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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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Manuscripts

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7 2 **longitudinal follow-up study using a national sample cohort**
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4 36 **Mortality and cause of death in Parkinson's disease patient: A**
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7 37 **longitudinal follow-up study using a national sample cohort**
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11 39 **ABSTRACT**

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14 40 *Objective:* The prevalence of Parkinson's disease (PD) is growing rapidly owing to the aging
15
16 41 population. We investigated the mortality rates and causes of death in South Korean patients
17
18 42 with PD.

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20
21 43 *Design:* We investigated a national cohort using the nationwide insurance database.

22
23 44 *Setting:* Korean Health Insurance Review and Assessment Service - National Sample Cohort.

24
25 45 *Participants:* We included 4,169 participants ≥ 60 years of age who were diagnosed with PD
26
27 46 between 2002 and 2013, as well as 1,121,522 matched controls.

28
29
30 47 *Interventions:* None

31
32 48 *Primary and secondary outcome measures:* A Cox proportional hazards model was used to
33
34 49 evaluate patients with PD who were matched 1:4 with non-PD control subjects adjusted for
35
36 50 age, sex, income, and region of residence. The causes of death were grouped into 12
37
38 51 classifications.

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41 52 *Results:* The adjusted hazard ratio (HR) for mortality in the PD group was 2.26 (95%
42
43 53 confidence interval [CI] = 2.11–2.42, $P < 0.001$). Subgroup analysis according to age (<75
44
45 54 years vs. ≥ 75 years) and sex revealed that patients with PD showed higher adjusted HRs for
46
47 55 mortality across all subgroups. Mortalities caused by metabolic, mental, neurologic, disease,
48
49 56 disease, and genitourinary diseases, as well as trauma, were more common in the PD group
50
51 57 than in the control group, with the highest odds ratio observed in patients with neurologic
52
53 58 disease.
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3 59 *Conclusions:* We demonstrated that PD in South Korean patients ≥ 60 years of age was
4
5 60 associated with increased mortality in both sexes regardless of age.
6
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8 61

9
10 62 Key words: Parkinson's disease, mortality, Korean
11
12 63

13 64 **Strengths and limitations of this study**

- 14
15 65 • Our study dataset encompassed 1,125,691 subjects registered over a 12-year period in
16
17 66 a national insurance database.
- 18
19 67 • The study encompassed all registered patients with PD who were treated at least
20
21 68 twice.
- 22
23 69 • The patients were not restricted to only those who were hospitalized.
- 24
25 70 • The patients with PD were matched 1:4 with control subjects based on age, group,
26
27 71 sex, income group, regions of residence, and the past medical histories.
- 28
29 72 • We were unable to determine the severity of PD, and some confounding factors (e.g.,
30
31 73 smoking status, alcohol consumption, and obesity) were not adjusted for.
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41 75 **INTRODUCTION**

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43 76 Parkinson's disease (PD) is the second most common neurodegenerative disorder, and is
44
45 77 characterized by the 4 cardinal motor signs: tremor at rest, bradykinesia, rigidity, and postural
46
47 78 instability, as well as other non-motor clinical manifestations [1, 2]. Despite the remarkable
48
49 79 symptom-relieving benefits provided by levodopa over the past 30 years, recent studies have
50
51 80 demonstrated that the mortality rates among PD patients remain higher than in individuals
52
53 81 without PD [3, 4]. PD is one of the fastest growing diseases in terms of prevalence, disability,
54
55 82 and mortality; the rapidly aging population has contributed to an increase in crude PD
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3 83 prevalence rates [5]. As such, a better understanding of the rates and causes of mortality in
4
5 84 patients with PD is important to better estimate the social burden and medical care costs [6].
6

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8 85 Even though PD is associated with increased mortality in general, previous studies show
9
10 86 inconsistent data, with mortality rates ranging from 0.80 to 3.50 [2]. Some studies performed
11
12 87 in the post-levodopa era even reported “super-normal” survival rather than increased
13
14 88 mortality among PD patients [2]. Furthermore, the causes of death in patients with PD remain
15
16 89 unclear [7]. The heterogeneity observed in studies of mortality as related to PD could be
17
18 90 caused by the variable methodology and patient selection criteria. Different studies tend to be
19
20 91 hospital-, pharmaceutical trial- or community-based, and thus yield results that are not very
21
22 92 representative of the general population [6].
23
24

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26 93 According to Global Burden of Disease, Injuries, and Risk Factors Study of 2016, the
27
28 94 death rate, prevalence, and disability-adjusted life-years of patients with PD varied depending
29
30 95 on ethnicity and/or geography [5]. Among high-income Asia Pacific countries, South Korea
31
32 96 showed the highest percentage change in age-standardized mortality rates between 1990 and
33
34 97 2016 (24.6%) compared to Brunei (17.9%), Japan (10.2%), and Singapore (11.3%), even
35
36 98 though the percentage change in age-standardized rates of prevalence during the same time
37
38 99 period (21.0%) was similar to that of Japan (21.3%) [5]. Thus, analyses focused on a
39
40 100 particular ethnic/geographic group is important to estimate the social burden of PD and the
41
42 101 patient management plan in each country. However, a large cohort-based investigation of PD-
43
44 102 related mortality rates and causes of death in South Korea has never been performed.
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49 103 To better understand the natural courses and prognoses of patients with PD, and to
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51 104 provide valuable information on the planning the distribution of health resources, we
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53 105 investigated the mortality rates and causes of death in patients with PD using a representative
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55 106 PD population in South Korea. We performed a large-scale longitudinal follow-up study with
56
57 107 a maximum follow-up duration of 12 years, using national cohort data.
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109 MATERIALS AND METHODS

110 Study Population and Data Collection

111 The ethics committee of Hallym University (2014-I148) approved the use of these data.

112 Written informed consent was exempted by the Institutional Review Board.

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

129 Because all Korean citizens are recognized by a 13-digit resident registration number
130 from birth to death, exact population statistics can be determined using this database. It is
131 mandatory for all Koreans to enroll in the NHIS. All Korean hospitals and clinics use the 13-
132 digit resident registration number to register individual patients in the medical insurance

