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Risk of Parkinson disease after depression

A nationwide population-based study

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ABSTRACT

Objective: To evaluate the risk of Parkinson disease (PD) among patients with depression by using the Taiwan National Health Insurance Research Database (NHIRD).

Methods: We conducted a retrospective study of a matched cohort of 23,180 participants (4,634 patients with depression and 18,544 control patients) who were selected from the NHIRD. Patients were observed for a maximum of 10 years to determine the rates of new-onset PD, and Cox regression was used to identify the predictors of PD. We also examined the risk of PD after excluding patients who were diagnosed with PD within 2 or 5 years after their depression diagnosis. A logistic regression model was used to identify risk factors associated with PD onset in patients with depression.

Results: During the 10-year follow-up period, 66 patients with depression (1.42%) and 97 control patients (0.52%) were diagnosed with PD. After adjusting for age and sex, patients with depression were 3.24 times more likely to develop PD (95% confidence interval 2.36–4.44, $p < 0.001$) compared with the control patients. After excluding patients who were diagnosed with PD within 2 or 5 years after their depression diagnosis, patients with depression had a higher hazard ratio for developing PD than the control patients. The odds ratios for age (1.09) and difficult-to-treat depression (2.18) showed that each is an independent risk factor for PD in patients with depression.

Conclusion: The likelihood of developing PD is greater among patients with depression than patients without depression. Depression may be an independent risk factor for PD. ***Neurology***® **2013;81:1–7**

GLOSSARY

CI = confidence interval; **HR** = hazard ratio; ***ICD-9-CM*** = *International Classification of Diseases*, ninth revision, Clinical Modification; **LHID 2005** = Longitudinal Health Insurance Database 2005; **NHI** = National Health Insurance; **NHIRD** = National Health Insurance Research Database; **OR** = odds ratio; **PD** = Parkinson disease.

Parkinson disease (PD) is the second most common neurodegenerative disease after Alzheimer disease, and its worldwide prevalence is estimated to be 1% to 2% for people older than 65 years.[1] Depression has been reported to be more common in patients with PD than in the general population,[2,3] and a considerable number of studies have evaluated the prevalence of depression,[2,3] the impact of depression on the quality of life,[4] and the treatment of depression[5] in patients with PD.

Depression increases the subsequent risk of many physical illnesses, such as cancer[6] and stroke,[7] and studies have shown that depression precedes PD development, indicating that it may be a risk factor for PD.[8–17] However, such evidence has originated primarily from case-control studies[11–17] that were limited by a small sample size and recall bias of the depression diagnosis. In addition, whether depression is an independent risk factor for PD or merely an early manifestation of the neurodegenerative disease remains unclear.[11,12]

Supplemental data at www.neurology.org

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We performed a population-based retrospective cohort study using data derived from the National Health Insurance (NHI) system in Taiwan. The aim of our study was to determine whether clinical depressive disorder was associated with an increased risk of PD. Independent risk factors for newly diagnosed PD in patients with depression were also surveyed.

METHODS

Data source. Instituted in 1995, the NHI program is a mandatory health insurance program that offers comprehensive medical care coverage, including outpatient, inpatient, emergency, and traditional Chinese medicine, to all residents of Taiwan, with a coverage rate of up to 98%.[18,19] The NHI research database (NHIRD) contains comprehensive information regarding clinical visits, including prescription details and diagnostic codes based on the A code and *ICD-9-CM*. The NHIRD is managed by the National Health Research Institutes, and confidentiality is maintained according to the directives of the Bureau of NHI. We used the Longitudinal Health Insurance Database 2005 (LHID 2005) as the data source for our study, which is a dataset released by the National Health Research Institutes that contains all original claims data for 1 million randomly selected beneficiaries in the 2005 Registry of Beneficiaries.

Standard protocol approvals, registrations, and patient consents. The Institutional Review Board of Taipei Veterans General Hospital approved this study (2013-04-036BC). Written consent from study subjects was not obtained because the NHI dataset consists of deidentified secondary data for research purposes and the Institutional Review Board of Taipei Veterans General Hospital issued a formal written waiver for the need for consent.

