ORIGINAL ARTICLE

# *Clostridium difficile* infection and risk of Parkinson's disease: a Swedish population-based cohort study

X. Kang[a], A. Ploner[a], J. F. Ludvigsson[a,b], D. M. Williams[a,c], H. Larsson[a,d], N. L. Pedersen[a] and K. Wirdefeldt[a,e]

[a]*Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm;* [b]*Department of Pediatrics, Örebro University Hospital, Örebro, Sweden;* [c]*MRC Unit for Lifelong Health and Ageing at UCL, University College London, London, UK;* [d]*School of Medical Sciences, Örebro University, Örebro; and* [e]*Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden*

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**Background and purpose:** Gastrointestinal inflammation has been implicated in Parkinson's disease (PD). The aim of this study was to examine whether individuals with a history of *Clostridium difficile* infection (CDI) are at elevated risk of PD.

**Methods:** We performed a population-based cohort study using Swedish national register data. Adults aged ≥35 years were identified from the Swedish Population and Housing Census 1990 and followed during the period 1997–2013. Diagnoses of CDI and PD were extracted from the National Patient Register. Associations of CDI history with PD risk were estimated using Cox proportional hazards regression. We also explored whether the association differed by the source of CDI diagnosis (inpatient vs. outpatient), presence of recurrent infections, and pre-infection use of antibiotics.

**Results:** Amongst the study population ($N$ = 4 670 423), 34 868 (0.75%) had a history of CDI. A total of 165 and 47 035 incident PD cases were identified from individuals with and without CDI history, respectively. Across the entire follow-up, a 16% elevation of PD risk was observed among the CDI group [hazard ratio 1.16, 95% confidence interval (CI)1.00–1.36], which was mainly driven by increased PD risk within the first 2 years after CDI diagnosis (hazard ratio 1.38, 95% CI 1.12–1.69). In longer follow-up, CDI was not associated with subsequent PD occurrence. This temporal pattern of CDI–PD associations was generally observed across all CDI subgroups.

**Conclusions:** *Clostridium difficile* may be associated with an increased short-term PD risk, but this might be explained by reverse causation and/or surveillance bias. Our results do not imply that CDI history affects long-term PD risk.

## Introduction

Parkinson's disease (PD) is an age-related neurodegenerative disorder, characterized by the cardinal motor signs tremor, rigidity and bradykinesia [1]. The etiology underlying PD remains unclear, but pathological hallmarks are the degeneration of dopaminergic neurons in the substantia nigra and abnormal aggregation of α-synuclein into Lewy bodies [2]. Apart from the motor symptoms, a broad spectrum of non-motor symptoms is now recognized [3,4], which can precede the onset of motor symptoms by many years [5]. In 2003, Braak *et al.* [6-8] hypothesized that PD pathology may originate partly in the gut and then spread to the brain via the vagus nerve. Evidence showing that α-synuclein is detectable in the gastrointestinal (GI) tract [9,10] and can be transmitted from cell to cell in a prion-like manner [11,12] supports this

Correspondence: X. Kang, Department of Medical Epidemiology and Biostatistics, Box 281, Karolinska Institutet, SE-171 77, Stockholm, Sweden (tel.: +46-8-524 85000; fax: +46-8-31 49 75: e-mail: xiaoying.kang@ki.se)





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hypothesis. Epidemiological studies have also suggested that vagotomy might reduce later PD risk [13,14].

Systemic inflammation, specifically inflammation in the GI tract, may be involved in the development of PD through various mechanisms [15,16]. Epidemiological studies have reported elevated PD risk among patients with inflammatory bowel disease (IBD), although part of that increase may be attributable to surveillance bias [17,18]. Genetic and pharmacoepidemiological evidence has also linked the gut–brain and neuro-immune axes in PD [19,20]. Furthermore, due to emerging observations of gut dysbiosis and dysregulated enteric neuronal function in PD, considerable attention has been given to the role of gut microbiota in PD [21-24].

