors or high-dose antipsychotics or have a history of fracture, falling, low BMI or renal disease.

Keywords Epidemiology · Falls · Fracture · Parkinson's disease

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Introduction

Parkinson's disease (PD) is a movement disorder with a prevalence of about 1 % in people over 60 years of age [1]. PD is characterized by loss of dopaminergic neurons in the nigrostriatal pathway, which causes symptoms like bradykinesia, resting tremor, stiffness and postural instability [2]. Subsequently, these symptoms explain the observed association between PD and an increased risk of falling [3, 4]. PD has also been associated with other indirect detrimental effects on bone [5, 6]. A possible explanation may be that in PD patients, reduced 25-hydroxyvitamin D levels and compensatory higher parathyroid hormone levels were observed, which may have reduced bone mineral density (BMD) [5]. This may be due to sunlight deprivation or decreased dietary intake

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of vitamin D [5, 7]. Both falling and reduced BMD are recognized determinants for an increased fracture risk. Common drugs used in the treatment of PD are also associated with falling (e.g. levodopa and dopamine agonists). This is caused by side effects like postural hypotension and slow mentation or confusion, which result in loss of protective reflexes during falling [8, 9]. Associations between PD and depression, anxiety, dementia, hallucinations and psychosis have been reported [10–13]. These comorbidities and concomitant treatment (e.g. antidepressants and antipsychotics) are risk factors of fracture [14–16].

The association between PD and fracture risk has been described in previous studies [17–21]. Vestergaard et al. and Arbouw et al. observed an increased fracture risk in, respectively, a Danish and a Dutch case control study among patients who used antiparkinson drugs. Fracture risk further increased with concomitant use of antidepressants and with high-dose neuroleptics [22, 23]. However, both studies were unable to focus specifically on PD patients and did not test the role of PD severity. Therefore, the aim of this study was to determine fracture risk in a cohort of incident PD patients, stratified by severity and duration of disease, PD medication and CNS comorbidity.

Methods

Data source

Information for this study was obtained from the General Practice Research Database (GPRD), which comprises computerized medical records of patients derived from primary care practices throughout the UK which were linked to the national Hospital Episode Statistics (HES). These records include the patient's demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and major outcomes [24]. HES includes information on the date, main discharge diagnosis and duration of hospitalisation, as provided by the hospitals. Previous studies of GPRD data have shown a high level of data validity with respect to the reporting of fractures (>90 % of fractures were confirmed) [25, 26].

Study population

The study population consisted of all incident PD patients aged 40 years or older, with their first recorded diagnosis of PD between 1987 and 2011 at least 1 year after the start of valid data collection. They had at least two records of a prescription for antiparkinson medication after diagnosis (levodopa, dopamine agonists, MAO-B inhibitors, amantadine, apomorphine, anticholinergic drugs [procyclidine, trihexyphenidyl, orphenadrine, methixine, biperiden or benzatropin] or catechol-*O*-methyl transferase (COMT) inhibitors [entacapone or tolcapone]). A total of 2,694 patients were excluded who had only one record of a prescription for antiparkinson medication after diagnosis. These excluded patients may have received a wrong diagnosis. Patients who had more than one record for a prescription of PD treatment before PD diagnosis were also excluded (n=1,827).

Each PD patient was matched by year of birth, sex and practice to a patient without a history of PD in GPRD. If no control was found, this age-matching criterion was expanded stepwise, in age increments of 1 year, to a maximum of 5 years. The index date of PD diagnosis was the date of the first record of PD after the start of GPRD data collection. Control patients had to be enrolled in the GPRD at the time of the index date of their matched PD patient. Patients were followed up for the occurrence of fracture from their index date to either the end of GPRD data collection, the date of transfer of the patient out of the practice area or the patient's death, whichever came first. Fracture types were classified according to the International Classification of Diseases, Tenth Revision categories. A clinical osteoporotic fracture was defined as a fracture of the radius/ulna, humerus, rib, femur/hip, pelvis or vertebrae. All other fractures were classified as non-osteoporotic [27].

