Parkinson’s disease or Parkinson symptoms following seasonal influenza

Stephen Toovey, a Susan S. Jick, b Christoph R. Meier, b,c,d

a Division of Infection and Immunity, Royal Free and University College Medical School, Academic Centre for Travel Medicine and Vaccines, London, UK. b Boston Collaborative Drug Surveillance Program, Boston University Medical Center, Lexington, MA, USA. c Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland. d Hospital Pharmacy, University Hospital Basel, Basel, Switzerland

Correspondence: Professor Christoph R. Meier, PhD, MSc, Basel Pharmacoepidemiology Unit, Hospital Pharmacy, University Hospital Basel, Spitalstrasse 26, CH - 4031 Basel, Switzerland. E-mail: meierch@uhbs.ch

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Background Influenza may cause neurological sequelae and has been associated with encephalitis lethargica, an entity displaying Parkinson’s disease (PD) signs and symptoms that followed the 1918 influenza pandemic. We studied the association between diagnosed influenza and idiopathic PD or Parkinson symptoms (PS) not followed by a firm PD diagnosis.

Methods We used the UK-based General Practice Research Database to perform a case–control analysis. We identified cases who developed an incident diagnosis of PD or PS between 1994 and March 2007, and we matched four controls on age, gender, general practice, calendar time, and history in the database to each case. We calculated odds ratios (OR) with 95% confidence intervals (CI) using conditional logistic regression to assess the relative risk of developing PD or PS in association with previous influenza diagnoses.

Results We identified 3976 PD cases and 18 336 PS cases. The risk of developing PD was not associated with previous influenza infections. However, PS was associated with recent influenza (last infection 0–29 days: OR 3.03, 95% CI 1.94–4.74; 30–364 days: OR 1.36, 95% CI 1.14–1.63), number of influenza episodes (1 attack: OR 1.20, 95% CI 1.12–1.28; 2 attacks: OR 1.52, 95% CI 1.28–1.81; ≥3 attacks: OR 2.00, 95% CI 1.45–2.75), and severity of preceding influenza infections (≥1 severe attack: OR 1.45, 95% CI 1.25–1.68).

Conclusions Influenza is associated with PD-like symptoms such as tremor, particularly in the month after an infection, but not with an increased risk of developing idiopathic PD.

Keywords Case–control studies, influenza, Parkinson’s disease, parkinsonism.

Introduction Parkinson’s disease (PD) afflicts 1–2% of the population over the age of 50.1 Although some familial forms are known, the etiology remains largely unknown. The total annual costs for society related to PD are substantial.2 That influenza may be associated with neurological complications has been known for some time, with influenza-associated encephalopathy (IAE) being one well-recognized complication of acute influenza.3,4 It has also been speculated that the wave of encephalitis lethargica (“von Economo’s disease”) that swept the world in the wake of the 1918 “Spanish flu” pandemic was in some way caused by infection with the pandemic influenza strain.

More recently, acute neuropsychiatric symptoms during an influenza infection were related to treatment with antiviral drugs, but investigators concluded that these neuropsychiatric symptoms were more likely associated with the influenza infection itself, rather than being related to antiviral treatment, because they occurred also in the absence of antiviral drug exposure.5 A study of American health claims databases revealed that treatment of influenza with the antiviral drug oseltamivir was associated with a reduction in the number of neuropsychiatric reactions.6 In addition, a review of the literature suggested that immune responses provoked by influenza might be responsible for neurological injury.7

We examined the hypothesis that influenza infection might be associated with the development of idiopathic PD or Parkinson symptoms (PS), using a large database from the UK. Parkinson symptoms refer to conditions mimicking PD, such as tremor, ataxia, and bradykinesia, but which did not lead to a firm diagnosis of PD in our study population.
Methods

