

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-025274
Article Type:	Research
Date Submitted by the Author:	10-Jul-2018
Complete List of Authors:	Liu, Chih-Ching; National Cheng Kung University, College of Medicine, Department of Public Health Sun, Yu; En Chu Kong Hospital, Department of Neurology Lee, Pei-Chen; National Taipei University of Nursing and Health Sciences, Department of Health Care Management Li, Chung-Yi; National Cheng Kung University, College of Medicine, Department of Public Health Hu, Susan; National Cheng Kung University, College of Medicine, Department of Public Health
Keywords:	retrospective cohort study, Parkinson's disease, Dementia < NEUROLOGY, competing risk, EPIDEMIOLOGY

SCHOLARONE™  
Manuscripts

1  
2 **Risk of Dementia after Parkinson's Disease in Taiwan: A Population-based Nationwide**  
3  
4 **Cohort Study**  
5

6 Chih-Ching Liu, MSc<sup>a</sup>, Yu Sun, MD, PhD<sup>b</sup>, Pei-Chen Lee, PhD<sup>c</sup>,

7  
8 Chung-Yi Li, PhD<sup>a,d</sup>, Susan C. Hu, PhD<sup>a\*</sup>  
9

10  
11  
12 <sup>a</sup> Department of Public Health, College of Medicine, National Cheng Kung University, Tainan,  
13  
14 Taiwan  
15

16  
17 <sup>b</sup>Department of Neurology, En Chu Kong Hospital, Sanxia District, New Taipei City, Taiwan  
18

19 <sup>c</sup>Department of Health Care Management, National Taipei University of Nursing and Health  
20  
21 Sciences, Taipei, Taiwan  
22

23 <sup>d</sup>Department of Public Health, College of Public Health, China Medical University, Taichung,  
24  
25 Taiwan  
26

27  
28 \*Chung-Yi Li and Susan C. Hu contributed equally to this article.  
29

30  
31  
32 **Running title:** Risk of Dementia after Parkinson's disease  
33

34 **Word count:** text 3800  
35

36  
37  
38 **Correspondence address:**  
39

40 Dr. Susan C. Hu  
41

42 Department of Public Health, College of Medicine, National Cheng Kung University  
43

44 Tel.: 886-6-2353535 ext. 5599, Fax: 886-6-2359033  
45

46 E-mail: shuhu@mail.ncku.edu.tw  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 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 ( $\leq 1$  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<sup>1</sup>. Some studies have reported that older age<sup>2-12</sup> and male gender<sup>2-5</sup> 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<sup>2-8 10-17</sup>, 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<sup>2-18</sup>, and most previous cohort studies involved a limited number of person-years with a limited follow-up period<sup>3-6 8-12 15-17</sup>. 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<sup>5 16-18</sup>. However, little research has examined medical comorbidities as a potential confounding factor to control<sup>5 9 18</sup> and none has considered death as a competing risk<sup>3-17</sup>, 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<sup>18</sup>. 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<sup>19</sup> 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<sup>19</sup>. 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<sup>20</sup>. 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

1  
2 included all cases with at least 3 medical claims (either outpatient or inpatient care) with a  
3  
4 diagnostic code of PD (ICD-9-CM: 332.0) who had received 3 or more courses of  
5  
6 anti-Parkinsonism medications, including L-dopa or dopamine agonist prescriptions after  
7  
8 first-time diagnosis between 2002 and 2003. Moreover, the first and last outpatient or  
9  
10 inpatient visits and anti-Parkinsonism medication records were separated by at least 90 days  
11  
12 to avoid accidental inclusion of miscoded patients.  
13

14  
15 We further made the following exclusions to ensure the validity of the PD diagnosis: (1)  
16  
17 an age on the index date of less than 40 years, who are more likely to have a genetic etiology;  
18  
19 (2) a diagnostic code of secondary Parkinsonism (ICD-9-CM code: 332.1) during the study  
20  
21 period; (3) receipt of any neuroleptic medication 180 days prior to the index date, and (4) 3 or  
22  
23 more medical claims (either ambulatory or inpatient care) with diagnostic codes of dementia  
24  
25 prior to the index date. The first date of initial diagnosis for PD in the period of 2002 to 2003  
26  
27 was set as the index date.  
28

29  
30 The control subjects were selected from those who had never been diagnosed with PD  
31  
32 between 1999 and 2011 and met the same exclusion criteria as those set for the patients with  
33  
34 PD. These control subjects were matched by age (each 5-year span), sex, and year of index  
35  
36 date for patients with PD at a 5:1 ratio. As a result, 29,645 control subjects were identified.  
37  
38 For the control groups, the index date was either January 1, 2002 or January 1, 2003.  
39

40  
41 Baseline comorbidities that may be associated with an increased risk of dementia were  
42  
43 identified for the PD and control groups, including hypertension, diabetes, CAD, stroke,  
44  
45 hyperlipidemia, and COPD observed before the index date. Information on the geographic  
46  
47 area, urbanization level, occupational status, and salary-based insurance premium at the index  
48  
49 date was also obtained from the registry for beneficiaries. The number of medical visits  
50  
51 within one year after the index date was adjusted to decrease the potential presence of  
52  
53 surveillance bias because subjects with PD visit clinics more frequently and thus may have  
54  
55 more opportunities to be diagnosed as having dementia.  
56



## 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  $\geq 3$  ambulatory visits or  $\geq 1$  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<sup>21</sup>. 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<sup>22-24</sup>. 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<sup>25</sup>, 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  $\leq 1$  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

1  
2 significant.

### 3 4 **RESULTS**

5  
6 Gender, age, geographic area, and urbanization levels were similar in both groups. The  
7 prevalence rates of the risk factors for dementia were high in patients with PD. The PD cohort  
8 had fewer white-collar workers (25.0% vs 31.2%), a higher prevalence of dependence (39.9%  
9 vs 33.8%), a lower insurance premium, and a higher frequency of medical visits (26.5 vs 19.7  
10 per year) than the control group (Table 1).  
11  
12  
13  
14  
15

16  
17 Figure 1 shows the cumulative incidence of dementia in patients with and without PD.  
18 The cumulative incidence of dementia for PD was significantly higher than the corresponding  
19 data observed in the non-PD group (log-rank test,  $p < 0.0001$ ).  
20  
21  
22

23 The median duration from the first diagnosis of PD to the development of dementia was  
24 9.02 years. In the period within 1 year after the index date (i.e., the first time partition), the  
25 corresponding incidence densities of dementia for the PD and control groups were 114.49 and  
26 9.76 per 1,000 person-years, respectively. Noticeably, the incidence density of dementia  
27 increased with age irrespective of PD status and sex, and the highest incidence was observed  
28 in those aged  $\geq 80$  years. The adjusted HR of dementia in relation to PD was significantly  
29 increased at 9.62 (95%CI 7.95-11.64) and was higher in men than in women (HR: 11.28 vs.  
30 5.64). In addition, there was a significant interaction of PD with age on the risk of dementia  
31 for both men ( $P = 0.0147$ ) and women ( $P < 0.0001$ ) (Table 2).  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41

42 In the years following the PD diagnosis (i.e., the second time partition), the overall  
43 incidence density of dementia was much lower (Table 2). The change in incidence density  
44 between the first and the second partition was more pronounced in the PD group (from 114.49  
45 to 30.99 per 1,000 person-years) than in the control group (from 9.76 to 10.83 per 1,000  
46 person-years). The age- and sex- specific incidence densities had a similar pattern in terms of  
47 change. However, no significant difference in the sex-specific HRs (hazard ratios) of  
48 dementia was observed ( $p = 0.7064$ ). There was a significant interaction of PD status with age  
49  
50  
51  
52  
53  
54  
55  
56

( $P < 0.0001$ ) 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)

1  
2 of dementia was significantly higher within 1 year after the initial PD diagnosis (HR =9.62,  
3 95%CI=7.59-11.64). However, the magnitude of association varied according to different age  
4 and sex stratifications. In general, the risk of dementia was higher in men in the first partition  
5 but was similar in both sexes in the second partition. However, the increased risk was highest  
6 in both male and female participants aged <70 years in any given partition time. The study  
7 results can provide physicians and patients with valuable information and also demonstrate  
8 the need for guidelines for detection of dementia risk after the initial diagnosis of PD.  
9

10  
11 Potential mechanisms contributing to dementia in patients with PD are still poorly  
12 understood. The site pathology for dementia in PD includes brain stem nuclei, limbic  
13 structures, and the cerebral cortex, and the types of pathological changes have been described  
14 as Lewy body (LB) degeneration and Alzheimer-type changes<sup>26</sup>. Regardless of whether there  
15 is additional Alzheimer's pathology (amyloid  $\beta$  (A $\beta$ ) plaques and tau neurofibrillary tangles  
16 (NFTs))<sup>22-24</sup>, the main pathology associated with dementia in PD are Lewy body degeneration  
17 in the limbic structures and cerebral cortex, with  $\alpha$ -synuclein<sup>26</sup>. Deficits in dopaminergic,  
18 noradrenergic, serotonergic, and cholinergic neurochemicals are known to be the cause of  
19 cognition impairment in PD<sup>26</sup>.  
20  
21

22  
23 Some former studies have revealed that the fact that the risk of dementia increases with  
24 the disease duration of PD may be due to the Lewy pathology as PD progresses temporally  
25 and spatially from the brain stem through the forebrain and limbic system to the neocortex,  
26 which is supported by the Braak pathology staging hypothesis<sup>27 28</sup>. However, our study  
27 showed a sharply increased hazard of dementia within 1 year after first diagnosis of PD, which  
28 is clinically and biologically unbelievable; this situation is probably because a large  
29 proportion of patients with dementia remain undiagnosed before the index date of their first  
30 clinical visit for PD. Nevertheless, a reasonably increased hazard of dementia more than one  
31 year after diagnosis of PD is more likely to be real and may suggest evidence of the  
32 mechanisms supported by the Braak pathology staging hypothesis<sup>27 28</sup>. Our findings were  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56

1  
2 similar to another population-based case control study in Taiwan<sup>18</sup>, which showed the risk of  
3  
4 developing dementia in prevalent Parkinsonism was highest in the first 6 months (AOR:11.98,  
5  
6 95%CI:8.51-16.68) and then became lower in the following months to years after diagnosis.  
7

8 Age is known to be a risk factor for dementia not only in the general population<sup>29 30</sup> but  
9  
10 also in PD patient population<sup>2-12</sup>. This may be caused by aging of non-dopaminergic  
11  
12 structures (i.e., the locus ceruleus and pedunculopontine nucleus)<sup>31</sup>. However, a modifying  
13  
14 effect of age on the risk of dementia after PD may be present in our study. For example, we  
15  
16 found that patients with PD had a significantly higher overall risk of dementia than those in  
17  
18 the control group, particularly in subjects aged < 70 years. This result is similar to the findings  
19  
20 of some prior studies<sup>11 12</sup>.  
21  
22

23 Male gender is sometimes identified as a risk factor for dementia in PD<sup>2 5</sup>; however,  
24  
25 there is no clear explanation for this finding. In our study, we found no significant role of  
26  
27 gender in the first-diagnosed PD patients one year later. Accordingly, patients with PD,  
28  
29 especially younger patients in both sexes, could be selected as a target population to evaluate  
30  
31 whether interventions are effective in decreasing the risk of dementia after diagnosis of PD in  
32  
33 future studies.  
34  
35

36 Our study also shows that the overall risk of dementia was more than double (adjusted  
37  
38 HR 2.37) among subjects with first-diagnosed PD 1 year later for up to 11 years. After  
39  
40 accounting for the competing risk of death and adjustment for the number of medical visits,  
41  
42 the findings were similar to those of Perezet al., who reported a higher relative risk of incident  
43  
44 dementia (2.31, 95%CI 1.48-3.61) in patients with PD as compared to non-PD subjects<sup>13</sup>.  
45  
46 However, other cohort studies have shown a relative risk of 1.7 (95%CI:1.1–2.7) to 5.9  
47  
48 (95%CI:3.9–9.1) for incident dementia in PD groups compared with the general population<sup>7 8</sup>  
49  
50 <sup>10-12 15</sup>, which is different from our findings. Noticeably, most previous studies were limited  
51  
52 by a relatively small sample size<sup>3-17</sup>, shorter follow-up time<sup>3-6 8-12 15-17</sup>, the lack of a matched  
53  
54 control<sup>3-6 9 14 16 17</sup>, failure to account for the competing risk of death<sup>3-17</sup>, or a lack of adjustment  
55  
56  
57  
58  
59  
60

1  
2 for the number of medical visits to control for surveillance bias<sup>7 8 10-13 15</sup>, rendering the risk  
3  
4 that the estimates were more likely to be imprecise and biased.  
5

6 We found the incidence of dementia increased with number of comorbidities, including  
7  
8 hypertension, diabetes mellitus, CAD, stroke, hyperlipidemia and COPD. However, of the  
9  
10 patients with PD in our study, PD alone also has more positive effects on dementia in most  
11  
12 circumstances, although effect modifiers such as hypertension, diabetes, stroke, CAD,  
13  
14 hyperlipidemia, and COPD had positive effects for dementia. Prior studies regarding the  
15  
16 relationship between patients with PD and those comorbidities remain controversial<sup>5 16-18</sup>. For  
17  
18 example, although a study in Taiwan has demonstrated those cerebrovascular or  
19  
20 cardiovascular comorbidities in patients with PD had lower risk of dementia onset than  
21  
22 patients with PD alone<sup>18</sup>, which is similar our findings, other studies have failed to relate  
23  
24 those cerebrovascular or cardiovascular risk factors<sup>16 17</sup>. Besides, some previous studies have  
25  
26 revealed that PD with cardiovascular dysautonomia (such as hypertension, diabetes mellitus,  
27  
28 and CAD) and COPD might cause substantial cerebral hypoperfusion and hypoxia,  
29  
30 respectively<sup>32-34</sup>. Hypoxia and hypotension in the brain might cause neuronal damage and  
31  
32 increase accumulation of pathologic proteins such as  $\beta$ -amyloid, which result in increased risk  
33  
34 of dementia onset<sup>32 33</sup>. Therefore, future perspective studies focusing on needed the causal  
35  
36 relationship between those comorbidities and the risk of dementia in PD are warranted.  
37  
38

39  
40 There were several strengths in our study. First, we obtained a large, nationwide number  
41  
42 of participants by using NHIR datasets, which made it possible to reduce selection bias, to  
43  
44 obtain higher statistical power, to obtain a highly representative study population, to have a  
45  
46 lower rate of nonresponse or loss to follow-up, and to facilitate the age-, sex- and  
47  
48 comorbidities-stratified analyses with an ample simple size to satisfy requirements. To the  
49  
50 best of our knowledge, this study is the first to report the age- and sex- specific incidence  
51  
52 rates of dementia in a PD group. Secondly, we conducted a longitudinal and retrospective  
53  
54 cohort study for 11 years, which is a longer time during which to observe the development of  
55  
56

1  
2 dementia than that in many other prior studies<sup>3-6 8-12 15-17</sup>. Thirdly, more accurate estimates for  
3  
4 the incidence rates of dementia in the PD group are available in this study due to the usage of  
5  
6 the first diagnosed PD cases rather than the prevalent PD cases, as this might reduce the  
7  
8 variations in the incidence of dementia across various PD durations. Fourth, this study used  
9  
10 multivariate Cox proportional hazard regression with competing risk analysis to control the  
11  
12 confounding bias and account for the competing risk of death.  
13

14  
15 Still, our study had some limitations. First, because we selected dementia patients only  
16  
17 by using NHIR datasets, we might have missed some patients who had been waiting for a  
18  
19 pathological diagnosis, which may have resulted in an underestimation of the incidence of  
20  
21 dementia. Also, because patients with PD may utilize the health care system more often than  
22  
23 control groups, surveillance bias may be present. To address this concern, we calculated the  
24  
25 number of medical visits for 1 year after the index date and adjusted for it in the multivariate  
26  
27 regression model. Secondly, the severity of dementia is not available in the database, and we  
28  
29 could not distinguish subtypes of dementia in our datasets. Therefore, it is essential for  
30  
31 patients with PD, particular in high risk groups such as subjects aged <70 years, to have  
32  
33 regular cognitive assessments including combinations of neuropsychological markers  
34  
35 throughout the early disease stages, which not only would provide benefits for identification  
36  
37 of the subtypes in dementia but would also decrease underestimation of risk for dementia in  
38  
39 PD. Thirdly, due to the limited information available from the claims data, we were unable to  
40  
41 consider a comprehensive list of potential confounders such as smoking, educational level,  
42  
43 physical function, and genes in the analysis, which may have resulted in residual confounding  
44  
45 bias. To reduce such bias, we used COPD and occupational status as surrogates for smoking  
46  
47 and educational level, respectively.  
48  
49

50  
51 In conclusion, it was found that PD confers a high risk of dementia than non-PD patients,  
52  
53 especially in the group of aged < 70 years in both sexes. Regular monitoring for the  
54  
55 development of dementia in patients with PD in a long-time follow-up, particularly risk  
56



1  
2 groups, is recommended. Future research should include further evaluation of the underlying  
3  
4 mechanism and subtypes for dementia development after diagnosis of PD.  
5  
6  
7

8 **Acknowledgements** We thank the Bureau of National Health Insurance in the Ministry of  
9  
10 Health and Welfare, and the National Health Research Institutes by providing the National  
11  
12 Health Insurance Research Database for this study. The interpretation and conclusions  
13  
14 contained herein do not represent those of the Bureau of National Health Insurance, Ministry  
15  
16 of Health and Welfare, or National Health Research Institutes.  
17  
18

19 **Author contributions** Chih-Ching Liu analyzed the data and wrote the draft of the  
20  
21 manuscript. Yu Sun and Pei-Chen Lee provided further data analyses and interpretation.  
22  
23 Chung-Yi Li and Susan C. Hu advised the study and revised the manuscript. All authors have  
24  
25 approved the final version of the manuscript.  
26

27 **Funding** This study was supported by a grant from Taiwan Ministry of Science and  
28  
29 Technology (MOST 106-2314-B-227-010).  
30

31 **Disclaimer** The funder had no role in study design, data collection and analysis, and the  
32  
33 preparation of the manuscript.  
34

35 **Competing interests** None.  
36

37 **Patient consent** Not required.  
38

39 **Ethics approval** Full review by our institutional review board was not required because the  
40  
41 encryption on the identification numbers makes it impossible to identify individuals. Access  
42  
43 to the National Health Insurance Research Database datasets is approved by the National  
44  
45 Health Research Institutes Review Committee.  
46  
47

48 **Provenance and peer review** Not commissioned; externally peer reviewed.  
49

50 **Data sharing statement** We, as the authors of this original research article, state that there is  
51  
52 no additional, unpublished data available from this study. Raw data sharing from National  
53  
54 Health Insurance Research Database is prohibited, according to the policy of National Health  
55  
56



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Research Institutes (NHRI) in Taiwan.