Gastrointestinal infection is a common cause of gut inflammation and is frequently coupled with an altered gut microbiome. *Clostridium difficile*, an anaerobic bacillus that can colonize the colon when the normal gut microbiota is compromised, is the leading cause of nosocomial infectious diarrhea [25]. By releasing two inflammatory toxins, TcdA and TcdB, *C. difficile* can trigger a profound host immune response [26]. Susceptibility to *C. difficile* infection (CDI) increases substantially with age [27]. Other risk factors for CDI include exposure to antibiotics (a well-established modulator of the intestinal microbiota) [28,29], IBD and celiac disease [30,31]. Although a connection between GI infections and PD has been suggested [32,33], the specific relationship between CDI and PD risk has not been explored.

We therefore examined the association between CDI history and future PD risk by analysing Swedish national register data in a population-based cohort design. As secondary objectives, we also assessed whether the association differed by source of infection diagnosis (inpatient or outpatient), presence of recurrent infections and pre-infection use of antibiotics.

## Methods

### Data sources and study design

We conducted a population-based cohort study with data from several Swedish national registers [34-37]. The Swedish Population and Housing Census was a nationwide survey performed by Statistics Sweden every 5 years between 1960–1990 and was mandatory for all Swedish residents aged 16 or older [38]. Information on CDI and PD diagnoses was extracted from the Swedish National Patient Register (NPR), which was established in 1964, gradually expanded and achieved effectively 100% coverage for nationwide inpatient care in 1987. Since 2001, outpatient hospital visits have also been registered in the NPR (primary care data are not included). Diagnoses in the NPR are coded according to the International Classification of Diseases (ICD). Demographic data were obtained from the Total Population Register, which contains nationwide data on life events such as birth and migration since 1968 and from the Cause of Death Register, which contains information about dates and causes of death in Sweden since 1961. Information on antibiotics use was retrieved from the Prescribed Drug Register (PDR), which has registered drug prescriptions in Sweden since July 2005. However, it is worth noting that hospital-administered medications are not covered by the PDR. Data from different registers were linked at individual level via the unique personal identity number assigned to all Swedish residents [39].

We constructed our study cohort using individuals in the 1990 census as the study base (Fig. 1). Study entry was defined as 1 January 1997, when CDI diagnoses (exposure) were first registered in the NPR. Individuals with PD who had died or emigrated out of Sweden prior to the study entry were excluded. To focus our study on idiopathic PD rather than young-onset PD that is commonly of genetic origin, we also excluded those younger than 35 years at study entry [40]. To investigate the impact of pre-CDI antibiotic use (restricted to those prescribed within 180 days prior to the CDI diagnosis) on any association, we also created a subset cohort by applying the same exclusion criteria to a re-defined study entry on 1 January 2006, approximately 180 days following the initiation of the PDR. Individuals in both cohorts were followed up from the study entry to the diagnosis of incident PD, death, emigration or 31 December 2013, whichever occurred first.

### Ascertainment of CDI

*Clostridium difficile* was identified by the Swedish version ICD code A04.7 (ICD-10). All individuals with at least one registered CDI diagnosis were considered as having CDI history. The date of the first CDI diagnosis was used as the index date of CDI. The ICD-10 code-based identification of CDI was reported to have low sensitivity (35.6%) but high specificity (99.9%), compared to laboratory test-based diagnosis [41].

In stratified analyses, CDI was further categorized: (i) by source of diagnosis (as a proxy for the source of infection acquisition) into inpatient (hospital-acquired) or outpatient (community-acquired); (ii) by presence of recurrent infection into recurrent or non-recurrent; and (iii) in the subcohort with antibiotics data, by pre-infection use of antibiotics into antibiotics (−) or antibiotics

