Autoimmune disease and risk for Parkinson disease

A population-based case-control study

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ABSTRACT

Objective: Inflammatory mediators are increased in autoimmune diseases and may activate microglia and might cause an inflammatory state and degeneration of dopaminergic neurons in the brain. Thus, we evaluated whether having an autoimmune disease increases the risk for developing Parkinson disease (PD).

Methods: A population based case-control study was conducted in Denmark of 13,695 patients with a primary diagnosis of PD recorded in the Danish National Hospital Register during the period 1986–2006. Each case was matched on year of birth and sex to 5 population controls selected at random from among inhabitants of Denmark who were alive at the date of the patient's diagnosis. The main exposure measure was a hospital diagnosis of 1 of 32 selected autoimmune diseases recorded 5 or more years before the index date in the files of the Danish Hospital Register.

Results: We observed no overall association between a diagnosis of autoimmune disease and risk for subsequent PD (odds ratio 0.96, 95% confidence interval 0.85–1.08). In a subgroup of patients with autoimmune diseases with systemic involvement, primarily rheumatoid arthritis, we saw a decrease in risk for PD of 30%.

Conclusions: Our results do not support the hypothesis that autoimmune diseases increase the risk for Parkinson disease. The decreased risk observed among patients with rheumatoid arthritis might be explained by underdiagnosis of movement disorders such as Parkinson disease in this patient group or by a protective effect of the treatment with anti-inflammatory drugs over prolonged periods. *Neurology*® 2009;73:1462–1468

GLOSSARY

CI = confidence interval; COPD = chronic obstructive pulmonary disease; ICD-8 = International Classification of Diseases, 8th revision; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio; PD = Parkinson disease.

Parkinson disease (PD) is a movement disorder that exhibits clinically signs of rigidity, bradykinesia, postural instability, and tremor, as well as a large number of nonmotor features, including dementia and depression.^{1,2} The patient's brain characteristically lacks the neurotransmitter dopamine because of the deaths of dopaminergic neurons. The etiology of the disease is largely unknown, except that a small percentage of younger-onset cases are caused by rare genetic mutations.³ One hypothesis is that inflammatory mediators activate immune cells in the brain (microglia), which may cause or contribute to the degeneration of neurons.⁴ Patients with autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, produce chronically high concentrations of inflammatory mediators over long periods of time,⁵ and it has been hypothesized that these patients may be at increased risk for neurodegenerative diseases such as PD.^{6–8} This hypothesis is supported by studies on brains taken postmortem from parkinsonian patients that demonstrated increased levels of proinflammatory mediators and apoptosis-related proteins in the striatal dopaminergic regions of the brain.^{9–11} However, it was unclear whether the inflammation was a cause or a

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consequence of PD. Recently, higher serum levels of the inflammatory mediator interleukin 6 during a 5-year interval before diagnosis were found to be associated with an increased risk for PD.¹² In addition, epidemiologic studies have suggested that regular use of anti-inflammatory drugs may be associated with a decreased risk for PD.¹³⁻¹⁵ To address the possible link between immunologically induced inflammation and PD, we examined associations between autoimmune diseases and risk for PD in a nationwide, population-based case-control study.

METHODS Danish Hospital Register. The Danish National Hospital Register contains information on all persons admitted to nonpsychiatric hospitals since 1977.¹⁶ Information on visits to outpatient clinics at hospitals, including visits to emergency rooms, was added to the register on January 1, 1995. The information of the hospital register includes the personal identification number of the patient, the dates of admission and discharge (inpatient registration), the dates of first and last contact (outpatient registrations), a code for the primary diagnosis made at the hospital contact, and codes for up to 19 supplementary diagnoses. The personal identification number, which is unique to every Danish citizen, incorporates sex and date of birth and permits accurate linkage between registers. The diagnoses, established at discharge from hospital or outpatient clinic, are coded according to the Danish version of the *International Classification of Diseases, 8th revision (ICD-8)*, until the end of 1993 and the 10th revision thereafter. Information on diagnoses made exclusively at private practicing neurologists or general practitioners is not covered by the register.

