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Anti–Tumor Necrosis Factor Therapy and Incidence of Parkinson Disease Among Patients With Inflammatory Bowel Disease

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IMPORTANCE Despite established genetic and pathophysiologic links between inflammatory bowel disease (IBD) and Parkinson disease (PD), clinical data supporting this association remain scarce. Although systemic inflammation is considered a potential biological mechanism shared between the 2 diseases, the role of reduced systemic inflammation through IBD-directed anti–tumor necrosis factor (anti-TNF) therapy in PD risk is largely unknown.

OBJECTIVE To compare the incidence of PD among individuals with or without IBD and to assess whether PD risk among patients with IBD is altered by anti-TNF therapy.

DESIGN, SETTING, AND PARTICIPANTS This is a retrospective cohort study analyzing information in the Truven Health MarketScan administrative claims database and the Medicare Supplemental Database between January 1, 2000, and March 31, 2016. Individuals were selected who had at least 2 claims for IBD diagnoses, at least 6 months of follow-up, and no prior diagnosis of PD on or before the IBD index date. Exposure to Anti-TNF therapy was measured from the anti-TNF index date to the last date of anti-TNF coverage or the end of enrollment or PD index date, whichever was earliest. Incidence rates per 1000 person-years were calculated, and crude and adjusted incidence rate ratios were estimated by Poisson regression models and presented with 95% CIs.

MAIN OUTCOMES AND MEASURES Incidence of PD among patients with IBD with or without exposure to anti-TNF therapy.

RESULTS In total, 144 018 individuals with IBD were matched on age, sex, and year of index date with 720 090 unaffected controls. Of them, 1796 individuals had at least 2 PD diagnoses and at least 1 filled PD-related prescription. The mean (SD) age of individuals with IBD was 51 (17) years, and 44% were men. The incidence of PD among patients with IBD was 28% higher than that among unaffected matched controls (adjusted incidence rate ratio, 1.28; 95% CI, 1.14-1.44; $P < .001$). A 78% reduction in the incidence rate of PD was detected among patients with IBD who were exposed to anti-TNF therapy compared with those who were not exposed (adjusted incidence rate ratio, 0.22; 95% CI, 0.05-0.88; $P = .03$).

CONCLUSIONS AND RELEVANCE A higher incidence of PD was observed among patients with IBD than among individuals without IBD. Early exposure to antiinflammatory anti-TNF therapy was associated with substantially reduced PD incidence. These findings support a role of systemic inflammation in the pathogenesis of both diseases. Further studies are required to determine whether anti-TNF treatment administered to high-risk individuals may mitigate PD risk.

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Supplemental content

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Recent advances in the fields of genetics and genomics have identified thousands of variants at genomic loci associated with numerous complex diseases and traits. Substantial evidence has emerged for genetic pleiotropy, meaning a single gene contributing to multiple phenotypic traits, igniting a search for pathophysiologically associated diseases.[1] Consequently, a shared genetic basis has been reported for autoimmune diseases,[2] psychiatric disorders,[3] cancers and metabolic and inflammatory traits,[4,5] neurodegenerative, psychiatric, and immune-related diseases,[6-8] hematologic and blood pressure traits,[9] cardiovascular disease risk factors,[10,11] and bone-related traits,[12] among others, suggesting that following the leads for shared genetic risks may provide novel, comparative insight into underlying biological mechanisms across various conditions.

