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Mortality and cause of death in Parkinson's disease patients: A longitudinal follow-up study using a national sample cohort

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ABSTRACT

Objective: The prevalence of Parkinson's disease (PD) is growing rapidly owing to the aging population. We investigated the mortality rates and causes of death in South Korean patients with PD.

Design: We investigated a national cohort using the nationwide insurance database.

Setting: Korean Health Insurance Review and Assessment Service - National Sample Cohort.

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.

Interventions: None

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.

Results: The adjusted hazard ratio (HR) for mortality in the PD group was 2.26 (95% confidence interval [CI] = 2.11–2.42, P < 0.001). Subgroup analysis according to age (<75 years vs. ≥75 years) and sex revealed that patients with PD showed higher adjusted HRs for mortality across all subgroups. Mortalities caused by metabolic, mental, neurologic, disease, disease, and genitourinary diseases, as well as trauma, were more common in the PD group than in the control group, with the highest odds ratio observed in patients with neurologic disease.

Conclusions: We demonstrated that PD in South Korean patients ≥60 years of age was associated with increased mortality in both sexes regardless of age.

Key words: Parkinson's disease, mortality, Korean

Strengths and limitations of this study

- Our study dataset encompassed 1,125,691 subjects registered over a 12-year period in a national insurance database.
- The study encompassed all registered patients with PD who were treated at least twice.
- The patients were not restricted to only those who were hospitalized.
- The patients with PD were matched 1:4 with control subjects based on age, group, sex, income group, regions of residence, and the past medical histories.
- We were unable to determine the severity of PD, and some confounding factors (e.g., smoking status, alcohol consumption, and obesity) were not adjusted for.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder, and is characterized by the 4 cardinal motor signs: tremor at rest, bradykinesia, rigidity, and postural instability, as well as other non-motor clinical manifestations [1, 2]. Despite the remarkable symptom-relieving benefits provided by levodopa over the past 30 years, recent studies have demonstrated that the mortality rates among PD patients remain higher than in individuals without PD [3, 4]. PD is one of the fastest growing diseases in terms of prevalence, disability, and mortality; the rapidly aging population has contributed to an increase in crude PD

prevalence rates [5]. As such, a better understanding of the rates and causes of mortality in patients with PD is important to better estimate the social burden and medical care costs [6].

Even though PD is associated with increased mortality in general, previous studies show inconsistent data, with mortality rates ranging from 0.80 to 3.50 [2]. Some studies performed in the post-levodopa era even reported "super-normal" survival rather than increased mortality among PD patients [2]. Furthermore, the causes of death in patients with PD remain unclear [7]. The heterogeneity observed in studies of mortality as related to PD could be caused by the variable methodology and patient selection criteria. Different studies tend to be hospital-, pharmaceutical trial- or community-based, and thus yield results that are not very representative of the general population [6].

According to Global Burden of Disease, Injuries, and Risk Factors Study of 2016, the death rate, prevalence, and disability-adjusted life-years of patients with PD varied depending on ethnicity and/or geography [5]. Among high-income Asia Pacific countries, South Korea showed the highest percentage change in age-standardized mortality rates between 1990 and 2016 (24.6%) compared to Brunei (17.9%), Japan (10.2%), and Singapore (11.3%), even though the percentage change in age-standardized rates of prevalence during the same time period (21.0%) was similar to that of Japan (21.3%) [5]. Thus, analyses focused on a particular ethnic/geographic group is important to estimate the social burden of PD and the patient management plan in each country. However, a large cohort-based investigation of PD-related mortality rates and causes of death in South Korea has never been performed.

To better understand the natural courses and prognoses of patients with PD, and to provide valuable information on the planning the distribution of health resources, we investigated the mortality rates and causes of death in patients with PD using a representative PD population in South Korea. We performed a large-scale longitudinal follow-up study with a maximum follow-up duration of 12 years, using national cohort data.

MATERIALS AND METHODS

Study Population and Data Collection

The ethics committee of Hallym University (2014-I148) approved the use of these data. Written informed consent was exempted by the Institutional Review Board.

This national cohort study relies on data from the Korean Health Insurance Review and Assessment Service - National Sample Cohort (HIRA-NSC). The Korean National Health Insurance Service (NHIS) selects samples directly from the entire population database to prevent non-sampling errors. Approximately 2% of the samples (one million) were selected from the entire Korean population (50 million). This selected data can be classified at 1,476 levels (age [18 categories], sex [2 categories], and income level [41 categories]) using randomized stratified systematic sampling methods via proportional allocation to represent the entire population. After data selection, the appropriateness of the sample was verified by a statistician who compared the data from the entire Korean population to the sample data. The details of the methods used to perform these procedures are provided by the National Health Insurance Sharing Service [8]. This cohort database included (i) personal information, (ii) health insurance claim codes (procedures and prescriptions), (iii) diagnostic codes using the International Classification of Disease-10 (ICD-10), (iv) death records from the Korean National Statistical Office (using the Korean Standard Classification of disease), (v) socio-economic data (residence and income), and (vi) medical examination data for each participant over a period ranging from 2002 to 2013.

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 register individual patients in the medical insurance

system. Therefore, the risk of overlapping medical records is minimal, even if a patient moves from one place to another. Moreover, all medical treatments in Korea can be tracked without exception using the HIRA system. In Korea, notice of death to an administrative entity is legally required before a funeral can be held. Causes of death and date are recorded by medical doctors on a death certificate.

Participants Selection

Out of 1,125,691 cases with 114,369,638 medical claim codes, we included participants who were diagnosed as PD from 2002 through 2013 (n = 4,169). PD was categorized using ICD-10 codes (Parkinson's disease: G20). For the accuracy of diagnosis, we only selected if the participants were treated ≥ 2 times. The control participants were extracted from 1,121,522 participants who were never diagnosed PD from 2002 through 2013 among this cohort.

The PD participants were matched 1:4 with control group. The matches were processed for age, group, sex, income group, region of residence, the past medical histories of hypertension, diabetes mellitus, and dyslipidemia. To prevent selection bias when selecting the matched participants, the control group participants were sorted using a random number order, and they were then selected from top to bottom. It was assumed that the matched control participants were involved at the same time of each matched PD participants. Therefore, the control group who died before the involvement time of the matched PD participant was excluded. The PD participants for whom we could not identify enough matching participants were excluded (n = 40). The participants who were diagnosed as PD under 60 years old were excluded (n = 619) in that the prevalence of PD was relatively low under that ages [9]. Finally, 1:4 matching resulted in the inclusion of 3,510 of PD participants and 14,040 control participants (Fig. 1).

Variables

The age groups were classified using 5-year intervals: 60-64, 65-69, 70-74…, and 85+ years old. A total of 6 age groups were designated. The income groups were initially divided into 41 classes (one health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were re-categorized into 11 classes (class 1 [lowest income]-11 [highest income]). Region of residence was divided into 16 areas according to administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

Cause of death were classified following Korean standard classification of diseases (KCD), which was developed based on the International Statistical Classification of Diseases and Related Health Problems (ICD) by World Health Organization (WHO). Therefore, the causes of death were categorized by 12 classification and we added one (others), which had the limited the number of participants: (i) Infection (Certain infections and parasitic diseases, A00-B99); (ii) Neoplasm (Neoplasm, C00-D48); (iii) Metabolic disease (Endocrine, nutritional and metabolic diseases, E00-E90); (iv) Mental disease (Mental and behavioural disorders, F00-F99); (v) Neurologic disease (Diseases of the nervous system, G00-G99); (vi) Circulatory disease (Diseases of the circulatory system, I00-I99); (vii) Respiratory disease (Diseases of the respiratory system, J00-J99); (viii) Digestive disease (Diseases of the digestive system, K00-K93); (ix) Muscular disease (Diseases of the musculoskeletal system and connective tissue, M00-M99); (x) Genitourinary disease (Diseases of the genitourinary system, N00-N99); (xi) Abnormal finding (Symptoms, signs and abnormal clinical and laboratory findings, NEC, R00-R99); (xii) Trauma (Injury, poisoning and certain other consequences of external causes, S00-T98); (xiii) Others (Diseases of the blood and blood-

forming organs and certain disorders involving the immune mechanism, D50-D89; Diseases of the skin and subcutaneous tissue, L00-L99).

The past medical histories of participants were evaluated using ICD-10 codes. For the accuracy of diagnosis, hypertension (I10 and I15), diabetes (E10-E14), and hyperlipidemia (E78) were checked if the participants were treated ≥ 2 times.

Statistical Analyses

Chi-square test was used to compare the general characteristics of participants.

Chi-square test or Fisher's exact test was used to compare the rate of mortality between PD and control group according to cause of death. In this analysis, to adjust expected value of wrong declined null hypothesis, false discovery rate was used.

To analyze the hazard ratio (HR) of PD on mortality, 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. 95% confidence interval (CI) were calculated. Two-tailed analyses were conducted, and P values less than 0.05 were considered to indicate significance. The results were statistically analyzed using SPSS v. 21.0 (IBM, Armonk, NY, USA).

RESULTS

The mean follow-up duration was 49.6 months (standard deviation [SD] = 37.3 months) in the PD group and 57.3 (SD = 40.6) months in the matched control group.

Age, sex, income level, region of residence, hypertension status, diabetes status, and dyslipidemia status 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% and 19.0%, respectively, $P < 0.001$).

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 $P < 0.05$

The crude and adjusted HRs for mortality in the PD group were 2.14 (95% CI = 2.00–2.29, $P < 0.001$) and 2.26 (95% CI = 2.11–2.42, $P < 0.001$), respectively (Table 2). When categorizing patients according to age (<75 years vs. ≥75 years) and sex, PD patients in all the subgroups showed higher crude and adjusted HRs for mortality than did the control patients (Table 3). 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.

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

Analysis of mortality rates according to the cause of death revealed an odds ratio (OR) for overall mortality of 2.26 (95% CI = 2.08–2.45, P < 0.001) in the PD group (Table 4); the detailed data are presented in Supplementary Table 1. Mortalities caused by metabolic disease, mental diseases, neurologic disease, circulatory disease, respiratory disease, genitourinary disease and trauma were higher in the PD group than in the control group (the false discovery rate-adjusted P-value was <0.05 for each). The OR for mortality was highest for neurologic disease (20.87, 95% CI = 16.05–27.14, P < 0.001); among these neurologic diseases, extrapyramidal and movement disorders were the most common (294/328, 89.6%). Mortalities caused by infection, neoplasm, digestive disease, muscular disease, and other causes were not significantly different between the PD and control groups.

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

DISCUSSION

Our findings were consistent with those of previous studies, most of which found higher mortality rates in patients with PD with HRs ranging from 1.2 to 2.4 [10, 11]. However, most such studies were performed in Western countries, and data from Asian patients have rarely been reported. A recent study in China found that the standardized mortality rate of patients with PD was 0.62 (95% CI = 0.32–1.07), implying that the 5-year mortality ratio of patients with PD was not significantly higher than that of the general urban Chinese population [2]. However, we cannot compare their results to ours given their different study design; the Chinese study comprised 157 PD patients who were referred to - or diagnosed at - a particular tertiary hospital. To our knowledge, ours is the first study to demonstrate that mortality rates are higher in Korean PD patients using a national cohort, and is also the largest study of its kind to date. The adjusted HR of our study (2.26) was relatively higher than in previous studies considering that most reported HRs fall between 1.2 and 2.4, however, this is of little relevance owing to the major heterogeneity among the study methodologies. Nevertheless, our data still show that the mortality of patients with PD is higher than that in control populations despite recent advances in the treatment of this disease. This indicates that, while current treatment modalities relieve motor symptoms, they do not necessarily improve mortality rates and/or the life expectancies of patients with PD.

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].