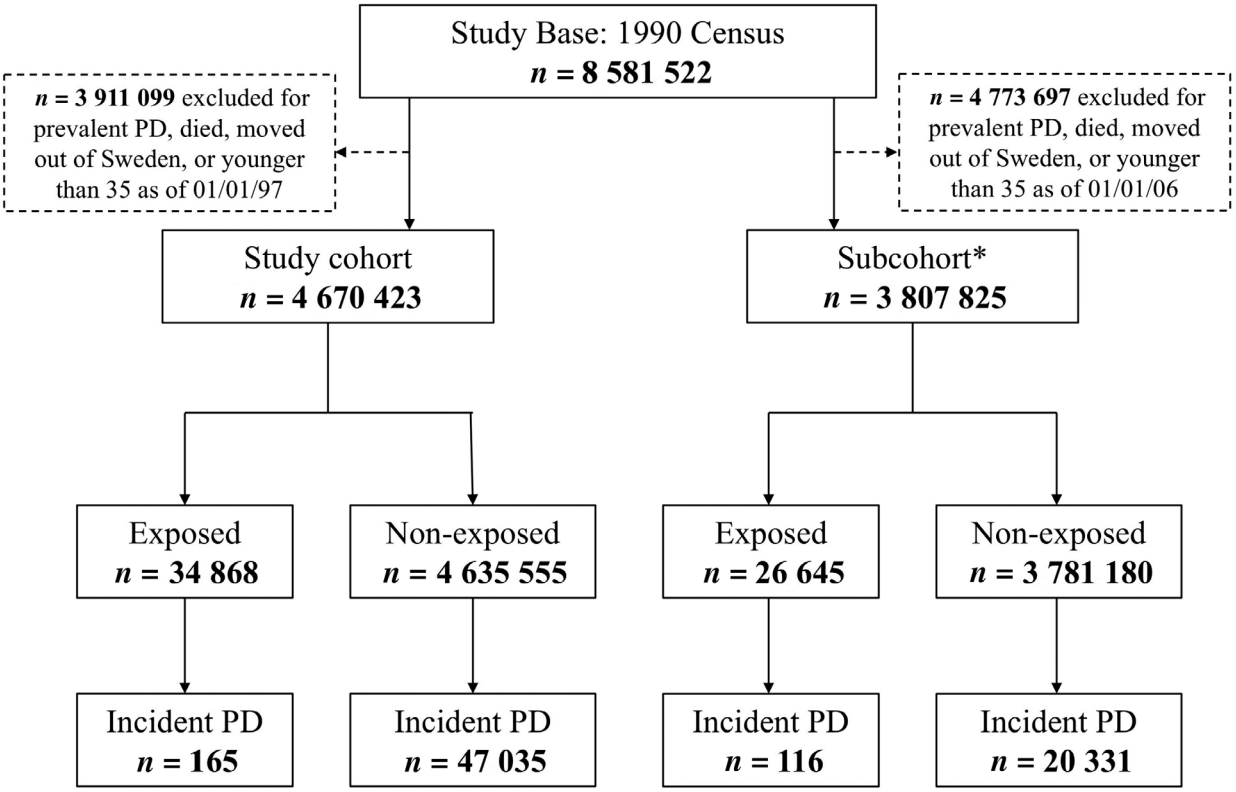


**Figure 1** Flowchart of the study. Exposure refers to a history of register diagnosis of *Clostridium difficile* infection. Subcohort* denotes the cohort constructed using 1 January 2006 as the study entry for the analysis of pre-infection use of antibiotics. PD, Parkinson's disease.

(+). The source of the first CDI diagnostic record was used for individuals with multiple registered diagnoses. A minimum of 60 days between two adjacent CDI diagnoses were required for the latter infection to be counted as recurrent. Antibiotics were identified from the PDR using the Anatomical Therapeutic Chemical classification system code J01. Only those dispensed within 180 days prior to a CDI diagnosis were regarded as pre-infection use. The date of the first recurrent infection was defined as the index date of recurrent CDI; whereas for other CDI subgroups, the date of the very first CDI diagnosis was used.

#### Ascertainment of PD

To identify PD, we used the Swedish version ICD codes 350 (ICD-7), 342 (ICD-8), 332.0 (ICD-9), and G20 (ICD-10). Individuals with at least one registered PD diagnosis, considering both inpatient and outpatient records and both primary and secondary diagnoses, were defined as PD cases. The index date of PD was defined as the date of the first PD diagnosis. When PD was diagnosed on the index date of CDI, the case was deemed to be incident PD without CDI history. We have previously tested the validity of register-based PD diagnoses against clinical diagnoses, showing a positive predictive value of 70.8% [42].

