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Relationship between Erectile Dysfunction, Comorbidity, and Parkinson's Disease: Evidence from a Population-Based Longitudinal Study

Yuwan Yang[a,b]
Hsinho Liu[c,d]
Tienhuang Lin[c,d]
Yuhung Kuo[c,e]
Tengfu Hsieh[c,d,e]

[a]Department of Neurology, China Medical University Hospital, Taichung, Taiwan
[b]School of Medicine, China Medical University, Taichung, Taiwan
[c]Departments of Urology and [e]Research, Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taichung, Taiwan
[d]School of Medicine, Tzu Chi University, Hualian, Taiwan

Background and Purpose To determine the risk of Parkinson's disease (PD) in relation to erectile dysfunction (ED) based on the National Health Insurance Research Database in Taiwan.

Methods We identified 3,153 patients who were newly diagnosed with ED between January 1, 2004 and December 31, 2010. A total of 12,612 randomly selected people without ED served as healthy controls. All of the study subjects were followed-up from the index date to the date of PD diagnosis, withdrawal from the National Health Insurance program, or the end of 2012 whichever occurred first.

Results The incidence density rate of PD was 1.52-fold higher in the ED cohort than the non-ED cohort (3.44 vs. 1.64 per 1,000 person-years), with an adjusted hazard ratio (HR) of 1.52 [95% confidence interval (CI)=1.09−2.12]. The combined effects on patients with ED and diabetes as well as hypertension showed a significant combined association with the PD risk compared with patients without ED, counterpart comorbidities, or medication use. The adjusted HR of PD for ED was higher for diabetes (2.82, 95% CI=1.42−5.63) and hypertension (2.19, 95% CI=1.35−3.55).

Conclusions ED leads to an increased risk of PD. ED patients with diabetes or hypertension have an elevated risk of PD.

Key Words comorbidity, diabetes, erectile dysfunction, Parkinson's disease, risk.

INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to achieve or maintain a penile erection sufficient to permit successful sexual intercourse, and it is a complex and heterogeneous disorder.[1] The incidence of ED is increasing globally, and it mainly affects men who are older than 40 years. It has been reported that approximately 150 million men worldwide suffer from ED.[2,3] ED has also been found to be a symptom of serious illnesses such as cardiovascular diseases, diabetes, metabolic syndromes, and all-cause mortality.[4,5]

Erectile function is controlled by the autonomic system, which is frequently compromised in patients with ED. Parkinson's disease (PD) is another disease commonly affected by the autonomic nervous system,[6] and ED is a common nonmotor symptom in PD. In contrast to motor disorders, ED is often unresponsive to levodopa treatment.[7] Previous studies have found that ED can be detected several years before a diagnosis of PD.[6,8] A retrospective analysis of a large cohort (32,616 men) found ED to be associated with a higher future risk of developing PD, and the authors hypothesized that the autonomic nervous system can be impaired for years before PD is clinically identified.[6] However, the findings of that study might be unreliable due to recall bias.

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Correspondence
Tengfu Hsieh, MD, PhD
Departments of Urology and Research, Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, No.88 Sec.1 Fengxing Rd. Tanzi Dist. Taichung 42743, Taiwan
Tel +886-4-3606-0666 ext 3181
Fax +886-4-3606-5928
E-mail hdf95@yahoo.com.tw

To identify the relationship between ED and the subsequent risk of PD, we conducted a nationwide population-based retrospective cohort study using a data set from the Taiwan National Health Insurance (NHI) program. The National Health Insurance Research Database (NHIRD) is a well-validated nationwide population-based data set that allows researchers to trace the medical service usage history of all citizens in Taiwan.[9-11] Several studies have used the NHIRD to investigate associations between different diseases;[12,13] the present study used NHIRD data to examine the possible association between ED and the risk of PD.