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3 133 system. Therefore, the risk of overlapping medical records is minimal, even if a patient
4
5 134 moves from one place to another. Moreover, all medical treatments in Korea can be tracked
6
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8 135 without exception using the HIRA system. In Korea, notice of death to an administrative
9
10 136 entity is legally required before a funeral can be held. Causes of death and date are recorded
11
12 137 by medical doctors on a death certificate.
13
14
15 138

17 139 **Participants Selection**

18
19 140 Out of 1,125,691 cases with 114,369,638 medical claim codes, we included participants who
20
21 141 were diagnosed as PD from 2002 through 2013 (n = 4,169). PD was categorized using ICD-
22
23 142 10 codes (Parkinson's disease: G20). For the accuracy of diagnosis, we only selected if the
24
25
26 143 participants were treated ≥ 2 times. The control participants were extracted from 1,121,522
27
28 144 participants who were never diagnosed PD from 2002 through 2013 among this cohort.

29
30 145 The PD participants were matched 1:4 with control group. The matches were processed
31
32
33 146 for age, group, sex, income group, region of residence, the past medical histories of
34
35 147 hypertension, diabetes mellitus, and dyslipidemia. To prevent selection bias when selecting
36
37 148 the matched participants, the control group participants were sorted using a random number
38
39 149 order, and they were then selected from top to bottom. It was assumed that the matched
40
41
42 150 control participants were involved at the same time of each matched PD participants.
43
44 151 Therefore, the control group who died before the involvement time of the matched PD
45
46 152 participant was excluded. The PD participants for whom we could not identify enough
47
48 153 matching participants were excluded (n = 40). The participants who were diagnosed as PD
49
50 154 under 60 years old were excluded (n = 619) in that the prevalence of PD was relatively low
51
52
53 155 under that ages [9]. Finally, 1:4 matching resulted in the inclusion of 3,510 of PD participants
54
55
56 156 and 14,040 control participants (Fig. 1).
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158 **Variables**

159 The age groups were classified using 5-year intervals: 60-64, 65-69, 70-74..., and 85+ years
160 old. A total of 6 age groups were designated. The income groups were initially divided into
161 41 classes (one health aid class, 20 self-employment health insurance classes, and 20
162 employment health insurance classes). These groups were re-categorized into 11 classes
163 (class 1 [lowest income]-11 [highest income]). Region of residence was divided into 16 areas
164 according to administrative district. These regions were regrouped into urban (Seoul, Busan,
165 Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon,
166 Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk,
167 Gyeongsangnam, and Jeju) areas.

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

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

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

188

189 **Statistical Analyses**

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

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

194 To analyze the hazard ratio (HR) of PD on mortality, Cox-proportional hazard model was
195 used. In this analysis, crude (simple) and adjusted (age, sex, income, region of residence,
196 hypertension, diabetes, and dyslipidemia) model was used. 95% confidence interval (CI)
197 were calculated. Two-tailed analyses were conducted, and P values less than 0.05 were
198 considered to indicate significance. The results were statistically analyzed using SPSS v. 21.0
199 (IBM, Armonk, NY, USA).

200

201 **RESULTS**

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

204 Age, sex, income level, region of residence, hypertension status, diabetes status, and
205 dyslipidemia status were matched between the PD and control groups (Table 1). The
206 mortality rate was significantly higher in the PD group than that in the control group (34.6%
207 and 19.0%, respectively, $P < 0.001$).

209 **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)	

210

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

212

213 The crude and adjusted HRs for mortality in the PD group were 2.14 (95% CI = 2.00–2.29,

214 $P < 0.001$) and 2.26 (95% CI = 2.11–2.42, $P < 0.001$), respectively (Table 2). When215 categorizing patients according to age (<75 years vs. ≥ 75 years) and sex, PD patients in all

216 the subgroups showed higher crude and adjusted HRs for mortality than did the control

217 patients (Table 3). The crude and adjusted HRs were significantly higher in PD patients ≥ 75

218 years of age than in those <75 years regardless of sex. Moreover, the crude and adjusted HRs

219 trended slightly higher in women than in men regardless of age; however, the 95% CIs

220 overlapped.

222 **Table 2** Crude and adjusted hazard ratios (95% confidence interval) of Parkinson's disease
 223 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	

224
 225 *Cox-proportional hazard regression model, Significance at P < 0.05

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

228

229 **Table 3** Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of
 230 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	

231

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

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

235

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

247 **Table 4** The difference of mortality rate between Parkinson's disease and control group
 248 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

249

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

251 CI: confidence interval

252

253

254 DISCUSSION

255 Our findings were consistent with those of previous studies, most of which found higher
 256 mortality rates in patients with PD with HRs ranging from 1.2 to 2.4 [10, 11]. However, most
 257 such studies were performed in Western countries, and data from Asian patients have rarely
 258 been reported. A recent study in China found that the standardized mortality rate of patients
 259 with PD was 0.62 (95% CI = 0.32–1.07), implying that the 5-year mortality ratio of patients
 260 with PD was not significantly higher than that of the general urban Chinese population [2].

261 However, we cannot compare their results to ours given their different study design; the
 262 Chinese study comprised 157 PD patients who were referred to - or diagnosed at - a particular
 263 tertiary hospital. To our knowledge, ours is the first study to demonstrate that mortality rates
 264 are higher in Korean PD patients using a national cohort, and is also the largest study of its
 265 kind to date. The adjusted HR of our study (2.26) was relatively higher than in previous
 266 studies considering that most reported HRs fall between 1.2 and 2.4, however, this is of little
 267 relevance owing to the major heterogeneity among the study methodologies. Nevertheless,
 268 our data still show that the mortality of patients with PD is higher than that in control
 269 populations despite recent advances in the treatment of this disease. This indicates that, while
 270 current treatment modalities relieve motor symptoms, they do not necessarily improve
 271 mortality rates and/or the life expectancies of patients with PD.

