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Risk of Dementia after Parkinson's Disease in Taiwan: A Population-based Nationwide Cohort Study

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Abstract

Objectives A nationwide cohort study on the risk of dementia onset after first diagnosis of Parkinson's disease (PD) is lacking. This study aims to assess 11 years of incidence and the relative risks for developing dementia in patients with PD compared with matched controls.

Design Population-based cohort study.

Setting National Health Insurance database in Taiwan.

Participants A total of 5,932 patients with PD was identified and 29,645 age-, sex-, and index year-matched PD-free individuals were randomly selected.

Intervention None

Outcome measures All subjects were linked to the claim data to identify the first diagnosis of dementia. The Poisson assumption was used to estimate the incidence rate. Fine-Gray proportional hazards models with a partitioning of time at 1 year to account for proportionality were used to estimate the risk of dementia onset.

Results The median duration from the first diagnosis of PD to the development of dementia was 9.02 years. In the first partition (≦1 years), the incidence of dementia in PD and control groups was 114.49 and 9.76 per 1,000 person-years, respectively, with an adjusted hazard ratio of 9.62 (95%CI, 7.95-11.64). In the second partition (>1 year), the incidence of dementia in PD and control groups was 30.99 and 10.83 per 1,000 person-years, with an adjusted hazard ratio of 2.37 (95%CI, 2.20-2.57). Notably, in the second partition, both man and women aged<70 had the highest hazard ratio (3.79, 95%CI=2.77-5.18 and 4.18, 95%CI=3.17-5.51, respectively).

Conclusions The risk of dementia onset increases twofold one year after the first diagnosis of PD.

Keywords: epidemiology, retrospective cohort study, Parkinson's disease, dementia, competing risk

Article Summary

Strengths and limitations of this study

- The study strengths include a nationwide and retrospective cohort design for 11 years and more accurate estimates for incidence rates of dementia by using the first diagnosed PD cases rather than the prevalent cases as study subjects.
- Multivariate Cox proportional hazard regression with competing risk analysis was used to control the confounding bias and account for the competing risk of death.
- We were unable to consider a comprehensive list of potential confounders such as smoking, educational level, physical function, and genes in the analysis because of the limited information available from the claims data.
- Another limitation is the lack of clinical symptoms and subtypes of dementia.

INTRODUCTION

Parkinson's disease (PD) has been associated with developing cognition impairments[1]. Some studies have reported that older age[2-12]and male gender[2 5]are related to increased dementia risk in PD; however, information regarding the age- and sex- stratified dementia incidence rate in PD is scant. In addition, most previous studies on the association between PD and dementia risk were conducted in western countries[2-8 10-17], and information for Asian PD populations is lacking. Moreover, to identify robust relative risks of dementia in PD requires a large sample size cohort and a sufficiently long follow-up time to observe the development of symptoms for dementia. To the best of our knowledge, there has been no nationwide cohort study on this topic[2-18], and most previous cohort studies involved a limited number of person-years with a limited follow-up period[3-6 8-12 15-17]. Nevertheless, many PD patients have medical comorbidities such as stroke, hypertension, diabetes mellitus, hyperlipidemia, and coronary heart disease, which may have modification effects on the relationship between dementia and PD[5 16-18]. However, little research has examined medical comorbidities as a potential confounding factor to control[5 9 18]and none has considered death as a competing risk[3-17], which may induce potential attrition bias and tend to distort the study results.

In Taiwan, the only population-based study with a case-control design showed a positive association between PD and the risk of dementia[18]. However, this Taiwanese study recruited prevalent PD cases at various disease stages to investigate the relative risks of developing dementia in PD, which may have caused survival bias. Therefore, a nationwide population-based cohort study was conducted to estimate 11 years of incidence in this study and the relative risks for development of dementia in patients with first-diagnosed PD by age- and sex- specific and selected comorbidities (i.e., hypertension, diabetes, coronary artery disease (CAD), stroke, hyperlipidemia, and chronic obstructive pulmonary disease (COPD)) after accounting for the competing risk of death.

METHODS

Data Source

The dataset were from ambulatory care claims, inpatient claims and the updated registry for beneficiaries retrieving from Taiwan's National Health Insurance Research Database (NHIRD), as provided by the National Health Insurance Administration (NHIA), Ministry of Health and Welfare, Taiwan. A universal National Health Insurance (NHI) program has been implemented in Taiwan since 1995, which more than 99% of Taiwan residents have enrolled in the NHI program after 2000, and the National Health Insurance Administration have contracted with 92.5% of hospitals and clinics[19] The NHIA performs quarterly expert reviews on a random sample of every 50-100 ambulatory and inpatient claims in each hospital and clinic to ensure the accuracy of the claims data[19]. False reports of diagnoses result in a severe penalty from the NHIA. Therefore, information obtained from NHIRD is considered to be complete and accurate. Access to the NHIRD has been approved by the National Health Research Institutes Review Committee.

Patient and public involvement

We conducted this study by using the National Health Insurance Research Database. No patients or public were involved in development of the research question and outcome measures. Also, no patients or public were involved in setting out the design of this study, nor were they involved in the recruitment to and conduct of the study. The study results were not disseminated to study subjects.

Study design, Cohorts and Covariates

This was a retrospective cohort study from 2002-2012. We selected 5,932 eligible PD patients between 2002 and 2003 from a previous study for which sample selection details were discussed previously[20]. The method for identifying PD cases has been validated and found to have a good sensitivity, specificity, positive predictive value, and negative predictive value of 97.6%, 92.3%, 98.8%, and 85.7%, respectively. In brief, the PD cohort in this study

included all cases with at least 3 medical claims (either outpatient or inpatient care) with a diagnostic code of PD (ICD-9-CM: 332.0) who had received 3 or more courses of anti-Parkinsonism medications, including L-dopa or dopamine agonist prescriptions after first-time diagnosis between 2002 and 2003. Moreover, the first and last outpatient or inpatient visits and anti-Parkinsonism medication records were separated by at least 90 days to avoid accidental inclusion of miscoded patients.

We further made the following exclusions to ensure the validity of the PD diagnosis: (1) an age on the index date of less than 40 years, who are more likely to have a genetic etiology; (2) a diagnostic code of secondary Parkinsonism (ICD-9-CM code: 332.1) during the study period; (3) receipt of any neuroleptic medication 180 days prior to the index date, and (4) 3 or more medical claims (either ambulatory or inpatient care) with diagnostic codes of dementia prior to the index date. The first date of initial diagnosis for PD in the period of 2002 to 2003 was set as the index date.

The control subjects were selected from those who had never been diagnosed with PD between 1999 and 2011 and met the same exclusion criteria as those set for the patients with PD. These control subjects were matched by age (each 5-year span), sex, and year of index date for patients with PD at a 5:1 ratio. As a result, 29,645 control subjects were identified. For the control groups, the index date was either January 1, 2002 or January 1, 2003.

Baseline comorbidities that may be associated with an increased risk of dementia were identified for the PD and control groups, including hypertension, diabetes, CAD, stroke, hyperlipidemia, and COPD observed before the index date. Information on the geographic area, urbanization level, occupational status, and salary-based insurance premium at the index date was also obtained from the registry for beneficiaries. The number of medical visits within one year after the index date was adjusted to decrease the potential presence of surveillance bias because subjects with PD visit clinics more frequently and thus may have more opportunities to be diagnosed as having dementia.

End point and Statistical analysis

The main outcome variable was initial occurrence of dementia (ICD-9-CM code: 290, 294.1, 331.0, and 331.82). To increase the validity of dementia identification, only dementia cases diagnosed with≥3 ambulatory visits or ≥1 hospitalization were included in this study. We do not distinguish the subtypes of dementia because it is not clear differences between AD and vascular dementia in certain situations[21]. Also, it is not easy to distinguish the major common type of dementia after PD by using ICD-9-CM codes because there is no specific ICD-9-CM diagnosis codes for Parkinson's disease dementia and the major common type of dementia after PD may be coexist[22-24].We followed the study subjects from the index date to the first diagnosed dementia, withdrawal from the NHI, or December 31, 2012, whichever came first. The incidence density of dementia was calculated using an age- and sex- specific and comorbidity-specific stratified analysis based on the Poisson assumption. The cumulative events and rates of dementia according to the PD status over the study period were calculated using a Kaplan-Meier analysis, and the log-rank test was used to test the between-group differences. A Cox proportional hazard regression with competing risk models, according to Fine and Gray's proportional sub-hazards models[25], was performed to assess the hazard ratio (HR) of dementia in relation to PD. In addition, we performed sex- and age- stratified analysis and comorbidity-stratified analysis to examine the potential effect-modifications by age, sex, and comorbidity on the association between PD and the risk of dementia. Plots of log (-log (survival function)) vs. log (time) were drawn to test for violations of the proportional-hazards assumption. Therefore, separate time-partitioned models were created, and the hazards within each partition were assessed. Proportionality was held for the new models partitioned at 1 year. If we modeled the hazards for ≤1 year (i.e., the first time partition), the censoring day for subsequent events was 1 year. If we modeled the hazards for>1 year (i.e., the second time partition), subjects with earlier events were included and considered to be censors (because the exclusion of these subjects may lead to a survival bias). A $p<0.05$ was considered

significant.

RESULTS

Gender, age, geographic area, and urbanization levels were similar in both groups. The prevalence rates of the risk factors for dementia were high in patients with PD. The PD cohort had fewer white-collar workers (25.0% vs 31.2%), a higher prevalence of dependence (39.9% vs 33.8%), a lower insurance premium, and a higher frequency of medical visits (26.5 vs 19.7 per year) than the control group (Table 1).

Figure 1 shows the cumulative incidence of dementia in patients with and without PD. The cumulative incidence of dementia for PD was significantly higher than the corresponding data observed in the non-PD group (log-rank test, $p<0.0001$).

The median duration from the first diagnosis of PD to the development of dementia was 9.02years. In the period within 1 year after the index date (i.e., the first time partition), the corresponding incidence densities of dementia for the PD and control groups were 114.49 and 9.76 per 1,000 person-years, respectively. Noticeably, the incidence density of dementia increased with age irrespective of PD status and sex, and the highest incidence was observed in those aged ≧80 years. The adjusted HR of dementia in relation to PD was significantly increased at 9.62 (95%CI 7.95-11.64) and was higher in men than in women (HR: 11.28 vs. 5.64). In addition, there was a significant interaction of PD with age on the risk of dementia for both men ($P = 0.0147$) and women ($P<0.0001$) (Table 2).

In the years following the PD diagnosis (i.e., the second time partition), the overall incidence density of dementia was much lower (Table 2). The change in incidence density between the first and the second partition was more pronounced in the PD group (from 114.49 to 30.99 per 1,000 person-years) than in the control group (from 9.76 to 10.83 per 1,000 person-years). The age- and sex- specific incidence densities had a similar pattern in terms of change. However, no significant difference in the sex-specific HRs (hazard ratios) of dementia was observed ($p = 0.7064$). There was a significant interaction of PD status with age

(P <0.0001) in both sexes. Age- and sex-specific HRs showed the highest HR to be in PD females aged <70 years (HR: 4.18; 95% CI 3.17-5.51).

Impact of PD on the risk of dementia by selected medical comorbidities was shown in Table 3. Irrespective of various partition of time, the incidence of dementia increased with the number of comorbidities in both groups. The PD group had the highest risk of dementia across various medical comorbidities stratifications after adjusting baseline characteristics. In the first partition of time, the interaction of PD with diabetes (P=0.0070) and COPD (P=0.0033) on the risk of dementia was statistically significant, indicating that subjects without diabetes and COPD had a higher adjusted HR irrespective of PD status. However, although the adjusted HR were also higher in subjects without hypertension, CAD, stroke, and hyperlipidemia than in those with the medical comorbidities, there was no statistically significant modification effect by hypertension, CAD, stroke, and hyperlipidemia on the association between PD and the risk of dementia.

In the second partition of time, effect-modification by hypertension (P<0.0001), CAD (P=0.0111) and stroke (P<0.0001) was statistically significant for dementia, indicating that subjects without those medical comorbidities had a higher adjusted HR irrespective of PD status. Among diabetes, hyperlipidemia, or COPD patients, adjusted HR for dementia also showed statistically significant high risk from 1.97 (95% CI=1.64–2.36) to 2.09 (95% CI=1.81–2.42), but no significant modification effect was found for those with medical comorbidities on the association between PD and the risk of dementia. Whether medical comorbidities exist or not, the HRs were greater in the first partition of time but were smaller in the second partition than those analyzed for all PD.

DISCUSSION

To the best of our knowledge, this is the first nationwide population-based cohort study to demonstrate that patients with the first diagnosis of PD are associated with increased risk of dementia compared with non-PD patients. In this study, we found that the hazard ratio (HR)

of dementia was significantly higher within 1 year after the initial PD diagnosis (HR =9.62, 95%CI=7.59-11.64). However, the magnitude of association varied according to different age and sex stratifications. In general, the risk of dementia was higher in men in the first partition but was similar in both sexes in the second partition. However, the increased risk was highest in both male and female participants aged <70 years in any given partition time. The study results can provide physicians and patients with valuable information and also demonstrate the need for guidelines for detection of dementia risk after the initial diagnosis of PD.

Potential mechanisms contributing to dementia in patients with PD are still poorly understood. The site pathology for dementia in PD includes brain stem nuclei, limbic structures, and the cerebral cortex, and the types of pathological changes have been described as Lewy body (LB) degeneration and Alzheimer-type changes[26]. Regardless of whether there is additional Alzheimer's pathology (amyloid β (Aβ) plaques and tau neurofibrillary tangles (NFTs))[22-24], the main pathology associated with dementia in PD are Lewy body degeneration in the limbic structures and cerebral cortex, with α-synuclein[26]. Deficits in dopaminergic, noradrenergic, serotoninergic, and cholinergic neurochemicals are known to be the cause of cognition impairment in PD[26].

Some former studies have revealed that the fact that the risk of dementia increases with the disease duration of PD may be due to the Lewy pathology as PD progresses temporally and spatially from the brain stem through the forebrain and limbic system to the neocortex, which is supported by the Braak pathology staging hypothesis[27 28]. However, our study showed a sharply increased hazard of dementia within1 year after first diagnosis of PD, which is clinically and biologically unbelievable; this situation is probably because a large proportion of patients with dementia remain undiagnosed before the index date of their first clinical visit for PD. Nevertheless, a reasonably increased hazard of dementia more than one year after diagnosis of PD is more likely to be real and may suggest evidence of the mechanisms supported by the Braak pathology staging hypothesis[27 28]. Our findings were

similar to another population-based case control study in Taiwan[18], which showed the risk of developing dementia in prevalent Parkinsonism was highest in the first 6 months (AOR:11.98, 95%CI:8.51-16.68) and then became lower in the following months to years after diagnosis.

Age is known to be a risk factor for dementia not only in the general population[29 30] but also in PD patient population[2-12]. This may be caused by aging of non-dopaminergic structures (i.e., the locus ceruleus and pedunculopontine nucleus)[31]. However, a modifying effect of age on the risk of dementia after PD may be present in our study. For example, we found that patients with PD had a significantly higher overall risk of dementia than those in the control group, particularly in subjects aged < 70 years. This result is similar to the findings of some prior studies[11 12].

Male gender is sometimes identified as a risk factor for dementia in PD[2 5]; however, there is no clear explanation for this finding. In our study, we found no significant role of gender in the first-diagnosed PD patients one year later. Accordingly, patients with PD, especially younger patients in both sexes, could be selected as a target population to evaluate whether interventions are effective in decreasing the risk of dementia after diagnosis of PD in future studies.