For peer review only

## REFERENCES

1. Kalia LV, Lang AE. Parkinson's disease. *Lancet* 2015;386:896-912.
2. Xu Y, Yang J, Shang H. Meta-analysis of risk factors for Parkinson's disease dementia. *Transl Neurodegener* 2016;5:11.
3. Domellof ME, Ekman U, Forsgren L, *et al.* Cognitive function in the early phase of Parkinson's disease, a five-year follow-up. *Acta Neurol Scand* 2015;132:79-88.
4. Kwon KY, Kang SH, Kim M, *et al.* Nonmotor Symptoms and Cognitive Decline in de novo Parkinson's Disease. *Can J Neurol Sci* 2014;41:597-602.
5. Anang JB, Gagnon JF, Bertrand JA, *et al.* Predictors of dementia in Parkinson disease: a prospective cohort study. *Neurology* 2014;83:1253-60.
6. Zhu K, van Hilten JJ, Marinus J. Predictors of dementia in Parkinson's disease; findings from a 5-year prospective study using the SCOPA-COG. *Parkinsonism Rel Disord* 2014;20:980-5.
7. Williams-Gray CH, Mason SL, Evans JR, *et al.* The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. *J Neurol Neurosurg Ps* 2013;84:1258-64.
8. Aarsland D, Andersen K, Larsen JP, *et al.* Risk of dementia in Parkinson's disease: a community-based, prospective study. *Neurology* 2001;56:730-6.
9. Lee SY, Ryu HJ, Seo JW, *et al.* Dementia-Free Survival and Risk Factors for Dementia in a Hospital-Based Korean Parkinson's Disease Cohort. *J Clin Neurol* 2017;13:21-26.
10. Hobson P, Meara J. Risk and incidence of dementia in a cohort of older subjects with Parkinson's disease in the United Kingdom. *Mov Disord* 2004;19:1043-9.
11. Marder K, Tang MX, Cote L, *et al.* The frequency and associated risk factors for dementia in patients with Parkinson's disease. *Arch Neurol* 1995;52:695-701.
12. Levy G, Schupf N, Tang MX, *et al.* Combined effect of age and severity on the risk of dementia in Parkinson's disease. *Ann Neurol* 2002;51:722-9.
13. Perez F, Helmer C, Foubert-Samier A, *et al.* Risk of dementia in an elderly population of Parkinson's disease patients: a 15-year population-based study. *Alzheimers Dement* 2012;8:463-9.
14. Auyeung M, Tsoi TH, Mok V, *et al.* Ten year survival and outcomes in a prospective cohort of new onset Chinese Parkinson's disease patients. *J Neurol Neurosurg Ps* 2012;83:607-11.
15. de Lau LM, Schipper CM, Hofman A, *et al.* Prognosis of Parkinson disease: risk of dementia and mortality: the Rotterdam Study. *Arch Neurol* 2005;62:1265-9.
16. Haugarvoll K, Aarsland D, Wentzel-Larsen T, *et al.* The influence of cerebrovascular risk factors on incident dementia in patients with Parkinson's disease. *Acta Neurol Scand* 2005;112:386-90.
17. Levy G, Tang MX, Cote LJ, *et al.* Do risk factors for Alzheimer's disease predict dementia in Parkinson's disease? An exploratory study. *Mov Disord* 2002;17:250-7.

18. Huang YC, Wu ST, Lin JJ, *et al.* Prevalence and risk factors of cognitive impairment in Parkinson disease: a population-based case-control study in Taiwan. *Medicine (Baltimore)* 2015;94:e782.
19. National Health Insurance Administration. Universal Health Coverage in Taiwan. [https://www.nhi.gov.tw/English/Content\\_List.aspx?n=8FC0974BBFEFA56D&topn=E4A30E51A609E49](https://www.nhi.gov.tw/English/Content_List.aspx?n=8FC0974BBFEFA56D&topn=E4A30E51A609E49) (accessed May 8 2018).
20. Liu CC, Li CY, Lee PC, *et al.* Variations in Incidence and Prevalence of Parkinson's Disease in Taiwan: A Population-Based Nationwide Study. *Parkinson's dis* 2016;2016:8756359.
21. Aguero-Torres H, Winblad B. Alzheimer's disease and vascular dementia. Some points of confluence. *Ann N Y Acad Sci* 2000;903:547-52.
22. Compta Y, Parkkinen L, O'Sullivan SS, *et al.* Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? *Brain* 2011;134:1493-505.
23. Jellinger KA, Attems J. Prevalence and impact of vascular and Alzheimer pathologies in Lewy body disease. *Acta Neuropathol* 2008;115:427-36.
24. Jellinger KA, Seppi K, Wenning GK, *et al.* Impact of coexistent Alzheimer pathology on the natural history of Parkinson's disease. *J Neural Transm* 2002;109:329-39.
25. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496-509.
26. Emre M. What causes mental dysfunction in Parkinson's disease? *Mov Disord* 2003;18:63-71.
27. Braak H, Del Tredici K, Bratzke H, *et al.* Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages). *J Neurol* 2002;249:1-5.
28. Braak H, Del Tredici K, Rub U, *et al.* Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003;24:197-211.
29. Matthews FE, Stephan BC, Robinson L, *et al.* A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II. *Nat Commun* 2016;7:11398.
30. Solomon A, Mangialasche F, Richard E, *et al.* Advances in the prevention of Alzheimer's disease and dementia. *J Intern Med* 2014;275:229-50.
31. Levy G, Tang MX, Cote LJ, *et al.* Motor impairment in PD: relationship to incident dementia and age. *Neurology* 2000;55:539-44.
32. de la Torre JC. Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. *Cardiovasc Psychiatry Neurol* 2012;2012:367516.
33. Liu H, Xing A, Wang X, *et al.* Regulation of beta-amyloid level in the brain of rats with cerebrovascular hypoperfusion. *Neurobiol Aging* 2012;33:826.e31-42.
34. Grant I, Heaton RK, McSweeney AJ, *et al.* Neuropsychologic findings in hypoxemic chronic obstructive pulmonary disease. *Arch Intern Med* 1982;142:1470-6.

Table 1. Characteristics of the study subjects

Variables <sup>a</sup>	PD group		Control group		P value
	n	%	n	%	
Age (years)					
<70	1852	31.2	4220	31.2	1.00 <sup>d</sup>
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) <sup>b</sup>		72.5±9.4		70.8±12.7	
Sex					1.00 <sup>d</sup>
Male	3116	52.6	15580	52.6	
Female	2813	47.4	14065	47.4	
Insurance premium (NTD) <sup>b</sup>					<0.0001 <sup>e</sup>
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) <sup>c</sup>		7102.6±11122.9		10194.0±13197.8	
Urbanization status					0.0007 <sup>d</sup>
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 <sup>d</sup>
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 <sup>d</sup>
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 <sup>d</sup>
Hypertension	3578	60.3	11431	38.6	<0.0001 <sup>d</sup>
Diabetes	1430	24.1	4112	13.9	<0.0001 <sup>d</sup>
CAD	1955	33.0	4890	16.5	<0.0001 <sup>d</sup>
Stroke	1977	33.3	2924	9.9	<0.0001 <sup>d</sup>
Hyperlipidemia	1089	18.4	3013	10.2	<0.0001 <sup>d</sup>
COPD	1719	29.0	5624	19.0	<0.0001 <sup>d</sup>

1					
2	Mean number of medical	39.6	26.5	21.9	19.7
3	visits				<0.0001 <sup>e</sup>
4					
5	Total	5932	100.0	29645	100.0

6 <sup>a</sup>Inconsistency between total population and population summed for individual variables was  
7 due to missing information.

8 <sup>b</sup>SD=Standard deviation; NTD=New Taiwan Dollars; CAD=Coronary artery disease ;  
9 COPD=chronic obstructive pulmonary disease

10 <sup>c</sup>The dependent insurers were not included.

11 <sup>d</sup>Based on  $\chi^2$  test

12 <sup>e</sup>Based on student's t test

13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

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

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

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

In the first time partition ( $\leq 1$  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 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 ( $p = 0.7064$ ).

<sup>a</sup>ID= incidence density(per 1,000 person-years), CI=confidence interval, AHR=adjusted hazard ratio, HR=hazard ratio,

<sup>b</sup>Based on Poisson assumption

<sup>c</sup>Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for age and sex.

<sup>d</sup>Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for sex.

<sup>e</sup>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) <sup>a,b</sup>		Crude HR (95% CI)	AHR (95% CI)	ID (95% CI) <sup>a,b</sup>		Crude HR (95% CI)	AHR (95% CI)
	Control group	PD group			Control group	PD group		
<b>Hypertension</b>								
No	7.49 (6.23-8.76)	110.98 (96.94-125.02)	14.58 (11.82-17.99)	7.84 (6.13-10.01) <sup>c</sup>	8.57 (8.13-9.01)	27.99 (25.45-30.53)	3.18 (2.86-3.53)	2.94 (2.60-3.33) <sup>c</sup>
Yes	13.40 (11.26-15.55)	116.81 (105.12-128.49)	8.64 (7.16-10.43)	7.76 (6.16-9.79) <sup>c</sup>	14.80 (14.03-15.56)	33.14 (30.81-35.48)	2.15 (1.97-2.35)	2.02 (1.83-2.22) <sup>c</sup>
				Interaction: p=0.3336				Interaction: p<0.0001
<b>Diabetes</b>								
No	9.13 (7.95-10.31)	115.65 (105.28-126.02)	12.49 (10.68-14.61)	10.52 (8.55-12.94) <sup>c</sup>	10.15 (9.74-10.56)	29.39 (27.48-31.29)	2.78 (2.58-3.01)	2.45 (2.24-2.67) <sup>c</sup>
Yes	13.69 (10.07-17.31)	110.87 (92.88-128.85)	8.05 (5.91-10.96)	4.50 (3.22-6.29) <sup>c</sup>	15.46 (14.13-16.79)	36.57 (32.61-40.53)	2.24 (1.95-2.58)	2.09 (1.78-2.44) <sup>c</sup>
				Interaction: p= 0.0070				Interaction: p= 0.1674
<b>CAD</b>								
No	8.47 (7.31-9.62)	107.08 (96.49-117.67)	12.49 (10.56-14.77)	7.41 (6.13- 8.96) <sup>c</sup>	10.11 (9.69-10.52)	29.77 (27.73-31.81)	2.82 (2.60-3.05)	2.47 (2.26-2.71) <sup>c</sup>
Yes	16.39 (12.75-20.02)	129.78 (113.04-146.52)	7.86 (6.08- 10.15)	7.06 (5.15- 9.70) <sup>c</sup>	14.85 (13.66-16.04)	33.69 (30.47-36.91)	2.21 (1.95-2.50)	2.02 (1.76-2.32) <sup>c</sup>
				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) <sup>c</sup>	9.99 (9.59-10.39)	29.39 (27.37-31.40)	2.85 (2.63-3.09)	2.60 (2.38- 2.84) <sup>c</sup>
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) <sup>c</sup>	19.94 (18.09-21.80)	34.66 (31.36-37.97)	1.71 (1.50-1.96)	1.68 (1.47-1.93) <sup>c</sup>
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) <sup>c</sup>	10.49 (10.08-10.90)	30.64 (28.73-32.54)	2.76 (2.56-2.97)	2.45 (2.25-2.67) <sup>c</sup>
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) <sup>c</sup>	13.82 (12.40-15.23)	32.52 (28.46-36.58)	2.30 (1.95-2.70)	1.97 (1.64-2.36) <sup>c</sup>
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) <sup>c</sup>	10.21 (9.79-10.63)	29.59 (27.62-31.56)	2.79 (2.57-3.02)	2.48 (2.27-2.72) <sup>c</sup>
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) <sup>c</sup>	13.77 (12.70-14.84)	34.86 (31.31-38.41)	2.41 (2.12-2.75)	2.09 (1.81- 2.42) <sup>c</sup>
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) <sup>d</sup>	7.48 (7.01-7.96)	24.63 (21.32-27.94)	3.28 (2.82-3.82)	3.34 (2.83-3.95) <sup>d</sup>
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) <sup>d</sup>	(10.87-12.65)	(24.94-32.27)	(2.06-2.77)	(2.17-2.98) <sup>d</sup>
$\geq 2$	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) <sup>d</sup>	(14.43-16.12)	(31.83-36.60)	(1.98-2.36)	(1.89-2.29) <sup>d</sup>
	Interaction: p= 0.0743				Interaction: p<0.0001			

<sup>a</sup>ID= incidence density, CI=confidence interval

<sup>b</sup>Based on Poisson assumption

<sup>c</sup>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.

<sup>d</sup>Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for comorbidities.

\*  $P < 0.05$

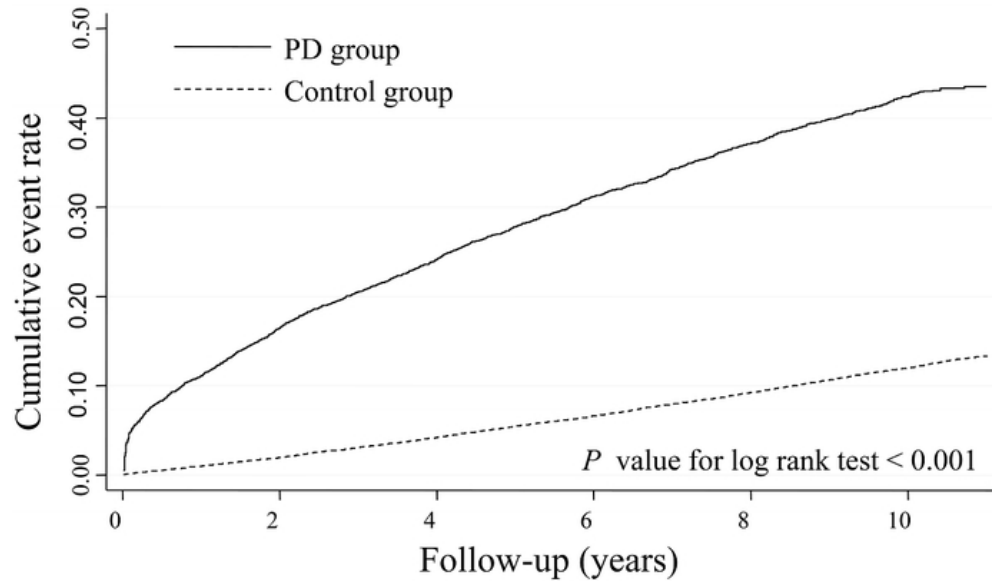


Figure 1 Comparison of Kaplan-Meier failure estimates of dementia onset between the two groups. PD, Parkinson's disease.

59x34mm (300 x 300 DPI)

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

	Item No	Page No	Recommendation
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants
		6	(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy
		-	(e) Describe any sensitivity analyses

<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	15*	8-9	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time
		-	<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure
		-	<i>Cross-sectional study</i> —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
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-025274.R1
Article Type:	Research
Date Submitted by the Author:	17-Oct-2018
Complete List of Authors:	Liu, Chih-Ching; National Cheng Kung University, College of Medicine, Department of Public Health Sun, Yu; En Chu Kong Hospital, Department of Neurology Lee, Pei-Chen; National Taipei University of Nursing and Health Sciences, Department of Health Care Management Li, Chung-Yi; National Cheng Kung University, College of Medicine, Department of Public Health Hu, Susan; National Cheng Kung University, College of Medicine, Department of Public Health
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Neurology, Public health
Keywords:	retrospective cohort study, Parkinson's disease, Dementia < NEUROLOGY, competing risk, EPIDEMIOLOGY

SCHOLARONE™  
Manuscripts

1  
2  
3 1 **Risk of Dementia after Parkinson's Disease in Taiwan: A Population-based Retrospective**  
4  
5 2 Cohort Study Using National Health Insurance Claims  
6

7 3  
8  
9 4 Chih-Ching Liu, MSc<sup>a</sup>, Yu Sun, MD, PhD<sup>b</sup>, Pei-Chen Lee, PhD<sup>c</sup>,  
10  
11 5 Chung-Yi Li, PhD<sup>a,d</sup>, Susan C. Hu, PhD<sup>a\*</sup>  
12  
13 6

14  
15  
16 7 <sup>a</sup> Department of Public Health, College of Medicine, National Cheng Kung University, Tainan,  
17  
18 8 Taiwan

19  
20 9 <sup>b</sup>Department of Neurology, En Chu Kong Hospital, Sanxia District, New Taipei City, Taiwan

21  
22  
23 10 <sup>c</sup>Department of Health Care Management, National Taipei University of Nursing and Health  
24  
25 11 Sciences, Taipei, Taiwan

26  
27 12 <sup>d</sup> Department of Public Health, College of Public Health, China Medical University, Taichung,  
28  
29 13 Taiwan

30  
31  
32 14 \*Chung-Yi Li and Susan C. Hu contributed equally to this article.  
33

34 15  
35  
36 16 **Running title:** Risk of Dementia after Parkinson's disease

37  
38 17 **Word count:** text 4399  
39  
40  
41 18

42  
43 19 **Correspondence address:**

44  
45 20 Dr. Susan C. Hu

46  
47 21 Department of Public Health, College of Medicine, National Cheng Kung University

48  
49 22 Tel.: 886-6-2353535 ext. 5599, Fax: 886-6-2359033

50  
51 23 E-mail: shuhu@mail.ncku.edu.tw  
52  
53  
54 24

## 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 ( $\leq 1$  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



1  
2 **1 Article Summary**  
3

4 2

5  
6 **3 Strengths and limitations of this study**  
7

- 8 4 ■ The study strengths include the fact that it is a nationwide, retrospective cohort design for 11  
9 years with more accurate estimates of the incidence rates of dementia by using the first  
10 diagnosed PD cases rather than the prevalent cases as study subjects.  
11  
12 5  
13 6  
14 7 ■ A multivariate Cox proportional hazard regression with a competing risk analysis was used to  
15 control the confounding bias and account for the competing risk of death.  
16  
17 8  
18 9 ■ We were unable to consider a comprehensive list of potential confounders, such as smoking,  
19 educational level, physical function, and genes in the analysis because of the limited  
20 information available from the claims data.  
21  
22 10  
23 11  
24 12 ■ Another limitation is the lack of clinical symptoms and subtypes of dementia.  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## INTRODUCTION

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

Parkinson's disease (PD) has been associated with developing cognitive impairments<sup>4</sup>. However, most previous studies on the association between PD and dementia risk were conducted in western countries<sup>5-19</sup>, 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<sup>5-23</sup>, 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<sup>19</sup>. 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)<sup>9</sup>.