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2
3 272 The adjusted HRs for mortality were significantly higher in patients ≥ 75 years of age at
4
5 273 the time of PD diagnosis than in those < 75 years when diagnosed in both men and women.
6
7 274 Older age at onset was most consistently found to be an independent predictor of mortality
8
9 275 across studies [4, 12-17]. One study by Morgan et al. produced a contrasting result in that
10
11 276 patients with early PD onset (of ages 50 years or younger) appeared to have higher mortality
12
13 277 rates than patients with later PD onset [3]; however, we could not compare our results to
14
15 278 theirs because we excluded subjects younger than 60 years. While it is unclear why the age of
16
17 279 onset affects the mortality rate in the PD patients, a possible explanation is that patients aged
18
19 280 ≥ 75 years at onset may be affected by mortality-causing conditions that were not adjusted for
20
21
22 281 in our study to a greater extent than those < 75 years.

23
24
25 282 As we did not make a direct comparison between men and women in subgroup analysis,
26
27 283 we were unable to ascertain whether sex is a factor affecting the mortality rates of patients
28
29 284 with PD. While some studies have found that male sex was associated with increased
30
31 285 mortality in patients with PD [12-17], others showed this not to be the case [3, 18]. More
32
33 286 recent data suggest that, because the general life expectancy of women in general is longer
34
35 287 than that of men, the formers' higher mortality rates and greater reductions in lifespan are
36
37 288 more apparent when they are afflicted with PD; this would imply that PD progression
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39 289 patterns are not actually different between the sexes with respect to mortality [3].

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42 290 In our study, patients with PD died more frequently of certain diseases and of trauma
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44 291 than their counterparts in the control population. Neurologic diseases (particularly
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46 292 extrapyramidal and movement disorders) were the most common causes of death, implying
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48 293 that PD features themselves were most responsible for death among PD patients in South
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50 294 Korea. Such studies of the outcomes of PD patients are scarce. In a study of mortality among
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52 295 211 levodopa-treated patients with PD in the United Kingdom, Morgan et al. showed that the
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54 296 most common cause of death was PD itself (52.6%) [3]. They interpreted this to indicate that,
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3 297 even though levodopa might improve motor symptoms such as tremor, bradykinesia, and
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5 298 rigidity, it did not slow disease progression [19]. As the PD progressed, levodopa-resistant
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7 299 motor symptoms (speech/swallowing impairment, gait, and balance problems) and nonmotor
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9 300 symptoms (autonomic dysfunction, mood disorders, cognitive impairment, sleep disorders,
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11 301 and psychosis) become more prevalent and may contribute to the increased morbidity and
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13 302 mortality [20]. Although our study cohort was not necessarily confined to levodopa-treated
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15 303 subjects, it is highly likely that a significant proportion of our patients might have been
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17 304 treated by levodopa, as we only selected patients who were treated ≥ 2 times for PD. Our
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19 305 findings are different from those of other groups that found pneumonia to be the most
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21 306 common cause of death in PD patients [21-24]. The most likely explanation for this
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23 307 difference could be the varying methods of patient recruitment: we recruited our subjects
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25 308 based on their PD treatment history regardless of whether they were hospitalized; therefore,
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27 309 the cause of death among our patients; i.e., neurologic disease that may have included PD
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29 310 itself, may also reflect patients having died of other (perhaps natural) causes while afflicted
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31 311 with PD. However, the causes of death in hospitalized or nursing home-bound PD patients
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33 312 may have had a greater likelihood of being reported as pneumonia because of their orthostatic
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35 313 lability. Furthermore, our indication that PD-group patients did not necessarily die of
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37 314 pneumonia is true insofar as being compared to the control group, and is not a general
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39 315 statement, since we calculated the ORs of the cause of mortality. The significance of other
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41 316 causes of death such as cancer and circulation-impeding ischemic heart disease remain
42
43 317 controversial [1, 2, 21-25]; the ORs for these conditions were not significant in our study.
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45 318 Nevertheless, our most important findings include (i) the overall death rate was higher in the
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47 319 PD group than that in the control group, and (ii) metabolic disease, mental diseases,
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49 320 neurologic disease, circulatory disease, respiratory disease, genitourinary disease, and trauma
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3 321 are common causes of death in PD patients in addition to PD itself. Our findings ought to be
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5 322 valuable for PD patient caregivers in both hospital and community settings.
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8 323 A limitation of our study was that we were unable to determine the severity of PD. In the
9
10 324 same context, we did not stratify patients by their hospitalization histories or disease
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12 325 durations, which may have skewed the mortality data. Furthermore, some confounding
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14 326 factors that can influence mortality, such as smoking status, alcohol consumption, and
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16 327 obesity, were not adjusted for [26-28].
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19 328 Despite these limitations, our data are nevertheless robust because we used a
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21 329 representative, large-scale sample from a cohort database comprising over 1 million subjects
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23 330 over a 12-year follow-up period. Another strength of our study is that our approach
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25 331 minimized the risk of recall bias or missing information, as the dataset was based on claims
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27 332 to the compulsory HIRA nationwide health insurance system. We chose matched controls
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29 333 adjusted for the potential confounding factors of age, sex, income, and region of residence.
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31 334 Our subjects' comorbidity data were consistent with those of previous epidemiologic studies
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33 335 in the Korean population, which was further evidence of our study's reliability [29, 30].
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40 337 **CONCLUSION**