Exposure

In GPRD, longitudinal prescription data are available, while clinical symptoms, as described in the Hoehn and Yahr [28] classification of PD severity, are often missing. Therefore, a proxy for the severity of PD over time (stratified into mild, moderate and severe PD) was based on the treatment prescribed during the different stages of PD, according to the National Institute for Health and Clinical Excellence (NICE) guideline on PD [29]. During follow-up, PD was classified as "mild" among patients who had not used COMT inhibitors or apomorphine injections and who were using only one of the following substances at the same time (within 3 months of a new time interval): low-dose levodopa (<600 mg per day), dopamine agonists, amantadine, anticholinergics or MAO-B inhibitors. PD was classified as "moderate" for patients without a history of COMT inhibitors or apomorphine injections and who were using either high-dose levodopa alone (≥600 mg per day) or more than one of the following substances at the same time: low-dose levodopa (<600 mg per day), dopamine agonists, amantadine, anticholinergics or MAO-B inhibitors. The use of a COMT inhibitor or apomorphine injections or continuous infusions ever before defined "severe" PD.

The total period of follow-up was divided into periods of 30 days, starting at the index date. At the start of each period, the presence of risk factors and indicators of PD severity were assessed by reviewing the computerized medical records for any record of risk factors prior to each period. Furthermore, PD disease duration was noted, as

measured from the index date (first record of PD). The use of dopaminergic and CNS medication was stratified to average daily dose during the 6 months before. WHO-defined daily dosages were used to add up dose equivalences between the various medications [30]. Within the 6 months before each interval, the average daily dose was calculated by dividing the cumulative dose by the time between the oldest prescription and the start date of the period.

General risk factors included age, gender, body mass index (BMI), smoking status and the use of >2 units alcohol/day, a history of fracture ever before PD diagnosis or history of falls within 3–12 months before PD diagnosis, history of chronic diseases ever before (asthma/chronic obstructive pulmonary disease [COPD], rheumatoid arthritis, thyroid disorders, renal disease [acute renal failure and chronic impaired renal function], cancer, congestive heart failure, cerebrovascular disease, diabetes mellitus, inflammatory bowel disease, dementia) and a prescription in the previous 6 months for CNS medications (antidepressants, antipsychotics, anxiolytics/hypnotics, anticonvulsants), opioids, oral glucocorticoids and other immunosuppressants (azathioprine, ciclosporin, tacrolimus, mycophenolate mofetil, methotrexate).

Statistical analysis

Time-dependent Cox proportional hazards regression was used in order to estimate hazard ratios (HRs) of fracture risk. Fracture risk in PD patients was compared with control patients to yield an estimate of the relative risk, which was expressed as hazard ratios. All characteristics, except age, were included as categorical variables in the regression models. Adjustments were made if any potential confounder showed a change in HR exceeding 1 %. For each analysis, the regression model was fitted with the general risk factors. These characteristics were treated as time-dependent variables in the analysis, in which the total period of follow-up was divided into periods of 30 days, starting at the index date. Within the group of PD patients, analyses were stratified to severity, history of dementia, history of drug use (including PD and CNS medication) 6 months before, history of fracture before the PD diagnosis and history of falls within 3–12 months before PD diagnosis. Stratification to each group of PD medication was adjusted for other PD medications.

Sensitivity analysis

Besides the main analysis, a sensitivity analysis was performed according to the algorithm of Hernan et al. to identify incident PD patients. Hernan et al. confirmed the PD diagnosis in 90 % of PD patients included in their cohort (n=1,019) [31]. Besides the current inclusion criteria, PD patients needed to have at least 3 years of follow-up in the GPRD prior to their first PD diagnosis and were not allowed to have a history of a drug for the treatment of PD or any treatment which induces parkinsonism (antiparkinson treatment, anticholinergics, "typical" antipsychotics, prochlorperazine, metoclopramide, amiodarone, reserpine, methyldopa and cinnarizine) ever before their PD diagnosis.

