PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk of Dementia after Parkinson's Disease in Taiwan: A Population-based Retrospective Cohort Study Using National Health Insurance Claims
AUTHORS	Liu, Chih-Ching; Sun, Yu; Lee, Pei-Chen; Li, Chung-Yi; Hu, Susan

VERSION 1 – REVIEW

REVIEWER	Oliver Riedel Leibniz-Institute for Prevention Resarch and Epidemiology, Germany
REVIEW RETURNED	02-Aug-2018

GENERAL COMMENTS	The presented study investigated the incidence of dementia in incident cases of Parkinson's disease as compared to matched controls without PD. The analyses were based on national health claims data, covering more than ten data years. The authors report a significant increased risk of dementia in PD patients as compared to controls, especially within the first year after the initial PD diagnosis. The paper is well written, the editing of the data is fine, and the underlying study has a sound methodology, taking several source of bias into account. All conclusions as drawn from the data are appropriate. I have only few comments: 1. One major drawback of the paper is that in my opinion the authors do not make the novelty aspects of their work clear enough. The fact that PD is associated with an elevated risk of dementia has been reported previously (eg. in the Rotterdam study, which is cited by the authors or by the works of Murat Emre and colleagues). The authors should work out more the benefits of their approach, especially in the introduction. 2. While considering and investigating the impact of single comorbidities on the risk of developing dementia, sum scores such as the Elixhauser measure or the Charlson Comorbidity index (both of which can be generated with claims data), would have also been of interest. If possible these should

	added at least descriptively. Minor comments refer to: 3. Page 12, line 15: "….positive effects for dementia….". What do the authors mean by that? Positive effects in terms of increasing the risk for dementia or positive effects in terms of protective factors? This is not clear and should be specified. 4. Page 7, line 36: I suggest the authors either use the plural forms ("analyses") or add "an" to each "analysis"

REVIEWER	Gerhard Ransmayr Dept. of Neurology II, Kepler University Hospital, A-4020 Linz, Austria
REVIEW RETURNED	10-Aug-2018

GENERAL COMMENTS	This is a retrospective national study on PD patients examined and recruited from sources from the national health insurance system of Taiwan. PD patients are compared to controls. One should comment on the potential differences between inpatient and outpatient recruitment of PD patients, the differences in the vascular risk profile, insurance premium, urbanization status, geogaphic area and occupational status between the PD patients and the controls. It should be clarified by a statistician whether these differences could be ruled out by statistical methods (multivar. Cox . The manuscript should be edited by a language expert in medical English for linguistic flaws. The conclusion in the abstract is a repetition of the results. Were PD patients with and without dementia at 1st diagnosis included or not? The discussion deals partly with aspect which are not part of the study, such as degenerative pathology in PD dementia page 10.

REVIEWER	Dr Peter Hobson Academic Unit, Betsi Cadwaladr University Health Board North Wales United Kingdom
REVIEW RETURNED	15-Aug-2018

GENERAL COMMENTS	This investigation sets explore the incidence and relative risks (RR) for the development of dementia in patients with Parkinson's disease (PD) by selected demographic and co-morbid risks. However, since it is a retrospective analysis of a National Health Insurance (NHI) program relying on ICD coding alone, it inevitably lacks a lot of clinical detail, such as autonomic dysfunction, medication response/side effects, disease severity, HRQoL, neuropsychiatric disturbance, occupational and or environmental exposure, genetic, etc, which are normally explored in population studies. This manuscript in general also suffers from grammatical and typographical errors. I am aware that the English language may not be the first language of the authors and would therefore suggest that they seek some assistance to address these issues. I have outlined a number of points the authors may wish to

	consider. Title: The title needs to clearly state that this is a retrospective cohort study drawn solely from the Taiwan NHI program. Introduction: This is a reasonably good review of the existing literature and as the authors point out there is a lack of reported studies from Asia. I could not quite follow the statements made in P4 lines 32-36. , where, it is suggested that death is a competing risk factor for dementia in PD. I assume that they mean cases who die during a period of observation are censored, thus potentially over or underestimating the true risk for dementia in PD. This sentence (assuming this is what it means), would need to be edited for greater clarity. Methods: Data source: The sample of PD and controls was drawn exclusively from the Taiwan NHIA databases where 99% of the population are enrolled. It is not exactly clear to me what information is held on patients in the database, but from what I can gather all of the recorded information is based upon ICD-9 coding alone. Perhaps the authors could give some further detail on what is collected for greater clarity for the reader. Study design, Cohorts & Covariates. P5 lines 51-55, suggest that the method they used to identify PD cases is a valid method. There is no clear rationale for this and there is no reference for this statement. This needs to be expanded and justified with supportive empirical evidence. PD diagnosis: 1. This is based I believe, solely on the recorded ICD codes. I find this difficult to accept that even in the best clinical hands the accuracy of diagnosis rarely (if ever!) exceeds 90%. Readers need to know exactly how the diagnosis of PD was reached and by whom and in addition, the criteria employed to reach the diagnosis. In addition, first recorded diagnosis (ICD code), is not necessarily the onset of PD symptoms. I feel that this is a major methodological weakness of the current investigation because the majority of previous population investigations have physically examined and reviewed the diagnosis of their patients in a clinical or population setting, rather than relying upon ICD data entry codes alone to confirm a diagnosis. 2. It would be useful to know how many of the cohort had their diagnosis reviewed and was changed to for example,

	parkinsonism, dementia with Lewy bodies Alzheimer's disease, or were deceased at the end of the study. I would be surprised if the entire baseline cohort's PD diagnosis remained stable. I suggest that the number of patients who had their diagnosis changed or died during the study is reported. In addition, a number of the control cohort will inevitably have developed PD or parkinsonism over the period of observation. It would be helpful if readers know how many developed PD or parkinsonism and how this was controlled for in the longitudinal analysis. 3. The assertion that incident cases of PD were identified based upon medical claims (p6 2-12) is probably not as accurate as the authors suggest, especially in view of the results, which I will discuss later. Dementia diagnosis: 1. The dementia diagnosis is based upon ICD coding alone. Again it is hard to determine the true accuracy of this diagnosis, because most population's base their findings on clinical assessment and application of criteria for dementia. 2. I would suggest that they consult with a clinician to assist in the description on how a "dementia" diagnosis is reached in clinics in Taiwan. Statistical analysis: Main outcome, dementia is clearly defined. Fine and Gray's proportional method is very poorly described and in general and I am not convinced that this was the most appropriate method for analysis, although marginally better than a cause specific HR model. The outline of the statistical analysis is not clearly described and in view of statistical analysis employed, I would suggest that an expert in epidemiology and or biostatistics is consulted to review the accuracy of the statistical methodology and outcomes reported in this investigation. The Hazard ratio (HR) models reported throughout the manuscript I assume are being interpreted as the relative risk (RR). Although the HR and RR are often reported as being one and the same, they are not and the terms should interchangeable. I would suggest removing RR throughout the text replacing it with HR's. Results: P 8 paragraph 1: When reporting differences within the cohort the p-values should be reported. P8 paragraph 3: Person-years, and HR results 95% CI's should be reported. I feel that the finding that the HR reported for dementia within one year of being reported on the NHI program serves to highlight the methodological weakness of the study. I suspect a number of patients with pre-existing cognitive impairment and PD were classed as new cases because their condition