41
42 338 We performed the largest study on the risk of mortality in South Korean PD patients
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44 339 with clearly defined inclusion criteria. We found that PD increased the risk of mortality
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46 340 regardless of age and sex. The mortality rate was higher in patients ≥ 75 years old than in
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48 341 those < 75 years for both sexes. Common causes of death in patients with PD included
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50 342 metabolic, mental, neurologic, circulatory, respiratory, and genitourinary diseases as well as
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52 343 trauma; the highest OR observed was for neurologic disease.
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12 349 **Conflict of Interest**
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14 350 The authors do not have any conflict of interest to disclose.
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18
19 352 **Author contributions:**
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21 353 Choi HG composed the manuscript, Lim JS provided neurologist's perspective, and Sim S
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23 354 and Kim M designed and supervised the study.
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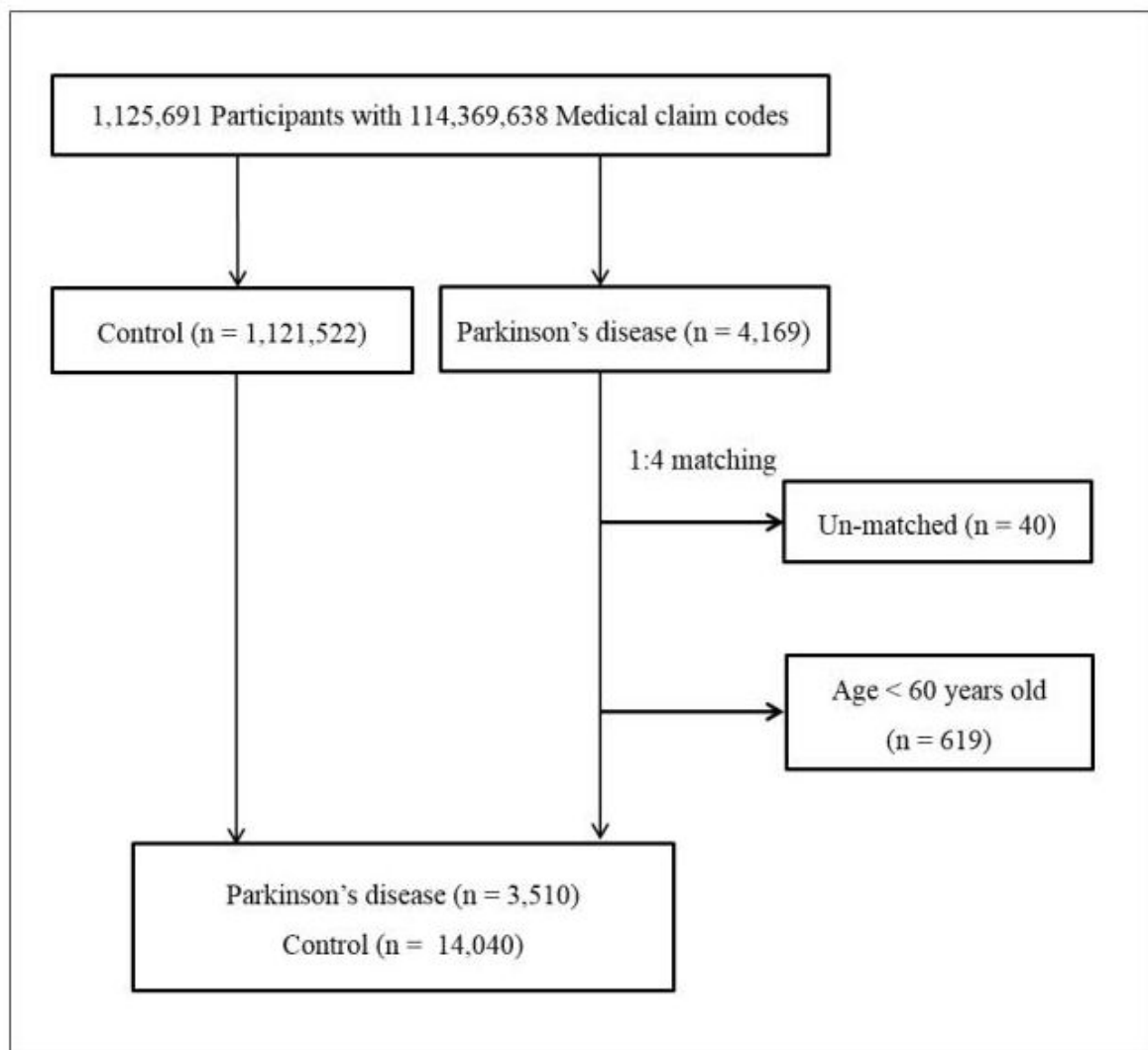
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428 **Figure legend**

429 **Fig. 1** A schematic illustration of the participant selection process that was used in the present
430 study. Out of a total of 1,125,691 participants, 4,169 PD participants were selected. The PD
431 participants were matched 1:4 with a control group that were not diagnosed as PD. Finally,
432 3,510 PD and 14,040 control participants were included.

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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
Helminthiasis	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 mesothelial 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

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4	Benign neoplasms	D10-D36	1	2
5	Neoplasms of uncertain or unknown behaviour	D37-D48	6	6
6				
7	Metabolic disease	E00-E90		
8	Disorders of thyroid gland	E00-E07	1	0
9	Diabetes mellitus	E10-E14	71	154
10				
11	Other disorders of glucose regulation and pancreatic internal secretion	E15-E16	0	0
12	Disorders of other endocrine glands	E20-E35	2	0
13	Malnutrition	E40-E46	0	1
14	Other nutritional deficiencies	E50-E64	1	0
15	Obesity and other hyperalimentation	E65-E68	0	0
16	Metabolic disorders	E70-E90	1	6
17				
18	Mental disease	F00-F99		
19				
20	Organic, including symptomatic	F00-F09	29	46
21	mental disorders	F10-F19	2	3
22	Mental and behavioral disorders	F20-F29	2	0
23	due to psychoactive substance use	F30-F39	0	0
24	Schizophrenia, schizotypal and	F40-F48	0	0
25	delusional disorders	F50-F59	0	0
26	Mood[affective] disorders	F60-F69	0	0
27	Neurotic, stress-related and	F70-F79	0	0
28	somatoform disorders	F80-F89	0	0
29	Behavioral syndromes associated	F90-F98	0	0
30	with physiological disturbances and	F99	0	0
31				
32				
33				
34	Neurologic disease	G00-G99		
35	Inflammatory diseases of the central nervous system	G00-G09	1	1
36	Systemic atrophies primarily affecting the central nervous system	G10-G14	4	3
37	Extrapyramidal and movement disorders	G20-G26	294	7
38	Other degenerative diseases of the nervous system	G30-G32	22	51
39	Demyelinating diseases of the central nervous system	G35-G37	0	0
40	Episodic and paroxysmal disorders	G40-G47	1	4
41	Nerve, nerve root and plexus disorders	G50-G59	0	0
42	Polyneuropathies and other disorders of the peripheral nervous system	G60-G64	0	1
43	Diseases of myoneural junction and muscle	G70-G73	0	0
44	Cerebral palsy and other paralytic syndromes	G80-G83	1	1
45	Other disorders of the nervous system	G90-G99	5	1
46				
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49	Circulatory disease	I00-I99		
50				
51	Acute rheumatic fever	I00-I02	0	0
52	Chronic rheumatic heart diseases	I05-I09	0	3
53	Hypertensive diseases	I10-I15	31	75
54	Ischemic heart diseases	I20-I25	54	148
55	Pulmonary heart disease and diseases of pulmonary circulation	I26-I28	1	5
56	Other forms of heart disease	I30-I52	39	102
57	Cerebrovascular diseases	I60-I69	150	359
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59	Diseases of arteries, arterioles and capillaries	I70-I79	2	13
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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-interstitial diseases	N10-N16	2	4
Renal failure	N17-N19	18	38