Study population. A total of 13,739 patients with a primary diagnosis of PD (*ICD-8* code 342 and *ICD-10* code G20) during the period 1986–2006 were identified in the files of the Hospital Register. Only patients with a primary diagnosis of PD were included in this study, because a primary diagnosis is considered to be more reliable and accurate compared with supplementary diagnoses. This is further supported by the fact that 65% of patients with a primary diagnosis had a diagnosis of PD at a neurologic department, whereas the corresponding number for patients with a supplementary diagnosis was 7%. We restricted the case population to patients who received their first primary diagnosis of PD after 1985, to eliminate prevalent cases, which were included in the Hospital Register in the first years of registration (1977–1985). After further exclusion of 1 patient who was a citizen of Greenland and 43 patients who were younger than 35 years at the time of first hospital contact for PD, a case population of 13,695 patients (7,423 men and 6,272 women) remained (table 1). Patients with a primary diagnosis of PD were assigned an index date, defined as the date of the first recorded hospital contact under a diagnosis of PD. This backdating of the contact date for patients registered with a supplementary diagnosis of PD before the primary diagnosis was done to approximate the true date of start of PD symptoms. For each case, we selected 5 control subjects at random from the Danish Central Population Register among all Danish inhabitants of the same sex and year of birth who were alive and without PD at the index date of the case. Although we aimed to recruit 5 control subjects per case, 26 patients were matched

Table 1 Characteristics of 13,695 patients with Parkinson disease and 68,445 population controls

Characteristic	Patients		Controls	
	No.	%	No.	%
Sex				
Men	7,423	54.2	37,101	54.2
Women	6,272	45.8	31,344	45.8
Age at index date*				
35–44 y	149	1.1	725	1.1
45–54 y	506	3.7	2,535	3.7
55–64 y	1,658	12.1	8,265	12.1
65–74 y	4,575	33.4	22,882	33.4
75–84 y	5,723	41.8	28,547	41.7
85–94 y	1,070	7.8	5,429	7.9
95–99 y	14	0.1	62	0.1
Year of birth				
<1900	54	0.4	270	0.4
1900–1909	1,406	10.3	7,030	10.3
1910–1919	4,749	34.7	23,741	34.7
1920–1929	4,379	32.0	21,887	32.0
1930–1939	2,044	14.9	10,218	14.9
1940–1949	819	6.0	4,089	6.0
1950–1959	194	1.4	965	1.4
1960–1969	50	0.4	245	0.4
Autoimmune disease (5-year lag interval)				
No	13,349	97.5	66,640	97.4
Yes	346	2.5	1,805	2.6
Men				
Men	151	2.0	821	2.2
Women				
Women	195	3.1	984	3.1
COPD (5-year lag interval)				
COPD (5-year lag interval)	211	1.5	1,424	2.1
Charlson comorbidity index (5-year lag interval)				
None	11,199	81.8	55,731	81.4
1	1,452	10.6	7,303	10.7
≥2	1,044	7.6	5,411	7.9

*Date of first hospital contact for patients with Parkinson disease and an equivalent date for controls.

COPD = chronic obstructive pulmonary disease.

with either 2, 3, or 4 control subjects, yielding a total of 68,445 controls (table 1).

Standard protocol approvals. The study protocol was approved by the Danish Data Protection Agency (no. 2002-41-2112) and the University of California at Los Angeles institutional review board for human subjects.

Ascertainment and classification of autoimmune and other diseases. From the Hospital Register, we obtained for cases and matched controls information on any hospital contact