#### Covariates

Three demographic variables were adjusted for as time-constant covariates: birth country (categorized as born in Sweden or not); education attainment (compulsory, secondary, and post-secondary or postgraduate); and sex. In addition, we adjusted for four comorbidities as time-varying covariates. Chronic obstructive pulmonary disease (COPD) was adjusted for as a proxy for smoking, a factor that is associated with both CDI [43] and PD [44]. Diabetes and cancer were adjusted for because hospitalization, a leading risk factor for CDI, is more common among patients with either of these two conditions; meanwhile, diabetes has also been suggested as a risk factor for PD [45]. IBD was included as it has been reported to increase both CDI [30] and PD [18] risks. For all of the four selected comorbidities, both prevalent conditions at study entry and those developed during the follow-up were included. The date of the first diagnosis of each condition was used as the index date of the corresponding disease. ICD codes used to identify the

four conditions are listed in the Supporting Information (Table S1).

### Statistical analysis

The associations between CDI and PD risk were estimated as hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazards models, with attained age as the underlying timescale, adjusting for covariates. We started the modeling by assuming proportional hazards throughout the entire follow-up period. Schoenfeld residual test was performed to check whether the assumption was satisfied. Covariates that violated the assumption were then stratified in the model to allow for stratum-specific baseline hazards. Stratified Cox models with and without CDI-by-sex interaction were also compared to detect any heterogeneity of CDI effect between men and women. Model selection was determined by the Wald test result of the interaction term as well as the likelihood ratio test for the nested models.

Next, we explored the time-varying effect of CDI on two scales: dependence on age at CDI diagnosis and time since CDI diagnosis. The age-dependent CDI effect was examined by fitting an interaction term between CDI and age at CDI diagnosis into the stratified Cox model. To explore the dependence of the CDI effect on time since CDI diagnosis, we split the follow-up time since CDI diagnosis into three time bands (0–2 years, 2–5 years and >5 years) and fit an interaction term between CDI and the generated time-band variable in the stratified Cox model. For each time band, we estimated the HRs and 95% CIs. The joint effect of the two timescales was then tested in one stratified model incorporating both interaction terms. We used the Wald test and likelihood ratio test for model selection.

Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

The study was approved by the Regional Ethics Review Board, Stockholm, Sweden. All research was performed in accordance with relevant guidelines and regulations. As the study was based solely on data from national registers (in which registration is mandatory for all Swedish residents), informed consent was not required.

## Results

### Characteristics of the study population

In total, 4 670 423 Swedish residents were included in the study cohort, of whom 34 868 (0.75%) had a history of CDI (Fig. 1, Table 1). Compared to those without CDI history, the proportions of Swedish-born individuals and women were slightly higher among those with CDI, who were, on average, 9 years older (mean ± SD age at entry 66.7 ± 12.3 vs. 57.8 ± 14.8 years) and experienced more comorbidities and higher mortality as well. Missingness of education was common in both groups, but more frequent among those with CDI history. In addition, the proportion of those who completed secondary or higher education was lower among individuals with CDI. In the subcohort with antibiotics data, the proportion of individuals with CDI and the distributions of demographic variables were comparable to the full cohort (Table S2).

The vast majority of individuals with CDI were diagnosed in hospital (93.3%) and had only one CDI diagnosis record (92.6%) (Table S2). Individuals with outpatient CDI were on average ~8 years younger than those with inpatient CDI at their first CDI diagnosis. Among individuals with CDI in the antibiotics subcohort, 48.1% were prescribed antibiotics within 180 days before the infection (Table S2).

**Table 1** Characteristics of study population

| | Individuals with CDI history | Individuals without CDI history |
|---|---|---|
| Total, *n* (%) | 34 868 (100) | 4 635 555 (100) |
| Women, *n* (%) | 19 632 (56) | 2 417 243 (52) |
| Born in Sweden, *n* (%) | 32 448 (93) | 4 179 520 (90) |
| Mean (SD) age at entry[a], years | 66.7 (12.3) | 57.8 (14.8) |
| Mean follow-up years | 3.2 | 14.1 |
| Mortality, per 100 PYs | 20.5 | 2.2 |
| Incident PD, *n* (%) | 165 (0.5) | 47 035 (1.0) |
| Type of PD diagnosis, *n* (% among total number of incident PDs) | | |
| Only primary diagnosis | 27 (16.4) | 10 613 (22.6) |
| Only secondary diagnosis | 95 (57.6) | 14 027 (29.8) |
| Both | 43 (26.1) | 22 395 (47.6) |
| Education attainment, *n* (%) | | |
| Compulsory | 11 105 (32) | 1 442 712 (31) |
| Secondary | 6858 (20) | 1 591 616 (34) |
| Post-secondary and postgraduate | 1386 (4) | 404 921 (9) |
| No information | 15 519 (44) | 1 196 306 (26) |
| Comorbidities[b], *n* (%) | | |
| IBD | 1488 (4.3) | 62 902 (1.4) |
| Diabetes | 8678 (24.9) | 524 592 (11.3) |
| Cancer | 13 146 (37.7) | 1 053 222 (22.7) |
| COPD | 5542 (15.9) | 260 365 (5.6) |