Our study also shows that the overall risk of dementia was more than double (adjusted HR 2.37) among subjects with first-diagnosed PD 1 year later for up to 11 years. After accounting for the competing risk of death and adjustment for the number of medical visits, the findings were similar to those of Perezet al., who reported a higher relative risk of incident dementia (2.31, 95%CI 1.48-3.61) in patients with PD as compared to non-PD subjects[13]. However, other cohort studies have shown a relative risk of 1.7 (95%CI:1.1–2.7) to5.9 (95%CI:3.9–9.1) for incident dementia in PD groups compared with the general population[7 8 10-12 15], which is different from our findings. Noticeably, most previous studies were limited by a relatively small sample size[3-17], shorter follow-up time[3-6 8-12 15-17], the lack of a matched control[3-6 9 14 16 17], failure to account for the competing risk of death[3-17], or a lack of adjustment

for the number of medical visits to control for surveillance bias[7 8 10-13 15], rendering the risk that the estimates were more likely to be imprecise and biased.

We found the incidence of dementia increased with number of comorbidities, including hypertension, diabetes mellitus, CAD, stroke, hyperlipidemia and COPD. However, of the patients with PD in our study, PD alone also has more positive effects on dementia in most circumstances, although effect modifiers such as hypertension, diabetes, stroke, CAD, hyperlipidemia, and COPD had positive effects for dementia. Prior studies regarding the relationship between patients with PD and those comorbidities remain controversial[5 16-18]. For example, although a study in Taiwan has demonstrated those cerebrovascular or cardiovascular comorbidities in patients with PD had lower risk of dementia onset than patients with PD alone[18], which is similar our findings, other studies have failed to relate those cerebrovascular or cardiovascular risk factors[16 17]. Besides, some previous studies have revealed that PD with cardiovascular dysautonomia (such as hypertension, diabetes mellitus, and CAD) and COPD might cause substantial cerebral hypoperfusion and hypoxia, respectively[32-34]. Hypoxia and hypotension in the brain might cause neuronal damage and increase accumulation of pathologic proteins such as β-amyloid, which result in increased risk of dementia onset[32 33].Therefore, future perspective studies focusing on needed the causal relationship between those comorbidities and the risk of dementia in PD are warranted.

There were several strengths in our study. First, we obtained a large, nationwide number of participants by using NHIR datasets, which made it possible to reduce selection bias, to obtain higher statistical power, to obtain a highly representative study population, to have a lower rate of nonresponse or loss to follow-up, and to facilitate the age-, sex- and comorbidities-stratified analyses with an ample simple size to satisfy requirements. To the best of our knowledge, this study is the first to report the age- and sex- specific incidence rates of dementia in a PD group. Secondly, we conducted a longitudinal and retrospective cohort study for 11 years, which is a longer time during which to observe the development of

dementia than that in many other prior studies[3-6 8-12 15-17]. Thirdly, more accurate estimates for the incidence rates of dementia in the PD group are available in this study due to the usage of the first diagnosed PD cases rather than the prevalent PD cases, as this might reduce the variations in the incidence of dementia across various PD durations. Fourth, this study used multivariate Cox proportional hazard regression with competing risk analysis to control the confounding bias and account for the competing risk of death.

Still, our study had some limitations. First, because we selected dementia patients only by using NHIR datasets, we might have missed some patients who had been waiting for a pathological diagnosis, which may have resulted in an underestimation of the incidence of dementia. Also, because patients with PD may utilize the health care system more often than control groups, surveillance bias may be present. To address this concern, we calculated the number of medical visits for 1 year after the index date and adjusted for it in the multivariate regression model. Secondly, the severity of dementia is not available in the database, and we could not distinguish subtypes of dementia in our datasets. Therefore, it is essential for patients with PD, particular in high risk groups such as subjects aged <70 years, to have regular cognitive assessments including combinations of neuropsychological markers throughout the early disease stages, which not only would provide benefits for identification of the subtypes in dementia but would also decrease underestimation of risk for dementia in PD. Thirdly, due to the limited information available from the claims data, we were unable to consider a comprehensive list of potential confounders such as smoking, educational level, physical function, and genes in the analysis, which may have resulted in residual confounding bias. To reduce such bias, we used COPD and occupational status as surrogates for smoking and educational level, respectively.

In conclusion, it was found that PD confers a high risk of dementia than non-PD patients, especially in the group of aged< 70 years in both sexes. Regular monitoring for the development of dementia in patients with PD in a long-time follow-up, particularly risk

groups, is recommended. Future research should include further evaluation of the underlying mechanism and subtypes for dementia development after diagnosis of PD.

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Author contributions Chih-Ching Liu analyzed the data and wrote the draft of the manuscript. Yu Sun and Pei-Chen Lee provided further data analyses and interpretation. Chung-Yi Li and Susan C. Hu advised the study and revised the manuscript. All authors have approved the final version of the manuscript.

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Competing interests None.

Patient consent Not required.

Ethics approval Full review by our institutional review board was not required because the encryption on the identification numbers makes it impossible to identify individuals. Access to the National Health Insurance Research Database datasets is approved by the National Health Research Institutes Review Committee.

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Data sharing statement We, as the authors of this original research article, state that there is no additional, unpublished data available from this study. Raw data sharing from National Health Insurance Research Database is prohibited, according to the policy of National Health

Research Institutes (NHRI) in Taiwan.

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Table 1. Characteristics of the study subjects

Variables[a]	PD group n	PD group %	Control group n	Control group %	P value
Age (years)					
<70	1852	31.2	4220	31.2	1.00 [d]
70-74	1314	21.2	6570	21.2	
75-79	1460	24.6	7300	24.6	
≧80	1306	22.0	6515	22.0	
Mean (±SD) [b]		72.5±9.4		70.8±12.7	
Sex					1.00 [d]
Male	3116	52.6	15580	52.6	
Female	2813	47.4	14065	47.4	
Insurance premium (NTD)[b]					<0.0001 [e]
Dependent	2333	39.9	9721	33.8	
<Median (19,200)	1734	29.6	7753	26.2	
>=Median	1787	30.5	12171	41.0	
Mean (±SD)[c]		7102.6±11122.9		10194.0±13197.8	
Urbanization status					0.0007 [d]
Urban	3203	54.7	15197	51.8	
Satellite city/town	2085	35.6	9741	33.2	
Rural area	566	9.8	4424	15.0	
Geographic area					<0.0001 [d]
Northern	2670	45.6	13130	44.8	
Central	1491	25.5	7288	24.9	
Southern	1519	25.9	7957	27.1	
Eastern	174	3.0	931	3.2	
Occupational status					<0.0001 [d]
White collar	1482	25.0	9242	31.2	
Blue collar	2075	35.0	11846	40.0	
Others	2375	40.0	8557	28.8	
History of comorbidity					
Without comorbidities	1151	19.4	16393	55.3	<0.0001 [d]
Hypertension	3578	60.3	11431	38.6	<0.0001 [d]
Diabetes	1430	24.1	4112	13.9	<0.0001 [d]
CAD	1955	33.0	4890	16.5	<0.0001 [d]
Stroke	1977	33.3	2924	9.9	<0.0001 [d]
Hyperlipidemia	1089	18.4	3013	10.2	<0.0001 [d]
COPD	1719	29.0	5624	19.0	<0.0001 [d]

Mean number of medical visits	39.6	26.5	21.9	19.7	<0.0001 [e]
Total	5932	100.0	29645	100.0	

[a]Inconsistency between total population and population summed for individual variables was due to missing information.

[b]SD=Standard deviation; NTD=New Taiwan Dollars; CAD=Coronary artery disease ; COPD=chronic obstructive pulmonary disease

[c]The dependent insurers were not included.

[d]Based on χ^2 test

[e]Based on student's t test

Table 2. Age- and sex- specific incidence densities of dementia (ICD-9: 290, 294.1, 331.0, 331.82)in the Parkinson's disease and control groups

Variables	≦1 years				>1 years			
	ID (95% CI)[a,b]		Crude HR	AHR	ID (95% CI)[a,b]		Crude HR	AHR
	Control group	PD group	(95% CI)	(95% CI)	Control group	PD group	(95% CI)	(95% CI)
Male								
<70	1.61	56.23	34.48	16.06	2.61	17.57	6.46	3.79
	(0.42-2.81)	(40.16-72.31)	(15.60-76.23)	(6.82-37.79)[d]	(2.13-3.09)	(14.48-20.67)	(5.02-8.33)	(2.77- 5.18)[c]
70-74	5.61	111.38	19.47	13.03	9.23	32.27	3.27	2.83
	(3.08-8.13)	(85.29-137.47)	(11.75-32.26)	(7.59-22.37)[d]	(8.16-10.30)	(27.02-37.52)	(2.68-4.00)	(2.23-3.58)[c]
75-79	7.59	129.62	16.71	9.55	14.01	38.05	2.47	2.04
	(4.92-10.27)	(103.83-155.42)	(11.18-24.99)	(6.12-14.88)[d]	(12.77-15.25)	(32.58-43.51)	(2.08-2.94)	(1.67-2.48)[c]
≧80	22.18	196.24	8.73	6.92	18.94	41.87	2.01	1.88
	(17.26-27.10)	(161.70-230.78)	(6.58-11.57)	(4.93-9.70)[d]	(17.31-20.57)	(35.34-48.40)	(1.68-2.41)	(1.54-2.29)[c]
Total	8.81	118.82	13.28	11.28	10.27	30.33	2.74	2.36
	(7.32-10.29)	(106.16-131.49)	(10.88-16.20)	(8.74-14.55)[e]	(9.74-10.81)	(27.93-32.73)	(2.49-3.02)	(2.11-2.63)[d]
Female								
<70	1.43	51.66	35.85	11.04	3.35	22.23	6.75	4.18
	(0.37-2.49)	(37.20-66.12)	(16.24-79.13)	(4.46-27.30)[d]	(2.85-3.86)	(18.98-25.49)	(5.48-8.33)	(3.17-5.51)[c]
70-74	7.37	89.93	12.06	4.66	10.81	33.61	3.03	2.69
	(4.36-10.38)	(65.72-114.14)	(7.41-19.63)	(2.66-8.18)[d]	(9.62-12.00)	(28.25-38.97)	(2.49- 3.68)	(2.15-3.38)[c]

75-79	10.92	165.75	14.86	8.31	17.61	43.22	2.40	2.22
	(7.25-14.59)	(132.06-199.4)	(10.06-21.96)	(5.42-12.76)[d]	(16.04-19.18)	(36.70-49.70)	(2.01-2.87)	(1.82-2.70)[c]
≧80	31.19	180.68	5.75	3.31	22.99	38.74	1.63	1.53
	(24.60-37.79)	(143.56-217.8)	(4.29-7.72)	(2.29-4.78)[d]	(20.97-25.02)	(32.00-45.47)	(1.34-1.99)	(1.23-1.91)[c]
Total	10.80	109.89	10.07	5.64	11.41	31.72	2.71	2.37
	(9.08-12.53)	(97.16-122.63)	(8.27-12.26)	(4.48-7.08)[e]	(10.83-12.00)	(29.24-34.21)	(2.46-2.98)	(2.12-2.64)[d]
Overall	9.76	114.49	11.58	9.62	10.83	30.99	2.72	2.37
	(8.62-10.89)	(105.51-123.4)	(10.07-13.32)	(7.95-11.64)[f]	(10.43-11.22)	(29.27-32.72)	(2.55- 2.91)	(2.20- 2.57)[e]

In the first time partition (≦1 years), the interactions were significant for PD with age (p<0.0001)and with sex (p=0.0010),with age in men (p=0.0147), and with age in women (p<0.0001). In the secondtime partition (>1 years), the interactions were significant for PD with age (p<0.0001),with age in men (p<0.0001), and with age in women ((p<0.0001), but not for PD with sex (p=0.7064).

[a]ID= incidence density(per 1,000 person-years), CI=confidence interval, AHR=adjusted hazard ratio, HR=hazard ratio,

[b]Based on Poisson assumption

[c]Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for age and sex.

[d]Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for sex.

[e]Based on Cox proportional hazard regression with competing risk analysis and adjusted for age, sex, insurance premium, urbanization status, geographic area,occupational status, status of hypertension, diabetes, CAD, stroke, hyperlipidemia, COPD, and number of medical visits.

*P<0.05

Table 3. Impact of Parkinson's disease on the risk of dementia by comorbidities

Variables	≦1 years				>1 years			
	ID (95% CI)[a,b]		Crude HR	AHR	ID (95% CI)[a,b]		Crude HR	AHR
	Control group	PD group	(95% CI)	(95% CI)	Control group	PD group	(95% CI)	(95% CI)
Hypertension								
No	7.49	110.98	14.58	7.84	8.57	27.99	3.18	2.94
	(6.23-8.76)	(96.94-125.02)	(11.82-17.99)	(6.13-10.01)[c]	(8.13-9.01)	(25.45-30.53)	(2.86-3.53)	(2.60-3.33)[c]
Yes	13.40	116.81	8.64	7.76	14.80	33.14	2.15	2.02
	(11.26-15.55)	(105.12-128.49)	(7.16-10.43)	(6.16-9.79)[c]	(14.03-15.56)	(30.81-35.48)	(1.97-2.35)	(1.83-2.22)[c]
			Interaction: p=0.3336				Interaction: p<0.0001	
Diabetes								
No	9.13	115.65	12.49	10.52	10.15	29.39	2.78	2.45
	(7.95-10.31)	(105.28-126.02)	(10.68-14.61)	(8.55-12.94)[c]	(9.74-10.56)	(27.48-31.29)	(2.58-3.01)	(2.24-2.67)[c]
Yes	13.69	110.87	8.05	4.50	15.46	36.57	2.24	2.09
	(10.07-17.31)	(92.88-128.85)	(5.91-10.96)	(3.22-6.29)[c]	(14.13-16.79)	(32.61-40.53)	(1.95-2.58)	(1.78-2.44)[c]
			Interaction: p= 0.0070				Interaction: p= 0.1674	
CAD								
No	8.47	107.08	12.49	7.41	10.11	29.77	2.82	2.47
	(7.31-9.62)	(96.49-117.67)	(10.56-14.77)	(6.13- 8.96)[c]	(9.69-10.52)	(27.73-31.81)	(2.60-3.05)	(2.26-2.71)[c]
Yes	16.39	129.78	7.86	7.06	14.85	33.69	2.21	2.02
	(12.75-20.02)	(113.04-146.52)	(6.08- 10.15)	(5.15- 9.70)[c]	(13.66-16.04)	(30.47-36.91)	(1.95-2.50)	(1.76-2.32)[c]
			Interaction: p= 0.5289				Interaction: p=0.0111	