(primary and secondary diagnoses) for autoimmune and related diseases (in the following defined as “autoimmune diseases”), chronic obstructive pulmonary disease (COPD; *ICD-8* codes 490–492, *ICD-10* codes J40–J44), and other diseases included in the Charlson comorbidity index¹⁷ occurring 5 or more years before the index date. The Charlson comorbidity index is an index based on the presence of 19 selected medical conditions, which are all related to an increased risk of mortality. Patients free from all 19 conditions get the score 0, and patients with 1 or more of the diseases included in the index get a score in the range 1 to 6, depending on number and severity of the conditions.¹⁷ A diagnosis of COPD was taken as a proxy for smoking. A 5-year lag interval was chosen on the basis of the results of a previous study by our group, which showed that treatment with anti-Parkinson drugs started on average 3 years before the first hospital contact for PD, indicating that the diagnosis often was made in the primary health care system months to several years before the first hospital contact.¹⁸ By applying a 5-year lag interval, we were confident that the autoimmune disease occurred before PD. We grouped the autoimmune diseases into 3 categories according to a classification used in 2 previous studies by our group^{19,20}: category A: diseases in which autoantibodies were detectable and with systemic involvement; category B: diseases in which autoantibodies were detectable and with organ involvement; and category C: diseases with no detectable autoantibodies. Diagnoses of 32 different autoimmune diseases among cases and controls occurring 5 or more years before the index date were identified in the Hospital Register. Category A diseases included rheumatoid arthritis (63 cases/456 controls), polymyositis or dermatomyositis (2/7), Sjögren syndrome (2/20), systemic lupus erythematosus (3/20), and systemic sclerosis (4/5); category B included Addison disease (2/14), amyotrophic lateral sclerosis (0/3), autoimmune hemolytic anemia (2/7), chronic rheumatic heart disease (30/188), discoid lupus erythematosus (1/6), Graves disease (22/82), Hashimoto thyroiditis (0/11), immune thrombocytopenic purpura (1/10), insulin-dependent diabetes mellitus (48/223), localized scleroderma (0/2), lupoid hepatitis (0/0), multiple sclerosis (7/72), myasthenia gravis (2/12), pernicious anemia (21/89), polyarteritis nodosa (0/11), primary biliary cirrhosis (2/7), and Wegener granulomatosis (0/6); and category C included ankylosing spondylitis (9/21), Behçet disease (0/0), celiac disease (2/9), chorea minor (0/1), Crohn disease (10/47), polymyalgia rheumatica (65/326), psoriasis (6/24), Reiter disease (0/6), sarcoidosis (21/55), and ulcerative colitis (42/164). The hospital records did not allow differentiation between types I and II insulin-dependent diabetes mellitus.

Analyses. We compared the prevalence of a history of hospital contacts for autoimmune diseases among 13,695 patients with a primary diagnosis of PD and their population controls between 1977 and 5 years before the index date. The association was expressed as odds ratio (OR) with a 95% confidence interval (CI) derived from a conditional logistic regression analysis for matched sets with and without adjusting for COPD. To explore the impact of the duration of having had an autoimmune disease, the presumed duration of treatment for an autoimmune disease, and the potential for diagnostic bias, ORs were estimated overall and for various intervals (5–9 years, 10–14 years, and ≥15 years) between the date of first hospital contact for a given autoimmune disease and the date of first hospital contact for PD.

We analyzed risk for 3 levels of autoimmune disease: 1) any autoimmune disease, based on the first recorded diagnosis; 2) by category (A, B, or C), based on the first recorded category-

specific diagnosis, i.e., study subjects can occur once in each category; and 3) by disease, i.e., subjects with more than 1 autoimmune disease appear in the analysis of each disease. Analyses were performed for each sex separately and for both sexes combined. Calculations were performed with SAS software version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS Table 1 shows the distribution of case patients with a primary diagnosis of PD and matched control subjects by age at the index date and by year of birth. The mean age at first hospital contact for PD was 73.0 years (72.5 for men and 73.6 for women), and almost 80% of the patients were born before 1930. Of the 13,695 patients with PD, 346 (2.5%) had at least 1 autoimmune disease recorded 5 or more years before the hospital contact for PD. The corresponding figure for the 68,445 population controls was 1,805 (2.6%). More controls (2.1%) than patients (1.5%) had a prior diagnosis of COPD, whereas the Charlson comorbidity index was similar among patients and controls (table 1).

Table 2 shows that there was no difference between cases and controls in the prevalence of any type of autoimmune disease 5 or more years before diagnosis of PD compared with controls (OR 0.96, 95% CI 0.85–1.08). The analysis adjusted for COPD resulted in a similar risk estimate (OR 0.96, 95% CI 0.86–1.08; not shown in the table).

Table 2 also shows that the neutral overall risk estimate associated with a history of autoimmune disease resulted from a significantly decreased risk for PD among persons with a previous autoimmune disease with detectable autoantibodies and systemic involvement (category A), a close to neutral effect among persons with an autoimmune disease with detectable autoantibodies and organ involvement (category B), and a slightly increased risk among persons with an autoimmune disease with no detectable autoantibodies (category C). The risk pattern was similar in both sexes in categories A and C; however, for category B diseases, we found an overall decreased risk for PD in men and an increased risk in women. The overall decrease in risk for PD among persons with a category A autoimmune disease was seen in both sexes and in all lag intervals.