METHODS

Ethics statement

The Institutional Review Board of Taichung Tzu Chi General Hospital in Taiwan approved the study protocol (approval no. REC103-43). Because personal identifiers were not included in the secondary files, informed consent did not need to be obtained.

Data sources

This study sampled cohort data from the NHIRD. The NHI program has provided comprehensive health-care coverage in Taiwan since 1995. Enrollment in this government-run, universal, single-payer insurance system is mandatory, and currently around 99% of the 23 million residents of Taiwan receive medical care through the NHI program. In addition, more than 97% of the hospitals and clinics in Taiwan are contracted to provide health-care services[14] that are reimbursed by the NHI Bureau, and all data related to these services are collected and input to the NHIRD by the National Health Research Institutes (NHRI; www.nhri.org.tw) so as to provide a comprehensive record of medical care. The data consist of outpatient care records, inpatient care records, and the registration files of the insured, and the database includes all claims data from the NHI program. The NHI Bureau randomly reviews the charts of 1 out of every 100 outpatient cases and 1 out of every 20 inpatient cases, as well as performing patient interviews to verify the accuracy of diagnoses.[15] The NHRI follows strict confidentiality guidelines for the protection of personal electronic data and maintains the NHI reimbursement data as anonymized files suitable for research use.

Study population

We conducted a population-based retrospective cohort study that included two groups. We initially identified patients who had been newly diagnosed with organic ED [International Classification of Diseases, ninth revision, clinical Modification (ICD-9-CM) code 607.84] or psychogenic ED (ICD-9-CM code 302.72) from inpatient and outpatient files in at least two consistent diagnoses in outpatient care and who were followed up between January 1, 2004 and December 31, 2010. Similar methods for identifying patients with ED have been used in other studies.[16,17] We used the date of ED diagnosis as the index date of the patient.

The control cohort included four non-ED patients per ED patient, who were selected from the same data set with propensity-score matching in order to reduce selection bias by bundling many confounding covariates that may be present in an observational study with this number of variables.

Charlson Comorbidity Index Score

The Charlson Comorbidity Index Score (CCIS) is a widely accepted measure for risk adjustment in administrative-claims data sets.[18,19] The CCIS was calculated for each patient by assigning 1 point for each of myocardial infarct, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective-tissue disease, ulcer, chronic liver disease, and diabetes; 2 points for each of hemiplegia, moderate or severe kidney disease, diabetes with end-organ damage, tumor, leukemia, and lymphoma; 3 points for moderate or severe liver disease; and 6 points for each of malignant tumor, metastasis, and acquired immune deficiency syndrome.

Variables

The independent variables were age, CCIS, comorbidities (e.g., diabetes, hypertension, hyperlipidemia, anxiety, depression, alcoholism, obesity, bipolar disorder, and schizophrenia), drugs causing parkinsonism (i.e., diazepam, alprazolam, and haloperidol),[20] antipsychotic medications (i.e., zolpidem, metoclopramide, and flunarizine),[13] other premotor symptoms [i.e., constipation, rapid-eye-movement-sleep behavior disorder (RBD), and hyposomnia],[21] geographic area of residence, and insurance premiums.[22]

Research outcomes

The main outcome of the study was the occurrence of PD (ICD-9-CM code 332.0), which was determined by linking records with outpatient and inpatient care data in the NHIRD. This method has been used in other studies to identify PD patients.[13,23,24] In Taiwan, secondary PD (including drug-induced or vascular) is recorded as ICD-9-CM code 332.1, and multiple-system atrophy with predominant parkinsonism is recorded as ICD-9-CM code 333. As described in detail previously, patients who diagnosed as PD and those receiving antiparkinsonism medication for more than 60 days are defined as the occurrence of PD.[13,23,24] All patients were observed from the index date to the date of PD diagnosis, with-

drawal from the NHI program, or the end of 2012 whichever occurred first.[25,26]