In our study, patients with PD died more frequently of certain diseases and of trauma than their counterparts in the control population. Neurologic diseases (particularly extrapyramidal and movement disorders) were the most common causes of death, implying that PD features themselves were most responsible for death among PD patients in South Korea. Such studies of the outcomes of PD patients are scarce. In a study of mortality among 211 levodopa-treated patients with PD in the United Kingdom, Morgan et al. showed that the most common cause of death was PD itself (52.6%) [3]. They interpreted this to indicate that,

even though levodopa might improve motor symptoms such as tremor, bradykinesia, and rigidity, it did not slow disease progression [19]. As the PD progressed, levodopa-resistant motor symptoms (speech/swallowing impairment, gait, and balance problems) and nonmotor symptoms (autonomic dysfunction, mood disorders, cognitive impairment, sleep disorders, and psychosis) become more prevalent and may contribute to the increased morbidity and mortality [20]. Although our study cohort was not necessarily confined to levodopa-treated subjects, it is highly likely that a significant proportion of our patients might have been treated by levodopa, as we only selected patients who were treated ≥2 times for PD. Our findings are different from those of other groups that found pneumonia to be the most common cause of death in PD patients [21-24]. The most likely explanation for this difference could be the varying methods of patient recruitment: we recruited our subjects based on their PD treatment history regardless of whether they were hospitalized; therefore, the cause of death among our patients; i.e., neurologic disease that may have included PD itself, may also reflect patients having died of other (perhaps natural) causes while afflicted with PD. However, the causes of death in hospitalized or nursing home-bound PD patients may have had a greater likelihood of being reported as pneumonia because of their orthostatic lability. Furthermore, our indication that PD-group patients did not necessarily die of pneumonia is true insofar as being compared to the control group, and is not a general statement, since we calculated the ORs of the cause of mortality. The significance of other causes of death such as cancer and circulation-impeding ischemic heart disease remain controversial [1, 2, 21-25]; the ORs for these conditions were not significant in our study. Nevertheless, our most important findings include (i) the overall death rate was higher in the PD group than that in the control group, and (ii) metabolic disease, mental diseases, neurologic disease, circulatory disease, respiratory disease, genitourinary disease, and trauma

are common causes of death in PD patients in addition to PD itself. Our findings ought to be valuable for PD patient caregivers in both hospital and community settings.

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].

Despite these limitations, our data are nevertheless robust because we used a representative, large-scale sample from a cohort database comprising over 1 million subjects over a 12-year follow-up period. 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 to the compulsory HIRA nationwide health insurance system. We chose matched controls adjusted for the potential confounding factors of age, sex, income, and region of residence. Our subjects' comorbidity data were consistent with those of previous epidemiologic studies in the Korean population, which was further evidence of our study's reliability [29, 30].

CONCLUSION`

We performed the largest study on the risk of mortality in South Korean PD patients with clearly defined inclusion criteria. We found that PD increased the risk of mortality regardless of age and sex. The mortality rate was higher in patients ≥75 years old than in those <75 years for both sexes. Common causes of death in patients with PD included metabolic, mental, neurologic, circulatory, respiratory, and genitourinary diseases as well as trauma; the highest OR observed was for neurologic disease.

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Conflict of Interest

The authors do not have any conflict of interest to disclose.

Author contributions:

Choi HG composed the manuscript, Lim JS provided neurologist's perspective, and Sim S and Kim M designed and supervised the study.

REFERENECES

1. Doi Y, Yokoyama T, Nakamura Y, Nagai M, Fujimoto K, Nakano I. How can the national burden of Parkinson's disease comorbidity and mortality be estimated for the Japanese population? J Epidemiol. 2011;21(3):211-6.
2. Wang G, Li XJ, Hu YS, Cheng Q, Wang CF, Xiao Q, Liu J, Ma JF, Zhou HY, Pan J, Tan YY, Wang Y, Chen SD. Mortality from Parkinson's disease in China: Findings from a five-year follow up study in Shanghai. Can J Neurol Sci. 2015 Jul;42(4):242-7.
3. Morgan JC, Currie LJ, Harrison MB, Bennett JP Jr, Trugman JM, Wooten GF. Mortality in levodopa-treated Parkinson's disease.Parkinsons Dis. 2014;2014:426976.
4. CLarke CE. Mortality from Parkinson's disease. J Neurol Neurosurg Psychiatry. 2000 Feb;68(2):254-5.
5. GBD 2016 Parkinson's Disease Collaborators. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018 Nov;17(11):939-953.
6. de Lau LM, Schipper CM, Hofman A, Koudstaal PJ, Breteler MM. Prognosis of Parkinson disease: risk of dementia and mortality: the Rotterdam Study. Arch Neurol. 2005 Aug;62(8):1265-9.
7. Pennington S, Snell K, Lee M, Walker R. The cause of death in idiopathic Parkinson's disease. Parkinsonism Relat Disord. 2010 Aug;16(7):434-7.
8. The National Health Insurance Sharing Service of Korea. 2014. Available at: https://nhiss.nhis.or.kr/bd/ab/bdaba022eng.do. Accessed November 1, 2018.
9. Driver JA, Logroscino G, Gaziano JM, Kurth T. Incidence and remaining lifetime risk of Parkinson disease in advanced age. Neurology. 2009 Feb 3;72(5):432-8.

10. Ishihara LS, Cheesbrough A, Brayne C, Schrag A. Estimated life expectancy of Parkinson's patients compared with the UK population. J Neurol Neurosurg Psychiatry. 2007 Dec;78(12):1304-9.
11. Macleod AD, Taylor KS, Counsell CE. Mortality in Parkinson's disease: a systematic review and meta-analysis. Mov Disord. 2014 Nov;29(13):1615-22.
12. Rajput AH, Uitti RJ, Rajput AH, Offord KP. Timely levodopa (LD) administration prolongs survival in Parkinson's disease. Parkinsonism Relat Disord. 1997 Nov;3(3):159-65.
13. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials. 1986;7:177-188.
14. Rybicki BA, Johnson CC, Gorell JM. Demographic differences in referral rates to neurologists of patients with suspected Parkinson's disease: implications for case-control study design. Neuroepidemiology. 1995;14:72-81.
15. Herlofson K, Lie SA, Arsland D, Larsen JP. Mortality and Parkinson disease: A community based study. Neurology. 2004 Mar 23;62(6):937-42.
16. Goldman DA, Brender JD. Are standardized mortality ratios valid for public health data analysis? Stat Med. 2000;19:1081-1088.
17. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. J R Stat Soc Series A. 2009;172:137-159.
18. Wooten GF, Currie LJ, Bovbjerg VE, Lee JK, Patrie J. Are men at greater risk for Parkinson's disease than women? J Neurol Neurosurg Psychiatry. 2004 Apr;75(4):637-9.
19. Olanow CW. The scientific basis for the current treatment of Parkinson's disease. Annu Rev Med. 2004;55:41-60.

20. Rascol O, Payoux P, Ory F, Ferreira JJ, Brefel-Courbon C, Montastruc JL. Limitations of current Parkinson's disease therapy. Ann Neurol. 2003;53 Suppl 3:S3-12; discussion S12-5.

21. Hobson P, Meara J. Mortality and quality of death certification in a cohort of patients with Parkinson's disease and matched controls in North Wales, UK at 18 years: a community-based cohort study. BMJ Open. 2018 Feb 14;8(2):e018969.

22. D'Amelio M, Ragonese P, Morgante L, Reggio A, Callari G, Salemi G, Savettieri G. Long-term survival of Parkinson's disease: a population-based study. J Neurol. 2006 Jan;253(1):33-7.

23. Fall PA, Saleh A, Fredrickson M, Olsson JE, Granérus AK. Survival time, mortality, and cause of death in elderly patients with Parkinson's disease: a 9-year follow-up. Mov Disord. 2003 Nov;18(11):1312-6.

24. Beyer MK, Herlofson K, Aarsland D, Larsen JP. Causes of death in a community based study of Parkinson’s disease. Acta Neurol Scand. 2001;103:7e11.

25. Ben-Shlomo Y, Marmot MG. Survival and cause of death in a cohort of patients with parkinsonism: possible clues to aetiology? J Neurol Neurosurg Psychiatr. 1995;58(3):293e9.

26. Ma C, Liu Y, Neumann S, Gao X. Nicotine from cigarette smoking and diet and Parkinson disease: a review. Transl Neurodegener. 2017 Jul 2;6:18.

27. Bettiol SS, Rose TC, Hughes CJ, Smith LA. Alcohol Consumption and Parkinson's Disease Risk: A Review of Recent Findings. J Parkinsons Dis. 2015;5(3):425-42.

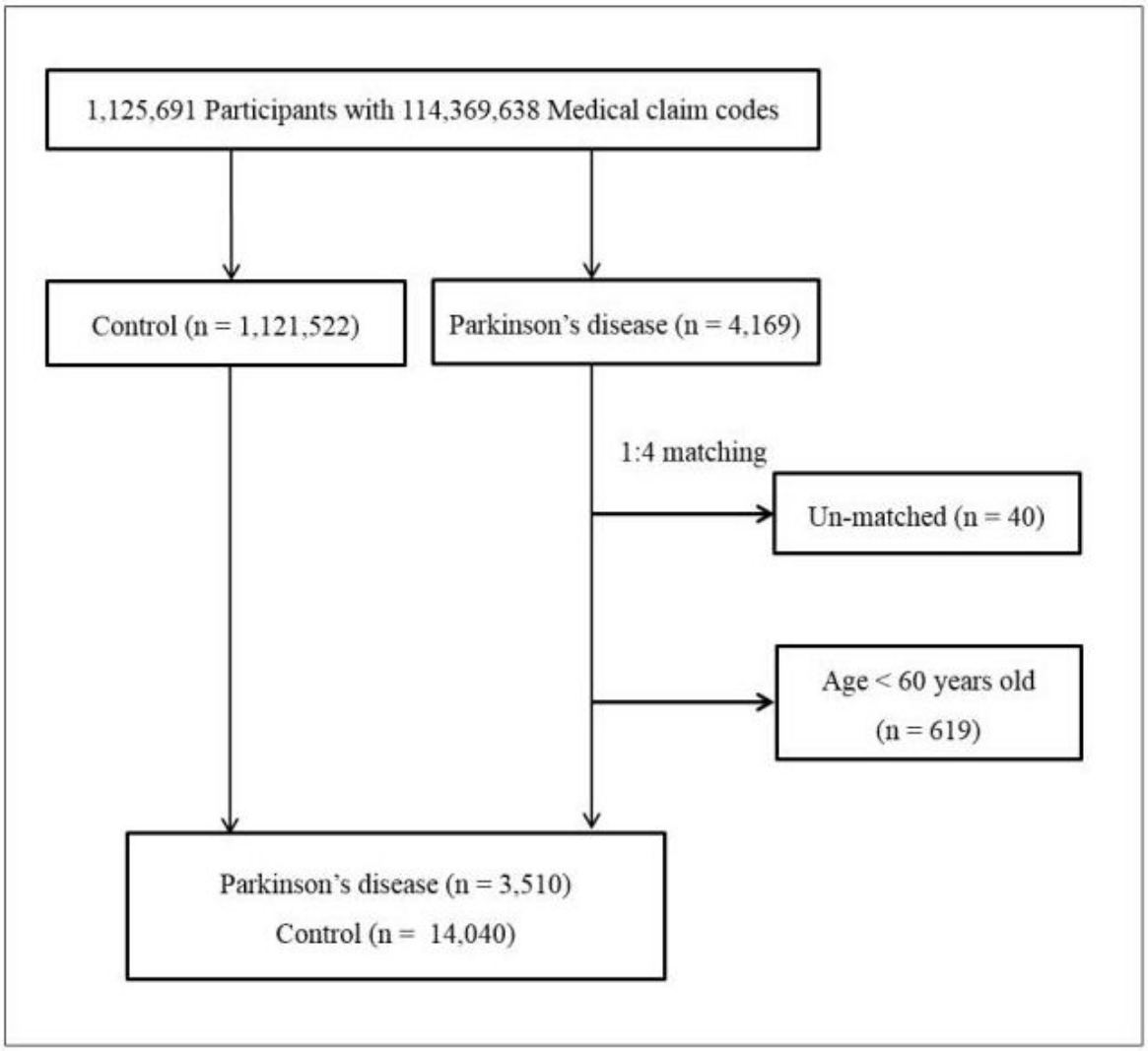
28. Chen J, Guan Z, Wang L, Song G, Ma B, Wang Y. Meta-analysis: overweight, obesity, and Parkinson's disease. Int J Endocrinol. 2014;2014:203930.

29. Kim DJ. The epidemiology of diabetes in Korea. Diabetes Metab J 2011;35:303-8.

426 **30.** Lee HY, Park JB. The Korean Society of Hypertension Guidelines for the Management
427 of hypertension in 2013: Its essentials and key points. Pulse (Basel) 2015;3:21-8.

Figure legend

Fig. 1 A schematic illustration of the participant selection process that was used in the present study. Out of a total of 1,125,691 participants, 4,169 PD participants were selected. The PD participants were matched 1:4 with a control group that were not diagnosed as PD. Finally, 3,510 PD and 14,040 control participants were included.