Moreover, many studies have included prevalent PD cases at varying disease stages to investigate the risk of dementia, which may have caused survival bias<sup>6-8 10 12-15 17 18 20 22 23</sup>. 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<sup>14</sup>. In Taiwan, the only population-based study with a case-control design also showed a

1  
2  
3 1 positive association between PD and the risk of dementia<sup>22</sup>. However, potential survival bias  
4  
5 2 resulting from recruitment of prevalent PD cases at various disease stages may have been present  
6  
7 3 in these studies.

8  
9 4 Some studies have reported that older age<sup>5-10 13 15 20 23</sup> and male gender<sup>5</sup> are related to increased  
10  
11 5 dementia risk in PD; however, information regarding the age- and sex- stratified dementia  
12  
13 6 incidence rate in PD is scant. In addition, many PD patients have medical comorbidities such as  
14  
15 7 stroke, hypertension, diabetes mellitus, hyperlipidemia, and coronary heart disease, which may  
16  
17 8 have modification effects on the relationship between dementia and PD<sup>7 16 17 22</sup>. However, little  
18  
19 9 research has examined medical comorbidities as a potential confounding factor that should be  
20  
21 10 controlled for<sup>7 22 23</sup>. Moreover, because of the increased age and co-morbidities in a long-term  
22  
23 11 follow-up study, competing risk of death should be considered. However, none of studies on this  
24  
25 12 topic has considered death as a competing risk<sup>6-21 23</sup>, which may induce potential attrition bias and  
26  
27 13 tend to distort the study results.

28  
29  
30  
31 14 Given the abovementioned methodological problems and limited information on this topic,  
32  
33 15 the association between PD and the risk of dementia needs to be further explored. Therefore, in  
34  
35 16 this study, a nationwide population-based cohort study was conducted to estimate 11 years of  
36  
37 17 incidence and the hazard ratios for development of dementia in patients with first-diagnosed PD  
38  
39 18 by age and sex and by comorbidities (i.e., hypertension, diabetes, coronary artery disease (CAD),  
40  
41 19 stroke, hyperlipidemia, and chronic obstructive pulmonary disease (COPD)), after accounting for  
42  
43 20 the competing risk of death.

## 44 45 46 47 48 49 50 22 **METHODS**

### 51 52 23 **Data Source**

53  
54 24 The dataset was from ambulatory care claims, inpatient claims, and the updated registry for  
55  
56 25 beneficiaries retrieved from Taiwan's National Health Insurance Research Database (NHIRD), as

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

### 11 **Patient and public involvement**

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

### 17 **Study design, Cohorts and Covariates**

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

1  
2  
3 1 We further made the following exclusions to ensure the validity of the PD diagnosis: (1) an  
4  
5 2 age on the index date of less than 40 years, who are more likely to have a genetic etiology; (2) a  
6  
7 3 diagnostic code of secondary Parkinsonism (ICD-9-CM code: 332.1) during the study period; (3)  
8  
9 4 receipt of any neuroleptic medication 180 days prior to the index date, and (4) 3 or more medical  
10  
11 5 claims (either ambulatory or inpatient care) with diagnostic codes of dementia prior to the index  
12  
13  
14 6 date. The first date of initial diagnosis of PD in the period of 2002 to 2003 was set as the index  
15  
16 7 date.

17  
18 8 We previously conducted a pilot study to validate the accuracy of the ICD-9 coding in PD  
19  
20 9 patients<sup>28</sup>. In the validation study, medical records including symptoms/signs, diagnostic  
21  
22  
23 10 procedures, use of anti-parkinsonism medication, as well as response to medication of 290  
24  
25 11 randomly selected patients with ICD-9-CM coded 332.0 were examined in detail by three  
26  
27 12 experienced neurologists from January 2012 to October 2012. Among these 290 cases, 245 were  
28  
29 13 confirmed as PD patients based on the aforementioned clinical information. The sensitivity,  
30  
31 14 specificity, positive predictive value, and negative predictive value were 97.6%, 92.3%, 98.8% and  
32  
33 15 85.7%, respectively. The accuracy of our method for identifying PD cases was 96.9%. Moreover,  
34  
35 16 cases in this study were not only ascertained using the ICD code but also required having been  
36  
37 17 prescribed at least 3 courses of anti-parkinsonism medication including L-dopa or a dopamine  
38  
39 18 agonist to minimize the possibility of miscoding.

40  
41  
42  
43 19 The control subjects were selected from those who had not been diagnosed with PD or treated  
44  
45 20 with any anti-PD medications during the entire study period and met the same exclusion criteria as  
46  
47 21 those set for the patients with PD. These control subjects were matched by age (each 5-year span),  
48  
49 22 sex, and year of index date for patients with PD at a 5:1 ratio. As a result, 29,645 control subjects  
50  
51 23 were identified. For the control groups, the index date was either January 1, 2002 or January 1,  
52  
53 24 2003.

54  
55  
56 25 Baseline comorbidities that may be associated with an increased risk of dementia were

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

## 10 **End point and Statistical analysis**

11 The main outcome variable was the initial occurrence of dementia (ICD-9-CM code: 290,  
12 294.1, 331.0, and 331.82). A Taiwanese study reported that the diagnostic accuracy of dementia is  
13 approximately 90% when relying on diagnosis codes (ICD-9-CM) to identify dementia<sup>27</sup>. To  
14 increase the validity of dementia identification, only dementia cases diagnosed with  $\geq 3$  ambulatory  
15 visits or  $\geq 1$  hospitalization were included in this study. We did not distinguish the subtypes of  
16 dementia because of data limitations due to a lack of information regarding symptoms/signs, lab  
17 data, and image findings, and further outcome analyses with dementia subtype classifications, such  
18 as dementia with Lewy bodies (DLB), Alzheimer's dementia, frontotemporal dementia, or just  
19 Parkinson's disease dementia (PDD), were not performed. However, according to the criteria set  
20 forth by the consensus report of the Lewy Body Consortium<sup>32</sup>, clinicians and researchers use the  
21 "1-year rule" to help verify the diagnoses of DLB and PDD. Thus, we analyzed the dementia  
22 incidence within and after one year of PD diagnosis, respectively.

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

1  
2  
3 1 based on the Poisson assumption. The cumulative events and rates of dementia according to the  
4  
5 2 PD status over the study period were calculated using a Kaplan-Meier analysis, and the log-rank  
6  
7 3 test was used to test the between-group differences.

8  
9 4 Since death is the competing risk of dementia occurrence in this long-term follow-up study,  
10  
11 5 analytical approaches used in competing risk settings must be used to assess the association  
12  
13 6 between PD and the risk of dementia. Cause-specific hazards models, one of the most common  
14  
15 7 analytical methods used in competing risk settings, are better suited for studying the etiology of  
16  
17 8 diseases<sup>33</sup>. The cause-specific hazard is the instantaneous risk of dying from a particular cause  $k$   
18  
19 9 given that the subject is still alive at time  $t$ <sup>34</sup>. Thus, in this study, a Cox proportional hazard  
20  
21 10 regression with competing risk models, according to cause-specific hazards models, was performed  
22  
23 11 to assess the hazard ratio (HR) of dementia in relation to PD.

24  
25  
26  
27 12 In addition, we performed a sex- and age- stratified analysis and a comorbidity-stratified  
28  
29 13 analysis to examine the potential effect-modifications by age, sex, and comorbidity on the  
30  
31 14 association between PD and the risk of dementia. Plots of  $\log(-\log(\text{survival function}))$  vs.  $\log(\text{time})$   
32  
33 15 were drawn to test for violations of the proportional-hazards assumption. Therefore, separate time-  
34  
35 16 partitioned models were created, and the hazards within each partition were assessed.  
36  
37 17 Proportionality was held for the new models partitioned at 1 year. If we modeled the hazards for  
38  
39 18  $\leq 1$  year (i.e., the first time partition), the censoring day for subsequent events was 1 year. If we  
40  
41 19 modeled the hazards for  $> 1$  year (i.e., the second time partition), subjects with earlier events were  
42  
43 20 included and considered to be censors (because the exclusion of these subjects may lead to a  
44  
45 21 survival bias). A  $p < 0.05$  was considered significant.

## 22 23 **RESULTS**

24  
25 24 Gender, age, geographic area, and urbanization levels were similar in both groups. The  
26  
27 25 prevalence rates of the risk factors for dementia were high in patients with PD. The PD cohort had

1  
2  
3 1 fewer white-collar workers (25.0% vs. 31.2%,  $p<0.0001$ ), a higher prevalence of dependence  
4  
5 2 (39.9% vs. 33.8%,  $p<0.0001$ ), a lower insurance premium (percentage with none or a lower than  
6  
7 3 median insurance premium: 69.5 vs. 60.0,  $p<0.0001$ ), a higher Charlson's score (percentage with  
8  
9 4 score of 1 to  $\geq 2$  : 52.1% vs. 25.4%,  $p<0.0001$ ), and a higher frequency of medical visits (39.6 vs.  
10  
11 5 21.9 per year,  $p<0.0001$ ) than the control group (Table 1).

12  
13  
14 6 Figure 1 shows the cumulative incidence of dementia in patients with and without PD. The  
15  
16 7 cumulative incidence of dementia for PD was significantly higher than the corresponding data  
17  
18 8 observed in the non-PD group (log-rank test,  $p<0.0001$ ).

19  
20 9 Among the total of 5,932 first diagnosed PD cases, only 492 of these cases (8.3%) were  
21  
22 10 derived from inpatient records. The adjusted hazard ratios of dementia either in the overall PD  
23  
24 11 cases or in the PD cases only enrolled in an outpatient group were significantly higher than those  
25  
26 12 in the control group without PD. The median duration from the overall first diagnosis of PD to the  
27  
28 13 development of dementia was 9.02 years.

29  
30  
31 14 During the 11 years of follow-up, a total of 1,836 PD patients developed dementia, and 1,226  
32  
33 15 PD patients died without developing dementia. In the same period, a total of 3,159 control subjects  
34  
35 16 developed dementia, and 5,223 control subjects died without developing dementia. In the period  
36  
37 17 within 1 year after the index date (i.e., the first time partition), a total of 5,932 PD subjects  
38  
39 18 encountered 624 medical episodes due to first diagnosed dementia in the 5,450.09 person-years  
40  
41 19 observed, representing incidence densities of dementia of 114.49 per 1,000 person-years. In the  
42  
43 20 same period, a total of 29,645 PD subjects encountered 285 medical episodes due to first diagnosed  
44  
45 21 dementia in 29,208.39 person-years observed, representing incidence densities of dementia of 9.76  
46  
47 22 per 1,000 person-years. Noticeably, the incidence density of dementia increased with age  
48  
49 23 irrespective of PD status and sex, and the highest incidence was observed in those aged  $\geq 80$  years.  
50  
51 24 The adjusted HR of dementia in relation to PD was significantly increased at 6.43 (95%CI 5.46-  
52  
53 25 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-



1  
2  
3 1 6.99). In addition, there was a significant interaction of PD with age on the risk of dementia for  
4  
5 2 both men ( $p=0.0149$ ) and women ( $p<0.0001$ ) (Table 2).

6  
7 3 In the years following the PD diagnosis (i.e., the second time partition), the overall incidence  
8  
9 4 density of dementia was much lower (Table 2). The change in incidence density between the first  
10  
11 5 and the second partition was more pronounced in the PD group (from 114.49 to 30.99 per 1,000  
12  
13 6 person-years) than in the control group (from 9.76 to 10.83 per 1,000 person-years). The age- and  
14  
15 7 sex- specific incidence densities had a similar pattern in terms of change. However, no significant  
16  
17 8 difference in the sex-specific HRs of dementia was observed ( $p=0.2267$ ). There was a significant  
18  
19 9 interaction of PD status with age ( $p<0.0001$ ) in both sexes. Age- and sex-specific HRs showed the  
20  
21 10 highest HR to be in PD females aged  $<70$  years (HR: 4.27; 95% CI 3.25-5.63).

22  
23  
24  
25 11 Impact of PD on the risk of dementia by comorbidity is shown in Table 3. Irrespective of the  
26  
27 12 various time partitions, the incidence of dementia increased with the number of comorbidities in  
28  
29 13 both groups. The PD group had the highest risk of dementia across various medical comorbidity  
30  
31 14 stratifications or Charlson's scores after adjusting for baseline characteristics. In the first time  
32  
33 15 partition, the interaction of PD with hypertension ( $p=0.0058$ ), CAD ( $p=0.0196$ ), stroke ( $p<0.0001$ ),  
34  
35 16 and COPD ( $p=0.0400$ ) on the risk of dementia also was statistically significant, indicating that  
36  
37 17 subjects without hypertension, CAD, stroke, and COPD had a higher adjusted HR for dementia.  
38  
39 18 However, although the adjusted HR for dementia was also higher in subjects without diabetes and  
40  
41 19 hyperlipidemia than in those with medical comorbidities, there was no statistically significant  
42  
43 20 modification effect by diabetes and hyperlipidemia on the association between PD and the risk of  
44  
45 21 dementia. In terms of the Charlson's scores, subjects with scores of 0 had a higher adjusted HR for  
46  
47 22 dementia than those with scores of 1 and  $\geq 2$ . The interactions were significant for PD with  
48  
49 23 Charlson's score ( $p=0.0003$ ) on the risk of dementia.

50  
51  
52  
53  
54 24 In the second time partition, effect-modification by hypertension ( $p<0.0001$ ), CAD ( $p=0.0048$ )  
55  
56 25 and stroke ( $p<0.0001$ ) was statistically significant for dementia, indicating that subjects without  
57  
58  
59  
60

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

## 11 DISCUSSION

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

18 In other words, many patients with pre-existing cognitive impairment and PD were classed as  
19 new PD cases because their condition had deteriorated and had only been recognized because they  
20 had been referred for an expert opinion. This is also supported by the decline in the number of PD  
21 patients with dementia in the subsequent period of observation. In this study, we found that the  
22 overall risk of dementia onset increased nearly twofold in up to 11 years (adjusted HR 2.42, 95%CI  
23 2.23- 2.61) among those who survived at least 1 year and had an initial PD diagnosis thereafter.  
24 The magnitude of this association varied according to different age and sex stratifications. In  
25 general, the risk of dementia was higher in men in the first partition but was similar in both sexes

1  
2  
3 1 in the second partition. However, the increased risk was highest in both male and female  
4  
5 2 participants aged <70 years in any given partition time. The study results can provide physicians  
6  
7 3 and patients with valuable information and also demonstrate the need for guidelines for detection  
8  
9 4 of dementia risk after the initial diagnosis of PD.

10  
11 5 Our study shows that a reasonably increased hazard of dementia more than one year after  
12  
13 6 diagnosis of PD is more likely to be real and may suggest evidence of the mechanisms supported  
14  
15 7 by the Braak pathology staging hypothesis<sup>35 36</sup>. Our findings were similar to another population-  
16  
17 8 based case control study in Taiwan<sup>22</sup>, which showed the risk of developing dementia in prevalent  
18  
19 9 Parkinsonism was highest in the first 6 months (AOR:11.98, 95%CI:8.51-16.68) and then became  
20  
21 10 lower in the following months to years after diagnosis.

22  
23  
24  
25 11 Age is known to be a risk factor for dementia not only in the general population<sup>37 38</sup> but also  
26  
27 12 in the PD patient population<sup>5-10 13 15 20 23</sup>. This may be caused by aging of non-dopaminergic  
28  
29 13 structures (i.e., the locus ceruleus and pedunculo pontine nucleus)<sup>39</sup>. However, a modifying effect  
30  
31 14 of age on the risk of dementia after PD may be present in our study. For example, we found that  
32  
33 15 patients with PD had a significantly higher overall risk of dementia than those in the control group,  
34  
35 16 particularly in subjects aged < 70 years. This result is similar to the findings of some prior studies<sup>13</sup>  
36  
37 17 <sup>18</sup>.

38  
39  
40  
41 18 Male gender is sometimes identified as a risk factor for dementia in PD<sup>5</sup>; however, there is no  
42  
43 19 clear explanation for this finding. In our study, we found no significant role of gender in the first-  
44  
45 20 diagnosed PD patients one year later. Accordingly, patients with PD, especially younger patients  
46  
47 21 in both sexes, could be selected in future studies as a target population to evaluate whether  
48  
49 22 interventions are effective in decreasing the risk of dementia after diagnosis of PD.

50  
51  
52 23 Our study also shows that the overall risk of dementia was more than double (adjusted HR  
53  
54 24 2.42) among subjects with first-diagnosed PD 1 year later for up to 11 years. After accounting for  
55  
56 25 the competing risk of death and adjustment for the number of medical visits, the findings were

1  
2  
3 1 similar to those of Perez et al., who reported a higher hazard ratio of incident dementia (2.47,  
4  
5 2 95%CI 1.55-3.59) in patients with PD as compared to non-PD subjects<sup>11</sup>. However, other cohort  
6  
7 3 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  
8  
9 4 incident dementia in PD groups compared with the general population<sup>9 10 12-15 18</sup>, which is different  
10  
11 5 from our findings. Noticeably, most previous studies were limited by a relatively small sample  
12  
13 6 size<sup>6-17 19-21 23</sup>, shorter follow-up time<sup>6-8 10 12-18 20</sup>, the lack of a matched control<sup>6-8 16 17 19-21 23</sup>, failure  
14  
15 7 to account for the competing risk of death<sup>6-21 23</sup>, or a lack of adjustment for the number of medical  
16  
17 8 visits to control for surveillance bias<sup>9-15 18</sup>, rendering the risk that the estimates were more likely to  
18  
19 9 be imprecise and biased.