Statistical analysis

Pearson's chi-square test was applied to categorical variables such as age, insurance premiums, drugs causing parkinsonism, antipsychotic medications, geographic region of residence, and comorbidities. Continuous variables were analyzed using one-way ANOVA. The cumulative risk of PD was estimated using Kaplan-Meier survival curves. A Cox proportional-hazards regression model adjusted for patient characteristics was used to analyze the association of ED with subsequent PD during the 7-year follow-up period. We calculated hazard ratios (HRs) along with 95% confidence intervals (CIs), and used a two-sided p value of <0.05 as a significance cutoff. All of these analyses were conducted using SPSS software (version 15, SPSS Inc., Chicago, IL, USA).

RESULTS

In total, 15,765 patients were included in our study cohort, of whom 3,153 had ED and 12,612 did not have ED (Supplementary Fig. 1 in the online-only Data Supplement). The demographic characteristics and selected morbidities for the two cohorts are presented in Table 1. The mean ages of the ED and non-ED cohorts were 56.7 and 53.4 years, respectively. The patients with ED were more likely to reside in northern and central Taiwan, have more comorbidities, use more medications, and have higher insurance premiums than those without ED.

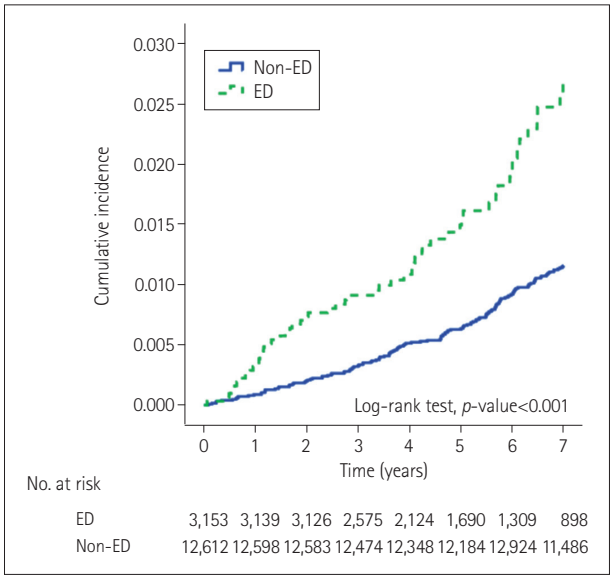

Fig. 1. Cumulative incidence of Parkinson's disease estimated using the Kaplan-Meier method for patients with and without ED. ED: erectile dysfunction.

Kaplan-Meier analysis demonstrated that the cumulative incidence of PD was significantly higher in the ED cohort than in the non-ED cohort (log-rank test p<0.001) (Fig. 1). The follow-up periods for the ED and non-ED cohorts were 5.07±1.77 and 6.83±0.70 years (mean±SD), respectively, and the incidence rates of PD were 3.44 and 1.64 per 1,000 person-years. Multivariate Cox proportional-hazards regression analyses revealed that the risk of PD was 1.52-fold higher in ED patients than in non-ED patients after adjusting for age and comorbidities (95% CI=1.07–2.10) (Table 2). Since ED is an important variable, we applied the Cox proportional-hazards model to stratify by age and CCIS. Compared with the non-ED cohort, the ED cohort still had a higher risk of PD, with an adjusted HR of 1.38 (95% CI=1.02–1.86) (Table 3).

We further explored the association between ED and PD by stratifying age, CCIS, insurance premiums, comorbidity of diabetes, hypertension, hyperlipidemia, anxiety, depression, alcoholism, bipolar disorder, schizophrenia, drugs causing parkinsonism, antipsychotic medications, residence area, and geographic region (Table 4). The adjusted HR of PD for ED was higher for the presence of diabetes (2.82, 95% CI=1.42–5.63) and hypertension (2.19, 95% CI=1.35–3.55), and the absence of anxiety (1.71, 95% CI=1.20–2.45), depression (1.65, 95% CI=1.17–2.33), bipolar disorder (1.56, 95% CI=1.11–2.20), schizophrenia (1.58, 95% CI=1.12–2.23), constipation (1.54, 95% CI=1.08–2.19), RBD (1.49, 95% CI=1.04–2.15), and hyposomnia (1.71, 95% CI=1.19–2.45).

