Parkinson Disease and the Risk of Epileptic Seizures

Katharina Gruntz, MD,[1] Marlene Bloechliger, PhD,[1] Claudia Becker, PhD,[1] Susan S. Jick, DSc,[2,3] Peter Fuhr, MD,[4] Christoph R. Meier, PhD,[1,2,5] and Stephan Rüegg, MD[4]

Objective: To assess the association between incident Parkinson disease (PD) and subsequent incident epileptic seizures.
Methods: We conducted a retrospective cohort study with a nested case–control analysis using data from the U.K. Clinical Practice Research Datalink. We identified patients aged ≥40 years with an incident diagnosis of PD between 1995 and 2016 and a matched comparison group of PD-free individuals. We calculated crude incidence rates (IRs) with 95% confidence intervals (CIs) of epileptic seizures in PD patients and the PD-free comparison group, and corresponding crude incidence rate ratios (IRRs). In the nested case–control analysis, we calculated adjusted odds ratios (adj. ORs) of incident PD among cases with incident epileptic seizures and seizure-free controls overall and stratified by various seizure-provoking comorbidities.
Results: Among 23,086 incident PD patients and 92,343 PD-free individuals, we identified 898 patients with incident epileptic seizures. The crude IR of epileptic seizures in PD patients was 266.7/100,000 person-years (95% CI = 235.6–297.7), and in PD-free individuals it was 112.4/100,000 person-years (95% CI = 103.5–121.3; IRR = 2.37, 95% CI = 2.06–2.73). The adj. OR of epileptic seizures was 1.68 (95% CI = 1.43–1.98) in PD patients compared with PD-free individuals. PD patients with comorbid brain disorders (adj. OR = 12.36, 95% CI = 8.74–17.48) or with > 1 seizure-provoking comorbidity (adj. OR = 13.24, 95% CI = 10.15-17.25) were at the highest risk of epileptic seizures compared with PD-free individuals with no seizure-provoking comorbidities.
Interpretation: This study suggests that incident PD is associated with an increased risk of incident epileptic seizures.

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A potential association between Parkinson disease (PD) and epilepsy was first reported in 1928.[1] In a case series, 4 epilepsy patients underwent a decrease in seizure frequency after developing parkinsonism (a syndrome characterized by bradykinesia, resting tremor, rigidity, and postural instability[2]). In a further case report published in 2000, a patient with childhood epilepsy had fewer epileptic seizures after developing parkinsonian symptoms.[3]

More recently, the results of 3 observational studies indicated that the prevalence of epilepsy in PD patients (3 of 125 [2.4%], 31 of 1215 [2.6%], and 7 of 500 [1.4%], respectively) [4–6] was higher than the estimated prevalence in the general population (0.4–1.0%).[7–11] However, the authors of the first study omitted 3 patients when calculating the epilepsy prevalence among PD patients, because these patients had comorbidities (stroke, brain tumor, traumatic brain injury) potentially provoking epileptic seizures; as a result, the prevalence of epilepsy among patients with PD was lower than among the general population.[4] Moreover, without further explanation, the authors of the second study concluded that

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Address correspondence to Dr Meier, Basel Pharmacoepidemiology Unit, Hospital Pharmacy, University Hospital Basel, Spitalstrasse 26, CH-4031 Basel, Switzerland. E-mail: christoph.meier@usb.ch

From the [1]Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland; [2]Boston Collaborative Drug Surveillance Program, Lexington, MA; [3]Boston University School of Public Health, Boston, MA; [4]Division of Clinical Neurophysiology, Department of Neurology, University Hospital Basel, Basel, Switzerland; and [5]Hospital Pharmacy, University Hospital Basel, Basel, Switzerland

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their results suggest a lower prevalence of epilepsy in patients with PD than in the general population of the same age (mean age = 67 ± 9.7 years),[5] although the prevalence of epilepsy in the Western European general population aged 55 to 75 years ranges between 0.4 and 0.6%.[7,11] On the contrary, results of a cross-sectional study based on data from the U.K. General Practice Research Database (now called Clinical Practice Research Datalink [CPRD]) suggested that PD was about 3 times more prevalent in patients with epilepsy than in patients without epilepsy.[10] An additional nested case–control study, also based on data from the CPRD, suggested that comorbid PD among adult patients with depression was associated with a higher risk of incident epileptic seizures (crude odds ratio [OR] = 2.43) compared with depression without comorbid PD.[12]

In summary, existing observational studies on the potential association between PD and epileptic seizures or epilepsy were based on small and heterogeneous study populations, cross-sectional data, or results that were not adjusted for confounding factors. We therefore conducted a large longitudinal study to assess crude incidence rates (IRs) of epileptic seizures among incident PD patients and among a matched comparison group of individuals without PD, and a nested case-control analysis to further explore the association between PD and epileptic seizures, and to study the potential influence of the presence or absence of additional risk factors for epileptic seizures.