Study population. Using data extracted from the LHID 2005, we conducted a retrospective cohort study of patients aged 20 years and older who were newly diagnosed with depressive disorder by a psychiatrist between January 1, 2000 and December 31, 2001. The definition of depressive disorder included major depressive disorder (*ICD-9-CM* codes: 296.2 and 296.3), dysthymic disorder (*ICD-9-CM* code: 300.4), and depressive disorder not elsewhere classified (*ICD-9-CM* code: 311). We excluded patients who were diagnosed with depressive disorders (A code: A212 and A214; *ICD-9-CM* codes: 296.2, 296.3, 300.4, and 311), bipolar disorders (A code: A212; *ICD-9-CM* codes: 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8, 296.80, and 296.89), or PD (A code: A221; *ICD-9-CM* code: 332) between January 1, 1996 and December 31, 1999. For each patient with depression included in the final cohort, 4 age- and sex-matched control patients without psychiatric disease were randomly selected from the LHID 2005 between 2000 and 2001. All depression and control patients were observed until diagnosed with PD, death, withdrawal from the NHI system, or December 31, 2009. The data from patients who were diagnosed with PD, death, and withdrawal from the NHI system were viewed as censored data. The primary clinical outcome assessed was neurologist-diagnosed PD. For sensitivity analyses, we also included a cohort of newly diagnosed depressive patients who were diagnosed by psychiatrists or nonpsychiatrists.

Statistical analysis. The incidence of newly diagnosed PD in the depression and control patients was calculated, and independent t tests and χ^2 tests were used to examine the differences in the demographic characteristics between the depression and control patients.

A Cox proportional-hazards regression model was used to identify variables that predicted the length of time between the index date and the date of PD diagnosis after controlling for age and sex. To evaluate whether depression is an independent risk factor for PD or an early manifestation of PD, we also performed Cox proportional-hazards regression after excluding depression patients who were diagnosed with PD within 2 or 5 years of being diagnosed with depression.

We also used univariate and multivariate logistic regression models to identify the risk factors for PD in the patients with depression. Control variables such as age, sex, and common comorbidities including hypertension, diabetes mellitus, and dyslipidemia were included as covariates in the univariate model. In addition, we added antidepressant use, number of psychiatric hospitalizations, and difficult-to-treat depression[20] in the analysis. We identified antidepressants according to the Anatomical Therapeutic Chemical classification system.[21] Antidepressants were classified into 4 groups according to their proposed mechanisms of action: tricyclic antidepressants (N06AA), selective serotonin reuptake inhibitors (N06AB), monoamine oxidase inhibitors (N06AF and N06AG), and other antidepressants (N06AX). "Other antidepressants" included serotonin norepinephrine reuptake inhibitors, mirtazapine, bupropion, and so on. The definition of difficult-to-treat depression is defined as depression patients whose antidepressant treatment regimen was altered 2 or more times in the first 2 years of being diagnosed with depression. In addition, these antidepressants must be used for more than 60 consecutive days, which represents an adequate trial.[20] Factors that demonstrated a moderately significant statistical relationship in the univariate analysis ($p < 0.1$) were included in the multivariate analysis.[22]

The SAS statistical software for Windows, version 9.3 (SAS Institute, Cary, NC), was used for data extraction, computation, data linkage, processing, and sampling. All other statistical analyses were performed using the SPSS statistical software for Windows, version 20 (IBM, Armonk, NY). The results of comparisons with a p value of <0.05 were considered to indicate a statistically significant relationship.