Results

We identified 4,687 incident PD patients and 4,687 controls between 1987 and 2011 with a mean age of 74 years, and 42 % were female. Approximately 90 % of PD patients were diagnosed after the age of 60 years, and average follow-up was 4 years. Table 1 shows age and gender distribution among PD patients and controls and provides information on BMI, smoking and alcohol status and history of comorbidities and drug use.

Table 2 shows the risk of fracture at different sites among PD patients as compared to controls. Risk of fracture was stratified to age and gender. The risks of fracture were almost doubled for any adjusted hazard ratio [AHR] (1.89, 95 % confidence interval [CI]; 1.67–2.14) and osteoporotic fracture (AHR 1.99; 95% CI, 1.72–2.30) compared to control patients. Risk for hip fracture was threefold increased when compared to controls (AHR of 3.08; 95%, CI 2.43–3.89). There was no effect of modification by gender for any or osteoporotic fracture. PD patients with an age between 75 and 85 years were at highest risk of any fracture yielding AHRs of 2.15 (95 % CI; 1.57–2.93) for male and 2.10 (95 % CI; 1.65–2.67) for female patients compared to controls. Similar findings were observed for osteoporotic fracture. Hip fracture risk was highest among male PD patients between 75 and 85 years (AHR, 3.67; 95 % CI, 2.14–6.31) compared to AHR of 2.67 (95 % CI, 1.75–4.06) for female patients.

Figure 1 displays the corresponding Kaplan–Meier survival curve for risk of osteoporotic fracture. Osteoporotic fracture risk increased non-significantly from an AHR of 1.51 (95 % CI; 1.14–2.00) in the first year, towards an AHR of 2.10 (95 % CI; 1.71–2.57) between 1 and 5 years, up to an AHR of 2.17 (95 % CI; 1.57–3.00) more than 5 years after PD diagnosis as compared with control patients.

In Table 3, the reference group changed from control patients towards PD patients who were unexposed to the treatment of interest. It shows that osteoporotic fracture risk further increased when PD patients were treated with MAO-B inhibitors, antidepressants or high-dose antipsychotics. PD patients exposed to selective serotonin re-uptake inhibitors (SSRI) had an increased risk of osteoporotic fracture (AHR, 1.72; 95 % CI, 1.38–2.15), whereas PD patients exposed to tricyclic antidepressants (TCA) had no further increased risk of osteoporotic fracture (AHR, 1.09; 95 % CI, 0.83–1.35). No

Table 1 Baseline characteristics of patients with PD and control patients

Characteristics	PD patients (n=4,687)	Controls (n=4,687)
Female (%)	42.3	42.3
Mean age (years)	73.9	73.9
BMI (%)		
<20	4.2	4.1
>30	11.6	14.3
Unknown	21.1	20.2
Smoking status (%)		
Never	55.8	46.4
Current	16.4	21.5
Ex	23.0	27.2
Unknown	4.8	4.8
Alcohol status (%)		
Never	18.4	16.6
Current	64.5	67.8
Ex	3.3	2.7
Unknown	13.8	12.8
Fracture history (%)		
Any fracture	19.2	18.7
Fracture at osteoporotic sites	11.3	10.7
Hip fracture	2.0	1.6
Vertebral fracture	1.1	1.0
Radius/ulna fracture	5.6	5.2
Comorbidity ever before index date (%)		
Asthma	11.2	12.6
COPD	4.6	6.9
Congestive heart failure	5.2	6.2
Diabetes mellitus	9.0	10.0
Rheumatoid arthritis	1.4	1.9
Renal disease	1.4	1.9
Cerebrovascular disease	13.3	9.8
Inflammatory bowel disease	0.8	1.0
Cancer (excluding skin cancer)	21.2	22.0
Dementia	5.1	1.9
Ischaemic heart disease	19.2	19.1
Drug use in 6 months before index date (%)		
Oral glucocorticoids	3.5	4.0
Antidepressants	21.0	9.9
Antipsychotics	5.1	2.0
Anxiolytics	12.1	8.4
Anticonvulsants	4.3	2.2
Bisphosphonates	4.3	3.8
Hormone replacement therapy	1.9	1.6