Subjects and Methods

Study Design and Data Source

We performed a retrospective population-based cohort study with a nested case–control analysis using data from the U.K.-based CPRD. The CPRD was established in 1987, encompasses deidentified computerized data on >11 million patients from almost 700 general practitioners (GPs), and includes information on demographics (eg, age, sex), medical diagnoses (recorded as "Read codes"), drug prescriptions, and behavioral factors (eg, body mass index [BMI], smoking status). Specialist and hospital care (eg, comorbidities diagnosed by specialists or at the hospital) are routinely reported back to the GPs, who enter the data into the computer system. The patients enrolled in the CPRD are representative of the U.K. general population in terms of age, sex, and ethnicity.[13] The database has repeatedly been validated and proven to be of high quality.[14–16] Numerous observational studies on PD[17,18] and on epileptic seizures[12,19] have been conducted using the CPRD.

The study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency research (London, U.K.; protocol number: 17_084).

Study Population

The study population comprised all patients aged ≥40 years in the CPRD who had a first ever diagnosis of PD between January 1995 and December 2016. PD was defined as a first recording of a Read code corresponding to the International Classification of Diseases version 10 (ICD-10) code G20 "Parkinson disease" (see Supplement 1). The date of the PD diagnosis will subsequently be referred to as the "cohort entry date." If a patient had at least 1 prescription for an antiparkinsonian drug within 1 year before the recording of the Read code for PD, we shifted the cohort entry date to the date of the first prescription within that year. To increase the likelihood of including only incident PD patients, they had to have at least 1 year of recorded active history on the database prior to the cohort entry date. We excluded all patients with a history of epileptic seizures at any time before the cohort entry date.

The study population also included a PD-free comparison group comprising 4 PD-free individuals matched to each PD patient on age (same year of birth), sex, GP practice, and cohort entry date. PD-free individuals were required to have no diagnosis of PD and no prescriptions for an antiparkinsonian medication at any time in their patient records up to December 2016.

We applied the same exclusion criteria to the PD-free comparison group as to PD patients. We did not exclude PD patients or PD-free individuals with seizure-provoking comorbidities (eg, brain disorders, psychiatric disorders, dementia),[19–22] because in addition to investigating the overall association between PD and epileptic seizures, we also planned to investigate the association between PD and epileptic seizures in association with the presence or absence of comorbidities.

Follow-up and Definition of Seizure Cases

We followed all patients (PD patients and PD-free individuals) from the cohort entry date until (1) they had a Read code for an incident epileptic seizure or epilepsy (corresponding to ICD-10 codes G40 “Epilepsy,” G41 “Status epilepticus,” or R65.8 “Other and unspecified convulsions”; see Supplement 2); (2) they had a Read code indicating a suspected epileptic seizure (eg, “On examination—a seizure”), which was followed by ≥2 prescriptions for anticonvulsant drugs within 6 months thereafter; (3) they died; (4) they left the practice; or (5) the end of the last data collection (December 2016). Patients whose follow-up ended because of (1) or (2) will subsequently be called “cases,” and the date of their first case qualifying code will be referred to as the “index date.”

Nested Case–Control Analysis

Definition of Controls

For each seizure case, we identified at random up to 10 controls from the study population who did not have a record of epileptic seizures prior to the case index date (risk set sampling). Controls were matched to cases on age (±2 years), sex, calendar time (by assigning the index date of the cases to their controls), years of history in the CPRD prior to the index date (±2 years), and duration

of follow-up (duration between the cohort entry date and the index date, ±2 years).

Definition of Exposure and Covariates

For cases and controls, we assessed the prevalence of diagnosed PD and classified patients with PD by the presence or absence of antiparkinsonian treatment prior to the index date. We further classified patients treated with an antiparkinsonian drug into those receiving dopa (or dopa derivatives), dopamine agonists, other antiparkinsonian drugs (eg, anticholinergics, monoamine oxidase inhibitors), or mixed use of antiparkinsonian drugs.

We assessed BMI (<18.5, 18.5–24.9, 25–29.9, ≥ 30kg/m^2, unknown), smoking status (nonsmoker, current smoker, former smoker, unknown), and alcohol consumption (nondrinker, 1–14U/wk, > 14U/wk, unknown) prior to the index date in cases and controls. Furthermore, we assessed diagnoses of known seizure-provoking comorbidities, that is, substance abuse (alcoholism or drug abuse), brain disorders (brain infections, brain surgery, brain tumors, head trauma, stroke/transient ischemic attack, intracranial hemorrhage, multiple sclerosis), psychiatric disorders (depression, anxiety disorders, schizophrenic disorders, bipolar and manic disorders, obsessive–compulsive disorders, suicide or suicidal ideation), dementia, and metabolic disturbances (hypo- and hypernatremia, hypo- and hyperglycemia, diabetic ketoacidosis, fever, hypocalcemia, uremia, disequilibrium syndrome) prior to the index date in cases and controls.[19–22] Finally, we also assessed the exposure to any of the following groups of drugs that potentially alter the risk of epileptic seizures prior to the index date in cases and controls: anticonvulsants, anti-infectives (antibiotics, antimalarials, or antivirals), antipsychotics, antidepressants, anticholinergics, antidiabetics provoking hypoglycemia (sulfonylureas, glinides, insulin), opioids, antiarrhythmics, and hypnotics.[23–26] We classified drug exposure according to the timing of the last prescription prior to the index date; "current users" received the last prescription ≤90 days prior to the index date, "past users" received it > 90 days prior to the index date, and "nonusers" were patients who had never received a prescription prior to the index date.

