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Inflammatory Bowel Disease and Risk of Parkinson's Disease in Medicare Beneficiaries

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Abstract

Introduction—Gastrointestinal (GI) dysfunction precedes the motor symptoms of Parkinson's disease (PD) by several years. PD patients have abnormal aggregation of intestinal α-synuclein, the accumulation of which may be promoted by inflammation. The relationship between intestinal α-synuclein aggregates and central nervous system neuropathology is unknown. Recently, we observed a possible inverse association between inflammatory bowel disease (IBD) and PD as part of a predictive model of PD. Therefore, the objective of this study was to examine the relationship between PD risk and IBD and IBD-associated conditions and treatment.

Methods—Using a case-control design, we identified 89,790 newly diagnosed PD cases and 118,095 population-based controls > 65 years of age using comprehensive Medicare data from 2004–2009 including detailed claims data. We classified IBD using International Classification of Diseases version 9 (ICD-9) diagnosis codes. We used logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to evaluate the association between PD and IBD. Covariates included age, sex, race/ethnicity, smoking, Elixhauser comorbidities, and health care use.

Results—PD was inversely associated with IBD overall (OR = 0.85, 95% CI 0.80–0.91) and with both Crohn's disease (OR = 0.83, 95% CI 0.74–0.93) and ulcerative colitis (OR = 0.88, 95% CI 0.82– 0.96). Among beneficiaries with ≥ 2 ICD-9 codes for IBD, there was an inverse dose-

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response association between number of IBD ICD-9 codes, as a potential proxy for IBD severity, and PD (p-for-trend = 0.006).

Conclusion—IBD is associated with a lower risk of developing PD.

Keywords

Parkinson's disease; Prodromal period; Inflammatory bowel disease; Medicare beneficiaries

Introduction

Gastrointestinal (GI) dysfunction precedes the onset of motor symptoms in Parkinson's disease (PD) by several years [1]; however, the etiology of GI dysfunction in PD and the role of GI pathology in the central nervous system (CNS) manifestations of PD are not well understood. Proposed theories for the mechanism of PD related GI dysfunction include abnormal protein aggregation with consequent degeneration of the enteric nervous system, destruction of the motor nucleus of the vagus nerve known to control the parasympathetic output to the GI tract, and/or chronic inflammation [2–6]. Abnormal α-synuclein aggregates in the intestine may propagate via the vagus nerve into the CNS, potentially contributing to the accumulation of α-synuclein in the brain. Supporting this hypothesis, patients who have undergone truncal vagotomy may have a lower risk of developing PD [7]. Furthermore, chronic intestinal inflammation may allow for rapid mobilization of abnormal protein between the gut and the brain [8].

Inflammatory bowel diseases (IBD) predominantly affect the GI tract but can also be associated with systemic inflammation and extraintestinal manifestations [9]. The two main types of IBD are Crohn's disease (CD) and ulcerative colitis (UC), which can differ in distribution in the gut and depth of inflammation. More severe disease may require immunosuppressant agents, biologic medications, and/or surgery. Given the potentially critical role of GI pathology in PD pathogenesis, there is reason to suspect that IBD or its treatments may impact PD risk. Recently, we observed a possible inverse association between IBD and PD while developing a predictive model of PD [10]. Therefore, in the present work, we hypothesized that patients with IBD would have a lower risk of developing PD than comparable controls without IBD, and that IBD-associated treatments such as GI surgery or immunosuppressant use may also be associated with a lower PD risk.

Methods

Protection of human subjects

This study was approved by the Washington University IRB and Centers for Medicare & Medicaid Services (CMS). All records were de-identified prior to release from CMS.