One example that has attracted considerable attention is the gene for the multifunctional leucine-rich repeat kinase 2 (*LRRK2*) because variants in this gene are recognized as risk factors for Parkinson disease (PD). Parkinson disease is a multifactorial neurodegenerative movement disorder characterized clinically by resting tremor, bradykinesia, rigidity, and postural instability[13,14]; it ranks among the most common late-life neurodegenerative diseases, affecting approximately 1% to 2% of people 60 years or older. Variations in the *LRRK2* locus have been recently independently linked to Crohn disease (CD)[15] and other conditions (for review, see Bae and Lee[15]). Ulcerative colitis (UC) and CD are types of inflammatory bowel disease (IBD), a complex chronic disorder resulting from impaired regulation of intestinal mucosal immune responses among genetically susceptible individuals.[16-18] More than 1.8 million adults in the United States are reportedly affected with IBD,[19] with most diagnosed before age 35. Patients with IBD usually present with recurrent abdominal pain, diarrhea, rectal bleeding, weight loss, or anemia. Most commonly, CD affects the ileum or colon, whereas UC involves the colon only and is confined to the mucosa. In a large case-control study,[20] we previously identified in a cohort of more than 24 500 individuals numerous *LRRK2* variants that are independently associated with PD and CD, further supporting shared biological mechanisms associated with the development of these 2 seemingly unrelated diseases.

Experimental data suggest that *LRRK2* is an important modulator in the immune system, pathophysiologically linking PD and IBD. Specifically, numerous studies have pointed toward the role of neuroinflammation in PD pathogenesis and progression and have reported elevated levels of proinflammatory mediators in the cerebrospinal fluid, striatum, and substantia nigra of experimental animal models and of postmortem brains from patients with PD (for review, see Olmos and Lladó[21]). Likewise, systemic inflammation and impaired autophagy have also been identified as crucial components of IBD pathogenesis.[22,23] Reducing inflammation is a major therapeutic target of IBD therapy.

However, despite consistent genetic and functional connections established between PD and IBD, clinical data on comorbid IBD and PD remain scarce. The goal of this retrospective cohort study was to assess the incidence of PD among patients with IBD and to identify whether IBD treatment with anti–tumor necrosis factor (anti-TNF) alters the risk of PD. A better understanding of the clinical link between IBD and PD may provide refined insight into the pathogenesis of both diseases and may have significant implications for the treatment and prevention of PD.

Key Points

Question Among patients with inflammatory bowel disease, what is the incidence of Parkinson disease, and does earlier exposure to anti–tumor necrosis factor therapy mitigate their risk of Parkinson disease?

Findings In this cohort study analyzing administrative claims from more than 170 million health care–covered lives, patients with inflammatory bowel disease were 28% more likely than matched individuals without inflammatory bowel disease to develop Parkinson disease. Patients with inflammatory bowel disease exposed to antitumor necrosis factor therapy had a 78% reduction in Parkinson disease incidence rates compared with unexposed patients.

Meaning Reducing systemic inflammation in at-risk individuals may decrease the incidence of Parkinson disease.

Methods

Data Sources

Data for the study were drawn from 2 large administrative claims databases: the Truven Health MarketScan Commercial Database and the Medicare Supplemental Database. The former contains the inpatient, outpatient, and outpatient prescription drug experience of employees and their dependents from all US census regions who are covered under a variety of fee-for-service and capitated health plans, including exclusive provider organization, preferred provider organization, and point of service plans as well as indemnity plans and health maintenance organization plans. The Medicare Supplemental Database contains the health care experience of individuals with Medicare supplemental insurance paid for by employers. Both the Medicare-covered portion of payment and the employer-paid portion are included in this database. The MarketScan Commercial and Medicare databases included in the present study span from January 1, 2000, to March 31, 2016. The MarketScan Commercial database contained 163.2 million covered lives across the entire period, whereas the Medicare database included 12.6 million covered lives in the same period. The data were fully deidentified prior to analysis in compliance with Health Insurance Portability and Accountability Act regulations; thus, neither institutional review board approval nor informed patient consent was sought or required.

Study Participants

From the health care claims databases, we selected patients with IBD who were at least 18 years old. Inflammatory bowel disease was defined as at least 2 claims of *International Classification of Diseases, Ninth Revision* (*ICD-9*) diagnosis codes

(CD, 555.xx; UC, 556.xx) or *Tenth Revision* (*ICD-10*) diagnosis codes (CD, K50.x; UC, K51.x). To distinguish between UC and CD, the disease associated with the majority of the participant's inpatient claims was used. If a distinction could not be made using only inpatient claims, then the disease associated with the majority of the outpatient claims was used. If a distinction could not be made using these criteria, the case was designated as indeterminate IBD.