S1Table Cause of death in Parkinson's disease and control groups

Cause of death	Codes	Total participants	
		Parkinson (n = 3,510)	Control (n = 14,040)
Infection	A00-B99		
Intestinal Infectious Diseases	A00-A09	6	9
Tuberculosis	A15-A19	3	25
Certain Zoonotic Bacterial diseases	A20-A28	0	0
Other bacterial diseases	A30- A49	13	26
Infections with a predominantly sexual mode of transmission	A50-A64	0	0
Other spirochaetal diseases	A65-A69	0	0
Other diseases caused by chlamydiae	A70-A74	0	0
Rickettsioses	A75-A79	0	2
Viral infections of the central nervous system	A80-A89	0	0
Arthropod-borne viral fevers and viral hemorrhagic fevers	A92-A99	0	0
Viral infections characterized by skin and mucous membrane lesions	B00-B09	0	2
Viral hepatitis	B15-B19	1	9
Human immunodeficiency virus[HIV] disease	B20-B24	0	0
Other viral diseases	B25-B34	0	0
Mycoses	B35-B49	0	0
Protozoal diseases	B50-B64	0	0
Helminthiases	B65-B83	0	0
Pediculosis, acariasis and other infestations	B85-B89	0	0
Sequelae of infectious and parasitic diseases	B90-B94	0	1
Bacterial, viral and other infectious agents	B95-B98	0	0
Other infectious diseases	B99	0	0
Neoplasm	C00-D48		
Malignant neoplasm of lip, oral cavity and pharynx	C00-C14	5	5
Malignant neoplasms of digestive organs	C15-C26	67	366
Malignant neoplasms of respiratory and intrathoracic organs	C30-C39	28	158
Malignant neoplasm of bone and articular cartilage	C40-C41	1	2
Melanoma and other malignant neoplasms of skin	C43-C44	1	1
Malignant neoplasms of mesthelial and soft tissue	C45-C49	1	5
Malignant neoplasm of breast	C50	2	3
Malignant neoplasm of female genital organs	C51-C58	8	11
Malignant neoplasm of male genital organs	C60-C63	4	29
Malignant neoplasm of urinary tract	C64-C68	4	28
Malignant neoplasm of eye, brain and other parts of central nervous system	C69-C72	1	6
Malignant neoplasm of thyroid and other endocrine gland	C73-C75	3	5
Malignant neoplasm of ill-defined, secondary and unspecified sites	C76-C80	8	11
Malignant neoplasms of lymphoid, hematopoietic and related tissue	C81-C96	10	26
Malignant neoplasm of independent (primary) multiple sites	C97	1	2
In situ neoplasms	D00-D09	0	1

Benign neoplasms	D10-D36	1	2
Neoplasms of uncertain or unknown behaviour	D37-D48	6	6
Metabolic disease	E00-E90		
Disorders of thyroid gland	E00-E07	1	0
Diabetes mellitus	E10-E14	71	154
Other diorders of glucose regulation and pancreatic internal secretion	E15-E16	0	0
Disorders of other endocrine glands	E20-E35	2	0
Malnutrition	E40-E46	0	1
Other nutritional deficiencies	E50-E64	1	0
Obesity and other hyperalimentation	E65-E68	0	0
Metabolic disorders	E70-E90	1	6
Mental disease	F00-F99		
Organic, including symptomatic	F00-F09	29	46
mental disorders	F10-F19	2	3
Mental and behavioral disorders	F20-F29	2	0
due to psychoactive substance use	F30-F39	0	0
Schizophrenia, schizotypal and	F40-F48	0	0
delusional disorders	F50-F59	0	0
Mood[affective] disorders	F60-F69	0	0
Neurotic, stress-related and	F70-F79	0	0
somatoform disorders	F80-F89	0	0
Behavioral syndromes associated	F90-F98	0	0
with physiological disturbances and	F99	0	0
Neurologic disease	G00-G99		
Inflammatory diseases of the central nervous system	G00-G09	1	1
Systemic atrophies primarily affecting the central nervous system	G10-G14	4	3
Extrapyramidal and movement disorders	G20-G26	294	7
Other degenerative diseases of the nervous system	G30-G32	22	51
Demyelinating diseases of the central nervous system	G35-G37	0	0
Episodic and paroxysmal disorders	G40-G47	1	4
Nerve, nerve root and plexus disorders	G50-G59	0	0
Polyneuropathies and other disorders of the peripheral nervous system	G60-G64	0	1
Diseases of myoneural junction and muscle	G70-G73	0	0
Cerebral palsy and other paralytic syndromes	G80-G83	1	1
Other disorders of the nervous system	G90-G99	5	1
Circulatory disease	I00-I99		
Acute rheumatic fever	I00-I02	0	0
Chronic rheumatic heart diseases	I05-I09	0	3
Hypertensive diseases	I10-I15	31	75
Ischemic heart diseases	I20-I25	54	148
Pulmonary heart disease and diseases of pulmonary circulation	I26-I28	1	5
Other forms of heart disease	I30-I52	39	102
Cerebrovascular diseases	I60-I69	150	359
Diseases of arteries, arterioles and capilaries	I70-I79	2	13

Diseases of veins, lymphatic vessels and lymph nodes, NEC	I80-I89	0	0
Other and unspecified disorders of the circulatory system	I95-I99	0	0
Respiratory disease	J00-J99		
Acute upper respiratory infections	J00-J06	0	0
Influenza and pneumonia	J09-J18	48	105
Other acute lower respiratory infections	J20-J22	0	0
Other diseases of upper respiratory tract	J30-J39	0	0
Chronic lower respiratory diseases	J40-J47	31	106
Lung diseases due to external agents	J60-J70	13	20
Other respiratory diseases principally affecting the interstitium	J80-J84	3	11
Suppurative and necrotic conditions of lower respiratory tract	J85-J86	1	1
Other diseases of pleura	J90-J94	0	0
Other diseases of the respiratory system	J95-J99	1	5
Digestive disease	K00-K93		
Diseases of oral cavity, salivary glands and jaws	K00-K14	0	0
Diseases of oesophagus, stomach and duodenum	K20-K31	3	12
Disease of appendix	K35-K38	0	0
Hernia	K40-K46	0	0
Noninfective enteritis and colitis	K50-K52	1	0
Other diseases of intestines	K55-K64	7	12
Diseases of peritoneum	K65-K67	0	2
Diseases of liver	K70-K77	10	35
Disorders of gallbladder, biliary tract and pancreas	K80-K87	4	21
Other diseases of the digestive system	K90-K93	5	6
Muscular disease	M00-M99		
Infectious arthropathies	M00-M03	0	0
Inflammatory polyarthropathies	M05-M14	2	3
Arthrosis	M15-M19	0	0
Other joint disorders	M20-M25	0	0
Systemic connective tissue disorder	M30-M36	0	1
Deformin dorsopathies	M40-M43	0	0
Spondylopathies	M45-M49	1	0
Other dorsopathies	M50-M54	0	1
Disorders of muscles	M60-M63	0	2
Disorders of synovium and tendon	M65-M68	0	0
Other soft tissue disorders	M70-M79	0	1
Disorders of bone density and structure	M80-M85	5	6
Other osteopathies	M86-M90	0	1
Chondropathies	M91-M94	0	0
Other disorders of the musculoskeletal system and connective tissue	M95-M99	0	0
Genitourinary disease	N00-N99		
Glomerular diseases	N00-N08	0	0
Renal tubulo-inerstitial diseases	N10-N16	2	4
Renal failure	N17-N19	18	38

Urolithiasis	N20-N23	1	0
Other disorders of kidney and ureter	N25-N29	0	0
Other diseases of the urinary system	N30-N39	4	5
Diseases of male genital organs	N40-N51	0	3
Disorders of breast	N60-N64	0	0
Inflammatory diseases of female pelvic organs	N70-N77	0	0
Noninflammatory disorders of female genital tract	N80-N98	0	0
Other disorders of te genitourinary system	N99	0	0
Abnormal finding	R00-R99		
Symptoms and signs involving the circulatory and respitatory systems	R00-R09	9	15
Symptoms and signs involving the digestive system and abdomen	R10-R19	0	0
Symptoms and signs involving the skin and subcutaneous tissue	R20-R23	0	0
symptoms and signs involving the nervous and musculoskeletal systems	R25-R29	0	0
symptoms and signs involving the urinary system	R30-R39	0	0
Symptoms and signs involving cognition, perception, emotional state and behaviour	R40-R46	0	0
Symptoms and signs involving speech and voice	R47-R49	0	0
General symptoms and signs	R50-R69	71	266
Abnormal findings on examination of blood, without diagnosis	R70-R79	0	0
Abnormal findings on examination of urine, without diagnosis	R80-R82	0	0
Abnormal findings on examination of other body fluids, substances and tissues, without diagnosis	R83-R89	0	0
Abnormal findings on diagnostic imaging and in function studies, without diagnosis	R90-R94	0	0
Ill-defined and unknown causes of mortality	R95-R99	5	48
Trauma	S00-T98		
Injuries to the head	S00-S09	10	32
Injuries to the neck	S10-S19	0	1
Injuries to the thorax	S20-S29	2	12
Injuries to the abdomen, lower back, lumbar spine and pelvis	S30-S39	0	3
Injuries to the shoulder and upper arm	S40-S49	0	1
Injuries to the elbow and forearm	S50-S59	1	0
Injuries to the wrist and hand	S60-S69	0	0
Injuries to th hip and thigh	S70-S79	7	16
Injuries to the knee and lower leg	S80-S89	0	2
Injuries to the ankle and foot	S90-S99	0	0
Injuries involving multiple body regions	T00-T07	7	17
Injuries to uspecitied part of trunk, limb or body region	T08-T14	3	8
Effects of foreign body entering throgh natural orifice	T15-T19	6	2
Burns and corrosions of external body suface, specified by site	T20-T25	0	0
Burn and corrosions confined to eye and internal organs	T26-T28	0	1
Burns and corrosions of multiple and unspecified of multiple and unspeccified body regions	T29-T32	2	0
Frostbite	T33-T35	0	0

	Poisoning by drugs, medicaments and biological substances	T36-T50	1	1
	Toxic effects of sustances chiefly nonmedicinal as to source	T51-T65	6	23
	Other and unspecified effects of external causes	T66-T78	18	33
	Certain early complications of trauma	T79	0	0
	Complications of surgical and medical care, NEC	T80-T88	1	0
	Sequelae of injures, of poisoning and of other consequences of external causes	T90-T98	0	2
Others		D50-D89, L00-L99		
	Nutritional anemias	D50-D53	0	0
	Hemolytic anemias	D55-D59	0	0
	Aplastic and other anemias	D60-D64	1	3
	Coagulation defect,purpura and other hemorrhage conditions	D65-D69	1	0
	Other disease of blood and blood-forming organs	D70-D77	1	3
	Certain disorders involving the immune mechanism	D80-D89	0	2
	Other disorders of the skin and subcutaneous tissue	L80-L99	2	1
	missing		12	2

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Mortality and cause of death in South Korean patients with Parkinson's disease: A longitudinal follow-up study using a national sample cohort

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Mortality and cause of death in South Korean patients with Parkinson's disease: A longitudinal follow-up study using a national sample cohort

ABSTRACT

Objective: The incidence rate of Parkinson's disease (PD) is growing rapidly owing to the aging population. We investigated the mortality rates and causes of death in South Korean patients with PD.

Design: We investigated a national cohort using the nationwide insurance database.

Setting: Korean Health Insurance Review and Assessment Service - National Sample Cohort.

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.

Interventions: None

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.

Results: The adjusted hazard ratio (HR) for mortality in the PD group was 2.09 (95% confidence interval [CI] = 1.94–2.24, P < 0.001). Subgroup analysis according to age (<70 years, 70–79 years, and ≥80 years) and sex revealed that patients with PD showed higher adjusted HRs for mortality across all subgroups. Mortalities caused by metabolic, mental, neurologic, circulatory, respiratory, and genitourinary diseases, as well as trauma, were more common in the PD group than in the control group, with the highest odds ratio observed in patients with neurologic disease.

Conclusions: We demonstrated that PD in South Korean patients ≥60 years of age was associated with increased mortality in both sexes regardless of age.

Key words: Parkinson's disease, mortality, Korean

Strengths and limitations of this study

- Our study dataset encompassed 1,125,691 subjects registered over a 12-year period in a national insurance database.
- The study encompassed all registered patients with PD who visited outpatient clinics, were hospitalized, or both at least twice.
- The patients were not restricted to only those who were hospitalized.
- The patients with PD were matched 1:4 with control subjects based on age, group, sex, income group, regions of residence, and the past medical histories.
- We were unable to determine the severity of PD, and some confounding factors (e.g., smoking status, alcohol consumption, and obesity) were not adjusted for.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder, and is characterized by the 4 cardinal motor signs: tremor at rest, bradykinesia, rigidity, and postural instability, as well as other non-motor clinical manifestations [1, 2]. Despite the remarkable symptom-relieving benefits provided by levodopa over the past 30 years, recent studies have demonstrated that the mortality rates among PD patients remain higher than in individuals without PD [3, 4]. PD is one of the fastest growing diseases in terms of prevalence, disability, and mortality; the rapidly aging population has contributed to an increase in crude PD prevalence rates [5]. As such, a better understanding of the rates and causes of mortality in patients with PD is important to better estimate the social burden and medical care costs [6].