RESULTS

Participant selection. Our study included 4,636 patients with depression and 18,544 control patients without depression, among whom 62% were female. The comparisons of the demographic and clinical variables between the depression and control patients are presented in table 1. Between 2002 and 2009 during the follow-up period, 66 patients with depression (1.42%) and 97 control patients (0.52%) were diagnosed with PD ($p < 0.001$). In 4,636 patients with depression, 4,292 patients (92.6%) had been treated with antidepressants during the follow-up period and the mean duration of antidepressant use was 397.4 days (SD = 618.4 days). The antidepressant types most frequently used in the depression cohort were selective serotonin reuptake inhibitors (45.3%), followed by other antidepressants (37.1%), then tricyclic antidepressants (13.9%).

Clinical depression on PD risks after adjusting for age and sex. After adjusting for age and sex, the hazard ratio (HR) for developing PD during the follow-up period was 3.24 times (95% confidence interval [CI] 2.36–4.44, $p < 0.001$) greater for the patients

Table 1 Demographic data, comorbidities, and PD in patients with depression and matched controls

	Patients with depression (n = 4,636)	Matched controls (n = 18,544)	*p* Values
Age at enrollment, y, mean (SD)	41.47 (15.08)	41.47 (15.08)	1
Distribution according to age, n (%)			
20–39 y	2,395 (51.66)	9,580 (51.66)	1
40–59 y	1,560 (33.65)	6,240 (33.65)	1
≥60 y	681 (14.69)	2,724 (14.69)	1
Sex, n (%)			
Male	1,781 (38)	7,124 (38)	1
Female	2,855 (62)	11,420 (62)	1
Follow-up, y, median (IQR)	8.84 (8.41–9.39)	9.84 (9.51–9.94)	<0.001[a]
Newly diagnosed PD			
No. (%)	66 (1.42)	97 (0.52)	<0.001[a]
Age at enrollment, y, mean (SD)	63.76 (13.29)	63.94 (10.84)	0.052
Age at diagnosis of PD, y, mean (SD)	69.03 (12.77)	69.84 (10.34)	0.658
Distribution of age of PD			
30–39 y	1	1	
40–49 y	4	5	
50–59 y	9	9	
60–69 y	13	27	
70–79 y	26	42	
≥80 y	13	13	
Sex of PD, n (%)			
Male	31 (47)	42 (43)	0.644
Female	35 (53)	55 (57)	
Duration from enrollment to PD, mean (SD)	5.26 (2.23)	6.33 (2.36)	0.600

Abbreviations: IQR = interquartile range; PD = Parkinson disease.
[a] Statistical significance.

with depression than for the control patients (table 2 and figure). After excluding patients diagnosed with PD within the first 2 or 5 years of the follow-up period, the HRs for the development of PD in the remaining patients with depression were still higher than that of the control patients (HR = 3.10, 95% CI 2.31–4.30, $p < 0.001$; HR = 2.84, 95% CI 1.89–4.27, $p < 0.001$, respectively).

Sensitivity analyses. Included in the analyses were 8,786 patients with depression who were diagnosed by a psychiatrist or nonpsychiatrist and 35,144 control patients without depression, among whom 62% were female. During the follow-up period, 148 patients with depression (1.68%) and 286 control patients (0.52%) were diagnosed with PD ($p < 0.001$). After adjusting for age and sex, the HR for developing PD during the follow-up period was 2.52 times (95% CI 2.06–3.08, $p < 0.001$) greater for the patients with depression than for the control patients (tables e-1 and e-2 on the *Neurology*® Web site at www.neurology.org).

Risk factors for PD in patients with depression. The results in table 3 show the comparisons of the demographic and clinical variables between the depression patients with PD and depression patients without PD and reveal that the depression patients with PD were older than depression patients without PD. The results of the univariate analysis in table 4 show that age (odds ratio [OR] = 1.09, 95% CI 1.07–1.11, $p < 0.001$), difficult-to-treat depression (OR = 2.46, 95% CI 1.37–4.40, $p = 0.003$), hypertension (OR = 4.05, 95% CI 2.48–6.60, $p < 0.001$), dyslipidemia (OR = 2.22, 95% CI 1.24–3.97, $p = 0.007$), and diabetes mellitus (OR = 2.73, 95% CI 1.52–4.89, $p = 0.001$) were associated with the development of PD in patients with depression.