relation with dose was observed with use of SSRIs or TCAs. Patients who were prescribed <10 mg fluoxetine equivalents per day for SSRIs showed an equivalent risk of osteoporotic fracture (AHR, 2.04; 95 % CI, 1.33–3.13), as compared with patients who were prescribed ≥20 mg fluoxetine equivalents per day (AHR, 1.68; 95 % CI, 1.24–2.26). Patients in the lowest-dose group of TCA use had an equivalent risk (AHR, 1.15; 95 % CI, 0.82–1.63) as compared with patients in the highest-dose group (AHR, 1.05; 95 % CI, 0.70–1.55). PD patients exposed to other types of antidepressants were at 1.5-fold non-significantly increased risk (AHR, 1.51; 95 % CI, 0.92–2.46). Hip fracture risk further increased when patients received high-dose antidepressants or high-dose antipsychotics. Furthermore, PD patients with a BMI <20 had a significant increased risk for osteoporotic fracture (AHR, 1.76; 95 % CI, 1.24–2.50) and hip fracture (AHR, 2.80; 95 %, CI, 1.82–4.30) as compared to PD patients with a BMI ≥20. Osteoporotic fracture risk was significantly increased in patients with a history of renal disease (AHR, 1.85; 95 % CI, 1.19–2.87), a recent history of falling (AHR, 1.87; 95 % CI, 1.48–2.37) and a history of fracture before PD diagnosis (AHR, 1.29; 95 % CI, 1.05–1.58). Hip fracture risk was significantly increased among PD patients with a history of renal disease (AHR, 2.05; 95 % CI, 1.17–3.61) and a recent history of falling (AHR, 2.04; 95 % CI, 1.49–2.78). None of the other general risk factors showed statistically significant associations with fracture.

Severe PD patients tended to have a 1.5-fold increased risk of hip fracture as compared to mild PD patients (Table 4), although the AHR did not reach statistical significance. A sensitivity analysis was performed according to the validated algorithm of Hernan et al. [30] to include only incident PD patients (follow-up in GPRD ≥3 years before first PD diagnosis and unexposed to parkinsonism-inducing drugs ever before first PD diagnosis). With this definition, 2,083 PD patients were identified. The observed risks for the various types of fracture were similar to those presented in Table 2 (any, AHR, 1.94; 95 % CI, 1.57–2.40), osteoporotic (AHR, 2.05; 95 % CI, 1.60–2.63) and hip fracture (AHR, 3.24; 95 % CI, 2.15–4.90).

Discussion

This study found an almost doubled risk of any fracture and osteoporotic fracture, and a tripled risk of hip fracture in patients with PD as compared to the control population. Among patients with PD, the risk of osteoporotic fracture further increased with the use of MAO-B inhibitors, SSRIs, high-dose antipsychotics, history of fracture, falling, low BMI and renal disease. We could not detect an association between the duration of PD, its severity and risk of fracture.

Our study adds up to the observed increased fracture risk in other studies [18–21]. The observed increased fracture risk is in line with recent findings from a Danish (Vestergaard et al. [22]) and a Dutch (Arbouw et al. [23]) case–control study that evaluated fracture risk among cases exposed to antiparkinson

Table 2 Risk of fracture in PD patients by type of fracture, gender and age compared to patients without PD

