PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Mortality and cause of death in South Korean patients with Parkinson's disease: A longitudinal follow-up study using a national sample cohort
AUTHORS	Kim, Miyoung; Choi, Hyo Geun; Lim, Jae-Sung; Lee, Young Kyung; Sim, Songyong

VERSION 1 – REVIEW

REVIEWER	Angus Macleod University of Aberdeen, UK.
REVIEW RETURNED	22-Feb-2019

GENERAL COMMENTS	This study uses a large population dataset, but unfortunately the description of methods is unclear in places and there are errors in the interpretation of the results. It would need a major revision to bring this up to publishable standard. Also, it should be proofread by a native English speaker. A STROBE checklist would be a useful addition. Specific comments. Abstract line 45. Numbers here are misleading. Put in the number of patients and controls you actually analysed. It is simply false to say there were 1.1m matched controls. Methods Line 140. Cases is not the best word to describe the population. Perhaps better to say individuals. Line 141. It isn't clear how PD cases were identified. Was ICD coding for PD from Hospital admissions, clinic visits, general practitioner visits? Please provide details about treatment in the identification of PD patients – pts had to be treated 2 or more times, but it is not stated where the details of PD treatment were obtained from. Line 141: Please clarify how cases diagnosed 2002-13 were distinguished from the cases diagnosed before 2002 Line 143: The numbers of PD diagnoses 2002-13, and then number of controls add up to the total individuals in the sample. What about those diagnosed with PD before 2002? Line 145. Re matching. Please clarify the time point at which the matching was done – presumably the matching was done at the time of patients' diagnosis, but this is not stated. The main issue here is age and co-morbidity.

	Line 149: “It was assumed that the matched control participants were involved at the same time of each matched PD participants.” It isn’t clear what this sentence means. Line 152: I think it would be useful and informative to include the young-onset PD. Please give your rationale for excluding this group of patients. Line 181: Please explain what NEC stands for. Line 194: was a standard Cox model or a stratified Cox model used? If stratified Cox model was not used to adjust for matching, please explain why not. Line 194: How were assumptions of Cox regression tested? Table 1: It would be informative to have a column listing the characteristics of the whole population sample. Listing the P-values for comparisons between matched variables is completely pointless. Sex distribution here is exceptional for Parkinson’s. Most studies have shown Male to female ratios of 1.5:1 or 2:1. Some studies, particularly Asian studies have sex ratios of about 1:1. Please check your coding for sex here as the male to female ratio here is 0.6:1. I am not aware of any previous study in PD showing a substantially higher incidence of PD in females than men. Results: Line 217: You say “The crude and adjusted HRs were significantly higher in PD patients ≥75 years of age than in those <75 years regardless of sex.”. Table 3 shows higher HRs in the under 75 than in the over 75s. I suggest you combine table 2 and table 3 into one table. Discussion: Line 216: you could expand this to point out that factors influencing referral to a tertiary hospital are likely to lead to selection bias which are likely to underestimate mortality in PD. Line 272: Again, this is the wrong way round. Line 274: I think you are confusing higher mortality rates and higher mortality relative to controls. Line 276: please clarify whether this should read higher mortality rates or higher relative mortality. Please revise this paragraph in light of the correct interpretation of your data about HRs and age group. Line 340: please revise. You haven’t reported any mortality rates, and this (again) appears to be the wrong way round.

REVIEWER	Dr. Walter Pirker Department of Neurology, Wilhelminenspital, Vienna, Austria
REVIEW RETURNED	25-Feb-2019

GENERAL COMMENTS	This is an interesting study on the mortality of Parkinson's disease in South Korea. The large population based patient and control sample included was drawn from a nationwide insurance database. Mortality hazard ratio for PD was within the expected range (2.26). In addition to higher mortality caused by neurologic and respiratory disease in PD vs. controls, metabolic, mental, circulatory and genitourinary disease and trauma, were more common in the PD group. The paper is well written. However, I have a question regarding the epidemiology of PD in South Korea. In addition, I have some reservation regarding the interpretation of the causes of death in PD and their discussion: Whereas many studies show a somewhat higher prevalence of PD in men, the proportion of males in this population-based study is only 38.1%. Does this reflect the gender distribution in the general Korean population of that age? Cause of death in table 4 is presented as percentage of all PD subjects involved in the study. Presenting individual causes of death as percentage of the deceased PD (or control) subjects may help the reader to get a faster overview. When recalculating the data, neurologic disease (probably PD) was the cause of death in 27% of the deceased PD subjects. In contrast to other studies which found pneumonia to be a prominent cause of death in PD, respiratory disease was rated as primary cause of death in only 8% of the deceased PD subjects (a fact discussed by the authors). At the end of the discussion the authors state that metabolic disease, mental diseases, circulatory disease, respiratory disease, genitourinary disease, and trauma are common causes of death in PD patients in addition to PD itself. However, the data presented in Table 4 show that the primary cause of death was attributed to mental and genitourinary diseases in only 2.7 and 2.1% of the deceased PD patients. Taking into account that the majority of PD subjects develop dementia the rate of dementia as primary cause of death seems therefore rather low. In clinical practice, it is often difficult to attribute the primary cause of death in PD to a single system and sometimes even autopsy does not reveal the primary cause of death. These limitations in a study relying on diagnoses from clinical death certificates should be pointed out in the discussion.

REVIEWER	Giancarlo Logroscino University of Bari - Italy
REVIEW RETURNED	04-Mar-2019

GENERAL COMMENTS	The authors should provide information on the diagnosis of PD in this system. If they don't, they should provide eventually information on a validation study on diagnosis of PD in this cohort. It would be interesting to study age and mortality across more than two categories (> ansd < 75 years). The change across different categories could be important. It would be useful to know the completeness of the information on causes of death in the death certificate in this cohort. Do the authors have any information on the presence of cognitive impairment in their cases and controls? It is not clear if the authors take into account comorbidities in the estimate of risk of death.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Angus Macleod

Institution and Country: University of Aberdeen, UK.

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This study uses a large population dataset, but unfortunately the description of methods is unclear in places and there are errors in the interpretation of the results. It would need a major revision to bring this up to publishable standard. Also, it should be proofread by a native English speaker. A STROBE checklist would be a useful addition.

Specific comments.

Abstract line 45. Numbers here are misleading. Put in the number of patients and controls you actually analysed. It is simply false to say there were 1.1m matched controls.

▸The numbers of participants have been corrected; we thank the reviewer for pointing this out.
▣ Abstract, page 3, line 46-47 [Before revision] Participants: We included 4,169 participants ≥60 years of age who were diagnosed with PD between

2002 and 2013, as well as 1,121,522 matched controls.

[After revision]

Participants: We included 3,510 participants ≥60 years of age who were diagnosed with PD between 2002 and 2013, as well as 14,040 matched controls.

Methods

Line 140. Cases is not the best word to describe the population. Perhaps better to say individuals.

▸We have revised our word choice as recommended.

▣ Materials and methods, page 7, line 143

[Before revision]

Out of 1,125,691 cases with 114,369,638 medical claim codes, we included participants…

[After revision]

From among 1,125,691 individuals with 114,369,638 medical claim codes, we included participants…

Line 141. It isn't clear how PD cases were identified. Was ICD coding for PD from Hospital admissions, clinic visits, general practitioner visits? Please provide details about treatment in the identification of PD patients – pts had to be treated 2 or more times, but it is not stated where the details of PD treatment were obtained from.

▸We included participants who visited outpatient clinics, were hospitalized, or both ≥2 times for reasons having to do directly with the diagnosis of PD. Based on our criteria, the incidence was 30.86 per 100,000 person-years in those aged ≥60 years. According to the only available nationwide study on the incidence and the prevalence of PD in Korea [J Clin Neurol. 2018 Oct; 14(4): 478–486], the incidence of PD ranged from 10.3 to 17.4 at different time points among participants aged ≥40 years. Even though we do not have data for the incidence of PD in Korean populations aged ≥60 years, it is assumed that the incidence in this age group would be higher than in those aged ≥40 years because PD is a disease that is predominant in elderly individuals. Our findings are in line with previously published data from other Asian countries even though there could be ethnicity-based differences between Koreans and other Asians [J Epidemiol. 2009;19(6):281-93]. The sentence in question has been revised and clarified as recommended.

▣ Strengths and limitations of this study, page 4, lines 68–69

[Before revision]

• The study encompassed all registered patients with PD who were treated at least twice.

[After revision]

• The study encompassed all registered patients with PD who visited outpatient clinics, were hospitalized, or both at least twice.

▣ Materials and methods, page 7, lines 145–146

[Before revision]

For the accuracy of diagnosis, we only selected if the participants were treated ≥ 2 times.

[After revision]

For accurate diagnoses, we only selected participants who visited outpatient clinics, were hospitalized, or both at least twice because of PD.

Line 141: Please clarify how cases diagnosed 2002-13 were distinguished from the cases diagnosed before 2002

▸We do not have any data from before 2002; hence, it was not a consideration in our study.

Line 143: The numbers of PD diagnoses 2002-13, and then number of controls add up to the total individuals in the sample. What about those diagnosed with PD before 2002?

▸We do not have any data from before the year 2002, as stated above. Therefore, the study population included those who were newly diagnosed with PD within the study period and also those who were diagnosed with PD before 2002 but still visited clinics (≥2 times) for PD-related matters.

Line 145. Re matching. Please clarify the time point at which the matching was done – presumably the matching was done at the time of patients' diagnosis, but this is not stated. The main issue here is age and co-morbidity.

