Inflammatory Bowel Disease and Parkinson's Disease: A Nationwide Swedish Cohort Study

*Petra Weimers, MD,[*] Jonas Halfvarson, PhD,[†] Michael C. Sachs, PhD,[‡] Rachel Saunders-Pullman, MD,[§] Jonas F. Ludvigsson, PhD,[¶,‖] Inga Peter, PhD,[**,a] Johan Burisch, PhD,[*,a] and Ola Olén, PhD[††,‡‡,§§,a]*

Background: Few studies have examined the association between inflammatory bowel disease (IBD) and Parkinson's disease (PD).

Methods: To estimate the incidence and relative risk of PD development in a cohort of adult IBD, we included all incident IBD patients (n = 39,652) in the Swedish National Patient Register (NPR) between 2002 and 2014 (ulcerative colitis [UC]: n = 24,422; Crohn's disease [CD]: n = 11,418; IBD-unclassified [IBD-U]: n = 3812). Each IBD patient was matched for sex, age, year, and place of residence with up to 10 reference individuals (n = 396,520). In a cohort design, all incident PD occurring after the index date was included from the NPR. In a case-control design, all incident PD occurring before the index date was included. The association between IBD and PD and vice versa was investigated by multivariable Cox and logistic regression.

Results: In IBD, there were 103 cases of incident PD, resulting in hazard ratios (HRs) for PD of 1.3 (95% confidence interval [CI], 1.0–1.7; $P = 0.04$) in UC, 1.1 (95% CI, 0.7–1.7) in CD, and 1.7 (95% CI, 0.8–3.0) in IBD-U. However, these effects disappeared when adjusting for number of medical visits during follow-up to minimize potential surveillance bias. In a case-control analysis, IBD patients were more likely to have prevalent PD at the time of IBD diagnosis than matched controls, with odds ratios of 1.4 (95% CI, 1.2–1.8) in all IBD patients, 1.4 (95% CI, 1.1–1.9) for UC, and 1.6 (95% CI, 1.1–2.3) for CD patients alone.

Conclusions: IBD is associated with an increased risk of PD, but some of this association might be explained by surveillance bias.

Key Words: inflammatory bowel disease, Parkinson's disease, population-based cohort

INTRODUCTION

Inflammatory bowel disease (IBD), that is, Crohn's disease (CD) and ulcerative colitis (UC), is a chronic condition affecting all ages.[1, 2] The disease is characterized by a remitting and relapsing course of abdominal pain, diarrhea, rectal bleeding, and weight loss.[3] Medical treatment aims to relieve and prevent gastrointestinal inflammation and consists of mesalamine compounds, corticosteroids, immunomodulators, and biologics targeting cytokine signaling pathways.[4] The highest

Received for publications March 23, 2018; Editorial Decision April 19, 2018.

From the *Department of Gastroenterology, North Zealand University Hospital, Frederikssund, Denmark; †Department of Gastroenterology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden; ‡Unit of Biostatistics, Institute of Environmental Medicine, ¶Department Medical Epidemiology and Biostatistics, ††Clinical Epidemiology Unit, Department of Medicine Solna, and §§Department of Clinical Science and Education Södersjukhuset, Karolinska Institutet, Stockholm, Sweden; §Department of Neurology and **Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, New York, USA; ‖Department of Pediatrics, Örebro University Hospital, Örebro, Sweden; ‡‡Department of Pediatric gastroenterology and nutrition, Sachs' Children and Youth Hospital, Stockholm, Sweden

[a]Equal contribution

Conflicts of interest: Petra Weimers has received grants from Ferring lægemidler and Tillotts Pharma and nonfinancial support from Janssen-Cilag A/S, Calpro AS, Pharmacosmos A/S, and Vifor Pharma Nordiska AB. Jonas Halfvarson has received consulting fees from Abbvie, Celgene, Ferring, Hospira, Janssen, Medivir, MSD, Pfizer, RenapharmaVifor, Sandoz, Shire Takeda, and Tillotts Pharma; lecture fees from Abbvie, Ferring, Janssen, MSD, RenapharmaVifor, Shire, Takeda, and Tillotts Pharma; and research grants from Janssen, MSD, and Takeda. Michael C. Sachs has no conflicts to declare. Rachel Saunders-Pullman has no conflicts to declare. Jonas F. Ludvigsson has no conflicts to declare. Inga Peter has no conflicts to declare. Johan Burisch has received consulting fees from Celgene, Janssen-Cilag, Abbvie, and Ferring; lecture fees from Abbvie, Pfizer, MSD, and Takeda; and an unrestricted grant from Takeda. Karolinska Institutet has received fees for lectures held by Ola Olén on occasions organized by Takeda and Ferring. Karolinska Institutet received fees when Ola Olén participated as an expert in a panel discussing possibilities with register-based research. Karolinska Institutet performed an observational study (Ola Olén, PI) financed in part by an unrestricted grant from Janssen Pharmaceuticals and an observational report financed by Pfizer.

Supported by: This project was partly financed by grants from the Swedish Medical Society (project grants, the Fund for Research in Gastroenterology and the Ihre Foundation), Mag-tarmfonden, the Jane and Dan Olsson Foundation, The Bengt Ihre Research Fellowship in gastroenterology, Karolinska Institutet Foundations, the Leona M. Harry B. Helmsley Charitable Fund, and the Michael J Fox Foundation. Financial support was also provided through the regional agreement on medical training and clinical research between Stockholm County Council and the Karolinska Institutet (A.L.F.). None of the funding organizations had any role in the design or conduct of the study; in the collection, management, or analysis of the data; or in the preparation, review, or approval of the manuscript.

Authors contributions: I.P. and J.B. conceived study. O.O., J.B., J.H., M.C.S., J.F.L., and I.P. designed the study. O.O. was responsible for the acquisition of data. M.C.S. and O.O. analyzed the data. P.W., J.B., JH., and I.P. drafted the manuscript. All authors interpreted the data, contributed to critical revision of the manuscript for important intellectual content, and approval the final version. O.O. is the guarantor of the article.

Address correspondence to: Petra Weimers, Department of Gastroenterology, North Zealand University Hospital, Frederikssundsvej 30, 3600 Frederikssund, Denmark (malin.petra.ulfsdotter.weimers.01@regionh.dk).

© 2018 Crohn's & Colitis Foundation. Published by Oxford University Press. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com.

doi: 10.1093/ibd/izy190
Published online 16 May 2018

Downloaded from https://academic.oup.com/ibdjournal/article/25/1/111/4996912 by guest on 20 March 2024

prevalence and incidence of IBD are traditionally found in countries of the Western world; however, during the last decades, a dramatic increase has also been observed in newly industrialized countries, and worldwide some 5 million people are believed to have IBD.[5, 6]

IBD has a complex etiology resulting from impaired regulation of intestinal mucosal immune responses in genetically susceptible individuals.[3] Genome-wide association studies (GWAS) have identified more than 200 loci associated with IBD,[7, 8] some of which have also been associated with Parkinson's disease (PD).[9] PD is a neurodegenerative disorder characterized by cardinal motor features of bradykinesia, rigidity, rest tremor, and postural instability. Nonmotor features, including obstipation, depression, anxiety, and cognitive decline may also be present. A majority of the patients are diagnosed between 65 and 70 years of age, and it is estimated that 1% of the population older than age 60 years is affected by PD.[10]

Specifically, mutations in the leucine-rich repeat kinase 2 (*LRRK2*) gene, involved in the regulation of the immune system and recently associated with IBD,[7, 11, 12] have been recognized as a major risk factor for the development of PD.[13] Moreover, the P268S variant in the *NOD2* gene has also been associated with development of sporadic PD and CD.[14, 15] In addition, variation in the HLA-DPA1 gene has been reported in both IBD and PD patients.[16, 17] PD and IBD also share potential features in terms of pathogenesis and risk factors of disease development. Tumor necrosis factor–α (TNF-α) and interleukin 1β are cytokines of great importance in the inflammation process of IBD and have been implicated in PD as well, with anti-TNFs being used with success in the treatment of UC and CD.[18–20]

Further understanding of the mechanisms and association between the diseases could eventually lead to revelations of new targets for interventions that may modulate the incidence and/or disease course. However, despite accumulating evidence providing common biological mechanisms involved in the development and pathogenesis of IBD and PD, limited and conflicting data exist on the clinical co-occurrence of IBD and PD.[21–23] Previous studies investigating the possible association between IBD and PD have been based on administrative claims databases and are therefore not representative of the general IBD population. Hence, the aim of this study was to estimate the incidence of PD in overall IBD and subtypes as compared with the general population in a Swedish nationwide population-based cohort. A secondary aim was to estimate the association between PD and later IBD in a case-control design.