Although sex was not determined to be a statistical risk factor for PD in the univariate analysis, we included it in the multivariate analysis because previous studies have shown a male preponderance in the risk of PD in the general population.[23] The multivariate analysis confirmed that age (OR = 1.09, 95% CI

Table 2 HRs of time until PD during a 10-year follow-up period

	Unadjusted HR (95% CI, *p* value)	Adjusted HR (95% CI, *p* value)
Including all patients diagnosed with PD in the study period		
Sex (male = 1, female = 0)	1.32 (0.97–1.80, 0.076)	0.99 (0.72–1.35, 0.941)
Age	1.09 (1.08–1.10, <0.001[a])	1.09 (1.08–1.10, <0.001[a])
Depression (1 = depression, 0 = control)	3.13 (2.28–4.29, <0.001[a])	3.24 (2.36–4.44, <0.001[a])
Excluding patients diagnosed with PD in the first 2 y after enrollment		
Sex (male = 1, female = 0)	1.21 (0.88–1.66, 0.25)	0.91 (0.66–1.26, 0.576)
Age	1.09 (1.08–1.10, <0.001[a])	1.09 (1.08–1.10, <0.001[a])
Depression (1 = depression, 0 = control)	2.99 (2.15–4.15, <0.001[a])	3.10 (2.23–4.30, <0.001[a])
Excluding patients diagnosed with PD in the first 5 y after enrollment		
Sex (male = 1, female = 0)	1.36 (0.92–2.00, 0.12)	1.05 (0.71–1.55, 0.794)
Age	1.08 (1.07–1.10, <0.001[a])	1.08 (1.07–1.10, <0.001[a])
Depression (1 = depression, 0 = control)	2.73 (1.82–4.10, <0.001[a])	2.84 (1.89–4.27, <0.001[a])

Abbreviations: CI = confidence interval; HR = hazard ratio; PD = Parkinson disease.
[a] Statistical significance.

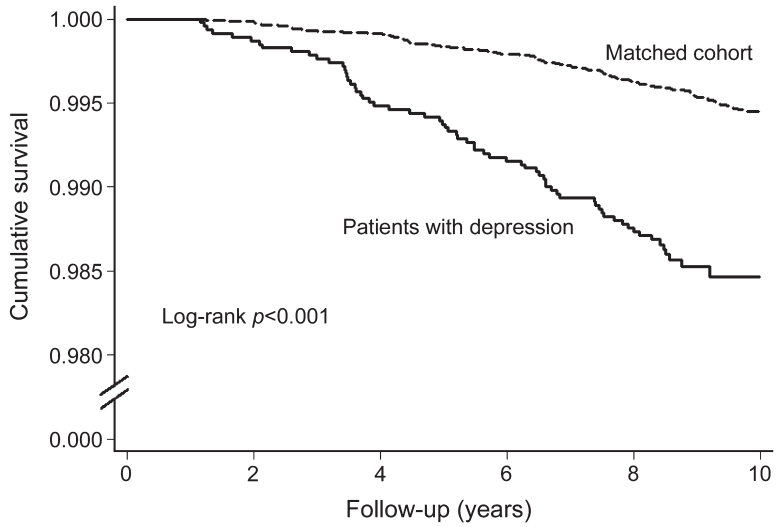
1.07–1.11, $p < 0.001$) and difficult-to-treat depression (OR = 2.18, 95% CI 1.18–4.02, $p = 0.013$) were independent risk factors for PD in patients with depression.

DISCUSSION The key findings in our study are that 1) the risk of PD was increased when patients had psychiatrist-diagnosed clinical depression (HR = 3.24); 2) the long-term risk of developing PD was greater in patients with depression, as evidenced by a higher HR for patients with depression diagnosed with PD at more than 2 or 5 years after their depression diagnosis; 3) the age was higher in depression patients with PD than in depression patients without PD; and 4) age (OR = 1.09) and difficult-to-treat depression (OR = 2.18) were independent risk factors for PD in patients with depression.