Patients with IBD were required to have enrollment with medical and pharmacy benefits for at least 12 months before the IBD index date (preperiod), defined as first date of diagnosis for IBD, and at least 6 months after the index date (postperiod). Cases and controls were excluded if they had any PD-related claims on or before the IBD index date. The non-IBD controls were each randomly assigned an index date based on the distribution of IBD index dates. The non-IBD controls were required to have enrollment with medical and pharmacy benefits for at least 12 months before the assigned index date and at least 6 months after the assigned index date, and no PD-related claims on or before the assigned index dates. We selected unaffected controls using a 1:5 ratio to match the IBD cohort to a non-IBD cohort on age, sex, and index year of IBD.

The anti-TNF therapies included in this analysis were adalimumab, certolizumab, golimumab, and infliximab. Person-time attributed to the anti-TNF cohort started from the anti-TNF index date to the last date of anti-TNF coverage or end of enrollment or PD index date, whichever was earliest. Person-time attributed to the non-anti-TNF cohort included (1) person-time for individuals who had never used anti-TNF and (2) person-time before the anti-TNF index date and after the last anti-TNF coverage date for anti-TNF users. Individuals were allowed to contribute person-time to both anti-TNF and non-anti-TNF cohorts, given the relatively acute reduction of systemic inflammation by anti-TNFs owing to its 1- to 2-week half-life.

Study Outcomes

Parkinson disease was defined as at least 2 claims for PD (*ICD-9* code, G20; and *ICD-10* code, 332.0) and at least 1 prescription claim for therapy associated with PD. We defined PD therapy as levodopa, carbidopa, or the carbidopa-levodopa combination; amantadine; dopamine agonists apomorphine, bromocriptine, rotigotine, ropinirole, and pramipexole; monoamine oxidase B inhibitors selegiline, rasagiline, and safinamide; anticholinergic drugs benztropine mesylate, trihexyphenidyl hydrochloride, orphenadrine citrate, and procyclidine hydrochloride; or catechol *O*-methyltransferase inhibitors entacapone and tolcapone. Participants were followed up until a PD event, the end of enrollment, or March 31, 2016, whichever was earliest.

Statistical Analysis

The incidence rate ratio (IRR) of PD in the IBD cohort vs the non-IBD cohort was measured using Poisson regression, adjusting for time-varying age group and sex, and offset by time at risk. Subgroup analyses were performed comparing patients with CD or UC with their respective matched controls. The analyses followed all individuals from the IBD index date to the end of enrollment or to the PD index date, whichever was earliest.

The IRR of PD during the anti-TNF–exposure time vs the non–anti-TNF time for patients with IBD was measured using Poisson regression, adjusting for sex and time-varying age group, and offset by TNF exposure time or non-exposure time. All data management and analyses were performed using SAS, version 9.4 (SAS Institute Inc). Two-sided values of $P < .05$ were considered statistically significant.