Statistical Analysis

In the cohort study, we calculated crude IRs of epileptic seizures per 100,000 person-years (PYs) with 95% confidence intervals (CIs) in PD patients and PD-free individuals overall, and we stratified IRs by age at the index date (40–59 years, 60–79 years, ≥ 80 years) and by sex. Furthermore, we calculated crude incidence rate ratios (IRRs) with 95% CIs of epileptic seizures in PD patients compared with PD-free individuals.

In the nested case–control analysis, we conducted conditional logistic regression analyses to explore the association between PD and the risk of epileptic seizures in more detail. We calculated ORs with 95% CIs of PD among cases with epileptic seizures compared to controls. We additionally calculated ORs stratified by treated versus untreated PD (reference group: patients without PD). Based on pre-existing literature, we a priori adjusted multivariate models for brain disorders, psychiatric disorders, dementia, and current use of anticonvulsants.[19–22,25,27–29] We tested additional potential confounders (substance abuse, metabolic disturbances, anti-infectives, antipsychotics, antidepressants, anticholinergics, antidiabetics that may provoke hypoglycemia, opioids, antiarrhythmics, and hypnotics),[23–26,28,30–33] but did not include them in the final model as they did not alter the risk estimates by >5%.

In a further analysis, we calculated ORs stratified by presence or absence of PD and of known potentially seizure-provoking comorbidities such as brain disorders, psychiatric disorders, dementia, metabolic disturbances, or substance abuse, to investigate patterns of comorbidities with the highest risk of epileptic seizures among PD patients and patients without PD (reference group: patients without PD and without any of these comorbidities). We adjusted these analyses for current use of anticonvulsants.

We also conducted a sensitivity analysis in which we applied additional criteria to assess the accuracy of the PD definition. In this analysis, we only included PD patients if (1) they had no record of any prescriptions for a drug that may cause parkinsonism[28] recorded within 180 days before the recorded PD diagnosis, and (2) they received at least 2 prescriptions for treatment of PD any time on or after the date of the PD diagnosis. A validation study conducted in the CPRD in 2004 found that PD diagnoses that were accompanied by ≥2 prescriptions for an antiparkinsonian drug were confirmed by review of medical records in 90% of cases.[34] In a second sensitivity analysis, we applied a definition of incident epilepsy used by authors of another CPRD-based study,[35] where a patient was required to have at least 2 anticonvulsant prescriptions recorded within 1 month before or up to 6 months after a Read code for an epileptic seizure, epilepsy, or status epilepticus.

We used SAS statistical software (v9.4; SAS Institute, Cary, NC) to conduct our analyses.

Results

In the cohort study, we identified 23,086 patients with incident PD and 92,343 matched individuals without PD. During follow-up, we identified 284 (1.2%) patients with incident epileptic seizures among PD patients and 614 (0.7%) patients with incident epileptic seizures in the PD-free comparison group.

TABLE 1. Crude IRs per 100,000 PYs of Epileptic Seizures in Patients with and without PD, and Corresponding IRRs, Stratified by Sex and Age at the Index Date

	Cases, n = 898	PYs	IR[a]	95% CI	IRR	95% CI
No PD, n = 92,343						
All	614	546,410.3	112.37	103.48–121.26	1	Reference
Men	380	302,291.4	125.71	113.07–138.35	1	Reference
Women	234	244,118.9	95.85	83.57–108.14	1	Reference
Age = 40–59 years	16	28,955.4	55.26	28.18–82.33	1	Reference
Age = 60–79 years	249	282,713.6	88.07	77.14–99.01	1	Reference
Age ≥ 80 years	349	234,741.2	148.67	133.08–164.27	1	Reference
PD, n = 23,086						
All	284	106,507.4	266.65	235.64–297.66	2.37	2.06–2.73
Men	149	59,595.7	250.02	209.87–290.16	1.99	1.65–2.40
Women	135	46,911.6	287.78	239.23–336.32	3.00	2.43–3.71
Age = 40–59 years	13	7,246.8	179.39	81.87–276.91	3.25	1.56–6.75
Age = 60–79 years	147	62,269.5	236.07	197.91–274.23	2.68	2.19–3.29
Age ≥ 80 years	124	36,991.1	335.22	276.21–394.22	2.25	1.84–2.77

[a]Per 100,000 PYs.
CI = confidence interval; IR = incidence rate; IRR = incidence rate ratio; PD = Parkinson disease; PY = person-year.