Considering that ED is related to neurodegeneration in the premotor stage, we included organic ED in the analysis. The non-ED group was matched with the propensity score. The patient's age, CCIS, diabetes, hypertension, hyperlipidemia, anxiety, depression, alcoholism, obesity, bipolar disorder, schizophrenia, constipation, RBD, hyposomnia, drugs causing parkinsonism, antipsychotic medications, insurance premiums, residence area, and geographic region were used for propensity-score matching. The patients with organic ED still had a 1.43-fold higher risk of PD than non-ED patients after the adjustment (95% CI=1.06–1.93). The full results are presented in Supplementary Tables 1 and 2 (in the online-only Data Supplement).

DISCUSSION

This study evaluated independent and combined associations between ED and comorbidities (as well as medications) on PD in a large prospective cohort during a 7-year follow-up period. The findings add to the existing literature by showing a 1.52-fold higher risk of PD in all ED patients after adjusting for age, sex, insurance premiums, residence area, CCIS, co-

Table 1. Demographic characteristics of and comorbidities in patients with and without ED in Taiwan from 2004 to 2010 (n=15,765)

Variable	ED (n=3,153)	Non-ED (n=12,612)	p
	n (%)	n (%)	
Age (years), mean±SD	56.7±9.8	53.4±10.5	<0.006
Follow-up duration (years), mean±SD	5.07±1.77	6.83±0.70	<0.0001
CCIS			<0.0001
0 or 1	2,607 (82.7)	11,813 (93.7)	
2 or 3	463 (14.7)	675 (5.3)	
>3	83 (2.6)	124 (1.0)	
Comorbidity			
Diabetes	634 (20.1)	837 (6.6)	<0.0001
Hypertension	1,051 (33.3)	1,924 (15.3)	<0.0001
Hyperlipidemia	578 (18.3)	734 (5.8)	<0.0001
Anxiety	351 (11.1)	437 (3.5)	<0.0001
Depression	140 (4.4)	136 (1.1)	<0.0001
Alcoholism	8 (0.3)	20 (0.2)	0.256
Obesity	11 (0.3)	7 (0.1)	<0.0001
Bipolar disorder	34 (1.1)	33 (0.3)	<0.0001
Schizophrenia	22 (0.7)	54 (0.4)	0.051
Constipation	140 (4.4)	183 (1.5)	<0.001
RBD	408 (12.9)	498 (3.9)	<0.001
Hyposomnia	355 (11.3)	464 (3.7)	<0.001
Drugs causing parkinsonism	2,256 (71.6)	6,629 (52.6)	<0.0001
Antipsychotic medications	2,175 (69.0)	5,857 (46.4)	<0.0001
Insurance premium			<0.0001
<17,500 NTD/month	884 (28.0)	2,856 (30.6)	
17,500–25,000 NTD/month	883 (28.0)	4,334 (34.4)	
>25,000 NTD/month	1,386 (44.0)	4,422 (35.0)	
Residence area			<0.0001
Urban	1,085 (34.4)	3,791 (30.1)	
Suburban	1,461 (46.3)	5,774 (45.8)	
Rural	607 (19.3)	3,047 (24.2)	
Geographic region			<0.0001
Northern/central	2,302 (73.0)	8,505 (67.4)	
Southern/eastern	851 (27.0)	4,107 (32.6)	

CCIS: Charlson Comorbidity Index Score, ED: erectile dysfunction, NTD: New Taiwan Dollar, RBD: rapid eye movement sleep behavior disorder.

morbidities, and medications.