Stroke								
No	7.84 (6.77-8.91)	99.07 (88.88-109.26)	12.48 (10.52-14.79)	7.86 (6.52- 9.49)[c]	9.99 (9.59-10.39)	29.39 (27.37-31.40)	2.85 (2.63-3.09)	2.60 (2.38- 2.84)[c]
Yes	27.73 (21.57-33.88)	146.13 (128.41-163.86)	5.26 (4.09- 6.77)	5.84 (4.32- 7.88)[c]	19.94 (18.09-21.80)	34.66 (31.36-37.97)	1.71 (1.50-1.96)	1.68 (1.47-1.93)[c]
			Interaction: p= 0.4950				Interaction: p= <0.0001	
Hyperlipidemia								
No	9.83 (8.63-11.03)	118.50 (108.36-128.63)	11.88 (10.24- 13.78)	9.66 (7.92- 11.78)[c]	10.49 (10.08-10.90)	30.64 (28.73-32.54)	2.76 (2.56-2.97)	2.45 (2.25-2.67)[c]
Yes	9.08 (5.66-12.51)	97.10 (77.97-116.23)	10.62 (6.95- 16.24)	5.97 (3.72- 9.57)[c]	13.82 (12.40-15.23)	32.52 (28.46-36.58)	2.30 (1.95-2.70)	1.97 (1.64-2.36)[c]
			Interaction: p= 0.4354				Interaction: p= 0.2713	
COPD								
No	8.72 (7.53-9.91)	108.70 (98.33-119.07)	12.28 (10.41-14.50)	10.62 (8.56- 13.16)[c]	10.21 (9.79-10.63)	29.59 (27.62-31.56)	2.79 (2.57-3.02)	2.48 (2.27-2.72)[c]
Yes	14.27 (11.10-17.43)	128.85 (111.08-146.02)	9.00 (6.94- 11.68)	5.50 (4.10- 7.40)[c]	13.77 (12.70-14.84)	34.86 (31.31-38.41)	2.41 (2.12-2.75)	2.09 (1.81- 2.42)[c]
			Interaction: p= 0.0033				Interaction: p= 0.1116	
Number of Comorbidities								
0	5.88 (4.56-7.19)	99.30 (80.40-118.21)	16.68 (12.45-22.35)	8.61 (6.24-11.87)[d]	7.48 (7.01-7.96)	24.63 (21.32-27.94)	3.28 (2.82-3.82)	3.34 (2.83-3.95)[d]
1	9.60	104.64	10.77	7.93	11.76	28.61	2.39	2.54

	(7.19-12.00)	(85.26-124.02)	(7.90-14.70)	(5.74-10.95)[d]	(10.87-12.65)	(24.94-32.27)	(2.06-2.77)	(2.17-2.98)[d]
≧2	15.08	122.57	8.07	7.83	15.28	34.21	2.16	2.08
	(12.65-17.52)	(110.65-134.5)	(6.69-9.74)	(6.26-9.80)[d]	(14.43-16.12)	(31.83-36.60)	(1.98-2.36)	(1.89-2.29)[d]
			Interaction: p= 0.0743				Interaction: p<0.0001	

[a]ID= incidence density, CI=confidence interval

[b]Based on Poisson assumption

[c]Based on Cox proportional hazard regression with competing risk analysis and adjusted for age, sex, insurance premium, urbanization status, geographic area, occupational status, status of hypertension, diabetes, CAD, stroke, hyperlipidemia, COPD, and number of medical visits.

[d]Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for comorbidities.

* $P<0.05$

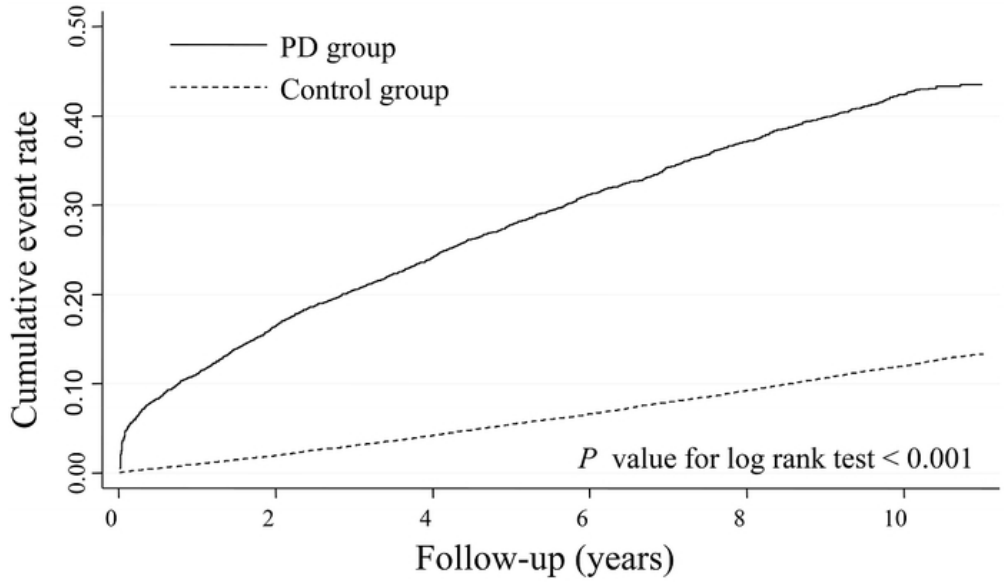

Figure 1 Comparison of Kaplan-Meier failure estimates of dementia onset between the two groups. PD, Parkinson's disease.

59x34mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Page No	Recommendation
Title and abstract	1	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		2	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction			
Background/rationale	2	4	Explain the scientific background and rationale for the investigation being reported
Objectives	3	4	State specific objectives, including any prespecified hypotheses
Methods			
Study design	4	5	Present key elements of study design early in the paper
Setting	5	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	5-6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		6	(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	6-7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	5-7	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	6	Describe any efforts to address potential sources of bias
Study size	10	5-6	Explain how the study size was arrived at
Quantitative variables	11	7	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	7	(*a*) Describe all statistical methods, including those used to control for confounding
		7	(*b*) Describe any methods used to examine subgroups and interactions
		-	(*c*) Explain how missing data were addressed
		-	(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		-	(*e*) Describe any sensitivity analyses

		Results	
Participants	13*	5-6	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		-	(b) Give reasons for non-participation at each stage
		-	(c) Consider use of a flow diagram
Descriptive data	14*	8	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		18-19	(b) Indicate number of participants with missing data for each variable of interest
		8	(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*8-9*	*Cohort study*—Report numbers of outcome events or summary measures over time
		-	*Case-control study*—Report numbers in each exposure category, or summary measures of exposure
		-	*Cross-sectional study*—Report numbers of outcome events or summary measures
Main results	16	8-9	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		8-9	(*b*) Report category boundaries when continuous variables were categorized
		8-9	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	8-9	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
		Discussion	
Key results	18	9	Summarise key results with reference to study objectives
Limitations	19	13	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	9-14	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	9-14	Discuss the generalisability (external validity) of the study results
		Other information	
Funding	22	14	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Risk of Dementia after Parkinson's Disease in Taiwan: A Population-based Retrospective Cohort Study Using National Health Insurance Claims

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Risk of Dementia after Parkinson's Disease in Taiwan: A Population-based Retrospective Cohort Study Using National Health Insurance Claims

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Abstract

Objectives: A nationwide cohort study on the risk of dementia onset after first diagnosis of Parkinson's disease (PD) is lacking. This study aims to assess 11 years of incidence and the hazard ratios for developing dementia in patients with PD compared with matched controls.

Design: A population-based cohort study.

Setting: National Health Insurance database in Taiwan.

Participants: A total of 5,932 patients with PD were identified, and 29,645 age-, sex-, and index year-matched PD-free individuals were randomly selected.

Intervention: None

Outcome measures: All subjects were linked to the claim data to identify the first diagnosis of dementia. The Poisson assumption was used to estimate the incidence rate. Cause-specific hazards models with a partitioning of time at 1 year to account for proportionality were used to estimate the risk of dementia onset.

Results: The median duration from the first diagnosis of PD to the development of dementia was 9.02 years. In the first partition (≦1 years), the incidence of dementia in the PD and control groups was 114.49 and 9.76 per 1,000 person-years, respectively, with an adjusted hazard ratio of 6.43 (95%CI 5.46-7.57). In the second partition (>1 year), the incidence of dementia in the PD and control groups was 30.99 and 10.83 per 1,000 person-years, with an adjusted hazard ratio of 2.42 (95%CI 2.23-2.61). Notably, in the second partition, both men and women aged<70 had the highest hazard ratio (3.82, 95%CI 2.79-5.22 and 4.27, 95%CI 3.25-5.63, respectively).

Conclusions: The risk of dementia in PD subjects was higher in men in the first partition, but it was similar in both genders in the second partition. The increased risk was highest in subjects aged <70 years in the case of both men and women at any given partition time.

Keywords: epidemiology, retrospective cohort study, Parkinson's disease, dementia, competing risk

Article Summary

Strengths and limitations of this study

- The study strengths include the fact that it is a nationwide, retrospective cohort design for 11 years with more accurate estimates of the incidence rates of dementia by using the first diagnosed PD cases rather than the prevalent cases as study subjects.
- A multivariate Cox proportional hazard regression with a competing risk analysis was used to control the confounding bias and account for the competing risk of death.
- We were unable to consider a comprehensive list of potential confounders, such as smoking, educational level, physical function, and genes in the analysis because of the limited information available from the claims data.
- Another limitation is the lack of clinical symptoms and subtypes of dementia.

INTRODUCTION

Dementia, a symptom of cognitive disturbances, can be potentially disabling and can also related to increased mortality rates and costs[1 2]. Thus, information about which patients will eventually develop dementia is an important issue in public health and clinical practice[3].

Parkinson's disease (PD) has been associated with developing cognitive impairments[4]. However, most previous studies on the association between PD and dementia risk were conducted in western countries[5-19], and information for Asian PD populations is lacking. Moreover, to identify robust hazard ratios (HRs) of dementia in PD requires a large sample size cohort and a sufficiently long follow-up time to observe the development of symptoms of dementia in incident cases of PD.

To the best of our knowledge, there has been no whole population-based nationwide cohort study on this topic[5-23], and only few cohort studies have involved incident cases of PD to investigate the frequency of dementia with a follow-up period of more than 10 years. The Sydney Multicentre Study of PD followed 136 newly diagnosed PD patients more than 20 years and reported that 83% of the 30 survivors developed dementia. However, only PD cases who received low-dose levodopa or low-dose bromocriptine were included in this study, which may not represent PD within the population as a whole[19]. The CamPaIGN study followed 121 newly diagnosed PD cases for 10 years, of which 41 PD cases developed dementia. This study estimated dementia incidence in PD subjects was 54.7 per 1,000 person-years (95% CI 35.4 to 74.1), which was 2.6-fold higher than that in an age- and geographically- matched population. However, this study also only included only a few newly diagnosed PD cases (n=121)[9].

Moreover, many studies have included prevalent PD cases at varying disease stages to investigate the risk of dementia, which may have caused survival bias[6-8 10 12-15 17 18 20 22 23]. For example, the Rotterdam study recruited 72 prevalent and 67 incident PD cases with only an overall mean follow-up time of 6.9 years and found a positive association between PD and dementia incidence[14]. In Taiwan, the only population-based study with a case-control design also showed a

positive association between PD and the risk of dementia[22]. However, potential survival bias resulting from recruitment of prevalent PD cases at various disease stages may have been present in these studies.

Some studies have reported that older age[5-10 13 15 20 23] and male gender[5] are related to increased dementia risk in PD; however, information regarding the age- and sex- stratified dementia incidence rate in PD is scant. In addition, many PD patients have medical comorbidities such as stroke, hypertension, diabetes mellitus, hyperlipidemia, and coronary heart disease, which may have modification effects on the relationship between dementia and PD[7 16 17 22]. However, little research has examined medical comorbidities as a potential confounding factor that should be controlled for[7 22 23]. Moreover, because of the increased age and co-morbidities in a long-term follow-up study, competing risk of death should be considered. However, none of studies on this topic has considered death as a competing risk[6-21 23], which may induce potential attrition bias and tend to distort the study results.

Given the abovementioned methodological problems and limited information on this topic, the association between PD and the risk of dementia needs to be further explored. Therefore, in this study, a nationwide population-based cohort study was conducted to estimate 11 years of incidence and the hazard ratios for development of dementia in patients with first-diagnosed PD by age and sex and by comorbidities (i.e., hypertension, diabetes, coronary artery disease (CAD), stroke, hyperlipidemia, and chronic obstructive pulmonary disease (COPD)), after accounting for the competing risk of death.

METHODS

Data Source

The dataset was from ambulatory care claims, inpatient claims, and the updated registry for beneficiaries retrieved from Taiwan's National Health Insurance Research Database (NHIRD), as

provided by the National Health Insurance Administration (NHIA), Ministry of Health and Welfare, Taiwan. A universal National Health Insurance (NHI) program has been implemented in Taiwan since 1995, and more than 99% of Taiwan residents enrolled in the NHI program after 2000. The National Health Insurance Administration has contracted with 92.5% of the hospitals and clinics in Taiwan[24]. The NHIA performs quarterly expert reviews on a random sample of every 50-100 ambulatory and inpatient claims in each hospital and clinic to ensure the accuracy of the claims data[24]. False reports of diagnoses result in a severe penalty from the NHIA. Therefore, information obtained from the NHIRD is considered to be complete and accurate. The NHI datasets have been used in many published epidemiologic studies on PD[25 26] and dementia[27]. Access to the NHIRD was approved by the National Health Research Institutes Review Committee.

Patient and public involvement

We conducted this study by using the National Health Insurance Research Database. No patients or members of the public were involved in the development of the research question and outcome measures. Also, no patients or members of the public were involved in setting out the design of this study, nor were they involved in the recruitment of and conducting of the study. The study results were not disseminated to the study subjects.

Study design, Cohorts and Covariates

This was a retrospective cohort study from 2002-2012. We selected 5,932 eligible PD patients between 2002 and 2003 from a previous study for which sample selection details were discussed previously[28]. In brief, the PD cohort in this study included all cases with at least 3 medical claims (either outpatient or inpatient care) with a diagnostic code of PD (ICD-9-CM: 332.0) who had received 3 or more courses of anti-Parkinsonism medications, including L-dopa or dopamine agonist prescriptions after a first-time diagnosis between 2002 and 2003. Moreover, the first and last outpatient or inpatient visits and anti-Parkinsonism medication records were separated by at least 90 days to avoid accidental inclusion of miscoded patients.

We further made the following exclusions to ensure the validity of the PD diagnosis: (1) an age on the index date of less than 40 years, who are more likely to have a genetic etiology; (2) a diagnostic code of secondary Parkinsonism (ICD-9-CM code: 332.1) during the study period; (3) receipt of any neuroleptic medication 180 days prior to the index date, and (4) 3 or more medical claims (either ambulatory or inpatient care) with diagnostic codes of dementia prior to the index date. The first date of initial diagnosis of PD in the period of 2002 to 2003 was set as the index date.

We previously conducted a pilot study to validate the accuracy of the ICD-9 coding in PD patients[28]. In the validation study, medical records including symptoms/signs, diagnostic procedures, use of anti-parkinsonism medication, as well as response to medication of 290 randomly selected patients with ICD-9-CM coded 332.0 were examined in detail by three experienced neurologists from January 2012 to October 2012. Among these 290 cases, 245 were confirmed as PD patients based on the aforementioned clinical information. The sensitivity, specificity, positive predictive value, and negative predictive value were 97.6%, 92.3%, 98.8% and 85.7%, respectively. The accuracy of our method for identifying PD cases was 96.9%. Moreover, cases in this study were not only ascertained using the ICD code but also required having been prescribed at least 3 courses of anti-parkinsonism medication including L-dopa or a dopamine agonist to minimize the possibility of miscoding.

The control subjects were selected from those who had not been diagnosed with PD or treated with any anti-PD medications during the entire study period and met the same exclusion criteria as those set for the patients with PD. These control subjects were matched by age (each 5-year span), sex, and year of index date for patients with PD at a 5:1 ratio. As a result, 29,645 control subjects were identified. For the control groups, the index date was either January 1, 2002 or January 1, 2003.