Incidence Rates

Table 1 displays crude IRs of epileptic seizures in PD patients and in the PD-free comparison group, as well as crude IRRs comparing these 2 groups (overall and stratified by sex and age). The crude overall IRR of epileptic seizures in PD patients compared with the PD-free comparison group was 2.37 (95% CI = 2.06–2.73). In PD and PD-free patients, incidence rates tended to be higher in older than in younger individuals. Female PD patients had a slightly (but statistically not significantly) higher crude IR of epileptic seizures than male PD patients, whereas the opposite was observed in the PD-free comparison group. The IRR of epileptic seizures in female PD patients compared to female PD-free individuals was significantly higher than the IRR of epileptic seizures in male PD patients compared to male PD-free individuals.

Nested Case–Control Analysis

The nested case–control analysis encompassed 897 cases with an incident diagnosis of epileptic seizures and 8,937 matched controls (1 case could not be matched to suitable controls and was not included in the nested case–control analysis). Mean age of cases was 79.1 years (±8.7 years), and 58.9% of cases were male.

Having prevalent diagnoses of brain disorders, dementia, metabolic disturbances, psychiatric disorders, and substance abuse was independently associated with increased risks of epileptic seizures (Table 2). Similarly, current use of anticonvulsants, anti-infectives, antidepressants, antipsychotics, opioids, and hypnotics was independently associated with increased risks of epileptic seizures, compared to past use or nonuse (Table 3). The adjusted OR for developing first-time epileptic seizures in association with PD was 1.68 (95% CI = 1.43–1.98) compared with no PD (Table 4). Furthermore, the adjusted OR of developing epileptic seizures was higher in untreated than in treated PD patients, compared with PD-free individuals. PD patients who did not have any seizure-provoking comorbidity had an adjusted OR of epileptic seizures of 2.24 (95% CI = 1.62–3.08) compared with PD-free individuals without any seizure-provoking comorbidity (Table 5). The OR of developing epileptic seizures was highest in patients with PD and comorbid brain disorders, dementia, or >1 seizure-provoking comorbidity compared with PD-free individuals without any seizure-provoking comorbidity. Brain disorders and >1 seizure-provoking comorbidity tended to be more strongly associated with epileptic seizures in PD patients than in PD-free individuals (see Table 5).

TABLE 2. Characteristics, Lifestyle Factors, and Potentially Seizure-Provoking Comorbidities of Cases with Epileptic Seizures and Matched Controls at the Index Date

Characteristic	Cases, n = 897, No. (%)	Controls, n = 8,937, No. (%)	Crude OR	95% CI
Sex				
Male	528 (58.9)	5,260 (58.9)	NA	NA
Female	369 (41.1)	3,677 (41.1)	NA	NA
Age, years				
40–59	29 (3.2)	261 (2.9)	NA	NA
60–79	396 (44.2)	3,950 (44.2)	NA	NA
≥80	472 (52.6)	4,726 (52.9)	NA	NA
Body mass index, kg/m^2				
<18.5	24 (2.7)	213 (2.4)	1.03	0.67–1.57
18.5–24.9	319 (35.6)	2,914 (32.6)	1	Reference
25–29.9	251 (28.0)	2,929 (32.8)	0.78	0.66–0.92
≥30	128 (14.3)	1,401 (15.7)	0.82	0.67–1.01
Unknown	175 (19.5)	1,480 (16.6)	1.13	0.93–1.38
Smoking status				
Nonsmoker	395 (44.0)	4,002 (44.8)	1	Reference
Current smoker	82 (9.1)	841 (9.4)	0.99	0.78–1.26
Former smoker	346 (38.6)	3,389 (37.9)	1.04	0.89–1.20
Unknown	74 (8.3)	705 (7.9)	1.07	0.82–1.39
Alcohol consumption				
Nondrinker	463 (51.6)	4,367 (48.9)	1	Reference
1–14U/wk	248 (27.7)	2,764 (30.9)	0.84	0.72–0.98
>14U/wk	64 (7.1)	686 (7.7)	0.87	0.67–1.13
Unknown	122 (13.6)	1,120 (12.5)	1.03	0.84–1.27
Substance abuse[a]				
No	817 (91.1)	8,341 (93.3)	1	Reference
Yes	80 (8.9)	596 (6.7)	1.39	1.09–1.75
Brain disorders[b]				
No	445 (49.6)	7,474 (83.6)	1	Reference
Yes	452 (50.4)	1,463 (16.4)	5.52	4.81–6.34
Psychiatric disorders[c]				
No	585 (65.2)	6,877 (77.0)	1	Reference
Yes	312 (34.8)	2,060 (23.1)	1.83	1.59–2.10
Dementia[d]				
No	723 (80.6)	8,519 (95.3)	1	Reference
Yes	174 (19.4)	418 (4.7)	5.31	4.42–6.37
Metabolic disturbances[e]				
No	817 (91.1)	8,544 (95.6)	1	Reference
Yes	80 (8.9)	393 (4.4)	2.16	1.70–2.75