METHODS

Study Design

We investigated the association between IBD and subsequent PD in a cohort study design consisting of a nationwide cohort of IBD patients. In a case-control design, consisting of all Swedish IBD patients and matched general population controls, we assessed the odds ratio (OR) for being exposed to PD before IBD.

Data Sources

All Swedish inhabitants since 1947 have received a unique personal identification number at birth or upon immigration.[24] Using the personal identification number, we linked data from national and virtually complete administrative and clinical registers on demographics, medical treatment, and morbidity. This study was based on the following registries, which cover the entire Swedish population of approximately 10 million people.[25]

The National Patient Registry (NPR) was established in 1964 and covers in-patient data from 1964 onward (nationwide since 1987), surgical day care data from 1997 onward, and outpatient data from 2001 onward.[26] Health care in Sweden is publicly founded, and all data regarding hospitalization, outpatient visits, and hospital procedures are registered in the NPR and linked to the patient by their personal identification number.

The Prescribed Drug Register covers data on the dispensation of all prescribed drugs since 2005. However, infusions of biologics are covered to a lesser extent in the register, and drugs dispensed in the hospital or bought over the counter are not registered at all.[27] Although noninfusion biologicals such as adalimumab, an inhibitor of TNF, have 100% coverage in the Prescribed Drug Register, only 20% of infliximab (infusion) use was registered in 2009. However, regional differences in the registration of biological treatments do occur, and some counties, for example, Stockholm County, have complete coverage of Infliximab since 2007.[28]

The Total Population Register includes data on age, sex, place of residence, date of birth and death, and emigration status of the Swedish population.[25] The registry was also used to identify reference individuals for the IBD cohort.

The Swedish Multigeneration Register contains information on people and their biological parents. We used this register to assess the occurrence of IBD and PD in first-degree relatives to study the potential effect modification of family history.[29]

Study Population

All individuals diagnosed with incident IBD in Sweden between January 1, 2002, and December 31, 2014, were identified in the NPR using International Classification of Disease (ICD) codes representing IBD (Supplementary Table 1). IBD was defined as at least 2 diagnostic listings of IBD (main or contributory diagnoses in inpatient or outpatient care). This approach has previously been shown to increase the accuracy of patient identification and has a positive predictive value (PPV) of 93% (95% confidence interval [CI], 87–97).[30, 31]

The definitions of exposures should not "look into the future." Subtypes of IBD at the start of follow-up (UC, CD, and IBD unclassified [IBD-U]) were therefore defined using the first 2 diagnostic codes only (Supplementary Table 1). All analyses of PD incidence in IBD were based on this definition. For

Downloaded from https://academic.oup.com/ibdjournal/article/25/1/111/4996912 by guest on 20 March 2024

descriptive purposes, we also defined subtypes of IBD according to all available information at the end of follow-up: different IBD diagnoses might be documented during a patient's medical history; either due to difficulties distinguishing between UC and CD or simply because of incorrect registration in the records. Patients with a mix of codes for UC, CD, or indeterminate colitis (ICD-10 code K52.3) during follow-up were hence defined as IBD-U. Moreover, patients who only shifted between UC and CD (and vice versa) and who had been diagnosed with only UC or CD during the last 5 years of follow-up were classified as UC or CD. Finally, patients who had a diagnostic or procedure code typical of CD (eg, small bowel resection or CD of the small bowel) (Supplementary Table 2) were classified as CD. All patients diagnosed with IBD before the inclusion date were excluded. Inclusion and exclusion of the study population are illustrated in Figure 1.

Up to 10 reference individuals were matched to index individuals with IBD by sex, age, calendar year, and place of residence. Reference individuals with an IBD diagnosis before their matching date were excluded, and individuals diagnosed with IBD between 2002 and 2014 were censored in the analysis.

Parkinson's Disease

PD was defined as at least 1 diagnostic listing of PD (main or contributory diagnosis in inpatient or outpatient care) between 2002 and 2014 in the NPR. Furthermore, to calculate the OR for being exposed to PD before IBD, patients diagnosed with PD between 1964 and 2014 were included in the analysis.

The Montreal Classification and Extra-intestinal Manifestations

In descriptive tables, patients' phenotype was identified by the highest ever possible degree of extent, location, or behavior according to the Montreal classification[32] using ICD-codes (Supplementary Table 3). Patients without a code representing a specific phenotype of UC or CD were classified as unspecified. Extra-intestinal manifestations related to IBD were identified

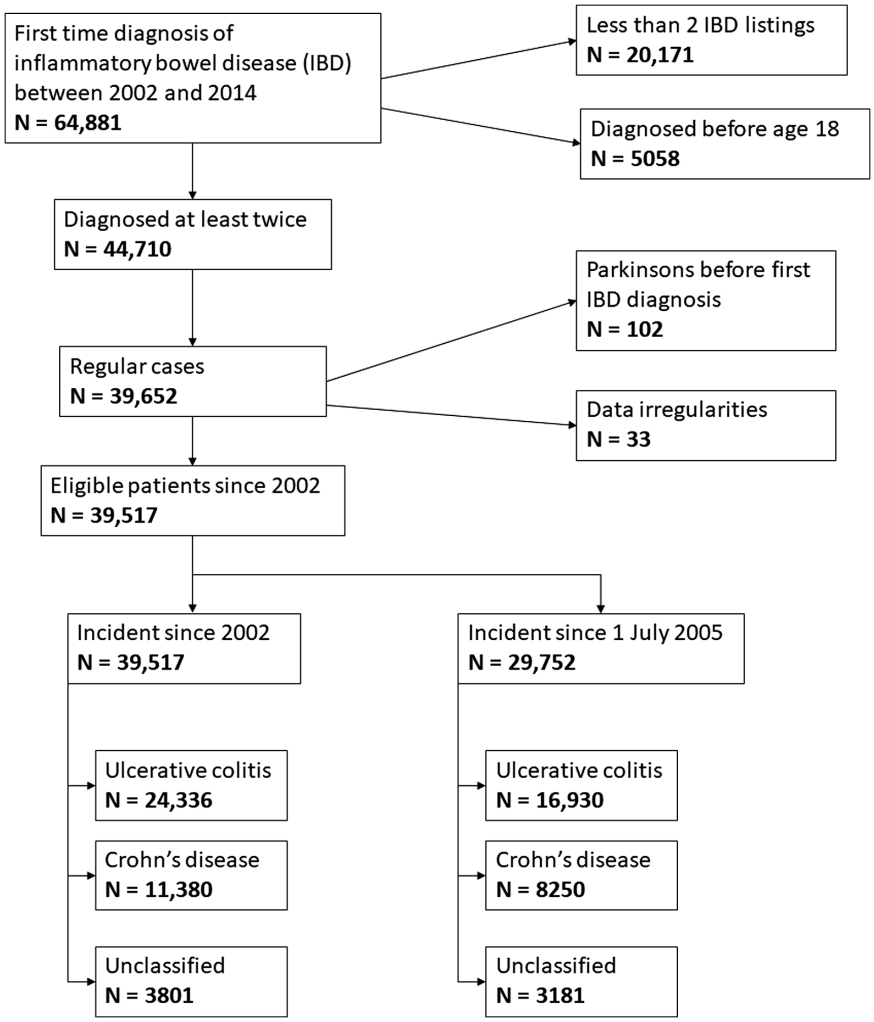

FIGURE 1. Inclusions and exclusions in the study population.