Even though PD is associated with increased mortality in general, previous studies show inconsistent data, with mortality rates ranging from 0.80 to 3.50 [2]. Some studies performed in the post-levodopa era even reported "super-normal" survival rather than increased mortality among PD patients [2]. Furthermore, the causes of death in patients with PD remain unclear [7]. The heterogeneity observed in studies of mortality as related to PD could be caused by the variable methodology and patient selection criteria. Different studies tend to be hospital-, pharmaceutical trial- or community-based, and thus yield results that are not very representative of the general population [6].

According to the Global Burden of Disease, Injuries, and Risk Factors Study of 2016, the death rate, prevalence, and disability-adjusted life-years of patients with PD varied depending on ethnicity and/or geography [5]. Among high-income Asia Pacific countries, South Korea showed the highest percentage change in age-standardized mortality rates between 1990 and 2016 (24.6%) compared to Brunei (17.9%), Japan (10.2%), and Singapore (11.3%), even though the percentage change in the age-standardized rates of prevalence during the same time period (21.0%) was similar to that of Japan (21.3%) [5]. Thus, analyses focused on a particular ethnic/geographic group is important to estimate the social burden of PD and the patient management plan in each country. However, a large cohort-based investigation of PD-related mortality rates and causes of death in South Korea has never been performed.

To better understand the natural courses and prognoses of patients with PD, and to provide valuable information on planning the distribution of health resources, we investigated the mortality rates and causes of death in patients with PD using a representative PD population in South Korea. We performed a large-scale longitudinal follow-up study, with a maximum follow-up duration of 12 years, using national cohort data.

MATERIALS AND METHODS

Patient and Public Involvement

No patient involved.

Study Population and Data Collection

The ethics committee of Hallym University approved the use of these data (approval number 2014-I148). The requirement for written informed consent was waived by the Institutional Review Board.

This national cohort study relied on data from the Korean Health Insurance Review and Assessment Service (HIRA) National Sample Cohort. The Korean National Health Insurance Service (NHIS) selects samples directly from the entire population database to prevent non-sampling errors. Approximately 2% of the samples (1 million) were selected from the entire Korean population (50 million). These selected data were classified into 1,476 levels (age [18 categories], sex [2 categories], and income level [41 categories]) using randomized stratified systematic sampling methods via proportional allocation to represent the entire population. After data selection, the appropriateness of the sample was verified by a statistician who compared the data from the entire Korean population to the sample data. The details of the methods used to perform these procedures are provided by the National Health Insurance Sharing Service [8]. The cohort database included (i) personal information, (ii) health insurance claim codes (procedures and prescriptions), (iii) diagnostic codes using the International Classification of Disease, 10th edition (ICD-10), (iv) death records from the Korean National Statistical Office (using the Korean Standard Classification of Disease), (v) socio-economic data (residence and income), and (vi) medical examination data for each participant over a period ranging from 2002 to 2013.

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.

Participant Selection

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). PD was categorized using ICD-10 codes (Parkinson's disease: G20). For accurate diagnoses, we only selected participants who visited outpatient clinics, were hospitalized, or both at least twice because of PD. The control participants were extracted from 1,121,522 participants who had no diagnoses of PD between 2002 and 2013.

Participants with PD were matched 1:4 with the control group. The matches were adjusted for age group, sex, income, region of residence, and medical histories of hypertension, diabetes mellitus, and dyslipidemia. 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. To prevent selection bias, participants in the control group were sorted using a random number, and were then selected in descending order. It was assumed that the matched control participants were involved at the same time of each matched PD participant; therefore, participants in the control group

who died before the time of involvement of the matched PD participant were excluded. Forty PD participants for whom we could not identify a sufficient number of matching participants were also excluded, as were 619 participants who were diagnosed with PD while under the age of 60 years since the prevalence of PD is relatively low in younger individuals [9]. Ultimately 3,510 PD participants matched 1:4 with 14,040 control participants were included (Fig. 1).

Variables

Age groups were classified by 5-year intervals into 6 age groups: 60–64, 65–69, 70–74, 75–79, 80–84, and 85+ years old. The income groups were initially divided into 41 classes (1 health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were re-categorized into 11 classes (class 1 [lowest income] to class 11 [highest income]). Regions of residence were divided into 16 areas according to the administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

The causes of death were classified according to the Korean standard classification of diseases, developed by the World Health Organization based on the ICD, into 12 classifications: (i) Infection (certain infections and parasitic diseases, A00–B99); (ii) Neoplasm (neoplasms, C00–D48); (iii) Metabolic disease (endocrine, nutritional, and metabolic diseases, E00–E90); (iv) Mental disease (mental and behavioural disorders, F00–F99); (v) Neurologic disease (diseases of the nervous system, G00–G99); (vi) Circulatory disease (diseases of the circulatory system, I00–I99); (vii) Respiratory disease (diseases of the respiratory system, J00–J99); (viii) Digestive disease (diseases of the digestive system, K00–K93); (ix) Muscular disease (diseases of the musculoskeletal system and connective

tissue, M00–M99); (x) Genitourinary disease (diseases of the genitourinary system, N00–N99); (xi) Abnormal finding (symptoms, signs and abnormal clinical and laboratory findings 'not elsewhere classified', R00–R99); and (xii) Trauma (injury, poisoning, and certain other consequences of external causes, S00–T98). We also added 1 more category: (xiii) Others (diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism, D50–D89; diseases of the skin and subcutaneous tissue, L00–L99). The Charlson comorbidity index was used for 17 comorbidities as a continuous variable (0 [no comorbidity] through 29 [multiple comorbidities]) [**10]**].

Statistical Analyses.

The chi-square or Fisher's exact test was used to compare the general characteristics of participants in the PD and control groups, as well as to compare their mortality rates according to the cause of death. The false discovery rate was used to adjust for incorrect rejections of the null hypothesis.

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. Two-tailed P-values less than 0.05 were considered significant. Statistical analyses were conducted using the SPSS software, version 21.0 (IBM, Armonk, NY, USA).

RESULTS

The mean follow-up duration was 49.6 months (standard deviation [SD] = 37.3 months) in the PD group and 57.3 (SD = 40.6) months in the matched control group.

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).

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).

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). When categorizing patients according to age (<70 years, 70–79 years and ≥80 years) and sex, PD patients in all the subgroups showed higher crude and adjusted HRs for mortality than did the control patients.

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	

223

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

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

226 ‡ Model adjusted for the Charlson comorbidity index.

HR, hazard ratio; CI, confidence interval.

Analysis of mortality rates according to the cause of death revealed an odds ratio (OR) for overall mortality of 2.26 (95% CI = 2.08–2.45, P < 0.001) in the PD group (Table 3); the detailed data are presented in Supplementary Table 1. Mortalities caused by metabolic disease, mental diseases, neurologic disease, circulatory disease, respiratory disease, genitourinary disease and trauma were higher in the PD group than in the control group (the false discovery rate-adjusted P-value was <0.05 for each). The OR for mortality was highest for neurologic disease (20.87, 95% CI = 16.05–27.14, P < 0.001); among these neurologic diseases, extrapyramidal and movement disorders were the most common (294/328, 89.6%). Mortalities caused by infection, neoplasm, digestive disease, muscular disease, and other causes were not significantly different between the PD and control groups.

240 **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.

DISCUSSION

Our findings were consistent with those of previous studies, most of which found higher mortality rates in patients with PD with HRs ranging from 1.2 to 2.4 [11,12]. However, most such studies were performed in Western countries, and data from Asian patients have rarely been reported. A recent study in China found that the standardized mortality rate of patients with PD was 0.62 (95% CI = 0.32–1.07), implying that the 5-year mortality ratio of patients with PD was not significantly higher than that of the general urban Chinese population [2]. However, we cannot compare their results to ours given their different study design; the Chinese study comprised 157 PD patients who were referred to - or diagnosed at - a particular tertiary hospital. To our knowledge, ours is the first study to demonstrate that mortality rates are higher in Korean PD patients using a national cohort, and is also the largest study of its kind to date. The adjusted HR of our study (2.09) was relatively higher than in previous studies considering that most reported HRs fall between 1.2 and 2.4, however, this is of little relevance owing to the major heterogeneity among the study methodologies. Nevertheless, our data still show that the mortality of patients with PD is higher than that in control populations despite recent advances in the treatment of this disease. This indicates that, while current treatment modalities relieve motor symptoms, they do not necessarily improve mortality rates and/or the life expectancies of patients with PD.

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.

In our study, patients with PD died more frequently of certain diseases and of trauma than their counterparts in the control population. Neurologic diseases (particularly extrapyramidal and movement disorders) were the most common causes of death, implying that PD features themselves were most responsible for death among PD patients in South Korea. Such studies of the outcomes of PD patients are scarce. In a study of mortality among 211 levodopa-treated patients with PD in the United Kingdom, Morgan et al. showed that the most common cause of death was PD itself (52.6%) [3]. They interpreted this to indicate that, even though levodopa might improve motor symptoms such as tremor, bradykinesia, and rigidity, it did not slow disease progression [13]. As the PD progressed, levodopa-resistant motor symptoms (speech/swallowing impairment, gait, and balance problems) and nonmotor symptoms (autonomic dysfunction, mood disorders, cognitive impairment, sleep disorders, and psychosis) become more prevalent and may contribute to the increased morbidity and mortality [14]. Although our study cohort was not necessarily confined to levodopa-treated subjects, it is highly likely that a significant proportion of our patients were being treated with

levodopa, as we only selected patients who were treated ≥2 times for PD. Our findings are different from those of other groups that described pneumonia to be the most common cause of death in PD patients [15-18]. The most likely explanation for this difference could be the varying methods of patient recruitment: we recruited our subjects based on their PD treatment history regardless of whether they were hospitalized; therefore, the cause of death among our patients; i.e., neurologic disease that may have included PD itself, may also reflect patients having died of other (perhaps natural) causes while afflicted with PD. However, the causes of death in hospitalized or nursing home-bound PD patients may have had a greater likelihood of being reported as pneumonia because of their orthostatic lability. Furthermore, our indication that PD-group patients did not necessarily die of pneumonia is true insofar as being compared to the control group, and is not a general statement, since we calculated the ORs of the cause of mortality. The significance of other causes of death such as cancer and circulation-impeding ischemic heart disease remain controversial [1, 2, 15-19]; the ORs for these conditions were not significant in our study. Nevertheless, our most important findings include (i) the overall death rate was higher in the PD group than that in the control group, and (ii) metabolic disease, mental diseases, neurologic disease, circulatory disease, respiratory disease, genitourinary disease, and trauma are common causes of death in PD patients in addition to PD itself. Our findings ought to be valuable for PD patient caregivers in both hospital and community settings.

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 [20-22]. 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.

Despite these limitations, our data are nevertheless robust because we used a representative, large-scale sample from a cohort database comprising over 1 million subjects over a 12-year follow-up period. 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. We chose matched controls adjusted for the potential confounding factors of age, sex, income, and region of residence. Our subjects' comorbidity data were consistent with those of previous epidemiologic studies in the Korean population, which was further evidence of our study's reliability [23, 24].

CONCLUSION

We performed the largest study on the risk of mortality in South Korean PD patients with clearly defined inclusion criteria. We found that PD increased the risk of mortality regardless of age and sex. Common causes of death in patients with PD included metabolic, mental, neurologic, circulatory, respiratory, and genitourinary diseases as well as trauma; the highest OR observed was for neurologic disease.

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Conflict of Interest

The authors do not have any conflict of interest to disclose.

Author contributions:

Choi HG composed the manuscript, Lim JS provided neurologists' perspectives, Lee YK reviewed the result, and Sim S and Kim M designed and supervised the study.

Data sharing

The data used for this study are available from the Korea National Health Insurance Sharing Service (https://nhiss.nhis.or.kr) subject to their requirements and fees.