▸ We set the index date as that of the diagnosis of PD in the PD group. Individuals in the control group were also followed from the same index date as their matched PD patient. For example, a participant with PD was diagnosed with the disease on May 3, 2009, which became the date of involvement with this study. We hypothesized that his/her 4 matched control participants were also involved with this study beginning on May 3 2009. We have further clarified this as recommended.

▣ Materials and methods, page 7, lines 151–153

[After revision]

We set the index date as that of the diagnosis of PD in the PD group; participants from the control group were also followed from the same index date as their matched counterparts with PD.

Line 149: “It was assumed that the matched control participants were involved at the same time of each matched PD participants.” It isn’t clear what this sentence means.

▸ This comment is addressed immediately above. To reiterate, we clarified the text as shown below.

▣ Materials and methods, page 7, lines 1451–153

[After revision]

We set the index date as that of the diagnosis of PD in the PD group; participants from the control group were also followed from the same index date as their matched counterparts with PD.

Line 152: I think it would be useful and informative to include the young-onset PD. Please give your rationale for excluding this group of patients.

▸ It may indeed be informative to include patients with young-onset PD. However, we decided to exclude this group because the diagnosis of PD in younger individuals might be less reliable than in older populations owing to the rarity of this disease among younger age groups.

Line 181: Please explain what NEC stands for.

▸ NEC stands for “not elsewhere classified”. We have now spelled it out in the text and defined it in Supplementary Table 1.

▣ Materials and methods, page 8, lines 183–184

[Before revision]

(xi) Abnormal finding (Symptoms, signs and abnormal clinical and laboratory findings, NEC, R00-R99);

[After revision]

(xi) Abnormal finding (symptoms, signs and abnormal clinical and laboratory findings ‘not elsewhere classified’, R00–R99);

▣ Table S1

[Before revision]

Diseases of veins, lymphatic vessels and lymph nodes, NEC

Complications of surgical and medical care, NEC

[After revision]

Diseases of veins, lymphatic vessels and lymph nodes, Not Elsewhere Classified (NEC)

Complications of surgical and medical care, Not Elsewhere Classified (NEC)

Line 194: was a standard Cox model or a stratified Cox model used? If stratified Cox model was not used to adjust for matching, please explain why not.

▸ We reanalyzed the data using a stratified Cox model and described it as below. All the figures, tables, and relevant text were modified accordingly.

▣ Abstract, page 3, line 49

[Before revision]

Primary and secondary outcome measures: A Cox proportional hazards model was used to evaluate patients with PD who were matched 1:4 with non-PD control subjects adjusted for age, sex, income, and region of residence. The causes of death were grouped into 12 classifications.

[After revision]

Primary and secondary outcome measures: A stratified Cox proportional hazards model was used to evaluate patients with PD who were matched 1:4 with non-PD control subjects adjusted for age, sex, income, and region of residence. The causes of death were grouped into 12 classifications.

▣ Materials and methods, page 9, line 196

[Before revision]

To analyze the hazard ratio (HR) of PD on mortality, a Cox-proportional hazard model was used. In this analysis, crude (simple) and adjusted (age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia) model was used.

[After revision]

To determine hazard ratios (HRs) for mortality as a function of PD, a stratified Cox-proportional hazards model, both crude (simple) and adjusted for the Charlson comorbidity index, was used. Age, sex, income, and region of residence were stratified.

▣ Results, page 10, lines 205–207

[Before revision]

The mortality rate was significantly higher in the PD group than that in the control group (34.6%

[1,214/3,510] and 19.0% [2,661/14,040], respectively, P < 0.001). Age, sex, income level, region of residence, hypertension status, diabetes status, and dyslipidemia status were matched between the PD and control groups (Table 1).

[After revision]

Age, sex, income level, and region of residence were matched between the PD and control groups (Table 1). The mortality rate was significantly higher in the PD group than that in the control group (34.6% [1,214/3,510] and 19.0% [2,661/14,040], respectively, P < 0.001).

▣ Results, page 11, lines 214–215

[Before revision]

The crude and adjusted HRs for mortality in the PD group were 2.14 (95% CI = 2. 00–2.29, P < 0.001) and 2.09 (95% CI = 2.11–2.42, P < 0.001), respectively (Table 2).

[After revision]

The crude and adjusted HRs for mortality in the PD group were 2.29 (95% CI = 2.13–2.45, P < 0.001) and 2.09 (95% CI = 1.94–2.24, P < 0.001), respectively (Table 2).

▣ New Table 2.

[After revision]

Table 2 Cox proportional hazards analyses of mortality due to Parkinson's disease

Characteristics	Hazard ratio (95% CI)			
	Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 17,550)				
Parkinson's disease	2.29 (2.13-2.45)	< 0.001*	2.09 (1.94-2.24)	< 0.001*
Control	1.00		1.00	
Age < 70 years old, men (n = 2,115)				
Parkinson's disease	3.04 (2.45-3.77)	< 0.001*	2.77 (2.23-3.45)	< 0.001*
Control	1.00		1.00	
Age < 70 years old, women (n = 3,125)				
Parkinson's disease	4.11 (3.24-5.21)	< 0.001*	3.32 (2.60-4.25)	< 0.001*
Control	1.00		1.00	
Age 70-79 years old, men (n = 3,280)				
Parkinson's disease	2.27 (1.96-2.63)	< 0.001*	2.07 (1.78-2.41)	< 0.001*
Control	1.00		1.00	
Age 70-79 years old, women (n = 5,410)				
Parkinson's disease	2.41 (2.10-2.78)	< 0.001*	2.22 (1.92-2.55)	< 0.001*
Control	1.00		1.00	

Age ≥ 80 years old, men (n = 1,285)				
Parkinson's disease	1.53 (1.25-1.88)	< 0.001*	1.47 (1.20-1.82)	< 0.001*
Control	1.00		1.00	
Age ≥ 80 years old, women (n = 2,335)				
Parkinson's disease	1.83 (1.55-2.17)	< 0.001*	1.73 (1.46-2.05)	< 0.001*
Control	1.00		1.00	

*Cox-proportional hazard regression model; significance at P < 0.05

† Stratified model for age, sex, income, and region of residence.

‡ Model adjusted for the Charlson comorbidity index.

HR, hazard ratio; CI, confidence interval.

Line 194: How were assumptions of Cox regression tested?

▸Cox regression analyses were performed under the assumption of proportionality as shown by the log minus plot below. The risk in one group increases in parallel with the other, demonstrating that the hypothesis of the Cox model was true.

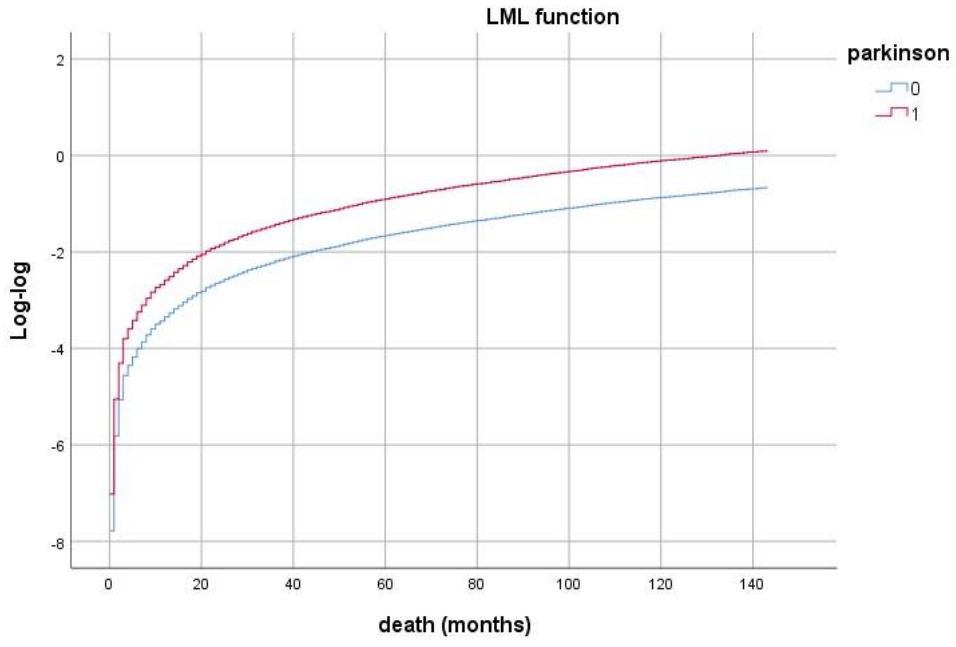

Table 1: It would be informative to have a column listing the characteristics of the whole population sample. Listing the P-values for comparisons between matched variables is completely pointless.

▸ We agree to the reviewer, and have realized that listing the P-values for comparisons between matched variables is not informative. We included the Charlson comorbidity index scores with P-values are <0.001, along with the death rates, in the revised Table 1 and wanted to share this information with our readers. The data is presentable only when there are 2 separate columns for the PD group and the control group.