Downloaded from https://academic.oup.com/ibdjournal/article/25/1/111/4996912 by guest on 20 March 2024

via ICD codes in the NPR and are listed in Supplementary Table 4.

Treatment

Data on medical treatment, including 5-aminosalicylate/sulfasalazine, corticosteroids, immunomodulators, and biologics for IBD (Supplementary Table 5), were retrieved from the Swedish Prescribed Drug Registry using the appropriate Anatomical Therapeutic Chemical Classification (ATC) codes. To cover treatment with infusion biologics, procedure code DT016 was used, followed by the ATC codes in the NPR.

Surgical procedures related to IBD, such as colectomy, resection of the intestine, resection of the rectum, strictureplasty, and stoma and pouch operations, were identified using procedure codes in the NPR (Supplementary Table 6).

Statistical Methods

In the cohort analyses, patients were considered at risk of PD from their first visit with an IBD diagnosis (or the corresponding index date for reference individuals) until a first-ever PD diagnostic listing or censoring due to death, emigration, end of follow-up, or change of IBD status (ie, reference individuals who were later diagnosed with IBD), whichever came first. As IBD was defined as at least 2 diagnostic listings of IBD, all reference individuals were required to be alive and living in Sweden at the date of the second IBD listing for their respective IBD patient case (to avoid immortal time bias).

The outpatient part of the NPR started in 2001, and patients with a first-ever diagnostic listing of IBD in 2001 will therefore be a mixture of incident and prevalent cases. To identify only truly incident IBD cases, we allowed for a 1-year washout period and restricted our study population to those with adult-onset IBD (age ≥18 years) starting on January 1, 2002, or later and their matched reference individuals, as described previously.[33]

Individuals with a PD diagnosis before the index date were excluded from the time-to-event analysis. To compare the risk of PD in IBD cases and non-IBD reference individuals, we computed hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazards models adjusted for sex, age, index date, and place of residency. The proportional hazards assumption was checked for the main results by testing the Schoenfeld residuals, followed by visual inspection of the complementary log-log survival curves. No marked departures from the assumption were observed.

To assess the impact of increased surveillance of IBD patients, we performed an additional analysis in which we included the number of medical care visits as a time-dependent covariate and thereby adjusted the association between IBD and PD in groups for health care usage.

In the case-control analyses, we used logistic regression to estimate the OR for a PD diagnosis before the onset of IBD. This analysis included all cases of IBD and their matched controls sampled from the general population. In these analyses, all PD diagnoses before IBD were counted (but PD diagnoses after IBD onset were not).

Statistical analyses were performed using R statistical software (version 3.3.1; R Foundation for Statistical Computing, Vienna, Austria) and the survival package (version 2.38; https://CRAN.R-project.org/package = survival). An HR with 95% CI excluding 1 was considered statistically significant.

This study was approved by the Ethics Review Board in Stockholm, Sweden (2007/785-31/5; 2011/1509-32; 2015/0004-31). Because this study was strictly register based, according to Swedish law, individual informed consent was not necessary.

RESULTS

Overall, 39,652 patients (UC: n = 24,422; CD: n = 11,418; IBD-U: n = 3812), were identified in the Swedish NPR from 2002 to 2014 (Fig. 1) and were matched to 396,520 reference individuals from the general population. Characteristics of the study population at start and end of follow-up are summarized in Tables 1 and 2. Among IBD patients, 102 (49.8 %) were diagnosed with PD before the IBD diagnosis, and 103 (50.2%) after. The mean age at diagnosis and sex distribution seemed to be similar in both IBD patients and reference individuals. Although IBD patients who developed PD were much older at the end of follow-up (88% vs 35% at age ≥60 years; $P < 0.001$) and more likely to never have received thiopurine or anti-TNF compared with those without PD (88% vs 66%; $P < 0.001$), no differences by PD status or IBD location were observed in health care usage during follow-up, as assessed by the Montreal classification (Table 3).

Incidence of PD in IBD Patients

During 249,784 person-years of follow-up in IBD patients, there were 103 cases of incident PD, corresponding to an absolute incidence rate for PD of 0.4 (95% CI, 0.3–0.5) per 1000 person-years for IBD patients. This compared with 830 first-ever PD diagnostic listings in reference individuals during 2,490,979 person-years of follow-up and an absolute incidence rate of 0.3 (95% CI, 0.3–0.4) per 1000 person-years (Table 4). This difference corresponds to 1 extra case of PD for every 10,000 IBD patients (≥18 years) followed for a year (1/(risk difference)) compared with reference individuals.

The incidence of PD increased with age at IBD onset in UC, CD, and IBD-U, with the highest incidence in patients aged 60 years or older (80% of PD events occurred in patients with IBD onset ≥60 years). However, the incidence remained rather stable, especially in IBD patients overall, when comparing length of follow-up (Table 4). The cumulative incidence of PD in IBD patients and reference individuals (by age at first IBD diagnosis) is illustrated in Figure 2, with a statistically significant ($P = 0.024$) difference observed in individuals older than age 60 years.

Downloaded from https://academic.oup.com/ibdjournal/article/25/1/111/4996912 by guest on 20 March 2024

TABLE 1: Characteristics of All Adult-Onset Inflammatory Bowel Disease Patients in Sweden 2002–2014, No. (%) if Not Otherwise Stated

	IBD	UC	CD	IBD-U	Reference Individuals
	39,652 (9.1)	24,422 (5.6)	11,418 (2.6)	3812 (0.9)	396,520 (90.9)
Parkinson's disease	205 (0.5)	133 (0.5)	53 (0.5)	19 (0.5)	1556 (0.4)
PD before IBD	102 (0.3)	64 (0.3)	30 (0.3)	8 (0.2)	714 (0.2)
Age at PD before IBD, mean (SD), y	68 (11)	69 (10)	69 (11)	62 (18)	67 (11)
Age at PD before IBD, median (IQR), y	70 (62–75)	71 (64–75)	70 (61–75)	67 (60–70)	68 (61–75)
PD after IBD	103 (0.3)	69 (0.3)	23 (0.2)	11 (0.3)	839 (0.2)
Age at PD after IBD, mean (SD), y	72 (10)	71 (10)	75 (10)	74 (9)	72 (10)
Age at PD after IBD, median (IQR), y	74 (68–79)	73 (67–78)	76 (70–81)	76 (72–80)	74 (66–79)
Sex and age at first IBD diagnosis					
Male	20,099 (50.7)	12,776 (52.3)	5429 (47.5)	1894 (49.7)	200,990 (50.7)
Female	19,553 (49.3)	11,646 (47.7)	5989 (52.5)	1918 (50.3)	195,530 (49.3)
Age at first IBD diagnosis, mean (SD), y	45 (18)	46 (18)	44 (19)	47 (20)	45 (18)
Age at first IBD diagnosis, median (IQR), y	43 (29–60)	43 (30–60)	41 (27–59)	46 (30–63)	43 (29–60)
≥18–<40	18,059 (45.5)	11,002 (45.0)	5462 (47.8)	1595 (41.8)	180,590 (45.5)
≥40–<50	5952 (15.0)	3785 (15.5)	1663 (14.6)	504 (13.2)	59,520 (15.0)
≥50–<60	5880 (14.8)	3686 (15.1)	1619 (14.2)	575 (15.1)	58,800 (14.8)
≥60	9761 (24.6)	5949 (24.4)	2674 (23.4)	1138 (29.9)	97,610 (24.6)
Heredity					
Parent or sibling with PD	880 (2.2)	530 (2.2)	264 (2.3)	86 (2.3)	8301 (2.1)
Parent or sibling with IBD	4326 (13.0)	2632 (12.9)	1308 (13.7)	386 (12.1)	16,188 (5.0)
Smoking status[a]					
Missing	30,996 (78.2)	19,054 (78.0)	8881 (77.8)	3061 (80.3)	309,405 (78.0)
Nonsmoker	6580 (76.0)	4239 (79.0)	1787 (70.4)	554 (73.8)	70,716 (81.2)
1–9 cigarettes/d	1265 (14.6)	706 (13.2)	442 (17.4)	117 (15.6)	9869 (11.3)
≥10 cigarettes/d	811 (9.4)	423 (7.9)	308 (12.1)	80 (10.7)	6530 (7.5)

Type of IBD (ulcerative colitis, Crohn's disease, or IBD-unclassified) defined by the 2 first diagnostic listings only.
[a]Based on self-reported smoking habits in early pregnancy.