	Fractures (*n*)	(%)	Age–sex-adjusted HR (95 % CI)	Fully adjusted HR (95 % CI)
No PD	411	8.8	1.00	1.00
PD (any fracture)	717	15.3	2.18 (1.93–2.46)	1.89 (1.67–2.14)
Fracture at osteoporotic sites	544	11.6	2.32 (2.01–2.67)	1.99 (1.72–2.30)
Hip fracture	275	5.9	3.57 (2.84–4.48)	3.08 (2.43–3.89)
Vertebral fracture	46	1.0	1.68 (1.08–2.63)	1.54 (0.97–2.45)
Radius/ulna fracture	77	1.6	1.28 (0.93–1.76)	1.10 (0.79–1.53)
Other fracture	157	3.3	2.00 (1.55–2.58)	1.77 (1.35–2.30)
Fracture at non-osteoporotic sites	173	3.7	1.82 (1.44–2.31)	1.62 (1.27–2.07)
By gender[a]				
Male	282	10.4	2.11 (1.74–2.57)	1.87 (1.53–2.29)
≤75 years	121	4.5	1.96 (1.45–2.64)	1.56 (1.14–2.13)
76–85 years	121	4.5	2.31 (1.71–3.13)	2.15 (1.57–2.93)
>85 years	40	1.5	1.57 (0.97–2.53)	1.39 (0.85–2.27)
Female	435	21.9	2.21 (1.89–2.58)	1.92 (1.64–2.25)
≤75 years	178	9.0	2.20 (1.71–2.84)	1.93 (1.48–2.50)
76–85 years	198	10.0	2.43 (1.92–3.08)	2.10 (1.65–2.67)
>85 years	59	3.0	1.46 (1.01–2.13)	1.27 (0.86–1.86)

[a]Male PD patients are compared with male controls of the same age group and female PD patients with female controls of the same age group

medication. The Danish study showed an adjusted odds ratio of 1.18 (95 % CI, 1.01–1.37) for any fracture, but adjusted in their main analyses for the use of anticholinergics, dopamine agonists, levodopa-containing drugs, MAO-B inhibitors and neuroleptics. When we adjusted our main analysis for any fracture for the same covariates, our AHR for any fracture decreased slightly from 1.89 (95 % CI, 1.67–2.14) to 1.85 (95 % CI, 1.54–2.23). It is hypothesized that the absence of non-PD patients receiving antiparkinson drugs in our cohort could further explain the different outcome. For example, in the Danish study also, patients treated with antiparkinson medication for restless legs syndrome may have been included. The Dutch case–control study showed an adjusted odds ratio of 1.76 (95 % CI, 1.39–2.22) for risk of hip fracture with current dopaminergic drug use. The use of MAO-B inhibitors, COMT inhibitors and amantadine was treated as a potential confounder. When we adjusted our main analysis of hip fracture for these covariates, our AHR for hip fracture decreased from 3.08 (95 % CI, 2.43–3.89) to 2.80 (95 % CI, 2.20–3.56). Again, the absence of non-PD patients receiving antiparkinson drugs in our cohort could further explain the difference in results.

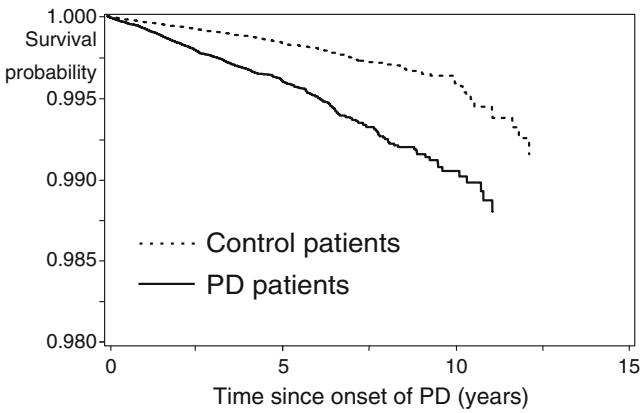

Fig. 1 Kaplan–Meier curves showing the survival of osteoporotic fracture among PD patients and control patients after their index date

Duration of PD did not show a clear association with fracture risk over time. However, patients seemed to have a higher risk in the first half year after onset of PD. This suggests that falls may be responsible for the increased fracture risk observed among PD patients instead of decreased BMD. This is in line with our finding that the highest proportion of falls was reported during the first 6 months after PD diagnosis, although differences are small as compared with the amount reported between 6 and 12 months after PD diagnosis (6.0 % versus 5.3 %, respectively). The difference may be caused by side effects of PD after onset. For example, tremor may take some time before being properly treated [8]. Arbouw et al. also observed the highest risk of hip fracture, immediately after start of antidopaminergic treatment [23].