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4	Urolithiasis	N20-N23	1	0
5	Other disorders of kidney and ureter	N25-N29	0	0
6	Other diseases of the urinary system	N30-N39	4	5
7	Diseases of male genital organs	N40-N51	0	3
8	Disorders of breast	N60-N64	0	0
9	Inflammatory diseases of female pelvic organs	N70-N77	0	0
10	Noninflammatory disorders of female genital tract	N80-N98	0	0
11	Other disorders of the genitourinary system	N99	0	0
12				
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14	Abnormal finding	R00-R99		
15				
16	Symptoms and signs involving the circulatory and respiratory systems	R00-R09	9	15
17	Symptoms and signs involving the digestive system and abdomen	R10-R19	0	0
18	Symptoms and signs involving the skin and subcutaneous tissue	R20-R23	0	0
19	symptoms and signs involving the nervous and musculoskeletal systems	R25-R29	0	0
20	symptoms and signs involving the urinary system	R30-R39	0	0
21	Symptoms and signs involving cognition, perception, emotional state and			
22	behaviour	R40-R46	0	0
23	Symptoms and signs involving speech and voice	R47-R49	0	0
24	General symptoms and signs	R50-R69	71	266
25	Abnormal findings on examination of blood, without diagnosis	R70-R79	0	0
26	Abnormal findings on examination of urine, without diagnosis	R80-R82	0	0
27	Abnormal findings on examination of other body fluids, substances and tissues,			
28	without diagnosis	R83-R89	0	0
29	Abnormal findings on diagnostic imaging and in function studies, without			
30	diagnosis	R90-R94	0	0
31	Ill-defined and unknown causes of mortality	R95-R99	5	48
32				
33	Trauma	S00-T98		
34				
35	Injuries to the head	S00-S09	10	32
36	Injuries to the neck	S10-S19	0	1
37	Injuries to the thorax	S20-S29	2	12
38	Injuries to the abdomen, lower back, lumbar spine and pelvis	S30-S39	0	3
39	Injuries to the shoulder and upper arm	S40-S49	0	1
40	Injuries to the elbow and forearm	S50-S59	1	0
41	Injuries to the wrist and hand	S60-S69	0	0
42	Injuries to the hip and thigh	S70-S79	7	16
43	Injuries to the knee and lower leg	S80-S89	0	2
44	Injuries to the ankle and foot	S90-S99	0	0
45	Injuries involving multiple body regions	T00-T07	7	17
46	Injuries to unspecified part of trunk, limb or body region	T08-T14	3	8
47	Effects of foreign body entering through natural orifice	T15-T19	6	2
48	Burns and corrosions of external body surface, specified by site	T20-T25	0	0
49	Burn and corrosions confined to eye and internal organs	T26-T28	0	1
50	Burns and corrosions of multiple and unspecified of multiple and unspecified			
51	body regions	T29-T32	2	0
52	Frostbite	T33-T35	0	0
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4	Poisoning by drugs, medicaments and biological substances	T36-T50	1	1
5	Toxic effects of sustances chiefly nonmedicinal as to source	T51-T65	6	23
6	Other and unspecified effects of external causes	T66-T78	18	33
7	Certain early complications of trauma	T79	0	0
8	Complications of surgical and medical care, NEC	T80-T88	1	0
9	Sequelae of injures, of poisoning and of other consequences of external causes	T90-T98	0	2
10		D50-D89,		
11		L00-L99		
12	Others			
13	Nutritional anemias	D50-D53	0	0
14	Hemolytic anemias	D55-D59	0	0
15	Aplastic and other anemias	D60-D64	1	3
16	Coagulation defect, purpura and other hemorrhage conditions	D65-D69	1	0
17	Other disease of blood and blood-forming organs	D70-D77	1	3
18	Certain disorders involving the immune mechanism	D80-D89	0	2
19	Other disorders of the skin and subcutaneous tissue	L80-L99	2	1
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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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3 **1 Mortality and cause of death in South Korean patients with Parkinson's disease: A**
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5 **2 longitudinal follow-up study using a national sample cohort**
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3 37 **Mortality and cause of death in South Korean patients with Parkinson's disease: A**
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5 38 **longitudinal follow-up study using a national sample cohort**
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10 40 **ABSTRACT**
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12 41 *Objective:* The incidence rate of Parkinson's disease (PD) is growing rapidly owing to the
13
14 42 aging population. We investigated the mortality rates and causes of death in South Korean
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17 43 patients with PD.