Risk of PD in IBD Patients Compared With the Background Population

The overall risk of PD was 30% higher in IBD patients compared with reference individuals, with an HR of 1.3 (95% CI, 1.0–1.6; $P = 0.02$) per 1000 person-years. For UC patients, the HR was 1.3 (95% CI, 1.0–1.7; $P = 0.04$); for CD, it was 1.1 (95% CI, 0.7–1.7); and for IBD-U, it was 1.7 (95% CI, 0.8–3.0), as illustrated in Figure 3 and the corresponding Supplementary Table 7. UC patients with up to 1 year of follow-up and IBD-U patients diagnosed at age 60 years or older carried a 2-fold risk of developing PD compared with the general population. However, when adjusted for number of medical care visits during follow-up as a time-dependent covariate, the overall relative risk for IBD patients developing PD decreased to 0.9 (95% CI, 0.7–1.1), as shown in Table 5.

When investigating the risk of PD with regards to IBD medication use, IBD patients never exposed to thiopurines or anti-TNF were 60% more likely to develop PD (HR, 1.6; 95% CI, 1.2–2.2) than their matched reference individuals. This increase in incident PD risk was 2.3-fold in patients with CD (HR, 2.3; 95% CI, 1.2–3.9), as shown in Supplementary Table 7. There were too few events to estimate the association of individual or combined anti-TNF/thiopurine use, nor could any conclusions be drawn with regards to hereditary risks of PD development.

PD and Subsequent IBD

In the case-control part of our study, we calculated the OR for PD diagnosis before IBD onset compared with reference individuals. The OR of being exposed to a first-ever PD diagnosis was 1.4 (95% CI, 1.2–1.8) in all IBD

Downloaded from https://academic.oup.com/ibdjournal/article/25/1/111/4996912 by guest on 20 March 2024

TABLE 2: Characteristics at End of Follow-up in Adult-Onset Inflammatory Bowel Disease Patients Diagnosed in Sweden Since 2002, Followed up Through 2014, No. (%) if Not Otherwise Stated

	IBD	UC	CD	IBD-U
	39,517 (100.0)	24,336 (61.6)	11,380 (28.8)	3801 (9.6)
Age at end of follow-up, y				
Mean (SD)	52 (18)	52 (18)	50 (18)	53 (19)
Median (IQR)	50 (36–66)	50 (37–67)	48 (34–65)	52 (35–68)
Reason for end of follow-up				
PD	103 (0.3)	69 (0.3)	23 (0.2)	11 (0.3)
Death	3010 (7.6)	1798 (7.4)	888 (7.8)	324 (8.5)
Emigration	409 (1.0)	252 (1.0)	123 (1.1)	34 (0.9)
December 31, 2014	35,998 (91.1)	22,219 (91.3)	10,346 (90.9)	3433 (90.3)
Length of follow-up, y				
≥0–<1	2855 (7.2)	1554 (6.4)	886 (7.8)	415 (10.9)
≥1–<5	13,326 (33.7)	7717 (31.7)	3939 (34.6)	1670 (43.9)
≥5–<10	14,785 (37.4)	9322 (38.3)	4236 (37.2)	1227 (32.3)
≥10	8551 (21.6)	5743 (23.6)	2319 (20.4)	489 (12.9)
Health care usage, mean (SD) No. visits during follow-up				
Total	23 (28)	22 (27)	26 (28)	23 (31)
Outpatient	20 (25)	19 (25)	22 (25)	20 (28)
Inpatient	3 (6)	3 (5)	4 (7)	3 (6)
Age at end of follow-up, y				
≥18–<40	13,092 (33.1)	7688 (31.6)	4148 (36.4)	1256 (33.0)
≥40–<50	6838 (17.3)	4437 (18.2)	1853 (16.3)	548 (14.4)
≥50–<60	5832 (14.8)	3650 (15.0)	1670 (14.7)	512 (13.5)
≥60	13,755 (34.8)	8561 (35.2)	3709 (32.6)	1485 (39.1)
IBD classification in last 5 y of follow-up				
UC	22,752 (57.6)	22,325 (91.7)	98 (0.9)	329 (8.7)
CD	12,423 (31.4)	659 (2.7)	10,834 (95.2)	930 (24.5)
IBD-U	4342 (11.0)	1352 (5.6)	448 (3.9)	2542 (66.9)
Maximum Montreal classification during follow-up				
No.	–	23,761	11,320	2881
E1 (ulcerative proctitis)	–	4377 (18.4)	–	235 (8.2)
E2 (left-sided UC)	–	6334 (26.7)	–	393 (13.6)
E3 (extensive colitis)	–	8721 (36.7)	–	742 (25.8)
EX (extent not defined)	–	4256 (17.9)	–	1501 (52.1)
L1 (terminal ileum)	–	–	4072 (36.0)	–
L2 (colon)	–	–	3880 (34.3)	–
L3 or LX (ileocecal/not defined)	–	–	3337 (29.5)	–
P (perianal disease)	–	–	1076 (9.5)	–
Complications during follow-up				
Primary sclerosing cholangitis	740 (1.9)	542 (2.2)	128 (1.1)	70 (1.8)
Other extra-intestinal manifestations	1868 (4.7)	940 (3.9)	771 (6.8)	157 (4.1)
IBD surgery (not mutually exclusive categories)				
Colectomy	971 (2.5)	769 (3.2)	128 (1.1)	74 (1.9)
Other bowel surgery	5360 (13.6)	2205 (9.1)	2708 (23.8)	447 (11.8)
IBD medications since July 1, 2005				
Incident cases since July 1, 2005	28,361 (71.8)	16,930 (69.6)	8250 (72.5)	3181 (83.7)
Never thiopurine or anti-TNF	18,597 (65.6)	12,330 (72.8)	4182 (50.7)	2085 (65.5)
Only thiopurine	7367 (26.0)	3591 (21.2)	2929 (35.5)	847 (26.6)
Thiopurine and anti-TNF	2079 (7.3)	859 (5.1)	1008 (12.2)	212 (6.7)
Only anti-TNF	318 (1.1)	150 (0.9)	131 (1.6)	37 (1.2)

Downloaded from https://academic.oup.com/ibdjournal/article/25/1/111/4996912 by guest on 20 March 2024

TABLE 3: Characteristics at End of Follow-up in Adult-Onset Inflammatory Bowel Disease Patients Diagnosed in Sweden Since 2002, Followed up Through 2014, No. (%) if not Otherwise Stated

	PD After IBD	No PD	*P*
UC	64 (62.1)	22,688 (57.6)	0.402
CD	27 (26.2)	12,396 (31.5)	0.300
IBD-U	12 (11.7)	4330 (11.0)	0.954
Health care usage, mean (SD) No. visits during follow-up			
Total	23 (25)	23 (28)	0.843
Outpatient	19 (22)	20 (25)	0.511
Inpatient	4 (5)	3 (6)	0.073
Age at end of follow-up, y			
≥18–<40	1 (1.0)	13,091 (33.2)	<0.001
≥40–<50	0 (0.0)	6838 (17.3)	<0.001
≥50–<60	11 (10.7)	5821 (14.8)	0.303
≥60	91 (88.3)	13,664 (34.7)	<0.001
Maximum Montreal classification during follow-up			
No.	103	39,414	
E1 (ulcerative proctitis)	10 (13.2)	4640 (17.2)	0.438
E2 (left-sided UC)	14 (18.4)	6757 (25.0)	0.233
E3 (extensive colitis)	27 (35.5)	9652 (35.7)	1.000
EX (extent not defined)	22 (28.9)	5953 (22.0)	0.189
L1 (terminal ileum)	7 (17.9)	4515 (27.0)	0.275
L2 (colon)	13 (33.3)	5605 (33.5)	1.000
L3 or LX (ileocecal/not defined)	13 (33.3)	4920 (29.4)	0.719
P (perianal disease)	1 (2.6)	1412 (8.4)	0.302
Complications during follow-up			
Primary sclerosing cholangitis	0 (0.0)	740 (1.9)	0.298
Other extra-intestinal manifestations	0 (0.0)	1868 (4.7)	0.042
IBD surgery (not mutually exclusive categories)			
Colectomy	0 (0.0)	971 (2.5)	0.196
Other bowel surgery	12 (11.7)	5348 (13.6)	0.672
IBD medications since July 1, 2005			
Incident cases since July 1, 2005	56 (54.4)	28,305 (71.8)	
Never thiopurine or anti-TNF	49 (87.5)	18,548 (65.5)	<0.001
Only thiopurine	6 (10.7)	7361 (26.0)	0.014
Anti-TNF with or without thiopurine	1 (1.8)	2396 (8.5)	0.120