In the analyses of specific diseases (table 3), we observed a significantly decreased risk for PD with a previous diagnosis of rheumatoid arthritis (OR 0.7, 95% CI 0.5–0.9), which constituted the vast majority (85%) of autoimmune disease cases in category A. The risk estimates did not change materially with increasing lag intervals for a diagnosis of rheumatoid arthritis. For both sexes combined, no associations were apparent for specific category B diseases, including chronic rheumatic heart disease, Graves disease, insulin-dependent diabetes mellitus, or pernicious

Table 2 Odds ratios and 95% confidence intervals for Parkinson disease by main diagnostic category of autoimmune disease and lag interval between the 2 diseases

Type of autoimmune disease Lag interval, y	Both sexes		Men		Women	
	No. of cases/ controls	OR (95% CI)	No. of cases/ controls	OR (95% CI)	No. of cases/ controls	OR (95% CI)
Any	346/1,805	0.96 (0.85–1.08)	151/821	0.92 (0.84–1.00)	195/984	1.00 (0.92–1.09)
Autoantibodies detectable and systemic involvement (category A)						
All (≥ 5)	73/503	0.7 (0.6–0.9)	25/162	0.8 (0.5–1.2)	48/341	0.7 (0.5–0.95)
5–9	37/227	0.8 (0.6–1.2)	12/69	0.9 (0.5–1.6)	25/158	0.8 (0.5–1.2)
10–14	13/142	0.5 (0.3–0.8)	5/46	0.6 (0.2–1.4)	8/96	0.4 (0.2–0.9)
≥ 15	23/134	0.9 (0.6–1.3)	8/47	0.9 (0.4–1.8)	15/87	0.9 (0.5–1.5)
Autoantibodies detectable and organ involvement (category B)						
All (≥ 5)	136/730	0.9 (0.8–1.1)	54/385	0.7 (0.5–0.9)	82/345	1.2 (0.9–1.5)
5–9	77/416	0.9 (0.7–1.2)	27/233	0.6 (0.4–0.9)	50/183	1.4 (1.00–1.9)
10–14	41/181	1.1 (0.8–1.6)	17/97	0.9 (0.5–1.5)	24/84	1.4 (0.9–2.2)
≥ 15	18/133	0.7 (0.4–1.1)	10/55	0.9 (0.5–1.8)	8/78	0.5 (0.3–1.1)
Autoantibodies not detectable (category C)						
All (≥ 5)	149/637	1.2 (0.98–1.4)	76/291	1.3 (1.02–1.7)	73/346	1.1 (0.8–1.4)
5–9	75/292	1.3 (1.00–1.7)	41/124	1.7 (0.2–2.4)	34/168	1.0 (0.7–1.5)
10–14	34/198	0.9 (0.6–1.2)	13/95	0.7 (0.4–1.2)	21/103	1.0 (0.6–1.6)
≥ 15	40/147	1.4 (0.96–1.9)	22/72	1.5 (0.95–2.5)	18/75	1.2 (0.7–2.0)

OR = odds ratio; CI = confidence interval.

anemia. However, women with previous Graves disease, insulin-dependent diabetes mellitus, or pernicious anemia exhibited an up to 2-fold increase in risk for developing PD. Among category C diseases, we estimated increases in risk for subjects with sarcoidosis (OR 1.9, 95% CI 1.2–3.2); however, there was no apparent trend by lag interval except that the most recently diagnosed cases exhibited the largest risk.

DISCUSSION Results from postmortem studies have suggested that inflammation plays an important role in the pathogenesis of PD,^{9–11} and an animal study has shown that the inflammatory mediators tumor necrosis factor α and interleukin 1- β can cause degeneration of the dopaminergic neurons.²¹ In this nationwide, population-based case-control study of more than 13,000 patients with a primary hospital contact for PD and 68,000 population controls, we did not find an overall link between PD and a prior hospital contact for an autoimmune disease. On the contrary, in the subcategory of patients who had autoimmune diseases with detectable autoantibodies and systemic involvement, a disease category predominated by cases of rheumatoid arthritis, we saw

an overall 30% reduction in risk for developing PD. The risk reduction was present for both sexes and for all lag intervals between the 2 diseases. The observation of a reduced risk for PD in patients with rheumatoid arthritis contrasts with the hypothesis that these patients are at increased risk for PD⁶ and the suggestion that circulating inflammatory mediators produced by some autoimmune diseases may trigger an inflammatory process in the brain that leads specifically to the degeneration of dopaminergic neurons of the substantia nigra.⁴