Study design

We constructed a population-based case-control study using 2009 Medicare base file (BASF) and inpatient, outpatient, physician/supplier, skilled nursing facility, home health care, and durable medical equipment claims data from age-eligible Medicare beneficiaries in 2004–2009 as detailed previously [10]. We required all cases and controls to be enrolled in

Medicare Part A and/or B without health maintenance organization coverage, live in the U.S., and to be age-eligible for Medicare for at least two years (age ≥ 66 years, 11 months) at PD diagnosis or control reference date. Those who met these criteria, had an International Classification of Diseases version 9 (ICD-9) code 332 or 332.0 in 2009 and no prior year, and did not have an ICD-9 code for secondary or atypical parkinsonism, were included as incident PD cases (N = 89,790). Controls (N = 118,095) were a random sample of remaining beneficiaries with none of the above ICD-9 codes in 2004–2009 and meeting the same inclusion criteria. The case-control study was originally formed to develop a predictive model of PD, and we avoided matching so that model coefficients for known PD risk factors would be unbiased when applying the model to future cohorts. The inclusion and exclusion criteria were designed to ensure complete ascertainment of incident PD cases, the selection of comparable controls, and that both were population-based samples rather than disability- or clinic-based samples.

Assessment of IBD and covariates

We extracted ICD-9 diagnosis and procedure codes, Healthcare Common Procedure Coding System (HCPCS) codes and Current Procedural Terminology (CPT) codes from all available claims data up to the PD diagnosis/control reference date. We created a dichotomous variable for each code observed in 2004–2009 prior to this date. We classified the beneficiary as having IBD if they had ≥ 1 of the following ICD-9 codes: 555.0–555.9, 556.0–556.9. We sub-classified IBD into CD (555.0–555.9) or UC (556.0–556.9) [11, 12]. We also identified beneficiaries with at least two codes on separate dates for IBD as a method of improving accuracy and stability of IBD diagnosis. We calculated the total number of occurrences of an IBD ICD-9 code, as a proxy for IBD severity, in order to consider a dose-response relationship between IBD and PD. We then classified all beneficiaries as having a condition known to be associated with IBD [11] if they had any of the following ICD-9 and/or CPT codes: arthropathy (713.1), pyoderma gangrenosum (686.01), erythema nodosum (695.2), oral aphthous ulcers (528.2), cholangitis (576.1), or fistulae (ICD-9 537.4, 565.1, 569.81, 596.1, 599.1, 619.1, 46.72, 46.74, 49.73, 46.76, 48.73, 48.93, CPT codes 45800, 45820, 45825, 45805, 43880, 44640, 44650, 46706). We included these diagnoses to ensure a consistent association with PD. We also identified procedure codes for an ileostomy or colectomy, surgical procedures commonly used to treat IBD. Because IBD is commonly treated with immunosuppressants, we investigated whether immunosuppressants were associated with a lower risk of PD. We identified HCPCS, CPT, and ICD-9 codes associated with steroid (e.g., long-term use of steroids, systemic corticosteroids, dexamethasone, methylprednisolone, and hydrocortisone) and immunosuppressant use (e.g., infliximab, daclizumab, adalimumab, rituximab, azathioprine, methotrexate, and cyclosporine). We categorized immunosuppressant use into traditional, biologic, and steroid. Traditional immunosuppressants are commonly used synthetic disease modifying agents which include methotrexate, azathioprine, and cyclosporine. Biologics are newer immunosuppressant medications made from live biological systems and categorized based on their mechanism of action. We did not have Medicare Part D (prescription coverage) claims data to verify immunosuppressant use and were only able to ascertain immunosuppressant use through Medicare Part A/B.

We calculated age and obtained sex and race from the 2009 BASF. We calculated the probability of having ever regularly smoked (a continuous variable, hereafter "smoking probability") for all cases and controls. We estimated the latter by assigning beneficiaries with a code specific to tobacco (ICD-9 V15.82, ICD-9 305.1, CPT 99406, CPT 99407) a probability of 100%. We calculated other participants' probability using a logistic regression predictive model for ever/never smoking that we developed within another nationwide, population-based dataset [13]. This model had 17 predictor variables, which we made in the Medicare dataset from > 650 ICD-9 codes. We applied this predictive model to our Medicare data and validated smoking probability against (1) tobacco-specific codes before factoring them in, (2) county level smoking [14], and (3) diagnoses associated with smoking but in Medicare data only [10]. We defined comorbidities using a modified Elixhauser index, a validated measure of medical comorbidities when using claims data [15]. Finally, we counted the total number of unique types of providers/diagnosis codes seen in 2004–2009 to quantify beneficiaries' use of medical care, which can bias associations between two medical conditions [16]. The smoking, Elixhauser, and use of care variables were based on all claims data up to the PD diagnosis/control reference date.