▣ Table 1

[Before revision]

Characteristics	Total participants		
	Parkinson's disease (n, %)	Control (n, %)	P-value
Age (years old)			1.000
60-64	388 (11.1)	1,552 (11.1)	
65-69	660 (18.8)	2,640 (18.8)	
70-74	903 (25.7)	3,612 (25.7)	
75-79	835 (23.8)	3,340 (23.8)	
80-84	498 (14.2)	1,992 (14.2)	
85+	226 (6.4)	904 (6.4)	
Sex			1.000
Male	1,336 (38.1)	5,344 (38.1)	
Female	2,174 (61.9)	8,696 (61.9)	
Income			1.000
1 (lowest)	325 (9.3)	1,300 (9.3)	
2	283 (8.1)	1,132 (8.1)	
3	145 (4.1)	580 (4.1)	
4	154 (4.4)	616 (4.4)	
5	179 (5.1)	716 (5.1)	
6	190 (5.4)	760 (5.4)	
7	251 (7.2)	1,004 (7.2)	
8	256 (7.3)	1,024 (7.3)	
9	383 (10.9)	1,532 (10.9)	
10	584 (16.6)	2,336 (16.6)	
11 (highest)	760 (21.7)	3,040 (21.7)	
Region of residence			1.000
Urban	1,467 (41.8)	5,868 (41.8)	
Rural	2,043 (58.2)	8,172 (58.2)	
Hypertension			1.000
Yes	2,544 (72.5)	10,176 (72.5)	

No	966 (27.5)	3,864 (27.5)	
Diabetes			1.000
Yes	1,386 (39.5)	5,544 (39.5)	
No	2,124 (60.5)	8,496 (60.5)	
Dyslipidemia			1.000
Yes	1,185 (33.8)	4,740 (33.8)	
No	2,325 (66.2)	9,300 (66.2)	
Death			<0.001*
Yes	1,214 (34.6)	2,661 (19.0)	
No	2,296 (65.4)	11,379 (81.0)	

*Chi-square test or Fisher's exact test. Significance at P < 0.05

[After revision]

Characteristics	Total participants		
	Parkinson's disease (n, %)	Control (n, %)	P-value
Age (years old)			1.000
60-64	388 (11.1)	1,552 (11.1)	
65-69	660 (18.8)	2,640 (18.8)	
70-74	903 (25.7)	3,612 (25.7)	
75-79	835 (23.8)	3,340 (23.8)	
80-84	498 (14.2)	1,992 (14.2)	
85+	226 (6.4)	904 (6.4)	
Sex			1.000
Male	1,336 (38.1)	5,344 (38.1)	
Female	2,174 (61.9)	8,696 (61.9)	
Income			1.000
1 (lowest)	325 (9.3)	1,300 (9.3)	
2	283 (8.1)	1,132 (8.1)	
3	145 (4.1)	580 (4.1)	
4	154 (4.4)	616 (4.4)	
5	179 (5.1)	716 (5.1)	
6	190 (5.4)	760 (5.4)	
7	251 (7.2)	1,004 (7.2)	
8	256 (7.3)	1,024 (7.3)	
9	383 (10.9)	1,532 (10.9)	
10	584 (16.6)	2,336 (16.6)	
11 (highest)	760 (21.7)	3,040 (21.7)	
Region of residence			1.000
Urban	1,467 (41.8)	5,868 (41.8)	

Rural	2,043 (58.2)	8,172 (58.2)	
† CCI score			<0.001*
0	325 (9.3)	3,049 (21.7)	
1	132 (3.8)	659 (4.7)	
2	240 (6.8)	1,173 (8.4)	
≥ 3	2,813 (80.1)	9,159 (65.2)	
Death	1,214 (34.6)	2,661 (19.0)	<0.001*

*Chi-square test or Fisher's exact test. Significance at P < 0.05

† CCI: Charlson Comorbidity Index (calculated without including pulmonary disease).

Sex distribution here is exceptional for Parkinson's. Most studies have shown Male to female ratios of 1.5:1 or 2:1. Some studies, particularly Asian studies have sex ratios of about 1:1. Please check your coding for sex here as the male to female ratio here is 0.6:1. I am not aware of any previous study in PD showing a substantially higher incidence of PD in females than men.

▸ According to the only available study on this topic in Korea, the male-to-female ratio among patients with Parkinson's disease is approximately 0.6 (0.634 in the year 2009, 0.640 in 2010, 0.637 in 2011, 0.648 in 2012, and 0.655 in 2013) (Parkinsonism Relat Disord. 2018;46;e64-e81).These data correspond well with our results.

Results:

Line 217: You say "The crude and adjusted HRs were significantly higher in PD patients ≥75 years of age than in those <75 years regardless of sex.".

▸ Our original interpretation when comparing HRs in different subpopulations was inappropriate. Therefore, we removed the relevant sentences throughout the manuscript and added a more suitable interpretation.

▣ Result, page 11, line 221

[Removed]

The crude and adjusted HRs were significantly higher in PD patients ≥75 years of age than in those <75 years regardless of sex. Moreover, the crude and adjusted HRs trended slightly higher in women than in men regardless of age; however, the 95% CIs overlapped.

▣ Discussion, page 16, line 264

[Removed]

The adjusted HRs for mortality were significantly higher in patients ≥75 years of age at the time of PD diagnosis than in those <75 years when diagnosed in both men and women. Older age at onset

was most consistently found to be an independent predictor of mortality across studies [4, 12-17]. One study by Morgan et al. produced a contrasting result in that patients with early PD onset (of ages 50 years or younger) appeared to have higher mortality rates than patients with later PD onset [3]; however, we could not compare our results to theirs because we excluded subjects younger than 60 years. While it is unclear why the age of onset affects the mortality rate in the PD patients, a possible explanation is that patients aged ≥75 years at onset may be affected by mortality-causing conditions that were not adjusted for in our study to a greater extent than those <75 years.

As we did not make a direct comparison between men and women in subgroup analysis, we were unable to ascertain whether sex is a factor affecting the mortality rates of patients with PD. While some studies have found that male sex was associated with increased mortality in patients with PD [12-17], others showed this not to be the case [3, 18]. More recent data suggest that, because the general life expectancy of women in general is longer than that of men, the formers' higher mortality rates and greater reductions in lifespan are more apparent when they are afflicted with PD; this would imply that PD progression patterns are not actually different between the sexes with respect to mortality [3].

▣ Discussion, page 16, line 263–page 17 line 280

[Added]

Our subgroup analyses showed that patients with PD had higher mortality rates across all age groups and in both sexes. Previous studies have produced similar data, demonstrating that PD is a risk factor for increased mortality regardless of age and sex [11, 12]. The adjusted HRs were relatively high in patients with PD aged <70 years (2.77 in men and 3.32 in women) but were relatively low in patients with PD aged 70–79 years (2.07 in men and 2.22 in women) and even lower in patients with PD aged >80 years (1.47 in men and 1.73 in women). This phenomenon could be attributed to the death rates themselves increasing in both the control and PD groups as individuals age, which dilutes the impact of PD on the mortality rate of older individuals. A previous literature review by Ishihara et al. on the estimated life expectancies of UK and European individuals with PD showed that, as the age of PD onset increased, the standardized mortality ratio dropped gradually from 7.3 in men and 6.7 in women in their twenties to 2.5 in both men and in women in their nineties [11]. However, this finding may be controversial, as a systematic review and meta-analysis by Macleod et al. found that, in 15 of 17 studies, older age either at onset or recruitment was associated with increased mortality [12]. This discrepancy could be related to the differing ethnicities of subjects in these studies, as well as the involved countries' economic statuses, study populations, and research methods. The differences in adjusted HRs between men and women were not notable in any of the age groups.

▣ Conclusion, page 19, line 342

[Removed]

The mortality rate was higher in patients ≥75 years old than in those <75 years for both sexes.

Table 3 shows higher HRs in the under 75 than in the over 75s. I suggest you combine table 2 and table 3 into one table.

▸ We merged Tables 2 and 3, and created a new Table 2 as shown below.

▣ New Table 2.

[After revision]

Table 2 Cox proportional hazards analyses of mortality due to Parkinson's disease

Characteristics	Hazard ratio (95% CI)			
	Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 17,550)				
Parkinson's disease	2.29 (2.13-2.45)	< 0.001*	2.09 (1.94-2.24)	< 0.001*
Control	1.00		1.00	
Age < 70 years old, men (n = 2,115)				
Parkinson's disease	3.04 (2.45-3.77)	< 0.001*	2.77 (2.23-3.45)	< 0.001*
Control	1.00		1.00	
Age < 70 years old, women (n = 3,125)				
Parkinson's disease	4.11 (3.24-5.21)	< 0.001*	3.32 (2.60-4.25)	< 0.001*
Control	1.00		1.00	
Age 70-79 years old, men (n = 3,280)				
Parkinson's disease	2.27 (1.96-2.63)	< 0.001*	2.07 (1.78-2.41)	< 0.001*
Control	1.00		1.00	
Age 70-79 years old, women (n = 5,410)				
Parkinson's disease	2.41 (2.10-2.78)	< 0.001*	2.22 (1.92-2.55)	< 0.001*
Control	1.00		1.00	
Age ≥ 80 years old, men (n = 1,285)				
Parkinson's disease	1.53 (1.25-1.88)	< 0.001*	1.47 (1.20-1.82)	< 0.001*
Control	1.00		1.00	
Age ≥ 80 years old, women (n = 2,335)				
Parkinson's disease	1.83 (1.55-2.17)	< 0.001*	1.73 (1.46-2.05)	< 0.001*
Control	1.00		1.00	

*Cox-proportional hazard regression model; significance at P < 0.05

† Stratified model for age, sex, income, and region of residence.

‡ Model adjusted for the Charlson comorbidity index.

HR, hazard ratio; CI, confidence interval.

Discussion:

Line 216: you could expand this to point out that factors influencing referral to a tertiary hospital are likely to lead to selection bias which are likely to underestimate mortality in PD.

▸ As stated in the Methods and Discussion sections, the selection bias ought to be minimal because we extracted the data from our National Health Insurance Sharing Service. It is a compulsory system that encompasses not only tertiary hospitals but all medical care institutions in South Korea.