In the absence of a causal link between systemic autoimmune-based inflammation and PD, we would expect a neutral estimate for patients with systemic autoimmunity. We observed, however, a significant decrease in risk, which can be explained either by the existence of a protective factor or by bias inherent in the study design. One such bias might be underdiagnosis of PD among patients with rheumatoid arthritis. If the symptoms of PD are masked by the physical consequences of rheumatoid arthritis or if patients with rheumatoid arthritis are less aware of the symptoms of PD, underdiagnosis among these patients could occur. There is no literature, however,

Table 3 Odds ratios and 95% confidence intervals for Parkinson disease by type of most prevalent autoimmune disease and lag interval between the 2 diseases

Autoimmune disease* Lag interval, y	No. of cases/controls	OR (95% CI)			
		Both sexes	Men	Women	
Autoantibodies detectable and systemic involvement (category A)					
Rheumatoid arthritis (712.09–712.39, 712.59)					
All (≥5)	63/456	0.7 (0.5–0.9)	0.8 (0.5–1.2)	0.7 (0.5–0.9)	
5–9	31/202	0.8 (0.5–1.1)	0.9 (0.5–1.7)	0.7 (0.4–1.1)	
10–14	12/127	0.5 (0.3–0.9)	0.4 (0.1–1.1)	0.5 (0.3–1.1)	
≥15	20/127	0.8 (0.5–1.3)	0.9 (0.4–1.8)	0.7 (0.4–1.4)	
Autoantibodies detectable and organ involvement (category B)					
Chronic rheumatic heart disease (393–398)					
All (≥ 5)	30/188	0.8 (0.5–1.2)	0.9 (0.6–1.4)	0.7 (0.4–1.3)	
5–9	15/93	0.8 (0.5–1.4)	0.7 (0.3–1.5)	1.0 (0.4–2.3)	
10–14	12/53	1.1 (0.6–2.1)	1.3 (0.6–2.8)	0.8 (0.2–2.7)	
≥15	3/42	0.4 (0.1–1.2)	0.7 (0.2–2.3)	—	
Graves disease (242.00)					
All (≥5)	22/82	1.3 (0.8–2.1)	—	2.1 (1.3–3.5)	
5–9	15/46	1.6 (0.9–2.9)	—	2.5 (1.3–4.6)	
10–14	4/17	1.2 (0.4–3.5)	—	1.8 (0.6–5.7)	
≥15	3/19	0.8 (0.2–2.7)	—	1.4 (0.4–4.9)	
Insulin-dependent diabetes mellitus (249)					
All (≥5)	48/223	1.1 (0.8–1.5)	0.8 (0.5–1.2)	1.6 (1.02–2.5)	
5–9	31/161	1.0 (0.7–1.4)	0.7 (0.4–1.2)	1.5 (0.8–2.5)	
10–14	15/51	1.5 (0.8–2.6)	1.0 (0.4–2.3)	2.3 (1.02–4.9)	
≥15	2/11	0.9 (0.2–4.2)	1.3 (0.1–11.2)	0.7 (0.1–6.0)	
Pernicious anemia (281.00–09)					
All (≥5)	21/89	1.2 (0.7–1.9)	0.6 (0.2–1.4)	1.8 (1.01–3.2)	
5–9	13/54	1.2 (0.7–2.2)	0.5 (0.2–1.8)	1.9 (0.9–4.0)	
10–14	7/23	1.5 (0.7–3.6)	0.5 (0.1–3.5)	2.5 (0.9–6.7)	
≥15	1/12	0.4 (0.1–3.2)	1.0 (0.1–8.6)	—	
Autoantibodies not detectable (category C)					
Polymyalgia rheumatica (446.30–39)					
All (≥5)	65/326	1.0 (0.8–1.3)	1.1 (0.7–1.7)	1.0 (0.7–1.3)	
5–9	39/182	1.1 (0.8–1.5)	1.3 (0.8–2.2)	0.9 (0.6–1.5)	
10–14	17/95	0.9 (0.5–1.5)	0.5 (0.2–1.5)	1.1 (0.6–2.0)	
≥15	9/49	0.9 (0.5–1.9)	1.3 (0.4–4.0)	0.7 (0.3–1.9)	
Sarcoidosis (135.99)					
All (≥5)	21/55	1.9 (1.2–3.2)	1.4 (0.7–3.0)	2.6 (1.3–5.2)	
5–9	9/14	3.2 (1.4–7.4)	2.2 (0.7–7.2)	5.0 (1.5–17.3)	
10–14	5/19	1.3 (0.5–3.5)	0.5 (0.1–3.9)	2.2 (0.7–7.2)	
≥15	7/22	1.6 (0.7–3.7)	1.5 (0.5–4.7)	1.7 (0.5–6.2)	
Ulcerative colitis (563.19, 569.04)					
All (≥5)	42/164	1.3 (0.9–1.8)	1.5 (0.9–2.2)	1.1 (0.6–1.9)	
5–9	16/63	1.3 (0.7–2.2)	1.8 (0.9–3.5)	0.8 (0.3–2.0)	
10–14	7/49	0.7 (0.3–1.6)	0.8 (0.3–2.2)	0.5 (0.1–2.3)	
≥15	19/52	1.8 (1.1–3.1)	1.7 (0.8–3.6)	2.0 (0.9–4.2)	