	had deteriorated and had only been recognised because they had been referred for an expert opinion. In other words, many would have had the condition for a number of years before seeking medical intervention. This is also supported by the decline in the numbers of PD patients with dementia in the subsequent period of observation. This may also explain the differences observed on the risk of dementia by co-morbidly (Table 3), between the < 1 years and > 1 year cohorts. In other words the > 1 year cohort had a longer period of time to develop significant co-morbidities. Discussion: As I have discussed in the results section, I do not feel that the finding that the HR for dementia was much higher within one year of an ICD code being entered into the NHI database, is reliable. Despite this, the findings reported here are important and support previous investigations reports on the significant association with PD and dementia. In particular, the call for earlier assessment and detection for cognitive impairment in PD is and excellent suggestion. Perhaps the authors could in light of re-structure their discussion to reflect this. I feel that the methodology overall weakens the investigation because of the other known risk factors, particularly non-motor symptoms (apart from the co-morbidities reported), are equally if not more important predictors for the development of dementia in PD. In addition, it is known that a significant proportion of PD patients have mild a cognitive impairment (ICD-9 code: 331.83), which in longitudinal investigations has been shown to progresses to dementia. The authors do not seem to have considered this in their analysis or discussion and should be addressed. In general, the discussion is quite long could be edited because some parts tend to drift off in speculation rather than focusing on the aims of the investigation. Conclusion. This is a publishable study, which I feel with careful editing, particularly addressing the methodological shortcomings will add to the strong association with PD and dementia in the literature. I do hope that the authors do re-submit and do not feel too despondent with my comments.

VERSION 1 – AUTHOR RESPONSE

Dear Dr. Riedel (Reviewer 1):

Thank you very much for reviewing our manuscript. Your suggestions are indeed very helpful for us to clarify the content of the study. We have revised our manuscript according to your comments and would like to describe our change as follows:

#1. One major drawback of the paper is that in my opinion the authors do not make the novelty aspects of their work clear enough. The fact that PD is associated with an elevated risk of dementia has been reported previously (e.g. in the Rotterdam study, which is cited by the authors or by the works of Murat Emre and colleagues). The authors should work out more the benefits of their approach, especially in the introduction.

Authors' reply:

Thank you very much for pointing out this important perspective. The novelty of this study is as follows: First, instead of using prevalent cases of PD as in previous studies, we estimated the incident dementia case among patients with newly diagnosed PD. We aimed to assess the time of developing dementia in patients with PD diagnosed within and after one year. Second, age- and sex- specific and selected comorbidity stratified dementia incidence rate in PD were analysed in present study to see if there are gender differences in dementia incidence and the diagnosed age of PD. Third, because of the increased age and co-morbidities in this long-term follow-up study, competing risk of death should be considered. The competing risk approach in this study made it different from previous studies with the traditional Cox proportional hazards model. We revised the manuscript in the Introduction section to clearly explain the novelty of this study (Page 4, Line 5-25; Page 5, Line 1-13).

#2. While considering and investigating the impact of single comorbidities on the risk of developing dementia, sum scores such as the Elixhauser measure or the Charlson Comorbidity index (both of which can be generated with claims data), would have also been of interest. If possible these should added at least descriptively.

Authors' reply:

This is very good suggestion. We followed the Reviewer's suggestion by investigating the effect of the Charlson Comorbidity Index on the risk of developing dementia. The

Charlson Comorbidity Index is described in the Methods section (Page 8, lines 2-5), and the results of the re-analysis using Charlson Comorbidity index as an independent variable are provided in the revised manuscript (Revised Table 1, Table 3, and text on Page 10, lines3-4; Page 11, lines 14, 22-25; Page 11, lines 21-23).

#3. Page 12, line 15: "….positive effects for dementia….". What do the authors mean by that? Positive effects in terms of increasing the risk for dementia or positive effects in terms of protective factors? This is not clear and should be specified.

Authors' reply:

Thanks for your comment. We revised the statement "….positive effects for dementia…." to "….increasing the risk of dementia." (Page 14, Line 14)

#4. Page 7, line 36: I suggest the authors either use the plural forms ("analyses") or add "an" to each "analysis"

Authors' reply:

We corrected the errors (Page 9, line 12).

Dear Dr. Ransmayr (Reviewer 2):

Thank you very much for reviewing our article. Your suggestions are very constructive. We revised our manuscript according to your comments and would like to describe our changes as follows:

#1. One should comment on the potential differences between inpatient and outpatient recruitment of PD patients, the differences in the vascular risk profile, insurance premium, urbanization status, geogaphic area and occupational status between the PD patients and the controls. It should be clarified by a statistician whether these differences could be ruled out by statistical methods (multivar. Cox)

Authors' reply:

Thanks you very much for this constructive suggestion. The objective of this study was to assess incident dementia among PD cases. Both inpatient and outpatient PD cases were recruited to minimize the selection bias. We compared these characteristics between the inpatient and outpatient recruitment of PD patients and found that inpatient PD patients had higher prevalent rates of vascular risk factors for dementia, a lower insurance premium, and fewer white-collar workers than the outpatient PD patients. Urbanization status and geographic area were similar in both groups. The adjusted hazard ratios of dementia both in the overall PD cases and in the PD cases only enrolled in the outpatient group were significantly higher than those in the control group without PD. Please see the following Table. We summarized the above information in the revised manuscript (Page 10, lines 9-12).

Table A. Characteristics of inpatient PD patients vs. outpatient PD patients.

	PD group		Control group		
Variables[a]	n	%	n	%	P value
History of comorbidity					
Without comorbidities	1113	20.5	37	7.5	<0.0001 [d]

Hypertension	3231	59.4	347	70.5	<0.0001 [d]
Diabetes	1283	23.6	147	29.9	<0.0001 [d]
CAD	1765	32.4	190	38.6	0.0053 [d]
Stroke	1705	31.3	272	55.3	<0.0001 [d]
Hyperlipidemia	981	18.0	108	21.6	0.0316 [d]
COPD	1551	28.5	168	34.2	0.0083 [d]
Insurance premium (NTD)[b]					<0.0001 [e]
Dependent	2151	40.1	182	37.1	
<Median (19,200)	1540	28.7	194	39.6	
>=Median	1673	31.2	114	23.3	
Mean (±SD)[c]	7261.3±11259.6		5365.4±9332.9		
Urbanization status					0.3560[d]
Urban	2935	54.7	268	54.7	
Satellite city/town	1902	35.5	183	37.4	
Rural area	527	9.8	39	8.0	
Geographic area					0.1571 [d]
Northern	2456	45.8	214	43.7	
Central	1355	25.2	136	27.7	
Southern	1400	26.1	119	24.3	
Eastern	153	2.9	21	4.3	
Occupational status					0.0003 [d]
White collar	1374	25.3	108	22.0	
Blue collar	1930	35.5	145	29.5	
Others	2136	39.3	239	48.6	
Total	5440	100.0	492	100.0	

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

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

[c]The dependent insurers were not included.