The strengths of our study are the large sample size, the long follow-up period, and the diagnosis of clinical depressive disorders by specialists. In addition, our study design included an unbiased participant selection process. Because participation in the NHI is mandatory and all residents of Taiwan can access health care with low copayments, referral bias is low and follow-up compliance is high.

Consistent with previous studies,[8–16] we found that the risk of PD in patients with clinical depression was higher than that in the control patients without

Figure Cox regression survival plots for subjects with and without depression



Patients with depression (solid line) were more likely to be diagnosed with Parkinson disease over time than subjects without depression (dashed line). The x-axis represents the time in years, and the y-axis the percentage survival.

Table 3 Characteristics of depression patients with or without PD

	Depression with PD (n = 66)	Depression without PD (n = 4,570)	*p* Values
Age, y, mean ± SD	63.76 ± 13.29	41.15 ± 14.86	<0.001[a]
Sex, n (%)			
Male	31 (47)	1,750 (38)	0.15
Female	35 (53)	2,820 (62)	
Antidepressant use, n (%)	64 (97)	4,228 (92.5)	0.17
No. of psychiatric hospitalizations, mean (SD)	0.09 (0.42)	0.13 (1.03)	0.78
Difficult-to-treat depression, n (%)	15 (22.7)	489 (10.7)	0.002[a]
Comorbidity, n (%)			
Hypertension	32 (48.5)	862 (18.9)	<0.001[a]
Dyslipidemia	15 (22.7)	535 (11.7)	0.006[a]
Diabetes mellitus	15 (22.7)	445 (9.7)	<0.001[a]

Abbreviation: PD = Parkinson disease.
[a] Statistical significance.

depression. Separate studies of depression and PD have shown that impaired monoaminergic neurotransmission may contribute to the underlying pathology in each.[24] Thus, the 2 diseases may share similar pathologic mechanisms. In addition, previous studies have shown that depression is correlated with chronic inflammation,[25,26] and chronic inflammation has been reported to increase the risk of PD.[27]

Whether depression is an independent risk factor for PD or merely an early manifestation during the prodromal phase of PD is unclear.[11,12] Estimates of the duration of the prodromal phase of PD vary from 3 to 20 years,[28,29] and the onset of classic parkinsonism has been proposed to be frequently preceded by a prodromal phase lasting from 4 to 6 years.[28] Consistent with the hypothesis proposed in one previous study,[12] we found that the long-term risk of developing PD was greater in patients with depression, after excluding patients who were diagnosed with PD at more than 2 or 5 years after their depression diagnosis, indicating that depression may be an independent risk factor for PD. However, neurodegenerative disorders such as PD may initiate 10 to 20 years before they become symptomatic, and depression in PD may have some unusual characteristics that make the diagnosis of depression in PD very difficult; therefore, we cannot obviate the possibility that depression is also an early symptom of PD from our study results.

It is possible that use of antidepressants may increase the risk of PD, which may partially account for our observation on depression and PD. Two studies found that PD and the use of antiparkinson drugs were independently associated with the use of antidepressant drugs for 6 months[30] and 2 years,[31] respectively. However, the risk of PD was not increased after the use of antidepressants for 2 years. Our study showed that the risk of PD remained higher in patients with depression who had received treatment for depression for more than 2 years. In addition, we also found that antidepressant use was not an independent risk factor for PD in patients with depression. Thus, factors other than the use of antidepressant drugs may have contributed to the increased HR for PD in patients with depression.