Data source
We used the General Practice Research Database (GPRD), which contains computerized longitudinal medical records of some five million patients. In the UK, GPs are responsible for primary health care, referrals to specialists, and hospitalizations. They record patient demographics, diagnoses, drug prescriptions, as well as some lifestyle information (e.g., smoking status) and personal characteristics (e.g., body mass index, BMI). Information on drug exposure and diagnoses in the GPRD has been validated repeatedly and proven to be of high quality. The GPRD is managed by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK. The patients enrolled in the GPRD are representative of the UK population with regard to age, gender, geographic distribution, and annual turnover rate. GPRD data have been used in previous studies on PD and influenza. The study protocol was reviewed and approved by the Independent Scientific Advisory Committee for MHRA database research (ISAC). The investigators had access only to anonymized information.

Study population
We identified within the GPRD two groups of case patients, (i) patients with an incident diagnosis of “idiopathic PD” and (ii) patients with an incident diagnosis of “PD-like symptoms” between January 1, 1994, and March 31, 2007. The date of the first diagnosis of PD or PS will subsequently be referred to as “index date”. Cases with PD or PS had to have been registered on computer for at least 3 years to be eligible for this study.

We defined “idiopathic PD” as follows: the patient with PD must not have had ≥1 prescription for an antiparkinson medication recorded prior to the diagnosis date, which was characterized by the first recording of an OXMIS-OMIS (Oxford Medical Information System) code 342 (“Paralysis agitans”) or 342 D (“idiopathic parkinsonism”) or Read codes F12.00 (“Parkinson’s disease”), F12z.00 (“Parkinson’s disease NOS”) or F12.00 (“Paralysis agitans”), must not have received prescriptions for drugs known to induce parkinsonism (such as “typical” antipsychotic drugs, metoclopramide, or cinnarizine) within 180 days before the recorded PD diagnosis, and must have received ≥2 prescriptions for drugs to treat PD after the diagnosis date in order to be included in the analysis. The validity of PD diagnoses in the GPRD has been documented in previous studies, and we again used a similar algorithm to identify patients with a recorded PD diagnosis.

Patients in the group with symptoms suggestive of PD (the PS group) had an incident diagnosis of tremor, ataxia, or dyskinesia, but these patients never had a formal diagnosis of PD recorded. In addition, they also must not have received any prescriptions for drugs known to induce parkinsonism within 180 days prior to the recorded diagnosis of the Parkinson symptom.

In addition to these two mutually exclusive case groups, we identified at random four controls to each case with PD or PS who also had to be recorded in the database for at least 3 years prior to the index date. We matched these controls to cases on age (same year of birth), gender, general practice attended, diagnosis date, and years of history in the GPRD prior to the index date. All cases and controls in the study population had to have at least three years of medical history in the computer record prior to the index date.

Statistical analysis
From the computer records, we assessed the number of influenza infections and the timing of the last influenza infection prior to the index date for all cases and controls. If a patient had more than one influenza diagnosis recorded, we considered them to be two separate infections if they were recorded more than 30 days apart. We further assessed whether any previous influenza infections were accompanied by diagnosed clinical complications such as sepsis, meningitis, encephalitis, pneumonia, or other respiratory tract infections within 30 days after the influenza diagnosis; we referred to such episodes as “influenza with complications”. We further assessed for all cases and controls the smoking status (non, current, ex-, unknown), body mass index (BMI) (<25, 25–29.9, 30+ kg/m² or unknown), and the history of various comorbidities at or prior to the index date in order to explore whether these parameters confounded the association between influenza infections and the risk of developing PD or PS.

We conducted conditional logistic regression analyses to explore the relative risk of an outcome of interest in association with previously recorded influenza infections, expressed as odds ratios (ORs) with 95% CI. P values are 2-sided and were considered statistically significant if less than .05. All statistical analyses were performed with SAS software, version 9.1 (SAS Institute, Cary, NC, USA).