[d]Based on χ^2 test

Table B: Impact of Parkinson's disease on the risk of dementia by recruitment sources of PD patients

Variables	≦1 years		>1 years	
	Crude HR [a] (95% CI)	AHR [a,b] (95% CI)	Crude HR [a] (95% CI)	AHR [a,b] (95% CI)
Overall (Inclusion of inpatient and outpatient PD patients)	11.54 (10.04-13.27)	6.43 (5.46-7.57)[b]	2.93 (2.75- 3.14)	2.42 (2.23- 2.61)[b]
Overall (Only inclusion of outpatient PD patients)	10.88 (9.43-12.55)	6.24 (5.28-7.38) [b]	2.91 (2.71- 3.12)	2.42 (2.24- 2.63) [b]

[a]AHR=adjusted hazard ratio, HR=hazard ratio,

[b]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.

*P<0.05

#2. The manuscript should be edited by a language expert in medical English for linguistic flaws.

Authors' reply:

Thank you for the comment. This revised manuscript has been edited by a professional native English editor from the Foreign Language Center at National Cheng Kung University. Revisions related to the linguistic flaws have been made according to suggestions from this medical English expert. All the changes made in the revised manuscript are marked with 'tracked changes'. We also showed a clean copy of these revision in the main document file of revised manuscript (page 2, lines 6, 18, 20; page 3, lines 4-5, 7; page 4, lines 9-10; page 5, lines 9-12, 24-25; page 6, lines 3-5,7,10, 13-16, 23; page 7, line 6; page 8, lines 1,11,15; page10, line 12; page11, lines 11-12, 14, 17-18, 24; page 12, lines 1-2, 8; page 13, lines 5,

12, 21; page 14, lines 3, 10,12,16-19, 24; page 15, lines 11-12, 25; page 16, lines 3, 5, 15-16, 22-23; page 17, lines 11, 18-19; page 22, line7; page 25, line1).

#3. The conclusion in the abstract is a repetition of the results.

Authors' reply:

We revised the conclusion as" "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" (Page 2, Lines 22-24).

#4. Were PD patients with and without dementia at 1st diagnosis included or not?

Authors' reply:

This study was aimed toward assessing 11 years of incidence and the relative risks for developing dementia in patients with PD compared with matched controls. Thus, we only included PD patients without dementia at first diagnosis at baseline in this study. We excluded those who had three or more medical claims (either ambulatory or inpatient care) with diagnostic codes of dementia prior to the index date. We provided this information in the original Methods section (Page 7, lines 4-6).

#5. The discussion deals partly with aspect which are not part of the study, such as degenerative pathology in PD dementia page 10.

Authors' reply:

Thanks for your expert commentary. As suggested, we eliminated the text regarding potential mechanisms contributing to dementia in patients with PD in the discussion, which was not focused on the aims of the study.

Dear Dr. Hobson (reviewer 3):

Thank you so much for reviewing our article. We appreciate your great contributions in the field of epidemiology and evaluation. Your suggestions are very constructive. We have revised our manuscript according to your comments and would like to discuss our changes as follows:

#1. This investigation sets explore the incidence and relative risks (RR) for the development of dementia in patients with Parkinson's disease (PD) by selected demographic and co-morbid risks. However, since it is a retrospective analysis of a National Health Insurance (NHI) program relying on ICD coding alone, it inevitably lacks a lot of clinical detail, such as autonomic dysfunction, medication response/side effects, disease severity, HRQoL, neuropsychiatric disturbance, occupational and or environmental exposure, genetic, etc, which are normally explored in population studies.

Authors' reply:

Thanks for your comprehensive review of this paper. This is a retrospective cohort study aimed to compare the dementia incidence between PD and control cohorts. Since the control subjects were selected from those who had never been diagnosed with PD during the whole study period, we don't need to consider the condition of PD related symptoms, PD severity, response or side effects to PD medicine and PD related exposure risk factors in the control cohort. Thus, whether performing detailed analyses on the aforementioned characteristics only in PD cohort did not affect the final results of this study.

#2. This manuscript in general also suffers from grammatical and typographical errors. I am aware that the English language may not be the first language of the authors and would therefore suggest that they seek some assistance to address these issues.

Authors' reply:

Thank you for the comment. This revised manuscript was edited by a professional native English editor from the Foreign Language Center at National Cheng Kung University. Revisions related to linguistic flaws have been made according to the suggestions from this medical English expert. All the changes made in the revised manuscript are marked with 'tracked changes'. We also showed a clean copy of these revision in the main document file of revised manuscript (page 2, lines 6, 18, 20; page 3, lines 4-5, 7; page 4, lines 9-10; page 5, lines 9-12, 24-25; page 6, lines 3-5,7,10, 13-16, 23; page 7, line 6; page 8, lines 1,11,15; page10, line 12; page11, lines 11-12, 14, 17-18, 24; page 12, lines 1-2, 8; page 13, lines 5, 12, 21; page 14, lines 3, 10,12,16-19, 24; page 15, lines 11-12, 25; page 16, lines 3, 5, 15-16, 22-23; page 17, lines 11, 18-19; page 22, line7; page 25, line1).

#3. Title: The title needs to clearly state that this is a retrospective cohort study drawn solely from the Taiwan NHI program.

Authors' reply:

Thanks for your valuable suggestions. We revised the title to be: "Risk of Dementia after Parkinson's Disease: A Population-based Retrospective Cohort Study Using National Health Insurance Claims" (Page 1, lines 1-2).

#4. Introduction: This is a reasonably good review of the existing literature and as the authors point out there is a lack of reported studies from Asia. I could not quite follow the statements made in P4 lines 32-36. , where, it is suggested that death is a competing risk factor for dementia in PD. I assume that they mean cases who die during a period of observation are censored, thus potentially over or underestimating the true risk for dementia in PD. This sentence (assuming this is what it means), would need to be edited for greater clarity.

Authors' reply:

Thank you for pointing out this important fact. As has been mentioned, mean cases who die during a period of observation are censored, thus potentially over or underestimating the true risk for dementia in PD. Therefore, it is suggested that death is a competing risk factor for dementia in PD. We provided the above clarifications in the revised manuscript (Page 5, lines10-11). We also added the following text in the revised manuscript: "because of the increased age and co-morbidities in the long-term follow-up study, competing risk of death should be considered." (Page 5, lines10-11)

#5. Methods/ Data source: The sample of PD and controls was drawn exclusively from the Taiwan NHIA databases where 99% of the population are enrolled. It is not exactly clear to me what information is held on patients in the database, but from what I can gather all of the recorded information is based upon ICD-9 coding alone. Perhaps the authors could give some further detail on what is collected for greater clarity for the reader.

Authors' reply:

Thanks for pointing out the unclear descriptions. The data analysed in this study were retrospectively retrieved from NHI dataset claims, which provide inpatient and ambulatory medical records mainly including patient demographics (gender, date of birth), medical facility visited, department visited, ICD-9-CM codes, procedure (ex. drug or diagnostic procedure), date of hospitalization and discharge, operational code, for around 99% of the Taiwanese people. These data provide important resources for disease prevalence and comorbidity measurement. Other major strengths of using NHI data are the use of a large, nationally representative population-based cohort, with little possibility of recall and selection bias and little likelihood of nonresponsive and loss to follow-up of cohort members [1-2]. The information has been described in the original manuscript (Page 14, line 25; Page 15, lines 1-4). Additionally, the NHI datasets have been used in many published epidemiologic studies on PD [1-2] and dementia [3]. We added the above statements into the revised manuscript (Page 6, lines 8-9).