Statistical analysis

We used logistic regression, with PD as our outcome variable, to determine the associations between PD and each medical condition or treatment. We reported the odds ratio (OR) and respective 95% confidence interval (CI) as an estimate of relative risk. We adjusted for age (continuously as two linear splines), race (seven categories), sex, and probability of ever smoking *a priori* because of their known associations with PD [17]. We adjusted for comorbidities using the Elixhauser index and total number of types of providers seen. For models of PD and IBD-associated conditions/treatments, we stratified by presence of IBD status, since associated conditions/treatments could be present in other disease processes. Finally, we performed three sensitivity analyses. First, we used stringent PD diagnostic criteria to identify incident PD requiring at least one ICD-9 code from a neurologist or ≥ 3 PD codes in 2009 [10]. Second, we restricted analyses to those without constipation given that constipation can be a symptom of PD and may have masked IBD symptoms. Third, we applied three-year exposure lag, similar to a prior study of autoimmune diseases and PD [18].

Results

Our PD cases demonstrated typical demographic associations [10]. Female sex (OR = 0.57, 95% CI 0.56–0.58) and smoking (OR = 0.57, 95% CI 0.56–0.59) were associated with a lower risk of PD. Additionally, PD cases demonstrated greater use of medical care than controls (Table 1).

PD was inversely associated with any IBD diagnosis (OR = 0.85, 95% CI 0.80–0.91) (Table 2). When considering specific IBD sub-types, we observed an inverse association between PD and both CD (OR = 0.83, 95% CI 0.74–0.93) and UC (OR = 0.88, 95% CI 0.82–0.96). The association between PD and CD was more apparent for women (OR = 0.79, 95% CI 0.68–0.92) than men (OR = 0.87, 95% CI 0.73–1.05) whereas the association between PD

and UC was more apparent for men (OR = 0.84, 95% CI 0.74–0.95) than women (OR = 0.92, 95% CI 0.82–1.02).

In the sensitivity analysis requiring PD cases to have had at least one code from a neurologist or ≥ 3 PD codes, PD remained inversely associated with any IBD (OR = 0.82, 95% CI 0.76–0.88), CD (OR = 0.83, 95% CI 0.72–0.95) and UC (OR=0.84, 95% CI 0.77–0.93). In the second sensitivity analysis, in beneficiaries without an ICD-9 code for constipation, PD remained inversely associated with any IBD (OR = 0.82, 95% CI 0.76–0.89), CD (OR = 0.79, 95% CI 0.68–0.91), and UC (OR = 0.86, 95% CI 0.77–0.95). When we repeated the primary analysis requiring the use of at least two ICD-9 codes to identify IBD, the PD-IBD OR was 0.82 (95% CI 0.75–0.89). Moreover, among beneficiaries with ≥ 2 codes for IBD, there was an inverse dose-response association between number of IBD ICD-9 codes and PD (p-for-trend = 0.006). Finally, in the last sensitivity analysis, the PD-IBD association was similar when we lagged exposure by three years.

When we investigated the relationship between IBD-associated medical conditions, we found that PD was inversely associated with IBD-associated medical conditions for both beneficiaries with and without IBD. We also found that PD was inversely associated with all IBD-associated surgical procedures, for both beneficiaries with and without IBD (Table 3). The inverse relationships between PD and IBD overall (OR = 0.86, 95% CI 0.81–0.92), CD (OR = 0.84, 95% CI 0.74–0.94), and UC (OR = 0.89, 95% CI 0.82–0.97) remained when we excluded beneficiaries with IBD-associated surgery.