We also found that the risk of PD was higher for patients with ED along with diabetes or hypertension than for patients without ED or counterpart comorbidities. ED has been reported as a risk factor for the development of PD,[6,8] but this association has so far been described as an independent effect. Some previous studies accounted for diabetes and hypertension,[27,28] but none considered their combined effect with ED on PD. It is unclear whether ED and other comorbidities play significant combined roles. Our research showed that diabetes and hypertension are jointly associated with ED in producing 2.53- and 2.17-fold higher risks of PD, respectively.

ED is a complex and heterogeneous disorder that possibly has arterial, neurogenic, hormonal, cavernous, iatrogenic, and psychogenic causes. ED could also be associated with not only cardiovascular disease but also neurological disorders including migraine, epilepsy, and dementia.[1,17,29,30] Furthermore, many studies have indicated that ED can be detected several years prior to a PD diagnosis.[6,8] These findings and the present results can be combined in ongoing efforts to identify individuals at the earliest phase of PD.

ED is diagnosed by self-reporting. It is not easy to reliably classify organic ED and psychogenic ED clinically because all sexual dysfunctions involve the mind as well as the relationship with a sexual partner.[31] For these reasons, we performed the analysis using both organic and psychogenic ED, and found that ED leads to an increased risk of PD.

The incidence of ED was lower in our patients than among those included in other studies. This is because ED is a taboo subject in Taiwan, with patients being reluctant to discuss sex.[17] Thus, the control group may have included some unidentified ED cases. The risk of PD was still clearly demonstrated despite this possible confounding effect, but the true risk may be even greater when every ED case can be clearly identified.

A previous study found ED to be associated with PD diagnosed more than 10 years later.[6] However, significant recall bias might have been present in that study. The present nationwide population-based cross-sectional study was able to avoid recall bias since it involved a large and representative sample. The NHIRD data set covers more than 99% of the

Table 2. Results from the Cox proportional-hazards model measuring HRs and 95% CIs of PD associated with patients with ED

Characteristic	Crude			Adjusted		
	HR	(95% CI)	*p*	HR	(95% CI)	*p*
ED	2.34	(1.71–3.21)	<0.0001	1.50	(1.07–2.10)	0.019
Comorbidity						
Hypertension	3.04	(2.28–4.04)	<0.0001	1.11	(0.81–1.52)	0.512
Depression	4.61	(2.63–8.09)	<0.0001	1.58	(0.77–3.23)	0.214
Schizophrenia	14.94	(8.33–26.79)	<0.0001	19.44	(10.35–36.54)	<0.0001
Constipation	5.03	(3.06–8.28)	<0.0001	1.42	(0.84–2.39)	0.193
Hyposomnia	2.73	(1.78–4.19)	<0.0001	1.50	(0.90–2.51)	0.123
Insurance premiums						
<17,500 NTD/month	1.00	Reference		1.00	Reference	
17,500–25,000 NTD/month	0.71	(0.51–0.98)	0.038	1.01	(0.71–1.44)	0.938
>25,000 NTD/month	0.50	(0.35–0.71)	<0.0001	0.99	(0.68–1.45)	0.960
Geographic region						
Northern/central	1.00	reference		1.00	Reference	
Southern/eastern	1.10	(0.82–1.47)	0.546	0.99	(0.73–1.36)	0.982

Adjusted HR: adjusted for ED, age, CCIS, insurance premiums, comorbidity of diabetes, hypertension, hyperlipidemia, anxiety, depression, alcoholism, bipolar disorder, schizophrenia, drugs causing parkinsonism, antipsychotic medications, constipation, RBD, and hyposomnia in Cox proportional-hazards regression.
CCIS: Charlson Comorbidity Index Score, CI: confidence interval, ED: erectile dysfunction, HR: hazard ratio, NTD: New Taiwan Dollar, PD: Parkinson's disease, RBD: rapid-eye-movement-sleep behavior disorder.