Comparison of those who developed Parkinson's disease with those who did not during follow-up. *P* values are from a *t* test for continuous variables and a chi-square test of proportions for categorical ones.

patients and 1.4 (95% CI, 1.1–1.9) for UC and 1.6 (95% CI, 1.1–2.3) for CD patients alone (Table 6). Although only 1 event was detected in patients diagnosed with IBD between 18 and 40 years of age, UC and CD patients diagnosed ≥60 years were at statistically significantly greater risk of having been diagnosed with PD before IBD, with ORs of 1.4 (95% CI, 1.1–1.9) and 1.7 (95% CI, 1.1–2.5), respectively. Interestingly, we observed a stronger association between PD and IBD in women than men (OR, 1.8; 95% CI, 1.3–2.3; vs OR, 1.2; 95% CI, 0.9–1.6), respectively (Table 6).

DISCUSSION

Main Findings

This nationwide population-based study of more than 39,000 patients with IBD found a 1.3-fold increased incidence of PD compared with the general population. We also observed an increased OR of being diagnosed with PD before IBD. The relative risk of future PD in IBD was highest among patients diagnosed with IBD at age 60 years or older. However, when adjusted for number of health care visits, the risk of PD in IBD patients was reduced, and an association was no longer observed.

Downloaded from https://academic.oup.com/ibdjournal/article/25/1/111/4996912 by guest on 20 March 2024

TABLE 4: Absolute Incidence Rates per 1000 Person-Years (95% CIs) for First-Ever Parkinson's Disease in Incident Cases of Adult-Onset Inflammatory Bowel Disease Patients and Matched General Population Reference Individuals From 2002 to 2014

	IBD	UC	CD	IBD-U	Gen. Pop.
Total No.	39,517	24,336	11,380	3801	387,960
No. events	103	69	23	11	830
Incidence proportion, %	0.3	0.3	0.2	0.3	0.2
Person-years	249,784.4	159,923.5	70,305.32	19,555.63	2,490,979
Incidence rate	0.4 (0.3–0.5)	0.4 (0.3–0.5)	0.3 (0.2–0.5)	0.6 (0.3–1.0)	0.3 (0.3–0.4)
Sex					
Female	0.4 (0.3–0.5)	0.4 (0.3–0.5)	0.3 (0.1–0.5)	0.6 (0.3–1.4)	0.3 (0.2–0.3)
Male	0.5 (0.4–0.6)	0.5 (0.3–0.6)	0.4 (0.2–0.7)	0.5 (0.2–1.2)	0.4 (0.4–0.4)
Age at first IBD diagnosis, y					
≥18–<40	0.0 (0.0–0.1)	0.0 (0.0–0.1)	0 (–)	0 (–)	0.0 (0.0–0.0)
≥40–<50	0.1 (0.0–0.3)	0.1 (0.0–0.3)	0.1 (0.0–0.6)	0 (–)	0.1 (0.1–0.1)
≥50–<60	0.4 (0.2–0.6)	0.5 (0.3–0.8)	0.2 (0.0–0.8)	0.3 (0.0–2.2)	0.3 (0.3–0.4)
≥60	1.6 (1.3–2.0)	1.6 (1.2–2.1)	1.4 (0.9–2.2)	2.2 (1.2–4.1)	1.2 (1.1–1.3)
Length of follow-up, y					
0–<1	0.4 (0.2–0.7)	0.6 (0.3–0.9)	0.2 (0.0–0.7)	0 (–)	0.3 (0.2–0.3)
1–<5	0.4 (0.3–0.5)	0.4 (0.3–0.6)	0.4 (0.2–0.7)	0.6 (0.3–1.3)	0.3 (0.3–0.4)
5–<10	0.4 (0.3–0.6)	0.4 (0.3–0.6)	0.3 (0.2–0.7)	1.0 (0.4–2.4)	0.4 (0.3–0.4)
≥10	0.5 (0.2–1.1)	0.8 (0.4–1.6)	0 (–)	0 (–)	0.3 (0.3–0.5)
Complications during follow-up					
Primary sclerosing cholangitis	0 (–)	0 (–)	0 (–)	0 (–)	–
Other extra-intestinal manifestations	0 (–)	0 (–)	0 (–)	0 (–)	–
IBD surgery					
Colectomy	0 (–)	0 (–)	0 (–)	0 (–)	–
Other bowel surgery	0.3 (0.2–0.6)	0.5 (0.2–1.0)	0.2 (0.1–0.6)	0.4 (0.1–2.6)	–
IBD medication					
No. incident cases since July 1, 2005	28,361	16,930	8250	3181	–
Never thiopurines or anti-TNF	0.6 (0.4–0.8)	0.5 (0.4–0.7)	0.8 (0.4–1.3)	0.8 (0.3–1.7)	–
Only thiopurine	0.2 (0.1–0.4)	0.2 (0.1–0.5)	0.2 (0.1–0.7)	0 (–)	–
Anti-TNF with or without thiopurines	0.1 (0.0–0.6)	0.2 (0.0–1.3)	0 (–)	0 (–)	–
At least 1 first-degree relative with:					
IBD	0.1 (0.0–0.3)	0.1 (0.0–0.4)	0 (–)	0 (–)	–
PD	0 (–)	0 (–)	0 (–)	0 (–)	–

Comparison With Previous Results

The incidence of PD has previously been investigated in patients with other immune-mediated disorders, such as psoriasis, rheumatoid arthritis, and diabetes.[34–36] A Taiwanese cohort study of psoriasis patients reported an increased risk of developing PD compared with the general population.[35] However, in a systemic review and meta-analysis on the association between diabetes and PD, no conclusive evidence between the 2 diseases was found.[36]

To our knowledge, the association between PD and IBD has only been investigated by 3 independent groups.[21–23] First, a Taiwanese retrospective cohort study observed a 1.35-fold higher risk for IBD patients to develop PD compared with the general population.[22] Male sex and comorbidities such as hypertension and coronary artery disease were independent risk factors of PD. This study was based on data from the Taiwanese National Health Insurance Database, and IBD patients were matched to 4 reference individuals (without IBD or PD history).

Second, a case-control study from the United States of newly diagnosed American PD patients and PD-free controls found an association between IBD and subsequent PD, with a prevalence of IBD in 2.9% of PD patients and 2.0% in the PD-free controls.[21] The study population was restricted to patients age >65 years and was based on Medicare data between 2004 and 2009, and hence was not representative of the general IBD population.