[a]The group comprised alcoholism (82.6%) and drug abuse or mixed drug abuse/alcoholism (17.4%).
[b]The group comprised ischemic/hemorrhagic stroke/transient ischemic attack (79.6%), traumatic head injury (17.2%), and other brain disorders (including multiple sclerosis, brain tumors, and brain infections, 3.1%).
[c]The group comprised affective disorders (depression, bipolar, and manic disorders, 46.1%), anxiety disorders (21.9%), mixed affective and anxiety disorders (28.3%), and other psychiatric disorders (schizophrenic disorders, compulsive disorders, and suicide/suicidal ideation, 3.7%).
[d]The group comprised Alzheimer dementia (35.0%), vascular dementia (15.5%), and other forms of dementia (49.5%).
[e]The group comprised hyponatremia (30.4%), fever (26.4%), hypoglycemia (18.2%), hyperglycemia and diabetic ketoacidosis (15.9%), and hypocalcemia, uremia, hypernatremia, and disequilibrium syndrome (9.1%).
CI = confidence interval; OR = odds ratio; NA = not applicable.

TABLE 3. ORs for Current[a] and Past Use[b]/Nonuse of Comedication of Cases with Epileptic Seizures and Matched Controls prior to the Index Date

	Cases, n = 897, No. (%)	Controls, n = 8,937, No. (%)	Crude OR	95% CI
Anticonvulsants				
Past use/nonuse	726 (80.9)	8,716 (97.5)	1	Reference
Current use	171 (19.1)	221 (2.5)	9.21	7.62–11.13
Anti-infectives[c]				
Past use/nonuse	614 (68.5)	7,253 (81.2)	1	Reference
Current use	283 (31.6)	1,684 (18.8)	2.01	1.74–2.32
Antidepressants				
Past use/nonuse	687 (76.6)	7,862 (88.0)	1	Reference
Current use	210 (23.4)	1,075 (12.0)	2.25	1.92–2.63
Antipsychotics				
Past use/nonuse	806 (89.9)	8,656 (96.9)	1	Reference
Current use	91 (10.1)	281 (3.1)	3.51	2.81–4.39
Anticholinergics[d]				
Past use/nonuse	826 (92.1)	8,316 (93.1)	1	Reference
Current use	71 (7.9)	621 (7.0)	1.15	0.90–1.46
Antidiabetics[e]				
Past use/nonuse	839 (93.5)	8,421 (94.2)	1	Reference
Current use	58 (6.5)	516 (5.8)	1.13	0.87–1.48
Opioids				
Past use/nonuse	709 (79.0)	7,333 (82.1)	1	Reference
Current use	188 (21.0)	1,604 (18.0)	1.21	1.03–1.43
Antiarrhythmics				
Past use/nonuse	793 (88.4)	7,978 (89.3)	1	Reference
Current use	104 (11.6)	959 (10.7)	1.10	0.89–1.34
Hypnotics				
Past use/nonuse	797 (88.9)	8,433 (94.4)	1	Reference
Current use	100 (11.2)	504 (5.6)	2.13	1.72–2.64

[a]Defined as last prescription ≤90 days ago.
[b]Defined as last prescription >90 days ago.
[c]The group comprised antibiotics (76.3%), antivirals or antimalarials (1.3%), and mixed use (22.4%).
[d]The group comprised anticholinergics for urinary incontinence (35.1%), anticholinergic antiparkinsonian drugs (7.2%), anticholinergic bronchodilators (31.3%), anticholinergic antidiarrheals (9.5%), and other anticholinergics (17.0%).
[e]Only antidiabetics that may provoke hypoglycemia, ie, sulfonylureas, glinides, insulin.
CI = confidence interval; OR = odds ratio.

Results of the sensitivity analyses with stricter exposure or case definition were similar to the main analysis. However, neither sensitivity analysis found material differences in the risk of epileptic seizures among treated PD patients compared to untreated PD patients (Tables 6 and 7).

TABLE 4. ORs for Developing Epileptic Seizures in Patients with PD Compared to Patients without PD, Stratified by Treated versus Untreated PD

	Cases, n = 897, No. (%)	Controls, n = 8,937, No. (%)	Crude OR	95% CI	Adjusted OR[a]	95% CI
No PD	613 (68.3)	7,520 (84.1)	1	Reference	1	Reference
PD	284 (31.7)	1,417 (15.9)	2.47	2.14–2.86	1.68	1.43–1.98
Treatment prior to the index date						
No antiparkinsonian drugs	56 (6.2)	187 (2.1)	3.73	2.82–4.94	2.46	1.81–3.36
Antiparkinsonian drugs	228 (25.4)	1,230 (13.8)	2.29	1.96–2.68	1.56	1.31–1.86
Dopa [derivatives]/dopamine agonists	134 (14.9)	687 (7.7)	2.45	2.01–2.99	1.72	1.37–2.15
Other antiparkinsonian drugs[b]	9 (1.0)	46 (0.5)	2.40	1.26–4.60	1.72	0.91–3.26
Mixed use of antiparkinsonian drugs[c]	85 (9.5)	497 (5.6)	2.07	1.64–2.61	1.34	1.04–1.74

[a]Adjusted for brain disorders (yes/no), psychiatric disorders (yes/no), dementia (yes/no), anticonvulsants (current use/past use or nonuse).
[b]For example, anticholinergics, monoamine oxidase inhibitors.
[c]Any combination of the abovementioned antiparkinsonian drugs.
CI = confidence interval; OR = odds ratio; PD = Parkinson disease.