Results
We identified 3976 cases with an incident diagnosis of idiopathic PD and 18 336 cases with one or more symptoms suggestive of PD, i.e., the PS group, who never received a firm PD diagnosis. The analysis further encompassed 89 211 matched controls, i.e., patients who neither had a PD diagnosis nor PD symptoms recorded at any time during the study period. The age and sex distribution as well as the distribution of smoking status and BMI of PD and PS cases and their controls is summarized in Table 1. PD cases tended to be older at the index date than PS cases.
(67% vs. 39.7% aged 70 years or older, respectively). In the PD case group, men (58.5%) were over-represented, while there were more women (58.0%) among PS cases. As reported previously, current and ex-smokers were also under-represented in PD cases as compared to their controls, while the opposite was seen in PS cases (Table 1).

| Table 1. Characteristics of cases with Parkinson or Parkinson-like symptoms and their matched controls |
|-----------------------------------------------|
| **Idiopathic Parkinson’s disease** | **Parkinson’s disease-like symptoms** |
| Cases | Controls | OR (95% CI) | Cases | Controls | OR (95% CI) |
| (n = 3976) | (n = 15 891) | | (n = 18 336) | (n = 73 320) | |
| **Age <50** | 76 (1.9) | 305 (1.9) | – | 4945 (27.0) | 19 787 (27.0) | – |
| **50–69** | 1236 (31.1) | 4944 (31.1) | – | 6115 (33.3) | 24 462 (33.3) | – |
| **70+** | 2664 (67.0) | 10 642 (67.0) | – | 7276 (39.7) | 29 071 (39.7) | – |
| **Men** | 2327 (58.5) | 9299 (58.5) | – | 7693 (42.0) | 30 766 (42.0) | – |
| **Women** | 1649 (41.5) | 6592 (41.5) | – | 10 643 (58.0) | 42 554 (58.0) | – |
| **BMI <25 kg/m²** | 2402 (60.4) | 8076 (50.8) | 1.0 | 9174 (50.0) | 37 997 (51.8) | 1.0 |
| **Current smoker** | 342 (8.6) | 2261 (14.2) | 0.50 (0.44–0.56) | 3886 (21.2) | 12 886 (17.6) | 1.26 (1.21–1.32) |
| **Ex-smoker** | 690 (17.4) | 3192 (20.1) | 0.71 (0.64–0.78) | 3258 (17.8) | 12 418 (16.9) | 1.10 (1.05–1.16) |
| **Unknown** | 542 (13.6) | 2362 (14.9) | 0.75 (0.67–0.84) | 2018 (11.0) | 10 019 (13.7) | 0.77 (0.72–0.81) |
| **BMI <25 kg/m²** | 1189 (29.9) | 4339 (27.3) | 1.0 | 6167 (33.6) | 22 837 (31.2) | 1.0 |
| **25–29.9** | 1322 (33.2) | 5241 (33.0) | 0.92 (0.84–1.01) | 5577 (30.4) | 22 039 (30.0) | 0.94 (0.90–0.98) |
| **30–59.9** | 516 (13.0) | 2290 (14.4) | 0.82 (0.73–0.92) | 2969 (16.2) | 11 720 (16.0) | 0.94 (0.89–0.99) |
| **Unknown** | 949 (23.9) | 4021 (25.3) | 0.85 (0.76–0.94) | 3623 (19.8) | 16 724 (22.8) | 0.77 (0.73–0.81) |