[Materials and Methods, page 6, line 132–page 7, line 140]

Because all Korean citizens are recognized by a 13-digit resident registration number from birth to death, exact population statistics can be determined using this database. It is mandatory for all Koreans to enroll in the NHIS. All Korean hospitals and clinics use the 13-digit resident registration number to record individual patients in the medical insurance system. Therefore, the risk of overlapping medical records is minimal, even if a patient relocates to another geographical region. Moreover, all medical treatments in Korea can be tracked without exception using the HIRA system. In Korea, a notice of death must legally be delivered to an administrative entity before a funeral can be held. Causes and dates of death are recorded by medical doctors on death certificates.

[Discussion, page 19, line 328-330]

Another strength of our study is that our approach minimized the risk of recall bias or missing information, as the dataset was based on claims made to the compulsory HIRA nationwide health insurance system.

Line 272: Again, this is the wrong way round.

▸ As pointed out above, we have revised these sections (the changes are reproduced below).

▣ Result, page 11, line 221

[Removed]

The crude and adjusted HRs were significantly higher in PD patients ≥75 years of age than in those <75 years regardless of sex. Moreover, the crude and adjusted HRs trended slightly higher in women than in men regardless of age; however, the 95% CIs overlapped.

▣ Discussion, page 16, line 264

[Removed]

The adjusted HRs for mortality were significantly higher in patients ≥75 years of age at the time of PD diagnosis than in those <75 years when diagnosed in both men and women. Older age at onset was most consistently found to be an independent predictor of mortality across studies [4, 12-17]. One study by Morgan et al. produced a contrasting result in that patients with early PD onset (of ages 50 years or younger) appeared to have higher mortality rates than patients with later PD onset [3]; however, we could not compare our results to theirs because we excluded subjects younger than 60

years. While it is unclear why the age of onset affects the mortality rate in the PD patients, a possible explanation is that patients aged ≥75 years at onset may be affected by mortality-causing conditions that were not adjusted for in our study to a greater extent than those <75 years.

As we did not make a direct comparison between men and women in subgroup analysis, we were unable to ascertain whether sex is a factor affecting the mortality rates of patients with PD. While some studies have found that male sex was associated with increased mortality in patients with PD [12-17], others showed this not to be the case [3, 18]. More recent data suggest that, because the general life expectancy of women in general is longer than that of men, the formers' higher mortality rates and greater reductions in lifespan are more apparent when they are afflicted with PD; this would imply that PD progression patterns are not actually different between the sexes with respect to mortality [3].

▣ Discussion, page 16, line 263–page 17 line 280

[Added]

Our subgroup analyses showed that patients with PD had higher mortality rates across all age groups and in both sexes. Previous studies have produced similar data, demonstrating that PD is a risk factor for increased mortality regardless of age and sex [11, 12]. The adjusted HRs were relatively high in patients with PD aged <70 years (2.77 in men and 3.32 in women) but were relatively low in patients with PD aged 70–79 years (2.07 in men and 2.22 in women) and even lower in patients with PD aged >80 years (1.47 in men and 1.73 in women). This phenomenon could be attributed to the death rates themselves increasing in both the control and PD groups as individuals age, which dilutes the impact of PD on the mortality rate of older individuals. A previous literature review by Ishihara et al. on the estimated life expectancies of UK and European individuals with PD showed that, as the age of PD onset increased, the standardized mortality ratio dropped gradually from 7.3 in men and 6.7 in women in their twenties to 2.5 in both men and in women in their nineties [11]. However, this finding may be controversial, as a systematic review and meta-analysis by Macleod et al. found that, in 15 of 17 studies, older age either at onset or recruitment was associated with increased mortality [12]. This discrepancy could be related to the differing ethnicities of subjects in these studies, as well as the involved countries' economic statuses, study populations, and research methods. The differences in adjusted HRs between men and women were not notable in any of the age groups.

▣ Conclusion, page 19, line 342

[Removed]

The mortality rate was higher in patients ≥75 years old than in those <75 years for both sexes.

Line 274: I think you are confusing higher mortality rates and higher mortality relative to controls.

▸ We appreciate the reviewer's point. As described in our response to the reviewer's comment on page 16 above, we have revised our interpretations.

▣ Result, page 11, line 221

[Removed]

The crude and adjusted HRs were significantly higher in PD patients ≥75 years of age than in those <75 years regardless of sex. Moreover, the crude and adjusted HRs trended slightly higher in women than in men regardless of age; however, the 95% CIs overlapped.

▣ Discussion, page 16, line 264

[Removed]

The adjusted HRs for mortality were significantly higher in patients ≥75 years of age at the time of PD diagnosis than in those <75 years when diagnosed in both men and women. Older age at onset was most consistently found to be an independent predictor of mortality across studies [4, 12-17]. One study by Morgan et al. produced a contrasting result in that patients with early PD onset (of ages 50 years or younger) appeared to have higher mortality rates than patients with later PD onset [3]; however, we could not compare our results to theirs because we excluded subjects younger than 60 years. While it is unclear why the age of onset affects the mortality rate in the PD patients, a possible explanation is that patients aged ≥75 years at onset may be affected by mortality-causing conditions that were not adjusted for in our study to a greater extent than those <75 years.

As we did not make a direct comparison between men and women in subgroup analysis, we were unable to ascertain whether sex is a factor affecting the mortality rates of patients with PD. While some studies have found that male sex was associated with increased mortality in patients with PD [12-17], others showed this not to be the case [3, 18]. More recent data suggest that, because the general life expectancy of women in general is longer than that of men, the formers' higher mortality rates and greater reductions in lifespan are more apparent when they are afflicted with PD; this would imply that PD progression patterns are not actually different between the sexes with respect to mortality [3].

▣ Discussion, page 16, line 263–page 17 line 280

[Added]

Our subgroup analyses showed that patients with PD had higher mortality rates across all age groups and in both sexes. Previous studies have produced similar data, demonstrating that PD is a risk factor for increased mortality regardless of age and sex [11, 12]. The adjusted HRs were relatively

high in patients with PD aged <70 years (2.77 in men and 3.32 in women) but were relatively low in patients with PD aged 70–79 years (2.07 in men and 2.22 in women) and even lower in patients with PD aged >80 years (1.47 in men and 1.73 in women). This phenomenon could be attributed to the death rates themselves increasing in both the control and PD groups as individuals age, which dilutes the impact of PD on the mortality rate of older individuals. A previous literature review by Ishihara et al. on the estimated life expectancies of UK and European individuals with PD showed that, as the age of PD onset increased, the standardized mortality ratio dropped gradually from 7.3 in men and 6.7 in women in their twenties to 2.5 in both men and in women in their nineties [11]. However, this finding may be controversial, as a systematic review and meta-analysis by Macleod et al. found that, in 15 of 17 studies, older age either at onset or recruitment was associated with increased mortality [12]. This discrepancy could be related to the differing ethnicities of subjects in these studies, as well as the involved countries' economic statuses, study populations, and research methods. The differences in adjusted HRs between men and women were not notable in any of the age groups.

▣ Conclusion, page 19, line 342

[Removed]

The mortality rate was higher in patients ≥75 years old than in those <75 years for both sexes.

Line 276: please clarify whether this should read higher mortality rates or higher relative mortality.

▸ We appreciate the reviewer's inquiry. Our revisions as described in our response to the reviewer's question on page 16 address this point.

▣ Result, page 11, line 221

[Removed]

The crude and adjusted HRs were significantly higher in PD patients ≥75 years of age than in those <75 years regardless of sex. Moreover, the crude and adjusted HRs trended slightly higher in women than in men regardless of age; however, the 95% CIs overlapped.

▣ Discussion, page 16, line 264

[Removed]

The adjusted HRs for mortality were significantly higher in patients ≥75 years of age at the time of PD diagnosis than in those <75 years when diagnosed in both men and women. Older age at onset was most consistently found to be an independent predictor of mortality across studies [4, 12-17]. One study by Morgan et al. produced a contrasting result in that patients with early PD onset (of ages 50 years or younger) appeared to have higher mortality rates than patients with later PD onset [3]; however, we could not compare our results to theirs because we excluded subjects younger than 60 years. While it is unclear why the age of onset affects the mortality rate in the PD patients, a possible

explanation is that patients aged ≥75 years at onset may be affected by mortality-causing conditions that were not adjusted for in our study to a greater extent than those <75 years.

As we did not make a direct comparison between men and women in subgroup analysis, we were unable to ascertain whether sex is a factor affecting the mortality rates of patients with PD. While some studies have found that male sex was associated with increased mortality in patients with PD [12-17], others showed this not to be the case [3, 18]. More recent data suggest that, because the general life expectancy of women in general is longer than that of men, the formers' higher mortality rates and greater reductions in lifespan are more apparent when they are afflicted with PD; this would imply that PD progression patterns are not actually different between the sexes with respect to mortality [3].

▣ Discussion, page 16, line 263–page 17 line 280

[Added]

Our subgroup analyses showed that patients with PD had higher mortality rates across all age groups and in both sexes. Previous studies have produced similar data, demonstrating that PD is a risk factor for increased mortality regardless of age and sex [11, 12]. The adjusted HRs were relatively high in patients with PD aged <70 years (2.77 in men and 3.32 in women) but were relatively low in patients with PD aged 70–79 years (2.07 in men and 2.22 in women) and even lower in patients with PD aged >80 years (1.47 in men and 1.73 in women). This phenomenon could be attributed to the death rates themselves increasing in both the control and PD groups as individuals age, which dilutes the impact of PD on the mortality rate of older individuals. A previous literature review by Ishihara et al. on the estimated life expectancies of UK and European individuals with PD showed that, as the age of PD onset increased, the standardized mortality ratio dropped gradually from 7.3 in men and 6.7 in women in their twenties to 2.5 in both men and in women in their nineties [10]. However, this finding may be controversial, as a systematic review and meta-analysis by Macleod et al. found that, in 15 of 17 studies, older age either at onset or recruitment was associated with increased mortality [11]. This discrepancy could be related to the differing ethnicities of subjects in these studies, as well as the involved countries' economic statuses, study populations, and research methods. The differences in adjusted HRs between men and women were not notable in any of the age groups.