20  
21  
22  
23 10 We found the incidence of dementia increased with the number of comorbidities, including  
24  
25 11 hypertension, diabetes mellitus, CAD, stroke, hyperlipidemia, and COPD. However, of the patients  
26  
27 12 with PD in our study, PD alone also had more positive effects on the risk of dementia in most  
28  
29 13 circumstances although effect modifiers such as hypertension, diabetes, stroke, CAD,  
30  
31 14 hyperlipidemia, and COPD had positive effects on increasing the risk of dementia. Prior studies  
32  
33 15 regarding the relationship between patients with PD and these comorbidities remain controversial<sup>7</sup>  
34  
35 16 <sup>16 17 22</sup>. For example, although a study in Taiwan demonstrated that patients with PD with  
36  
37 17 cerebrovascular or cardiovascular comorbidities had a lower risk of dementia onset than patients  
38  
39 18 with PD alone<sup>22</sup>, which is similar our findings, other studies have failed to find this relationship<sup>16</sup>  
40  
41 19 <sup>17</sup>. In addition, some previous studies have shown that PD with cardiovascular dysautonomia (such  
42  
43 20 as hypertension, diabetes mellitus, and CAD) and COPD might cause substantial cerebral  
44  
45 21 hypoperfusion and hypoxia, respectively<sup>40-42</sup>. Hypoxia and hypotension in the brain might cause  
46  
47 22 neuronal damage and increase accumulation of pathologic proteins such as  $\beta$ -amyloid, which result  
48  
49 23 in increased risk of dementia onset<sup>40 41</sup>. Therefore, future perspective studies focusing on the causal  
50  
51 24 relationship between such comorbidities and the risk of dementia in PD are warranted.

52  
53  
54  
55  
56 25 There were several strengths in our study. First, we obtained a large, nationwide number of  
57  
58  
59  
60

1  
2  
3 1 participants by using NHIR datasets, which made it possible to reduce selection bias, to obtain  
4  
5 2 higher statistical power, to obtain a highly representative study population, to have a lower rate of  
6  
7 3 nonresponse or loss to follow-up, and to facilitate the age-, sex- and comorbidities-stratified  
8  
9 4 analyses with an ample simple size to satisfy requirements. To the best of our knowledge, this study  
10  
11 5 is the first to report the age- and sex- specific incidence rates of dementia in a PD group. Secondly,  
12  
13 6 we conducted a longitudinal and retrospective cohort study for 11 years, which is a longer time  
14  
15 7 during which to observe the development of dementia than that in many other prior studies<sup>6-8 10 12-</sup>  
16  
17 8 <sup>18 20</sup>. Thirdly, more accurate estimates for the incidence rates of dementia in the PD group are  
18  
19 9 available in this study due to the usage of the first diagnosed PD cases rather than the prevalent PD  
20  
21 10 cases, as this might reduce the variations in the incidence of dementia across various PD durations.  
22  
23 11 Fourth, a multivariate Cox proportional hazard regression with a competing risk analysis was used  
24  
25 12 to control for the confounding bias and to account for the competing risk of death.

26  
27  
28  
29 13 Still, our study had some limitations. Firstly, we solely selected our PD cases according to  
30  
31 14 physician-recorded diagnosis and prescriptions reported in medical claims, which might have led  
32  
33 15 to potential disease misclassification. To avoid accidental inclusion of miscoded patients, we  
34  
35 16 managed to solely include PD patients who had at least three ambulatory or inpatient visits with  
36  
37 17 PD diagnosis and prescriptions with the first and last visits more than 90 days apart during the  
38  
39 18 study period, which would largely decrease the likelihood of disease misclassification. Similarly,  
40  
41 19 because we selected patients with dementia only by using NHIR datasets, potential disease  
42  
43 20 misclassification may be present. To address this concern, we only included dementia cases  
44  
45 21 diagnosed with  $\geq 3$  ambulatory visits or  $\geq 1$  hospitalization in this study to increase the validity of  
46  
47 22 dementia identification.

48  
49  
50  
51  
52 23 Also, because patients with PD may utilize the health care system more often than control  
53  
54 24 groups, surveillance bias may be present. To address this concern, we calculated the number of  
55  
56 25 medical visits for 1 year after the index date and adjusted for this in the multivariate regression

1  
2  
3 1 model. Secondly, the severity of dementia is not available in the database, and we could not  
4  
5 2 distinguish subtypes of dementia in our datasets. Therefore, it is essential for patients with PD,  
6  
7 3 particularly in high risk groups such as subjects aged <70 years, to have regular cognitive  
8  
9 4 assessments including combinations of neuropsychological markers throughout the early disease  
10  
11 5 stages, which not only will provide benefits for identification of the subtypes in dementia but will  
12  
13 6 also decrease underestimation of risk for dementia in PD.

14  
15  
16 7 Thirdly, due to the limited information available from the claims data, we were unable to  
17  
18 8 consider a comprehensive list of potential confounders such as smoking, educational level, physical  
19  
20 9 function, and genes in the analysis, which may have resulted in residual confounding bias. To  
21  
22 10 reduce such bias, we used COPD and occupational status as surrogates for smoking and educational  
23  
24 11 level, respectively. Fourthly, the disease symptoms of PD cases at different disease stages may play  
25  
26 12 a role, to some extent, in the relationship between PD and the risk of dementia. Because information  
27  
28 13 on the disease symptoms is unavailable from the NHI data, we have left this area (such as non-  
29  
30 14 motor symptoms) for further investigations.

31  
32  
33  
34 15 In conclusion, it was found that PD confers a higher risk of dementia than is the case for non-  
35  
36 16 PD patients, especially in those aged <70 years in both sexes. Regular monitoring for the  
37  
38 17 development of dementia in patients with PD in a long-time follow-up, particularly risk groups, is  
39  
40 18 recommended. Future research should include further evaluation of the underlying mechanism and  
41  
42 19 subtypes for dementia development after diagnosis of PD.

43  
44  
45 20  
46  
47 21 **Acknowledgements:** We thank the Bureau of National Health Insurance in the Ministry of Health  
48  
49 22 and Welfare and the National Health Research Institutes for providing the National Health  
50  
51 23 Insurance Research Database used in this study. The interpretation and conclusions contained  
52  
53 24 herein do not represent those of the Bureau of National Health Insurance, Ministry of Health and  
54  
55 25 Welfare, or National Health Research Institutes.

1  
2  
3 1 **Author contributions:** Chih-Ching Liu analyzed the data and wrote the draft of the manuscript.  
4  
5 2 Yu Sun and Pei-Chen Lee provided further data analyses and interpretation. Chung-Yi Li and  
6  
7 3 Susan C. Hu advised the study and revised the manuscript. All authors have approved the final  
8  
9 4 version of the manuscript.  
10  
11 5 **Funding:** This study was supported by a grant from Taiwan Ministry of Science and Technology  
12  
13 6 (MOST 106-2314-B-227-010).  
14  
15  
16 7 **Disclaimer:** The funder had no role in study design, data collection and analysis, and the  
17  
18 8 preparation of the manuscript.  
19  
20 9 **Competing interests:** None.  
21  
22  
23 10 **Patient consent:** Not required.  
24  
25 11 **Ethics approval:** A full review by the institutional review board was not required because the  
26  
27 12 encryption of the identification numbers makes it impossible to identify individuals. Access to the  
28  
29 13 National Health Insurance Research Database datasets is approved by the National Health Research  
30  
31 14 Institutes Review Committee.  
32  
33  
34 15 **Provenance and peer review:** Not commissioned; externally peer reviewed.  
35  
36 16 **Data sharing statement:** We, as the authors of this original research article, state that there is no  
37  
38 17 additional, unpublished data available from this study. Raw data sharing from National Health  
39  
40 18 Insurance Research Database is prohibited according to the National Health Research Institutes  
41  
42 19 (NHRI) policies in Taiwan.  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## 1 REFERENCES

- 1 2 1. World Health Organization. Dementia: a public health priority. 2012 [cited 2018 April  
3 2]. [http://www.who.int/mental\\_health/publications/dementia\\_report\\_2012/en/](http://www.who.int/mental_health/publications/dementia_report_2012/en/)
- 4 2 2. Alzheimer's Disease International. World Alzheimer Report 2015: The Global Impact of  
5 3  
6 4  
7 5  
8 6  
9 7  
10 8  
11 9  
12 10  
13 11  
14 12  
15 13  
16 14  
17 15  
18 16  
19 17  
20 18  
21 19  
22 20  
23 21  
24 22  
25 23  
26 24  
27 25  
28 26  
29 27  
30 28  
31 29  
32 30  
33 31  
34 32  
35 33  
36 34  
37 35  
38 36  
39 37  
40 38  
41 39  
42 40  
43 41  
44 42  
45 43  
46 44  
47 45  
48 46  
49 47  
50 48  
51 49  
52 50  
53 51  
54 52  
55 53  
56 54  
57 55  
58 56  
59 57  
60 58  
61 59  
62 60  
63 61  
64 62  
65 63  
66 64  
67 65  
68 66  
69 67  
70 68  
71 69  
72 70  
73 71  
74 72  
75 73  
76 74  
77 75  
78 76  
79 77  
80 78  
81 79  
82 80  
83 81  
84 82  
85 83  
86 84  
87 85  
88 86  
89 87  
90 88  
91 89  
92 90  
93 91  
94 92  
95 93  
96 94  
97 95  
98 96  
99 97  
100 98  
101 99  
102 100  
103 101  
104 102  
105 103  
106 104  
107 105  
108 106  
109 107  
110 108  
111 109  
112 110  
113 111  
114 112  
115 113  
116 114  
117 115  
118 116  
119 117  
120 118  
121 119  
122 120  
123 121  
124 122  
125 123  
126 124  
127 125  
128 126  
129 127  
130 128  
131 129  
132 130  
133 131  
134 132  
135 133  
136 134  
137 135  
138 136  
139 137  
140 138  
141 139  
142 140  
143 141  
144 142  
145 143  
146 144  
147 145  
148 146  
149 147  
150 148  
151 149  
152 150  
153 151  
154 152  
155 153  
156 154  
157 155  
158 156  
159 157  
160 158  
161 159  
162 160  
163 161  
164 162  
165 163  
166 164  
167 165  
168 166  
169 167  
170 168  
171 169  
172 170  
173 171  
174 172  
175 173  
176 174  
177 175  
178 176  
179 177  
180 178  
181 179  
182 180  
183 181  
184 182  
185 183  
186 184  
187 185  
188 186  
189 187  
190 188  
191 189  
192 190  
193 191  
194 192  
195 193  
196 194  
197 195  
198 196  
199 197  
200 198  
201 199  
202 200  
203 201  
204 202  
205 203  
206 204  
207 205  
208 206  
209 207  
210 208  
211 209  
212 210  
213 211  
214 212  
215 213  
216 214  
217 215  
218 216  
219 217  
220 218  
221 219  
222 220  
223 221  
224 222  
225 223  
226 224  
227 225  
228 226  
229 227  
230 228  
231 229  
232 230  
233 231  
234 232  
235 233  
236 234  
237 235  
238 236  
239 237  
240 238  
241 239  
242 240  
243 241  
244 242  
245 243  
246 244  
247 245  
248 246  
249 247  
250 248  
251 249  
252 250  
253 251  
254 252  
255 253  
256 254  
257 255  
258 256  
259 257  
260 258  
261 259  
262 260  
263 261  
264 262  
265 263  
266 264  
267 265  
268 266  
269 267  
270 268  
271 269  
272 270  
273 271  
274 272  
275 273  
276 274  
277 275  
278 276  
279 277  
280 278  
281 279  
282 280  
283 281  
284 282  
285 283  
286 284  
287 285  
288 286  
289 287  
290 288  
291 289  
292 290  
293 291  
294 292  
295 293  
296 294  
297 295  
298 296  
299 297  
300 298  
301 299  
302 300  
303 301  
304 302  
305 303  
306 304  
307 305  
308 306  
309 307  
310 308  
311 309  
312 310  
313 311  
314 312  
315 313  
316 314  
317 315  
318 316  
319 317  
320 318  
321 319  
322 320  
323 321  
324 322  
325 323  
326 324  
327 325  
328 326  
329 327  
330 328  
331 329  
332 330  
333 331  
334 332  
335 333  
336 334  
337 335  
338 336  
339 337  
340 338  
341 339  
342 340  
343 341  
344 342  
345 343  
346 344  
347 345  
348 346  
349 347  
350 348  
351 349  
352 350  
353 351  
354 352  
355 353  
356 354  
357 355  
358 356  
359 357  
360 358  
361 359  
362 360  
363 361  
364 362  
365 363  
366 364  
367 365  
368 366  
369 367  
370 368  
371 369  
372 370  
373 371  
374 372  
375 373  
376 374  
377 375  
378 376  
379 377  
380 378  
381 379  
382 380  
383 381  
384 382  
385 383  
386 384  
387 385  
388 386  
389 387  
390 388  
391 389  
392 390  
393 391  
394 392  
395 393  
396 394  
397 395  
398 396  
399 397  
400 398  
401 399  
402 400  
403 401  
404 402  
405 403  
406 404  
407 405  
408 406  
409 407  
410 408  
411 409  
412 410  
413 411  
414 412  
415 413  
416 414  
417 415  
418 416  
419 417  
420 418  
421 419  
422 420  
423 421  
424 422  
425 423  
426 424  
427 425  
428 426  
429 427  
430 428  
431 429  
432 430  
433 431  
434 432  
435 433  
436 434  
437 435  
438 436  
439 437  
440 438  
441 439  
442 440  
443 441  
444 442  
445 443  
446 444  
447 445  
448 446  
449 447  
450 448  
451 449  
452 450  
453 451  
454 452  
455 453  
456 454  
457 455  
458 456  
459 457  
460 458  
461 459  
462 460  
463 461  
464 462  
465 463  
466 464  
467 465  
468 466  
469 467  
470 468  
471 469  
472 470  
473 471  
474 472  
475 473  
476 474  
477 475  
478 476  
479 477  
480 478  
481 479  
482 480  
483 481  
484 482  
485 483  
486 484  
487 485  
488 486  
489 487  
490 488  
491 489  
492 490  
493 491  
494 492  
495 493  
496 494  
497 495  
498 496  
499 497  
500 498  
501 499  
502 500  
503 501  
504 502  
505 503  
506 504  
507 505  
508 506  
509 507  
510 508  
511 509  
512 510  
513 511  
514 512  
515 513  
516 514  
517 515  
518 516  
519 517  
520 518  
521 519  
522 520  
523 521  
524 522  
525 523  
526 524  
527 525  
528 526  
529 527  
530 528  
531 529  
532 530  
533 531  
534 532  
535 533  
536 534  
537 535  
538 536  
539 537  
540 538  
541 539  
542 540  
543 541  
544 542  
545 543  
546 544  
547 545  
548 546  
549 547  
550 548  
551 549  
552 550  
553 551  
554 552  
555 553  
556 554  
557 555  
558 556  
559 557  
560 558  
561 559  
562 560  
563 561  
564 562  
565 563  
566 564  
567 565  
568 566  
569 567  
570 568  
571 569  
572 570  
573 571  
574 572  
575 573  
576 574  
577 575  
578 576  
579 577  
580 578  
581 579  
582 580  
583 581  
584 582  
585 583  
586 584  
587 585  
588 586  
589 587  
590 588  
591 589  
592 590  
593 591  
594 592  
595 593  
596 594  
597 595  
598 596  
599 597  
600 598  
601 599  
602 600  
603 601  
604 602  
605 603  
606 604  
607 605  
608 606  
609 607  
610 608  
611 609  
612 610  
613 611  
614 612  
615 613  
616 614  
617 615  
618 616  
619 617  
620 618  
621 619  
622 620  
623 621  
624 622  
625 623  
626 624  
627 625  
628 626  
629 627  
630 628  
631 629  
632 630  
633 631  
634 632  
635 633  
636 634  
637 635  
638 636  
639 637  
640 638  
641 639  
642 640  
643 641  
644 642  
645 643  
646 644  
647 645  
648 646  
649 647  
650 648  
651 649  
652 650  
653 651  
654 652  
655 653  
656 654  
657 655  
658 656  
659 657  
660 658  
661 659  
662 660  
663 661  
664 662  
665 663  
666 664  
667 665  
668 666  
669 667  
670 668  
671 669  
672 670  
673 671  
674 672  
675 673  
676 674  
677 675  
678 676  
679 677  
680 678  
681 679  
682 680  
683 681  
684 682  
685 683  
686 684  
687 685  
688 686  
689 687  
690 688  
691 689  
692 690  
693 691  
694 692  
695 693  
696 694  
697 695  
698 696  
699 697  
700 698  
701 699  
702 700  
703 701  
704 702  
705 703  
706 704  
707 705  
708 706  
709 707  
710 708  
711 709  
712 710  
713 711  
714 712  
715 713  
716 714  
717 715  
718 716  
719 717  
720 718  
721 719  
722 720  
723 721  
724 722  
725 723  
726 724  
727 725  
728 726  
729 727  
730 728  
731 729  
732 730  
733 731  
734 732  
735 733  
736 734  
737 735  
738 736  
739 737  
740 738  
741 739  
742 740  
743 741  
744 742  
745 743  
746 744  
747 745  
748 746  
749 747  
750 748  
751 749  
752 750  
753 751  
754 752  
755 753  
756 754  
757 755  
758 756  
759 757  
760 758  
761 759  
762 760  
763 761  
764 762  
765 763  
766 764  
767 765  
768 766  
769 767  
770 768  
771 769  
772 770  
773 771  
774 772  
775 773  
776 774  
777 775  
778 776  
779 777  
780 778  
781 779  
782 780  
783 781  
784 782  
785 783  
786 784  
787 785  
788 786  
789 787  
790 788  
791 789  
792 790  
793 791  
794 792  
795 793  
796 794  
797 795  
798 796  
799 797  
800 798  
801 799  
802 800  
803 801  
804 802  
805 803  
806 804  
807 805  
808 806  
809 807  
810 808  
811 809  
812 810  
813 811  
814 812  
815 813  
816 814  
817 815  
818 816  
819 817  
820 818  
821 819  
822 820  
823 821  
824 822  
825 823  
826 824  
827 825  
828 826  
829 827  
830 828  
831 829  
832 830  
833 831  
834 832  
835 833  
836 834  
837 835  
838 836  
839 837  
840 838  
841 839  
842 840  
843 841  
844 842  
845 843  
846 844  
847 845  
848 846  
849 847  
850 848  
851 849  
852 850  
853 851  
854 852  
855 853  
856 854  
857 855  
858 856  
859 857  
860 858  
861 859  
862 860  
863 861  
864 862  
865 863  
866 864  
867 865  
868 866  
869 867  
870 868  
871 869  
872 870  
873 871  
874 872  
875 873  
876 874  
877 875  
878 876  
879 877  
880 878  
881 879  
882 880  
883 881  
884 882  
885 883  
886 884  
887 885  
888 886  
889 887  
890 888  
891 889  
892 890  
893 891  
894 892  
895 893  
896 894  
897 895  
898 896  
899 897  
900 898  
901 899  
902 900  
903 901  
904 902  
905 903  
906 904  
907 905  
908 906  
909 907  
910 908  
911 909  
912 910  
913 911  
914 912  
915 913  
916 914  
917 915  
918 916  
919 917  
920 918  
921 919  
922 920  
923 921  
924 922  
925 923  
926 924  
927 925  
928 926  
929 927  
930 928  
931 929  
932 930  
933 931  
934 932  
935 933  
936 934  
937 935  
938 936  
939 937  
940 938  
941 939  
942 940  
943 941  
944 942  
945 943  
946 944  
947 945  
948 946  
949 947  
950 948  
951 949  
952 950  
953 951  
954 952  
955 953  
956 954  
957 955  
958 956  
959 957  
960 958  
961 959  
962 960  
963 961  
964 962  
965 963  
966 964  
967 965  
968 966  
969 967  
970 968  
971 969  
972 970  
973 971  
974 972  
975 973  
976 974  
977 975  
978 976  
979 977  
980 978  
981 979  
982 980  
983 981  
984 982  
985 983  
986 984  
987 985  
988 986  
989 987  
990 988  
991 989  
992 990  
993 991  
994 992  
995 993  
996 994  
997 995  
998 996  
999 997  
1000 998