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19 44 *Design:* We investigated a national cohort using the nationwide insurance database.
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21 45 *Setting:* Korean Health Insurance Review and Assessment Service - National Sample Cohort.
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24 46 *Participants:* We included 3,510 participants ≥ 60 years of age who were diagnosed with PD
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26 47 between 2002 and 2013, as well as 14,040 matched controls.
27

28 48 *Interventions:* None
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30
31 49 *Primary and secondary outcome measures:* A stratified Cox proportional hazards model was
32
33 50 used to evaluate patients with PD who were matched 1:4 with non-PD control subjects
34
35 51 adjusted for age, sex, income, and region of residence. The causes of death were grouped into
36
37 52 12 classifications.
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39
40 53 *Results:* The adjusted hazard ratio (HR) for mortality in the PD group was 2.09 (95%
41
42 54 confidence interval [CI] = 1.94–2.24, $P < 0.001$). Subgroup analysis according to age (<70
43
44 55 years, 70–79 years, and ≥ 80 years) and sex revealed that patients with PD showed higher
45
46 56 adjusted HRs for mortality across all subgroups. Mortalities caused by metabolic, mental,
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48 57 neurologic, circulatory, respiratory, and genitourinary diseases, as well as trauma, were more
49
50 58 common in the PD group than in the control group, with the highest odds ratio observed in
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52 59 patients with neurologic disease.
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56 60 *Conclusions:* We demonstrated that PD in South Korean patients ≥ 60 years of age was
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58 61 associated with increased mortality in both sexes regardless of age.
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Key words: Parkinson's disease, mortality, Korean

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65 **Strengths and limitations of this study**

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

75

76 **INTRODUCTION**

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

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3 86 Even though PD is associated with increased mortality in general, previous studies show
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5 87 inconsistent data, with mortality rates ranging from 0.80 to 3.50 [2]. Some studies performed
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7 88 in the post-levodopa era even reported “super-normal” survival rather than increased
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10 89 mortality among PD patients [2]. Furthermore, the causes of death in patients with PD remain
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12 90 unclear [7]. The heterogeneity observed in studies of mortality as related to PD could be
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14 91 caused by the variable methodology and patient selection criteria. Different studies tend to be
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16 92 hospital-, pharmaceutical trial- or community-based, and thus yield results that are not very
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18 93 representative of the general population [6].

21 94 According to the Global Burden of Disease, Injuries, and Risk Factors Study of 2016,
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23 95 the death rate, prevalence, and disability-adjusted life-years of patients with PD varied
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25 96 depending on ethnicity and/or geography [5]. Among high-income Asia Pacific countries,
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27 97 South Korea showed the highest percentage change in age-standardized mortality rates
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29 98 between 1990 and 2016 (24.6%) compared to Brunei (17.9%), Japan (10.2%), and Singapore
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31 99 (11.3%), even though the percentage change in the age-standardized rates of prevalence
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33 100 during the same time period (21.0%) was similar to that of Japan (21.3%) [5]. Thus, analyses
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35 101 focused on a particular ethnic/geographic group is important to estimate the social burden of
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37 102 PD and the patient management plan in each country. However, a large cohort-based
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39 103 investigation of PD-related mortality rates and causes of death in South Korea has never been
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41 104 performed.

46 105 To better understand the natural courses and prognoses of patients with PD, and to
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48 106 provide valuable information on planning the distribution of health resources, we investigated
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50 107 the mortality rates and causes of death in patients with PD using a representative PD
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52 108 population in South Korea. We performed a large-scale longitudinal follow-up study, with a
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54 109 maximum follow-up duration of 12 years, using national cohort data.

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3 111 **MATERIALS AND METHODS**
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5 112 **Patient and Public Involvement**
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8 113 No patient involved.
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12 115 **Study Population and Data Collection**
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14 116 The ethics committee of Hallym University approved the use of these data (approval number
15 117 2014-I148). The requirement for written informed consent was waived by the Institutional
16 118 Review Board.
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21 119 This national cohort study relied on data from the Korean Health Insurance Review and
22 120 Assessment Service (HIRA) National Sample Cohort. The Korean National Health Insurance
23 121 Service (NHIS) selects samples directly from the entire population database to prevent non-
24 122 sampling errors. Approximately 2% of the samples (1 million) were selected from the entire
25 123 Korean population (50 million). These selected data were classified into 1,476 levels (age [18
26 124 categories], sex [2 categories], and income level [41 categories]) using randomized stratified
27 125 systematic sampling methods via proportional allocation to represent the entire population.
28 126 After data selection, the appropriateness of the sample was verified by a statistician who
29 127 compared the data from the entire Korean population to the sample data. The details of the
30 128 methods used to perform these procedures are provided by the National Health Insurance
31 129 Sharing Service [8]. The cohort database included (i) personal information, (ii) health
32 130 insurance claim codes (procedures and prescriptions), (iii) diagnostic codes using the
33 131 International Classification of Disease, 10th edition (ICD-10), (iv) death records from the
34 132 Korean National Statistical Office (using the Korean Standard Classification of Disease), (v)
35 133 socio-economic data (residence and income), and (vi) medical examination data for each
36 134 participant over a period ranging from 2002 to 2013.
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3 135 Because all Korean citizens are recognized by a 13-digit resident registration number
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5 136 from birth to death, exact population statistics can be determined using this database. It is
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7 137 mandatory for all Koreans to enroll in the NHIS. All Korean hospitals and clinics use the 13-
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9 138 digit resident registration number to record individual patients in the medical insurance
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11 139 system. Therefore, the risk of overlapping medical records is minimal, even if a patient
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13 140 relocates to another geographical region. Moreover, all medical treatments in Korea can be
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15 141 tracked without exception using the HIRA system. In Korea, a notice of death must legally be
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17 142 delivered to an administrative entity before a funeral can be held. Causes and dates of death
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19 143 are recorded by medical doctors on death certificates.
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25 26 145 **Participant Selection**