Results

Between January 1, 2000, and March 31, 2016, the MarketScan Commercial and Medicare databases included 657 637 patients who had received at least 2 IBD diagnoses (eTable 1 in the Supplement). Of them, 144 018 (21.9%) (84 436 with UC [58.6%], 56 507 with CD [39.2%], and 3075 with indeterminate IBD [2.1%]) were at least 18 years old on the IBD index date, had at least 12 months of enrollment with medical and pharmacy benefits before the IBD index date, had at least 6 months of follow-up, and had no prior PD on or before the IBD index date. The patients with IBD were matched on age, sex, and year of index date to 720 090 unaffected controls. Among the 864 108 individuals included in the study (both those with or without IBD), 1796 patients (0.2%) were identified as having PD. Patients with IBD were more likely to reside in the Northeast but were otherwise well matched on age, sex, and index year with the non-IBD study participants (**Table 1**). Follow-up times did not differ by IBD status after stratification by PD status. We found a statistically significant 28% increase in the incidence of PD among patients with IBD compared with the unaffected matched controls, after adjusting for age and sex (**Table 2**, **Figure**). The increased rate of PD was observed equally among patients with CD (adjusted IRR, 1.26; 95% CI, 1.03-1.53; $P = .02$) and among those with UC (adjusted IRR, 1.31; 95% CI, 1.14-1.51; $P < .001$; Table 2). Compared with non-IBD controls, a greater proportion of men with IBD developed PD (0.34% vs 0.25%). The proportion of women with or without IBD who developed PD was similar (0.19% vs 0.16%). In addition, 13 089 patients with IBD were exposed to anti-TNF therapy on or after the IBD index date. We observed a markedly lower PD incidence rate (0.08 per 1000 patient-years) among patients with IBD who were exposed to anti-TNF therapy compared with patients with IBD who were not exposed to anti-TNF therapy (0.76 per 1000 patient-years) (**Table 3**). Furthermore, a 78% reduction in the PD incidence rate was observed after adjustment for time-varying age group and sex (Table 3).

Discussion

In this study, we used 2 large health care administrative claim databases consisting of more than 170 million covered lives to assess the genetic and pathogenic links between IBD and PD. We detected a 28% higher incidence of PD among patients

Table 1. Demographic Characteristics

Characteristic	All Persons With IBD (n = 144 018)	Persons With CD (n = 56 507)	Persons With UC (n = 84 436)	Persons Without IBD[a] (n = 720 090)
Index age, y, No. (%)				
18-39	38 052 (26.4)	16 978 (30.0)	20 319 (24.1)	190 260 (26.4)
40-49	28 069 (19.5)	11 232 (19.9)	16 266 (19.3)	140 345 (19.5)
50-64	49 929 (34.7)	19 093 (33.8)	29 719 (35.2)	249 645 (34.7)
≥65	27 968 (19.4)	9204 (16.3)	18 132 (21.5)	139 840 (19.4)
Mean (SD)	50.8 (16.8)	48.9 (16.7)	52.0 (16.7)	50.8 (16.8)
Sex, No. (%)				
Male	62 827 (43.6)	24 013 (42.5)	37 590 (44.5)	314 135 (43.6)
Female	81 191 (56.4)	32 494 (57.5)	46 846 (55.5)	405 955 (56.4)
Index year, No. (%)				
2001	2622 (1.8)	975 (1.7)	1578 (1.9)	13 110 (1.8)
2002	3899 (2.7)	1473 (2.6)	2337 (2.8)	19 495 (2.7)
2003	5750 (4.0)	2227 (3.9)	3393 (4.0)	28 750 (4.0)
2004	7829 (5.4)	2910 (5.1)	4752 (5.6)	39 145 (5.4)
2005	8646 (6.0)	3303 (5.8)	5157 (6.1)	43 230 (6.0)
2006	7187 (5.0)	2752 (4.9)	4274 (5.1)	35 935 (5.0)
2007	7204 (5.0)	2781 (4.9)	4264 (5.0)	36 020 (5.0)
2008	10 030 (7.0)	3857 (6.8)	5938 (7.0)	50 150 (7.0)
2009	12 770 (8.9)	5082 (9.0)	7439 (8.8)	63 850 (8.9)
2010	13 046 (9.1)	5055 (8.9)	7706 (9.1)	65 230 (9.1)
2011	15 932 (11.1)	6368 (11.3)	9236 (10.9)	79 660 (11.1)
2012	15 363 (10.7)	6093 (10.8)	8939 (10.6)	76 815 (10.7)
2013	12 704 (8.8)	5143 (9.1)	7309 (8.7)	63 520 (8.8)
2014	12 891 (9.0)	5256 (9.3)	7356 (8.7)	64 455 (9.0)
2015	8145 (5.7)	3232 (5.7)	4758 (5.6)	40 725 (5.7)
US Geographic region, No. (%)				
Northeast	25 266 (17.5)	9941 (17.6)	14 681 (17.4)	96 497 (13.4)
North central	38 521 (26.7)	15 455 (27.4)	22 264 (26.4)	195 198 (27.1)
South	52 557 (36.5)	21 050 (37.3)	30 416 (36.0)	278 519 (38.7)
West	26 595 (18.5)	9570 (16.9)	16 510 (19.6)	144 756 (20.1)
Unknown	1079 (0.7)	491 (0.9)	565 (0.7)	5120 (0.7)