REFERENCES

1. Doi Y, Yokoyama T, Nakamura Y, Nagai M, Fujimoto K, Nakano I. How can the national burden of Parkinson's disease comorbidity and mortality be estimated for the Japanese population? J Epidemiol. 2011;21(3):211-6.
2. Wang G, Li XJ, Hu YS, Cheng Q, Wang CF, Xiao Q, Liu J, Ma JF, Zhou HY, Pan J, Tan YY, Wang Y, Chen SD. Mortality from Parkinson's disease in China: Findings from a five-year follow up study in Shanghai. Can J Neurol Sci. 2015 Jul;42(4):242-7.
3. Morgan JC, Currie LJ, Harrison MB, Bennett JP Jr, Trugman JM, Wooten GF. Mortality in levodopa-treated Parkinson's disease.Parkinsons Dis. 2014;2014:426976.
4. CLarke CE. Mortality from Parkinson's disease. J Neurol Neurosurg Psychiatry. 2000 Feb;68(2):254-5.
5. GBD 2016 Parkinson's Disease Collaborators. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018 Nov;17(11):939-953.
6. de Lau LM, Schipper CM, Hofman A, Koudstaal PJ, Breteler MM. Prognosis of Parkinson disease: risk of dementia and mortality: the Rotterdam Study. Arch Neurol. 2005 Aug;62(8):1265-9.
7. Pennington S, Snell K, Lee M, Walker R. The cause of death in idiopathic Parkinson's disease. Parkinsonism Relat Disord. 2010 Aug;16(7):434-7.
8. The National Health Insurance Sharing Service of Korea. 2014. Available at: https://nhiss.nhis.or.kr/bd/ab/bdaba022eng.do. Accessed November 1, 2018.
9. Driver JA, Logroscino G, Gaziano JM, Kurth T. Incidence and remaining lifetime risk of Parkinson disease in advanced age. Neurology. 2009 Feb 3;72(5):432-8.
10. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel JM, Sundararajan V. Updating and validating the Charlson comorbidity index and score for risk adjustment in

hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011 Mar 15;173(6):676-82.

11. Ishihara LS, Cheesbrough A, Brayne C, Schrag A. Estimated life expectancy of Parkinson's patients compared with the UK population. J Neurol Neurosurg Psychiatry. 2007 Dec;78(12):1304-9.
12. Macleod AD, Taylor KS, Counsell CE. Mortality in Parkinson's disease: a systematic review and meta-analysis. Mov Disord. 2014 Nov;29(13):1615-22.
13. Olanow CW. The scientific basis for the current treatment of Parkinson's disease. Annu Rev Med. 2004;55:41-60.
14. Rascol O, Payoux P, Ory F, Ferreira JJ, Brefel-Courbon C, Montastruc JL. Limitations of current Parkinson's disease therapy. Ann Neurol. 2003;53 Suppl 3:S3-12; discussion S12-5.
15. Hobson P, Meara J. Mortality and quality of death certification in a cohort of patients with Parkinson's disease and matched controls in North Wales, UK at 18 years: a community-based cohort study. BMJ Open. 2018 Feb 14;8(2):e018969.
16. D'Amelio M, Ragonese P, Morgante L, Reggio A, Callari G, Salemi G, Savettieri G. Long-term survival of Parkinson's disease: a population-based study. J Neurol. 2006 Jan;253(1):33-7.
17. Fall PA, Saleh A, Fredrickson M, Olsson JE, Granérus AK. Survival time, mortality, and cause of death in elderly patients with Parkinson's disease: a 9-year follow-up. Mov Disord. 2003 Nov;18(11):1312-6.
18. Beyer MK, Herlofson K, Aarsland D, Larsen JP. Causes of death in a community based study of Parkinson’s disease. Acta Neurol Scand. 2001;103:7e11.

19. Ben-Shlomo Y, Marmot MG. Survival and cause of death in a cohort of patients with parkinsonism: possible clues to aetiology? J Neurol Neurosurg Psychiatr. 1995;58(3):293e9.
20. Ma C, Liu Y, Neumann S, Gao X. Nicotine from cigarette smoking and diet and Parkinson disease: a review. Transl Neurodegener. 2017 Jul 2;6:18.
21. Bettiol SS, Rose TC, Hughes CJ, Smith LA. Alcohol Consumption and Parkinson's Disease Risk: A Review of Recent Findings. J Parkinsons Dis. 2015;5(3):425-42.
22. Chen J, Guan Z, Wang L, Song G, Ma B, Wang Y. Meta-analysis: overweight, obesity, and Parkinson's disease. Int J Endocrinol. 2014;2014:203930.
23. Kim DJ. The epidemiology of diabetes in Korea. Diabetes Metab J 2011;35:303-8.
24. Lee HY, Park JB. The Korean Society of Hypertension Guidelines for the Management of hypertension in 2013: Its essentials and key points. Pulse (Basel) 2015;3:21-8.

Figure legend

Fig. 1 A schematic illustration of the participant selection process that was used in the present study. Of the 1,125,691 total participants, 4,169 with Parkinson's disease (PD) were selected. Participants with PD were matched 1:4 with a control group comprising individuals not diagnosed with PD. Ultimately, 3,510 participants with PD and 14,040 control participants were included.

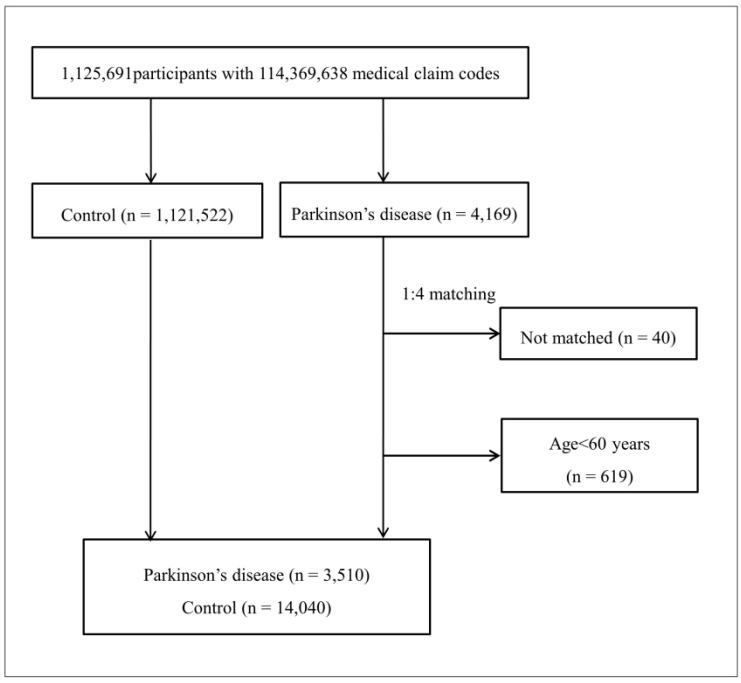

Figure 1

254x190mm (300 x 300 DPI)

S1Table Cause of death in dementia and control group

Cause of death	Codes	Total participants	
		Parkinson (n = 3,510)	Control (n = 14,040)
Infection	A00-B99		
Intestinal Infectious Diseases	A00-A09	6	9
Tuberculosis	A15-A19	3	25
Certain Zoonotic Bacterial diseases	A20-A28	0	0
Other bacterial diseases	A30- A49	13	26
Infections with a predominantly sexual mode of transmission	A50-A64	0	0
Other spirochaetal diseases	A65-A69	0	0
Other diseases caused by chlamydiae	A70-A74	0	0
Rickettsioses	A75-A79	0	2
Viral infections of the central nervous system	A80-A89	0	0
Arthropod-borne viral fevers and viral hemorrhagic fevers	A92-A99	0	0
Viral infections characterized by skin and mucous membrane lesions	B00-B09	0	2
Viral hepatitis	B15-B19	1	9
Human immunodeficiency virus[HIV] disease	B20-B24	0	0
Other viral diseases	B25-B34	0	0
Mycoses	B35-B49	0	0
Protozoal diseases	B50-B64	0	0
Helminthiases	B65-B83	0	0
Pediculosis, acariasis and other infestations	B85-B89	0	0
Sequelae of infectious and parasitic diseases	B90-B94	0	1
Bacterial, viral and other infectious agents	B95-B98	0	0
Other infectious diseases	B99	0	0
Neoplasm	C00-D48		
Malignant neoplasm of lip, oral cavity and pharynx	C00-C14	5	5
Malignant neoplasms of digestive organs	C15-C26	67	366
Malignant neoplasms of respiratory and intrathoracic organs	C30-C39	28	158
Malignant neoplasm of bone and articular cartilage	C40-C41	1	2
Melanoma and other malignant neoplasms of skin	C43-C44	1	1
Malignant neoplasms of mesthelial and soft tissue	C45-C49	1	5
Malignant neoplasm of breast	C50	2	3
Malignant neoplasm of female genital organs	C51-C58	8	11
Malignant neoplasm of male genital organs	C60-C63	4	29
Malignant neoplasm of urinary tract	C64-C68	4	28
Malignant neoplasm of eye, brain and other parts of central nervous system	C69-C72	1	6
Malignant neoplasm of thyroid and other endocrine gland	C73-C75	3	5
Malignant neoplasm of ill-defined, secondary and unspecified sites	C76-C80	8	11
Malignant neoplasms of lymphoid, hematopoietic and related tissue	C81-C96	10	26
Malignant neoplasm of independent (primary) multiple sites	C97	1	2
In situ neoplasms	D00-D09	0	1

Benign neoplasms	D10-D36	1	2
Neoplasms of uncertain or unknown behaviour	D37-D48	6	6
Metabolic disease	E00-E90		
Disorders of thyroid gland	E00-E07	1	0
Diabetes mellitus	E10-E14	71	154
Other diorders of glucose regulation and pancreatic internal secretion	E15-E16	0	0
Disorders of other endocrine glands	E20-E35	2	0
Malnutrition	E40-E46	0	1
Other nutritional deficiencies	E50-E64	1	0
Obesity and other hyperalimentation	E65-E68	0	0
Metabolic disorders	E70-E90	1	6
Mental disease	F00-F99		
Organic, including symptomatic	F00-F09	29	46
mental disorders	F10-F19	2	3
Mental and behavioral disorders	F20-F29	2	0
due to psychoactive substance use	F30-F39	0	0
Schizophrenia, schizotypal and	F40-F48	0	0
delusional disorders	F50-F59	0	0
Mood[affective] disorders	F60-F69	0	0
Neurotic, stress-related and	F70-F79	0	0
somatoform disorders	F80-F89	0	0
Behavioral syndromes associated	F90-F98	0	0
with physiological disturbances and	F99	0	0
Neurologic disease	G00-G99		
Inflammatory diseases of the central nervous system	G00-G09	1	1
Systemic atrophies primarily affecting the central nervous system	G10-G14	4	3
Extrapyramidal and movement disorders	G20-G26	294	7
Other degenerative diseases of the nervous system	G30-G32	22	51
Demyelinating diseases of the central nervous system	G35-G37	0	0
Episodic and paroxysmal disorders	G40-G47	1	4
Nerve, nerve root and plexus disorders	G50-G59	0	0
Polyneuropathies and other disorders of the peripheral nervous system	G60-G64	0	1
Diseases of myoneural junction and muscle	G70-G73	0	0
Cerebral palsy and other paralytic syndromes	G80-G83	1	1
Other disorders of the nervous system	G90-G99	5	1
Circulatory disease	I00-I99		
Acute rheumatic fever	I00-I02	0	0
Chronic rheumatic heart diseases	I05-I09	0	3
Hypertensive diseases	I10-I15	31	75
Ischemic heart diseases	I20-I25	54	148
Pulmonary heart disease and diseases of pulmonary circulation	I26-I28	1	5
Other forms of heart disease	I30-I52	39	102
Cerebrovascular diseases	I60-I69	150	359
Diseases of arteries, arterioles and capilaries	I70-I79	2	13

Diseases of veins, lymphatic vessels and lymph nodes, NEC	I80-I89	0	0
Other and unspecified disorders of the circulatory system	I95-I99	0	0
Respiratory disease	J00-J99		
Acute upper respiratory infections	J00-J06	0	0
Influenza and pneumonia	J09-J18	48	105
Other acute lower respiratory infections	J20-J22	0	0
Other diseases of upper respiratory tract	J30-J39	0	0
Chronic lower respiratory diseases	J40-J47	31	106
Lung diseases due to external agents	J60-J70	13	20
Other respiratory diseases principally affecting the interstitium	J80-J84	3	11
Suppurative and necrotic conditions of lower respiratory tract	J85-J86	1	1
Other diseases of pleura	J90-J94	0	0
Other diseases of the respiratory system	J95-J99	1	5
Digestive disease	K00-K93		
Diseases of oral cavity, salivary glands and jaws	K00-K14	0	0
Diseases of oesophagus, stomach and duodenum	K20-K31	3	12
Disease of appendix	K35-K38	0	0
Hernia	K40-K46	0	0
Noninfective enteritis and colitis	K50-K52	1	0
Other diseases of intestines	K55-K64	7	12
Diseases of peritoneum	K65-K67	0	2
Diseases of liver	K70-K77	10	35
Disorders of gallbladder, biliary tract and pancreas	K80-K87	4	21
Other diseases of the digestive system	K90-K93	5	6
Muscular disease	M00-M99		
Infectious arthropathies	M00-M03	0	0
Inflammatory polyarthropathies	M05-M14	2	3
Arthrosis	M15-M19	0	0
Other joint disorders	M20-M25	0	0
Systemic connective tissue disorder	M30-M36	0	1
Deformin dorsopathies	M40-M43	0	0
Spondylopathies	M45-M49	1	0
Other dorsopathies	M50-M54	0	1
Disorders of muscles	M60-M63	0	2
Disorders of synovium and tendon	M65-M68	0	0
Other soft tissue disorders	M70-M79	0	1
Disorders of bone density and structure	M80-M85	5	6
Other osteopathies	M86-M90	0	1
Chondropathies	M91-M94	0	0
Other disorders of the musculoskeletal system and connective tissue	M95-M99	0	0
Genitourinary disease	N00-N99		
Glomerular diseases	N00-N08	0	0
Renal tubulo-inerstitial diseases	N10-N16	2	4
Renal failure	N17-N19	18	38