Baseline comorbidities that may be associated with an increased risk of dementia were

identified for the PD and control groups. These comorbidities included hypertension, diabetes, CAD, stroke, hyperlipidemia, and COPD observed before the index date. The comorbidity score observed before the index date was calculated using the Charlson Comorbidity Index, a weighted summery measure of common comorbid conditions adopted for use with ICD-9-CM coded administrative databases[29-31]. Information on the geographic area, urbanization level, occupational status, and salary-based insurance premium at the index date was also obtained from the registry for beneficiaries. The number of medical visits within one year after the index date was adjusted to decrease the potential presence of surveillance bias because subjects with PD visit clinics more frequently and thus may have more opportunities to be diagnosed as having dementia.

End point and Statistical analysis

The main outcome variable was the initial occurrence of dementia (ICD-9-CM code: 290, 294.1, 331.0, and 331.82). A Taiwanese study reported that the diagnostic accuracy of dementia is approximately 90% when relying on diagnosis codes (ICD-9-CM) to identify dementia[27]. To increase the validity of dementia identification, only dementia cases diagnosed with ≥3 ambulatory visits or ≥1 hospitalization were included in this study. We did not distinguish the subtypes of dementia because of data limitations due to a lack of information regarding symptoms/signs, lab data, and image findings, and further outcome analyses with dementia subtype classifications, such as dementia with Lewy bodies (DLB), Alzheimer's dementia, frontotemporal dementia, or just Parkinson's disease dementia (PDD), were not performed. However, according to the criteria set forth by the consensus report of the Lewy Body Consortium[32], clinicians and researchers use the "1-year rule" to help verify the diagnoses of DLB and PDD. Thus, we analyzed the dementia incidence within and after one year of PD diagnosis, respectively.

We followed the study subjects from the index date to the first diagnosis of dementia, withdrawal from the NHI, or December 31, 2012, whichever came first. The incidence density of dementia was calculated using an age- and sex- specific and comorbidity-specific stratified analysis

based on the Poisson assumption. The cumulative events and rates of dementia according to the PD status over the study period were calculated using a Kaplan-Meier analysis, and the log-rank test was used to test the between-group differences.

Since death is the competing risk of dementia occurrence in this long-term follow-up study, analytical approaches used in competing risk settings must be used to assess the association between PD and the risk of dementia. Cause-specific hazards models, one of the most common analytical methods used in competing risk settings, are better suited for studying the etiology of diseases[33]. The cause-specific hazard is the instantaneous risk of dying from a particular cause k given that the subject is still alive at time t[34]. Thus, in this study, a Cox proportional hazard regression with competing risk models, according to cause-specific hazards models, was performed to assess the hazard ratio (HR) of dementia in relation to PD.

In addition, we performed a sex- and age- stratified analysis and a comorbidity-stratified analysis to examine the potential effect-modifications by age, sex, and comorbidity on the association between PD and the risk of dementia. Plots of log (-log(survival function)) vs. log(time) were drawn to test for violations of the proportional-hazards assumption. Therefore, separate time-partitioned models were created, and the hazards within each partition were assessed. Proportionality was held for the new models partitioned at 1 year. If we modeled the hazards for ≤1 year (i.e., the first time partition), the censoring day for subsequent events was 1 year. If we modeled the hazards for >1 year (i.e., the second time partition), subjects with earlier events were included and considered to be censors (because the exclusion of these subjects may lead to a survival bias). A $p<0.05$ was considered significant.

RESULTS

Gender, age, geographic area, and urbanization levels were similar in both groups. The prevalence rates of the risk factors for dementia were high in patients with PD. The PD cohort had

fewer white-collar workers (25.0% vs. 31.2%, $p<0.0001$), a higher prevalence of dependence (39.9% vs. 33.8%, $p<0.0001$), a lower insurance premium (percentage with none or a lower than median insurance premium: 69.5 vs. 60.0, $p<0.0001$), a higher Charlson's score (percentage with score of 1 to $\geqq 2$: 52.1% vs. 25.4%, $p<0.0001$), and a higher frequency of medical visits (39.6 vs. 21.9 per year, $p<0.0001$) than the control group (Table 1).

Figure 1 shows the cumulative incidence of dementia in patients with and without PD. The cumulative incidence of dementia for PD was significantly higher than the corresponding data observed in the non-PD group (log-rank test, $p<0.0001$).

Among the total of 5,932 first diagnosed PD cases, only 492 of these cases (8.3%) were derived from inpatient records. The adjusted hazard ratios of dementia either in the overall PD cases or in the PD cases only enrolled in an outpatient group were significantly higher than those in the control group without PD. The median duration from the overall first diagnosis of PD to the development of dementia was 9.02 years.

During the 11 years of follow-up, a total of 1,836 PD patients developed dementia, and 1,226 PD patients died without developing dementia. In the same period, a total of 3,l59 control subjects developed dementia, and 5,223 control subjects died without developing dementia. In the period within 1 year after the index date (i.e., the first time partition), a total of 5,932 PD subjects encountered 624 medical episodes due to first diagnosed dementia in the 5,450.09 person-years observed, representing incidence densities of dementia of 114.49 per 1,000 person-years. In the same period, a total of 29,645 PD subjects encountered 285 medical episodes due to first diagnosed dementia in 29,208.39 person-years observed, representing incidence densities of dementia of 9.76 per 1,000 person-years. Noticeably, the incidence density of dementia increased with age irrespective of PD status and sex, and the highest incidence was observed in those aged $\geqq 80$ years. The adjusted HR of dementia in relation to PD was significantly increased at 6.43 (95%CI 5.46-7.57) and was higher in men than in women (HR: 7.18, 95%CI 5.73-9.01 vs. 5.54, 95%CI 4.39-

6.99). In addition, there was a significant interaction of PD with age on the risk of dementia for both men (p=0.0149) and women (p<0.0001) (Table 2).

In the years following the PD diagnosis (i.e., the second time partition), the overall incidence density of dementia was much lower (Table 2). The change in incidence density between the first and the second partition was more pronounced in the PD group (from 114.49 to 30.99 per 1,000 person-years) than in the control group (from 9.76 to 10.83 per 1,000 person-years). The age- and sex- specific incidence densities had a similar pattern in terms of change. However, no significant difference in the sex-specific HRs of dementia was observed (p=0.2267). There was a significant interaction of PD status with age (p<0.0001) in both sexes. Age- and sex-specific HRs showed the highest HR to be in PD females aged <70 years (HR: 4.27; 95% CI 3.25-5.63).

Impact of PD on the risk of dementia by comorbidity is shown in Table 3. Irrespective of the various time partitions, the incidence of dementia increased with the number of comorbidities in both groups. The PD group had the highest risk of dementia across various medical comorbidity stratifications or Charlson's scores after adjusting for baseline characteristics. In the first time partition, the interaction of PD with hypertension (p=0.0058), CAD (p= 0.0196), stroke (p<0.0001), and COPD (p=0.0400) on the risk of dementia also was statistically significant, indicating that subjects without hypertension, CAD, stroke, and COPD had a higher adjusted HR for dementia. However, although the adjusted HR for dementia was also higher in subjects without diabetes and hyperlipidemia than in those with medical comorbidities, there was no statistically significant modification effect by diabetes and hyperlipidemia on the association between PD and the risk of dementia. In terms of the Charlson's scores, subjects with scores of 0 had a higher adjusted HR for dementia than those with scores of 1 and ≧2. The interactions were significant for PD with Charlson's score (p=0.0003) on the risk of dementia.

In the second time partition, effect-modification by hypertension (p<0.0001), CAD (p=0.0048) and stroke (p<0.0001) was statistically significant for dementia, indicating that subjects without

those medical comorbidities had a higher adjusted HR for dementia. Among diabetes, hyperlipidemia, or COPD patients, adjusted HR for dementia also showed a statistically significant high risk from 2.02 (95% CI=1.68–2.43) to 2.21 (95% CI=1.89–2.59), but no significant modification effect was found for those with medical comorbidities on the association between PD and the risk of dementia. In terms of the Charlson's scores, subjects with scores of 0 had a higher adjusted HR for dementia than those with scores of 1 and ≧2. Also, a significant modification effect of Charlson's scores on the association between PD and the risk of dementia (p=0.0059) was found. Regardless of whether medical comorbidities existed or not, the HRs for dementia were greater in the first time partition but were smaller in the second time partition.

DISCUSSION

To the best of our knowledge, this is the first nationwide population-based cohort study to demonstrate that patients with the first diagnosis of PD are associated with increased risk of dementia compared with non-PD patients. However, our study showed a sharply increased hazard of dementia within 1 year after the first diagnosis of PD, which is clinically and biologically unbelievable; this situation is probably because a large proportion of patients with dementia remain undiagnosed before the index date of their first clinical visit for PD.

In other words, many patients with pre-existing cognitive impairment and PD were classed as new PD cases because their condition had deteriorated and had only been recognized because they had been referred for an expert opinion. This is also supported by the decline in the number of PD patients with dementia in the subsequent period of observation. In this study, we found that the overall risk of dementia onset increased nearly twofold in up to 11 years (adjusted HR 2.42, 95%CI 2.23- 2.61) among those who survived at least 1 year and had an initial PD diagnosis thereafter. The magnitude of this association varied according to different age and sex stratifications. In general, the risk of dementia was higher in men in the first partition but was similar in both sexes

in the second partition. However, the increased risk was highest in both male and female participants aged <70 years in any given partition time. The study results can provide physicians and patients with valuable information and also demonstrate the need for guidelines for detection of dementia risk after the initial diagnosis of PD.

Our study shows that a reasonably increased hazard of dementia more than one year after diagnosis of PD is more likely to be real and may suggest evidence of the mechanisms supported by the Braak pathology staging hypothesis[35 36]. Our findings were similar to another population-based case control study in Taiwan[22], which showed the risk of developing dementia in prevalent Parkinsonism was highest in the first 6 months (AOR:11.98, 95%CI:8.51-16.68) and then became lower in the following months to years after diagnosis.

Age is known to be a risk factor for dementia not only in the general population[37 38] but also in the PD patient population[5-10 13 15 20 23]. This may be caused by aging of non-dopaminergic structures (i.e., the locus ceruleus and pedunculopontine nucleus)[39]. However, a modifying effect of age on the risk of dementia after PD may be present in our study. For example, we found that patients with PD had a significantly higher overall risk of dementia than those in the control group, particularly in subjects aged < 70 years. This result is similar to the findings of some prior studies[13 18].

Male gender is sometimes identified as a risk factor for dementia in PD[5]; however, there is no clear explanation for this finding. In our study, we found no significant role of gender in the first-diagnosed PD patients one year later. Accordingly, patients with PD, especially younger patients in both sexes, could be selected in future studies as a target population to evaluate whether interventions are effective in decreasing the risk of dementia after diagnosis of PD.

Our study also shows that the overall risk of dementia was more than double (adjusted HR 2.42) among subjects with first-diagnosed PD 1 year later for up to 11 years. After accounting for the competing risk of death and adjustment for the number of medical visits, the findings were

similar to those of Perez et al., who reported a higher hazard ratio of incident dementia (2.47, 95%CI 1.55-3.59) in patients with PD as compared to non-PD subjects[11]. However, other cohort studies have shown a hazard ratio ranging from 1.7 (95%CI 1.1–2.7) to 5.9 (95%CI 3.9–9.1) for incident dementia in PD groups compared with the general population[9 10 12-15 18], which is different from our findings. Noticeably, most previous studies were limited by a relatively small sample size[6-17 19-21 23], shorter follow-up time[6-8 10 12-18 20], the lack of a matched control[6-8 16 17 19-21 23], failure to account for the competing risk of death[6-21 23], or a lack of adjustment for the number of medical visits to control for surveillance bias[9-15 18], rendering the risk that the estimates were more likely to be imprecise and biased.

We found the incidence of dementia increased with the number of comorbidities, including hypertension, diabetes mellitus, CAD, stroke, hyperlipidemia, and COPD. However, of the patients with PD in our study, PD alone also had more positive effects on the risk of dementia in most circumstances although effect modifiers such as hypertension, diabetes, stroke, CAD, hyperlipidemia, and COPD had positive effects on increasing the risk of dementia. Prior studies regarding the relationship between patients with PD and these comorbidities remain controversial[7 16 17 22]. For example, although a study in Taiwan demonstrated that patients with PD with cerebrovascular or cardiovascular comorbidities had a lower risk of dementia onset than patients with PD alone[22], which is similar our findings, other studies have failed to find this relationship[16 17]. In addition, some previous studies have shown that PD with cardiovascular dysautonomia (such as hypertension, diabetes mellitus, and CAD) and COPD might cause substantial cerebral hypoperfusion and hypoxia, respectively[40-42]. Hypoxia and hypotension in the brain might cause neuronal damage and increase accumulation of pathologic proteins such as β-amyloid, which result in increased risk of dementia onset[40 41]. Therefore, future perspective studies focusing on the causal relationship between such comorbidities and the risk of dementia in PD are warranted.

There were several strengths in our study. First, we obtained a large, nationwide number of

participants by using NHIR datasets, which made it possible to reduce selection bias, to obtain higher statistical power, to obtain a highly representative study population, to have a lower rate of nonresponse or loss to follow-up, and to facilitate the age-, sex- and comorbidities-stratified analyses with an ample simple size to satisfy requirements. To the best of our knowledge, this study is the first to report the age- and sex- specific incidence rates of dementia in a PD group. Secondly, we conducted a longitudinal and retrospective cohort study for 11 years, which is a longer time during which to observe the development of dementia than that in many other prior studies[6-8 10 12-18 20]. Thirdly, more accurate estimates for the incidence rates of dementia in the PD group are available in this study due to the usage of the first diagnosed PD cases rather than the prevalent PD cases, as this might reduce the variations in the incidence of dementia across various PD durations. Fourth, a multivariate Cox proportional hazard regression with a competing risk analysis was used to control for the confounding bias and to account for the competing risk of death.

Still, our study had some limitations. Firstly, we solely selected our PD cases according to physician-recorded diagnosis and prescriptions reported in medical claims, which might have led to potential disease misclassification. To avoid accidental inclusion of miscoded patients, we managed to solely include PD patients who had at least three ambulatory or inpatient visits with PD diagnosis and prescriptions with the first and last visits more than 90 days apart during the study period, which would largely decrease the likelihood of disease misclassification. Similarly, because we selected patients with dementia only by using NHIR datasets, potential disease misclassification may be present. To address this concern, we only included dementia cases diagnosed with ≥3 ambulatory visits or ≥1 hospitalization in this study to increase the validity of dementia identification.

Also, because patients with PD may utilize the health care system more often than control groups, surveillance bias may be present. To address this concern, we calculated the number of medical visits for 1 year after the index date and adjusted for this in the multivariate regression

model. Secondly, the severity of dementia is not available in the database, and we could not distinguish subtypes of dementia in our datasets. Therefore, it is essential for patients with PD, particularly in high risk groups such as subjects aged <70 years, to have regular cognitive assessments including combinations of neuropsychological markers throughout the early disease stages, which not only will provide benefits for identification of the subtypes in dementia but will also decrease underestimation of risk for dementia in PD.

Thirdly, due to the limited information available from the claims data, we were unable to consider a comprehensive list of potential confounders such as smoking, educational level, physical function, and genes in the analysis, which may have resulted in residual confounding bias. To reduce such bias, we used COPD and occupational status as surrogates for smoking and educational level, respectively. Fourthly, the disease symptoms of PD cases at different disease stages may play a role, to some extent, in the relationship between PD and the risk of dementia. Because information on the disease symptoms is unavailable from the NHI data, we have left this area (such as non-motor symptoms) for further investigations.