Abbreviations: CD, Crohn disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

[a] Each person in the IBD cohort was matched on age, sex, and index year of IBD to 5 persons in the non-IBD cohort.

Table 2. Incidence of PD in Persons With IBD and in Matched Persons Without IBD

Variable	PD Event	Person-years[a]	Rate[b]	Univariate Poisson Model[c]		Multivariate Poisson Model[d]	
				Crude IR (95% CI)	*P* Value	Adjusted IR (95% CI)	*P* Value
All IBD							
Yes	371	508 033	0.73	1.28 (1.14-1.44)	<.001	1.28 (1.14-1.44)	<.001
Controls	1425	2 500 792	0.57	1 [Reference]		1 [Reference]	
Crohn disease							
Yes	122	194 865	0.63	1.26 (1.03-1.54)	.02	1.26 (1.03-1.53)	.02
Controls	480	966 379	0.50	1 [Reference]		1 [Reference]	
Ulcerative colitis							
Yes	243	302 512	0.80	1.30 (1.13-1.5)	<.001	1.31 (1.14-1.51)	<.001
Controls	913	1 480 956	0.62	1 [Reference]		1 [Reference]	

Abbreviations: IBD, inflammatory bowel disease; IR, incidence rate; PD, Parkinson disease.

[a] Crohn disease and ulcerative colitis stratified person-years do not add up to all IBD person-years because undetermined IBD cases are not presented.

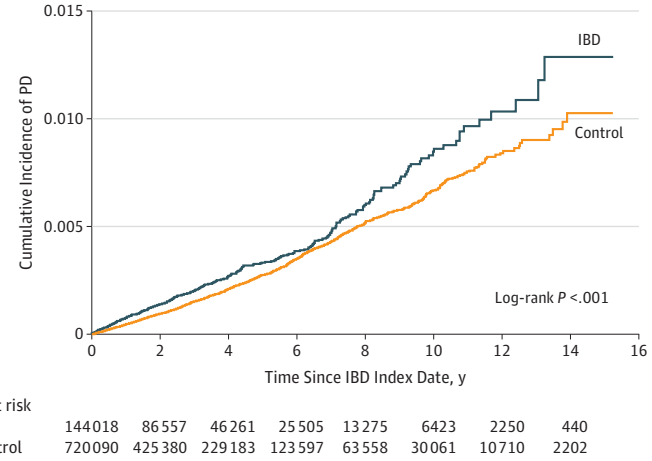
[b] Incidence rate per 1000 person-years.

[c] Analysis of patients with IBD vs matched controls, offset by time.

[d] Analysis adjusted for time-varying age group and sex, and offset by time.

with IBD compared with age-, sex-, and IBD index year–matched individuals without IBD. This association was observed for individuals with CD or UC. These findings support a previous report[24] from a Taiwanese National Registry showing a 35% increased incidence of PD among patients with IBD in a nationwide population-based cohort. Furthermore, we showed that those patients with IBD who were prescribed anti-TNF therapy had a lower risk of developing PD than those patients

Figure. Cumulative Incidence of Parkinson Disease (PD) Among Patients With or Without Inflammatory Bowel Disease (IBD)



No. at risk

IBD	144 018	86 557	46 261	25 505	13 275	6423	2250	440
Control	720 090	425 380	229 183	123 597	63 558	30 061	10 710	2202