In our study, we defined difficult-to-treat depression as patients with depression whose antidepressant treatment regimen was altered 2 or more times in the first 2 years of being diagnosed with depression and these antidepressants must be used for more than 60 consecutive days. The change of antidepressant in patients with depression may be related to many factors, and adverse effects and nonremission are the most frequent reasons for switching.[32,33] If the antidepressant was changed because of adverse effects, it was usually changed in the first few weeks after taking it. Therefore, it was reasonable to think that the

Table 4 Analyses of risk factors for PD in patients with depression

	Univariate analysis			Multivariate analysis		
Variable	OR	95% CI	*p* Value	OR	95% CI	*p* Value
Age	1.09	1.07-1.11	<0.001[a]	1.09	1.07-1.11	<0.001[a]
Sex	1.43	0.88-2.32	0.152	1.07	0.63-1.75	0.842
Antidepressant use	2.59	0.63-10.6	0.18	1.92	0.46-8.02	0.37
No. of psychiatric hospitalizations	0.95	0.67-1.34	0.78			
Difficult-to-treat depression	2.46	1.37-4.40	0.003[a]	2.18	1.18-4.02	0.013[a]
Comorbidity						
Hypertension	4.05	2.48-6.60	<0.001[a]	0.88	0.50-1.55	0.66
Dyslipidemia	2.22	1.24-3.97	0.007[a]	1.06	0.56-2.03	0.85
Diabetes mellitus	2.73	1.52-4.89	0.001[a]	1.10	0.58-2.10	0.77

Abbreviation: CI = confidence interval; OR = odds ratio; PD = Parkinson disease.
[a] Statistical significance.

change of antidepressant according to our definition was mainly attributable to nonremission. Previous studies have showed that neurotoxicity of depression was related to severity of depression, and repetition of depressive episodes.[34] In our study, we found that difficult-to-treat depression was an independent risk factor for PD in patients with depression, and this finding may imply that neurotoxicity of depression is related to the severity or resistance of depression, and the more resistance of depression, the more risk of PD in these patients.

We found that the incidence of PD was greater among older patients with depression, and that age is an independent risk factor for the development of PD in patients with depression. When we divided our cohort into 2 groups—younger age (<65 years) and older age (≥65 years)—and put this variable into a Cox proportional-hazards regression model, the HR for developing PD during the follow-up period was 10.39 times (95% CI 7.62–14.16, $p < 0.001$) greater for the older patients than for the younger patients. Our findings are consistent with results of previous studies that found age to be a primary risk factor for PD, and that the incidence of PD increases progressively with increasing age.[35] We did not find that sex is a risk factor for PD, which is contrary to data from Western studies that showed a higher prevalence of PD in men than in women.[36,37] However, a study of PD prevalence in Taiwan in 2001 reported no differences between men and women.[38] Thus, ethnic and environmental factors may also contribute to the risk of PD.

There are limitations to our findings. First, information regarding the family history of PD, lifestyle factors (tobacco and coffee use), and environmental factors (exposure to pesticides and herbicides) are not included in the NHIRD, all of which may be associated with the risk of PD.[23,39–41] Second, in studies using NHIRD, it was not clear how the diagnostic classification was performed. Therefore, the diagnostic accuracy of depression in our study could not be ascertained. Further studies with depression patients diagnosed by structured interview should be conducted to investigate the association between depression and the risk of PD. Third, the severity of depression and the length of depressive episode were unknown in our study, and whether these 2 factors influence the risk of developing PD warrants further study. Fourth, the duration of the follow-up period in our study may have been insufficient for detecting late-onset PD. Thus, future studies with longer follow-up periods are required to better elucidate the long-term risk of PD in patients with depression.

Our population-based retrospective cohort study found that both the short-term (<2 years) and long-term risks of PD are higher among patients with depression than in patients without depression, and that depression may be an independent risk factor for PD. Older age and difficult-to-treat depression are also independent risk factors for PD in patients with depression. Future population-based prospective studies with longer-duration observation are needed to further investigate the association between depression and the risk of PD.

AUTHOR CONTRIBUTIONS

Cheng-Che Shen: analysis and interpretation. Shih-Jen Tsai: study supervision, critical revision of the manuscript for important intellectual content. Chin-Lin Perng and Benjamin Ing-Tiau Kuo: analysis and interpretation. Albert C. Yang: acquisition of data, study concept and design.

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DISCLOSURE

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