In the general population, anxiolytics/hypnotics increase fracture risk by reducing balance [32]. However, in a PD population, which may already have poor balance, the excess increased risk of fracture caused by anxiolytic/hypnotic use may have been masked by the stronger effect of falling in the PD population. This may also explain the absence of a dose effect. In line with previous studies, fracture risk further increased with the use of SSRIs [15, 33, 34]. This may be caused by a further increased risk of falling. It may also be

Table 3 Risk of osteoporotic and hip fracture among PD patients stratified to drug use 6 months before

	Risk of osteoporotic fracture		Risk of hip fracture	
	Fractures (*n*)	Fully adjusted HR (95 % CI)[a]	Fractures (*n*)	Fully adjusted HR (95 % CI)[a]
Levodopa[b]	418	1.00 (0.82–1.23)	219	1.12 (0.83–1.52)
By average daily dose equivalents (eq.)				
<300 mg levodopa eq.	154	0.97 (0.76–1.24)	76	1.00 (0.70–1.42)
300–600 mg levodopa eq.	179	1.03 (0.82–1.30)	98	1.24 (0.88–1.73)
≥600 mg levodopa eq.	85	1.00 (0.74–1.33)	45	1.15 (0.76–1.74)
Dopamine agonists[b]	72	0.83 (0.64–1.09)	33	0.93 (0.63–1.38)
By average daily dose				
<3 mg ropinirole eq.	20	0.91 (0.58–1.43)	13	1.26 (0.72–2.23)
3–6 mg ropinirole eq.	19	0.87 (0.55–1.39)	6	0.67 (0.30–1.53)
≥6 mg ropinirole eq.	33	0.77 (0.53–1.12)	14	0.85 (0.48–1.51)
MAO-B inhibitors[b]	39	1.47 (1.05–2.05)	15	1.19 (0.70–2.02)
COMT inhibitors[b]	34	1.17 (0.82–1.67)	19	1.52 (0.94–2.47)
Amantadine[b]	14	1.13 (0.66–1.94)	7	1.38 (0.64–2.97)
Antidepressants	194	1.52 (1.26–1.82)	90	1.42 (1.10–1.83)
By average daily dose				
<10 mg fluoxetine eq.	60	1.52 (1.15–2.00)	25	1.30 (0.85–1.97)
10–20 mg fluoxetine eq.	47	1.34 (0.99–1.83)	23	1.32 (0.85–2.05)
≥20 mg fluoxetine eq.	87	1.64 (1.29–2.10)	42	1.57 (1.12–2.20)
Antipsychotics	44	1.28 (0.93–1.77)	22	1.24 (0.79–1.96)
By average daily dose				
<37.5 mg thioridazine eq.	15	1.00 (0.60–1.69)[c]	7	0.89 (0.42–1.91)[c]
37.5–150 mg thioridazine eq.	18	1.15 (0.71–1.85)[d]	8	1.00 (0.49–2.05)[d]
≥150 mg thioridazine eq.	11	2.98 (1.63–5.47)[cd]	7	3.84 (1.79–8.25)[cd]
Anxiolytics/hypnotics	111	1.23 (0.99–1.52)	46	0.97 (0.70–1.34)
By average daily dose				
<5 mg diazepam eq.	57	1.49 (1.13–1.98)	21	1.06 (0.67–1.67)
5–10 mg diazepam eq.	27	0.98 (0.66–1.46)	12	0.81 (0.45–1.47)
≥10 mg diazepam eq.	27	1.04 (0.70–1.56)	13	1.00 (0.56–1.77)