In conclusion, it was found that PD confers a higher risk of dementia than is the case for non-PD patients, especially in those aged <70 years in both sexes. Regular monitoring for the development of dementia in patients with PD in a long-time follow-up, particularly risk groups, is recommended. Future research should include further evaluation of the underlying mechanism and subtypes for dementia development after diagnosis of PD.

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Table 1. Characteristics of the study subjects

Variables[a]	PD group n	PD group %	Control group n	Control group %	*P* value
Age (years)					
<70	1852	31.2	4220	31.2	1.00 [d]
70-74	1314	21.2	6570	21.2	
75-79	1460	24.6	7300	24.6	
≧80	1306	22.0	6515	22.0	
Mean (±SD) [b]	72.5±9.4		70.8±12.7		
Sex					1.00 [d]
Male	3116	52.6	15580	52.6	
Female	2813	47.4	14065	47.4	
Insurance premium (NTD)[b]					<0.0001 [e]
Dependent	2333	39.9	9721	33.8	
<Median (19,200)	1734	29.6	7753	26.2	
>=Median	1787	30.5	12171	41.0	
Mean (±SD)[b,c]	7102.6±11122.9		10194.0±13197.8		
Urbanization status					0.0007 [d]
Urban	3203	54.7	15197	51.8	
Satellite city/town	2085	35.6	9741	33.2	
Rural area	566	9.8	4424	15.0	
Geographic area					<0.0001 [d]
Northern	2670	45.6	13130	44.8	
Central	1491	25.5	7288	24.9	
Southern	1519	25.9	7957	27.1	
Eastern	174	3.0	931	3.2	
Occupational status					<0.0001 [d]
White collar	1482	25.0	9242	31.2	
Blue collar	2075	35.0	11846	40.0	
Others	2375	40.0	8557	28.8	
History of comorbidity					
Without comorbidities	1151	19.4	16393	55.3	<0.0001 [d]
Hypertension	3578	60.3	11431	38.6	<0.0001 [d]
Diabetes	1430	24.1	4112	13.9	<0.0001 [d]
CAD	1955	33.0	4890	16.5	<0.0001 [d]
Stroke	1977	33.3	2924	9.9	<0.0001 [d]
Hyperlipidemia	1089	18.4	3013	10.2	<0.0001 [d]

COPD	1719	29.0	5624	19.0	<0.0001 [d]
Charlson's score					<0.0001 [d]
0	2841	47.9	22123	74.6	
1	1707	28.8	4640	15.7	
>=2	1384	23.3	2282	9.7	
Mean number of medical visits (±SD) [b]	39.6 (±26.5)		21.9 (±19.7)		<0.0001 [e]
Total	5932	100.0	29645	100.0	

[a]Inconsistency between the total population and the population summed for individual variables was due to missing information.

[b]SD=Standard deviation; NTD=New Taiwan Dollars; CAD=Coronary artery disease; COPD=chronic obstructive pulmonary disease

[c]The dependent insurers were not included.

[d]Based on χ^2 test

[e]Based on a Student's t test

Table 2. Age- and sex- specific incidence densities of dementia (ICD-9: 290, 294.1, 331.0, 331.82) in the Parkinson's disease and control groups

Variables	≦1 years				>1 years			
	ID (95% CI)[a,b]		Crude HR	AHR	ID (95% CI)[a,b]		Crude HR	AHR
	Control group	PD group	(95% CI)	(95% CI)	Control group	PD group	(95% CI)	(95% CI)
Male								
<70	1.61 (0.42-2.81)	56.23 (40.16-72.31)	34.44 (15.58-76.13)	15.74 (6.67-37.10)[c]	2.61 (2.13-3.09)	17.57 (14.48-20.67)	6.93 (5.38-8.93)	3.82 (2.79- 5.22)[c]
70-74	5.61 (3.08-8.13)	111.38 (85.29-137.47)	19.44 (11.73-32.21)	13.00 (7.59-22.26)[c]	9.23 (8.16-10.30)	32.27 (27.02-37.52)	3.65 (2.98-4.47)	3.06 (2.41-3.89)[c]
75-79	7.59 (4.92-10.27)	129.62 (103.83-155.42)	16.69 (11.16-24.95)	9.84 (6.27-15.46)[c]	14.01 (12.77-15.25)	38.05 (32.58-43.51)	2.87 (2.42-3.41)	2.26 (1.85-2.75)[c]
≧80	22.18 (17.26-27.10)	196.24 (161.70-230.78)	8.64 (6.58-11.57)	4.35 (3.13-6.05)[c]	18.94 (17.31-20.57)	41.87 (35.34-48.40)	2.25 (1.87-2.69)	1.90 (1.55-2.33)[c]
Total	8.81 (7.32-10.29)	118.82 (106.16-131.49)	13.23 (10.85-16.14)	7.18 (5.73-9.01)[d]	10.27 (9.74-10.81)	30.33 (27.93-32.73)	3.02 (2.75-3.33)	2.44 (2.19-2.73)[d]
Female								
<70	1.43 (0.37-2.49)	51.66 (37.20-66.12)	35.81 (16.24-79.13)	10.55 (4.21-26.45)[c]	3.35 (2.85-3.86)	22.23 (18.98-25.49)	7.14 (5.78-8.81)	4.27 (3.25-5.63)[c]
70-74	7.37 (4.36-10.38)	89.93 (65.72-114.14)	12.04 (7.40-19.60)	4.98 (2.84-8.74)[c]	10.81 (9.62-12.00)	33.61 (28.25-38.97)	3.29 (2.71- 4.01)	2.82 (2.25-3.53)[c]
75-79	10.92 (7.25-14.59)	165.75 (132.06-199.4)	14.81 (10.02-21.89)	8.09 (5.23-12.51)[c]	17.61 (16.04-19.18)	43.22 (36.70-49.70)	2.56 (2.14-3.07)	2.30 (1.88-2.81)[c]

≧80	31.19	180.68	5.69	3.17	22.99	38.74	1.68	1.49
	(24.60-37.79)	(143.56-217.8)	(4.24-7.64)	(2.18-4.62)[c]	(20.97-25.02)	(32.00-45.47)	(1.38-2.05)	(1.19-1.86)[c]
Total	10.80	109.89	10.03	5.54	11.41	31.72	2.85	2.41
	(9.08-12.53)	(97.16-122.63)	(8.23-12.21)	(4.39-6.99)[d]	(10.83-12.00)	(29.24-34.21)	(2.60-3.14)	(2.15-2.69)[d]
Overall	9.76	114.49	11.54	6.43	10.83	30.99	2.93	2.42
	(8.62-10.89)	(105.51-123.4)	(10.04-13.27)	(5.46-7.57)[e]	(10.43-11.22)	(29.27-32.72)	(2.75- 3.14)	(2.23- 2.61)[e]

In the first time partition (≦1 years), the interactions were significant for PD with age (p<0.0001) and with sex (p=0.0462), with age in men (p=0.0149), and with age in women (p<0.0001). In the second time partition (>1 years), the interactions were significant for PD with age (p<0.0001), with age in men (p<0.0001), and with age in women (p<0.0001), but not for PD with sex (p=0.2267).

[a]ID= incidence density (per 1,000 person-years), CI=confidence interval, AHR=adjusted hazard ratio, HR=hazard ratio,

[b]Based on Poisson assumption

[c]Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for age and sex.

[d]Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for sex.

[e]Based on Cox proportional hazard regression with competing risk analysis and adjusted for age, sex, insurance premium, urbanization status, geographic area, occupational status, hypertension status, diabetes, CAD, stroke, hyperlipidemia, COPD, Charlson's score, and number of medical visits.

*P<0.05

Table 3. Impact of Parkinson's disease on the risk of dementia by comorbidity

Variables	≦1 years				>1 years			
	ID (95% CI)[a,b]		Crude HR (95% CI)	AHR (95% CI)	ID (95% CI)[a,b]		Crude HR (95% CI)	AHR (95% CI)
	Control group	PD group			Control group	PD group		
Hypertension								
No	7.49 (6.23-8.76)	110.98 (96.94-125.02)	14.55 (11.79-17.95)	7.75 (6.05-9.94)[c]	8.57 (8.13-9.01)	27.99 (25.45-30.53)	3.36 (3.02-3.73)	3.05 (2.69-3.45)[c]
Yes	13.40 (11.26-15.55)	116.81 (105.12-128.49)	8.59 (7.12-10.37)	5.25 (4.26-6.47)[c]	14.80 (14.03-15.56)	33.14 (30.81-35.48)	2.29 (2.09-2.50)	2.07 (1.87-2.28)[c]
			Interaction: p=0.0058				Interaction: p<0.0001	
Diabetes								
No	9.13 (7.95-10.31)	115.65 (105.28-126.02)	12.45 (10.64-14.56)	6.99 (5.82-8.41)[c]	10.15 (9.74-10.56)	29.39 (27.48-31.29)	2.97 (2.75-3.21)	2.47 (2.26-2.70)[c]
Yes	13.69 (10.07-17.31)	110.87 (92.88-128.85)	7.99 (5.87-10.89)	4.43 (3.16-6.22)[c]	15.46 (14.13-16.79)	36.57 (32.61-40.53)	2.42 (2.10-2.78)	2.21 (1.89-2.59)[c]
			Interaction: p=0.0935				Interaction: p= 0.1891	
CAD								
No	8.47 (7.31-9.62)	107.08 (96.49-117.67)	12.45 (10.53-14.73)	7.38 (6.09- 8.95)[c]	10.11 (9.69-10.52)	29.77 (27.73-31.81)	3.02 (2.79-3.28)	2.58 (2.35-2.83)[c]
Yes	16.39 (12.75-20.02)	129.78 (113.04-146.52)	7.79 (6.03- 10.06)	4.16 (3.13- 5.55)[c]	14.85 (13.66-16.04)	33.69 (30.47-36.91)	2.32 (2.05-2.63)	2.04 (1.77-2.35)[c]
			Interaction: p= 0.0196				Interaction: p=0.0048	
Stroke								

No	7.84 (6.77-8.91)	99.07 (88.88-109.26)	12.44 (10.49-14.75)	7.79 (6.44- 9.42)[c]	9.99 (9.59-10.39)	29.39 (27.37-31.40)	3.03 (2.80-3.29)	2.71 (2.48- 2.97)[c]
Yes	27.73 (21.57-33.88)	146.13 (128.41-163.86)	5.20 (4.04- 6.69)	3.75 (2.87- 4.90)[c]	19.94 (18.09-21.80)	34.66 (31.36-37.97)	1.73 (1.52-1.98)	1.68 (1.46-1.94)[c]
			Interaction: $p<0.0001$				Interaction: $p<0.0001$	
Hyperlipidemia								
No	9.83 (8.63-11.03)	118.50 (108.36-128.63)	11.84 (10.20- 13.73)	6.50 (5.46- 7.73)[c]	10.49 (10.08-10.90)	30.64 (28.73-32.54)	2.99 (2.78-3.23)	2.51 (2.30-2.73)[c]
Yes	9.08 (5.66-12.51)	97.10 (77.97-116.23)	10.57 (6.91- 16.16)	5.83 (3.64-9.32)[c]	13.82 (12.40-15.23)	32.52 (28.46-36.58)	2.42 (2.05-2.84)	2.02 (1.68-2.43)[c]
			Interaction: $p= 0.9212$				Interaction: $p=0.1841$	
COPD								
No	8.72 (7.53-9.91)	108.70 (98.33-119.07)	12.25 (10.38-14.46)	6.78 (5.60- 8.21)[c]	10.21 (9.79-10.63)	29.59 (27.62-31.56)	2.98 (2.76-3.23)	2.54 (2.32-2.78)[c]
Yes	14.27 (11.10-17.43)	128.85 (111.08-146.02)	8.91 (6.87-11.56)	5.33 (3.94-7.19)[c]	13.77 (12.70-14.84)	34.86 (31.31-38.41)	2.56 (2.25-2.91)	2.11 (1.82- 2.45)[c]
			Interaction: $p= 0.0400$				Interaction: $p=0.0772$	
Number of Comorbidities								
0	5.88 (4.56-7.19)	99.30 (80.40-118.21)	16.66 (12.43-22.33)	8.68 (6.27-12.00)[d]	7.48 (7.01-7.96)	24.63 (21.32-27.94)	3.40 (2.93-3.96)	3.52 (2.97-4.16)[d]

1	9.60 (7.19-12.00)	104.64 (85.26-124.02)	10.73 (7.86-14.64)	7.70 (5.56-10.69)[d]	11.76 (10.87-12.65)	28.61 (24.94-32.27)	2.47 (2.13-2.87)	2.67 (2.27-3.13)[d]
≧2	15.08 (12.65-17.52)	122.57 (110.65-134.5)	8.01 (6.63-9.66)	4.90 (4.01-5.99)[d]	15.28 (14.43-16.12)	34.21 (31.83-36.60)	2.28 (2.08-2.49)	2.11 (1.92-2.32)[d]
			Interaction: p=0.0006				Interaction: p<0.0001	
Charlson's score								
0	7.16 (6.04-8.28)	95.08 (83.31-106.84)	13.07 (10.72-15.96)	7.34 (5.88-9.17)[e]	9.73 (9.30-10.15)	28.39 (26.09-30.70)	3.00 (2.73-3.29)	2.67 (2.41-2.97)[e]
1	16.55 (12.80-20.29)	120.17 (102.99-137.35)	7.15 (5.47-9.33)	4.36 (3.26-5.83)[e]	14.92 (13.70-16.13)	34.79 (31.34-38.25)	2.38 (2.09-2.71)	2.11 (1.83-2.44)[e]
≧2	19.33 (14.13-24.53)	148.51 (127.11-169.91)	7.60 (5.61-10.31)	5.08 (3.62-7.13)[e]	13.93 (12.36-15.51)	32.35 (28.45-36.24)	2.32 (1.96-2.73)	2.07 (1.71-2.51)[e]
			Interaction: p= 0.0003				Interaction: p=0.0059	

[a]ID= incidence density, CI=confidence interval

[b]Based on Poisson assumption

[c]Based on Cox proportional hazard regression with competing risk analysis and adjusted for age, sex, insurance premium, urbanization status, geographic area, occupational status, status of hypertension, diabetes, CAD, stroke, hyperlipidemia, COPD, Charlson's score, and number of medical visits.

[d]Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for comorbidities.

[e]Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for Charlson's score.

* P<0.05

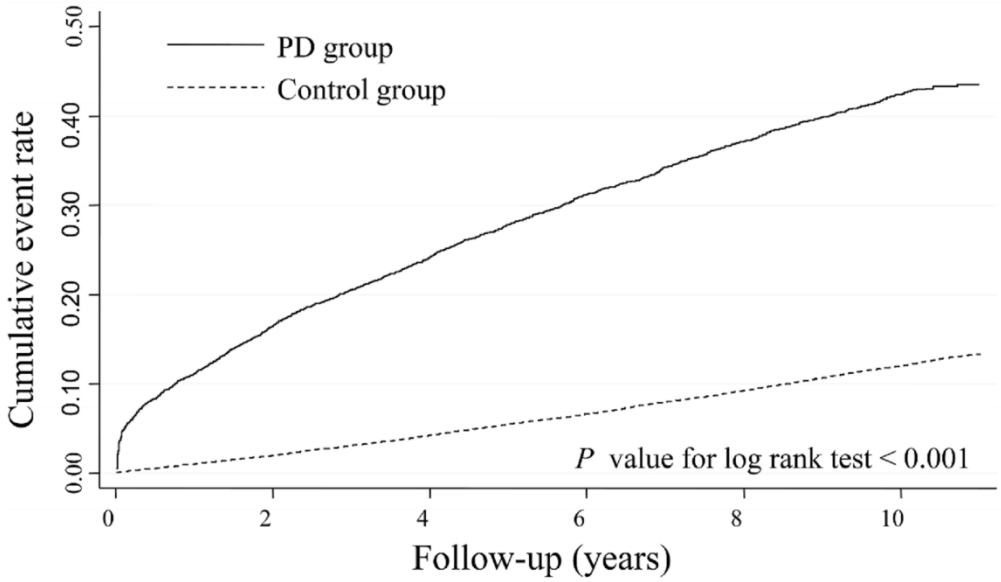

Figure 1 Comparison of Kaplan-Meier failure estimates of dementia onset between the two groups. PD, Parkinson's disease.