Urolithiasis	N20-N23	1	0
Other disorders of kidney and ureter	N25-N29	0	0
Other diseases of the urinary system	N30-N39	4	5
Diseases of male genital organs	N40-N51	0	3
Disorders of breast	N60-N64	0	0
Inflammatory diseases of female pelvic organs	N70-N77	0	0
Noninflammatory disorders of female genital tract	N80-N98	0	0
Other disorders of te genitourinary system	N99	0	0
Abnormal finding	R00-R99		
Symptoms and signs involving the circulatory and respitatory systems	R00-R09	9	15
Symptoms and signs involving the digestive system and abdomen	R10-R19	0	0
Symptoms and signs involving the skin and subcutaneous tissue	R20-R23	0	0
symptoms and signs involving the nervous and musculoskeletal systems	R25-R29	0	0
symptoms and signs involving the urinary system	R30-R39	0	0
Symptoms and signs involving cognition, perception, emotional state and behaviour	R40-R46	0	0
Symptoms and signs involving speech and voice	R47-R49	0	0
General symptoms and signs	R50-R69	71	266
Abnormal findings on examination of blood, without diagnosis	R70-R79	0	0
Abnormal findings on examination of urine, without diagnosis	R80-R82	0	0
Abnormal findings on examination of other body fluids, substances and tissues, without diagnosis	R83-R89	0	0
Abnormal findings on diagnostic imaging and in function studies, without diagnosis	R90-R94	0	0
Ill-defined and unknown causes of mortality	R95-R99	5	48
Trauma	S00-T98		
Injuries to the head	S00-S09	10	32
Injuries to the neck	S10-S19	0	1
Injuries to the thorax	S20-S29	2	12
Injuries to the abdomen, lower back, lumbar spine and pelvis	S30-S39	0	3
Injuries to the shoulder and upper arm	S40-S49	0	1
Injuries to the elbow and forearm	S50-S59	1	0
Injuries to the wrist and hand	S60-S69	0	0
Injuries to th hip and thigh	S70-S79	7	16
Injuries to the knee and lower leg	S80-S89	0	2
Injuries to the ankle and foot	S90-S99	0	0
Injuries involving multiple body regions	T00-T07	7	17
Injuries to uspecitied part of trunk, limb or body region	T08-T14	3	8
Effects of foreign body entering throgh natural orifice	T15-T19	6	2
Burns and corrosions of external body suface, specified by site	T20-T25	0	0
Burn and corrosions confined to eye and internal organs	T26-T28	0	1
Burns and corrosions of multiple and unspecified of multiple and unspeccified body regions	T29-T32	2	0
Frostbite	T33-T35	0	0

Poisoning by drugs, medicaments and biological substances	T36-T50	1	1
Toxic effects of sustances chiefly nonmedicinal as to source	T51-T65	6	23
Other and unspecified effects of external causes	T66-T78	18	33
Certain early complications of trauma	T79	0	0
Complications of surgical and medical care, NEC	T80-T88	1	0
Sequelae of injures, of poisoning and of other consequences of external causes	T90-T98	0	2
Others	D50-D89, L00-L99		
Nutritional anemias	D50-D53	0	0
Hemolytic anemias	D55-D59	0	0
Aplastic and other anemias	D60-D64	1	3
Coagulation defect,purpura and other hemorrhage conditions	D65-D69	1	0
Other disease of blood and blood-forming organs	D70-D77	1	3
Certain disorders involving the immune mechanism	D80-D89	0	2
Other disorders of the skin and subcutaneous tissue	L80-L99	2	1
missing		12	2

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	4–5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8–9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	Fig. 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10–11
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9–12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders	14–15

		were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18–19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for exposed and unexposed groups.

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

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Mortality and cause of death in South Korean patients with Parkinson's disease: A longitudinal follow-up study using a national sample cohort

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Mortality and cause of death in South Korean patients with Parkinson's disease: A longitudinal follow-up study using a national sample cohort

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Mortality and cause of death in South Korean patients with Parkinson's disease: A longitudinal follow-up study using a national sample cohort

ABSTRACT

Objective: The incidence rate of Parkinson's disease (PD) is growing rapidly owing to the aging population. We investigated the mortality rates and causes of death in South Korean patients with PD.

Design: We investigated a national cohort using the nationwide insurance database.

Setting: Korean Health Insurance Review and Assessment Service - National Sample Cohort.

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.

Interventions: None

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.

Results: The adjusted hazard ratio (HR) for mortality in the PD group was 2.09 (95% confidence interval [CI] = 1.94–2.24, P < 0.001). Subgroup analysis according to age (<70 years, 70–79 years, and ≥80 years) and sex revealed that patients with PD showed higher adjusted HRs for mortality across all subgroups. Mortalities caused by metabolic, mental, neurologic, circulatory, respiratory, and genitourinary diseases, as well as trauma, were more common in the PD group than in the control group, with the highest odds ratio observed in patients with neurologic disease.

Conclusions: We demonstrated that PD in South Korean patients ≥60 years of age was associated with increased mortality in both sexes regardless of age.

Key words: Parkinson's disease, mortality, Korean

Strengths and limitations of this study

- Our study dataset encompassed 1,125,691 subjects registered over a 12-year period in a national insurance database.
- The study encompassed all registered patients with PD who visited outpatient clinics, were hospitalized, or both at least twice.
- The patients were not restricted to only those who were hospitalized.
- The patients with PD were matched 1:4 with control subjects based on age, group, sex, income group, regions of residence, and the past medical histories.
- We were unable to determine the severity of PD, and some confounding factors (e.g., smoking status, alcohol consumption, and obesity) were not adjusted for.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder, and is characterized by the 4 cardinal motor signs: tremor at rest, bradykinesia, rigidity, and postural instability, as well as other non-motor clinical manifestations [1, 2]. Despite the remarkable symptom-relieving benefits provided by levodopa over the past 30 years, recent studies have demonstrated that the mortality rates among PD patients remain higher than in individuals without PD [3, 4]. PD is one of the fastest growing diseases in terms of prevalence, disability, and mortality; the rapidly aging population has contributed to an increase in crude PD prevalence rates [5]. As such, a better understanding of the rates and causes of mortality in patients with PD is important to better estimate the social burden and medical care costs [6].

Even though PD is associated with increased mortality in general, previous studies show inconsistent data, with mortality rates ranging from 0.80 to 3.50 [2]. Some studies performed in the post-levodopa era even reported "super-normal" survival rather than increased mortality among PD patients [2]. Furthermore, the causes of death in patients with PD remain unclear [7]. The heterogeneity observed in studies of mortality as related to PD could be caused by the variable methodology and patient selection criteria. Different studies tend to be hospital-, pharmaceutical trial- or community-based, and thus yield results that are not very representative of the general population [6].

According to the Global Burden of Disease, Injuries, and Risk Factors Study of 2016, the death rate, prevalence, and disability-adjusted life-years of patients with PD varied depending on ethnicity and/or geography [5]. Among high-income Asia Pacific countries, South Korea showed the highest percentage change in age-standardized mortality rates between 1990 and 2016 (24.6%) compared to Brunei (17.9%), Japan (10.2%), and Singapore (11.3%), even though the percentage change in the age-standardized rates of prevalence during the same time period (21.0%) was similar to that of Japan (21.3%) [5]. Thus, analyses focused on a particular ethnic/geographic group is important to estimate the social burden of PD and the patient management plan in each country. However, a large cohort-based investigation of PD-related mortality rates and causes of death in South Korea has never been performed.

To better understand the natural courses and prognoses of patients with PD, and to provide valuable information on planning the distribution of health resources, we investigated the mortality rates and causes of death in patients with PD using a representative PD population in South Korea. We performed a large-scale longitudinal follow-up study, with a maximum follow-up duration of 12 years, using national cohort data.

MATERIALS AND METHODS

Patient and Public Involvement

No patient involved.

Study Population and Data Collection

The ethics committee of Hallym University approved the use of these data (approval number 2014-I148). The requirement for written informed consent was waived by the Institutional Review Board.

This national cohort study relied on data from the Korean Health Insurance Review and Assessment Service (HIRA) National Sample Cohort. The Korean National Health Insurance Service (NHIS) selects samples directly from the entire population database to prevent non-sampling errors. Approximately 2% of the samples (1 million) were selected from the entire Korean population (50 million). These selected data were classified into 1,476 levels (age [18 categories], sex [2 categories], and income level [41 categories]) using randomized stratified systematic sampling methods via proportional allocation to represent the entire population. After data selection, the appropriateness of the sample was verified by a statistician who compared the data from the entire Korean population to the sample data. The details of the methods used to perform these procedures are provided by the National Health Insurance Sharing Service [8]. The cohort database included (i) personal information, (ii) health insurance claim codes (procedures and prescriptions), (iii) diagnostic codes using the International Classification of Disease, 10th edition (ICD-10), (iv) death records from the Korean National Statistical Office (using the Korean Standard Classification of Disease), (v) socio-economic data (residence and income), and (vi) medical examination data for each participant over a period ranging from 2002 to 2013.

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.

Participant Selection

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). PD was categorized using ICD-10 codes (Parkinson's disease: G20). For accurate diagnoses, we only selected participants who visited outpatient clinics, were hospitalized, or both at least twice because of PD. The control participants were extracted from 1,121,522 participants who had no diagnoses of PD between 2002 and 2013.

Participants with PD were matched 1:4 with the control group. The matches were adjusted for age group, sex, income, region of residence, and medical histories of hypertension, diabetes mellitus, and dyslipidemia. We set the index date as that of the first visit to a clinic or a hospital for PD during the study period in the PD group; participants from the control group were also followed from the same index date as their matched counterparts with PD. To prevent selection bias, participants in the control group were sorted using a random number, and were then selected in descending order. It was assumed that the matched control participants were involved at the same time of each matched PD participant;

therefore, participants in the control group who died before the time of involvement of the matched PD participant were excluded. Forty PD participants for whom we could not identify a sufficient number of matching participants were also excluded, as were 619 participants who were diagnosed with PD while under the age of 60 years since the prevalence of PD is relatively low in younger individuals [9]. Ultimately 3,510 PD participants matched 1:4 with 14,040 control participants were included (Fig. 1).

Variables

Age groups were classified by 5-year intervals into 6 age groups: 60–64, 65–69, 70–74, 75–79, 80–84, and 85+ years old. The income groups were initially divided into 41 classes (1 health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were re-categorized into 11 classes (class 1 [lowest income] to class 11 [highest income]). Regions of residence were divided into 16 areas according to the administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

The causes of death were classified according to the Korean standard classification of diseases, developed by the World Health Organization based on the ICD, into 12 classifications: (i) Infection (certain infections and parasitic diseases, A00–B99); (ii) Neoplasm (neoplasms, C00–D48); (iii) Metabolic disease (endocrine, nutritional, and metabolic diseases, E00–E90); (iv) Mental disease (mental and behavioural disorders, F00–F99); (v) Neurologic disease (diseases of the nervous system, G00–G99); (vi) Circulatory disease (diseases of the circulatory system, I00–I99); (vii) Respiratory disease (diseases of the respiratory system, J00–J99); (viii) Digestive disease (diseases of the digestive system, K00–K93); (ix) Muscular disease (diseases of the musculoskeletal system and connective

tissue, M00–M99); (x) Genitourinary disease (diseases of the genitourinary system, N00–N99); (xi) Abnormal finding (symptoms, signs and abnormal clinical and laboratory findings 'not elsewhere classified', R00–R99); and (xii) Trauma (injury, poisoning, and certain other consequences of external causes, S00–T98). We also added 1 more category: (xiii) Others (diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism, D50–D89; diseases of the skin and subcutaneous tissue, L00–L99). The Charlson comorbidity index was used for 17 comorbidities as a continuous variable (0 [no comorbidity] through 29 [multiple comorbidities]) [**10]**].