CDI, *Clostridium difficile* infection; COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease; PD, Parkinson's disease; PY, person-year. [a]Study entry was defined as 1 January 1997. [b]Comorbidities included both prevalent conditions and those developed during the follow-up.

### Crude incidence rate and cumulative incidence of PD

In total, 165 and 47 035 incident PD cases were identified from individuals with and without CDI history, respectively, during a mean follow-up time of 3.23 and 14.14 person-years (Table 1). The crude PD incidence rate (per 100 000 person-years) was 146.45 (95% CI 124.95–170.57) for the CDI group and 71.74 (95% CI 71.09–72.39) for the non-CDI group. More than 70% of PD patients identified from the non-CDI group were diagnosed with PD as a primary condition at least once, whereas almost 60% of PD cases identified from the CDI group were only diagnosed with PD as a secondary condition (Table 1). As expected, the incidence rate of PD was higher among those with recurrent CDI vs. those without, and among those who used antibiotics within 180 days prior to an infection vs. those who did not. By contrast, the PD incidence rate was lower among inpatient vs. outpatient CDIs (Table S2).

When stratified by age at entry, the cumulative incidence curves of PD were similar for CDI and non-CDI groups before 80 years of age, but diverged after age 80 years, with excess PD incidence observed among those without CDI history (results not shown).

### Association between CDI and PD risk

*Clostridium difficile* history was associated with a 16% increase in PD risk when a time-constant effect was assumed across the entire follow-up [HR 1.16, 95% CI 1.00–1.36; $P = 0.05$ (Fig. 2)]. The time-constant model did not violate the proportionality of hazards assumption. A subsequent test for CDI by sex interaction suggested no heterogeneity of the CDI effect between men and women. Nevertheless, when the CDI effect was allowed to vary with time since CDI diagnosis (0–2 years, 2–5 years and >5 years), we observed that the positive association was mainly driven by an increased PD risk within the first 2 years after CDI diagnosis (HR 1.38, 95% CI 1.12–1.69), which was no longer present when the outcome ascertainment was restricted to primary PD diagnosis (results not shown). After 2 years since diagnosis, CDI was no longer associated with PD (Table 2, Fig. 3). There was no notable evidence for modification of the CDI–PD association by age at CDI diagnosis (results not shown).

Over the entire follow-up, no association was observed for CDI subgroups, except for CDI with pre-infection antibiotic use (HR 1.37, 95% CI 1.03–1.82; Fig. 2). The increased PD risk within the first 2 years since CDI diagnosis was generally observed across all CDI subgroups, with suggestively stronger

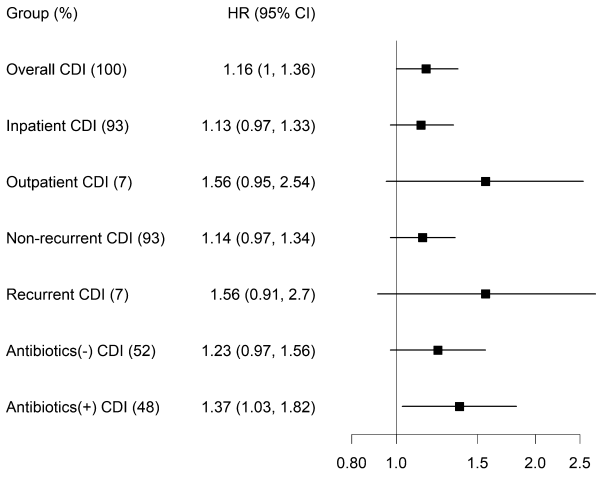


**Figure 2** Time-constant associations between history of *Clostridium difficile* infection (CDI), overall and by subgroup, and risk of Parkinson's disease. HR, hazard ratio; CI, confidence interval.

effects detected from outpatient, recurrent and antibiotics (+) CDIs compared to their comparison subgroups (Table 2, Fig. S1). Similar to the temporal relationship for the overall CDI–PD association, none of the CDI subgroups were associated with PD risk after 2 years since diagnosis, although power to detect modest associations in some of these subgroups may have been limited (Table 2, Fig. S1).