PD was inversely associated with all indicators of immunosuppressant and steroid use (Table 4). When excluding beneficiaries with IBD, both categories of medication were still inversely associated with PD. Among beneficiaries with IBD, there was an inverse association between PD and immunosuppressant and steroid use which did not reach statistical significance. The inverse relationship between PD and any IBD diagnosis remained when restricting the analysis to those individuals without immunosuppressant codes (OR = 0.83, 95% CI 0.76–0.90).

Discussion

In this large, population-based case-control study of prodromal PD, we observed an inverse association between IBD and PD, including both CD and UC. Similarly, there was an inverse association between PD and IBD-associated conditions, as well as IBD-associated surgical procedures and immunosuppressant use, even among beneficiaries without IBD. These conditions may be present in other autoimmune diseases. Our findings were similar or stronger when restricted to more stringent case definitions of PD. The findings that the surgical procedures and immunosuppressant use were associated with a lower risk of PD suggested that aggressive treatment may reduce the risk of PD.

Our findings are in contrast to another large population-based cohort study in Taiwan in which IBD was positively associated with PD [19]. We believe that a possible explanation for this positive association is bias by use of care [16], in which patients are more likely to be diagnosed with PD if they frequent the health care system, creating a surveillance bias.

We note that in the Taiwanese study, PD was not only positively associated with IBD but also with stroke and coronary heart disease. Given that these conditions are more common in smokers than non-smokers, they would be expected to be inversely associated with PD, at least after adequately accounting for the use of medical care and therefore not true causal associations. In contrast, our study included a lagged analysis and aggressively adjusted for use of care, improving our ability to interpret the observed inverse association between IBD and PD. Interestingly, another large population-based case-control study of PD in Denmark, found no association between autoimmune diseases, which included IBD and risk of PD. However, they did find an inverse association between PD and autoimmune diseases that involved detectable autoantibodies and systemic involvement [18]. The reduced risk of PD in this subgroup may reflect more aggressive treatment for a disease that manifests through widespread organ and tissue involvement. The Danish study applied exposure lagging, and this likely improved the accuracy of their risk estimates. When we restricted to beneficiaries who are the most likely to have IBD (≥ 2 IBD ICD-9 codes [11]) we again found an inverse association whereby PD risk decreased as the number of ICD-9 codes for IBD increased.

Nonetheless, the inverse association between IBD and PD is unexpected considering evidence that suggests a shared genetic risk profile between PD and IBD, which includes both *LRRK2* and *MAPT* genes [20, 21]. However, PD and IBD genetic profiles are not universally positively associated, as a polymorphism close to the *HLA* gene region demonstrated an inverse association between PD and IBD genes [21]. There are several possible explanations by which IBD may lower PD risk. Growing evidence suggests that abnormal α-synuclein aggregates may propagate through direct neuronal transport, via prion-like mechanisms [22]. The modified Braak hypothesis suggests that PD starts outside the CNS, in the GI tract [23]. Lewy bodies containing α-synuclein aggregates are found in the GI tract, including those of PD patients, and it is possible that α-synuclein may spread from the GI myenteric complex into the CNS via these prion-like mechanisms. It is possible that gut inflammation and/or alteration of the gut microbiome [24] in IBD may reduce α-synuclein spread by containing the protein aggregates to the GI tract. Alternatively, GI surgical procedures may remove tissue with higher concentrations of α-synuclein, thus limiting potential aberrant protein spread to the CNS. Finally, dysbiosis"imbalances" in the gut microbiome, associated with either IBD or IBD treatment may also lower PD risk through as-yet undefined mechanisms.