153x90mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Page No	Recommendation
Title and abstract	1	2	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		3	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction			
Background/rationale	2	4-5	Explain the scientific background and rationale for the investigation being reported
Objectives	3	5	State specific objectives, including any prespecified hypotheses
Methods			
Study design	4	6	Present key elements of study design early in the paper
Setting	5	5-6	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	6-7	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		6-7	(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	7-8	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	*5-8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	6-7	Describe any efforts to address potential sources of bias
Study size	10	5-6	Explain how the study size was arrived at
Quantitative variables	11	7-8	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	8-9	(*a*) Describe all statistical methods, including those used to control for confounding
		8-9	(*b*) Describe any methods used to examine subgroups and interactions
		-	(*c*) Explain how missing data were addressed
		-	(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and

	controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
-	(*e*) Describe any sensitivity analyses

		Results	
Participants	13*	5-7	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		-	(b) Give reasons for non-participation at each stage
		-	(c) Consider use of a flow diagram
Descriptive data	14*	9-10	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		21-22	(b) Indicate number of participants with missing data for each variable of interest
		10	(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*10-12*	*Cohort study*—Report numbers of outcome events or summary measures over time
		-	*Case-control study*—Report numbers in each exposure category, or summary measures of exposure
		-	*Cross-sectional study*—Report numbers of outcome events or summary measures
Main results	16	9-12	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		9-12	(*b*) Report category boundaries when continuous variables were categorized
		9-12	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	10-12	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
		Discussion	
Key results	18	12-13	Summarise key results with reference to study objectives
Limitations	19	15-16	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	12-16	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	12-16	Discuss the generalisability (external validity) of the study results
		Other information	
Funding	22	17	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely

available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Risk of Dementia after Parkinson's Disease in Taiwan: A Population-based Retrospective Cohort Study Using National Health Insurance Claims

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Risk of Dementia after Parkinson's Disease in Taiwan: A Population-based Retrospective Cohort Study Using National Health Insurance Claims

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Abstract

Objectives: A nationwide cohort study on the risk of dementia onset after first diagnosis of Parkinson's disease (PD) is lacking. This study aims to assess 11 years of incidence and the hazard ratios for developing dementia in patients with PD compared with matched controls.

Design: A population-based cohort study.

Setting: National Health Insurance database in Taiwan.

Participants: A total of 5,932 patients with PD were identified, and 29,645 age-, sex-, and index year-matched PD-free individuals were randomly selected.

Outcome measures: All subjects were linked to the claim data to identify the first diagnosis of dementia. The Poisson assumption was used to estimate the incidence rate. Cause-specific hazards models with a partitioning of time at one year to account for proportionality were used to estimate the risk of dementia onset.

Results: The median duration from the first diagnosis of PD to the development of dementia was 9.02 years. In the first partition ($\leqq$ one year), the incidence of dementia in the PD and control groups was 114.49 and 9.76 per 1,000 person-years, respectively, with an adjusted hazard ratio of 6.43 (95% CI 5.46 - 7.57). In the second partition (> one year), the incidence of dementia in the PD and control groups was 30.99 and 10.83 per 1,000 person-years, with an adjusted hazard ratio of 2.42 (95% CI 2.23 - 2.61). Notably, in the second partition, both men and women aged <70 had the highest hazard ratio (3.82, 95% CI 2.79 - 5.22 and 4.27, 95% CI 3.25 - 5.63, respectively).

Conclusions: This study noted an increased risk of dementia after a diagnosis of PD. The magnitude of effect estimation was higher in men in the first partition, but was similar in both genders in the second partition. PD patients aged <70 years have the highest risk of dementia in any given partition time.

Keywords: epidemiology, retrospective cohort study, Parkinson's disease, dementia, competing risk

Article Summary

Strengths and limitations of this study

- The study strengths include the fact that it is a nationwide, retrospective cohort design for 11 years with more accurate estimates of the incidence rates of dementia by using the first diagnosed PD cases rather than the prevalent cases as study subjects.
- A multivariate Cox proportional hazard regression with a competing risk analysis was used to control the confounding bias and account for the competing risk of death.
- We were unable to consider a comprehensive list of potential confounders, such as smoking, educational level, physical function, and genes in the analysis because of the limited information available from the claims data.
- Another limitation is the lack of clinical symptoms and subtypes of dementia.

INTRODUCTION

Dementia, a symptom of cognitive disturbances, can be potentially disabling and can also be related to increased mortality rates and costs.[1 2] Thus, information about which patients will eventually develop dementia is an important issue in public health and clinical practice.[3]

Parkinson's disease (PD) has been associated with the development of cognitive impairment.[4] However, most previous studies on the association between PD and dementia risk have been conducted in western countries,[5-19] and information for Asian PD populations is lacking. Moreover, to identify robust hazard ratios (HRs) of dementia in PD requires a large sample size cohort and a sufficiently long follow-up time to observe the development of symptoms of dementiain incident cases of PD.

To the best of our knowledge, there has been no whole population-based nationwide cohort study on this topic,[5-23] and only few cohort studies have involved incident cases of PD to investigate the frequency of dementia with a follow-up period of more than 10 years. The Sydney Multicentre Study of PD followed 136 newly diagnosed PD patients more than 20 years and reported that 83% of the 30 survivors developed dementia. However, only PD cases who received low-dose levodopa or low-dose bromocriptine were included in this study, which may not represent PD within the population as a whole.[19] The CamPaIGN study followed 121 newly diagnosed PD cases for 10 years, of which 41 PD cases developed dementia. This study estimated dementia incidence in PD subjects was 54.7 per 1,000 person-years (95% confidence interval (CI) 35.4 to 74.1), which was 2.6-fold higher than that in an age- and geographically- matched population. However, this study also only included only a few newly diagnosed PD cases (n=121).[9]

Moreover, many studies have included prevalent PD cases at varying disease stages to investigate the risk of dementia, which may have caused survival bias.[6-8 10 12-15 17 18 20 22 23] For example, the Rotterdam study recruited 72 prevalent and 67 incident PD cases with only an

overall mean follow-up time of 6.9 years and found a positive association between PD and dementia incidence.[14] In Taiwan, the only population-based study with a case-control design also showed a positive association between PD and the risk of dementia.[22] However, potential survival bias resulting from recruitment of prevalent PD cases at various disease stages may have been present in these studies.

Some studies have reported that older age[5-10 13 15 20 23] and male gender[5] are related to increased dementia risk in PD; however, information regarding the age- and sex- stratified dementia incidence rate in PD is scant. In addition, many PD patients may have medical comorbidities such as stroke, hypertension, diabetes mellitus, hyperlipidemia, and coronary heart disease, which may have modification effects on the relationship between dementia and PD.[7 16 17 22] However, little research has examined medical comorbidities as a potential confounding factor that should be controlled for.[7 22 23] Moreover, because of the increased age and co-morbidities in a long-term follow-up study, competing risk of death should be considered. However, none of studies on this topic have considered death as a competing risk, [6-21 23] which may induce potential attrition bias and tend to distort the study results.

Given the abovementioned methodological problems and limited information on this topic, the association between PD and the risk of dementia needs to be further explored. Therefore, in this study, a nationwide population-based cohort study was conducted to estimate 11 years of incidence and the HRs for development of dementia in patients with first-diagnosed PD by age and sex and by comorbidities (i.e., hypertension, diabetes, coronary artery disease (CAD), stroke, hyperlipidemia, and chronic obstructive pulmonary disease (COPD)), after accounting for the competing risk of death.

METHODS

Data Source

The dataset was drawn from ambulatory care claims, inpatient claims, and the updated

registry for beneficiaries retrieved from Taiwan's National Health Insurance Research Database (NHIRD), as provided by the National Health Insurance Administration (NHIA), Ministry of Health and Welfare, Taiwan. A universal National Health Insurance (NHI) program has been implemented in Taiwan since 1995, and more than 99% of Taiwan residents enrolled in the NHI program after 2000. The NHIA has contracts with 92.5% of the hospitals and clinics in Taiwan.[24] The NHIA performs quarterly expert reviews on a random sample of every 50-100 ambulatory and inpatient claims in each hospital and clinic to ensure the accuracy of the claims data.[24] Therefore, information obtained from the NHIRD is considered to be complete and accurate. The NHI datasets have been used in many published epidemiological studies on PD[25 26] and dementia[27]. Access to the NHIRD was approved by the National Health Research Institutes Review Committee.

Patient and public involvement

We conducted this study by using the National Health Insurance Research Database. No patients or members of the public were involved in the development of the research question and outcome measures. Also, no patients or members of the public were involved in setting out the design of this study, nor were they involved in the recruitment of and conducting of the study. The study results were not disseminated to the study subjects.

Study design, Cohorts and Covariates

This was a retrospective cohort study from 2002-2012. We selected 5,932 eligible PD patients between 2002 and 2003 from a previous study for which sample selection details were discussed previously.[28] In brief, the PD cohort in this study included all cases with at least three medical claims (either outpatientor inpatient care) with a diagnostic code of PD (ICD-9-CM: 332.0) who receiving at least three times of prescriptions of anti-Parkinsonism medications, including L-dopa or dopamine agonist prescriptions after a first-time diagnosis between 2002 and 2003. Moreover, the first and last outpatient or inpatient visits and anti-Parkinsonism medication records were separated by at least 90 days to avoid accidental

inclusion of miscoded patients.

To ensure that the PD diagnosis was reliable and consistent, cases were excluded if: (1) an age on the index date of less than 40 years, who are more likely to have a genetic etiology; (2) a diagnostic code of secondary Parkinsonism (ICD-9-CM code: 332.1) during the study period; (3) receipt of any neuroleptic medication 180 days prior to the index date, and (4) three or more medical claims (either ambulatory or inpatient care) with diagnostic codes of dementia prior to the index date. The first date of initial diagnosis of PD in the period of 2002 to 2003 was set as the index date.

We previously conducted a pilot study to validate the accuracy of the ICD-9 coding in PD patients.[28] In this study, medical records including symptoms/signs, diagnostic procedures, use of anti-parkinsonism medication, as well as response to medication of 290 randomly selected patients with ICD-9-CM coded 332.0 were examined in detail by three experienced neurologists from January to October 2012. Among these 290 cases, 245 were confirmed as PD patients based on the aforementioned clinical information. The sensitivity, specificity, positive predictive value, and negative predictive value were 97.6%, 92.3%, 98.8% and 85.7%, respectively. The accuracy of our method for identifying PD cases was 96.9%. Moreover, cases in this study were not only ascertained using the ICD code but also required having been prescribed at least three times of anti-parkinsonism medication including L-dopa or a dopamine agonist to minimize the possibility of miscoding.

The control subjects were selected from those who had not been diagnosed with PD or treated with any anti-PD medications during the entire study period and met the same exclusion criteria as those set for the patients with PD. These control subjects were matched by age (each five-year span), sex, and year of index date for patients with PD at a 5:1 ratio. As a result, 29,645 control subjects were identified. For the control groups, the index date was either January 1, 2002 or January 1, 2003.

Baseline comorbidities that may be associated with an increased risk of dementia were

identified for the PD and control groups. These included hypertension, diabetes, CAD, stroke, hyperlipidemia, and COPD observed before the index date. The comorbidity score observed before the index date was calculated using the Charlson Comorbidity Index, which is a weighted summery measure of common comorbid conditions adopted for use with ICD-9-CM coded administrative databases.[29-31] Information on the geographic area, urbanization level, occupational status, and salary-based insurance premium at the index date was also obtained from the registry for beneficiaries. The number of medical visits within one year after the index date was adjusted to decrease the potential presence of surveillance bias because subjects with PD visit clinics more frequently and thus may have more opportunities to be diagnosed as having dementia.

End point and Statistical analysis

The main outcome variable was the initial occurrence of dementia (ICD-9-CM code: 290, 294.1, 331.0, and 331.82). A Taiwanese has previously reported that the diagnostic accuracy of dementia is approximately 90% when relying on diagnosis codes (ICD-9-CM) to identify dementia.[27] To increase the validity of dementia identification, only dementia cases diagnosed with ≥ three ambulatory visits or ≥ one hospitalization were included in this study. We did not distinguish the subtypes of dementia because of data limitations due to a lack of information regarding symptoms/signs, lab data, and image findings, and further outcome analyses with dementia subtype classifications, such as dementia with Lewy bodies (DLB), Alzheimer's dementia, frontotemporal dementia, just Parkinson's disease dementia (PDD), were not performed. However, according to the criteria set forth by the consensus report of the Lewy Body Consortium,[32] clinicians and researchers use the "one-year rule" to help verify the diagnoses of DLB and PDD. Thus, we analyzed the dementia incidence within and after one year of PD diagnosis, respectively.

We followed the study subjects from the index date to the first diagnosis of dementia, withdrawal from the NHI, or December 31, 2012, whichever came first. The incidence

density of dementia was calculated using an age- and sex- specific and comorbidity-specific stratified analysis based on the Poisson assumption. The cumulative events and rates of dementia according to the PD status over the study period were calculated using a Kaplan-Meier analysis, and the log-rank test was used to test the between-group differences.

Since death is the competing risk of dementia occurrence in this long-term follow-up study, analytical approaches used in competing risk settings must be used to assess the association between PD and the risk of dementia. Cause-specific hazards models, one of the most common analytical methods used in competing risk settings, are better suited for studying the etiology of diseases.[33] The cause-specific hazard is the instantaneous risk of dying from a particular cause k given that the subject is still alive at time t.[34] Thus, in this study, a Cox proportional hazard regression with competing risk models, according to cause-specific hazards models, was performed to assess the hazard ratio of dementia in relation to PD.

In addition, we performed a sex- and age- stratified analysis and a comorbidity-stratified analysis to examine the potential effect-modifications by age, sex, and comorbidity on the association between PD and the risk of dementia. Plots of log (-log (survival function)) vs. log (time) were drawn to test for violations of the proportional-hazards assumption. Therefore, separate time-partitioned models were created, and the hazards within each partition were assessed. Proportionality was held for the new models partitioned at one year. If we modeled the hazards for ≤ one year (i.e., the first time partition), the censoring day for subsequent events was one year. If we modeled the hazards for > one year (i.e., the second time partition), subjects with earlier events were included and considered to be censors (because the exclusion of these subjects may lead to a survival bias). A $p<0.05$ was considered significant.