References:

1. Sun Y, Chang YH, Chen HF, Su YH, Su HF, Li CY. Risk of Parkinson disease onset in patients with diabetes: a 9-year population-based cohort study with age and sex stratifications. Diabetes Care. 2012 May;35(5):1047-9.
2. Shen CC, Tsai SJ, Perng CL, Kuo BI, Yang AC. Risk of Parkinson disease after depression: a nationwide population-based study. Neurology. 2013 Oct 22;81(17):1538-44.
3. Chiang CJ, Yip PK, Wu SC, Lu CS, Liou CW, Liu HC, et al. Midlife risk factors for subtypes of dementia: a nested case-control study in Taiwan. Am J Geriatr Psychiatry. 2007;15(9):762-71.

#6. Study design, Cohorts & Covariates: P5 lines 51-55, suggest that the method they used to identify PD cases is a valid method. There is no clear rationale for this and there is no reference for this statement. This needs to be expanded and justified with supportive empirical evidence.

Authors' reply:

Thanks for your constructive comments. We conducted a pilot study to validate the accuracy of ICD-9 coding in PD patients previously [1]. In the validation study, medical records including symptoms/signs, diagnostic procedure, use of anti-parkinsonism medication, as well as responses to medication of 290 randomly selected patients with ICD-9-CM coded 332.0 were examined in detail by three experienced neurologists from January 2012 to October 2012. Among these 290 cases, 245 were confirmed as PD patients based on the aforementioned clinical information. The sensitivity, specificity, positive predictive value, and negative predictive value were 97.6%, 92.3%, 98.8% and 85.7%, respectively. The accuracy of our method for identifying PD cases was 96.9%. We provided this information in the revised manuscript (Page 7, lines 8-18).

In addition, cases in this study were not only ascertained from the ICD code, but we also required patients to have had prescriptions with at least three courses of anti-Parkinsonism medication including L-dopa or dopamine agonist to minimize the possibility of miscoding. As for the onset time of PD, since PD is characterized by a gradual onset and is a slow, progressive degenerative disease, it is sometimes difficult to identify the exact onset time of

PD in clinical practice. Thus, we chose first diagnostic time as the main point in our study design. In this study using a nationwide dataset, we were able to precisely identify the exact diagnostic date of PD at nearly all the hospitals and clinics in Taiwan.

Reference:

[1] 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 disease 2016; 2016:8756359.

#7. PD diagnosis: This is based I believe, solely on the recorded ICD codes. I find this difficult to accept that even in the best clinical hands the accuracy of diagnosis rarely (if ever!) exceeds 90%. Readers need to know exactly how the diagnosis of PD was reached and by whom and in addition, the criteria employed to reach the diagnosis. In addition, first recorded diagnosis (ICD code), is not necessarily the onset of PD symptoms. I feel that this is a major methodological weakness of the current investigation because the majority of previous population investigations have physically examined and reviewed the diagnosis of their patients in a clinical or population setting, rather than relying upon ICD data entry codes alone to confirm a diagnosis.

Authors' reply:

Thanks for your insightful comments, and we totally agree with your criticism. Please see the authors' response to comment #6.

#8. It would be useful to know how many of the cohort had their diagnosis reviewed and was changed to for example, parkinsonism, dementia with Lewy bodies, Alzheimer's disease, or were deceased at the end of the study. I would be surprised if the entire baseline cohort's PD diagnosis remained stable. I suggest that the number of patients who had their diagnosis changed or died during the study is reported. In addition, a number of the control cohort will inevitably have developed PD or

Parkinsonism over the period of observation. It would be helpful if readers know how many developed PD or Parkinsonism and how this was controlled for in the longitudinal analysis.

Authors' reply:

Thanks for your suggestions. We considered the possibility of a change in diagnoses over follow-up time in clinical practice. Thus, the cases in this study had to have had at least three ambulatory or inpatient visits with PD diagnoses and prescriptions. The first and last visit had to be more than 90 days apart during the study period, which would largely decrease the likelihood of disease misclassification. Whether or not the PD cases would develop cognitive decline with an additional diagnosis of dementia is the primary outcome of this study.

During the study period, a total of 1,836 PD patients developed dementia, and 1,226 PD patients died without developing dementia. In the same study period, a total of 3,l59 control subjects developed dementia, and 5,223 control subjects died without developing dementia. We provided this information in the revised manuscript (Page 10, Lines 14-16).

However, because of a data limitation related to a lack of information on symptoms/signs, lab data, and image findings, further outcome analyses with dementia subtype classifications, such as dementia with Lewy bodies (DLB), Alzheimer's dementia, frontotemporal dementia, or simply Parkinson's disease dementia (PDD), were not conducted. However, according to the criteria set forth by the consensus report of the Lewy Body Consortium [1], clinicians and researchers use the "1-year rule" to help verify the diagnoses of DLB and PDD. This is one of the reasons why we analyzed dementia incidence within and after one year of PD diagnoses, respectively. We also added the above information in the revised manuscript (Page 8, lines 15-22).

Regarding the Reviewer's question about the diagnoses changing over time in the control subjects, the study design excluded any individual in the control group either having a PD diagnosis or having been treated with any anti-PD medications during the entire study period. We provided the above information in the revised manuscript (Page 7, Line19-20).

Reference:

1. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. Neurology (2017) 89:88–100.10.

#9. The assertion that incident cases of PD were identified based upon medical claims (p6 2-12) is probably not as accurate as the authors suggest, especially in view of the results, which I will discuss later.

Authors' reply:

Please see the authors' response to comment #6.

#10. Dementia diagnosis: The dementia diagnosis is based upon ICD coding alone. Again it is hard to determine the true accuracy of this diagnosis, because most population's base their findings on clinical assessment and application of criteria for dementia. I would suggest that they consult with a clinician to assist in the description on how a "dementia" diagnosis is reached in clinics in Taiwan.

Authors' reply:

Thanks for the comments. The main outcome variable was the initial occurrence of dementia (ICD-9-CM code: 290, 294.1, 331.0, and 331.82). To increase the validity of dementia identification, only dementia cases diagnosed with ≥3 ambulatory visits or ≥1 hospitalization were included in this study. We agree with the Reviewer that it is necessary to report the accuracy of dementia diagnosis when this diagnosis is based on ICD coding alone. A Taiwanese study reported that the diagnostic accuracy of dementia is approximately 90% when relying on diagnosis codes (ICD-9-CM) to identify dementia [1].

This study validated the diagnosis of dementia in NHI claims by analyzing the medical charts and neuroimaging records of dementia patients treated by neurologists or psychiatrists

in 48 hospitals from January 2000 to December 2002. Dementia diagnosis included senile dementia, Alzheimer's disease, and vascular dementia (ICD-9-CM codes of 290, 290.0, 290.1, 290.2, 290.3, 290.4, 294.8, 331.0). We provided this information in the revised manuscript (Page 8, lines 12-13).