## Discussion

To our knowledge, this is the first study of the association between CDI history and PD risk. We found that individuals with CDI history were at slightly higher risk of PD during the first 2 years since CDI diagnosis but there was no increased PD risk in long-term follow-up. The temporal pattern of the CDI–PD association was independent of source of CDI diagnosis, presence of recurrent infection and use of antibiotics before CDI.

One possible explanation for the short-term association is reverse causation. Considering a lag time between symptom onset and register PD diagnosis (on average 7.5 years for inpatient cases) [42], PD patients might have had PD for several years before their first registered diagnoses were recorded. Therefore, CDI might occur as a complication of hospital stay for reasons related to PD, such as other infections or falls. Awareness of a potential increased CDI risk among PD patients may lead to interventions to mitigate this excess risk. Surveillance bias may also be responsible. Both CDI and any underlying diseases require medical care [26], and the contact with healthcare providers

**Table 2** Time-varying associations between *Clostridium difficile* infections history, overall and by subgroups, and risk of Parkinson's disease

| | HR (95% CI) | | |
|---|---|---|---|
| CDI group (%) | 0–2 years since CDI | 2-5 years since CDI | >5 years since CDI |
| Overall (100) | 1.38 (1.12–1.69) | 0.95 (0.71–1.28) | 0.99 (0.68–1.44) |
| By source of diagnosis | | | |
| Inpatient (93) | 1.33 (1.07–1.64) | 0.94 (0.68–1.28) | 0.97 (0.66–1.44) |
| Outpatient (7) | 2.14 (1.11–4.11) | 1.11 (0.42–2.96) | 1.22 (0.39–3.77) |
| By presence of recurrent infections | | | |
| Non-recurrent (93) | 1.34 (1.08–1.65) | 0.94 (0.69–1.28) | 0.99 (0.68–1.45) |
| Recurrent (7) | 1.92 (1.00–3.69) | 1.18 (0.38–3.67) | 0.92 (0.13–6.55) |
| By pre-infection use of antibiotics | | | |
| Antibiotics (−) (52) | 1.52 (1.12–2.08) | 1.07 (0.69–1.63) | 0.75 (0.36–1.57) |
| Antibiotics (+) (48) | 1.71 (1.23–2.39) | 0.84 (0.45–1.56) | 1.11 (0.36–3.43) |

CDI, *Clostridium difficile* infection; CI, confidence interval; HR, hazard ratio. For all models, attained age was adjusted for as underlying timescale and interaction between CDI and age at CDI diagnosis was also included.

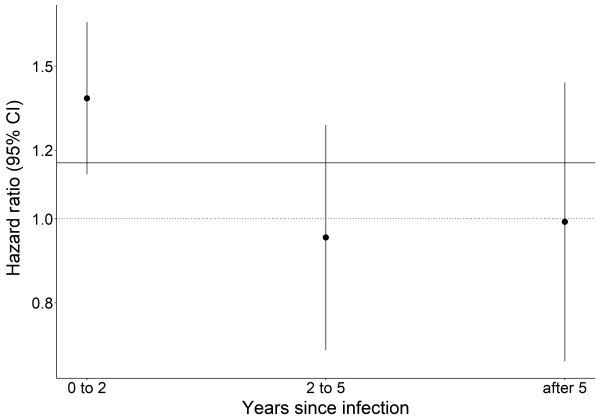


**Figure 3** Association between history of *Clostridium difficile* infection (CDI) and risk of Parkinson's disease over years since CDI diagnosis. The maximum length of follow-up since infection was 17 years. The horizontal dotted line denotes the null association at hazard ratio (HR) = 1, and the solid line represents the time-constant association across the entire follow-up at HR = 1.16. CI, confidence interval.

may increase the CDI patients' chances of being evaluated for other health problems, including PD. However, we adjusted for comorbidities related to CDI in our data, which should have controlled for surveillance bias to some extent.