RESULTS

The distributions of age and gender were no significant difference in both groups. The percentages of PD patients who lived in urban (54.7 vs. 51.8%) and suburban (35.6 vs. 33.2%) areas and in northern (45.6 vs. 44.8%) and central (25.5 vs. 24.9%) Taiwan were higher than those of the controls. The prevalence rates of the risk factors for dementia were high in patients with PD. The PD cohort had fewer white-collar workers (25.0% vs. 31.2%, $p<0.0001$), a lower insurance premium (percentage with none or a lower than median insurance premium: 69.5 vs. 60.0, $p<0.0001$), a higher Charlson's score (percentage with score of one to $\geqq$ two: 52.1% vs. 25.4%, $p<0.0001$), and a higher frequency of medical visits (39.6 vs. 21.9 per year, $p<0.0001$), than the control group (Table 1).

Figure 1 shows the cumulative incidence of dementia in patients with and without PD. The cumulative incidence of dementia for PD was significantly higher than the corresponding data observed in the non-PD group (log-rank test, $p<0.0001$).

Among the total of 5,932 first diagnosed PD cases, only 492 of these cases (8.3%) were derived from inpatient records. The adjusted hazard ratios of dementia either in the overall PD cases or in the PD cases only enrolled in an outpatient group were significantly higher than those in the control group without PD. The median duration from the overall first diagnosis of PD to the development of dementia was 9.02 years.

During the 11 years of follow-up, a total of 1,836 PD patients developed dementia, and 1,226 PD patients died without developing dementia. In the same period, a total of 3,159 control subjects developed dementia, and 5,223 control subjects died without developing dementia. In the period within one year after the index date (i.e.,the first time partition), a total of 5,932 PD subjects encountered 624 medical episodes due to first diagnosed dementia in the 5,450.09 person-years observed, representing incidence densities of dementia of 114.49 per 1,000 person-years. In the same period, a total of 29,645 PD subjects encountered 285 medical episodes due to first diagnosed dementia in 29,208.39 person-years observed, representing incidence densities of dementia of 9.76 per 1,000 person-years. Noticeably, the

incidence density of dementia increased with age irrespective of PD status and sex, and the highest incidence was observed in those aged ≧80 years. The adjusted HR of dementia in relation to PD was significantly increased at 6.43 (95% CI 5.46 - 7.57) and was higher in men than in women (HR: 7.18, 95% CI 5.73 - 9.01 vs. 5.54, 95% CI 4.39 - 6.99). In addition, there was a significant interaction of PD with age on the risk of dementia for both men (p=0.02) and women (p<0.0001) (Table 2).

In the years following the PD diagnosis (i.e., the second time partition), the overall incidence density of dementia was much lower (Table 2). The change in incidence density between the first and the second partition was more pronounced in the PD group (from 114.49 to 30.99 per 1,000 person-years) than in the control group (from 9.76 to 10.83 per 1,000 person-years). The age- and sex- specific incidence densities had a similar pattern in terms of change. However, no significant difference in the sex-specific HRs of dementia was observed (p=0.23). There was a significant interaction of PD status with age (p<0.0001) in both sexes. Further analyses of age- and sex-specific HRs showed the highest HR was observed in PD females aged <70 years (HR: 4.27; 95% CI 3.25 - 5.63).

Impact of PD on the risk of dementia by comorbidity is shown in Table 3. Irrespective of the various time partitions, the incidence of dementia increased with the number of comorbidities in both groups. The PD group had the highest risk of dementia across various medical comorbidity stratifications or Charlson's scores after adjusting for baseline characteristics. In the first time partition, the interaction of PD with hypertension (p=0.01), CAD (p=0.02), stroke (p<0.0001), and COPD (p=0.04) on the risk of dementia also was statistically significant, indicating that subjects without hypertension, CAD, stroke, and COPD had a higher adjusted HR for dementia. However, although the adjusted HR for dementia was also higher in subjects without diabetes and hyperlipidemia than in those with medical comorbidities, there was no statistically significant modification effect by diabetes and hyperlipidemia on the association between PD and the risk of dementia. In terms of the

Charlson's scores, subjects with scores of 0 had a higher adjusted HR for dementia than those with scores of one and ≧two. The interactions were significant for PD with Charlson's score (p=0.01) on the risk of dementia.

In the second time partition, effect-modification by hypertension (p<0.0001), CAD (p=0.01) and stroke (p<0.0001) was statistically significant for dementia, indicating that subjects without those medical comorbidities had a higher adjusted HR for dementia. Among diabetes, hyperlipidemia, or COPD patients, adjusted HR for dementia also showed a statistically significant high risk from 2.02 (95% CI=1.68 - 2.43) to 2.21 (95% CI=1.89 - 2.59), but no significant modification effect was found for those with medical comorbidities on the association between PD and the risk of dementia. In terms of the Charlson's scores, subjects with scores of 0 had a higher adjusted HR for dementia than those with scores of one and ≧ two. Also, a significant modification effect of Charlson's scores on the association between PD and the risk of dementia (p=0.01) was found. Regardless of whether medical comorbidities existed or not, the HRs for dementia were greater in the first time partition but were smaller in the second time partition.

DISCUSSION

To the best of our knowledge, this is the first nationwide population-based cohort study to demonstrate that patients with the first diagnosis of PD are associated with increased risk of dementia compared with non-PD patients. However, our study showed a sharply increased hazard of dementia within one year after the first diagnosis of PD, which is clinically and biologically questionable, probably because a large proportion of patients with dementia remain undiagnosed before the index date of their first clinical visit for PD.

In other words, many patients with pre-existing cognitive impairment and PD were classed as new PD cases because their condition had deteriorated and had only been recognized because they had been referred for an expert opinion. This is also supported by the

decline in the number of PD patients with dementia in the subsequent period of observation. In this study, we found that the overall risk of dementia onset increased nearly twofold in up to 11 years (adjusted HR: 2.42, 95% CI: 2.23 – 2.61) among those who survived at least one year and had an initial PD diagnosis thereafter. The magnitude of this association varied according to different age and sex stratifications. In general, the increased risk of dementia was higher in men in the first partition but was similar in both genders in the second partition. In addition, younger PD patients have the highest risk of dementia in any given partition time. The study results can provide physicians and patients with valuable information and also demonstrate the need for guidelines for detection of dementia risk after the initial diagnosis of PD.

Our study shows that a reasonably increased hazard of dementia more than one year after diagnosis of PD is more likely to be real and may suggest evidence of the mechanisms supported by the Braak pathology staging hypothesis.[35 36] Our findings were similar to another population-based case control study in Taiwan,[22] which showed the risk of developing dementia in prevalent Parkinsonism was highest in the first six months (adjusted odds ratio (AOR): 11.98, 95% CI: 8.51 – 16.68) and then became lower in the following months to years after diagnosis.

Age is known to be a risk factor for dementia not only in the general population[37 38] but also in the PD patient population[5-10 13 15 20 23]. This may be caused by aging of non-dopaminergic structures (i.e., the locus ceruleus and pedunculopontine nucleus).[39] However, a modifying effect of age on the risk of dementia after PD may be present in our study. For example, we found that patients with PD had a significantly higher overall risk of dementia than those in the control group, particularly in subjects aged < 70 years. This result is similar to the findings of some prior studies.[13 18]

Male sometimes is identified as a risk factor for dementia in PD;[5] however, there is no clear explanation for this finding. In our study, we found that the risk of dementia was similar

in both men and women who had first-diagnosed PD one year later (HR: 2.44, 95% CI 2.19 - 2.73 and HR: 2.41, 95% CI 2.15 - 2.69, respectively). Accordingly, patients with PD, especially younger patients in both sexes, could be selected in future studies as a target population to evaluate whether interventions are effective in decreasing the risk of dementia after diagnosis of PD.

Our study also shows that the overall risk of dementia was more than double (adjusted HR 2.42) among subjects with first-diagnosed PD one year later for up to 11 years. After accounting for the competing risk of death and adjustment for the number of medical visits, the findings were similar to those of Perezet al., who reported a higher HR of incident dementia (2.47, 95%CI 1.55 - 3.59) in patients with PD as compared to non-PD subjects.[11] However, other cohort studies have shown a HR ranging from 1.7 (95% CI 1.1 - 2.7) to 5.9 (95% CI 3.9 - 9.1) for incident dementia in PD groups compared with the general population,[9 10 12-15 18] which is different from our findings. Noticeably, most previous studies were limited by a relatively small sample size,[6-17 19-21 23] shorter follow-up time,[6-8 10 12-18 20] the lack of a matched control,[6-8 16 17 19-21 23] failure to account for the competing risk of death,[6-21 23] or a lack of adjustment for the number of medical visits to control for surveillance bias,[9-15 18] rendering the risk that the estimates were more likely to be imprecise and biased.

We found the incidence of dementia increased with the number of comorbidities, including hypertension, diabetes mellitus, CAD, stroke, hyperlipidemia, and COPD, irrespective of PD status. However, in our study, the adjusted HR for dementia was higher in PD alone than in those with medical comorbidities. The effect-modification by hypertension, CAD and stroke was statistically significant for the association between PD and dementia in any given partition time. Prior studies regarding the relationship between patients with PD and these comorbidities remain controversial.[7 16 17 22] For example, although a study in Taiwan demonstrated that patients with PD with cerebrovascular or cardiovascular comorbidities had a lower risk of dementia onset than patients with PD alone,[22] which is similar our findings,

other studies have failed to find this relationship.[16 17] In addition, some previous studies have shown that PD with cardiovascular dysautonomia (such as hypertension, diabetes mellitus, and CAD) and COPD might cause substantial cerebral hypoperfusion and hypoxia, respectively.[40-42] Hypoxia and hypotension in the brain might cause neuronal damage and increase accumulation of pathologic proteins such as β-amyloid, which result in increased risk of dementia onset.[40 41] Therefore, future perspective studies focusing on the causal relationship between such comorbidities and the risk of dementia in PD are warranted.

There were several strengths in our study. First, we obtained a large, nationwide number of participants by using NHIR datasets, which made it possible to reduce selection bias, to obtain higher statistical power, to obtain ahighly representative study population, to have a lower rate of nonresponse or loss to follow-up, and to facilitate the age-, sex- and comorbidities-stratified analyses with an ample simple size to satisfy requirements. To the best of our knowledge, this study is the first to report the age- and sex- specific incidence rates of dementia in a PD group. Secondly, we conducted a longitudinal and retrospective cohort study for 11 years, which is a longer time during which to observe the development of dementia than that in many other prior studies.[6-8 10 12-18 20] Thirdly, more accurate estimates for the incidence rates of dementia in the PD group are available in this study due to the usage of the first diagnosed PD cases rather than the prevalent PD cases, as this might reduce the variations in the incidence of dementia across various PD durations. Lastly, a multivariate Cox proportional hazard regression with a competing risk analysis was used to control for the confounding bias and to account for the competing risk of death.

Still, our study had some limitations. Firstly, we solely selected our PD cases according to physician-recorded diagnosis and prescriptions reported in medical claims, which might have led to potential disease misclassification. However, we used at least three PD-related diagnoses and prescriptions, with the first and last visits >90 days apart, which greatly decrease the likelihood of disease misclassification. Similarly, because we selected patients

with dementia only by using NHIR datasets, potential disease misclassification may be present. To address this concern, we only included dementia cases diagnosed with ≥ three ambulatory visits or ≥ one hospitalization in this study to increase the validity of dementia identification.

Secondly, because patients with PD may utilize the health care system more often than control groups, surveillance bias may be present. Thus, to address this concern, we calculated the number of medical visits for one year after the index date and adjusted for this in the multivariate regression model. Also, the severity of dementia is not available in the database, and we could not distinguish subtypes of dementia in our datasets. Therefore, it is essential for patients with PD, particularly in high risk groups such as subjects aged <70 years, to have regular cognitive assessments including combinations of neuropsychological markers throughout the early disease stages, which not only will provide benefits for identification of the subtypes in dementia but will also decrease underestimation of risk for dementia in PD.

Thirdly, due to the limited information available from the claims data, we were unable to consider a comprehensive list of potential confounders such as smoking, educational level, physical function, and genesin the analysis, which may have resulted in residual confounding bias. To reduce such bias, we used COPD and occupational status as surrogates for smoking and educational level, respectively. Finally, the disease symptoms of PD cases at different disease stages may play a role, to some extent, in the relationship between PD and the risk of dementia. However, because information on the disease symptoms is unavailable from the NHI data, we have left this area (such as non-motor symptoms) for further investigations.

In conclusion, it was found that PD confers a higher risk of dementia than the general population, especially in those aged <70 years in both sexes. Regular monitoring for the development of dementia in patients with PD longitudinally is recommended. Future research should include further evaluation of the underlying mechanism and subtypes for dementia development after diagnosis of PD.

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1 Table 1. Characteristics of the study subjects

Variables[a]	PD group n	PD group %	Control group n	Control group %	*P* value
Age (years)					
<70	1852	31.2	4220	31.2	1.00 [d]
70-74	1314	21.2	6570	21.2	
75-79	1460	24.6	7300	24.6	
≧80	1306	22.0	6515	22.0	
Mean (±SD) [b]	72.5±9.4		70.8±12.7		
Sex					1.00 [d]
Male	3116	52.6	15580	52.6	
Female	2813	47.4	14065	47.4	
Insurance premium (NTD)[b]					<0.0001 [d]
Dependent	2333	39.9	9721	33.8	
<Median (19,200)	1734	29.6	7753	26.2	
>=Median	1787	30.5	12171	41.0	
Mean (±SD)[b,c]	7102.6±11122.9		10194.0±13197.8		
Urbanization status					0.01 [d]
Urban	3203	54.7	15197	51.8	
Suburban	2085	35.6	9741	33.2	
Rural	566	9.8	4424	15.0	
Geographic area					<0.0001 [d]
Northern	2670	45.6	13130	44.8	
Central	1491	25.5	7288	24.9	
Southern	1519	25.9	7957	27.1	
Eastern	174	3.0	931	3.2	
Occupational status					<0.0001 [d]
White collar	1482	25.0	9242	31.2	
Blue collar	2075	35.0	11846	40.0	
Others	2375	40.0	8557	28.8	
History of comorbidity					
Without comorbidities	1151	19.4	16393	55.3	<0.0001 [d]
Hypertension	3578	60.3	11431	38.6	<0.0001 [d]
Diabetes	1430	24.1	4112	13.9	<0.0001 [d]
CAD	1955	33.0	4890	16.5	<0.0001 [d]
Stroke	1977	33.3	2924	9.9	<0.0001 [d]
Hyperlipidemia	1089	18.4	3013	10.2	<0.0001 [d]
COPD	1719	29.0	5624	19.0	<0.0001 [d]

Charlson's score					<0.0001 [d]
0	2841	47.9	22123	74.6	
1	1707	28.8	4640	15.7	
>=2	1384	23.3	2282	9.7	
Mean number of medical visits (±SD) [b]	39.6 (±26.5)		21.9 (±19.7)		<0.0001 [e]
Total	5932	100.0	29645	100.0	

[a]Inconsistency between the total population and the population summed forindividual variableswas due to missing information.

[b]SD=Standard deviation; NTD=New Taiwan Dollars; CAD=Coronary artery disease;COPD=chronic obstructive pulmonary disease

[c]The dependent insurers were not included.