Discussion

This large population-based observational study using data from the U.K.-based primary care database CPRD suggests that PD patients have increased crude IRs of epileptic seizures compared with PD-free individuals of similar age and sex. Crude IRRs comparing PD patients with PD-free individuals were highest in the youngest age group and in female patients. After adjusting for potential confounding, we still observed a 1.7-fold increased risk of epileptic seizures in patients with PD compared with PD-free individuals. PD patients with no seizure-provoking comorbidity were at a 2.2-fold increased risk of epileptic seizures compared with PD-free individuals without any seizure-provoking comorbidity, whereas PD patients with comorbid brain disorders, dementia, or >1 seizure-provoking comorbidity were at substantially increased risks of epileptic seizures compared with PD-free individuals without any seizure-provoking comorbidity (adjusted ORs ranged from 10.1 to 13.2).

Our findings contrast with some available literature that found a lower prevalence of epileptic seizures in patients with parkinsonism[1,3] or PD[4,5] compared with the general population. However, they are consistent with a cross-sectional study based on data from the CPRD, which reported a prevalence ratio of PD of 3.19 (95% CI = 2.44–4.18) in patients with epilepsy aged ≥16 years compared with nonepileptic individuals.[10] Our estimated crude IR in PD-free individuals aged 40 years or older lies within the reported range of IRs of epileptic seizures among the general population without age restriction (IR = 71–130/100,000 PYs).[36,37] Our results further suggest that irrespective of whether patients have PD, crude IRs of epileptic seizures increase with age, which is consistent with current literature.[36,38] We observed decreasing risks of epileptic seizures with increasing age for PD patients compared with PD-free individuals, which could be explained by the finding that older people have at baseline a higher risk of epileptic seizures. This is in part because of the higher prevalence of seizure-provoking comorbidities such as stroke or brain tumors,[39,40] where the addition of PD as another risk factor has less effect on the incidence rate of epileptic seizures. In the general population, the prevalence of epileptic seizures was reported to be higher in men than in women.[38] Interestingly, in our PD population, women had a higher crude IR of epileptic seizures than men.

In the nested case–control analysis, consistent with current literature, we observed increased risks of epileptic seizures in patients with brain disorders, dementia, psychiatric disorders, substance abuse, and metabolic disturbances.[19–22] Furthermore, as supported by other reports,[23–26] current use of anti-infectives, antidepressants, antipsychotics, anticholinergics, opioids, or hypnotics was associated with a higher OR of epileptic seizures compared with past use or nonuse. However, the association could also be related to the underlying diseases for which the drugs were indicated (eg, infections

TABLE 5. ORs for Developing Epileptic Seizures in Patients with PD Compared to Patients without PD, Stratified by Comorbidities That Are Known Risk Factors for Epileptic Seizures

	Cases, n = 897, No. (%)	Controls, n = 8,937, No. (%)	Crude OR	95% CI	Adjusted OR[a]	95% CI
No PD						
No SP comorbidity	144 (16.1)	4,516 (50.5)	1	Reference	1	Reference
SP comorbidities						
Brain disorders	163 (18.2)	686 (7.7)	7.92	6.27–10.01	7.35	5.81–9.30
Psychiatric disorders	63 (7.0)	1,009 (11.3)	2.02	1.50–2.73	1.83	1.37–2.47
Dementia	31 (3.5)	135 (1.5)	7.91	5.43–11.52	7.79	5.16–11.77
Metabolic disturbances	7 (0.8)	164 (1.8)	1.46	0.68–3.14	1.23	0.57–2.64
Substance abuse	16 (1.8)	282 (3.2)	1.77	1.05–2.99	1.63	0.98–2.71
>1 SP comorbidity[b]	189 (21.1)	728 (8.2)	8.82	7.05–11.04	7.95	6.31–10.00
PD						
No SP comorbidity	52 (5.8)	627 (7.0)	2.55	1.86–3.50	2.24	1.62–3.08
SP comorbidities						
Brain disorders	53 (5.9)	130 (1.5)	13.39	9.58–18.71	12.36	8.74–17.48
Psychiatric disorders	33 (3.7)	307 (3.4)	3.19	2.18–4.66	2.31	1.52–3.49
Dementia	16 (1.8)	46 (0.5)	10.38	5.92–18.19	10.14	5.75–17.88
Metabolic disturbances	5 (0.6)	24 (0.3)	7.66	2.99–19.59	5.93	2.38–14.78
Substance abuse	X	35 (0.4)	NA	NA	NA	NA
>1 SP comorbidity[b]	121 (13.5)	248 (2.8)	15.95	12.43–20.47	13.24	10.15–17.25

X cell contains < 5 patients (owing to ethics regulations to preserve confidentiality, we are not allowed to display cells with a count of <5 patients).

[a]Adjusted for anticonvulsants (current use/past use or nonuse).