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28 146 From among 1,125,691 individuals with 114,369,638 medical claim codes, we included
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30 147 participants who were diagnosed with PD between 2002 and 2013 ($n = 4,169$). PD was
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32 148 categorized using ICD-10 codes (Parkinson's disease: G20). For accurate diagnoses, we only
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34 149 selected participants who visited outpatient clinics, were hospitalized, or both at least twice
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36 150 because of PD. The control participants were extracted from 1,121,522 participants who had
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38 151 no diagnoses of PD between 2002 and 2013.
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42 152 Participants with PD were matched 1:4 with the control group. The matches were
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44 153 adjusted for age group, sex, income, region of residence, and medical histories of
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46 154 hypertension, diabetes mellitus, and dyslipidemia. We set the index date as that of the
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48 155 diagnosis of PD in the PD group; participants from the control group were also followed from
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50 156 the same index date as their matched counterparts with PD. To prevent selection bias,
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52 157 participants in the control group were sorted using a random number, and were then selected
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54 158 in descending order. It was assumed that the matched control participants were involved at
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56 159 the same time of each matched PD participant; therefore, participants in the control group
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3 160 who died before the time of involvement of the matched PD participant were excluded. Forty
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5 161 PD participants for whom we could not identify a sufficient number of matching participants
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8 162 were also excluded, as were 619 participants who were diagnosed with PD while under the
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10 163 age of 60 years since the prevalence of PD is relatively low in younger individuals [9].
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12 164 Ultimately 3,510 PD participants matched 1:4 with 14,040 control participants were included
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15 165 (Fig. 1).
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167 **Variables**

168 Age groups were classified by 5-year intervals into 6 age groups: 60–64, 65–69, 70–74, 75–
169 79, 80–84, and 85+ years old. The income groups were initially divided into 41 classes (1
170 health aid class, 20 self-employment health insurance classes, and 20 employment health
171 insurance classes). These groups were re-categorized into 11 classes (class 1 [lowest income]
172 to class 11 [highest income]). Regions of residence were divided into 16 areas according to
173 the administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu,
174 Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk,
175 Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

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

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3 185 tissue, M00–M99); (x) Genitourinary disease (diseases of the genitourinary system, N00–
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5 186 N99); (xi) Abnormal finding (symptoms, signs and abnormal clinical and laboratory findings
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7 187 ‘not elsewhere classified’, R00–R99); and (xii) Trauma (injury, poisoning, and certain other
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9 188 consequences of external causes, S00–T98). We also added 1 more category: (xiii) Others
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11 189 (diseases of the blood and blood-forming organs and certain disorders involving the immune
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13 190 mechanism, D50–D89; diseases of the skin and subcutaneous tissue, L00–L99). The Charlson
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15 191 comorbidity index was used for 17 comorbidities as a continuous variable (0 [no comorbidity]
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17 192 through 29 [multiple comorbidities]) [10].
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24 194 **Statistical Analyses.**

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26 195 The chi-square or Fisher’s exact test was used to compare the general characteristics of
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28 196 participants in the PD and control groups, as well as to compare their mortality rates
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30 197 according to the cause of death. The false discovery rate was used to adjust for incorrect
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32 198 rejections of the null hypothesis.
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35 199 To determine hazard ratios (HRs) for mortality as a function of PD, a stratified Cox-
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37 200 proportional hazards model, both crude (simple) and adjusted for the Charlson comorbidity
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39 201 index, was used. Age, sex, income, and region of residence were stratified. Two-tailed P-
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41 202 values less than 0.05 were considered significant. Statistical analyses were conducted using
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43 203 the SPSS software, version 21.0 (IBM, Armonk, NY, USA).
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49 205 **RESULTS**

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51 206 The mean follow-up duration was 49.6 months (standard deviation [SD] = 37.3 months) in
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53 207 the PD group and 57.3 (SD = 40.6) months in the matched control group.
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208 Age, sex, income level, and region of residence were matched between the PD and control
 209 groups (Table 1). The mortality rate was significantly higher in the PD group than that in the
 210 control group (34.6% [1,214/3,510] and 19.0% [2,661/14,040], respectively, $P < 0.001$).

211

212 **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*

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

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

216

217 The crude and adjusted HRs for mortality in the PD group were 2.29 (95% CI = 2.13–2.45,
 218 $P < 0.001$) and 2.09 (95% CI = 1.94–2.24, $P < 0.001$), respectively (Table 2). When
 219 categorizing patients according to age (<70 years, 70–79 years and ≥ 80 years) and sex, PD
 220 patients in all the subgroups showed higher crude and adjusted HRs for mortality than did the
 221 control patients.

222 **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	

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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.

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3 227 HR, hazard ratio; CI, confidence interval.
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8 229 Analysis of mortality rates according to the cause of death revealed an odds ratio (OR) for
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10 230 overall mortality of 2.26 (95% CI = 2.08–2.45, $P < 0.001$) in the PD group (Table 3); the
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12 231 detailed data are presented in Supplementary Table 1. Mortalities caused by metabolic
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14 232 disease, mental diseases, neurologic disease, circulatory disease, respiratory disease,
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16 233 genitourinary disease and trauma were higher in the PD group than in the control group (the
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19 234 false discovery rate-adjusted P-value was <0.05 for each). The OR for mortality was highest
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21 235 for neurologic disease (20.87, 95% CI = 16.05–27.14, $P < 0.001$); among these neurologic
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24 236 diseases, extrapyramidal and movement disorders were the most common (294/328, 89.6%).
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26 237 Mortalities caused by infection, neoplasm, digestive disease, muscular disease, and other
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28 238 causes were not significantly different between the PD and control groups.
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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				Odd ratio (95% CI)	P-value
	Parkinson's disease (total n = 3,510)		Control (total n = 14,040)			
	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*

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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

241

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

243 †%, calculated as the proportion of the number of deaths among all participants with/without mortality.

244 ‡%, calculated as the proportion of the number of deaths among participants with mortality.