[d]Based on χ^2 test

[e]Based on a Student's t test

Table 2. Age- and sex- specific incidence densities of dementia (ICD-9: 290, 294.1, 331.0, 331.82) in the Parkinson's disease and control groups

Variables	≦1 years				>1 years			
	ID (95% CI)[a,b]		Crude HR (95% CI)	AHR (95% CI)	ID (95% CI)[a,b]		Crude HR (95% CI)	AHR (95% CI)
	Control group	PD group			Control group	PD group		
Male								
<70	1.61 (0.42 - 2.81)	56.23 (40.16 - 72.31)	34.44 (15.58 - 76.13)	15.74 (6.67 - 37.10)[c]	2.61 (2.13 - 3.09)	17.57 (14.48 - 20.67)	6.93 (5.38 - 8.93)	3.82 (2.79 - 5.22)[c]
70-74	5.61 (3.08 - 8.13)	111.38 (85.29 - 137.47)	19.44 (11.73 - 32.21)	13.00 (7.59 - 22.26)[c]	9.23 (8.16 - 10.30)	32.27 (27.02 - 37.52)	3.65 (2.98 - 4.47)	3.06 (2.41 - 3.89)[c]
75-79	7.59 (4.92 - 10.27)	129.62 (103.83 - 155.42)	16.69 (11.16 - 24.95)	9.84 (6.27 - 15.46)[c]	14.01 (12.77 - 15.25)	38.05 (32.58 - 43.51)	2.87 (2.42 - 3.41)	2.26 (1.85 - 2.75)[c]
≧80	22.18 (17.26 - 27.10)	196.24 (161.70 - 230.78)	8.64 (6.58 - 11.57)	4.35 (3.13 - 6.05)[c]	18.94 (17.31 - 20.57)	41.87 (35.34 - 48.40)	2.25 (1.87 - 2.69)	1.90 (1.55 - 2.33)[c]
Total	8.81 (7.32 - 10.29)	118.82 (106.16 - 131.49)	13.23 (10.85 - 16.14)	7.18 (5.73 - 9.01)[d]	10.27 (9.74 - 10.81)	30.33 (27.93 - 32.73)	3.02 (2.75 - 3.33)	2.44 (2.19 - 2.73)[d]
Female								
<70	1.43 (0.37 - 2.49)	51.66 (37.20 - 66.12)	35.81 (16.24 - 79.13)	10.55 (4.21 - 26.45)[c]	3.35 (2.85 - 3.86)	22.23 (18.98 - 25.49)	7.14 (5.78 - 8.81)	4.27 (3.25 - 5.63)[c]
70-74	7.37 (4.36 - 10.38)	89.93 (65.72 - 114.14)	12.04 (7.40 - 19.60)	4.98 (2.84 - 8.74)[c]	10.81 (9.62 - 12.00)	33.61 (28.25 - 38.97)	3.29 (2.71 - 4.01)	2.82 (2.25 - 3.53)[c]
75-79	10.92 (7.25 - 14.59)	165.75 (132.06 - 199.4)	14.81 (10.02 - 21.89)	8.09 (5.23 - 12.51)[c]	17.61 (16.04 - 19.18)	43.22 (36.70 - 49.70)	2.56 (2.14 - 3.07)	2.30 (1.88 - 2.81)[c]

≧80	31.19	180.68	5.69	3.17	22.99	38.74	1.68	1.49
	(24.60 - 37.79)	(143.56 - 217.8)	(4.24 - 7.64)	(2.18 - 4.62)[c]	(20.97 - 25.02)	(32.00 - 45.47)	(1.38 - 2.05)	(1.19 - 1.86)[c]
Total	10.80	109.89	10.03	5.54	11.41	31.72	2.85	2.41
	(9.08 - 12.53)	(97.16 - 122.63)	(8.23 - 12.21)	(4.39 - 6.99)[d]	(10.83 - 12.00)	(29.24 - 34.21)	(2.60 - 3.14)	(2.15 - 2.69)[d]
Overall	9.76	114.49	11.54	6.43	10.83	30.99	2.93	2.42
	(8.62 - 10.89)	(105.51 - 123.4)	(10.04 - 13.27)	(5.46 - 7.57)[e]	(10.43 - 11.22)	(29.27 - 32.72)	(2.75 - 3.14)	(2.23 - 2.61)[e]

In the first time partition (≦1 years), the interactions were significant for PD with age (p<0.0001) and with sex (p=0.04), with age in men (p=0.02), and with age in women (p<0.0001). In the second time partition (>1 years), the interactions were significant for PD with age (p<0.0001), with age in men (p<0.0001), and with age in women (p<0.0001), but not for PD with sex (p=0.23).

[a]ID= incidence density (per 1,000 person-years), CI=confidence interval, AHR=adjusted hazard ratio, HR=hazard ratio

[b]Based on Poisson assumption

[c]Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for age and sex.

[d]Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for sex.

[e]Based on Cox proportional hazard regression with competing risk analysis and adjusted for age, sex, insurance premium, urbanization status, geographic area, occupational status, hypertension status, diabetes, CAD, stroke, hyperlipidemia, COPD, Charlson's score, and number of medical visits.

*P<0.05

Table 3. Impact of Parkinson's disease on the risk of dementia by comorbidity

Variables	≦1 years				>1 years			
	ID (95% CI)[a,b]		Crude HR (95% CI)	AHR (95% CI)	ID (95% CI)[a,b]		Crude HR (95% CI)	AHR (95% CI)
	Control group	PD group			Control group	PD group		
Hypertension								
No	7.49 (6.23 - 8.76)	110.98 (96.94 - 125.02)	14.55 (11.79 - 17.95)	7.75 (6.05 - 9.94)[c]	8.57 (8.13 - 9.01)	27.99 (25.45 - 30.53)	3.36 (3.02 - 3.73)	3.05 (2.69 - 3.45)[c]
Yes	13.40 (11.26 - 15.55)	116.81 (105.12 - 128.49)	8.59 (7.12 - 10.37)	5.25 (4.26 - 6.47)[c]	14.80 (14.03 - 15.56)	33.14 (30.81 - 35.48)	2.29 (2.09 - 2.50)	2.07 (1.87 - 2.28)[c]
			Interaction: p=0.01				Interaction: p<0.0001	
Diabetes								
No	9.13 (7.95 - 10.31)	115.65 (105.28 - 126.02)	12.45 (10.64 - 14.56)	6.99 (5.82 - 8.41)[c]	10.15 (9.74 - 10.56)	29.39 (27.48 - 31.29)	2.97 (2.75 - 3.21)	2.47 (2.26 - 2.70)[c]
Yes	13.69 (10.07 - 17.31)	110.87 (92.88 - 128.85)	7.99 (5.87 - 10.89)	4.43 (3.16 - 6.22)[c]	15.46 (14.13 - 16.79)	36.57 (32.61 - 40.53)	2.42 (2.10 - 2.78)	2.21 (1.89 - 2.59)[c]
			Interaction: p=0.09				Interaction: p=0.19	
CAD								
No	8.47 (7.31 - 9.62)	107.08 (96.49 - 117.67)	12.45 (10.53 - 14.73)	7.38 (6.09 - 8.95)[c]	10.11 (9.69 - 10.52)	29.77 (27.73 - 31.81)	3.02 (2.79 - 3.28)	2.58 (2.35 - 2.83)[c]
Yes	16.39 (12.75 - 20.02)	129.78 (113.04 - 146.52)	7.79 (6.03 - 10.06)	4.16 (3.13 - 5.55)[c]	14.85 (13.66 - 16.04)	33.69 (30.47 - 36.91)	2.32 (2.05 - 2.63)	2.04 (1.77 - 2.35)[c]
			Interaction: p=0.02				Interaction: p=0.01	
Stroke								

No	7.84 (6.77 - 8.91)	99.07 (88.88 - 109.26)	12.44 (10.49 - 14.75)	7.79 (6.44 - 9.42)[c]	9.99 (9.59 - 10.39)	29.39 (27.37 - 31.40)	3.03 (2.80 - 3.29)	2.71 (2.48 - 2.97)[c]
Yes	27.73 (21.57 - 33.88)	146.13 (128.41 - 163.86)	5.20 (4.04 - 6.69)	3.75 (2.87 - 4.90)[c]	19.94 (18.09 - 21.80)	34.66 (31.36 - 37.97)	1.73 (1.52 - 1.98)	1.68 (1.46 - 1.94)[c]
			Interaction: $p<0.0001$				Interaction: $p<0.0001$	
Hyperlipidemia								
No	9.83 (8.63 - 11.03)	118.50 (108.36 - 128.63)	11.84 (10.20 - 13.73)	6.50 (5.46 - 7.73)[c]	10.49 (10.08 - 10.90)	30.64 (28.73 - 32.54)	2.99 (2.78 - 3.23)	2.51 (2.30 - 2.73)[c]
Yes	9.08 (5.66 - 12.51)	97.10 (77.97 - 116.23)	10.57 (6.91 - 16.16)	5.83 (3.64 - 9.32)[c]	13.82 (12.40 - 15.23)	32.52 (28.46 - 36.58)	2.42 (2.05 - 2.84)	2.02 (1.68 - 2.43)[c]
			Interaction: $p=0.92$				Interaction: $p=0.18$	
COPD								
No	8.72 (7.53 - 9.91)	108.70 (98.33 - 119.07)	12.25 (10.38 - 14.46)	6.78 (5.60 - 8.21)[c]	10.21 (9.79 - 10.63)	29.59 (27.62 - 31.56)	2.98 (2.76 - 3.23)	2.54 (2.32 - 2.78)[c]
Yes	14.27 (11.10 - 17.43)	128.85 (111.08 - 146.02)	8.91 (6.87 - 11.56)	5.33 (3.94 - 7.19)[c]	13.77 (12.70 - 14.84)	34.86 (31.31 - 38.41)	2.56 (2.25 - 2.91)	2.11 (1.82 - 2.45)[c]
			Interaction: $p=0.04$				Interaction: $p=0.08$	
Number of Comorbidities								
0	5.88 (4.56 - 7.19)	99.30 (80.40 - 118.21)	16.66 (12.43 - 22.33)	8.68 (6.27 - 12.00)[d]	7.48 (7.01 - 7.96)	24.63 (21.32 - 27.94)	3.40 (2.93 - 3.96)	3.52 (2.97 - 4.16)[d]
1	9.60 (7.19 - 12.00)	104.64 (85.26 - 124.02)	10.73 (7.86 - 14.64)	7.70 (5.56 - 10.69)[d]	11.76 (10.87 - 12.65)	28.61 (24.94 - 32.27)	2.47 (2.13 - 2.87)	2.67 (2.27 - 3.13)[d]
≧2	15.08	122.57	8.01	4.90	15.28	34.21	2.28	2.11

	(12.65 - 17.52)	(110.65 - 134.5)	(6.63 - 9.66)	(4.01 - 5.99)[d]	(14.43 - 16.12)	(31.83 - 36.60)	(2.08 - 2.49)	(1.92 - 2.32) [d]
			Interaction: p=0.01				Interaction: p<0.0001	
Charlson's score								
0	7.16	95.08	13.07	7.34	9.73	28.39	3.00	2.67
	(6.04 - 8.28)	(83.31 - 106.84)	(10.72 - 15.96)	(5.88 - 9.17)[e]	(9.30 - 10.15)	(26.09 - 30.70)	(2.73 - 3.29)	(2.41 - 2.97)[e]
1	16.55	120.17	7.15	4.36	14.92	34.79	2.38	2.11
	(12.80 - 20.29)	(102.99 - 137.35)	(5.47 - 9.33)	(3.26 - 5.83)[e]	(13.70 - 16.13)	(31.34 - 38.25)	(2.09 - 2.71)	(1.83 - 2.44)[e]
≧2	19.33	148.51	7.60	5.08	13.93	32.35	2.32	2.07
	(14.13 - 24.53)	(127.11 - 169.91)	(5.61 - 10.31)	(3.62 - 7.13)[e]	(12.36 - 15.51)	(28.45 - 36.24)	(1.96 - 2.73)	(1.71 - 2.51)[e]
			Interaction: p=0.01				Interaction: p=0.01	

[a]ID= incidence density, CI=confidence interval

[b]Based on Poisson assumption

[c]Based on Cox proportional hazard regression with competing risk analysis and adjusted for age, sex, insurance premium, urbanization status, geographic area, occupational status, status of hypertension, diabetes, CAD, stroke, hyperlipidemia, COPD, Charlson's score,and number of medical visits.

[d]Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for comorbidities.

[e]Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for Charlson's score.

* P<0.05

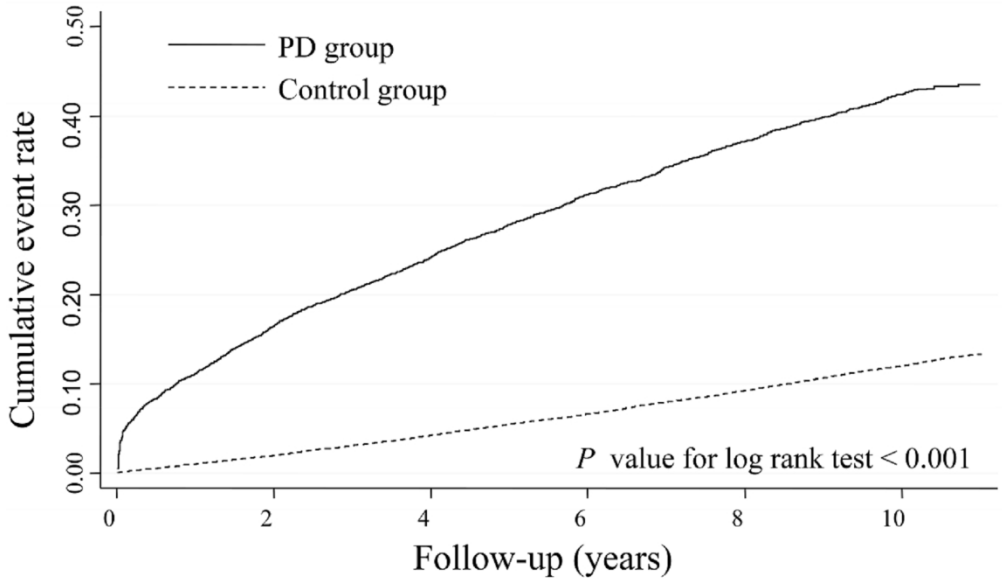

Figure 1 Comparison of Kaplan-Meier failure estimates of dementia onset between the two groups. PD, Parkinson's disease.

153x90mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Page No	Recommendation
Title and abstract	1	2	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		3	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction			
Background/rationale	2	4-5	Explain the scientific background and rationale for the investigation being reported
Objectives	3	5	State specific objectives, including any prespecified hypotheses
Methods			
Study design	4	6	Present key elements of study design early in the paper
Setting	5	5-6	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	6-7	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		6-7	(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	7-8	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	*5-8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	6-8	Describe any efforts to address potential sources of bias
Study size	10	5-6	Explain how the study size was arrived at
Quantitative variables	11	7-8	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	8-9	(*a*) Describe all statistical methods, including those used to control for confounding
		8-9	(*b*) Describe any methods used to examine subgroups and interactions
		-	(*c*) Explain how missing data were addressed
		-	(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		-	(*e*) Describe any sensitivity analyses

		Results	
Participants	13*	5-7	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		-	(b) Give reasons for non-participation at each stage
		-	(c) Consider use of a flow diagram
Descriptive data	14*	10	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		21-22	(b) Indicate number of participants with missing data for each variable of interest
		10	(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*10-12*	*Cohort study*—Report numbers of outcome events or summary measures over time
		-	*Case-control study*—Report numbers in each exposure category, or summary measures of exposure
		-	*Cross-sectional study*—Report numbers of outcome events or summary measures
Main results	16	10-12	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		10-12	(*b*) Report category boundaries when continuous variables were categorized
		10-12	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	10-12	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
		Discussion	
Key results	18	12-13	Summarise key results with reference to study objectives
Limitations	19	15-16	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	12-16	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	12-16	Discuss the generalisability (external validity) of the study results
		Other information	
Funding	22	17	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.