- 1  
2 1 2005;112:386-90.  
3  
4 2 17. Levy G, Tang MX, Cote LJ, *et al.* Do risk factors for Alzheimer's disease predict dementia  
5 3 in Parkinson's disease? An exploratory study. *Mov Disord* 2002;17:250-7.  
6  
7 4 18. Breteler MM, de Groot RR, van Romunde LK, *et al.* Risk of dementia in patients with  
8 5 Parkinson's disease, epilepsy, and severe head trauma: a register-based follow-up study.  
9 6 *Am J Epidemiol* 1995;142:1300-5.  
10  
11 7 19. Hely MA, Reid WG, Adena MA, *et al.* The Sydney multicenter study of Parkinson's  
12 8 disease: the inevitability of dementia at 20 years. *Mov Disord* 2008;23:837-44.  
13  
14 9 20. Kwon KY, Kang SH, Kim M, *et al.* Nonmotor Symptoms and Cognitive Decline in de novo  
15 10 Parkinson's Disease. *Can J Neurol Sci* 2014;41:597-602.  
16  
17 11 21. Auyeung M, Tsoi TH, Mok V, *et al.* Ten year survival and outcomes in a prospective  
18 12 cohort of new onset Chinese Parkinson's disease patients. *J Neurol Neurosurg Psychiatry*  
19 13 2012;83:607-11.  
20  
21 14 22. Huang YC, Wu ST, Lin JJ, *et al.* Prevalence and risk factors of cognitive impairment in  
22 15 Parkinson disease: a population-based case-control study in Taiwan. *Medicine*  
23 16 *(Baltimore)* 2015;94:e782.  
24  
25 17 23. Lee SY, Ryu HJ, Seo JW, *et al.* Dementia-Free Survival and Risk Factors for Dementia in a  
26 18 Hospital-Based Korean Parkinson's Disease Cohort. *J Clin Neurol* 2017;13:21-6.  
27  
28 19 24. National Health Insurance Administration. Universal Health Coverage in Taiwan. 2017  
29 20 [cited 2018 May 8].  
30  
31 21 [https://www.nhi.gov.tw/English/Content\\_List.aspx?n=8FC0974BBFEFA56D&topn=ED4A](https://www.nhi.gov.tw/English/Content_List.aspx?n=8FC0974BBFEFA56D&topn=ED4A30E51A609E49)  
32 22 [30E51A609E49](https://www.nhi.gov.tw/English/Content_List.aspx?n=8FC0974BBFEFA56D&topn=ED4A30E51A609E49)  
33  
34 23 25. Sun Y, Chang YH, Chen HF, *et al.* Risk of Parkinson disease onset in patients with  
35 24 diabetes: a 9-year population-based cohort study with age and sex stratifications.  
36 25 *Diabetes Care* 2012;35:1047-9.  
37  
38 26 26. Shen CC, Tsai SJ, Perng CL, *et al.* Risk of Parkinson disease after depression: a nationwide  
39 27 population-based study. *Neurology* 2013;81:1538-44.  
40  
41 28 27. Chiang CJ, Yip PK, Wu SC, *et al.* Midlife risk factors for subtypes of dementia: a nested  
42 29 case-control study in Taiwan. *Am J Geriatr Psychiatry* 2007;15:762-71.  
43  
44 30 28. Liu CC, Li CY, Lee PC, *et al.* Variations in Incidence and Prevalence of Parkinson's Disease  
45 31 in Taiwan: A Population-Based Nationwide Study. *Parkinsons Dis* 2016;2016:8756359.  
46  
47 32 29. Charlson ME, Pompei P, Ales KL, *et al.* A new method of classifying prognostic  
48 33 comorbidity in longitudinal studies: development and validation. *J Chronic Dis*  
49 34 1987;40:373-83.  
50  
51 35 30. Charlson M, Szatrowski TP, Peterson J, *et al.* Validation of a combined comorbidity index.  
52 36 *J Clin Epidemiol* 1994;47:1245-51.  
53  
54 37 31. Driver JA, Kurth T, Buring JE, *et al.* Parkinson disease and risk of mortality: a prospective  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1 comorbidity-matched cohort study. *Neurology* 2008;70:1423-30.
- 2 32. McKeith IG, Boeve BF, Dickson DW, *et al.* Diagnosis and management of dementia with  
3 Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology* 2017;89:88-  
4 100.
- 5 33. Noordzij M, Leffondre K, van Stralen KJ, *et al.* When do we need competing risks  
6 methods for survival analysis in nephrology? *Nephrol Dial Transplant* 2013;28:2670-7.
- 7 34. Prentice RL, Kalbfleisch JD, Peterson AV, Jr., *et al.* The analysis of failure times in the  
8 presence of competing risks. *Biometrics* 1978;34:541-54.
- 9 35. Braak H, Del Tredici K, Bratzke H, *et al.* Staging of the intracerebral inclusion body  
10 pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages).  
11 *J Neurol* 2002;249 Suppl 3:lil/1-5.
- 12 36. Braak H, Del Tredici K, Rub U, *et al.* Staging of brain pathology related to sporadic  
13 Parkinson's disease. *Neurobiol Aging* 2003;24:197-211.
- 14 37. Matthews FE, Stephan BC, Robinson L, *et al.* A two decade dementia incidence  
15 comparison from the Cognitive Function and Ageing Studies I and II. *Nat Commun*  
16 2016;7:11398.
- 17 38. Solomon A, Mangialasche F, Richard E, *et al.* Advances in the prevention of Alzheimer's  
18 disease and dementia. *J Intern Med* 2014;275:229-50.
- 19 39. Levy G, Tang MX, Cote LJ, *et al.* Motor impairment in PD: relationship to incident  
20 dementia and age. *Neurology* 2000;55:539-44.
- 21 40. de la Torre JC. Cardiovascular risk factors promote brain hypoperfusion leading to  
22 cognitive decline and dementia. *Cardiovasc Psychiatry Neurol* 2012;2012:367516.
- 23 41. Liu H, Xing A, Wang X, *et al.* Regulation of beta-amyloid level in the brain of rats with  
24 cerebrovascular hypoperfusion. *Neurobiol Aging* 2012;33:826.e31-42.
- 25 42. Grant I, Heaton RK, McSweeney AJ, *et al.* Neuropsychologic findings in hypoxemic chronic  
26 obstructive pulmonary disease. *Arch Intern Med* 1982;142:1470-6.

1 Table 1. Characteristics of the study subjects

Variables <sup>a</sup>	PD group		Control group		P value
	n	%	n	%	
Age (years)					
<70	1852	31.2	4220	31.2	1.00 <sup>d</sup>
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) <sup>b</sup>	72.5±9.4		70.8±12.7		
Sex					
Male	3116	52.6	15580	52.6	1.00 <sup>d</sup>
Female	2813	47.4	14065	47.4	
Insurance premium (NTD) <sup>b</sup>					
Dependent	2333	39.9	9721	33.8	<0.0001 <sup>e</sup>
<Median (19,200)	1734	29.6	7753	26.2	
≥Median	1787	30.5	12171	41.0	
Mean (±SD) <sup>b,c</sup>	7102.6±11122.9		10194.0±13197.8		
Urbanization status					
Urban	3203	54.7	15197	51.8	0.0007 <sup>d</sup>
Satellite city/town	2085	35.6	9741	33.2	
Rural area	566	9.8	4424	15.0	
Geographic area					
Northern	2670	45.6	13130	44.8	<0.0001 <sup>d</sup>
Central	1491	25.5	7288	24.9	
Southern	1519	25.9	7957	27.1	
Eastern	174	3.0	931	3.2	
Occupational status					
White collar	1482	25.0	9242	31.2	<0.0001 <sup>d</sup>
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 <sup>d</sup>
Hypertension	3578	60.3	11431	38.6	<0.0001 <sup>d</sup>
Diabetes	1430	24.1	4112	13.9	<0.0001 <sup>d</sup>
CAD	1955	33.0	4890	16.5	<0.0001 <sup>d</sup>
Stroke	1977	33.3	2924	9.9	<0.0001 <sup>d</sup>
Hyperlipidemia	1089	18.4	3013	10.2	<0.0001 <sup>d</sup>

COPD	1719	29.0	5624	19.0	<0.0001 <sup>d</sup>
Charlson's score					<0.0001 <sup>d</sup>
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) <sup>b</sup>	39.6 (±26.5)		21.9 (±19.7)		<0.0001 <sup>e</sup>
Total	5932	100.0	29645	100.0	

<sup>a</sup>Inconsistency between the total population and the population summed for individual variables was due to missing information.

<sup>b</sup>SD=Standard deviation; NTD=New Taiwan Dollars; CAD=Coronary artery disease; COPD=chronic obstructive pulmonary disease

<sup>c</sup>The dependent insurers were not included.

<sup>d</sup>Based on  $\chi^2$  test

<sup>e</sup>Based on a Student's t test

1  
2  
3  
4 1 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  
5  
6 2 groups  
7

Variables	≤ 1 years				>1 years			
	ID (95% CI) <sup>a,b</sup>		Crude HR (95% CI)	AHR (95% CI)	ID (95% CI) <sup>a,b</sup>		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) <sup>c</sup>	2.61 (2.13-3.09)	17.57 (14.48-20.67)	6.93 (5.38-8.93)	3.82 (2.79- 5.22) <sup>c</sup>
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) <sup>c</sup>	9.23 (8.16-10.30)	32.27 (27.02-37.52)	3.65 (2.98-4.47)	3.06 (2.41-3.89) <sup>c</sup>
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) <sup>c</sup>	14.01 (12.77-15.25)	38.05 (32.58-43.51)	2.87 (2.42-3.41)	2.26 (1.85-2.75) <sup>c</sup>
≥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) <sup>c</sup>	18.94 (17.31-20.57)	41.87 (35.34-48.40)	2.25 (1.87-2.69)	1.90 (1.55-2.33) <sup>c</sup>
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) <sup>d</sup>	10.27 (9.74-10.81)	30.33 (27.93-32.73)	3.02 (2.75-3.33)	2.44 (2.19-2.73) <sup>d</sup>
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) <sup>c</sup>	3.35 (2.85-3.86)	22.23 (18.98-25.49)	7.14 (5.78-8.81)	4.27 (3.25-5.63) <sup>c</sup>
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) <sup>c</sup>	10.81 (9.62-12.00)	33.61 (28.25-38.97)	3.29 (2.71- 4.01)	2.82 (2.25-3.53) <sup>c</sup>
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) <sup>c</sup>	17.61 (16.04-19.18)	43.22 (36.70-49.70)	2.56 (2.14-3.07)	2.30 (1.88-2.81) <sup>c</sup>

1									
2									
3	≥80	31.19	180.68	5.69	3.17	22.99	38.74	1.68	1.49
4		(24.60-37.79)	(143.56-217.8)	(4.24-7.64)	(2.18-4.62) <sup>c</sup>	(20.97-25.02)	(32.00-45.47)	(1.38-2.05)	(1.19-1.86) <sup>c</sup>
5	Total	10.80	109.89	10.03	5.54	11.41	31.72	2.85	2.41
6		(9.08-12.53)	(97.16-122.63)	(8.23-12.21)	(4.39-6.99) <sup>d</sup>	(10.83-12.00)	(29.24-34.21)	(2.60-3.14)	(2.15-2.69) <sup>d</sup>
7	Overall	9.76	114.49	11.54	6.43	10.83	30.99	2.93	2.42
8		(8.62-10.89)	(105.51-123.4)	(10.04-13.27)	(5.46-7.57) <sup>e</sup>	(10.43-11.22)	(29.27-32.72)	(2.75- 3.14)	(2.23- 2.61) <sup>e</sup>

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

4 <sup>a</sup>ID= incidence density (per 1,000 person-years), CI=confidence interval, AHR=adjusted hazard ratio, HR=hazard ratio,

5 <sup>b</sup>Based on Poisson assumption

6 <sup>c</sup>Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for age and sex.

7 <sup>d</sup>Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for sex.

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

11 \* $P<0.05$

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
1 Table 3. Impact of Parkinson's disease on the risk of dementia by comorbidity

Variables	≤ 1 years				>1 years			
	ID (95% CI) <sup>a,b</sup>		Crude HR (95% CI)	AHR (95% CI)	ID (95% CI) <sup>a,b</sup>		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) <sup>c</sup>	8.57 (8.13-9.01)	27.99 (25.45-30.53)	3.36 (3.02-3.73)	3.05 (2.69-3.45) <sup>c</sup>
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) <sup>c</sup>	14.80 (14.03-15.56)	33.14 (30.81-35.48)	2.29 (2.09-2.50)	2.07 (1.87-2.28) <sup>c</sup>
				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) <sup>c</sup>	10.15 (9.74-10.56)	29.39 (27.48-31.29)	2.97 (2.75-3.21)	2.47 (2.26-2.70) <sup>c</sup>
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) <sup>c</sup>	15.46 (14.13-16.79)	36.57 (32.61-40.53)	2.42 (2.10-2.78)	2.21 (1.89-2.59) <sup>c</sup>
				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) <sup>c</sup>	10.11 (9.69-10.52)	29.77 (27.73-31.81)	3.02 (2.79-3.28)	2.58 (2.35-2.83) <sup>c</sup>
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) <sup>c</sup>	14.85 (13.66-16.04)	33.69 (30.47-36.91)	2.32 (2.05-2.63)	2.04 (1.77-2.35) <sup>c</sup>
				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) <sup>c</sup>	9.99 (9.59-10.39)	29.39 (27.37-31.40)	3.03 (2.80-3.29)	2.71 (2.48- 2.97) <sup>c</sup>
	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) <sup>c</sup>	19.94 (18.09-21.80)	34.66 (31.36-37.97)	1.73 (1.52-1.98)	1.68 (1.46-1.94) <sup>c</sup>
				Interaction: $p < 0.0001$				Interaction: $p < 0.0001$	
<b>Hyperlipidemia</b>									
	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) <sup>c</sup>	10.49 (10.08-10.90)	30.64 (28.73-32.54)	2.99 (2.78-3.23)	2.51 (2.30-2.73) <sup>c</sup>
	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) <sup>c</sup>	13.82 (12.40-15.23)	32.52 (28.46-36.58)	2.42 (2.05-2.84)	2.02 (1.68-2.43) <sup>c</sup>
				Interaction: $p = 0.9212$				Interaction: $p = 0.1841$	
<b>COPD</b>									
	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) <sup>c</sup>	10.21 (9.79-10.63)	29.59 (27.62-31.56)	2.98 (2.76-3.23)	2.54 (2.32-2.78) <sup>c</sup>
	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) <sup>c</sup>	13.77 (12.70-14.84)	34.86 (31.31-38.41)	2.56 (2.25-2.91)	2.11 (1.82- 2.45) <sup>c</sup>
				Interaction: $p = 0.0400$				Interaction: $p = 0.0772$	
<b>Number of Comorbidities</b>									
	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) <sup>d</sup>	7.48 (7.01-7.96)	24.63 (21.32-27.94)	3.40 (2.93-3.96)	3.52 (2.97-4.16) <sup>d</sup>



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

Charlson's score	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) <sup>d</sup>	11.76 (10.87-12.65)	28.61 (24.94-32.27)	2.47 (2.13-2.87)	2.67 (2.27-3.13) <sup>d</sup>
	≥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) <sup>d</sup>	15.28 (14.43-16.12)	34.21 (31.83-36.60)	2.28 (2.08-2.49)	2.11 (1.92-2.32) <sup>d</sup>
	Interaction: <i>p</i> =0.0006				Interaction: <i>p</i> <0.0001				
	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) <sup>e</sup>	9.73 (9.30-10.15)	28.39 (26.09-30.70)	3.00 (2.73-3.29)	2.67 (2.41-2.97) <sup>e</sup>
	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) <sup>e</sup>	14.92 (13.70-16.13)	34.79 (31.34-38.25)	2.38 (2.09-2.71)	2.11 (1.83-2.44) <sup>e</sup>
	≥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) <sup>e</sup>	13.93 (12.36-15.51)	32.35 (28.45-36.24)	2.32 (1.96-2.73)	2.07 (1.71-2.51) <sup>e</sup>
	Interaction: <i>p</i> = 0.0003				Interaction: <i>p</i> =0.0059				

1 <sup>a</sup>ID= incidence density, CI=confidence interval

2 <sup>b</sup>Based on Poisson assumption

3 <sup>c</sup>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.