[b]Any combinations of the abovementioned comorbidities.

CI = confidence interval; NA = not applicable; OR = odds ratio; PD = Parkinson disease; SP = seizure-provoking.

and psychiatric disorders),[20–22] rather than representing true causal effects of these drugs. The observation that current use of anticonvulsants was associated with a 9-fold increased risk of epileptic seizures compared to nonuse or past use is likely attributable to records being made in reversed order, that is, patients had an epileptic seizure and subsequently received anticonvulsants, but the GP first recorded the prescription of anticonvulsants and only later the diagnosis of a first epileptic seizure after workup by a neurologist.

Individuals with PD were at an increased risk of epileptic seizures compared with PD-free individuals. This result suggests that even after adjusting for important confounders, PD patients remain at a higher risk of epileptic seizures than PD-free individuals. Surprisingly, the results of our main analysis suggest that PD patients without antiparkinsonian drugs prior to the index date have a slightly higher risk of epileptic seizures compared with PD patients receiving antiparkinsonian drugs. To assess the possibility that untreated PD patients were not true PD patients, we reviewed all profiles of these patients. Approximately 50% of these patients had a plausible PD diagnosis, determined based on additional Read codes (eg, "Tremor," "Complaining of stiffness") during follow-up or based on prescriptions of antiparkinsonian drugs after the index date. In the remaining 50% of untreated patients, the PD diagnosis could be explained by misclassification or by GPs not having entered treatment information, as the initiation of antiparkinsonian treatment in the U.K. can take place in secondary care. We also observed that untreated PD patients had on average a higher Charlson Comorbidity

TABLE 6. Sensitivity Analysis Restricted to PD Patients with More Strictly Defined PD[a]: ORs for Developing Epileptic Seizures in Patients with PD Compared to Patients without PD, Stratified by Treated versus Untreated PD

	Cases, n = 612, No. (%)	Controls, n = 6,099, No. (%)	Crude OR	95% CI	Adjusted OR[b]	95% CI
No PD	436 (71.2)	5,108 (83.8)	1	Reference	1	Reference
PD	176 (28.8)	991 (16.3)	2.09	1.75–2.49	1.60	1.31–1.95
Treatment prior to the index date						
No antiparkinsonian drugs[c]	9 (1.5)	53 (0.9)	1.98	1.03–3.82	1.81	0.92–3.58
Antiparkinsonian drugs	167 (27.3)	938 (15.4)	2.09	1.74–2.51	1.59	1.30–1.94
Dopa [derivatives]/dopamine agonists	95 (15.5)	499 (8.2)	2.25	1.79–2.82	1.73	1.35–2.22
Other antiparkinsonian drugs[d]	X	22 (0.4)	NA	NA	NA	NA
Mixed use of antiparkinsonian drugs[e]	70 (11.4)	417 (6.8)	1.96	1.52–2.53	1.44	1.09–1.91

X cell contains < 5 patients (owing to ethics regulations to preserve confidentiality, we are not allowed to display cells with a count of <5 patients).

[a]No prescriptions of drugs that may cause drug-induced parkinsonism within 180 days before the diagnosis of PD and ≥2 prescriptions of antiparkinsonian drugs any time after the diagnosis of PD.

[b]Adjusted for brain disorders (yes/no), psychiatric disorders (yes/no), dementia (yes/no), anticonvulsants (current use/past use or nonuse).

[c]These were PD patients who had no prescriptions for antiparkinsonian drugs prior to the index date but were prescribed antiparkinsonian drugs any time after the index date.

[d]For example, anticholinergics, monoamine oxidase inhibitors.

[e]Any combinations of the abovementioned antiparkinsonian drugs.

CI = confidence interval; NA = not applicable; OR = odds ratio; PD = Parkinson disease.

TABLE 7. Sensitivity Analysis Restricted to Patients with a More Strictly Defined Case Definition[a]: ORs for Developing Epilepsy in Patients with PD Compared to Patients without PD, Stratified by Treated versus Untreated PD

	Cases, n = 527, No. (%)	Controls, n = 5,268 (%)	Crude OR	95% CI	Adjusted OR[b]	95% CI
No PD	372 (70.6)	4,433 (84.2)	1	Reference	1	Reference
PD	155 (29.4)	835 (15.9)	2.22	1.83–2.70	1.68	1.36–2.08
Treatment prior to the index date						
No antiparkinsonian drugs	29 (5.5)	113 (2.2)	3.15	2.12–4.66	1.75	1.17–2.62
Antiparkinsonian drugs	126 (23.9)	722 (13.7)	2.08	1.69–2.57	1.67	1.32–2.10
Dopa [derivatives]/dopamine agonists	67 (12.7)	391 (7.4)	2.07	1.57–2.72	1.61	1.19–2.18
Other antiparkinsonian drugs[c]	8 (1.5)	29 (0.6)	3.24	1.61–6.49	2.78	1.26–6.16
Mixed use of antiparkinsonian drugs[d]	51 (9.7)	302 (5.7)	1.99	1.47–2.68	1.64	1.18–2.27

[a]≥2 prescriptions of anticonvulsants recorded within 1 month before until 6 months after a Read code of seizure, epilepsy, or status epilepticus.