A recent meta-analysis suggests that levels of peripheral inflammatory levels of some cytokines may be higher in PD patients than controls [25]. However, whether these inflammatory biomarkers precede the diagnosis of PD or are a consequence of it is unknown. If a host of inflammatory biomarkers are required to induce the pathological cascade of PD, early onset IBD may protect against PD through use of anti-inflammatory or immunosuppressant agents used to treat IBD. While we did not have specific Medicare Part D drug prescription data, we were able to use procedure codes for selected immunosuppressant medications used to treat IBD and other conditions. Although this information was limited, these codes were associated with a lower risk of PD, regardless of the presence of IBD. Since the relationship was similar when excluding people with IBD, immunosuppression may be neuroprotective against development of PD. Of course, confirming this association with Medicare Part D data will be required.

As with any administrative data study, there are several limitations. While Medicare is the only population-based, national health care program in the U.S., the data are only population-based when considering those aged 65 and older. We do not have diagnosis and procedure codes occurring when cases and controls were younger, when IBD incidence is high, since our study included only five years of data prior to PD diagnosis/reference. We cannot fully investigate the complete time course of patients' IBD, use of medications, or comorbidities. However, we have no reason to believe that misclassification of IBD would differ by PD case status. As such, this misclassification would bias the association between PD and IBD toward the null and, therefore, not account for the observed inverse association. On the other hand, because constipation is a common nonmotor symptom of PD and can be present decades before PD diagnosis, it is possible that IBD symptoms would be masked, thus leading to an inverse association. However, in our secondary analysis when we restricted to those beneficiaries without constipation, IBD remained inversely associated with PD. Finally, although codes for IBD have been validated in previous studies [11], the CPT codes suggestive of immunosuppressant use have not. As a result, we may have misclassified some beneficiaries given that we did not have Medicare Part D to verify the immunosuppressant-related codes.

Although replication of our findings is needed, this study provides compelling evidence of an inverse association between PD and IBD that may inform our understanding of disease risk. Replication of these findings could be done in countries with comprehensive population-based national health care systems that include both inpatient and outpatient data for a sufficient period of time. This would allow one to obtain information on medical conditions from early years, when IBD incidence initially peaks, through old age, when PD incidence is greatest and when a second smaller peak in IBD incidence characterized by milder disease has been described [26]. These data would allow one to assess the complete time course of IBD, IBD-associated medical conditions, and treatments. Nevertheless, the primary findings of an inverse relationship between PD and IBD and PD and immunosuppressant treatment clearly warrant further study as this may provide an important target for disease modifying therapies.

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Highlights

- We found an inverse association between PD and IBD.
- Both Crohn disease and Ulcerative colitis were inversely associated with PD.
- Potential indicators of disease severity were inversely associated with PD.

Table 1

Characteristics of incident Parkinson's disease (PD) cases and randomly selected controls, Medicare 2009

	PD Cases N = 89,790 %	Controls N = 118,095 %	Mutually adjusted ORs (95% CI)	P-values
Age, years				
66–69	8.1	18.3	1.0 (reference)	
70–74	19.5	28.9	1.48 (1.43–1.53)	<0.001
75–79	24.8	22.5	2.33 (2.26–2.41)	<0.001
80–84	26.9	18.2	2.99 (2.90–3.09)	<0.001
85–90	20.7	12.1	3.37 (3.26–3.49)	<0.001
Female	50.2	57.0	0.57 (0.56–0.58)	<0.001
Race/ethnicity				
White	88.8	86.4	1.0 (reference)	
Black	6.0	7.5	0.83 (0.80–0.86)	<0.001
Pacific Islander/Other	1.0	1.5	0.68 (0.63–0.74)	<0.001
Asian	1.7	2.2	0.73 (0.69–0.78)	<0.001
Hispanic	2.1	1.9	0.98 (0.92–1.05)	0.574
Native American	0.3	0.4	0.85 (0.73–0.99)	0.037
Unknown	0.09	0.09	0.88 (0.66–1.19)	0.411
Smoking Index[a] ≥ median	42.9	55.4	0.57 (0.56–0.59)	<0.001
	Mean (SD)	**Mean (SD)**		
Age, years	78.7 (6.1)	76.0 (6.2)		
Number of unique provider types seen, 2004–2009	19.3 (6.8)	14.2 (7.5)		

[a]Ever vs. never tobacco smoking, as an index calculated as the probability (0 to 1) of ever tobacco smoking derived from a logistic regression predictive model of smoking, divided by the total count of unique diagnosis codes observed for each beneficiary.