4 <sup>d</sup>Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for comorbidities.

5 <sup>e</sup>Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for Charlson's score.

6 \* *P*<0.05

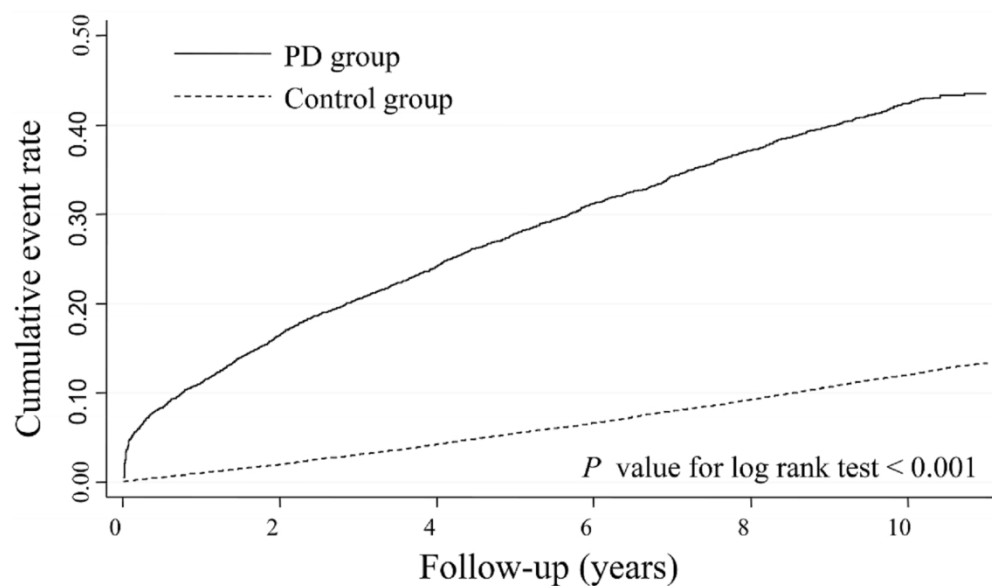


Figure 1 Comparison of Kaplan-Meier failure estimates of dementia onset between the two groups. PD, Parkinson's disease.

153x90mm (300 x 300 DPI)

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

	Item No	Page No	Recommendation
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants
		6-7	(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and

1  
2 controls was addressed

3 *Cross-sectional study*—If applicable, describe analytical methods taking  
4 account of sampling strategy  
5

---

- 6 - (e) Describe any sensitivity analyses  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	15*	10-12	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time
		-	<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure
		-	<i>Cross-sectional study</i> —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
<b>Discussion</b>			
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
<b>Other information</b>			
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

1  
2 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at  
3 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available  
4 at [www.strobe-statement.org](http://www.strobe-statement.org).  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-025274.R2
Article Type:	Research
Date Submitted by the Author:	08-Dec-2018
Complete List of Authors:	Liu, Chih-Ching; National Cheng Kung University, College of Medicine, Department of Public Health Sun, Yu; En Chu Kong Hospital, Department of Neurology Lee, Pei-Chen; National Taipei University of Nursing and Health Sciences, Department of Health Care Management Li, Chung-Yi; National Cheng Kung University, College of Medicine, Department of Public Health Hu, Susan; National Cheng Kung University, College of Medicine, Department of Public Health
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Neurology, Public health
Keywords:	retrospective cohort study, Parkinson's disease, Dementia < NEUROLOGY, competing risk, EPIDEMIOLOGY

SCHOLARONE™  
Manuscripts

1  
2  
3 1 **Risk of Dementia after Parkinson's Disease in Taiwan: A Population-based Retrospective**  
4  
5 2 Cohort Study Using National Health Insurance Claims  
6  
7 3

8  
9 4 Chih-Ching Liu, MSc<sup>a</sup>, Yu Sun, MD, PhD<sup>b</sup>, Pei-Chen Lee, PhD<sup>c</sup>,  
10  
11 5 Chung-Yi Li, PhD<sup>a,d</sup>, Susan C. Hu, PhD<sup>a\*</sup>  
12  
13 6

14  
15  
16 7 <sup>a</sup> Department of Public Health, College of Medicine, National Cheng Kung University,  
17  
18 8 Tainan, Taiwan

19  
20 9 <sup>b</sup> Department of Neurology, En Chu Kong Hospital, Sanxia District, New Taipei City, Taiwan

21  
22  
23 10 <sup>c</sup> Department of Health Care Management, National Taipei University of Nursing and Health  
24  
25 11 Sciences, Taipei, Taiwan

26  
27 12 <sup>d</sup> Department of Public Health, College of Public Health, China Medical University, Taichung,  
28  
29 13 Taiwan

30  
31  
32 14 \*Chung-Yi Li and Susan C. Hu contributed equally to this article.  
33  
34 15

35  
36 16 **Running title:** Risk of Dementia after Parkinson's disease

37  
38 17 **Word count:** text 4549  
39  
40 18

41  
42  
43 19 **Correspondence address:**

44  
45 20 Dr. Susan C. Hu

46  
47 21 Department of Public Health, College of Medicine, National Cheng Kung University

48  
49 22 Tel.: 886-6-2353535 ext. 5599, Fax: 886-6-2359033

50  
51 23 E-mail: shuhu@mail.ncku.edu.tw  
52  
53 24  
54  
55  
56  
57  
58  
59  
60



## 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 ( $\leq$  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

1  
2 **1 Article Summary**  
3

4  
5  
6 **3 Strengths and limitations of this study**  
7

- 8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- 4 ■ 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.
  - 7 ■ 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.
  - 9 ■ 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.
  - 12 ■ 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.<sup>1 2</sup> Thus, information about which patients will eventually develop dementia is an important issue in public health and clinical practice.<sup>3</sup>

Parkinson's disease (PD) has been associated with the development of cognitive impairment.<sup>4</sup> However, most previous studies on the association between PD and dementia risk have been conducted in western countries,<sup>5-19</sup> 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,<sup>5-23</sup> 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.<sup>19</sup> 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).<sup>9</sup>

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

1  
2  
3 1 overall mean follow-up time of 6.9 years and found a positive association between PD and  
4  
5 2 dementia incidence.<sup>14</sup> In Taiwan, the only population-based study with a case-control design  
6  
7 3 also showed a positive association between PD and the risk of dementia.<sup>22</sup> However, potential  
8  
9 4 survival bias resulting from recruitment of prevalent PD cases at various disease stages may  
10  
11 5 have been present in these studies.

12  
13  
14 6 Some studies have reported that older age<sup>5-10 13 15 20 23</sup> and male gender<sup>5</sup> are related to  
15  
16 7 increased dementia risk in PD; however, information regarding the age- and sex- stratified  
17  
18 8 dementia incidence rate in PD is scant. In addition, many PD patients may have medical  
19  
20 9 comorbidities such as stroke, hypertension, diabetes mellitus, hyperlipidemia, and coronary  
21  
22 10 heart disease, which may have modification effects on the relationship between dementia and  
23  
24 11 PD.<sup>7 16 17 22</sup> However, little research has examined medical comorbidities as a potential  
25  
26 12 confounding factor that should be controlled for.<sup>7 22 23</sup> Moreover, because of the increased age  
27  
28 13 and co-morbidities in a long-term follow-up study, competing risk of death should be  
29  
30 14 considered. However, none of studies on this topic have considered death as a competing risk,  
31  
32 15 <sup>6-21 23</sup> which may induce potential attrition bias and tend to distort the study results.

33  
34  
35  
36 16 Given the abovementioned methodological problems and limited information on this  
37  
38 17 topic, the association between PD and the risk of dementia needs to be further explored.  
39  
40 18 Therefore, in this study, a nationwide population-based cohort study was conducted to  
41  
42 19 estimate 11 years of incidence and the HRs for development of dementia in patients with  
43  
44 20 first-diagnosed PD by age and sex and by comorbidities (i.e., hypertension, diabetes, coronary  
45  
46 21 artery disease (CAD), stroke, hyperlipidemia, and chronic obstructive pulmonary disease  
47  
48 22 (COPD)), after accounting for the competing risk of death.

## 23 24 **METHODS**

### 25 **Data Source**

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

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

## 12 **Patient and public involvement**

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

## 18 **Study design, Cohorts and Covariates**

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

1  
2  
3 1 inclusion of miscoded patients.

4  
5 2 To ensure that the PD diagnosis was reliable and consistent, cases were excluded if: (1)  
6  
7 3 an age on the index date of less than 40 years, who are more likely to have a genetic etiology;  
8  
9 4 (2) a diagnostic code of secondary Parkinsonism (ICD-9-CM code: 332.1) during the study  
10  
11 5 period; (3) receipt of any neuroleptic medication 180 days prior to the index date, and (4)  
12  
13 6 three or more medical claims (either ambulatory or inpatient care) with diagnostic codes of  
14  
15 7 dementia prior to the index date. The first date of initial diagnosis of PD in the period of 2002  
16  
17 8 to 2003 was set as the index date.

18  
19  
20 9 We previously conducted a pilot study to validate the accuracy of the ICD-9 coding in  
21  
22 10 PD patients.<sup>28</sup> In this study, medical records including symptoms/signs, diagnostic procedures,  
23  
24 11 use of anti-parkinsonism medication, as well as response to medication of 290 randomly  
25  
26 12 selected patients with ICD-9-CM coded 332.0 were examined in detail by three experienced  
27  
28 13 neurologists from January to October 2012. Among these 290 cases, 245 were confirmed as  
29  
30 14 PD patients based on the aforementioned clinical information. The sensitivity, specificity,  
31  
32 15 positive predictive value, and negative predictive value were 97.6%, 92.3%, 98.8% and  
33  
34 16 85.7%, respectively. The accuracy of our method for identifying PD cases was 96.9%.  
35  
36 17 Moreover, cases in this study were not only ascertained using the ICD code but also required  
37  
38 18 having been prescribed at least three times of anti-parkinsonism medication including L-dopa  
39  
40 19 or a dopamine agonist to minimize the possibility of miscoding.

41  
42  
43 20 The control subjects were selected from those who had not been diagnosed with PD or  
44  
45 21 treated with any anti-PD medications during the entire study period and met the same  
46  
47 22 exclusion criteria as those set for the patients with PD. These control subjects were matched  
48  
49 23 by age (each five-year span), sex, and year of index date for patients with PD at a 5:1 ratio. As  
50  
51 24 a result, 29,645 control subjects were identified. For the control groups, the index date was  
52  
53 25 either January 1, 2002 or January 1, 2003.

54  
55 26 Baseline comorbidities that may be associated with an increased risk of dementia were  
56  
57  
58  
59  
60

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

### 11 **End point and Statistical analysis**

12 The main outcome variable was the initial occurrence of dementia (ICD-9-CM code: 290,  
13 294.1, 331.0, and 331.82). A Taiwanese has previously reported that the diagnostic accuracy  
14 of dementia is approximately 90% when relying on diagnosis codes (ICD-9-CM) to identify  
15 dementia.<sup>27</sup> To increase the validity of dementia identification, only dementia cases diagnosed  
16 with  $\geq$  three ambulatory visits or  $\geq$  one hospitalization were included in this study. We did not  
17 distinguish the subtypes of dementia because of data limitations due to a lack of information  
18 regarding symptoms/signs, lab data, and image findings, and further outcome analyses with  
19 dementia subtype classifications, such as dementia with Lewy bodies (DLB), Alzheimer's  
20 dementia, frontotemporal dementia, just Parkinson's disease dementia (PDD), were not  
21 performed. However, according to the criteria set forth by the consensus report of the Lewy  
22 Body Consortium,<sup>32</sup> clinicians and researchers use the "one-year rule" to help verify the  
23 diagnoses of DLB and PDD. Thus, we analyzed the dementia incidence within and after one  
24 year of PD diagnosis, respectively.

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

1  
2  
3 1 density of dementia was calculated using an age- and sex- specific and comorbidity-specific  
4  
5 2 stratified analysis based on the Poisson assumption. The cumulative events and rates of  
6  
7 3 dementia according to the PD status over the study period were calculated using a  
8  
9 4 Kaplan-Meier analysis, and the log-rank test was used to test the between-group differences.

10  
11 5 Since death is the competing risk of dementia occurrence in this long-term follow-up  
12  
13 6 study, analytical approaches used in competing risk settings must be used to assess the  
14  
15 7 association between PD and the risk of dementia. Cause-specific hazards models, one of the  
16  
17 8 most common analytical methods used in competing risk settings, are better suited for  
18  
19 9 studying the etiology of diseases.<sup>33</sup> The cause-specific hazard is the instantaneous risk of  
20  
21 10 dying from a particular cause  $k$  given that the subject is still alive at time  $t$ .<sup>34</sup> Thus, in this  
22  
23 11 study, a Cox proportional hazard regression with competing risk models, according to  
24  
25 12 cause-specific hazards models, was performed to assess the hazard ratio of dementia in  
26  
27 13 relation to PD.

28  
29  
30  
31 14 In addition, we performed a sex- and age- stratified analysis and a comorbidity-stratified  
32  
33 15 analysis to examine the potential effect-modifications by age, sex, and comorbidity on the  
34  
35 16 association between PD and the risk of dementia. Plots of  $\log(-\log(\text{survival function}))$  vs.  $\log$   
36  
37 17 (time) were drawn to test for violations of the proportional-hazards assumption. Therefore,  
38  
39 18 separate time-partitioned models were created, and the hazards within each partition were  
40  
41 19 assessed. Proportionality was held for the new models partitioned at one year. If we modeled  
42  
43 20 the hazards for  $\leq$  one year (i.e., the first time partition), the censoring day for subsequent  
44  
45 21 events was one year. If we modeled the hazards for  $>$  one year (i.e., the second time partition),  
46  
47 22 subjects with earlier events were included and considered to be censors (because the exclusion  
48  
49 23 of these subjects may lead to a survival bias). A  $p < 0.05$  was considered significant.

## 54 24

## 56 25 RESULTS



1  
2  
3 1 The distributions of age and gender were no significant difference in both groups. The  
4  
5 2 percentages of PD patients who lived in urban (54.7 vs. 51.8%) and suburban (35.6 vs. 33.2%)  
6  
7 3 areas and in northern (45.6 vs. 44.8%) and central (25.5 vs. 24.9%) Taiwan were higher than  
8  
9 4 those of the controls. The prevalence rates of the risk factors for dementia were high in  
10  
11 5 patients with PD. The PD cohort had fewer white-collar workers (25.0% vs. 31.2%,  
12  
13 6  $p<0.0001$ ), a lower insurance premium (percentage with none or a lower than median  
14  
15 7 insurance premium: 69.5 vs. 60.0,  $p<0.0001$ ), a higher Charlson's score (percentage with  
16  
17 8 score of one to  $\geq$  two: 52.1% vs. 25.4%,  $p<0.0001$ ), and a higher frequency of medical  
18  
19 9 visits (39.6 vs. 21.9 per year,  $p<0.0001$ ), than the control group (Table 1).  
20  
21  
22

23 10 Figure 1 shows the cumulative incidence of dementia in patients with and without PD.  
24  
25 11 The cumulative incidence of dementia for PD was significantly higher than the corresponding  
26  
27 12 data observed in the non-PD group (log-rank test,  $p<0.0001$ ).  
28

29 13 Among the total of 5,932 first diagnosed PD cases, only 492 of these cases (8.3%) were  
30  
31 14 derived from inpatient records. The adjusted hazard ratios of dementia either in the overall PD  
32  
33 15 cases or in the PD cases only enrolled in an outpatient group were significantly higher than  
34  
35 16 those in the control group without PD. The median duration from the overall first diagnosis of  
36  
37 17 PD to the development of dementia was 9.02 years.  
38  
39

40 18 During the 11 years of follow-up, a total of 1,836 PD patients developed dementia, and  
41  
42 19 1,226 PD patients died without developing dementia. In the same period, a total of 3,159  
43  
44 20 control subjects developed dementia, and 5,223 control subjects died without developing  
45  
46 21 dementia. In the period within one year after the index date (i.e., the first time partition), a  
47  
48 22 total of 5,932 PD subjects encountered 624 medical episodes due to first diagnosed dementia  
49  
50 23 in the 5,450.09 person-years observed, representing incidence densities of dementia of 114.49  
51  
52 24 per 1,000 person-years. In the same period, a total of 29,645 PD subjects encountered 285  
53  
54 25 medical episodes due to first diagnosed dementia in 29,208.39 person-years observed,  
55  
56 26 representing incidence densities of dementia of 9.76 per 1,000 person-years. Noticeably, the  
57  
58  
59  
60

1  
2  
3 1 incidence density of dementia increased with age irrespective of PD status and sex, and the  
4  
5 2 highest incidence was observed in those aged  $\geq 80$  years. The adjusted HR of dementia in  
6  
7 3 relation to PD was significantly increased at 6.43 (95% CI 5.46 - 7.57) and was higher in men  
8  
9 4 than in women (HR: 7.18, 95% CI 5.73 - 9.01 vs. 5.54, 95% CI 4.39 - 6.99). In addition, there  
10  
11 5 was a significant interaction of PD with age on the risk of dementia for both men ( $p=0.02$ )  
12  
13 6 and women ( $p<0.0001$ ) (Table 2).

14  
15  
16 7 In the years following the PD diagnosis (i.e., the second time partition), the overall  
17  
18 8 incidence density of dementia was much lower (Table 2). The change in incidence density  
19  
20 9 between the first and the second partition was more pronounced in the PD group (from 114.49  
21  
22 10 to 30.99 per 1,000 person-years) than in the control group (from 9.76 to 10.83 per 1,000  
23  
24 11 person-years). The age- and sex- specific incidence densities had a similar pattern in terms of  
25  
26 12 change. However, no significant difference in the sex-specific HRs of dementia was observed  
27  
28 13 ( $p=0.23$ ). There was a significant interaction of PD status with age ( $p<0.0001$ ) in both sexes.  
29  
30 14 Further analyses of age- and sex-specific HRs showed the highest HR was observed in PD  
31  
32 15 females aged  $<70$  years (HR: 4.27; 95% CI 3.25 - 5.63).