Reference:

1. Chiang CJ, Yip PK, Wu SC, Lu CS, Liou CW, Liu HC, et al. Midlife risk factors for subtypes of dementia: a nested case-control study in Taiwan. Am J Geriatr Psychiatry. 2007;15(9):762-71.

#11. Statistical analysis: Fine and Gray's proportional method is very poorly described and in general and I am not convinced that this was the most appropriate method for analysis, although marginally better than a cause specific HR model. The outline of the statistical analysis is not clearly described and in view of statistical analysis employed, I would suggest that an expert in epidemiology and or biostatistics is consulted to review the accuracy of the statistical methodology and outcomes reported in this investigation.

Authors' reply:

Thanks for your expert commentary. One of our corresponding authors is an epidemiologist provided expert advice for the analysis. In response to your comments, we compared the hazard ratios from the cause-specific and sub-distribution hazard models. In the first partition (≦1 years), the results of the association between PD and risk of dementia changed largely when we used the cause-specific hazard models. This may be due to the fact that only 86 PD patients (1.45%) and 522 control subjects (1.69%) died without developing dementia in the first partition (≦1 years). Thus, the competing risk was low in the first partition. If we employed the Fine and Gray's proportional method to estimate the association between PD and dementia incidence in the presence of competing risks, the findings would be largely different from the results analyzed from cause-specific hazard models where the competing event is removed.

In the second partition (> 1 years), 1,226PD patients (20.67%) and 5,223 control subjects (18.63%) died without developing dementia. Thus, death is the competing risk of dementia occurrence, so analytical approaches used in a competing risk setting were necessary to assess the association between PD and the risk of dementia in our study. The results of the association between PD and risk of dementia only changed slightly when we used the cause-specific hazard models in the second partition (> 1 years). Please see the following table. The impact of use of cause-specific hazards models on our findings is thus likely to be small in the second partition (> 1 years).

In general, cause-specific hazards models are better suited for studying the etiology of diseases, whereas the Fine-Gray model has use in prognostic research questions to calculate survival probability [1]. The major difference between cause-specific hazards models and the Fine and Gray approach is that the cause-specific hazard is the instantaneous risk of dying from a particular cause k given that the subject is still alive at time t [2]. The Fine-Gray model can be used to model the cumulative incidence function [1]. Since we were interested in the pure effect of how PD affects the risk of dementia, we preferred reporting the data using the cause-specific hazard model in our analysis. We added this information to the revised manuscript (Page 9, lines 4-11).

References:

A. Noordzij M, Leffondre K, van Stralen KJ, et al. When do we need competing risks methods for survival analysis in nephrology? Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2013;28(11):2670-7.
B. Prentice RL, Kalbfleisch JD, Peterson AV, Jr., et al. The analysis of failure times in the presence of competing risks. Biometrics 1978;34(4):541-54

Table C. 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			
	Cause-Specific Hazards Models		Subdistribution Hazards Models		Cause-Specific Hazards Models		Subdistribution Hazards Models	
	Crude HR (95% CI)	AHR (95% CI)	Crude SHR (95% CI)	ASHR (95% CI)	Crude HR (95% CI)	AHR (95% CI)	Crude SHR (95% CI)	ASHR (95% CI)
Male								
<70	34.44 (15.58-76.13)	15.74 (6.67-37.10)[c]	34.48 (15.60-76.23)	15.79 (6.70-37.22)[c]	6.93 (5.38-8.93)	3.82 (2.79- 5.22)[c]	6.46 (5.02-8.33)	3.78 (2.77- 5.17)[c]
70-74	19.44 (11.73-32.21)	13.00 (7.59-22.26)[c]	19.47 (11.75-32.26)	13.08 (7.64-22.38)[c]	3.65 (2.98-4.47)	3.06 (2.41-3.89)[c]	3.27 (2.68-4.00)	2.82 (2.23-3.58)[c]
75-79	16.69 (11.16-24.95)	9.84 (6.27-15.46)[c]	16.71 (11.18-24.99)	9.88 (6.30-15.50)[c]	2.87 (2.42-3.41)	2.26 (1.85-2.75)[c]	2.47 (2.08-2.94)	2.04 (1.68-2.48)[c]
≧80	8.64 (6.58-11.57)	4.35 (3.13-6.05)[c]	8.73 (6.58-11.57)	6.62 (4.70-9.31)[c]	2.25 (1.87-2.69)	1.90 (1.55-2.33)[c]	2.01 (1.68-2.41)	1.91 (1.57-2.33)[c]

Total	13.23	7.18	13.28	11.18	3.02	2.44	2.74	2.37
	(10.85-16.14)	(5.73-9.01)[d]	(10.88-16.20)	(8.64-14.46)[d]	(2.75-3.33)	(2.19-2.73)[d]	(2.49-3.02)	(2.12-2.64)[d]
Female								
<70	35.81	10.55	35.85	10.72	7.14	4.27	6.75	4.20
	(16.24-79.13)	(4.21-26.45)[c]	(16.24-79.13)	(4.29-26.81)[c]	(5.78-8.81)	(3.25-5.63)[c]	(5.48-8.33)	(3.19-5.52)[c]
70-74	12.04	4.98	12.06	5.01	3.29	2.82	3.03	2.71
	(7.40-19.60)	(2.84-8.74)[c]	(7.41-19.63)	(2.85-8.78)[c]	(2.71- 4.01)	(2.25-3.53)[c]	(2.49- 3.68)	(2.17-3.39)[c]
75-79	14.81	8.09	14.86	8.19	2.56	2.30	2.40	2.24
	(10.02-21.89)	(5.23-12.51)[c]	(10.06-21.96)	(5.30-12.64)[c]	(2.14-3.07)	(1.88-2.81)[c]	(2.01-2.87)	(1.84-2.74)[c]
≧80	5.69	3.17	5.75	3.29	1.68	1.49	.63	1.53
	(4.24-7.64)	(2.18-4.62)[c]	(4.29-7.72)	(2.28-4.77)[c]	(1.38-2.05)	(1.19-1.86)[c]	(1.34-1.99)	(1.23-1.91)[c]
Total	10.03	5.54	10.07	5.62	2.85	2.41	2.71	2.38
	(8.23-12.21)	(4.39-6.99)[d]	(8.27-12.26)	(4.46-7.09)[d]	(2.60-3.14)	(2.15-2.69)[d]	(2.46-2.98)	(2.13-2.65)[d]
Overall	11.54	6.43	11.58	9.52	2.93	2.42	2.72	2.38
	(10.04-13.27)	(5.46-7.57)[e]	(10.07-13.32)	(7.86-11.53)[e]	(2.75- 3.14)	(2.23- 2.61)[e]	(2.55- 2.91)	(2.21- 2.58)[e]