| Table 2. Parkinson or Parkinson-like symptoms and their association with previous influenza infections |
|-----------------------------------------------|
| **Idiopathic Parkinson’s disease** | **Parkinson’s disease-like symptoms** |
| Cases | Controls | OR (95% CI)* | Cases | Controls | OR (95% CI)* |
| (n = 3976) | (n = 15 891) | | (n = 18 336) | (n = 73 320) | |
| **Number of influenza attacks** | | | | | |
| 0 | 3753 (94.4) | 15 044 (94.6) | 1.0 | 16 794 (91.6) | 68 251 (93.1) | 1.0 |
| 1 | 196 (4.9) | 724 (4.6) | 1.08 (0.91–1.27) | 1298 (7.1) | 4426 (6.0) | 1.20 (1.12–1.28) |
| 2 | 23 (0.6) | 90 (0.6) | 1.03 (0.64–1.65) | 181 (1.0) | 498 (0.7) | 1.52 (1.28–1.81) |
| 3+ | 4 (0.1) | 33 (2.2) | 0.44 (0.14–1.32) | 83 (0.3) | 145 (0.2) | 2.00 (1.45–2.75) |
| **Timing of last influenza attack** | | | | | |
| 0 | 3753 (94.4) | 15 044 (94.7) | 1.0 | 16 794 (91.6) | 68 251 (93.1) | 1.0 |
| 1–29 | 5 (0.13) | 5 (0.03) | 4.33 (1.24–15.1) | 34 (0.2) | 46 (0.1) | 3.03 (1.94–4.74) |
| 30–364 | 16 (0.4) | 95 (0.6) | 0.64 (0.37–1.11) | 169 (0.9) | 509 (0.7) | 1.36 (1.14–1.63) |
| 365–729 | 22 (0.6) | 103 (0.6) | 0.84 (0.52–1.34) | 170 (0.9) | 537 (0.7) | 1.29 (1.08–1.54) |
| 730+ days | 180 (4.5) | 644 (4.1) | 1.13 (0.94–1.34) | 1169 (6.4) | 3977 (5.4) | 1.20 (1.12–1.29) |
| **Severe influenza followed by clinical complications** | | | | | |
| 0 | 3753 (94.4) | 15 044 (94.7) | 1.0 | 16 794 (91.6) | 68 251 (93.1) | 1.0 |
| 1+ | 28 (0.7) | 126 (8.0) | 0.91 (0.60–1.38) | 255 (1.4) | 715 (1.0) | 1.45 (1.25–1.68) |
| **Last severe influenza attack** | | | | | |
| 0 | 3753 (94.4) | 15 044 (94.7) | 1.0 | 16 794 (91.6) | 68 251 (93.1) | 1.0 |
| 1–29 | 1 (0.03) | 1 (0.01) | 4.43 (0.27–73) | 8 (0.04) | 6 (0.01) | 5.30 (1.83–15.3) |
| 30–364 | 2 (0.05) | 19 (0.1) | 0.42 (0.10–1.82) | 29 (0.16) | 68 (0.1) | 1.76 (1.14–2.73) |
| 365–729 | 0 (0) | 13 (0.1) | – | 34 (0.2) | 93 (0.1) | 1.47 (0.99–2.18) |
| 730+ days | 25 (0.6) | 93 (0.6) | 1.09 (0.70–1.70) | 184 (1.0) | 548 (0.8) | 1.36 (1.15–1.61) |

*Adjusted for smoking status (non, current, ex, unknown) and BMI (<25, 25–29.9, 30+ kg/m², unknown).
†Prior to the index date.
The relative risk estimates (ORs) of developing idiopathic PD or PS associated with the number of previously recorded influenza diagnoses are summarized in Table 2. While there was no evidence for an increase in the risk of developing PD in relation to an increasing number of influenza attacks prior to the index date, the risk of developing PS was statistically significantly increased (OR 2.00, 95% CI 1.45–2.75) for patients with three or more recorded influenza infections prior to the index date, as compared to those with no recorded infection (Table 2).

With respect to the timing of the last recorded influenza infection prior to the index date, the OR for developing a PD diagnosis shortly (1–29 days) after an influenza diagnosis was 4.33 (95% CI, 95% CI 1.24–15.1, P = 0.02) compared to having no infection. This OR, however, was based on only five exposed cases and five controls. There was no suggestion of an increased risk of those with a larger time lag between the last influenza infection and the index date. For patients with PS, the OR was also highest for those with a recent influenza infection (1–29 days ago; OR 3.03, 95% CI 1.94–4.74, P < 0.0001); the risk decreased gradually to 1.20 (95% CI 1.12–1.29, P < 0.0001) for those with a last influenza infection recorded more than 2 years ago (Table 2).