▣ Conclusion, page 19, line 342

[Removed]

The mortality rate was higher in patients ≥75 years old than in those <75 years for both sexes.

Please revise this paragraph in light of the correct interpretation of your data about HRs and age group.

▸ We have done so as described in our response to the reviewer's question on page 16.

▣ Result, page 11, line 221

[Removed]

The crude and adjusted HRs were significantly higher in PD patients ≥75 years of age than in those <75 years regardless of sex. Moreover, the crude and adjusted HRs trended slightly higher in women than in men regardless of age; however, the 95% CIs overlapped.

▣ Discussion, page 16, line 264

[Removed]

The adjusted HRs for mortality were significantly higher in patients ≥75 years of age at the time of PD diagnosis than in those <75 years when diagnosed in both men and women. Older age at onset was most consistently found to be an independent predictor of mortality across studies [4, 12-17]. One study by Morgan et al. produced a contrasting result in that patients with early PD onset (of ages 50 years or younger) appeared to have higher mortality rates than patients with later PD onset [3]; however, we could not compare our results to theirs because we excluded subjects younger than 60 years. While it is unclear why the age of onset affects the mortality rate in the PD patients, a possible explanation is that patients aged ≥75 years at onset may be affected by mortality-causing conditions that were not adjusted for in our study to a greater extent than those <75 years.

As we did not make a direct comparison between men and women in subgroup analysis, we were unable to ascertain whether sex is a factor affecting the mortality rates of patients with PD. While some studies have found that male sex was associated with increased mortality in patients with PD [12-17], others showed this not to be the case [3, 18]. More recent data suggest that, because the general life expectancy of women in general is longer than that of men, the formers' higher mortality rates and greater reductions in lifespan are more apparent when they are afflicted with PD; this would imply that PD progression patterns are not actually different between the sexes with respect to mortality [3].

▣ Discussion, page 16, line 263–page 17 line 280

[Added]

Our subgroup analyses showed that patients with PD had higher mortality rates across all age groups and in both sexes. Previous studies have produced similar data, demonstrating that PD is a risk factor for increased mortality regardless of age and sex [11, 12]. The adjusted HRs were relatively high in patients with PD aged <70 years (2.77 in men and 3.32 in women) but were relatively low in patients with PD aged 70–79 years (2.07 in men and 2.22 in women) and even lower in patients with PD aged >80 years (1.47 in men and 1.73 in women). This phenomenon could be attributed to the death rates themselves increasing in both the control and PD groups as individuals age, which dilutes the impact of PD on the mortality rate of older individuals. A previous literature review by Ishihara et

al. on the estimated life expectancies of UK and European individuals with PD showed that, as the age of PD onset increased, the standardized mortality ratio dropped gradually from 7.3 in men and 6.7 in women in their twenties to 2.5 in both men and in women in their nineties [11]. However, this finding may be controversial, as a systematic review and meta-analysis by Macleod et al. found that, in 15 of 17 studies, older age either at onset or recruitment was associated with increased mortality [12]. This discrepancy could be related to the differing 2ethnicities of subjects in these studies, as well as the involved countries' economic statuses, study populations, and research methods. The differences in adjusted HRs between men and women were not notable in any of the age groups.

▣ Conclusion, page 19, line 342

[Removed]

The mortality rate was higher in patients ≥75 years old than in those <75 years for both sexes.

Line 340: please revise. You haven't reported any mortality rates, and this (again) appears to be the wrong way round.

▸ The mortality rate was reported in the first paragraph of the result section and at the end of Table 1.

[Results, page 9, lines 206–207]

The mortality rate was significantly higher in the PD group than that in the control group (34.6% [1,214/3,510] and 19.0% [2,661/14,040], respectively, P < 0.001)

[Table 1]

Characteristics	Total participants		
	Parkinson's disease (n, %)	Control (n, %)	P-value
Death	1,214 (34.6)	2,661 (19.0)	<0.001*

▸ Moreover, our revisions in the Discussion section, as outlined above, also addressed this point.

Reviewer: 2
Reviewer Name: Dr. Walter Pirker
Institution and Country: Department of Neurology,
Wilhelminenspital, Vienna, Austria
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
This is an interesting study on the mortality of Parkinson’s disease in South Korea. The large population based patient and control sample included was drawn from a nationwide insurance database. Mortality hazard ratio for PD was within the expected range (2.26). In addition to higher mortality caused by neurologic and respiratory disease in PD vs. controls, metabolic, mental, circulatory and genitourinary disease and trauma, were more common in the PD group.
The paper is well written. However, I have a question regarding the epidemiology of PD in South Korea. In addition, I have some reservation regarding the interpretation of the causes of death in PD and their discussion:
Whereas many studies show a somewhat higher prevalence of PD in men, the proportion of males in this population-based study is only 38.1%. Does this reflect the gender distribution in the general Korean population of that age?

▸ According to the only available study on this topic in Korea, the male-to-female ratio among patients with Parkinson’s disease is approximately 0.6 (0.634 in the year 2009, 0.640 in 2010, 0.637 in 2011, 0.648 in 2012, and 0.655 in 2013) (Parkinsonism Relat Disord. 2018;46;e64-e81).These data correspond well with our results.

Cause of death in table 4 is presented as percentage of all PD subjects involved in the study. Presenting individual causes of death as percentage of the deceased PD (or control) subjects may help the reader to get a faster overview. When recalculating the data, neurologic disease (probably PD) was the cause of death in 27% of the deceased PD subjects. In contrast to other studies which found pneumonia to be a prominent cause of death in PD, respiratory disease was rated as primary cause of death in only 8% of the deceased PD subjects (a fact discussed by the authors).

▸ We have now presented the data in a format recommended by the reviewer (reproduced below). The relevant table in the revised paper is Table 3, as the former Tables 1 and 2 have been merged based on the recommendation of Reviewer 1.

▣ Table 3

[Before revision]

Table 4 The difference of mortality rate between Parkinson’s disease and control group according to cause of death

Cause of death	Total participants			
	Parkinson's disease (n = 3,510)	Control (n = 14,040)	Odd ratio (95% CI)	P-value
All of death (n, %)	1214 (34.6)	2661 (19.0)	2.26 (2.08-2.45)	<0.001*
Infection (n, %)	23 (0.7)	74 (0.5)	1.25 (0.78-1.99)	0.375
Neoplasm (n, %)	151 (4.3)	667 (4.8)	0.90 (0.75-1.08)	0.283
Metabolic Disease (n, %)	76 (2.2)	161 (1.1)	1.91 (1.45-2.51)	<0.001*
Mental diseases (n, %)	33 (0.9)	49 (0.3)	2.71 (1.74-4.22)	<0.001*
Neurologic disease (n, %)	328 (9.3)	69 (0.5)	20.87 (16.05-27.14)	<0.001*
Circulatory disease (n, %)	277 (7.9)	705 (5.0)	1.62 (1.40-1.87)	<0.001*
Respiratory disease (n, %)	97 (2.8)	248 (1.8)	1.58 (1.25-2.01)	<0.001*
Digestive disease (n, %)	30 (0.9)	88 (0.6)	1.37 (0.90-2.07)	0.139
Muscular disease (n, %)	8 (0.2)	15 (0.1)	2.14 (0.91-5.04)	0.076
Genitourinary disease (n, %)	25 (0.7)	50 (0.4)	2.01 (1.24-3.25)	0.004*
Trauma (n, %)	64 (1.8)	154 (1.1)	1.68 (1.25-2.25)	0.001*
Others (n, %)	102 (2.9)	381 (2.7)	1.07 (0.86-1.34)	0.533

* Chi-square test or Fisher's exact test. Significance at false discovery rate adjusted P < 0.05

CI: confidence interval

[After revision]

Table 3 Comparison of mortality rates between the Parkinson's disease and control patient groups according to the cause of death

Cause of death	Total participants					
	Parkinson's disease (total n = 3,510)		Control (total n = 14,040)		Odd ratio (95% CI)	P-value
	n of died individual, †%,	‡%	n of died individual, †%,	‡%		
All of death	1,214 (34.6)	100.0	2,661 (19.0)	100.0	2.26 (2.08-2.45)	<0.001*
Infection	23 (0.7)	1.9	74 (0.5)	2.8	1.25 (0.78-1.99)	0.375
Neoplasm	151 (4.3)	12.4	667 (4.8)	25.1	0.90 (0.75-1.08)	0.283
Metabolic Disease	76 (2.2)	6.2	161 (1.1)	6.1	1.91 (1.45-2.51)	<0.001*
Mental diseases	33 (0.9)	2.7	49 (0.3)	1.8	2.71 (1.74-4.22)	<0.001*
Neurologic disease	328 (9.3)	27.0	69 (0.5)	2.6	20.87 (16.05-27.14)	<0.001*
Circulatory disease	277 (7.9)	22.8	705 (5.0)	26.5	1.62 (1.40-1.87)	<0.001*
Respiratory disease	97 (2.8)	8.0	248 (1.8)	9.3	1.58 (1.25-2.01)	<0.001*
Digestive disease	30 (0.9)	2.5	88 (0.6)	3.3	1.37 (0.90-2.07)	0.139
Muscular disease	8 (0.2)	0.7	15 (0.1)	0.6	2.14 (0.91-5.04)	0.076
Genitourinary disease	25 (0.7)	2.1	50 (0.4)	1.9	2.01 (1.24-3.25)	0.004*
Trauma	64 (1.8)	5.3	154 (1.1)	5.8	1.68 (1.25-2.25)	0.001*
Others	102 (2.9)	8.4	381 (2.7)	14.3	1.07 (0.86-1.34)	0.533

* Chi-square test or Fisher's exact test. Significance at false discovery rate-adjusted P < 0.05.
†%, calculated as the proportion of the number of deaths among all participants with/without mortality.
‡% calculated as the proportion of the number of deaths among participants with mortality.
CI, confidence interval.