Table 3. Incidence Analysis of PD Among Patients With IBD by Anti-TNF Exposure

				Univariate Poisson Model[c]		Multivariate Poisson Model[d]	
Anti-TNF Exposure[a]	PD Event	Person-years	Rate[b]	Crude IRR (95% CI)	*P* Value	Adjusted IRR (95% CI)	*P* Value
Yes	2	23 610	0.08	0.11 (0.03-0.45)	.002	0.22 (0.05-0.88)	.03
No	369	484 423	0.76	1 [Reference]		1 [Reference]	

Abbreviations: anti-TNF, anti–tumor necrosis factor; IBD, inflammatory bowel disease; IRR, incidence rate ratio; PD, Parkinson disease.

[a] Anti-TNF exposure status was defined as yes for all days from anti-TNF exposure index date to last date of anti-TNF exposure coverage or end of enrollment or PD index date, whichever was earliest; otherwise the anti-TNF exposure status was defined as no.

[b] Incidence rate per 1000 person-years.

[c] Unadjusted incidence ratio, offset by time.

[d] Model adjusted for time-varying age group and sex, and offset by time.

with IBD who were not prescribed anti-TNF therapy. Although our study design does not allow for inferring causality, we hypothesize that a reduction of systemic inflammation contributed to the observed association.

The exact mechanism of PD development among patients with IBD is still unknown; however, some studies have suggested that inflammation is a risk factor for PD and that pathology is initiated in the intestine decades before progressing to the central nervous system. Systemic inflammation, which is a major component of IBD, is also thought to contribute to neuronal inflammation and dopaminergic neuron loss in PD through infiltration and accumulation of immune cells from the periphery (systemic inflammation). Intraperitoneal injection of bacterial lipopolysaccharide—shown to produce a systemic immune response in mice and to increase intestinal permeability, an important pathogenic factor of IBD,[25]—has also resulted in microglial activation and dopaminergic neuron loss.[26] Because lipopolysaccharide cannot enter the brain,[27] increased systemic cytokine production in response to the administered lipopolysaccharide likely contributes to neuroinflammation via proinflammatory cytokine (interleukin 1 [IL-1] and TNF) transport across the blood-brain barrier.[28] In addition, postmortem analyses of human samples and experimental animal studies have indicated that activation of glial cells and increases in proinflammatory factor levels, such as for TNF, IL-1β, IL-2, IL-4, and IL-6[29] (regional inflammation), are also common features of the PD brain. The proinflammatory cytokine profiles observed in the cerebrospinal fluid and peripheral blood, as well as in the striatum and substantia nigra pars compacta of patients with PD and of animals modeling PD,[30,31] including an increase in the expression of TNF, IL-1β, and IL-6, among others, are remarkably identical to those observed in patients with IBD.[29,32]

Anti-TNF therapies are currently approved as a standard treatment of a number of autoimmune disorders, including both CD and UC.[33,34] Current therapies for PD are focused on ameliorating symptoms, although investigative studies targeting underlying molecular mechanisms and disease modification are actively under way. Reducing inflammatory processes has been suggested as promising interventional targets for PD and other neurodegenerative diseases.[35,36] Clinical trials examining the effects of TNF inhibition among patients with multiple sclerosis, Alzheimer disease, or amyotrophic lateral sclerosis obtained promising effects among patients with Alzheimer disease, who showed significant cognitive and behavioral improvements,[37,38] whereas the treatment failed among patients with amyotrophic lateral sclerosis or multiple sclerosis.[39,40] No such trial has been conducted among patients with PD. In the present study, we observed a 78% reduction in the incidence of PD among patients with IBD who were exposed to anti-TNF medications. These findings call into question the notion that existing anti-TNF therapies have limited central nervous system

effects because these large molecule drugs do not cross the blood-brain barrier. Our data suggested the possibility that targeting peripheral TNF is sufficient to reduce neuroinflammation or that the blood-brain barrier may be compromised among patients with IBD such that anti-TNF compounds enter the brain through an already leaky blood-brain barrier. Peripheral administration of the selective inhibitor of soluble TNF XPro1595 has been shown to attenuate nigral cell loss and glial activation in hemiparkinsonian rats[41] and continues to be an active area of research. Taken together, these results suggest that targeting TNF could have disease-modifying potential in individuals at risk of PD.