We further identified all patients with one or more influenza infections with complications. In this analysis, the risk of developing idiopathic PD was unaltered in relation to previous influenza episodes with complications, as compared to those without any influenza infection. On the other hand, the OR of developing PS was 1.45 (95% CI 1.25–1.68, P < 0.0001) for patients with one or more previous influenza infections with complications, as compared to those with no recorded infection, and it was particularly high for patients who had such an infection within 30 days prior to the diagnosis of a PS (OR 5.30, 95% CI 1.83–15.3, P < 0.01) (Table 2).

All ORs were adjusted for smoking status and BMI. We further adjusted the analysis for a number of recorded comorbidities such as a history of hypertension, hypotension, stroke or transient ischemic attack, hyperlipidemia, asthma or COPD, diabetes mellitus, depression, psychosis, and urinary dysfunction. While some of these parameters were associated with an increased risk of developing idiopathic PD or PS, the ORs for the main association of interest (i.e. influenza and PD/PS) remained virtually unaltered and we did not include these parameters in the final model.

**Discussion**

The findings of this large observational study support the hypothesis that influenza is a contributory factor in the development of PS, while there was no material evidence of an increased PD risk associated with previous influenza infections. The PS case group differed considerably from the PD group with respect to several characteristics such as age, gender, or smoking status, suggesting that the PS group comprised a heterogeneous group of transient neurological symptoms largely unrelated to idiopathic PD.

With regard to PS, the likelihood of acquiring the diagnosis increased with the number of influenza attacks suffered and the risk appears to decay with increasing time from the last influenza attack suffered. These findings support a relationship between influenza and PS but do not indicate whether this influenza-associated effect is a direct or indirect result of infection with the virus. The intervals over which this association was seen, however, suggest an indirect effect, i.e., not an acute effect from direct viral invasion of the central nervous system (CNS), although influenza does seem in some way responsible for neurological injury. The increasing risk of developing PS with increasing number of influenza attacks suggests that influenza-associated neuronal injury may be a cumulative process, as do the associations with severe influenza.

The only relative risk estimate, which was increased for idiopathic PD, was seen in the analysis in which we assessed the timing of the last infection; the OR of developing a PD diagnosis shortly (1–29 days) after an influenza diagnosis was 4.33 (95% CI, 95% CI 1.24–15.1), which was based on only five exposed cases and five exposed controls. Whether the association is simply a chance finding, given the small numbers in the relevant cells, or whether the association represents a rare event, is not known. It is possible that influenza-induced inflammation could be the final insult precipitating frank PD, or it could be that it is acute influenza which brings individuals with previously undiagnosed, and unrelated, PD to medical attention. Given the long lag time from degeneration of first dopaminergic neurons in the substantia nigra until development of first PD symptoms, a causal association for this finding seems to be unlikely. Previous work by Postuma et al. did not find an association between season of birth and development of PD in later life, also arguing against influenza exposure in very early life being associated with PD.

There is evidence that could support and explain the association between influenza and neurological conditions with a parkinsonian component (PS group). There are sporadic reports of post-encephalitic parkinsonism with one of the best known examples being the emergence of encephalitis lethargica (“von Economo’s disease”) following the 1918 “Spanish flu” pandemic. It has been argued for many years that the encephalitis lethargica pandemic was a complication of influenza, although this has been questioned; similar speculation links an earlier pandemic of an encephalitis lethargica–like illness (“noma”) to the 1889 influenza pandemic. It has been observed that encephalitis lethargica victims often developed post-encephalitic parkinsonism. Lo et al. failed to find influenza genetic material in tissue...
specimens from the autopsied brains of encephalitis lethargica patients dating from the “Spanish influenza” pandemic. This negative finding was hypothesized by Lo et al. to be attributable to a possible “hit-and-run” effect of the influenza virus, a possible absence of an etiological role for the virus, or influenza exerting an effect in conjunction with other agents such as herpesviruses 6 or 7.25