33  
34  
35  
36 16 Impact of PD on the risk of dementia by comorbidity is shown in Table 3. Irrespective of  
37  
38 17 the various time partitions, the incidence of dementia increased with the number of  
39  
40 18 comorbidities in both groups. The PD group had the highest risk of dementia across various  
41  
42 19 medical comorbidity stratifications or Charlson's scores after adjusting for baseline  
43  
44 20 characteristics. In the first time partition, the interaction of PD with hypertension ( $p=0.01$ ),  
45  
46 21 CAD ( $p=0.02$ ), stroke ( $p<0.0001$ ), and COPD ( $p=0.04$ ) on the risk of dementia also was  
47  
48 22 statistically significant, indicating that subjects without hypertension, CAD, stroke, and  
49  
50 23 COPD had a higher adjusted HR for dementia. However, although the adjusted HR for  
51  
52 24 dementia was also higher in subjects without diabetes and hyperlipidemia than in those with  
53  
54 25 medical comorbidities, there was no statistically significant modification effect by diabetes  
55  
56 26 and hyperlipidemia on the association between PD and the risk of dementia. In terms of the  
57  
58  
59  
60

1  
2  
3 1 Charlson's scores, subjects with scores of 0 had a higher adjusted HR for dementia than those  
4  
5 2 with scores of one and  $\geq$ two. The interactions were significant for PD with Charlson's score  
6  
7 3 ( $p=0.01$ ) on the risk of dementia.

8  
9 4 In the second time partition, effect-modification by hypertension ( $p<0.0001$ ), CAD  
10  
11 5 ( $p=0.01$ ) and stroke ( $p<0.0001$ ) was statistically significant for dementia, indicating that  
12  
13 6 subjects without those medical comorbidities had a higher adjusted HR for dementia. Among  
14  
15 7 diabetes, hyperlipidemia, or COPD patients, adjusted HR for dementia also showed a  
16  
17 8 statistically significant high risk from 2.02 (95% CI=1.68 - 2.43) to 2.21 (95% CI=1.89 - 2.59),  
18  
19 9 but no significant modification effect was found for those with medical comorbidities on the  
20  
21 10 association between PD and the risk of dementia. In terms of the Charlson's scores, subjects  
22  
23 11 with scores of 0 had a higher adjusted HR for dementia than those with scores of one and  $\geq$   
24  
25 12 two. Also, a significant modification effect of Charlson's scores on the association between  
26  
27 13 PD and the risk of dementia ( $p=0.01$ ) was found. Regardless of whether medical  
28  
29 14 comorbidities existed or not, the HRs for dementia were greater in the first time partition but  
30  
31 15 were smaller in the second time partition.  
32  
33  
34  
35  
36  
37

## 38 17 **DISCUSSION**

39  
40 18 To the best of our knowledge, this is the first nationwide population-based cohort study  
41  
42 19 to demonstrate that patients with the first diagnosis of PD are associated with increased risk of  
43  
44 20 dementia compared with non-PD patients. However, our study showed a sharply increased  
45  
46 21 hazard of dementia within one year after the first diagnosis of PD, which is clinically and  
47  
48 22 biologically questionable, probably because a large proportion of patients with dementia  
49  
50 23 remain undiagnosed before the index date of their first clinical visit for PD.  
51  
52  
53

54 24 In other words, many patients with pre-existing cognitive impairment and PD were  
55  
56 25 classed as new PD cases because their condition had deteriorated and had only been  
57  
58 26 recognized because they had been referred for an expert opinion. This is also supported by the  
59  
60

1  
2  
3 1 decline in the number of PD patients with dementia in the subsequent period of observation.  
4  
5 2 In this study, we found that the overall risk of dementia onset increased nearly twofold in up  
6  
7 3 to 11 years (adjusted HR: 2.42, 95% CI: 2.23 - 2.61) among those who survived at least one  
8  
9 4 year and had an initial PD diagnosis thereafter. The magnitude of this association varied  
10  
11 5 according to different age and sex stratifications. In general, the increased risk of dementia  
12  
13 6 was higher in men in the first partition but was similar in both genders in the second partition.  
14  
15 7 In addition, younger PD patients have the highest risk of dementia in any given partition time.  
16  
17 8 The study results can provide physicians and patients with valuable information and also  
18  
19 9 demonstrate the need for guidelines for detection of dementia risk after the initial diagnosis of  
20  
21 10 PD.

22  
23  
24  
25 11 Our study shows that a reasonably increased hazard of dementia more than one year after  
26  
27 12 diagnosis of PD is more likely to be real and may suggest evidence of the mechanisms  
28  
29 13 supported by the Braak pathology staging hypothesis.<sup>35 36</sup> Our findings were similar to  
30  
31 14 another population-based case control study in Taiwan,<sup>22</sup> which showed the risk of  
32  
33 15 developing dementia in prevalent Parkinsonism was highest in the first six months (adjusted  
34  
35 16 odds ratio (AOR): 11.98, 95% CI: 8.51 - 16.68) and then became lower in the following  
36  
37 17 months to years after diagnosis.

38  
39  
40 18 Age is known to be a risk factor for dementia not only in the general population<sup>37 38</sup> but  
41  
42 19 also in the PD patient population<sup>5-10 13 15 20 23</sup>. This may be caused by aging of  
43  
44 20 non-dopaminergic structures (i.e., the locus ceruleus and pedunculopontine nucleus).<sup>39</sup>  
45  
46 21 However, a modifying effect of age on the risk of dementia after PD may be present in our  
47  
48 22 study. For example, we found that patients with PD had a significantly higher overall risk of  
49  
50 23 dementia than those in the control group, particularly in subjects aged < 70 years. This result  
51  
52 24 is similar to the findings of some prior studies.<sup>13 18</sup>

53  
54  
55  
56 25 Male sometimes is identified as a risk factor for dementia in PD;<sup>5</sup> however, there is no  
57  
58 26 clear explanation for this finding. In our study, we found that the risk of dementia was similar  
59  
60

1  
2  
3 1 in both men and women who had first-diagnosed PD one year later (HR: 2.44, 95% CI  
4  
5 2.19 - 2.73 and HR: 2.41, 95% CI 2.15 - 2.69, respectively). Accordingly, patients with PD,  
6  
7 3 especially younger patients in both sexes, could be selected in future studies as a target  
8  
9 4 population to evaluate whether interventions are effective in decreasing the risk of dementia  
10  
11 5 after diagnosis of PD.

12  
13  
14 6 Our study also shows that the overall risk of dementia was more than double (adjusted  
15  
16 7 HR 2.42) among subjects with first-diagnosed PD one year later for up to 11 years. After  
17  
18 8 accounting for the competing risk of death and adjustment for the number of medical visits,  
19  
20 9 the findings were similar to those of Perezet al., who reported a higher HR of incident  
21  
22 10 dementia (2.47, 95%CI 1.55 - 3.59) in patients with PD as compared to non-PD subjects.<sup>11</sup>  
23  
24 11 However, other cohort studies have shown a HR ranging from 1.7 (95% CI 1.1 - 2.7) to 5.9  
25  
26 12 (95% CI 3.9 - 9.1) for incident dementia in PD groups compared with the general population,<sup>9</sup>  
27  
28 13 <sup>10 12-15 18</sup> which is different from our findings. Noticeably, most previous studies were limited  
29  
30 14 by a relatively small sample size,<sup>6-17 19-21 23</sup> shorter follow-up time,<sup>6-8 10 12-18 20</sup> the lack of a  
31  
32 15 matched control,<sup>6-8 16 17 19-21 23</sup> failure to account for the competing risk of death,<sup>6-21 23</sup> or a lack  
33  
34 16 of adjustment for the number of medical visits to control for surveillance bias,<sup>9-15 18</sup> rendering  
35  
36 17 the risk that the estimates were more likely to be imprecise and biased.

37  
38  
39  
40 18 We found the incidence of dementia increased with the number of comorbidities,  
41  
42 19 including hypertension, diabetes mellitus, CAD, stroke, hyperlipidemia, and COPD,  
43  
44 20 irrespective of PD status. However, in our study, the adjusted HR for dementia was higher in  
45  
46 21 PD alone than in those with medical comorbidities. The effect-modification by hypertension,  
47  
48 22 CAD and stroke was statistically significant for the association between PD and dementia in  
49  
50 23 any given partition time. Prior studies regarding the relationship between patients with PD  
51  
52 24 and these comorbidities remain controversial.<sup>7 16 17 22</sup> For example, although a study in Taiwan  
53  
54 25 demonstrated that patients with PD with cerebrovascular or cardiovascular comorbidities had  
55  
56 26 a lower risk of dementia onset than patients with PD alone,<sup>22</sup> which is similar our findings,  
57  
58  
59  
60

1  
2  
3 1 other studies have failed to find this relationship.<sup>16 17</sup> In addition, some previous studies have  
4  
5 2 shown that PD with cardiovascular dysautonomia (such as hypertension, diabetes mellitus,  
6  
7 3 and CAD) and COPD might cause substantial cerebral hypoperfusion and hypoxia,  
8  
9 4 respectively.<sup>40-42</sup> Hypoxia and hypotension in the brain might cause neuronal damage and  
10  
11 5 increase accumulation of pathologic proteins such as  $\beta$ -amyloid, which result in increased risk  
12  
13 6 of dementia onset.<sup>40 41</sup> Therefore, future perspective studies focusing on the causal  
14  
15 7 relationship between such comorbidities and the risk of dementia in PD are warranted.

16  
17  
18 8 There were several strengths in our study. First, we obtained a large, nationwide number  
19  
20 9 of participants by using NHIR datasets, which made it possible to reduce selection bias, to  
21  
22 10 obtain higher statistical power, to obtain a highly representative study population, to have a  
23  
24 11 lower rate of nonresponse or loss to follow-up, and to facilitate the age-, sex- and  
25  
26 12 comorbidities-stratified analyses with an ample sample size to satisfy requirements. To the  
27  
28 13 best of our knowledge, this study is the first to report the age- and sex- specific incidence  
29  
30 14 rates of dementia in a PD group. Secondly, we conducted a longitudinal and retrospective  
31  
32 15 cohort study for 11 years, which is a longer time during which to observe the development of  
33  
34 16 dementia than that in many other prior studies.<sup>6-8 10 12-18 20</sup> Thirdly, more accurate estimates for  
35  
36 17 the incidence rates of dementia in the PD group are available in this study due to the usage of  
37  
38 18 the first diagnosed PD cases rather than the prevalent PD cases, as this might reduce the  
39  
40 19 variations in the incidence of dementia across various PD durations. Lastly, a multivariate  
41  
42 20 Cox proportional hazard regression with a competing risk analysis was used to control for the  
43  
44 21 confounding bias and to account for the competing risk of death.

45  
46  
47 22 Still, our study had some limitations. Firstly, we solely selected our PD cases according  
48  
49 23 to physician-recorded diagnosis and prescriptions reported in medical claims, which might  
50  
51 24 have led to potential disease misclassification. However, we used at least three PD-related  
52  
53 25 diagnoses and prescriptions, with the first and last visits >90 days apart, which greatly  
54  
55 26 decrease the likelihood of disease misclassification. Similarly, because we selected patients  
56  
57  
58  
59  
60

1  
2  
3 1 with dementia only by using NHIR datasets, potential disease misclassification may be  
4  
5 2 present. To address this concern, we only included dementia cases diagnosed with  $\geq$  three  
6  
7 3 ambulatory visits or  $\geq$  one hospitalization in this study to increase the validity of dementia  
8  
9 4 identification.

10  
11 5 Secondly, because patients with PD may utilize the health care system more often than  
12  
13 6 control groups, surveillance bias may be present. Thus, to address this concern, we calculated  
14  
15 7 the number of medical visits for one year after the index date and adjusted for this in the  
16  
17 8 multivariate regression model. Also, the severity of dementia is not available in the database,  
18  
19 9 and we could not distinguish subtypes of dementia in our datasets. Therefore, it is essential  
20  
21 10 for patients with PD, particularly in high risk groups such as subjects aged  $<70$  years, to have  
22  
23 11 regular cognitive assessments including combinations of neuropsychological markers  
24  
25 12 throughout the early disease stages, which not only will provide benefits for identification of  
26  
27 13 the subtypes in dementia but will also decrease underestimation of risk for dementia in PD.  
28  
29  
30

31  
32 14 Thirdly, due to the limited information available from the claims data, we were unable to  
33  
34 15 consider a comprehensive list of potential confounders such as smoking, educational level,  
35  
36 16 physical function, and genes in the analysis, which may have resulted in residual confounding  
37  
38 17 bias. To reduce such bias, we used COPD and occupational status as surrogates for smoking  
39  
40 18 and educational level, respectively. Finally, the disease symptoms of PD cases at different  
41  
42 19 disease stages may play a role, to some extent, in the relationship between PD and the risk of  
43  
44 20 dementia. However, because information on the disease symptoms is unavailable from the  
45  
46 21 NHI data, we have left this area (such as non-motor symptoms) for further investigations.  
47  
48  
49

50  
51 22 In conclusion, it was found that PD confers a higher risk of dementia than the general  
52  
53 23 population, especially in those aged  $<70$  years in both sexes. Regular monitoring for the  
54  
55 24 development of dementia in patients with PD longitudinally is recommended. Future research  
56  
57 25 should include further evaluation of the underlying mechanism and subtypes for dementia  
58  
59 26 development after diagnosis of PD.  
60



1  
2  
3 1  
4  
5 2 **Acknowledgements:** We thank the Bureau of National Health Insurance in the Ministry of  
6  
7 3 Health and Welfare and the National Health Research Institutes for providing the National  
8  
9 4 Health Insurance Research Database used in this study. The interpretation and conclusions  
10  
11 5 contained herein do not represent those of the Bureau of National Health Insurance, Ministry  
12  
13 6 of Health and Welfare, or National Health Research Institutes.

14  
15  
16 7 **Author contributions:** Chih-Ching Liu analyzed the data and wrote the draft of the  
17  
18 8 manuscript. Yu Sun and Pei-Chen Lee provided further data analyses and interpretation.  
19  
20 9 Chung-Yi Li and Susan C. Hu advised the study and revised the manuscript. All authors have  
21  
22 10 approved the final version of the manuscript.

23  
24  
25 11 **Funding:** This study was supported by a grant from Taiwan Ministry of Science and  
26  
27 12 Technology (MOST 106-2314-B-227-010).

28  
29 13 **Disclaimer:** The funder had no role in study design, data collection and analysis, and the  
30  
31 14 preparation of the manuscript.

32  
33 15 **Competing interests:** None.

34  
35 16 **Patient consent:** Not required.

36  
37 17 **Ethics approval:** A full review by the institutional review board was not required because the  
38  
39 18 encryption of the identification numbers makes it impossible to identify individuals. Access to  
40  
41 19 the National Health Insurance Research Database datasets is approved by the National Health  
42  
43 20 Research Institutes Review Committee.

44  
45 21 **Provenance and peer review:** Not commissioned; externally peer reviewed.

46  
47 22 **Data sharing statement:** We, as the authors of this original research article, state that there is  
48  
49 23 no additional, unpublished data available from this study. Raw data sharing from National  
50  
51 24 Health Insurance Research Database is prohibited according to the National Health Research  
52  
53 25 Institutes (NHRI) policies in Taiwan.



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
**1 REFERENCES**

1. World Health Organization. Dementia: a public health priority. 2012 [cited 2018 April 2]. [http://www.who.int/mental\\_health/publications/dementia\\_report\\_2012/en/](http://www.who.int/mental_health/publications/dementia_report_2012/en/)
2. Alzheimer's Disease International. World Alzheimer Report 2015: The Global Impact of Dementia. 2015 [cited 2018 April 1]. <https://www.alz.co.uk/research/world-report-2015>
3. Russell A, Drozdova A, Wang W, *et al*. The impact of dementia development concurrent with Parkinson's disease: a new perspective. *CNS Neurol Disord Drug Targets* 2014;13:1160-8.
4. Kalia LV, Lang AE. Parkinson's disease. *Lancet* 2015;386:896-912.
5. Xu Y, Yang J, Shang H. Meta-analysis of risk factors for Parkinson's disease dementia. *Transl Neurodegener* 2016;5:11.
6. Domellof ME, Ekman U, Forsgren L, *et al*. Cognitive function in the early phase of Parkinson's disease, a five-year follow-up. *Acta Neurol Scand* 2015;132:79-88.
7. Anang JB, Gagnon JF, Bertrand JA, *et al*. Predictors of dementia in Parkinson disease: a prospective cohort study. *Neurology* 2014;83:1253-60.
8. Zhu K, van Hilten JJ, Marinus J. Predictors of dementia in Parkinson's disease; findings from a 5-year prospective study using the SCOPA-COG. *Parkinsonism Relat Disord* 2014;20:980-5.
9. Williams-Gray CH, Mason SL, Evans JR, *et al*. The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. *J Neurol Neurosurg Psychiatry* 2013;84:1258-64.
10. Aarsland D, Andersen K, Larsen JP, *et al*. Risk of dementia in Parkinson's disease: a community-based, prospective study. *Neurology* 2001;56:730-6.
11. Perez F, Helmer C, Foubert-Samier A, *et al*. Risk of dementia in an elderly population of Parkinson's disease patients: a 15-year population-based study. *Alzheimers Dement* 2012;8:463-9.
12. Marder K, Tang MX, Cote L, *et al*. The frequency and associated risk factors for dementia in patients with Parkinson's disease. *Arch Neurol* 1995;52:695-701.
13. Levy G, Schupf N, Tang MX, *et al*. Combined effect of age and severity on the risk of dementia in Parkinson's disease. *Ann Neurol* 2002;51:722-9.
14. de Lau LM, Schipper CM, Hofman A, *et al*. Prognosis of Parkinson disease: risk of dementia and mortality: the Rotterdam Study. *Arch Neurol* 2005;62:1265-9.
15. Hobson P, Meara J. Risk and incidence of dementia in a cohort of older subjects with Parkinson's disease in the United Kingdom. *Mov Disord* 2004;19:1043-9.
16. Haugarvoll K, Aarsland D, Wentzel-Larsen T, *et al*. The influence of cerebrovascular risk factors on incident dementia in patients with Parkinson's disease. *Acta Neurol Scand* 2005;112:386-90.
17. Levy G, Tang MX, Cote LJ, *et al*. Do risk factors for Alzheimer's disease predict