For the cause-specific hazards models, in the first time partition (≦1 years), the interactions were significant for PD with age (p<0.0001) and with sex (p= 0.0462), with age in men (p <0.0001), and with age in women (p<0.0001). In the second time partition (>1 years), the interactions were significant for PD with age (p<0.0001), with age in men (p<0.0001), and with age in women ((p<0.0001), but not for PD with sex (p= 0.2267).
For the subdistribution hazards models, in the first time partition (≦1 years), the interactions were significant for PD with age (p<0.0001) and with sex (p=0.0010), with age in men (p=0.0149), and with age in women (p<0.0001). In the second time partition (>1 years), the interactions were significant for PD with age (p<0.0001), with age in men (p<0.0001), and with age in women (p<0.0001), but not for PD with sex (p=0.6428).
[a]ID= incidence density(per 1,000 person-years), CI=confidence interval, AHR=adjusted hazard ratio, HR=hazard ratio,
[b]Based on Poisson assumption
[c]Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for age and sex.
[d]Based on Cox proportional hazard regression with competing risk analysis and adjusted for all variables, except for sex.
[e]Based on Cox proportional hazard regression with competing risk analysis and adjusted for age, sex, insurance premium, urbanization status, geographic area, occupational status, status of hypertension, diabetes, CAD, stroke, hyperlipidemia, COPD, Charlson's score, and number of medical visits.
*P<0.05

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

Variables	≦1 years				>1 years			
	Cause-Specific Hazards Models		Subdistribution Hazards Models		Cause-Specific Hazards Models		Subdistribution Hazards Models	
	Crude HR (95% CI)	AHR (95% CI)	Crude HR (95% CI)	AHR (95% CI)	Crude HR (95% CI)	AHR (95% CI)	Crude HR (95% CI)	AHR (95% CI)
Hypertension								
No	14.55 (11.79-17.95)	7.75 (6.05-9.94)[c]	14.58 (11.82-17.99)	7.85 (6.14-10.05)[c]	3.36 (3.02-3.73)	3.05 (2.69-3.45)[c]	3.18 (2.86-3.53)	2.94 (2.60-3.32)[c]
Yes	8.59 (7.12-10.37)	5.25 (4.26-6.47)[c]	8.64 (7.16-10.43)	7.71 (6.11-9.74)[c]	2.29 (2.09-2.50)	2.07 (1.87-2.28)[c]	2.15 (1.97-2.35)	2.04 (1.85-2.25)[c]
	Interaction: p= 0.0058		Interaction: p= 0.3508		Interaction: p<0.0001		Interaction: p<0.0001	
Diabetes								
No	12.45 (10.64-14.56)	6.99 (5.82-8.41)[c]	12.49 (10.68-14.61)	10.39 (8.44-12.80)[c]	2.97 (2.75-3.21)	2.47 (2.26-2.70)[c]	2.78 (2.58-3.01)	2.45 (2.24-2.68)[c]

Yes	7.99	4.43	8.05	4.49	2.42	2.21	2.24	2.10
	(5.87-10.89)	(3.16-6.22)[c]	(5.91-10.96)	(3.21-6.29)[c]	(2.10-2.78)	(1.89-2.59) [c]	(1.95-2.58)	(1.80-2.46)[c]
	Interaction: p= 0.0935		Interaction: p= 0.0081		Interaction: p=0.1891		Interaction: p= 0.1702	
CAD								
No	12.45	7.38	12.49	7.46	3.02	2.58	2.82	2.48
	(10.53-14.73)	(6.09- 8.95)[c]	(10.56-14.77)	(6.16- 9.04)[c]	(2.79-3.28)	(2.35-2.83) [c]	(2.60-3.05)	(2.26-2.72)[c]
Yes	7.79	4.16	7.86	7.00	2.32	2.04	2.21	2.05
	(6.03- 10.06)	(3.13- 5.55)[c]	(6.08- 10.15)	(5.09- 9.63)[c]	(2.05-2.63)	(1.77-2.35) [c]	(1.95-2.50)	(1.79-2.35)[c]
	Interaction: p= 0.0196		Interaction: p= 0.5176		Interaction: p=0.0048		Interaction: p=0.0165	
Stroke								
No	12.44	7.79	12.48	7.88	3.03	2.71	2.85	2.60
	(10.49-14.75)	(6.44- 9.42)[c]	(10.52-14.79)	(6.53- 9.52)[c]	(2.80-3.29)	(2.48- 2.97) [c]	(2.63-3.09)	(2.38- 2.84)[c]
Yes	5.20	3.75	5.26	5.79	1.73	1.68	1.71	1.70
	(4.04- 6.69)	(2.87- 4.90)[c]	(4.09- 6.77)	(4.28- 7.85)[c]	(1.52-1.98)	(1.46-1.94) [c]	(1.50-1.96)	(1.48-1.96)[c]
	Interaction: p<0.0001		Interaction: p= 0.5060		Interaction: p<0.0001		Interaction: p <0.0001	

Hyperlipidemia								
No	11.84	6.50	11.88	9.58	2.99	2.51	2.76	3
	(10.20- 13.73)	(5.46- 7.73)[c]	(10.24- 13.78)	(7.84- 11.70)[c]	(2.78-3.23)	(2.30-2.73)[c]	(2.56-2.97)	(2.26-2.68)[c]
Yes	10.57	5.83	10.62	5.94	2.42	2.02	2.30	1.99
	(6.91- 16.16)	(3.64- 9.32)[c]	(6.95- 16.24)	(3.71- 9.51)[c]	(2.05-2.84)	(1.68-2.43)[c]	(1.95-2.70)	(1.65-2.38)[c]
	Interaction: p= 0.9212		Interaction: p= 0.4664		Interaction: p=0.1841		Interaction: p= 0.3100	
COPD								
No	12.25	6.78	28	10.59	2.98	2.54	2.79	2.50
	(10.38-14.46)	(5.60- 8.21)[c]	(10.41-14.50)	(8.53- 13.15)[c]	(2.76-3.23)	(2.32-2.78)[c]	(2.57-3.02)	(2.28-2.74)[c]
Yes	8.91	5.33	0	5.44	2.56	2.11	2.41	2.09
	(6.87- 11.56)	(3.94- 7.19)[c]	(6.94-11.68)	(4.04- 7.34)[c]	(2.25-2.91)	(1.82- 2.45)[c]	(2.12-2.75)	(1.81- 2.42)[c]
	Interaction: p= 0.0400		Interaction: p= 0.0040		Interaction: p=0.0772		Interaction: p= 0.1485	
Number of Comorbidities								
0	16.66	8.68	68	8.75	3.40	3.52	3.28	4
	(12.43-22.33)	(6.27-12.00)[d]	.45-22.35)	(6.34-12.09)[d]	(2.93-3.96)	(2.97-4.16)[d]	(2.82-3.82)	(2.83-3.95)[d]