[a]The reference group are PD patients unexposed to the investigated drug

[b]Additionally adjusted for PD medication, except for PD medication investigated

[c]Statistically significant difference Wald test ($p<0.05$)

[d]Statistically significant difference Wald test ($p<0.05$)

caused by decreased osteoblast proliferation, through 5-hydroxytryptamine receptor inhibition in bone [15]. No dose effect and no association between fracture risk and TCA use was observed, although their effect may also have been masked by the high general increased risk of falling of PD patients Fracture risk increased with concomitant use of high-dose antipyschotics (exceeding an average daily dose of 150 mg thioridazine equivalents). Vestergaard et al. stratified their Danish cohort to average daily dose of antipsychotics as well and observed the highest risks for osteoporotic and hip fracture among patients receiving high average daily doses exceeding 100 mg thioridazine equivalents [22]. Conversely, a Dutch case–control study did not observe a trend in average daily dose of antipsychotics, but their highest average daily

Table 4 Risk of fracture at osteoporotic sites and hip fracture among PD patients, by severity of PD

	Risk of any osteoporotic fracture		Risk of hip fracture	
	Number of fractures	Fully adjusted HR (95 % CI)	Number of fractures	Fully adjusted HR (95 % CI)
By severity of PD				
Mild PD	338	1.00	174	1.00
Moderate PD	162	0.98 (0.81–1.20)	75	1.01 (0.76–1.33)
Severe PD	44	1.13 (0.81–1.56)	26	1.51 (0.98–2.33)

dose group did not exceed 75 mg thioridazine equivalents [16]. This may be explained by the use of different antipsychotics in the UK as compared to the Netherlands.

Our study has several strengths. It investigated the risk of fracture in a substantial number of 4,687 incident PD patients compared to control patients. Our inclusion criteria are based on the validated inclusion criteria used by Hernan et al. to identify incident PD patients [31]. A sensitivity analysis on incident PD patients (follow-up in GPRD ≥3 years before first PD diagnosis and unexposed to parkinsonism-inducing drugs ever before first PD diagnosis) showed similar results for fracture risk in the main analyses. Furthermore, 95 % of PD patients had at least three records of a prescription for antiparkinson medication after diagnosis, which indicates that most diagnoses were correct and that early death was uncommon. Selection bias is unlikely, because each PD patient was compared with an age–gender-matched control. In contrast to other studies (Vestergaard et al. and Arbouw et.al), adjustment for well-known risk factors like smoking status and history of fracture was possible.

Our study had various limitations. We were unable to classify the severity of PD based on the Hoehn and Yahr classification [28]. Instead, an alternative approach, based on PD treatment prescribed in the different severity stages of PD, was used based on the NICE guideline [29]. A recent GPRD study by de Vries et al. [35] and a Dutch PHARMO study by Bazelier et al. [36] used a similar approach. Some PD patients may have been misclassified for mild, moderate or severe PD in our severity analysis. Moreover, it is likely that the most severe PD patients were not included in our cohort since mean follow-up did not exceed 4 years. No association between the dose of dopaminergic drugs and the risk of fracture was observed. However, we were unable to distinguish if these drugs were actually harmless or that an increasing dose ameliorated the symptoms of the disease and consequently prevented the risk of fracture. No data were present on femoral bone mineral density and history of hip fracture among the parents of patients.

In conclusion, PD patients are at an almost doubled risk of any fracture and osteoporotic fracture, and a tripled risk of hip fracture as compared to the control population. Bisphosphonates may be recommended in order to prevent hip fractures in PD patients [37]. Therefore, fracture risk assessment may be indicated among PD patients, who, besides the general risk factors for fracture, like increasing age and female gender, have recently used MAO-B inhibitors, SSRIs or high-dose antipsychotics or have a history of fracture, falling, low BMI or renal disease.

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