- 1  
2 1 dementia in Parkinson's disease? An exploratory study. *Mov Disord* 2002;17:250-7.  
3  
4 2 18. Breteler MM, de Groot RR, van Romunde LK, *et al.* Risk of dementia in patients with  
5 3 Parkinson's disease, epilepsy, and severe head trauma: a register-based follow-up  
6 4 study. *Am J Epidemiol* 1995;142:1300-5.  
7  
8 5 19. Hely MA, Reid WG, Adena MA, *et al.* The Sydney multicenter study of Parkinson's  
9 6 disease: the inevitability of dementia at 20 years. *Mov Disord* 2008;23:837-44.  
10 7 20. Kwon KY, Kang SH, Kim M, *et al.* Nonmotor Symptoms and Cognitive Decline in de  
11 8 novo Parkinson's Disease. *Can J Neurol Sci* 2014;41:597-602.  
12 9 21. Auyeung M, Tsoi TH, Mok V, *et al.* Ten year survival and outcomes in a prospective  
13 10 cohort of new onset Chinese Parkinson's disease patients. *J Neurol Neurosurg*  
14 11 *Psychiatry* 2012;83:607-11.  
15 12 22. Huang YC, Wu ST, Lin JJ, *et al.* Prevalence and risk factors of cognitive impairment  
16 13 in Parkinson disease: a population-based case-control study in Taiwan. *Medicine*  
17 14 *(Baltimore)* 2015;94:e782.  
18 15 23. Lee SY, Ryu HJ, Seo JW, *et al.* Dementia-Free Survival and Risk Factors for  
19 16 Dementia in a Hospital-Based Korean Parkinson's Disease Cohort. *J Clin Neurol*  
20 17 2017;13:21-6.  
21 18 24. National Health Insurance Administration. Universal Health Coverage in Taiwan.  
22 19 2017 [cited 2018 May 8].  
23 20 [https://www.nhi.gov.tw/English/Content\\_List.aspx?n=8FC0974BBFEFA56D&topn=](https://www.nhi.gov.tw/English/Content_List.aspx?n=8FC0974BBFEFA56D&topn=ED4A30E51A609E49)  
24 21 [ED4A30E51A609E49](https://www.nhi.gov.tw/English/Content_List.aspx?n=8FC0974BBFEFA56D&topn=ED4A30E51A609E49)  
25 22 25. Sun Y, Chang YH, Chen HF, *et al.* Risk of Parkinson disease onset in patients with  
26 23 diabetes: a 9-year population-based cohort study with age and sex stratifications.  
27 24 *Diabetes Care* 2012;35:1047-9.  
28 25 26. Shen CC, Tsai SJ, Perng CL, *et al.* Risk of Parkinson disease after depression: a  
29 26 nationwide population-based study. *Neurology* 2013;81:1538-44.  
30 27 27. Chiang CJ, Yip PK, Wu SC, *et al.* Midlife risk factors for subtypes of dementia: a  
31 28 nested case-control study in Taiwan. *Am J Geriatr Psychiatry* 2007;15:762-71.  
32 29 28. Liu CC, Li CY, Lee PC, *et al.* Variations in Incidence and Prevalence of Parkinson's  
33 30 Disease in Taiwan: A Population-Based Nationwide Study. *Parkinsons Dis*  
34 31 2016;2016:8756359.  
35 32 29. Charlson ME, Pompei P, Ales KL, *et al.* A new method of classifying prognostic  
36 33 comorbidity in longitudinal studies: development and validation. *J Chronic Dis*  
37 34 1987;40:373-83.  
38 35 30. Charlson M, Szatrowski TP, Peterson J, *et al.* Validation of a combined comorbidity  
39 36 index. *J Clin Epidemiol* 1994;47:1245-51.  
40 37 31. Driver JA, Kurth T, Buring JE, *et al.* Parkinson disease and risk of mortality: a  
41 38 prospective comorbidity-matched cohort study. *Neurology* 2008;70:1423-30.  
42 39 32. McKeith IG, Boeve BF, Dickson DW, *et al.* Diagnosis and management of dementia  
43 44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2 1 with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology*  
3 2017;89:88-100.  
4 2  
5 33. Noordzij M, Leffondre K, van Stralen KJ, *et al.* When do we need competing risks  
6 4 methods for survival analysis in nephrology? *Nephrol Dial Transplant*  
7 2013;28:2670-7.  
8 5  
9 34. Prentice RL, Kalbfleisch JD, Peterson AV, Jr., *et al.* The analysis of failure times in  
10 6 the presence of competing risks. *Biometrics* 1978;34:541-54.  
11 7  
12 35. Braak H, Del Tredici K, Bratzke H, *et al.* Staging of the intracerebral inclusion body  
13 8 pathology associated with idiopathic Parkinson's disease (preclinical and clinical  
14 9 stages). *J Neurol* 2002;249 Suppl 3:Iii/1-5.  
15 10  
16 36. Braak H, Del Tredici K, Rub U, *et al.* Staging of brain pathology related to sporadic  
17 11 Parkinson's disease. *Neurobiol Aging* 2003;24:197-211.  
18 12  
19 37. Matthews FE, Stephan BC, Robinson L, *et al.* A two decade dementia incidence  
20 13 comparison from the Cognitive Function and Ageing Studies I and II. *Nat Commun*  
21 14 2016;7:11398.  
22 15  
23 38. Solomon A, Mangialasche F, Richard E, *et al.* Advances in the prevention of  
24 16 Alzheimer's disease and dementia. *J Intern Med* 2014;275:229-50.  
25 17  
26 39. Levy G, Tang MX, Cote LJ, *et al.* Motor impairment in PD: relationship to incident  
27 18 dementia and age. *Neurology* 2000;55:539-44.  
28 19  
29 40. de la Torre JC. Cardiovascular risk factors promote brain hypoperfusion leading to  
30 20 cognitive decline and dementia. *Cardiovasc Psychiatry Neurol* 2012;2012:367516.  
31 21  
32 41. Liu H, Xing A, Wang X, *et al.* Regulation of beta-amyloid level in the brain of rats  
33 22 with cerebrovascular hypoperfusion. *Neurobiol Aging* 2012;33:826.e31-42.  
34 23  
35 42. Grant I, Heaton RK, McSweeney AJ, *et al.* Neuropsychologic findings in hypoxemic  
36 24 chronic obstructive pulmonary disease. *Arch Intern Med* 1982;142:1470-6.  
37 25  
38 26  
39 27  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1 Table 1. Characteristics of the study subjects

Variables <sup>a</sup>	PD group		Control group		P value
	n	%	n	%	
Age (years)					
<70	1852	31.2	4220	31.2	1.00 <sup>d</sup>
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) <sup>b</sup>	72.5±9.4		70.8±12.7		
Sex					
Male	3116	52.6	15580	52.6	1.00 <sup>d</sup>
Female	2813	47.4	14065	47.4	
Insurance premium (NTD) <sup>b</sup>					
Dependent	2333	39.9	9721	33.8	<0.0001 <sup>d</sup>
<Median (19,200)	1734	29.6	7753	26.2	
≥Median	1787	30.5	12171	41.0	
Mean (±SD) <sup>b,c</sup>	7102.6±11122.9		10194.0±13197.8		
Urbanization status					
Urban	3203	54.7	15197	51.8	0.01 <sup>d</sup>
Suburban	2085	35.6	9741	33.2	
Rural	566	9.8	4424	15.0	
Geographic area					
Northern	2670	45.6	13130	44.8	<0.0001 <sup>d</sup>
Central	1491	25.5	7288	24.9	
Southern	1519	25.9	7957	27.1	
Eastern	174	3.0	931	3.2	
Occupational status					
White collar	1482	25.0	9242	31.2	<0.0001 <sup>d</sup>
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 <sup>d</sup>
Hypertension	3578	60.3	11431	38.6	<0.0001 <sup>d</sup>
Diabetes	1430	24.1	4112	13.9	<0.0001 <sup>d</sup>
CAD	1955	33.0	4890	16.5	<0.0001 <sup>d</sup>
Stroke	1977	33.3	2924	9.9	<0.0001 <sup>d</sup>
Hyperlipidemia	1089	18.4	3013	10.2	<0.0001 <sup>d</sup>
COPD	1719	29.0	5624	19.0	<0.0001 <sup>d</sup>

Charlson's score					<0.0001 <sup>d</sup>
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) <sup>b</sup>	39.6 (±26.5)		21.9 (±19.7)		<0.0001 <sup>e</sup>
Total	5932	100.0	29645	100.0	

<sup>a</sup>Inconsistency between the total population and the population summed for individual variables was due to missing information.

<sup>b</sup>SD=Standard deviation; NTD=New Taiwan Dollars; CAD=Coronary artery disease; COPD=chronic obstructive pulmonary disease

<sup>c</sup>The dependent insurers were not included.

<sup>d</sup>Based on  $\chi^2$  test

<sup>e</sup>Based on a Student's t test

1 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) <sup>a,b</sup>		Crude HR (95% CI)	AHR (95% CI)	ID (95% CI) <sup>a,b</sup>		Crude HR (95% CI)	AHR (95% CI)
	Control group	PD group			Control group	PD group		
<b>Male</b>								
<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) <sup>c</sup>	2.61 (2.13 - 3.09)	17.57 (14.48 - 20.67)	6.93 (5.38 - 8.93)	3.82 (2.79 - 5.22) <sup>c</sup>
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) <sup>c</sup>	9.23 (8.16 - 10.30)	32.27 (27.02 - 37.52)	3.65 (2.98 - 4.47)	3.06 (2.41 - 3.89) <sup>c</sup>
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) <sup>c</sup>	14.01 (12.77 - 15.25)	38.05 (32.58 - 43.51)	2.87 (2.42 - 3.41)	2.26 (1.85 - 2.75) <sup>c</sup>
≥ 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) <sup>c</sup>	18.94 (17.31 - 20.57)	41.87 (35.34 - 48.40)	2.25 (1.87 - 2.69)	1.90 (1.55 - 2.33) <sup>c</sup>
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) <sup>d</sup>	10.27 (9.74 - 10.81)	30.33 (27.93 - 32.73)	3.02 (2.75 - 3.33)	2.44 (2.19 - 2.73) <sup>d</sup>
<b>Female</b>								
<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) <sup>c</sup>	3.35 (2.85 - 3.86)	22.23 (18.98 - 25.49)	7.14 (5.78 - 8.81)	4.27 (3.25 - 5.63) <sup>c</sup>
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) <sup>c</sup>	10.81 (9.62 - 12.00)	33.61 (28.25 - 38.97)	3.29 (2.71 - 4.01)	2.82 (2.25 - 3.53) <sup>c</sup>
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) <sup>c</sup>	17.61 (16.04 - 19.18)	43.22 (36.70 - 49.70)	2.56 (2.14 - 3.07)	2.30 (1.88 - 2.81) <sup>c</sup>

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

In the first time partition ( $\leq 1$  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 ( $p = 0.23$ ).

<sup>a</sup>ID= incidence density (per 1,000 person-years), CI=confidence interval, AHR=adjusted hazard ratio, HR=hazard ratio

<sup>b</sup>Based on Poisson assumption

<sup>c</sup>Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for age and sex.

<sup>d</sup>Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for sex.

<sup>e</sup>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.

\* $P < 0.05$

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

Variables	≤ 1 years				>1 years			
	ID (95% CI) <sup>a,b</sup>		Crude HR (95% CI)	AHR (95% CI)	ID (95% CI) <sup>a,b</sup>		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) <sup>c</sup>	8.57 (8.13 - 9.01)	27.99 (25.45 - 30.53)	3.36 (3.02 - 3.73)	3.05 (2.69 - 3.45) <sup>c</sup>
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) <sup>c</sup>	14.80 (14.03 - 15.56)	33.14 (30.81 - 35.48)	2.29 (2.09 - 2.50)	2.07 (1.87 - 2.28) <sup>c</sup>
				Interaction: <i>p</i> =0.01				Interaction: <i>p</i> <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) <sup>c</sup>	10.15 (9.74 - 10.56)	29.39 (27.48 - 31.29)	2.97 (2.75 - 3.21)	2.47 (2.26 - 2.70) <sup>c</sup>
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) <sup>c</sup>	15.46 (14.13 - 16.79)	36.57 (32.61 - 40.53)	2.42 (2.10 - 2.78)	2.21 (1.89 - 2.59) <sup>c</sup>
				Interaction: <i>p</i> =0.09				Interaction: <i>p</i> =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) <sup>c</sup>	10.11 (9.69 - 10.52)	29.77 (27.73 - 31.81)	3.02 (2.79 - 3.28)	2.58 (2.35 - 2.83) <sup>c</sup>
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) <sup>c</sup>	14.85 (13.66 - 16.04)	33.69 (30.47 - 36.91)	2.32 (2.05 - 2.63)	2.04 (1.77 - 2.35) <sup>c</sup>
				Interaction: <i>p</i> =0.02				Interaction: <i>p</i> =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) <sup>c</sup>	9.99 (9.59 - 10.39)	29.39 (27.37 - 31.40)	3.03 (2.80 - 3.29)	2.71 (2.48 - 2.97) <sup>c</sup>	
	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) <sup>c</sup>	19.94 (18.09 - 21.80)	34.66 (31.36 - 37.97)	1.73 (1.52 - 1.98)	1.68 (1.46 - 1.94) <sup>c</sup>	
				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) <sup>c</sup>	10.49 (10.08 - 10.90)	30.64 (28.73 - 32.54)	2.99 (2.78 - 3.23)	2.51 (2.30 - 2.73) <sup>c</sup>	
	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) <sup>c</sup>	13.82 (12.40 - 15.23)	32.52 (28.46 - 36.58)	2.42 (2.05 - 2.84)	2.02 (1.68 - 2.43) <sup>c</sup>	
				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) <sup>c</sup>	10.21 (9.79 - 10.63)	29.59 (27.62 - 31.56)	2.98 (2.76 - 3.23)	2.54 (2.32 - 2.78) <sup>c</sup>	
	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) <sup>c</sup>	13.77 (12.70 - 14.84)	34.86 (31.31 - 38.41)	2.56 (2.25 - 2.91)	2.11 (1.82 - 2.45) <sup>c</sup>	
				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) <sup>d</sup>	7.48 (7.01 - 7.96)	24.63 (21.32 - 27.94)	3.40 (2.93 - 3.96)	3.52 (2.97 - 4.16) <sup>d</sup>	
	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) <sup>d</sup>	11.76 (10.87 - 12.65)	28.61 (24.94 - 32.27)	2.47 (2.13 - 2.87)	2.67 (2.27 - 3.13) <sup>d</sup>	
	$\geq 2$	15.08	122.57	8.01	4.90	15.28	34.21	2.28	2.11	

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

	(12.65 - 17.52)	(110.65 - 134.5)	(6.63 - 9.66)	(4.01 - 5.99) <sup>d</sup>	(14.43 - 16.12)	(31.83 - 36.60)	(2.08 - 2.49)	(1.92 - 2.32) <sup>d</sup>
			Interaction: <i>p</i> =0.01				Interaction: <i>p</i> <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) <sup>e</sup>	9.73 (9.30 - 10.15)	28.39 (26.09 - 30.70)	3.00 (2.73 - 3.29)	2.67 (2.41 - 2.97) <sup>e</sup>
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) <sup>e</sup>	14.92 (13.70 - 16.13)	34.79 (31.34 - 38.25)	2.38 (2.09 - 2.71)	2.11 (1.83 - 2.44) <sup>e</sup>
≥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) <sup>e</sup>	13.93 (12.36 - 15.51)	32.35 (28.45 - 36.24)	2.32 (1.96 - 2.73)	2.07 (1.71 - 2.51) <sup>e</sup>
			Interaction: <i>p</i> =0.01				Interaction: <i>p</i> =0.01	

<sup>a</sup>ID= incidence density, CI=confidence interval

<sup>b</sup>Based on Poisson assumption

<sup>c</sup>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.

<sup>d</sup>Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for comorbidities.

<sup>e</sup>Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for Charlson's score.

\* *P*<0.05

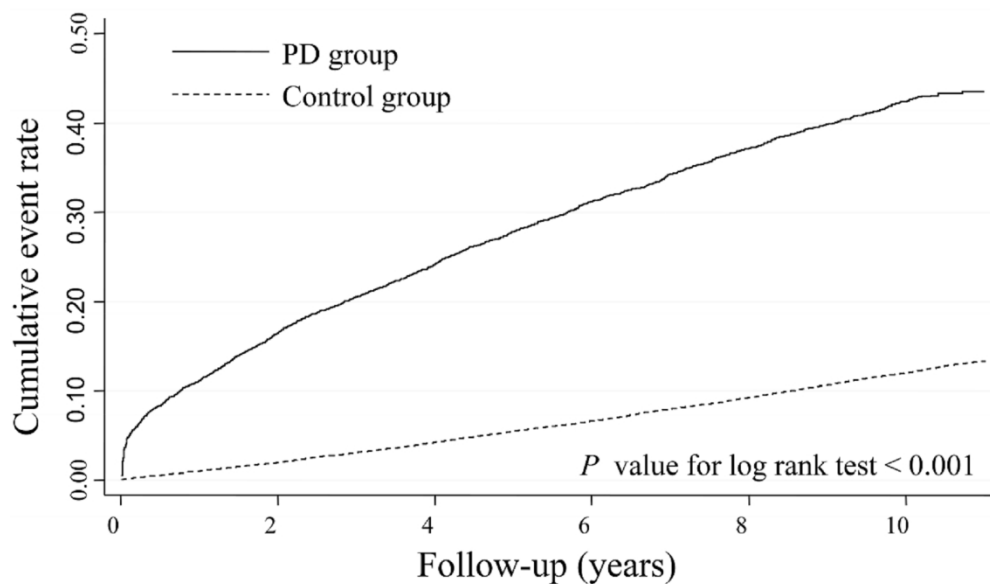


Figure 1 Comparison of Kaplan-Meier failure estimates of dementia onset between the two groups. PD, Parkinson's disease.

153x90mm (300 x 300 DPI)

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

	<b>Item No</b>	<b>Page No</b>	<b>Recommendation</b>
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants
		6-7	(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy
		-	(e) Describe any sensitivity analyses

<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	15*	10-12	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time
		-	<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure
		-	<i>Cross-sectional study</i> —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
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).