Although our results support a causal role of inflammation in PD and a potential benefit of targeting peripheral TNF, numerous questions remain unanswered. For example, despite the pleiotropic actions of numerous *LRRK2* mutations on IBD and PD risk, there is as yet no direct evidence demonstrating an increased risk of IBD among patients with PD or among families carrying identified PD-associated *LRRK2* variants. We also could not assess whether individuals with IBD who failed to respond or lost response to anti-TNF therapies (mean >40%[42]) differed in their risk of developing PD. Although constipation is a well-established precursor of PD that has been reported in 50% of PD cases,[43] IBD is largely characterized by diarrhea and bloody stool. Moreover, the use of anti-TNF therapy among patients with IBD has been associated with individual cases of induction or exacerbation of several neurological diseases (reviewed by Morís[44]), although a definite link between de novo development of neurologic adverse events and exposure to anti-TNF therapy has not been established.[45] In addition, most recent studies have reported gut dysbiosis in patients with PD[46] and in animal models of PD,[47] in line with the well-established signature of the low diversity in the gut microbiome among pediatric and adult patients with IBD.[48,49] The observed TNF inhibition could exert effects through changes in the microbiome. Further research will be needed to assess the role of the microbiome in IBD and PD comorbidity. Results of these studies could help generate early genetic, clinical, and microbiome biomarkers of PD that can apply not only to patients with IBD but also to the general population.

Limitations

A limitation of this study is that diagnostic clinical criteria, such as the UK Brain Bank for PD, were not available to identify cases. Nevertheless, the PD criteria used in this study are more stringent than those used in some other PD claims analyses,[50,51] allowing for greater specificity and precision in our analyses. We were unable to clinically phenotype patients with IBD who developed PD in terms of their disease location, progression, and severity. Moreover, the lack of access to DNA samples prevented us from characterizing the mutation status of *LRRK2* and other relevant genes for patients with both diseases. Another limitation is that the small number of events in the anti-TNF exposed cohort likely contributed to wide confidence intervals, despite the large effect sizes. We also did not have access to detailed demographic information associated with either diagnosis, such as race/ethnicity, access to health care, or exposure to other potential risk factors (eg, smoking,[52,53] caffeine intake,[53-56] infections, or head trauma). Future studies will be needed to determine whether the reported findings are sensitive to clinical diagnosis or differences in diet and lifestyle, whether the higher susceptibility of patients with IBD to PD is confined to those carriers with certain mutations, and whether meta-analyses may be warranted to increase the number of cases for analysis. Finally, although the follow-up time between patients with or without PD differed, the follow-up time of patients who developed PD was similar across the comparison groups (ie, IBD vs non-IBD and anti-TNF exposure vs no anti-TNF exposure). Similar follow-up times were also observed across comparison groups for patients who did not develop PD. Thus, these findings suggest that bias was not likely introduced by differences in follow-up time.

Conclusions

In summary, we showed a potential clinical link between IBD and PD, supporting shared mechanisms involved in the pathogenesis of these diseases. Moreover, our data suggested that early exposure to anti-TNF therapy may reduce the risk of PD among patients with IBD, potentially owing to a reduction in systemic inflammation. These findings should be further assessed and confirmed by other studies.

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Study concept and design: Peter, Park, Lu, Chen, Wang.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Peter, Park, Lu, Wang.
Critical revision of the manuscript for important intellectual content: Peter, Dubinsky, Bressman, Park, Chen, Wang.
Statistical analysis: Park, Lu, Chen, Wang.
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Study supervision: Peter, Park, Chen, Wang.

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