At the end of the discussion the authors state that metabolic disease, mental diseases, circulatory disease, respiratory disease, genitourinary disease, and trauma are common causes of death in PD patients in addition to PD itself. However, the data presented in Table 4 show that the primary cause of death was attributed to mental and genitourinary diseases in only 2.7 and 2.1% of the deceased PD patients. Taking into account that the majority of PD subjects develop dementia the rate of dementia as primary cause of death seems therefore rather low. In clinical practice, it is often difficult to attribute the primary cause of death in PD to a single system and sometimes even autopsy does not reveal the primary cause of death. These limitations in a study relying on diagnoses from clinical death certificates should be pointed out in the discussion.

▸ The causes of death may be a combination of different illnesses in PD patients. In South Korea, the physician who is the primary caretaker of a particular patient is responsible for signing the death certificate; when there are multiple comorbidities, this physician indicates only the single most likely cause of death on the certificate. Thus, the causes of death that we reported are the most likely causes of death of patients with PD. Nevertheless, this procedure may discount the role of other illnesses that may also have contributed to the death of the patient, and we mentioned this as a limitation in the Discussion section of the revised manuscript, as reproduced below.

▣ Discussion, page 18, line 318–page 19, line 325

[After revision]

Another limitation of our study was that the cause of death may not have encompassed all the different types of illnesses and complications that contributed to the death of a patient with PD. We retrieved the causes of death from death certificates, which only list a single condition. This may have resulted in the underestimation of other illnesses that contributed the death of the patient. Nevertheless, the cause of death reported on a death certificate was the most probable from among the multiple illnesses that may have contributed to the death of the patient; hence, our data ought to be representative in this regard.

Reviewer: 3
Reviewer Name: Giancarlo Logroscino
Institution and Country: University of Bari - Italy
Please state any competing interests or state 'None declared': none declared

Please leave your comments for the authors below
The authors should provide information on the diagnosis of PD in this system. If they don't, they should provide eventually information on a validation study on diagnosis of PD in this cohort.

▸We included participants who visited outpatient clinics, were hospitalized, or both ≥2 times for matters related to a diagnosis of PD. Based on our criteria, the incidence was 30.86 per 100,000 person-years in those aged ≥60 years. According to the only available nationwide study on the incidence and the prevalence of PD in Korea [J Clin Neurol. 2018 Oct; 14(4): 478–486], the incidence of PD ranged from 10.3 to 17.4 at different time points in participants aged ≥40 years. Even though we do not have data for the incidence of PD in Korean population aged ≥60 years, it is assumed that the incidence in this age group would be higher than in those aged ≥40 years because PD is a disease that is predominant in elderly individuals. Our findings are in line with previously published data from other Asian countries even though there could be ethnicity-based differences between Koreans and other Asians [J Epidemiol. 2009;19(6):281-93]. The sentence in question has been revised and clarified as recommended.

▣ Strengths and limitations of this study, page 4, line 68-69

[Before revision]

• The study encompassed all registered patients with PD who were treated at least twice.

[After revision]

• The study encompassed all registered patients with PD who visited outpatient clinics, were hospitalized, or both at least twice.

▣ Materials and methods, page 7, lines 145–146

[Before revision]

For the accuracy of diagnosis, we only selected if the participants were treated ≥ 2 times.

[After revision]

For accurate diagnoses, we only selected participants who visited outpatient clinics, were hospitalized, or both at least twice because of PD.

It would be interesting to study age and mortality across more than two categories (> ansd < 75 years). The change across different categories could be important.

▸ We performed a subgroup analysis of patients aged <70 years, 70–79 years, and ≥80 years as recommended. The results are now reported, as reproduced below.

▣ Table 2

[Before revision]

Table 3 Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of Parkinson's disease for mortality according to age

Characteristics	Hazard ratio (95% CI)			
	Crude	P-value	Adjusted†	P-value
Age < 75 years old, men (n = 3,895)				
Parkinson's disease		< 0.001*		< 0.001*
Yes	2.59 (2.24-2.98)		2.66 (2.31-3.06)	
No	1.00		1.00	
Age < 75 years old, women (n = 5,860)				
Parkinson's disease		< 0.001*		< 0.001*
Yes	3.26 (2.80-3.81)		3.37 (2.88-3.93)	
No	1.00		1.00	
Age ≥ 75 years old, men (n = 2,785)				
Parkinson's disease		< 0.001*		< 0.001*
Yes	1.73 (1.50-1.99)		1.77 (1.54-2.03)	
No	1.00		1.00	
Age ≥ 75 years old, women (n = 5,010)				
Parkinson's disease		< 0.001*		< 0.001*
Yes	1.89 (1.68-2.13)		1.96 (1.74-2.20)	
No	1.00		1.00	

*Cox-proportional hazard regression model, Significance at P < 0.05

†Adjusted model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia

[After revision]

Table 2 Cox proportional hazards analyses of mortality due to Parkinson's disease

Characteristics	Hazard ratio (95% CI)			
	Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 17,550)				
Parkinson's disease	2.29 (2.13-2.45)	< 0.001*	2.09 (1.94-2.24)	< 0.001*
Control	1.00		1.00	
Age < 70 years old, men (n = 2,115)				
Parkinson's disease	3.04 (2.45-3.77)	< 0.001*	2.77 (2.23-3.45)	< 0.001*
Control	1.00		1.00	
Age < 70 years old, women (n = 3,125)				
Parkinson's disease	4.11 (3.24-5.21)	< 0.001*	3.32 (2.60-4.25)	< 0.001*
Control	1.00		1.00	
Age 70-79 years old, men (n = 3,280)				
Parkinson's disease	2.27 (1.96-2.63)	< 0.001*	2.07 (1.78-2.41)	< 0.001*
Control	1.00		1.00	
Age 70-79 years old, women (n = 5,410)				
Parkinson's disease	2.41 (2.10-2.78)	< 0.001*	2.22 (1.92-2.55)	< 0.001*
Control	1.00		1.00	
Age ≥ 80 years old, men (n = 1,285)				
Parkinson's disease	1.53 (1.25-1.88)	< 0.001*	1.47 (1.20-1.82)	< 0.001*
Control	1.00		1.00	
Age ≥ 80 years old, women (n = 2,335)				
Parkinson's disease	1.83 (1.55-2.17)	< 0.001*	1.73 (1.46-2.05)	< 0.001*
Control	1.00		1.00	

*Cox-proportional hazard regression model; significance at P < 0.05

† Stratified model for age, sex, income, and region of residence.

‡ Model adjusted for the Charlson comorbidity index.

HR, hazard ratio; CI, confidence interval.

▣ Result, page 11, line 221

[Removed]

The crude and adjusted HRs were significantly higher in PD patients ≥75 years of age than in those <75 years regardless of sex. Moreover, the crude and adjusted HRs trended slightly higher in women

than in men regardless of age; however, the 95% CIs overlapped.

▣ Discussion, page 16, line 264

[Removed]

The adjusted HRs for mortality were significantly higher in patients ≥75 years of age at the time of PD diagnosis than in those <75 years when diagnosed in both men and women. Older age at onset was most consistently found to be an independent predictor of mortality across studies [4, 12-17]. One study by Morgan et al. produced a contrasting result in that patients with early PD onset (of ages 50 years or younger) appeared to have higher mortality rates than patients with later PD onset [3]; however, we could not compare our results to theirs because we excluded subjects younger than 60 years. While it is unclear why the age of onset affects the mortality rate in the PD patients, a possible explanation is that patients aged ≥75 years at onset may be affected by mortality-causing conditions that were not adjusted for in our study to a greater extent than those <75 years.

As we did not make a direct comparison between men and women in subgroup analysis, we were unable to ascertain whether sex is a factor affecting the mortality rates of patients with PD. While some studies have found that male sex was associated with increased mortality in patients with PD [12-17], others showed this not to be the case [3, 18]. More recent data suggest that, because the general life expectancy of women in general is longer than that of men, the formers' higher mortality rates and greater reductions in lifespan are more apparent when they are afflicted with PD; this would imply that PD progression patterns are not actually different between the sexes with respect to mortality [3].

▣ Discussion, page 16, line 263–page 17 line 280

[Added]

Our subgroup analyses showed that patients with PD had higher mortality rates across all age groups and in both sexes. Previous studies have produced similar data, demonstrating that PD is a risk factor for increased mortality regardless of age and sex [11, 12]. The adjusted HRs were relatively high in patients with PD aged <70 years (2.77 in men and 3.32 in women) but were relatively low in patients with PD aged 70–79 years (2.07 in men and 2.22 in women) and even lower in patients with PD aged >80 years (1.47 in men and 1.73 in women). This phenomenon could be attributed to the death rates themselves increasing in both the control and PD groups as individuals age, which dilutes the impact of PD on the mortality rate of older individuals. A previous literature review by Ishihara et al. on the estimated life expectancies of UK and European individuals with PD showed that, as the age of PD onset increased, the standardized mortality ratio dropped gradually from 7.3 in men and 6.7 in women in their twenties to 2.5 in both men and in women in their nineties [11]. However, this finding may be controversial, as a systematic review and meta-analysis by Macleod et al. found that, in 15 of 17 studies, older age either at onset or recruitment was associated with increased mortality [12]. This discrepancy could be related to the differing ethnicities of subjects in these studies, as well as the involved countries' economic statuses, study populations, and research methods. The

differences in adjusted HRs between men and women were not notable in any of the age groups.