Statistical Analyses.

The chi-square or Fisher's exact test was used to compare the general characteristics of participants in the PD and control groups, as well as to compare their mortality rates according to the cause of death. The false discovery rate was used to adjust for incorrect rejections of the null hypothesis.

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. Two-tailed P-values less than 0.05 were considered significant. Statistical analyses were conducted using the SPSS software, version 21.0 (IBM, Armonk, NY, USA).

RESULTS

The mean follow-up duration was 49.6 months (standard deviation [SD] = 37.3 months) in the PD group and 57.3 (SD = 40.6) months in the matched control group.

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).

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).

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). When categorizing patients according to age (<70 years, 70–79 years and ≥80 years) and sex, PD patients in all the subgroups showed higher crude and adjusted HRs for mortality than did the control patients.

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	

223

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

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

226 ‡ Model adjusted for the Charlson comorbidity index.

HR, hazard ratio; CI, confidence interval.

Analysis of mortality rates according to the cause of death revealed an odds ratio (OR) for overall mortality of 2.26 (95% CI = 2.08–2.45, P < 0.001) in the PD group (Table 3); the detailed data are presented in Supplementary Table 1. Mortalities caused by metabolic disease, mental diseases, neurologic disease, circulatory disease, respiratory disease, genitourinary disease and trauma were higher in the PD group than in the control group (the false discovery rate-adjusted P-value was <0.05 for each). The OR for mortality was highest for neurologic disease (20.87, 95% CI = 16.05–27.14, P < 0.001); among these neurologic diseases, extrapyramidal and movement disorders were the most common (294/328, 89.6%). Mortalities caused by infection, neoplasm, digestive disease, muscular disease, and other causes were not significantly different between the PD and control groups.

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.

DISCUSSION

Our findings were consistent with those of previous studies, most of which found higher mortality rates in patients with PD with HRs ranging from 1.2 to 2.4 [11,12]. However, most such studies were performed in Western countries, and data from Asian patients have rarely been reported. A recent study in China found that the standardized mortality rate of patients with PD was 0.62 (95% CI = 0.32–1.07), implying that the 5-year mortality ratio of patients with PD was not significantly higher than that of the general urban Chinese population [2]. However, we cannot compare their results to ours given their different study design; the Chinese study comprised 157 PD patients who were referred to - or diagnosed at - a particular tertiary hospital. To our knowledge, ours is the first study to demonstrate that mortality rates are higher in Korean PD patients using a national cohort, and is also the largest study of its kind to date. The adjusted HR of our study (2.09) was relatively higher than in previous studies considering that most reported HRs fall between 1.2 and 2.4, however, this is of little relevance owing to the major heterogeneity among the study methodologies. Nevertheless, our data still show that the mortality of patients with PD is higher than that in control populations despite recent advances in the treatment of this disease. This indicates that, while current treatment modalities relieve motor symptoms, they do not necessarily improve mortality rates and/or the life expectancies of patients with PD.

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.

In our study, patients with PD died more frequently of certain diseases and of trauma than their counterparts in the control population. Neurologic diseases (particularly extrapyramidal and movement disorders) were the most common causes of death, implying that PD features themselves were most responsible for death among PD patients in South Korea. Such studies of the outcomes of PD patients are scarce. In a study of mortality among 211 levodopa-treated patients with PD in the United Kingdom, Morgan et al. showed that the most common cause of death was PD itself (52.6%) [3]. They interpreted this to indicate that, even though levodopa might improve motor symptoms such as tremor, bradykinesia, and rigidity, it did not slow disease progression [13]. As the PD progressed, levodopa-resistant motor symptoms (speech/swallowing impairment, gait, and balance problems) and nonmotor symptoms (autonomic dysfunction, mood disorders, cognitive impairment, sleep disorders, and psychosis) become more prevalent and may contribute to the increased morbidity and mortality [14]. Although our study cohort was not necessarily confined to levodopa-treated subjects, it is highly likely that a significant proportion of our patients were being treated with

levodopa, as we only selected patients who were treated ≥2 times for PD. Our findings are different from those of other groups that described pneumonia to be the most common cause of death in PD patients [15-18]. The most likely explanation for this difference could be the varying methods of patient recruitment: we recruited our subjects based on their PD treatment history regardless of whether they were hospitalized; therefore, the cause of death among our patients; i.e., neurologic disease that may have included PD itself, may also reflect patients having died of other (perhaps natural) causes while afflicted with PD. However, the causes of death in hospitalized or nursing home-bound PD patients may have had a greater likelihood of being reported as pneumonia because of their orthostatic lability. Furthermore, our indication that PD-group patients did not necessarily die of pneumonia is true insofar as being compared to the control group, and is not a general statement, since we calculated the ORs of the cause of mortality. The significance of other causes of death such as cancer and circulation-impeding ischemic heart disease remain controversial [1, 2, 15-19]; the ORs for these conditions were not significant in our study. Nevertheless, our most important findings include (i) the overall death rate was higher in the PD group than that in the control group, and (ii) metabolic disease, mental diseases, neurologic disease, circulatory disease, respiratory disease, genitourinary disease, and trauma are common causes of death in PD patients in addition to PD itself. Our findings ought to be valuable for PD patient caregivers in both hospital and community settings.

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.

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 [23-25]. 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.

Despite these limitations, our data are nevertheless robust because we used a representative, large-scale sample from a cohort database comprising over 1 million subjects over a 12-year follow-up period. 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. We chose matched controls adjusted for the potential confounding factors of age, sex, income, and region of residence. Our subjects' comorbidity data were consistent with those of previous epidemiologic studies in the Korean population, which was further evidence of our study's reliability [26,27].

CONCLUSION

We performed the largest study on the risk of mortality in South Korean PD patients with clearly defined inclusion criteria. We found that PD increased the risk of mortality regardless of age and sex. Common causes of death in patients with PD included metabolic, mental, neurologic, circulatory, respiratory, and genitourinary diseases as well as trauma; the highest OR observed was for neurologic disease.

Acknowledgments

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Conflict of Interest

The authors do not have any conflict of interest to disclose.

Author contributions:

Choi HG composed the manuscript, Lim JS provided neurologists' perspectives, Lee YK reviewed the result, and Sim S and Kim M designed and supervised the study.

Data sharing

The data used for this study are available from the Korea National Health Insurance Sharing Service (https://nhiss.nhis.or.kr) subject to their requirements and fees.

REFERENCES

1. Doi Y, Yokoyama T, Nakamura Y, Nagai M, Fujimoto K, Nakano I. How can the national burden of Parkinson's disease comorbidity and mortality be estimated for the Japanese population? J Epidemiol. 2011;21(3):211-6.
2. Wang G, Li XJ, Hu YS, Cheng Q, Wang CF, Xiao Q, Liu J, Ma JF, Zhou HY, Pan J, Tan YY, Wang Y, Chen SD. Mortality from Parkinson's disease in China: Findings from a five-year follow up study in Shanghai. Can J Neurol Sci. 2015 Jul;42(4):242-7.
3. Morgan JC, Currie LJ, Harrison MB, Bennett JP Jr, Trugman JM, Wooten GF. Mortality in levodopa-treated Parkinson's disease. Parkinsons Dis. 2014;2014:426976.
4. CLarke CE. Mortality from Parkinson's disease. J Neurol Neurosurg Psychiatry. 2000 Feb;68(2):254-5.
5. GBD 2016 Parkinson's Disease Collaborators. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018 Nov;17(11):939-953.
6. de Lau LM, Schipper CM, Hofman A, Koudstaal PJ, Breteler MM. Prognosis of Parkinson disease: risk of dementia and mortality: the Rotterdam Study. Arch Neurol. 2005 Aug;62(8):1265-9.
7. Pennington S, Snell K, Lee M, Walker R. The cause of death in idiopathic Parkinson's disease. Parkinsonism Relat Disord. 2010 Aug;16(7):434-7.
8. The National Health Insurance Sharing Service of Korea. 2014. Available at: https://nhiss.nhis.or.kr/bd/ab/bdaba022eng.do. Accessed November 1, 2018.
9. Driver JA, Logroscino G, Gaziano JM, Kurth T. Incidence and remaining lifetime risk of Parkinson disease in advanced age. Neurology. 2009 Feb 3;72(5):432-8.
10. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel JM, Sundararajan V. Updating and validating the Charlson comorbidity index and score for risk adjustment in

hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011 Mar 15;173(6):676-82.

11. Ishihara LS, Cheesbrough A, Brayne C, Schrag A. Estimated life expectancy of Parkinson's patients compared with the UK population. J Neurol Neurosurg Psychiatry. 2007 Dec;78(12):1304-9.
12. Macleod AD, Taylor KS, Counsell CE. Mortality in Parkinson's disease: a systematic review and meta-analysis. Mov Disord. 2014 Nov;29(13):1615-22.
13. Olanow CW. The scientific basis for the current treatment of Parkinson's disease. Annu Rev Med. 2004;55:41-60.
14. Rascol O, Payoux P, Ory F, Ferreira JJ, Brefel-Courbon C, Montastruc JL. Limitations of current Parkinson's disease therapy. Ann Neurol. 2003;53 Suppl 3:S3-12; discussion S12-5.
15. Hobson P, Meara J. Mortality and quality of death certification in a cohort of patients with Parkinson's disease and matched controls in North Wales, UK at 18 years: a community-based cohort study. BMJ Open. 2018 Feb 14;8(2):e018969.
16. D'Amelio M, Ragonese P, Morgante L, Reggio A, Callari G, Salemi G, Savettieri G. Long-term survival of Parkinson's disease: a population-based study. J Neurol. 2006 Jan;253(1):33-7.
17. Fall PA, Saleh A, Fredrickson M, Olsson JE, Granérus AK. Survival time, mortality, and cause of death in elderly patients with Parkinson's disease: a 9-year follow-up. Mov Disord. 2003 Nov;18(11):1312-6.
18. Beyer MK, Herlofson K, Aarsland D, Larsen JP. Causes of death in a community based study of Parkinson’s disease. Acta Neurol Scand. 2001;103:7e11.

19. Ben-Shlomo Y, Marmot MG. Survival and cause of death in a cohort of patients with parkinsonism: possible clues to aetiology? J Neurol Neurosurg Psychiatr. 1995;58(3):293e9.

20. Lee JE, Choi J, Lim HS, Kim JH, Cho JH, Kim GS, Lee PH, Sohn YH, Lee JH. The prevalence and incidence of Parkinson′s Disease in South Korea: a 10-year nationwide population–based study. J Korean Neurol Assoc 2017; 35(4): 191-198.

21. Khang YH, Bahk J, Lim D, Kang HY, Lim HK, Kim YY, Park JH. Trends in inequality in life expectancy at birth between 2004 and 2017 and projections for 2030 in Korea: multiyear cross-sectional differences by income from national health insurance data. BMJ Open. 2019 Jul 3;9(7):e030683.

22. Vital Statistics Division, Statistics Korea ,Shin HY, Lee JY, Kim JE, Lee S, Youn H, Kim H, Lee J, Park MS, Huh S. Cause-of-death statistics in 2016 in the Republic of Korea. J Korean Med Assoc. 2018 Sep;61(9):573-584.

23. Ma C, Liu Y, Neumann S, Gao X. Nicotine from cigarette smoking and diet and Parkinson disease: a review. Transl Neurodegener. 2017 Jul 2;6:18.

24. Bettiol SS, Rose TC, Hughes CJ, Smith LA. Alcohol Consumption and Parkinson's Disease Risk: A Review of Recent Findings. J Parkinsons Dis. 2015;5(3):425-42.

25. Chen J, Guan Z, Wang L, Song G, Ma B, Wang Y. Meta-analysis: overweight, obesity, and Parkinson's disease. Int J Endocrinol. 2014;2014:203930.

26. Kim DJ. The epidemiology of diabetes in Korea. Diabetes Metab J 2011;35:303-8.

27. Lee HY, Park JB. The Korean Society of Hypertension Guidelines for the Management of hypertension in 2013: Its essentials and key points. Pulse (Basel) 2015;3:21-8.

Figure legend

Fig. 1 A schematic illustration of the participant selection process that was used in the present study. Of the 1,125,691 total participants, 4,169 with Parkinson's disease (PD) were selected. Participants with PD were matched 1:4 with a control group comprising individuals not diagnosed with PD. Ultimately, 3,510 participants with PD and 14,040 control participants were included.