[b]Adjusted for brain disorders (yes/no), psychiatric disorders (yes/no), dementia (yes/no).

[c]For example, anticholinergics, monoamine oxidase inhibitors.

[d]Any combinations of the abovementioned antiparkinsonian drugs.

CI = confidence interval; OR = odds ratio; PD = Parkinson disease.

Index,[41] that is, higher overall disease burden, than treated PD patients. A theoretical explanation for the higher risk of epileptic seizures among untreated patients could thus also have been higher overall disease burden in untreated PD patients compared with PD patients who had received antiparkinsonian treatment.[42] After defining exposure and outcome more strictly in the sensitivity analyses, untreated PD patients did not have a higher risk of epileptic seizures than treated PD patients, suggesting that the results of the main analysis were due to residual confounding and not due to a real association between antiparkinsonian treatment and epileptic seizures. However, data from animal models and case reports suggest an antiepileptic effect by activation of dopamine receptor type 2, which is mainly understimulated in PD, and a potential protective effect of antiparkinsonian drugs on epileptic seizures.[3,5,43–45] Furthermore, zonisamide, an antiepileptic drug with dopaminergic effect, was reported to have beneficial effect in motor dysfunction and fluctuation in PD.[46,47] On the contrary, antipsychotic drugs that reduce dopaminergic transmission have been associated with seizures.[26,48] Thus, further research on the potential association between dopamine and epileptic seizures is warranted.

PD patients with no seizure-provoking comorbidity had a 2-fold increased risk of epileptic seizures compared with PD-free individuals with no seizure-provoking comorbidity. Furthermore, patients with brain disorders, dementia, or >1 seizure-provoking comorbidity were at a substantially increased risk of epileptic seizures compared with patients with none of these comorbidities, irrespective of whether they had PD. Of interest, the risk of epileptic seizures in PD patients with comorbid brain disorders or with >1 seizure-provoking comorbidity was higher than the risk of epileptic seizures in PD-free individuals with these comorbidities. Our results therefore suggest that PD patients with comorbidities known to be risk factors for epileptic seizures are at an even higher risk of epileptic seizures than patients without PD with such comorbidities.

This study has some limitations. Although we aimed to minimize confounding by matching cases to controls on age, sex, calendar time, years of history in the CPRD prior to the index date, and duration of follow-up, and adjusting the nested case–control analyses for other important potential confounders known from the literature, there may still be residual confounding by unknown risk factors of epileptic seizures, such as patient frailty. In addition, some exposure or outcome misclassification may be present in this study. For example, as the onset of PD is insidious, PD is likely missed in early stages of the disease, which could have led to misclassification of some PD patients as PD-free individuals. However, the prevalence of PD is quite low and this would not have had a strong effect on our results. Moreover, patients with secondary parkinsonism could have been misdiagnosed as idiopathic PD patients. Additionally, a first epileptic seizure could have been missed if the patient did not recognize and report it to the GP, or the GP could have misinterpreted an epileptic seizure in a PD patient as a nonmotor symptom of PD.[49] However, the first scenario of misclassification would likely have been nondifferential, and the second scenario would have lessened an in reality even stronger association between PD and epileptic seizures. Furthermore, other medical conditions could have been misdiagnosed as epileptic seizures. However, the results of the sensitivity analyses in which we applied more rigorous criteria to the PD and epileptic seizure definitions, although limited in power, were not materially different from the main analysis.

To our knowledge, no other large study to date has investigated the risk of incident epileptic seizures in association with the risk of PD using "real life" observational data with long follow-up. The available studies on the risk of epileptic seizures in association with PD were either case reports,[1,3] did not have a primary objective to assess the association between PD and epileptic seizures,[10,12] or were observational studies based on a very limited number of patients.[4–6] Those observational studies claiming a lower prevalence of epileptic seizures associated with PD were based on cross-sectional data, did not have a matched PD-free comparison group, and did not adjust their results for potential confounding factors.[4,5] Our study is the first to report the absolute risk of epileptic seizures among patients with PD and among a matched comparison group of individuals without PD, with adjusted relative risk estimates of epileptic seizures among PD patients compared with PD-free individuals.

In conclusion, irrespective of whether seizure-inducing comorbidities were present, PD patients were at a higher risk of developing epileptic seizures than PD-free individuals in our study. Our study results are relevant for clinicians, indicating that PD is associated with an increased risk of epileptic seizures, and that the increased risk is particularly pronounced in PD patients with comorbid brain disorders, dementia, or >1 seizure-provoking comorbidity.

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Author Contributions

Conception and design of the study: K.G., M.B., C.B., S.S.J., C.R.M., S.R.; acquisition and analysis of data: all authors; drafting a significant portion of the manuscript: K.G., M.B., S.S.J., P.F., C.R.M., S.R. All authors approved the final version of the manuscript.

Potential Conflicts of Interest

Nothing to report.

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