Downloaded from https://academic.oup.com/ibdjournal/article/25/1/111/4996912 by guest on 20 March 2024

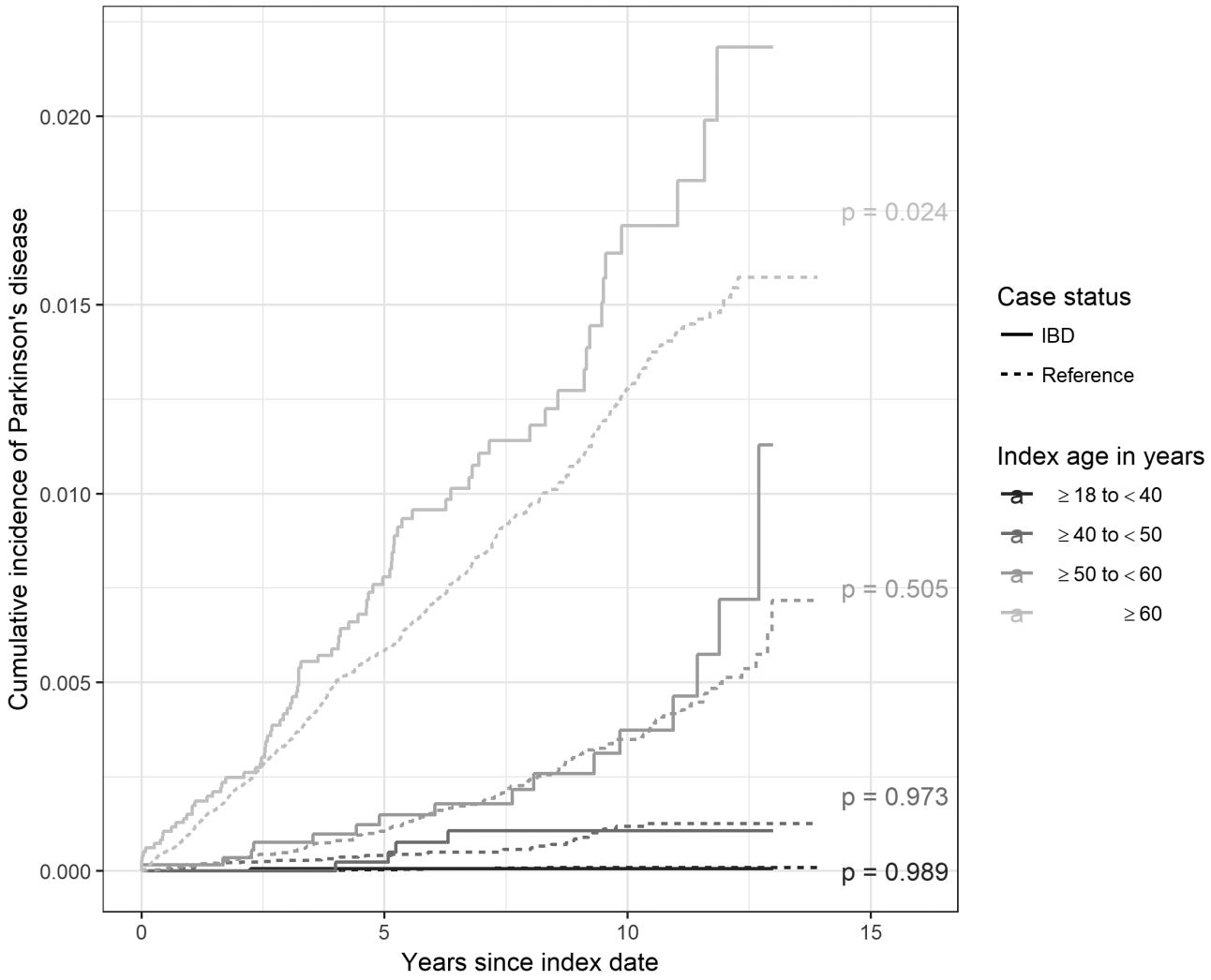

FIGURE 2. Cumulative incidence of Parkinson's disease since index date in IBD patients since 2002 and their matched reference individuals. Curves are stratified by age at first IBD diagnosis. *P* values are from log-rank tests stratified by age group.

Finally, a retrospective cohort study based on administrative claims databases from the United States observed a 28% higher incidence of PD in IBD patients compared with non-IBD controls.[23] Moreover, the group also reported an inverse association between anti-TNF exposure and development of PD.

Our study confirms the positive association between PD and IBD found in the aforementioned studies. The prevalence of PD in IBD patients was approximately 0.5% in our nationwide cohort, which is lower compared with the results generated by Lin et al. (1.3%)[22] and Camacho-Soto et al. (2.9%),[21] but higher than the prevalence reported by Peter et al. (0.3%).[23] Moreover, the HR of 1.3 found in our study was similar to that observed in the Taiwanese study and was statistically significant in both. Our study also confirmed the results generated by Peter et al.[23] when investigating the effect of anti-TNF therapy on the risk of PD development. Although Camacho-Soto et al.[21] investigated the association between IBD and later PD in a case-control design, our group studied both the association between IBD and later PD in a cohort design and the association between PD and later IBD in a case-control design.

Mechanism and Clinical Implications

The mechanism of PD development in IBD patients is not fully understood and is most likely multifactorial. The proinflammatory cytokines interleukin-1β and TNF-α have been suggested to be important effectors of neuroinflammation on degeneration of dopaminergic neurons in humans and mice models.[37, 38] In IBD, cytokines play an essential role by controlling multiple aspects of the inflammatory response.[19] During the last decades, medications targeting systemic inflammation through reduction in TNF-α activity or immunosuppression of key processes in T lymphocytes that lead to inflammation have been developed and used with success.[20, 39]

Downloaded from https://academic.oup.com/ibdjournal/article/25/1/111/4996912 by guest on 20 March 2024

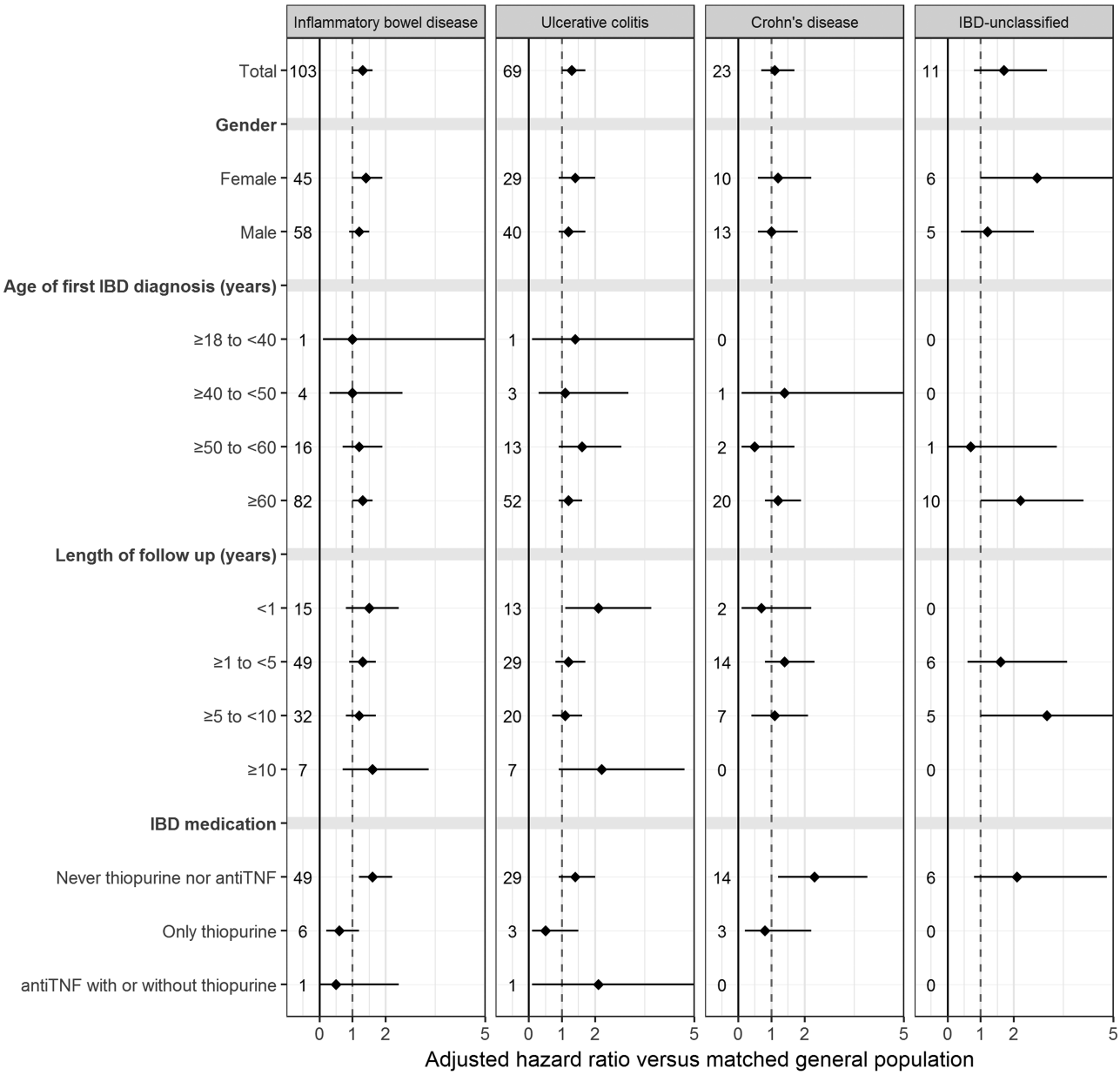

FIGURE 3. Hazard ratios (95% CIs) for first-ever Parkinson's disease in incident cases of adult-onset IBD patients and matched general population reference individuals between 2002 and 2014.