Although no prior work has examined the relationship between CDI and PD, several epidemiological studies investigated other GI infections in the context of PD. For instance, *Helicobacter pylori* infection has been reported to be more prevalent among PD patients than controls [46], and a Danish register-based study found a 45% increased risk of PD five or more years after prescription of *H. pylori* eradication drugs [47]. Similarly, a health insurance data-based study observed an association of *H. pylori* infection with higher PD risk (HR 2.29, 95% CI 1.44–3.66), but that study defined incident PD only 6 months following an infection, raising concerns about reverse causation [14]. Associations with a spectrum of other GI-related pathogens have also been investigated, but none has yet been established as causal for PD development [48].

The fact that PD risk may be increased with chronically inflamed gut (i.e. IBD) but not acute enteric infections, such as *H. pylori* infection and CDI, might suggest that only a cumulative effect of the inflammatory environment in the GI tract is relevant to the initiation of PD pathology. The distinct host immune responses to acute infection and chronic inflammation in the intestine might also be relevant. Indeed, the immune cell profile in CDI patients who later had recurrent infections was shown to be increasingly similar to that implicated in IBD over the course of disease [49]. Nonetheless, we did not observe differential PD risks in individuals with and without recurrent infections, possibly implying that the PD pathogenesis is driven by mechanisms besides chronic GI inflammation.

The present study has several strengths. First, the population-based study design makes the results readily generalizable to the general population. Second, our statistical analyses were carefully designed to characterize the temporal relationship between CDI and incident PD as well as the heterogenous associations across different CDI subgroups. Third, the study was based on a large sample size with long follow-up time.

Limitations of the study include measurement errors in the register data for both CDI and PD diagnoses, which may have influenced the findings. The low sensitivity of ICD-10 code-based ascertainment of CDI [41] can lead to misclassification of exposure, which may result in an underestimated association, whereas error in the measurement of confounders or outcome may bias a result in either direction. Due to the lack of primary care data and outpatient records before 2001, some CDI and PD diagnoses in the sample may have been missed. The date of PD diagnosis was also estimated imprecisely with register records, but we allowed for lag time periods of various durations between CDI and subsequent PD by estimating a time-varying effect of CDI since its diagnosis. Last,

information on several potential confounders, i.e. smoking, lifestyle and behavioral factors, is also lacking in the Swedish registers (although we included COPD as a proxy for smoking in the analysis).

In conclusion, the present study did not find evidence for CDI as a risk factor for PD. Further studies should be conducted to assess the replicability of our results.

## Acknowledgements

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## Disclosure of conflicts of interest

H.L. reports receiving research grants from Shire Pharmaceuticals and serving as a speaker for Evolan Pharma AB and Shire Pharmaceuticals outside the submitted work. X.K., A.P., J.L., D.W., N.P. and K.W. report no disclosures.

## Data availability statement

The original data for this study are held by the Swedish National Board of Health and Welfare and Statistics Sweden and we cannot make the data publicly available due to Swedish data privacy laws. Any researcher can obtain access to the original data by obtaining an ethical approval from a regional ethical review board and then making a request to the Swedish National Board of Health and Welfare and Statistics Sweden.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** The Swedish-version ICD codes for the selected four comorbidities.

**Table S2.** Description of individuals with a history of *Clostridium difficile* infection in the study cohort.

**Figure S1.** Associations between history of *Clostridium difficile* infection (CDI), by subgroup, and risk of Parkinson's disease over years since CDI diagnosis.

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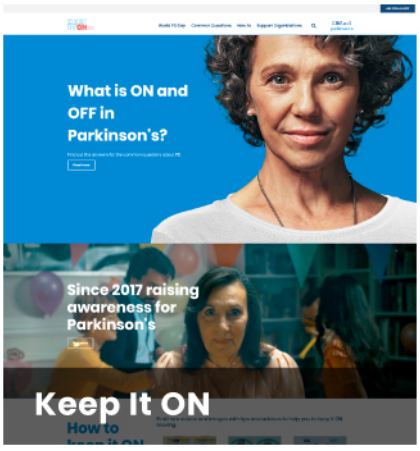


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