*Modified Danish version of the *International Classification of Diseases, 8th revision*.

OR = odds ratio; CI = confidence interval.

in support of this explanation. Another potential bias that we were unable to control directly for is confounding by smoking. Smoking seems to be a risk factor for rheumatic diseases²² and a possible protective factor for PD; thus, without controlling for smoking, an increased relative risk would be underestimated. However, when we in secondary analyses adjusted for COPD, as a proxy for heavy smoking, our results remained largely unchanged.

A number of epidemiologic studies have suggested that regular use of anti-inflammatory drugs could inhibit neurodegeneration and protect against the development of PD.^{13-15,23-26} In line with this suggestion, laboratory investigations have shown that nonsteroidal anti-inflammatory drugs (NSAIDs) decrease the formation of neurotoxic molecules²⁷ and inhibit activation of transcription factors that control the expression of genes involved in immune and inflammatory functions.²⁸ Anti-inflammatory drugs are often used in the treatment of rheumatoid arthritis,^{29,30} and given the results from laboratory and human studies, our observation of a decreased risk for PD among patients with rheumatoid arthritis might also—at least theoretically—be explained by a protective effect of the long-term treatment this group of patients adheres to. In the present investigation, however, no data were available on use of NSAIDs in the study population.

We noted an increased risk for PD among women with Graves disease, insulin-dependent diabetes mellitus, and pernicious anemia, and among patients of both sexes with sarcoidosis. We are unable to explain these findings and cannot exclude the possibility that these are chance findings. Further, the slightly non-significant increase in risk for insulin-dependent diabetes mellitus might be an underestimate, because diagnostic information was too crude to allow exclusion of the subgroup of patients having nonautoimmune type 2 diabetes mellitus, specifically.

The strengths of our study include its size, identification of patients from a national hospital register, unbiased selection of population controls through linkage to a nationwide population register, and unbiased ascertainment and validation of autoimmune diseases among patients and controls by linkage to the hospital register. Our study is limited by the fact that patients with less severe PD were potentially missing from our study population, implying that the autoimmune disease pattern of patients with PD is not fully representative of that of all patients with the disease. Further, we had no information on clinical details for patients with PD. Regarding the latter aspect, however, we previously found that 91% of patients with a primary diagnosis of PD in the national hospital register had received anti-Parkinson drugs,¹⁸ indicating lim-

ited misclassification. Also, we had no information on the date of first symptoms of PD. On the other hand, the drug prescription records revealed that treatment with anti-Parkinson drugs was often started some years before the first hospital contact for PD. We attempted to address this delay in diagnosis by introducing a lag interval of 5 years before the first primary or supplementary hospital diagnosis of PD. Finally, if patients with mild autoimmune disease were treated in the primary health care system and more severely affected patients were treated at hospitals, our results would apply only to the last group.

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DISCLOSURE

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