Our results suggested a potential protective effect of selective IBD-directed therapies, thiopurines, or anti-TNF-α on PD, as IBD patients never exposed to thiopurines or anti-TNF-α agents had a higher risk of developing PD compared with their matched reference individuals, whereas patients exposed to these drugs had a nonsignificantly decreased risk of PD. Similar results regarding a potential protective effect of anti-TNF therapy have been shown in the aforementioned study by Peter et al.[23] However, we did not have enough power to make any meaningful direct comparisons between IBD patients with different drug exposures. Any such comparisons in the future must also be adjusted for at least sex and age, as PD is predominantly diagnosed in the elderly and cases of elderly-onset IBD are to a much lesser extent exposed to thiopurines or anti-TNF-α agents.[2] Although the precise mechanism of any potential protection remains unclear and requires further investigation, reducing inflammatory processes has been suggested as promising for interventional targets for PD and other neurodegenerative diseases.[40]

Downloaded from https://academic.oup.com/ibdjournal/article/25/1/111/4996912 by guest on 20 March 2024

TABLE 5: Hazard Ratios (95% CIs) for First-Ever Parkinson's Disease in Incident Cases of Adult-Onset Inflammatory Bowel Disease Patients and Matched General Population Reference Individuals Between 2002 and 2014

	IBD	UC	CD	IBD-U
Total	0.9 (0.7–1.1)	0.8 (0.6–1.1)	0.9 (0.6–1.4)	1.0 (0.5–1.9)
Sex				
Female	1.0 (0.7–1.4)	0.9 (0.6–1.4)	1.0 (0.5–2.1)	1.6 (0.6–4.2)
Male	0.8 (0.6–1.0)	0.8 (0.6–1.1)	0.8 (0.4–1.5)	0.7 (0.3–1.8)
Age at IBD onset, y				
≥18–<40	0.9 (0.1–8.2)	1.0 (0.1–10.3)	0.0 (0.0–inf)	0.0 (0.0–inf)
≥40–<50	0.4 (0.1–1.3)	0.5 (0.1–1.6)	0.6 (0.1–5.5)	0.0 (0.0–inf)
≥50–<60	0.7 (0.4–1.2)	0.8 (0.4–1.6)	0.4 (0.1–1.7)	0.7 (0.1–5.6)
≥60	0.9 (0.7–1.2)	0.9 (0.6–1.2)	1.0 (0.6–1.7)	1.2 (0.6–2.4)

Model is adjusted for number of medical care visits as a time-dependent covariate.

TABLE 6: Odds Ratios (95% CIs) for Being Diagnosed With Parkinson's Disease Since January 1, 1964, Before a First-Ever Diagnosis of Inflammatory Bowel Disease (or Index Date in Matched General Population Controls) in Sweden Between 2002 and 2014

	IBD	UC	CD	IBD-U
	No.,[a] OR (95% CI)	No.,[a] OR (95% CI)	No.,[a] OR (95% CI)	No.,[a] OR (95% CI)
Total	102, 1.4 (1.2–1.8)	64, 1.4 (1.1–1.9)	30, 1.6 (1.1–2.3)	8, 1.1 (0.5–2.3)
Sex				
Female	54, 1.8 (1.3–2.3)	37, 2.0 (1.4–2.9)	11, 1.2 (0.7–2.3)	6, 1.7 (0.7–4.1)
Male	48, 1.2 (0.9–1.6)	27, 1.0 (0.7–1.5)	19, 1.9 (1.1–3.1)	2, 0.5 (0.1–2.2)
Age at IBD onset, y				
≥18–<40	1, 1.4 (0.2–11.6)	0, 0.0 (0.0–inf)	0, 0.0 (0.0–inf)	1, inf (0.0–inf)
≥40–<50	3, 2.3 (0.7–8.1)	2, 2.9 (0.6–13.8)	1, 2.0 (0.2–17.2)	0, 0.0 (0.0–inf)
≥50–<60	5, 0.9 (0.4–2.4)	5, 1.4 (0.5–3.5)	0, 0.0 (0.0–inf)	0, 0.0 (0.0–inf)
≥60	93, 1.5 (1.2–1.8)	57, 1.4 (1.1–1.9)	29, 1.7 (1.1–2.5)	7, 1.1 (0.5–2.3)
At least 1 first-degree relative with:				
IBD	3, 1.0 (0.3–3.4)	2, 0.9 (0.2–3.9)	1, 2.6 (0.3–25.0)	0, 0.0 (0.0–inf)
PD	0, 0.0 (0.0–inf)	0, 0.0 (0.0–inf)	0, 0.0 (0.0–inf)	0, 0.0 (0.0–inf)

[a]"No." indicates exposed inflammatory bowel disease cases.

However, in our study, the increased risk of developing PD vanished when adjusting for number of health care visits. This phenomenon is often referred to as surveillance bias, based on the idea "the more we look, the more we find."[41] Surveillance bias is an important and well-known source of error when evaluating outcome measures, although it is seldom included in published clinical studies.[42] Therefore, the association observed in the present study might to some extent be explained by this phenomenon. On the other hand, our case-control analysis also found an increased odds ratio of IBD patients being diagnosed with PD before IBD, which strengthens the notion that IBD and PD share risk factors.

Strengths and Limitations

Two of the most important strengths of our study are the number of participants and the reliability of our data source. Our study included more than 39,000 IBD patients who were identified in the NPR by a minimum of 2 diagnostic listings. This approach has recently been validated in the Swedish patient register, with a positive predictive value for a diagnosis of IBD of 93%.[31] The NPR was established in 1964 and contains outpatient data from 2001, and as PD is often used as an outpatient diagnosis, we allowed a 1-year washout period and included patients from 2002 to 2014 to ensure that only incident cases were included. Another strength of our study is the virtually complete coverage of

Downloaded from https://academic.oup.com/ibdjournal/article/25/1/111/4996912 by guest on 20 March 2024

the NPR in a setting with universal access to health care (regardless of income, severity of disease, or place of residence) and access to reference individuals by the total population register, which results in optimal generalizability.

Our study shares a limitation with previous studies, as Swedish nationwide registers only contain data on smoking in early pregnancy. Therefore, we have not been able to stratify for smoking in our analyses. As smoking protects against UC and PD but increases the risk of CD, smoking might be considered a confounder in the positive association between PD and UC. Moreover, we were not able to identify a particular IBD subphenotype and severity among PD patients We excluded IBD cases with age of onset <18 years, as the length of available follow-up (12 years) was considered too short for evaluating the risk of PD development. Also, we had no access to DNA samples to test whether individuals with IBD-PD comorbidity were more likely to carry polymorphisms in genes associated with IBD and/or PD.