Table 3. Results of the stratified Cox proportion-hazards model for PD associated with ED patients and non-ED patients

Characteristics	Crude			Adjusted		
	HR	(95% CI)	*p*	HR	(95% CI)	*p*
ED	1.42	1.08–1.88	0.011	1.38	1.02–1.86	0.034
Comorbidity						
Hypertension	1.50	1.36–1.66	<0.001	1.46	1.15–1.86	0.002
Depression	1.69	1.33–2.16	<0.001	1.79	1.12–2.87	0.015
Schizophrenia	9.20	7.08–11.96	<0.001	5.91	2.51–13.92	<0.001
Constipation	1.91	1.64–2.23	<0.001	1.62	1.14–2.31	0.007
Hyposomnia	1.38	1.15–1.65	<0.001	1.60	1.12–2.30	0.010
Insurance premiums						
<17,500 NTD/month	1.00			1.00		
17,500–25,000 NTD/month	0.74	0.66–0.82	<0.001	0.68	0.51–0.91	0.009
>25,000 NTD/month	0.77	0.69–0.87	<0.001	0.75	0.57–0.99	0.044
Geographic region						
Northern/central	1.00			1.00		
Southern/eastern	1.18	1.08–1.30	<0.001	1.29	1.02–1.65	0.037

Stratified by age and CCIS. Adjusted HR: adjusted for ED, age, CCIS, insurance premiums, comorbidity of diabetes, hypertension, hyperlipidemia, anxiety, depression, alcoholism, bipolar disorder, schizophrenia, drugs causing parkinsonism, antipsychotic medications, constipation, RBD, and hyposomnia in Cox proportional-hazards regression.
CCIS: Charlson Comorbidity Index Score, CI: confidence interval, ED: erectile dysfunction, HR: hazard ratio, NTD: New Taiwan Dollar, PD: Parkinson's disease, RBD: rapid-eye-movement-sleep behavior disorder.