1	10.73	7.70	77	7.79	2.47	2.67	2.39	5
	(7.86-14.64)	(5.56-10.69)[d]	90-14.70)	(5.62-10.79)[d]	(2.13-2.87)	(2.27-3.13)[d]	(2.06-2.77)	(2.17-2.99)[d]
≧2	8.01	4.90	7	7.51	2.28	2.11	2.16	9
	(6.63-9.66)	(4.01-5.99)[d]	59-9.74)	(5.97-9.45)[d]	(2.08-2.49)	(1.92-2.32) [d]	(1.98-2.36)	(1.90-2.30)[d]
	Interaction: p= 0.0006		Interaction: p= 0.0375		Interaction: p<0.0001		Interaction: p<0.0001	
Charlson's score								
0	13.07	7.34	01	7.39	3.00	2.67	2.87	2.56
	(10.72-15.96)	(5.88-9.17)[e]	.73-15.98)	(5.92-9.22)[e]	(2.73-3.29)	(2.41-2.97)[e]	(2.61-3.15)	(2.31-2.84)[e]
1	7.15	4.36	0	4.46	2.38	2.11	2.28	2.04
	(5.47-9.33)	(3.26-5.83)[e]	52-9.40)	(3.34-5.95)[e]	(2.09-2.71)	(1.83-2.44)[e]	(2.01-2.60)	(1.77-2.35)[e]
≧2	7.60	5.08	7	8.87	2.32	2.07	2.28	3
	(5.61-10.31)	(3.62-7.13)[e]	74-10.54)	(5.54-9.43)[e]	(1.96-2.73)	(1.71-2.51)[e]	(1.93-2.69)	(1.77-2.55)[e]
	Interaction: p= 0.0003		Interaction: p= 0.0003		Interaction: p=0.0031		Interaction: p=0.0059	

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

[b]Based on Poisson assumption

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

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

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

* $P<0.05$

#12. The Hazard ratio (HR) models reported throughout the manuscript I assume are being interpreted as the relative risk (RR). Although the HR and RR are often reported as being one and the same, they are not and the terms should interchangeable. I would suggest removing RR throughout the text replacing it with HR's.

Authors' reply:

Thanks for your suggestions. We complied with your suggestions by removing RR throughout the text and replacing it with HR's (Page 2, line 4-5; Page 4, line 8; Page 5, line 17; Page14, lines 3).

#13.Results: P.8 paragraph 1: When reporting differences within the cohort the p-values should be reported.

Authors' reply:

This was a very good recommendation. We responded by providing the p-values in the revised manuscript (Page 10, lines 1-5).

#14.P8 paragraph 3: Person-years, and HR results 95% CI's should be reported.

Authors' reply:

Thanks for the suggestions. We provided the person-years and HR results for the 95% CI's in the revised manuscript (Page 10, lines 16-22, 24-25; Page 11, line 1).

#15. I feel that the finding that the HR reported for dementia within one year of being reported on the NHI program serves to highlight the methodological weakness of the study. I suspect a number of patients with pre-existing cognitive impairment and PD were classed as new cases because their condition had deteriorated and had only been recognised because they had been referred for an expert opinion. In other words, many would have had the condition for a number of years before seeking medical intervention. This is also supported by the decline in the numbers of PD patients with dementia in the subsequent period of observation. This may also explain the differences observed on the risk of dementia by co-morbidly (Table 3), between the < 1 years and > 1 year cohorts. In other words the > 1 year cohort had a longer period of time to develop significant co-morbidities.

Authors' reply:

Thanks for your comment. We responded to the Reviewer's comments by re-structuring our study discussion to reflect your comments (Page 12, Lines 14-25; Page 27, lines 1-4).

#16. Discussion:As I have discussed in the results section, I do not feel that the finding that the HR for dementia was much higher within one year of an ICD code being entered into the NHI database, is reliable. Despite this, the findings reported here are important and support previous investigations reports on the significant association with PD and dementia. In particular, the call for earlier assessment and detection for cognitive impairment in PD is and excellent suggestion. Perhaps the authors could in light of re-structure their discussion to reflect this.

Authors' reply:

Please see the authors' response to comment #15.

#17. I feel that the methodology overall weakens the investigation because of the other known risk factors, particularly non-motor symptoms (apart from the co-morbidities reported), are equally if not more important predictors for the development of dementia in PD.

Authors' reply:

We agree with your comments suggesting that the other known risk factors, particularly non-motor symptoms, are also important predictors for the development of dementia in PD. Unfortunately, we are unable to further explore this from the NHI claims using specific information indicated by the Reviewer. Because information on disease symptoms are unavailable from the NHI data, we left some (such as non-motor symptoms) for further investigations. We added this as a limitation and provided further information in the revised manuscript (Page 16, lines 11-14).

#18. In addition, it is known that a significant proportion of PD patients have mild a cognitive impairment (ICD-9 code: 331.83), which in longitudinal investigations has been shown to progresses to dementia. The authors do not seem to have considered this in their analysis or discussion and should be addressed.

Authors' reply:

Thank you for the comments. However, we did not intend to assess the proportion of PD patients with mild cognitive impairment (ICD-9 code: 331.83) in this study. In addition, mild cognitive impairment is reversible, which makes it very difficult to set up an explicit number of mild cognitive impairment cases with meaningful separation.

#19. In general, the discussion is quite long could be edited because some parts tend to drift off in speculation rather than focusing on the aims of the investigation.

Authors' reply:

As suggested, we eliminated the text regarding potential mechanisms contributing to dementia in patients with PD in the discussion, which was not the focus of the study.

#20. Conclusion. This is a publishable study, which I feel with careful editing, particularly addressing the methodological shortcomings will add to the strong association with PD and dementia in the literature. I do hope that the authors do re-submit and do not feel too despondent with my comments.

Authors' reply:

Thank you for your encouragement. We really appreciate your detailed review of our manuscript and the fact that you have given us an opportunity to improve it. The alterations made in the revised manuscript are marked in red. Thanks again for your time and consideration related to the publication of our work.

VERSION 2 – REVIEW

REVIEWER	Oliver Riedel Leibniz-Institute for Prevention Research and Epidemiology - BIPS, Germany
REVIEW RETURNED	23-Oct-2018

GENERAL COMMENTS	All my concerns have been adequately addressed.

REVIEWER	Gerhard Ransmayr Dept. of Neurology 2 Kepler University Hospital, Linz, Austria
REVIEW RETURNED	26-Nov-2018

GENERAL COMMENTS	The effect of sex on dementia risk is somewhat unclear: Please compare the respective statements/results concerning the first and the second partition in the Abstract with the bottom of page 13 (manuscript version with corrections highlighted: "higher in men than in women"), page 14 lines 8-11 (highest in female PD patients aged <70), compared to the abstract "both men and women" highest hazard ratio or page 17 last complete paragraph "In our study, no significant role of gender..one year later". What does the term course of medication mean, such as "3 or more courses of anti-Parkinsonism medication" page 9

REVIEWER	Dr Peter Hobson Academic Unit Betsi Cadwaldr University Health BoardU nited Kingdom
REVIEW RETURNED	06-Nov-2018

GENERAL COMMENTS	I would like to congratulate the authors for taking to time and considerable effort to revise the manuscript. Overall I feel that this is publishable, however it still suffers in its standard of written English,; perhaps someone in the editorial can assist with this. I have a few other stylist, grammatical and typographical errors that would need to addressed. Abstract L16: ≦1 years, replace with ≦1 year