Abbreviations: CI = confidence interval; OR = odds ratio.

Table 2

Risk of Parkinson's Disease (PD) in relation to inflammatory bowel disease (IBD), overall and by IBD type

	All beneficiaries		
	PD Cases N = 89,790 n (%)	Controls N = 118,095 n (%)	OR (95% CI)[a]
Any IBD[b]	2599 (2.9)	2381 (2.0)	0.85 (0.80–0.91)
IBD, by type			
Crohn's disease only[c]	749 (0.8)	708 (0.6)	0.83 (0.74–0.93)
Ulcerative colitis only[d]	1583 (1.8)	1405 (1.2)	0.88 (0.82– 0.96)

[a] Odds ratio and 95% confidence interval for PD among those with vs. without IBD or IBD subtype, adjusted for age (two continuous splines), sex, race/ethnicity (seven categories), probability of ever/never smoking, number of different types of providers seen, and 18 Elixhauser dichotomous comorbidity indicators of chronic heart failure, diabetes, pulmonary circulation disorders, hypertension, paralysis, hypothyroidism, renal failure, metastatic cancer, solid tumor, rheumatoid arthritis, obesity, weight loss, fluid electrolyte disorders, deficiency anemias, other neurological disorders, psychoses, and depression.

[b] ICD-9 555.0–555.9 and/or 556.0–556.9.

[c] ICD-9 555.0–555.9 without other IBD ICD-9 codes.

[d] ICD-9 556.0–556.9 without other IBD ICD-9 codes.

Table 3

Risk of Parkinson's Disease (PD) in relation to medical conditions and surgical procedures related to inflammatory bowel disease (IBD), overall and by IBD diagnosis status

	All beneficiaries			Beneficiaries with IBD			Beneficiaries without IBD		
	PD Cases N=89,790	Controls N=118,095		PD Cases N=2,599	Controls N=2,381		PD Cases N=87,191	Controls N=115,714	
	n	n	OR (95% CI) [a]	n	n	OR (95% CI) [a]	n	n	OR (95% CI) [a]
IBD-associated condition[b] (ICD- 9 code)	2266	2191	0.79 (0.74–0.85)	164	159	0.69 (0.54– 0.89)	2102	2032	0.81 (0.75–0.87)
Arthropathy (713.1)	17	16	1.03 (0.47–2.26)	_ [c]					
Pyoderma gangrenosum (686.01)	60	51	0.87 (0.57–1.31)	_ [c]			57	44	1.00 (0.64–1.55)
Erythema nodosum (695.2)	62	82	0.73 (0.51–1.06)	_ [c]			55	76	0.73 (0.49–1.07)
Oral aphthous ulcers (528.2)	704	748	0.80 (0.71– 0.90)	38	29	0.95 (0.56–1.62)	666	719	0.79 (0.70–0.89)
Cholangitis (576.1)	437	363	0.77 (0.66–0.90)	31	30	0.76 (0.44–1.33)	406	333	0.78 (0.66–0.92)
Fistulae [d]	1039	957	0.83 (0.75– 0.92)	82	81	0.63 (0.45–0.90)	957	876	0.84 (0.77–0.94)
IBD-associated surgery [e]	1649	1763	0.73 (0.68–0.79)	216	200	0.78 (0.62–0.98)	1433	1563	0.74 (0.68–0.80)
Ileostomy[f]	350	346	0.68 (0.57–0.81)	117	113	0.74 (0.55–0.99)	233	233	0.71 (0.58–0.87)
Colectomy [g]	1419	1538	0.73 (0.67–0.79)	132	122	0.72 (0.54–0.95)	1287	1416	0.74 (0.68–0.81)