Table 4. Risk for PD in patients with and without ED

Variables	ED (*n*=3,153)			Non–ED (*n*=12,612)			IRR (95% CI)	Adjusted HR (95% CI)
	Event	Person years	IR	Event	Person years	IR		
Total	55	15,989	3.44	141	86,190	1.64	2.10 (1.54–2.87)†	1.50 (1.07–2.10)*
CCIS								
0 or 1	30	13,240	2.27	109	80,746	1.35	1.68 (1.12–2.51)*	1.25 (0.81–1.93)
2 or 3	22	2,372	9.27	28	4,591	6.10	1.52 (0.87–2.66)	2.17 (1.18–4.02)*
>4	3	377	7.96	4	852	4.69	1.70 (0.38–7.57)	3.44 (0.42–27.92)
Comorbidity								
Diabetes								
No	36	12,822	2.81	122	80,412	1.52	1.85 (1.28–2.68)†	1.20 (0.81–1.79)
Yes	19	3,166	6.00	19	5,779	3.29	1.83 (0.97–3.45)	2.82 (1.42–5.63)†
Hypertension								
No	23	10,815	2.13	95	72,905	1.30	1.63 (1.03–2.57)*	1.03 (0.63–1.69)
Yes	32	5,173	6.19	46	13,286	3.46	1.79 (1.14–2.81)*	2.19 (1.35–3.55)†
Hyperlipidemia								
No	40	13,204	3.03	126	81,101	1.55	1.95 (1.37–2.78)†	1.39 (0.95–2.04)
Yes	15	2,785	5.39	15	5,089	2.95	1.83 (0.89–3.74)	1.79 (0.83–3.86)
Anxiety								
No	48	14,181	3.38	123	83,172	1.48	2.29 (1.64–3.20)†	1.71 (1.20–2.45)†
Yes	7	1,808	3.87	18	3,018	5.96	0.65 (0.27–1.55)	0.69 (0.26–1.81)
Depression								
No	52	15,313	3.40	131	85,271	1.54	2.21 (1.60–3.05)†	1.65 (1.17–2.33)†
Yes	3	675	4.44	10	920	10.87	0.41 (0.11–1.49)	0.16 (0.02–1.13)
Alcoholism								
No	55	15,954	3.45	139	86,055	1.62	2.13 (1.56–2.92)†	1.51 (1.08–2.12)*
Yes	0	35	0	2	136	14.71	0	
Obesity								
No	55	15,941	3.45	141	86,141	1.64	2.11 (1.54–2.88)†	1.50 (1.18–1.90)†
Yes	0	48	0	0	49	0	0	
Bipolar disorder								
No	54	15,834	3.41	137	85,973	1.59	2.14 (1.56–2.93)†	1.56 (1.11–2.20)†
Yes	1	155	6.45	4	217	18.43	0.35 (0.04–3.13)	
Schizophrenia								
No	53	15,886	3.34	131	85,839	1.53	2.19 (1.59–3.01)†	1.58 (1.12–2.23)†
Yes	2	103	19.42	10	352	28.41	0.68 (0.15–3.12)	0.82 (0.11–6.31)
Constipation								
No	50	15,302	3.27	129	84,945	1.52	2.15 (1.55–2.98)†	1.54 (1.08–2.19)*
Yes	5	686	7.29	12	1,245	9.64	0.76 (1.27–2.15)	1.05 (0.32–3.37)
RBD								
No	44	13,939	3.16	128	82,744	1.55	2.04 (1.45–2.87)†	1.49 (1.04–2.15)*
Yes	11	2,049	5.37	13	3,445	3.77	1.42 (0.64–3.18)	1.68 (0.69–4.11)
Hyposomnia								
No	48	14,133	3.40	124	83,014	1.49	2.27 (1.63–3.17)†	1.71 (1.19–2.45)†
Yes	7	1,854	3.78	17	3,176	5.35	0.71 (0.29–1.70)	0.69 (0.27–1.75)
Drugs causing parkinsonism								
No	10	4,411	2.27	35	40,562	0.86	2.63 (1.30–5.31)†	1.49 (0.70–3.18)
Yes	45	11,578	3.89	106	45,629	2.32	1.67 (1.18–2.37)†	1.53 (1.05–2.23)*
Antipsychotic medications								
No	10	4,894	2.04	41	45,829	0.89	2.28 (1.14–4.56)*	1.44 (0.69–3.01)
Yes	45	11,094	4.06	100	40,361	2.48	1.64 (1.15–2.33)†	1.54 (1.05–2.24)*

Table 4. Risk for PD in patients with and without ED (continued)

Variables	ED (*n*=3,153)			Non-ED (*n*=12,612)			IRR (95% CI)	Adjusted HR (95% CI)
	Event	Person years	IR	Event	Person years	IR		
Insurance premium								
<17,500 NTD/month	26	4,498	5.78	55	25,929	2.12	2.73 (1.71–4.34)†	2.00 (1.21–3.29)†
17,500–25,000 NTD/month	11	4,517	2.44	54	29,746	1.82	1.34 (0.70–2.57)	0.96 (0.47–1.98)
>25,000 NTD/month	18	6,974	2.58	32	30,515	1.05	2.46 (1.38–4.38)†	1.44 (0.76–2.73)
Residence area								
Urban	19	5,507	3.45	39	25,928	1.50	2.29 (1.33–3.97)†	1.47 (0.80–2.70)
Suburban	28	7,438	3.76	55	39,484	1.39	2.70 (1.71–4.26)†	1.99 (1.22–3.27)†
Rural	8	3,044	2.63	47	20,778	2.26	1.16 (0.55–2.46)	0.89 (0.40–2.00)
Geographic region								
Northern/central	38	11,735	3.24	92	58,134	1.58	2.05 (1.40–2.99)	1.42 (0.94–2.14)
Southern/eastern	17	4,254	4.00	49	28,056	1.75	2.29 (1.32–3.97)	1.91 (1.05–3.46)*