	Introduction: P4 L3: missing “be” : can also be ……. P4 L5: with developing cognitive impairments,… replace: with the development cognitive impairment P4 L6: replace “were” with have been….. P5 L6: “PD patients have medical comorbidities….” : PD patients may have medical comorbidities P5 L12: “topic has considered…..” : topic have considered Methods: P5 L24: “The dataset was from…..” : The dataset was drawn from P6 L4 : replace National Health Insurance Administration with: NHIA P6 L4 : “has contracted…” : has contracts P6 L7 : False reports of diagnoses result in a severe penalty from the NHIA: this could be removed. P6 L9: replace epidemiologic with: epidemiological There are several instances of numbers rather than words for example P 6 L20 3 should be replaced with three. For general writing, most guides agree that you should use words for the numbers one through nine. The authors would need to check the manuscript for these inconsistencies. P7 L 1: Replace “We further made the following exclusions to ensure the validity of the PD diagnosis…” : To ensure that the PD Diagnosis was reliable and consistent, cases were excluded if: P7 L 9: Replace: “In the validation study,…”: In this study P7 L12: “January 2012 to October 2012” : January to October 2012 P8 L 1 : “These comorbidities included…” : These included P8 L 3: “Charlson Comorbidity Index, a weighted…..” : Charlson Comorbidity Index, which is a weighted P8 L 12: “A Taiwanese study reported….” : A Taiwanese has previously reported P8 L 18: “or just…” : just P10 L 5: 21.9 per year, p<0.0001): missing comma. Reporting of p-values: Throughout the results section p-values (with the exception of some p-values < 0.001), should be rounded to two decimal places. Example: P 11 L1: p=0.0149 : should read P + 0.015; P11 L 8: p=0.2267: 0.23, etc. P12 L 16: Replace: “unbelievable: this situation is…” with questionable, probably because….. P14 L’s 11-12: remove “of the patients with PD” Note: I would suggest editing lines 11-15. P15 L11: replace “Fourth,” with lastly, P15 L’s 15-18. This sentence is too long and needs to be reviewed and edited. P15 L 24. Insert “firstly” P16 L11: replace “Fourth,” with finally P16 L12: Insert However before because

	P16 L15-16: replace “is the case for non PD patients,”…. With: than the general population, P16 L 17: replace “in a long-time follow-up….” With: longitudinally Remove: “particularly risk groups, ….”

VERSION 2 – AUTHOR RESPONSE

Dear Dr. Ransmayr (Reviewer 2):

Thank you very much for reviewing our article. Your suggestions are indeed very helpful for us to clarify the content of the study. We revised our manuscript according to your comments and would like to describe our changes which are marked in red as follows:

#1.The effect of sex on dementia risk is somewhat unclear: Please compare the respective statements/results concerning the first and the second partition in the Abstract with the bottom of page 13 (manuscript version with corrections highlighted: "higher in men than in women"), page 14 lines 8-11 (highest in female PD patients aged <70), compared to the abstract "both men and women" highest hazard ratio or page 17 last complete paragraph "In our study, no significant role of gender..one year later".

Authors’ reply:

Thank you very much for the comments. To make the descriptions regarding effect of sex on dementia risk more clearly, the statement in the Abstracts section lines 21-24 was revised as “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.”

In corresponds to Abstracts section, the statement on page 13 was revised as “In general, the increased risk of dementia was higher in men in the first partition but was similar in both genders in the second partition. In addition, younger PD patients have the highest risk of dementia in any given partition time.”

We also revised the statement on page 11 line 14-15 (i.e., the reviewer mentioned page14, lines 8-11) as “Further analyses of age- and sex-specific HRs showed the highest HR was observed in PD females aged <70 years (HR: 4.27; 95% CI 3.25-5.63).” Moreover, the statement on page 13 line 26 and page 14 lines 1-2 (i.e., the reviewer mentioned page 17 last complete paragraph) was also revised as “In our study, we found that the risk of dementia was similar in both men and women who had first-diagnosed PD one year later (HR: 2.44, 95% CI 2.19-2.73 and HR: 2.41, 95% CI 2.15-2.69, respectively).”

#2. What does the term course of medication mean, such as "3 or more courses of anti-Parkinsonism medication" page 9

Authors' reply:

The term course of medication means PD cohort in this study had received at least three times of prescriptions of anti-Parkinsonism medications, including L-dopa or dopamine agonist prescriptions after the first PD diagnosis between 2002 and 2003.

In response to the reviewer's comment, we revised the statement "... 3 or more courses of anti-Parkinsonism medications,…" to **"….**at least three times of prescriptions of anti-Parkinsonism medications,….". (Page 6, Line23)

Dear Dr. Hobson (reviewer 3):

Thank you so much for correcting our grammatical or typoerrors. We have revised this manuscript according to your comments. All the changed made in the revised manuscript are used the track changes. Thanks again for your help.

#1.I have a few other stylist, grammatical and typographical errors that would need to addressed.

Abstract L16: ≦1 years, replace with ≦1 year

Introduction:

P4 L3: missing "be" : can also be …….
P4 L5: with developing cognitive impairments,… replace: with the development cognitive impairment
P4 L6: replace "were" with have been…..
P5 L6: "PD patients have medical comorbidities…." : PD patients may have medical comorbidities
P5 L12: "topic has considered….." : topic have considered

Methods:

P5 L24: "The dataset was from….." : The dataset was drawn from
P6 L4 : replace National Health Insurance Administration with: NHIA
P6 L4 : "has contracted…" : has contracts
P6 L7 : False reports of diagnoses result in a severe penalty from the NHIA: this could be removed.
P6 L9: replace epidemiologic with: epidemiological

Authors' reply:

Thanks very much for pointing out all these errors. We have revised all grammatical and typographical errors, accordingly.

#2.There are several instances of numbers rather than words for example P 6 L20 3 should be replaced with three. For general writing, most guides agree that you should use words for the numbers one through nine. The authors would need to check the manuscript for these inconsistencies.

Authors' reply:

Yes. We have corrected all of them.

#3.P7 L 1: Replace "We further made the following exclusions to ensure the validity of the PD diagnosis…" : To ensure that the PD Diagnosis was reliable and consistent, cases were excluded if:
P7 L 9: Replace: "In the validation study,…": In this study
P7 L12: "January 2012 to October 2012" : January to October 2012
P8 L 1 : "These comorbidities included…" : These included
P8 L 3: "Charlson Comorbidity Index, a weighted….." : Charlson Comorbidity Index, which is a weighted
P8 L 12: "A Taiwanese study reported…." : A Taiwanese has previously reported
P8 L 18: "or just…" : just
P10 L 5: 21.9 per year, p<0.0001): missing comma.

Authors' reply:

Thanks again for helping us to clarify the sentences. We have revised all of them.

#4.Reporting of p-values: Throughout the results section p-values (with the exception of some p-values < 0.001), should be rounded to two decimal places. Example: P 11 L1: p=0.0149 : should read P + 0.015; P11 L 8: p=0.2267: 0.23, etc.

Authors' reply:

Yes. We have corrected them.

#5.P12 L 16: Replace: "unbelievable: this situation is…" with questionable, probably because…..
P14 L's 11-12: remove "of the patients with PD"
Note: I would suggest editing lines 11-15.
P15 L11: replace "Fourth," with lastly,
P15 L's 15-18. This sentence is too long and needs to be reviewed and edited.
P15 L 24. Insert "firstly"
P16 L11: replace "Fourth," with finally
P16 L12: Insert However before because
P16 L15-16: replace "is the case for non PD patients,"…. With: than the general population,
P16 L 17: replace "in a long-time follow-up…." With: longitudinally
Remove: "particularly risk groups, …."

Authors' reply:

Thanks again for pointing out these unclear sentences. We have revised all of them, accordingly.