There is evidence to support a “hit-and-run” scenario for influenza. A considerable amount of work, principally in Japan, points to immunological mechanisms playing a role in the genesis of IAE, with IAE victims displaying elevations of plasma or cerebrospinal fluid (CSF) levels of a number of pro-inflammatory mediators, including interleukin-6 (IL-6) and soluble tumor necrosis factor receptor-1 (s-TNFR-1).26 The picture that emerges is that individuals with susceptible genetic makeup, most likely abnormalities of long-chain fatty acid metabolism,27 suffer immunologically mediated mitochondrial injury during influenza-induced hypercytokinemia and pyrexia, with collapse of the mitochondrial membrane potential, development of neuronal oxidative stress,28 opening of the mitochondrial transition pore, and consequent neuronal apoptosis. The outcome in IAE is associated with elevated CSF and serum levels of cytokine, a marker of mitochondrial injury.26 At the clinical level, Maricich et al., imaging with magnetic resonance spectroscopy, demonstrated an accumulation of lactate in the basal ganglia of a child during the acute phase of IAE, supporting the idea that oxidative stress secondary to mitochondrial injury occurs during acute IAE.29 Influenza-induced inflammation mediating neuronal damage may offer a plausible mechanism for the associations between influenza and neurological disorder found in this study.

Direct viral invasion of CNS, including the substantia nigra pars compacta, has been demonstrated in mice experimentally infected with avian influenza A H5N1 virus. Infected mice displayed neurological signs, with necropsy evidence of apoptotic neuronal loss and prolonged post-infection microgliosis.30 The authors of this study concluded that a “hit-and-run” mechanism may underlie viral-associated parkinsonism.

We used one of the largest and best validated databases in the world, the GPRD, to explore the association between influenza infections and the risk of developing idiopathic PD or PS. Even though there is no alternative to an observational study design for this study question, some limitations of our study need to be discussed.

First, influenza diagnosed by the GP is most often a clinical diagnosis and not supported by viral tests. Thus, we cannot rule out the possibility that some recorded influenza diagnoses were not caused by an influenza virus, but possibly by another infectious agent causing influenza-like illness.

Secondly, influenza is a disease that may be treated at home without GP involvement. Thus, it is likely that we missed influenza infections in the GPRD that never came to the attention of the GP. However, in a previous GPRD study on influenza, we documented that the rate of recorded influenza infections over a 6-year period was similar to the one derived from a UK sentinel system, which was considered to be the gold standard for assessing influenza rates in the UK at that time.3 Thus, the GPRD is well suited for observational studies on influenza, despite the limitation that some cases are not captured in this observational study.

Thirdly, it is also possible that some patients with the outcome of interest (PD or PS) were missed. While it is rather unlikely that we missed a substantial proportion of true cases of idiopathic PD, it is possible that we may not have captured all cases with PS, particularly if symptoms were mild or transient. Under the assumption that missing a certain proportion of cases occurred at random and independently of previous influenza infections, the relative risk estimates would have been driven toward the null; however, we cannot rule out the possibility that the elevated risk estimates of developing PS associated with a recent influenza infection may be slightly distorted by increased medical attention associated with a recent episode of clinical influenza. When we ran an analysis in which we additionally adjusted for the number of GP visits in the year preceding the index date (as a marker for medical attention), the relative risk estimates of interest remained statistically significantly increased.

In summary, the current large observational study provides evidence that influenza infections are associated with transient neurological sequelae such as tremor or gait disturbances. The relative risk of developing neurological PS was highest within the first few weeks after a diagnosed and recorded influenza infection. However, there was no evidence for an altered risk of developing a firm idiopathic PD diagnosis in association with the number or the severity of previous influenza infections.

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