Adjusted HR: adjusted for ED, age, CCIS, insurance premiums, comorbidity of diabetes, hypertension, hyperlipidemia, anxiety, depression, alcoholism, bipolar disorder, schizophrenia, drugs causing parkinsonism, antipsychotic medications, constipation, RBD and hyposomnia in Cox proportional-hazards regression.
*p<0.05, †p<0.01, ‡p<0.001.
CCIS: Charlson Comorbidity Index Score, CI: confidence interval, ED: erectile dysfunction, HR: hazard ratio, IR: incidence rates, per 1,000 person-years, IRR: incidence rate ratio, NTD: New Taiwan Dollar, PD: Parkinson's disease, RBD: rapid-eye-movement-sleep behavior disorder.

23.74 million residents of Taiwan and the NHIRD has been validated as being highly accurate.[11,32] The high coverage rate of the NHI program in our study could also have minimized the number of cohort subjects lost during follow-up. Given the considerable differences in age, medications, and comorbidities between the present ED and non-ED patients, the risk of PD increased in the Cox proportional-hazards model. Our results have provided further epidemiological evidence of the relationship between PD and ED.

Many antipsychotic drugs (e.g., flunarizine and zolpidem) and antiemetic drugs (e.g., metoclopramide) can cause PD, and previous studies have investigated the association between ED and the risk of developing PD.[6,8,13] However, most of these studies did not include potentially parkinsonism-causing medicines in the adjusted variables. In the current research, the ED patients took these medicines more frequently than non-ED patients (71.6% vs. 52.6% for parkinsonism-related drugs and 69.0% vs. 46.4% for antipsychotic medications, both p<0.0001)−the results may be misleading if the adjusted variables do not include these drugs. The present study also found an association between ED and PD in subgroups with and without the use of these medications.

While the present study was not able to identify the real connection between ED and PD, there are at least two possible mechanisms for a relationship between ED and PD. First, ED is one of manifestations of parasympathetic cholinergic failure,[33] and the findings of previous studies suggest that many nonmotor symptoms and autonomic dysfunction could be early signs of preclinical stages of PD development.[34] Second, testosterone levels are important for erectile function,[35] and lower testosterone levels are an important component of ED. Many authors have reported that testosterone deficiency is often observed in PD patients relative to age-matched controls.[36,37] Furthermore, beneficial effects of testosterone administration on both motor and nonmotor symptoms in PD patients have also been reported.[37-39]

One limitation of the present analysis is that the diagnoses of ED, PD, and comorbid conditions were completely dependent on ICD-9-CM codes, and so the presence of coding errors should be considered. However, the NHI Bureau randomly reviews patient charts and conducts patient interviews to verify the accuracy of diagnoses. Moreover, hospitals with outlier charges or practices may be audited, with subsequent heavy penalties for malpractice or discrepancies. Second, the database does not contain information on daily activity, dietary habits, tobacco use, education, or body mass index, which may also be risk factors for PD. Laboratory data are also not available in the database. Although we attempted to overcome these problems, they can only be addressed using observable variables, and unobservable variables may still have confounded our results. Further studies linking administrative-claims data and primary hospitalization information such as the severity of ischemic stroke and detailed risk factors are warranted. However, given the magnitude and statistical significance of the effects observed in this study, these limitations are unlikely to compromise the results.

In conclusion, the results of this population-based retrospective cohort study suggest that ED leads to an increased risk of PD. ED patients with diabetes or hypertension had an elevated risk of PD. Further research into the mechanisms underlying the effect of ED on PD is needed, but clinicians should already recognize the potential implications of ED

and stay vigilant for the onset of PD.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2017.13.3.250.

Conflicts of Interest

The authors have no financial conflicts of interest.

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