[a] Odds ratio and 95% confidence interval for PD among those with vs. without IBD or IBD subtype, adjusted for age (two continuous splines), sex, race/ethnicity (seven categories), ever/never smoking, number of different types of providers seen, and 18 Elixhauser dichotomous comorbidity indicators of chronic heart failure, diabetes, pulmonary circulation disorders, hypertension, paralysis, hypothyroidism, renal failure, metastatic cancer, solid tumor, rheumatoid arthritis, obesity, weight loss, fluid electrolyte disorders, deficiency anemias, other neurological disorders, psychoses, and depression.

[b] One or more of the conditions (ICD-9 codes) listed below.

[c] The number of cases and controls with both IBD and the specified condition was too few to report and analyze.

[d] Fistula as assessed by ICD-9 diagnosis codes 537.4, 569.81, 565.1, 619.1, 596.1, 599.1, ICD-9 procedure codes 48.73, 48.93, 46.72, 46.74, 46.76, 49.73, and CPT codes 45800, 45820, 45825, 45805, 43880, 44640, 44650, and 46706.

[e] Surgery as assessed by ileostomy and/or colectomy.

[f] Ileostomy as assessed by ICD-9 diagnosis codes V44.2 or V55.2, ICD-9 procedure codes 46.20, 46.21, 46.22, 46.23, or 46.51, CPT codes 44310, 44312, or 44314.

[g] Colectomy as assessed by ICD-9 procedure codes 45.80 45.81, 45.82, 45.83, or 45.95, or CPT codes 44140, 44141, 44143, 44144, 44145, 44146, 44147, 44150, 44151, 44155, 44156, 44157, 44158, 44204, 44205, 44206, 44207, 44208, 44210, 44211, 44212, or 45113.

Table 4

Risk of Parkinson's Disease (PD) in relation to immunosuppressant use, overall and by IBD diagnosis status

	All beneficiaries			Beneficiaries with IBD			Beneficiaries without IBD		
	PD Cases N=89,790	Controls N=118,095		PD Cases N=2,599	Controls N=2,381		PD Cases N=87,191	Controls N=115,714	
	n	n	OR (95% CI) [a]	n	n	OR (95% CI) [a]	n	n	OR (95% CI) [a]
Any biologic[b]	741	890	0.68 (0.61–0.76)	67	78	0.68 (0.46–0.99)	674	812	0.69 (0.62–0.78)
Any traditional[c]	489	599	0.70 (0.61–0.80)	21	26	0.54 (0.28–1.04)	468	573	0.71 (0.62–0.82)
Any steroid[d]	28694	31322	0.86 (0.85–0.89)	1063	909	0.90 (0.78–1.02)	27631	30413	0.86 (0.84–0.88)

[a] Odds ratio and 95% confidence interval for PD among those with vs. without IBD or IBD subtype, adjusted for age (two continuous splines), sex, race/ethnicity (seven categories), ever/never smoking, number of different types of providers seen, and 18 Elixhauser dichotomous comorbidity indicators of chronic heart failure, diabetes, pulmonary circulation disorders, hypertension, paralysis, hypothyroidism, renal failure, metastatic cancer, solid tumor, rheumatoid arthritis, obesity, weight loss, fluid electrolyte disorders, deficiency anemias, other neurological disorders, psychoses, and depression.

[b] HCPCS codes: J1745, J7513, J0135, J9310

[c] HCPCS, CPT and ICD-9 codes: J7500, J7501, J7599, J9250, J9260, J7502, J7515, 80158, V5812, J8610

[d] HCPCS, CPT and ICD-9 codes: J1020, J1030, J1040, J1094, J1100, J2920, J2930, J1700, J1710, J1720, J7509, J7510, 4193F, 4194F, V5865.