Conclusion

We demonstrated that incident IBD was associated with an increased relative risk of incident PD. We also observed that PD was a risk factor for future IBD. These findings are pathophysiologically interesting, even though the absolute excess risk compared with the general population was small. When adjusting for number of health care visits, the increased risk of incident PD in IBD patients disappeared. The positive association between IBD and PD found in previous studies might therefore, to some extent, be explained by surveillance bias. Future studies need to take this into account when investigating the correlation between IBD and PD.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

REFERENCES

1. Duricova D, Burisch J, Jess T, et al; ECCO-EpiCom. Age-related differences in presentation and course of inflammatory bowel disease: an update on the population-based literature. *J Crohns Colitis*. 2014;8:1351–1361.
2. Everhov ÅH, Halfvarson J, Myrelid P, et al. Incidence and treatment of patients diagnosed with inflammatory bowel diseases at 60 years or older in Sweden. *Gastroenterology*. 2018;154:518–528.e15.
3. Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med*. 2009;361:2066–2078.
4. Neurath MF. Current and emerging therapeutic targets for IBD. *Nat Rev Gastroenterol Hepatol*. 2017;14:269–278.
5. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet*. 2018;390:2769–2778.
6. Burisch J, Jess T, Martinato M, et al; ECCO -EpiCom. The burden of inflammatory bowel disease in Europe. *J Crohns Colitis*. 2013;7:322–337.
7. Jostins L, Ripke S, Weersma RK, et al; International IBD Genetics Consortium (IIBDGC). Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature*. 2012;491:119–124.
8. Liu JZ, van Sommeren S, Huang H, et al; International Multiple Sclerosis Genetics Consortium; International IBD Genetics Consortium. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet*. 2015;47:979–986.
9. Bialecka M, Kurzawski M, Klodowska-Duda G, et al. CARD15 variants in patients with sporadic Parkinson's disease. *Neurosci Res*. 2007;57:473–476.
10. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. *J Neural Transm (Vienna)*. 2017;124:901–905.
11. Franke A, McGovern DP, Barrett JC, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat Genet*. 2010;42:1118–1125.
12. Hui KY, Fernandez-Hernandez H, Hu J, et al. Functional variants in the LRRK2 gene confer shared effects on risk for Crohn's disease and Parkinson's disease. *Sci Transl Med*. In press.
13. Ross OA, Soto-Ortolaza AI, Heckman MG, et al; Genetic Epidemiology Of Parkinson's Disease (GEO-PD) Consortium. Association of LRRK2 exonic variants with susceptibility to Parkinson's disease: a case-control study. *Lancet Neurol*. 2011;10:898–908.
14. Long WY, Chen L, Zhang CL, et al. Association between NOD2/CARD15 gene polymorphisms and Crohn's disease in Chinese Zhuang patients. *World J Gastroenterol*. 2014;20:4737–4744.
15. Ma Q, An X, Li Z, et al. P268S in NOD2 associates with susceptibility to Parkinson's disease in Chinese population. *Behav Brain Funct*. 2013;9:19.
16. Goyette P, Boucher G, Mallon D, et al; International Inflammatory Bowel Disease Genetics Consortium; Australia and New Zealand IBDGC; Belgium IBD Genetics Consortium; Italian Group for IBD Genetic Consortium; NIDDK Inflammatory Bowel Disease Genetics Consortium; United Kingdom IBDGC; Wellcome Trust Case Control Consortium; Quebec IBD Genetics Consortium. High-density mapping of the MHC identifies a shared role for HLA-DRB1*01:03 in inflammatory bowel diseases and heterozygous advantage in ulcerative colitis. *Nat Genet*. 2015;47:172–179.
17. Ferrari R, Wang Y, Vandrovcova J, et al; International FTD-Genomics Consortium (IFGC), International Parkinson's Disease Genomics Consortium (IPDGC), International Genomics of Alzheimer's Project (IGAP). Genetic architecture of sporadic frontotemporal dementia and overlap with Alzheimer's and Parkinson's diseases. *J Neurol Neurosurg Psychiatry*. 2017;88:152–164.
18. Leal MC, Casabona JC, Puntel M, et al. Interleukin-1β and tumor necrosis factor-α: reliable targets for protective therapies in Parkinson's disease? *Front Cell Neurosci*. 2013;7:53.
19. Neurath MF. Cytokines in inflammatory bowel disease. *Nat Rev Immunol*. 2014;14:329–342.
20. Neurath MF. New targets for mucosal healing and therapy in inflammatory bowel diseases. *Mucosal Immunol*. 2014;7:6–19.
21. Camacho-Soto A, Gross A, Searles Nielsen S, et al. Inflammatory bowel disease and risk of Parkinson's disease in Medicare beneficiaries. *Parkinsonism Relat Disord*. In press.
22. Lin JC, Lin CS, Hsu CW, et al. Association between Parkinson's disease and inflammatory bowel disease: a nationwide Taiwanese retrospective cohort study. *Inflamm Bowel Dis*. 2016;22:1049–1055.
23. Peter I, Dubinsky M, Bressman S, et al. Anti-tumor necrosis factor therapy and the incidence of Parkinson disease among patients with inflammatory bowel disease. *JAMA Neurol*. In press.
24. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, et al. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol*. 2009;24:659–667.
25. Ludvigsson JF, Almqvist C, Bonamy AK, et al. Registers of the Swedish total population and their use in medical research. *Eur J Epidemiol*. 2016;31:125–136.
26. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11:450.
27. Wettermark B, Hammar N, Fored CM, et al. The new swedish prescribed drug register–opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf*. 2007;16:726–735.
28. Neovius M, Sundström A, Simard J, et al; ARTIS Study Group. Small-area variations in sales of TNF inhibitors in Sweden between 2000 and 2009. *Scand J Rheumatol*. 2011;40:8–15.
29. Ekbom A. The Swedish multi-generation register. *Methods Mol Biol*. 2011;675:215–220.
30. Lophaven SN, Lynge E, Burisch J. The incidence of inflammatory bowel disease in Denmark 1980–2013: a nationwide cohort study. *Aliment Pharmacol Ther*. 2017;45:961–972.
31. Jakobsson GL, Sternegård E, Olén O, et al. Validating inflammatory bowel disease (IBD) in the Swedish National Patient Register and the Swedish Quality Register for IBD (SWIBREG). *Scand J Gastroenterol*. 2017;52:216–221.
32. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a working party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol*. 2005;19(Suppl A):5A–36A.
33. Olén O, Askling J, Sachs MC, et al. Childhood onset inflammatory bowel disease and risk of cancer: a Swedish nationwide cohort study 1964–2014. *BMJ*. 2017;358:j3951.
34. Rugbjerg K, Friis S, Ritz B, et al. Autoimmune disease and risk for Parkinson disease: a population-based case-control study. *Neurology*. 2009;73:1462–1468.

Downloaded from https://academic.oup.com/ibdjournal/article/25/1/111/4996912 by guest on 20 March 2024

35. Sheu JJ, Wang KH, Lin HC, et al. Psoriasis is associated with an increased risk of Parkinsonism: a population-based 5-year follow-up study. *J Am Acad Dermatol*. 2013;68:992–999.
36. Cereda E, Barichella M, Pedrolli C, et al. Diabetes and risk of Parkinson's disease: a systematic review and meta-analysis. *Diabetes Care*. 2011;34:2614–2623.
37. Meredith GE, Rademacher DJ. MPTP mouse models of Parkinson's disease: an update. *J Parkinsons Dis*. 2011;1:19–33.
38. Mogi M, Harada M, Riederer P, et al. Tumor necrosis factor-alpha (TNF-alpha) increases both in the brain and in the cerebrospinal fluid from Parkinsonian patients. *Neurosci Lett*. 1994;165:208–210.
39. Neurath M. Thiopurines in IBD: what is their mechanism of action? *Gastroenterol Hepatol (N Y)*. 2010;6:435–436.
40. Wang Q, Liu Y, Zhou J. Neuroinflammation in Parkinson's disease and its potential as therapeutic target. *Transl Neurodegener*. 2015;4:19.
41. Pierce CA, Haut ER, Kardooni S, et al. Surveillance bias and deep vein thrombosis in the national trauma data bank: the more we look, the more we find. *J Trauma*. 2008;64:932–936; discussion 936.
42. Haut ER, Pronovost PJ. Surveillance bias in outcomes reporting. *JAMA*. 2011;305:2462–2463.

Downloaded from https://academic.oup.com/ibdjournal/article/25/1/111/4996912 by guest on 20 March 2024