▣ Conclusion, page 19, line 342

[Removed]

The mortality rate was higher in patients ≥75 years old than in those <75 years for both sexes.

It would be useful to know the completeness of the information on causes of death in the death certificate in this cohort.

▸ The causes of death may be a combination of different illnesses in PD patients. In South Korea, the physician who is primarily responsible for a particular patient is responsible for the signing the death certificate; when there are multiple comorbidities, this physician indicates only the single most likely cause of death on the certificate. Thus, the causes of death that we reported are the most likely causes of death of patients with PD. Nevertheless, this procedure may discount the role of other illnesses that may also have contributed the death of the patient, and we mentioned this as a limitation in the Discussion section of the revised manuscript, as reproduced below.

▣ Discussion, page 18, line 318–page 19, line 325

[After revision]

Another limitation of our study was that the cause of death may not have encompassed all the different types of illnesses and complications that contributed to the death of a patient with PD. We retrieved the causes of death from death certificates, which only list a single condition. This may have resulted in the underestimation of other illnesses that contributed the death of the patient. Nevertheless, the cause of death reported on a death certificate was the most probable from among the multiple illnesses that may have contributed to the death of the patient; hence, our data ought to be representative in this regard.

Do the authors have any information on the presence of cognitive impairment in their cases and controls?

▸ We appreciate the reviewer's question. While it would have been helpful to have information on the presence of cognitive impairment in our PD subjects and controls, these data were not available. We have now mentioned this as a limitation.

▣ Discussion, page 18, lines 314–318

[Before revision]

A limitation of our study was that we were unable to determine the severity of PD. In the same context, we did not stratify patients by their hospitalization histories or disease durations, which may have

skewed the mortality data. Furthermore, some confounding factors that can influence mortality, such as smoking status, alcohol consumption, and obesity, were not adjusted for [26-28].

[After revision]

A limitation of our study was that we were unable to determine the severity of PD. In the same context, we did not stratify patients by their hospitalization histories, disease durations, or the presence of mental illness, which may have skewed the mortality data. Furthermore, some confounding factors that can influence mortality, such as smoking status, alcohol consumption, and obesity, were not adjusted for [26-28].

It is not clear if the authors take into account comorbidities in the estimate of risk of death.

▸ We calculated the Charlson comorbidity index and accordingly adjusted the model for 17 disease categories. We appreciate this recommendation.

▣ Table 1

[Before revision]

Table 1 General Characteristics of Participants

Characteristics	Total participants		
	Parkinson's disease (n, %)	Control (n, %)	P-value
Age (years old)			1.000
60-64	388 (11.1)	1,552 (11.1)	
65-69	660 (18.8)	2,640 (18.8)	
70-74	903 (25.7)	3,612 (25.7)	
75-79	835 (23.8)	3,340 (23.8)	
80-84	498 (14.2)	1,992 (14.2)	
85+	226 (6.4)	904 (6.4)	
Sex			1.000
Male	1,336 (38.1)	5,344 (38.1)	
Female	2,174 (61.9)	8,696 (61.9)	
Income			1.000
1 (lowest)	325 (9.3)	1,300 (9.3)	
2	283 (8.1)	1,132 (8.1)	
3	145 (4.1)	580 (4.1)	
4	154 (4.4)	616 (4.4)	
5	179 (5.1)	716 (5.1)	
6	190 (5.4)	760 (5.4)	
7	251 (7.2)	1,004 (7.2)	
8	256 (7.3)	1,024 (7.3)	

9	383 (10.9)	1,532 (10.9)	
10	584 (16.6)	2,336 (16.6)	
11 (highest)	760 (21.7)	3,040 (21.7)	
Region of residence			1.000
Urban	1,467 (41.8)	5,868 (41.8)	
Rural	2,043 (58.2)	8,172 (58.2)	
Hypertension			1.000
Yes	2,544 (72.5)	10,176 (72.5)	
No	966 (27.5)	3,864 (27.5)	
Diabetes			1.000
Yes	1,386 (39.5)	5,544 (39.5)	
No	2,124 (60.5)	8,496 (60.5)	
Dyslipidemia			1.000
Yes	1,185 (33.8)	4,740 (33.8)	
No	2,325 (66.2)	9,300 (66.2)	
Death			<0.001*
Yes	1,214 (34.6)	2,661 (19.0)	
No	2,296 (65.4)	11,379 (81.0)	

*Chi-square test or Fisher's exact test. Significance at P < 0.05

[After revision]

Table 1 General characteristics of the participants

Characteristics	Total participants		
	Parkinson's disease (n, %)	Control (n, %)	P-value
Age (years old)			1.000
60-64	388 (11.1)	1,552 (11.1)	
65-69	660 (18.8)	2,640 (18.8)	
70-74	903 (25.7)	3,612 (25.7)	
75-79	835 (23.8)	3,340 (23.8)	
80-84	498 (14.2)	1,992 (14.2)	
85+	226 (6.4)	904 (6.4)	
Sex			1.000
Male	1,336 (38.1)	5,344 (38.1)	
Female	2,174 (61.9)	8,696 (61.9)	
Income			1.000
1 (lowest)	325 (9.3)	1,300 (9.3)	
2	283 (8.1)	1,132 (8.1)	
3	145 (4.1)	580 (4.1)	

4	154 (4.4)	616 (4.4)	
5	179 (5.1)	716 (5.1)	
6	190 (5.4)	760 (5.4)	
7	251 (7.2)	1,004 (7.2)	
8	256 (7.3)	1,024 (7.3)	
9	383 (10.9)	1,532 (10.9)	
10	584 (16.6)	2,336 (16.6)	
11 (highest)	760 (21.7)	3,040 (21.7)	
Region of residence			1.000
Urban	1,467 (41.8)	5,868 (41.8)	
Rural	2,043 (58.2)	8,172 (58.2)	
† CCI score			<0.001*
0	325 (9.3)	3,049 (21.7)	
1	132 (3.8)	659 (4.7)	
2	240 (6.8)	1,173 (8.4)	
≥ 3	2,813 (80.1)	9,159 (65.2)	
Death	1,214 (34.6)	2,661 (19.0)	<0.001*

*Chi-square test or Fisher's exact test. Significance at P < 0.05

† CCI, Charlson Comorbidity Index (calculated without including pulmonary disease).

▣ Table 2

[Before revision]

Table 2 Crude and adjusted hazard ratios (95% confidence interval) of Parkinson's disease for mortality

Characteristics	Hazard ratio (95% CI)			
	Crude	P-value	Adjusted†	P-value
Parkinson's disease		< 0.001*		< 0.001*
Yes	2.14 (2.00-2.29)		2.26 (2.11-2.42)	
No	1.00		1.00	

*Cox-proportional hazard regression model, Significance at P < 0.05

†Adjusted model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia

Table 3 Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of Parkinson's disease for mortality according to age

Characteristics	Hazard ratio (95% CI)			
	Crude	P-value	Adjusted†	P-value
Age < 75 years old, men (n = 3,895)				
Parkinson's disease		< 0.001*		< 0.001*
Yes	2.59 (2.24-2.98)		2.66 (2.31-3.06)	

No	1.00		1.00	
Age < 75 years old, women (n = 5,860)				
Parkinson's disease		< 0.001*		< 0.001*
Yes	3.26 (2.80-3.81)		3.37 (2.88-3.93)	
No	1.00		1.00	
Age ≥ 75 years old, men (n = 2,785)				
Parkinson's disease		< 0.001*		< 0.001*
Yes	1.73 (1.50-1.99)		1.77 (1.54-2.03)	
No	1.00		1.00	
Age ≥ 75 years old, women (n = 5,010)				
Parkinson's disease		< 0.001*		< 0.001*
Yes	1.89 (1.68-2.13)		1.96 (1.74-2.20)	
No	1.00		1.00	

*Cox-proportional hazard regression model, Significance at P < 0.05

†Adjusted model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia

[After revision]

Table 2 Cox proportional hazards analyses of mortality due to Parkinson's disease

Characteristics	Hazard ratio (95% CI)			
	Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 17,550)				
Parkinson's disease	2.29 (2.13-2.45)	< 0.001*	2.09 (1.94-2.24)	< 0.001*
Control	1.00		1.00	
Age < 70 years old, men (n = 2,115)				
Parkinson's disease	3.04 (2.45-3.77)	< 0.001*	2.77 (2.23-3.45)	< 0.001*
Control	1.00		1.00	
Age < 70 years old, women (n = 3,125)				
Parkinson's disease	4.11 (3.24-5.21)	< 0.001*	3.32 (2.60-4.25)	< 0.001*
Control	1.00		1.00	
Age 70-79 years old, men (n = 3,280)				
Parkinson's disease	2.27 (1.96-2.63)	< 0.001*	2.07 (1.78-2.41)	< 0.001*
Control	1.00		1.00	
Age 70-79 years old, women (n = 5,410)				
Parkinson's disease	2.41 (2.10-2.78)	< 0.001*	2.22 (1.92-2.55)	< 0.001*
Control	1.00		1.00	
Age ≥ 80 years old, men (n = 1,285)				
Parkinson's disease	1.53 (1.25-1.88)	< 0.001*	1.47 (1.20-1.82)	< 0.001*
Control	1.00		1.00	

Age ≥ 80 years old, women (n = 2,335)				
Parkinson's disease	1.83 (1.55-2.17)	< 0.001*	1.73 (1.46-2.05)	< 0.001*
Control	1.00		1.00	

*Cox-proportional hazard regression model; significance at P < 0.05

† Stratified model for age, sex, income, and region of residence.