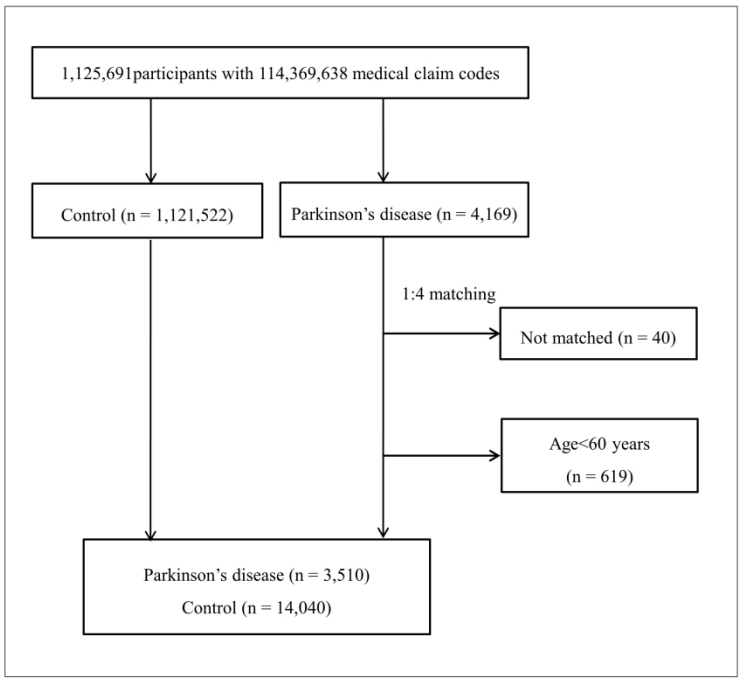

Figure 1

254x190mm (300 x 300 DPI)

S1Table Cause of death in dementia and control group

Cause of death	Codes	Total participants	
		Parkinson (n = 3,510)	Control (n = 14,040)
Infection	A00-B99		
Intestinal Infectious Diseases	A00-A09	6	9
Tuberculosis	A15-A19	3	25
Certain Zoonotic Bacterial diseases	A20-A28	0	0
Other bacterial diseases	A30- A49	13	26
Infections with a predominantly sexual mode of transmission	A50-A64	0	0
Other spirochaetal diseases	A65-A69	0	0
Other diseases caused by chlamydiae	A70-A74	0	0
Rickettsioses	A75-A79	0	2
Viral infections of the central nervous system	A80-A89	0	0
Arthropod-borne viral fevers and viral hemorrhagic fevers	A92-A99	0	0
Viral infections characterized by skin and mucous membrane lesions	B00-B09	0	2
Viral hepatitis	B15-B19	1	9
Human immunodeficiency virus[HIV] disease	B20-B24	0	0
Other viral diseases	B25-B34	0	0
Mycoses	B35-B49	0	0
Protozoal diseases	B50-B64	0	0
Helminthiases	B65-B83	0	0
Pediculosis, acariasis and other infestations	B85-B89	0	0
Sequelae of infectious and parasitic diseases	B90-B94	0	1
Bacterial, viral and other infectious agents	B95-B98	0	0
Other infectious diseases	B99	0	0
Neoplasm	C00-D48		
Malignant neoplasm of lip, oral cavity and pharynx	C00-C14	5	5
Malignant neoplasms of digestive organs	C15-C26	67	366
Malignant neoplasms of respiratory and intrathoracic organs	C30-C39	28	158
Malignant neoplasm of bone and articular cartilage	C40-C41	1	2
Melanoma and other malignant neoplasms of skin	C43-C44	1	1
Malignant neoplasms of mesthelial and soft tissue	C45-C49	1	5
Malignant neoplasm of breast	C50	2	3
Malignant neoplasm of female genital organs	C51-C58	8	11
Malignant neoplasm of male genital organs	C60-C63	4	29
Malignant neoplasm of urinary tract	C64-C68	4	28
Malignant neoplasm of eye, brain and other parts of central nervous system	C69-C72	1	6
Malignant neoplasm of thyroid and other endocrine gland	C73-C75	3	5
Malignant neoplasm of ill-defined, secondary and unspecified sites	C76-C80	8	11
Malignant neoplasms of lymphoid, hematopoietic and related tissue	C81-C96	10	26
Malignant neoplasm of independent (primary) multiple sites	C97	1	2
In situ neoplasms	D00-D09	0	1

Benign neoplasms	D10-D36	1	2
Neoplasms of uncertain or unknown behaviour	D37-D48	6	6
Metabolic disease	E00-E90		
Disorders of thyroid gland	E00-E07	1	0
Diabetes mellitus	E10-E14	71	154
Other diorders of glucose regulation and pancreatic internal secretion	E15-E16	0	0
Disorders of other endocrine glands	E20-E35	2	0
Malnutrition	E40-E46	0	1
Other nutritional deficiencies	E50-E64	1	0
Obesity and other hyperalimentation	E65-E68	0	0
Metabolic disorders	E70-E90	1	6
Mental disease	F00-F99		
Organic, including symptomatic	F00-F09	29	46
mental disorders	F10-F19	2	3
Mental and behavioral disorders	F20-F29	2	0
due to psychoactive substance use	F30-F39	0	0
Schizophrenia, schizotypal and	F40-F48	0	0
delusional disorders	F50-F59	0	0
Mood[affective] disorders	F60-F69	0	0
Neurotic, stress-related and	F70-F79	0	0
somatoform disorders	F80-F89	0	0
Behavioral syndromes associated	F90-F98	0	0
with physiological disturbances and	F99	0	0
Neurologic disease	G00-G99		
Inflammatory diseases of the central nervous system	G00-G09	1	1
Systemic atrophies primarily affecting the central nervous system	G10-G14	4	3
Extrapyramidal and movement disorders	G20-G26	294	7
Other degenerative diseases of the nervous system	G30-G32	22	51
Demyelinating diseases of the central nervous system	G35-G37	0	0
Episodic and paroxysmal disorders	G40-G47	1	4
Nerve, nerve root and plexus disorders	G50-G59	0	0
Polyneuropathies and other disorders of the peripheral nervous system	G60-G64	0	1
Diseases of myoneural junction and muscle	G70-G73	0	0
Cerebral palsy and other paralytic syndromes	G80-G83	1	1
Other disorders of the nervous system	G90-G99	5	1
Circulatory disease	I00-I99		
Acute rheumatic fever	I00-I02	0	0
Chronic rheumatic heart diseases	I05-I09	0	3
Hypertensive diseases	I10-I15	31	75
Ischemic heart diseases	I20-I25	54	148
Pulmonary heart disease and diseases of pulmonary circulation	I26-I28	1	5
Other forms of heart disease	I30-I52	39	102
Cerebrovascular diseases	I60-I69	150	359
Diseases of arteries, arterioles and capilaries	I70-I79	2	13

Diseases of veins, lymphatic vessels and lymph nodes, NEC	I80-I89	0	0
Other and unspecified disorders of the circulatory system	I95-I99	0	0
Respiratory disease	J00-J99		
Acute upper respiratory infections	J00-J06	0	0
Influenza and pneumonia	J09-J18	48	105
Other acute lower respiratory infections	J20-J22	0	0
Other diseases of upper respiratory tract	J30-J39	0	0
Chronic lower respiratory diseases	J40-J47	31	106
Lung diseases due to external agents	J60-J70	13	20
Other respiratory diseases principally affecting the interstitium	J80-J84	3	11
Suppurative and necrotic conditions of lower respiratory tract	J85-J86	1	1
Other diseases of pleura	J90-J94	0	0
Other diseases of the respiratory system	J95-J99	1	5
Digestive disease	K00-K93		
Diseases of oral cavity, salivary glands and jaws	K00-K14	0	0
Diseases of oesophagus, stomach and duodenum	K20-K31	3	12
Disease of appendix	K35-K38	0	0
Hernia	K40-K46	0	0
Noninfective enteritis and colitis	K50-K52	1	0
Other diseases of intestines	K55-K64	7	12
Diseases of peritoneum	K65-K67	0	2
Diseases of liver	K70-K77	10	35
Disorders of gallbladder, biliary tract and pancreas	K80-K87	4	21
Other diseases of the digestive system	K90-K93	5	6
Muscular disease	M00-M99		
Infectious arthropathies	M00-M03	0	0
Inflammatory polyarthropathies	M05-M14	2	3
Arthrosis	M15-M19	0	0
Other joint disorders	M20-M25	0	0
Systemic connective tissue disorder	M30-M36	0	1
Deformin dorsopathies	M40-M43	0	0
Spondylopathies	M45-M49	1	0
Other dorsopathies	M50-M54	0	1
Disorders of muscles	M60-M63	0	2
Disorders of synovium and tendon	M65-M68	0	0
Other soft tissue disorders	M70-M79	0	1
Disorders of bone density and structure	M80-M85	5	6
Other osteopathies	M86-M90	0	1
Chondropathies	M91-M94	0	0
Other disorders of the musculoskeletal system and connective tissue	M95-M99	0	0
Genitourinary disease	N00-N99		
Glomerular diseases	N00-N08	0	0
Renal tubulo-inerstitial diseases	N10-N16	2	4
Renal failure	N17-N19	18	38

Urolithiasis	N20-N23	1	0
Other disorders of kidney and ureter	N25-N29	0	0
Other diseases of the urinary system	N30-N39	4	5
Diseases of male genital organs	N40-N51	0	3
Disorders of breast	N60-N64	0	0
Inflammatory diseases of female pelvic organs	N70-N77	0	0
Noninflammatory disorders of female genital tract	N80-N98	0	0
Other disorders of te genitourinary system	N99	0	0
Abnormal finding	R00-R99		
Symptoms and signs involving the circulatory and respitatory systems	R00-R09	9	15
Symptoms and signs involving the digestive system and abdomen	R10-R19	0	0
Symptoms and signs involving the skin and subcutaneous tissue	R20-R23	0	0
symptoms and signs involving the nervous and musculoskeletal systems	R25-R29	0	0
symptoms and signs involving the urinary system	R30-R39	0	0
Symptoms and signs involving cognition, perception, emotional state and behaviour	R40-R46	0	0
Symptoms and signs involving speech and voice	R47-R49	0	0
General symptoms and signs	R50-R69	71	266
Abnormal findings on examination of blood, without diagnosis	R70-R79	0	0
Abnormal findings on examination of urine, without diagnosis	R80-R82	0	0
Abnormal findings on examination of other body fluids, substances and tissues, without diagnosis	R83-R89	0	0
Abnormal findings on diagnostic imaging and in function studies, without diagnosis	R90-R94	0	0
Ill-defined and unknown causes of mortality	R95-R99	5	48
Trauma	S00-T98		
Injuries to the head	S00-S09	10	32
Injuries to the neck	S10-S19	0	1
Injuries to the thorax	S20-S29	2	12
Injuries to the abdomen, lower back, lumbar spine and pelvis	S30-S39	0	3
Injuries to the shoulder and upper arm	S40-S49	0	1
Injuries to the elbow and forearm	S50-S59	1	0
Injuries to the wrist and hand	S60-S69	0	0
Injuries to th hip and thigh	S70-S79	7	16
Injuries to the knee and lower leg	S80-S89	0	2
Injuries to the ankle and foot	S90-S99	0	0
Injuries involving multiple body regions	T00-T07	7	17
Injuries to uspecitied part of trunk, limb or body region	T08-T14	3	8
Effects of foreign body entering throgh natural orifice	T15-T19	6	2
Burns and corrosions of external body suface, specified by site	T20-T25	0	0
Burn and corrosions confined to eye and internal organs	T26-T28	0	1
Burns and corrosions of multiple and unspecified of multiple and unspeccified body regions	T29-T32	2	0
Frostbite	T33-T35	0	0

Poisoning by drugs, medicaments and biological substances	T36-T50	1	1
Toxic effects of sustances chiefly nonmedicinal as to source	T51-T65	6	23
Other and unspecified effects of external causes	T66-T78	18	33
Certain early complications of trauma	T79	0	0
Complications of surgical and medical care, NEC	T80-T88	1	0
Sequelae of injures, of poisoning and of other consequences of external causes	T90-T98	0	2
Others	D50-D89, L00-L99		
Nutritional anemias	D50-D53	0	0
Hemolytic anemias	D55-D59	0	0
Aplastic and other anemias	D60-D64	1	3
Coagulation defect,purpura and other hemorrhage conditions	D65-D69	1	0
Other disease of blood and blood-forming organs	D70-D77	1	3
Certain disorders involving the immune mechanism	D80-D89	0	2
Other disorders of the skin and subcutaneous tissue	L80-L99	2	1
missing		12	2

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	4–5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8–9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	Fig. 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10–11
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9–12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders	14–15

		were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18–19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for exposed and unexposed groups.

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