‡ Model adjusted for the Charlson comorbidity index.

HR, hazard ratio; CI, confidence interval.

VERSION 2 – REVIEW

REVIEWER	Angus Macleod University of Aberdeen, UK
REVIEW RETURNED	16-May-2019

GENERAL COMMENTS	The changes have greatly improved this manuscript. I have only one change to suggest now. In line 159, you refer to the date of diagnosis of PD, and also in other places in the manuscript. This is incorrect for patients diagnosed before 2002, many of whom would have had PD for several years prior to their identification for the study. Please change date of diagnosis to date of identification, or index date, or similar.

REVIEWER	Walter Pirker Dept. of Neurology, Wilhelminenspital, Vienna, Austria
REVIEW RETURNED	30-Apr-2019

GENERAL COMMENTS	This is an interesting paper on the mortality of PD in South Korea. While most questions raised by the reviewers have been addressed by the authors, the sex distribution of the studied PD sample (38% male, 62% female) still puzzles me. Almost all epidemiological studies show a higher incidence of PD in males, especially in those with late onset of disease (see e.g. Savica, JAMA Neurol 2013;70:859-866). Is the reverse sex distribution in the study under review due to the general sex distribution in the elderly Korean population or due to methodological reasons? A discussion of this issue should be added to the manuscript.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name: Walter Pirker
Institution and Country: Dept. of Neurology, Wilhelminenspital, Vienna, Austria
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
This is an interesting paper on the mortality of PD in South Korea.
While most questions raised by the reviewers have been addressed by the authors, the sex distribution of the studied PD sample (38% male, 62% female) still puzzles me. Almost all epidemiological studies show a higher incidence of PD in males, especially in those with late onset of disease (see e.g. Savica, JAMA Neurol 2013;70:859-866). Is the reverse sex distribution in the study under review due to the general sex distribution in the elderly Korean population or due to methodological reasons? A discussion of this issue should be added to the manuscript.

▸ The prevalence of PD in Korea has not yet been extensively studied, and there are only a very few published reports on this topic. In a study using randomly selected individuals over 60 years of age in a rural city cohort, Seo et al. reported that the crude prevalence of PD was 498 and 271 per 100,000 population among men and women, respectively [J Clin Neurosci. 2007 Dec;14(12):1155-7.]. In a larger study of individuals ≥40 years of age using the National Health Insurance Service-National Sample Cohort Database, Lee et al. reported a slightly higher prevalence in women (47.4 per 100,000 population) than in men (35.4 per 100,000 population) in 2004; these rates gradually increased to 167.3 and 117.7 per 100,000 population , respectively, in 2013, with the same trend maintained throughout the intervening period [J Korean Neurol Assoc. 2017;35(4):191-198]. The authors also reported that the prevalence of PD dramatically increases with age; the rates in 2004 were 8.1 and 310.9 per 100,000 population in those 40–49 years and ≥80 years, respectively, and by 2013 rose to 20.9 and 1,226.3 per 100,000 population, respectively.
Nevertheless, the prevalence of PD in each sex group should be distinguished from the proportion of patients of each sex among PD patients. The higher proportion of female patients in our cohort does not necessarily mean that the prevalence of PD is higher in woman than in men in Korea. We are aware of no study that investigated the ratio of male to female patients with PD in Korea.
The reason for a higher proportion of women than men among patients with PD in our study could be attributable to the survival effect. The life expectancy of men is shorter than that of women in Korea (74.65 years vs. 81.48 years in 2004 and 80.01 years vs. 86.04 years in 2017) [BMJ Open. 2019 Jul 3;9(7):e030683.]. Shin et al. reported that, among individuals ≥80 years of age, 29.5% of deaths were among men whereas 58.0% were among women [J Korean Med Assoc 2018 September; 61(9):573-584]. Taken together, we can speculate that the population of women with PD is higher than that of men with PD among octogenarians.
Tables 1 and 2 in our paper support the reasoning above even though the proportions of PD

patients in our original study cohort differ from those in the abovementioned studies since we had our own patient selection criteria to ensure the inclusion only of those properly diagnosed with PD (as stated in the Materials and Methods section). There were relatively high numbers of patients in the 80–84 year and ≥85 year age groups (Table 1); however, the overall population of these age groups are likely be much lower than those in the 60–64 year and the 65–69 year age groups. It is also notable that the 70–74 year and 75–79 year age groups comprised the largest numbers of patients. The number of subjects of each sex in each age group reflects the number of PD patients within each as well, because 1:4 matched controls were selected (Table 2). This not only confirms that there were relatively high numbers of patients in the 80–84 year and ≥85 year age groups, but also shows that the male-to-female ratio of PD patients in those <70 years was higher than that in the 70–79 year group. Patients ≥80 years had the lowest male-to-female ratio. Again, the higher number of female patients with PD in our study ought to be attributable to the higher number of females than males in the general Korean population as well as the higher prevalence of PD in elderly individuals, particularly those over 80 years.

In our revised manuscript we have commented on this issue in the Discussion section, as below.

▣ Discussion

An interesting observation was that the proportion of female patients with PD was higher than that of their male counterparts (Table 1). No studies have investigated the sex ratio of patients with PD in Korea to date, so we had no records to compare our results to. However, this observation should be interpreted considering the prevalence of PD among each of the sexes in Korea, the prevalence of PD in different age groups, and the different life expectancies of men and women in Korea. A recent large-scale study utilizing the National Health Insurance Service-National Sample Cohort Database by Lee et al. found that the prevalence of PD in Korea was slightly higher among women (47.4 per 100,000 population) than among men (35.4 per 100,000 population) in 2004; these rates gradually increased to 167.3 and 117.7 per 100,000 population, respectively, in 2013 [20]. Lee et al.'s study also found that the prevalence of PD dramatically increased with age; the PD rates in 2004 were 8.1 and 310.9 per 100,000 population among 40–49- and ≥80-year-old subjects, respectively, and had risen to 20.9 and 1,226.3 per 100,000 population, respectively, in 2013. The proportion of individuals in our overall cohort who had PD was different from those in the abovementioned studies because, as stated in Materials and Methods, we used different criteria in selecting PD patients to ensure their actual diagnosis with the disease. Moreover, the life expectancy of men in Korea is shorter than that of women (74.65 vs. 81.48 years, respectively, in 2004 and 80.01 vs. 86.04 years, respectively, in 2017) [21]. Shin et al. reported that the rates of death among individuals ≥80 years of age were 29.5% for men and 58.0% for women [22].

Taken together, we can speculate that the relatively high proportion of women in both the general and PD patient populations in Korea (particularly older age groups, which have a higher prevalence of PD and longer life expectancy) could have resulted in a higher proportion of women with the disease than men. This reasoning is supported by the relatively high number of patients with PD in the older age groups as shown in Tables 1 and 2. Our results not only confirm that there were relatively high numbers of patients with PD in the 80–84- and ≥85-year age groups, but also show

that the male-to-female ratio among patients with PD who are <70 years was higher than that in patients 70–79 years; those ≥80 years showed the lowest male-to-female ratio. Further studies regarding the male/female proportions among patients with PD in different age groups would be helpful to clarify these patterns

Reviewer: 1
Reviewer Name: Angus Macleod
Institution and Country: University of Aberdeen, UK
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
The changes have greatly improved this manuscript. I have only one change to suggest now. In line 159, you refer to the date of diagnosis of PD, and also in other places in the manuscript. This is incorrect for patients diagnosed before 2002, many of whom would have had PD for several years prior to their identification for the study. Please change date of diagnosis to date of identification, or index date, or similar.

▸We thank the reviewer for pointing out that the term 'the date of diagnosis of PD' was misleading. We replaced these words with 'the date of the first clinic or hospital visit for PD during the study period' in the Participant Selection section.

▣ Materials and Methods, page 7, line 147
[Before revision]
From among 1,125,691 individuals with 114,369,638 medical claim codes, we included participants who were diagnosed with PD between 2002 and 2013 (n = 4,169).
[After revision]
From among 1,125,691 individuals with 114,369,638 medical claim codes, we included participants who visited a clinic or hospital for PD-related reasons between 2002 and 2013 (n = 4,169).

▣ Materials and Methods, page 7, line 154
[Before revision]
We set the index date as that of the diagnosis of PD in the PD group; participants from the control group were also followed from the same index date as their matched counterparts with PD.
[After revision]
We set the index date for the PD group as that of the first visit to a clinic or hospital for PD during the study period; participants from the control group were also followed from the same index date as their matched counterparts with PD.

VERSION 3 – REVIEW

REVIEWER	Walter Pirker Department of Neurology Wilhelminenspital Vienna, Austria
REVIEW RETURNED	31-Aug-2019

GENERAL COMMENTS	This is an important study on the mortality of Parkinson's disease in the Korean population. The authors have addressed all important issues raised by the reviewers including the unusual sex distribution in their PD population and the limitations of clinical diagnoses on death certificates. Overall the manuscript has greatly benefited from the revision and seems acceptable in the present form.