245 CI, confidence interval.

246 DISCUSSION

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

264 Our subgroup analyses showed that patients with PD had higher mortality rates across all
265 age groups and in both sexes. Previous studies have produced similar data, demonstrating that
266 PD is a risk factor for increased mortality regardless of age and sex [11, 12]. The adjusted
267 HRs were relatively high in patients with PD aged <70 years (2.77 in men and 3.32 in women)
268 but were relatively low in patients with PD aged 70–79 years (2.07 in men and 2.22 in
269 women) and even lower in patients with PD aged >80 years (1.47 in men and 1.73 in women).
270 This phenomenon could be attributed to the death rates themselves increasing in both the

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3 271 control and PD groups as individuals age, which dilutes the impact of PD on the mortality
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5 272 rate of older individuals. A previous literature review by Ishihara et al. on the estimated life
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7 273 expectancies of UK and European individuals with PD showed that, as the age of PD onset
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9 274 increased, the standardized mortality ratio dropped gradually from 7.3 in men and 6.7 in
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11 275 women in their twenties to 2.5 in both men and in women in their nineties [11]. However, this
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13 276 finding may be controversial, as a systematic review and meta-analysis by Macleod et al.
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15 277 found that, in 15 of 17 studies, older age either at onset or recruitment was associated with
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17 278 increased mortality [12]. This discrepancy could be related to the differing ethnicities of
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19 279 subjects in these studies, as well as the involved countries' economic statuses, study
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21 280 populations, and research methods. The differences in adjusted HRs between men and
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23 281 women were not notable in any of the age groups.

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28 282 In our study, patients with PD died more frequently of certain diseases and of trauma
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30 283 than their counterparts in the control population. Neurologic diseases (particularly
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32 284 extrapyramidal and movement disorders) were the most common causes of death, implying
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34 285 that PD features themselves were most responsible for death among PD patients in South
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36 286 Korea. Such studies of the outcomes of PD patients are scarce. In a study of mortality among
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38 287 211 levodopa-treated patients with PD in the United Kingdom, Morgan et al. showed that the
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40 288 most common cause of death was PD itself (52.6%) [3]. They interpreted this to indicate that,
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42 289 even though levodopa might improve motor symptoms such as tremor, bradykinesia, and
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44 290 rigidity, it did not slow disease progression [13]. As the PD progressed, levodopa-resistant
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46 291 motor symptoms (speech/swallowing impairment, gait, and balance problems) and nonmotor
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48 292 symptoms (autonomic dysfunction, mood disorders, cognitive impairment, sleep disorders,
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50 293 and psychosis) become more prevalent and may contribute to the increased morbidity and
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52 294 mortality [14]. Although our study cohort was not necessarily confined to levodopa-treated
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54 295 subjects, it is highly likely that a significant proportion of our patients were being treated with
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3 296 levodopa, as we only selected patients who were treated ≥ 2 times for PD. Our findings are
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5 297 different from those of other groups that described pneumonia to be the most common cause
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7 298 of death in PD patients [15-18]. The most likely explanation for this difference could be the
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10 299 varying methods of patient recruitment: we recruited our subjects based on their PD treatment
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12 300 history regardless of whether they were hospitalized; therefore, the cause of death among our
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14 301 patients; i.e., neurologic disease that may have included PD itself, may also reflect patients
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16 302 having died of other (perhaps natural) causes while afflicted with PD. However, the causes of
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18 303 death in hospitalized or nursing home-bound PD patients may have had a greater likelihood
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20 304 of being reported as pneumonia because of their orthostatic lability. Furthermore, our
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22 305 indication that PD-group patients did not necessarily die of pneumonia is true insofar as being
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24 306 compared to the control group, and is not a general statement, since we calculated the ORs of
25
26 307 the cause of mortality. The significance of other causes of death such as cancer and
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28 308 circulation-impeding ischemic heart disease remain controversial [1, 2, 15-19]; the ORs for
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30 309 these conditions were not significant in our study. Nevertheless, our most important findings
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32 310 include (i) the overall death rate was higher in the PD group than that in the control group,
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34 311 and (ii) metabolic disease, mental diseases, neurologic disease, circulatory disease,
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36 312 respiratory disease, genitourinary disease, and trauma are common causes of death in PD
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38 313 patients in addition to PD itself. Our findings ought to be valuable for PD patient caregivers
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40 314 in both hospital and community settings.

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42 315 A limitation of our study was that we were unable to determine the severity of PD. In the
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44 316 same context, we did not stratify patients by their hospitalization histories, disease durations,
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46 317 or the presence of mental illness, which may have skewed the mortality data. Furthermore,
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48 318 some confounding factors that can influence mortality, such as smoking status, alcohol
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50 319 consumption, and obesity, were not adjusted for [20-22]. Another limitation of our study was
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52 320 that the cause of death may not have encompassed all the different types of illnesses and
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3 321 complications that contributed to the death of a patient with PD. We retrieved the causes of
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5 322 death from death certificates, which only list a single condition. This may have resulted in the
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7 323 underestimation of other illnesses that contributed the death of the patient. Nevertheless, the
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9 324 cause of death reported on a death certificate was the most probable from among the multiple
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11 325 illnesses that may have contributed to the death of the patient; hence, our data ought to be
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13 326 representative in this regard.
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17 327 Despite these limitations, our data are nevertheless robust because we used a representative,
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19 328 large-scale sample from a cohort database comprising over 1 million subjects over a 12-year
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21 329 follow-up period. Another strength of our study is that our approach minimized the risk of
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23 330 recall bias or missing information, as the dataset was based on claims made to the
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25 331 compulsory HIRA nationwide health insurance system. We chose matched controls adjusted
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27 332 for the potential confounding factors of age, sex, income, and region of residence. Our
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29 333 subjects' comorbidity data were consistent with those of previous epidemiologic studies in
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31 334 the Korean population, which was further evidence of our study's reliability [23, 24].
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37 336 **CONCLUSION**

38
39 337 We performed the largest study on the risk of mortality in South Korean PD patients
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41 338 with clearly defined inclusion criteria. We found that PD increased the risk of mortality
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43 339 regardless of age and sex. Common causes of death in patients with PD included metabolic,
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45 340 mental, neurologic, circulatory, respiratory, and genitourinary diseases as well as trauma; the
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47 341 highest OR observed was for neurologic disease.
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52 343 **Acknowledgments**

53
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56 345 the National Research Foundation (NRF) of Korea.
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5 347 **Conflict of Interest**

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8 348 The authors do not have any conflict of interest to disclose.
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12 350 **Author contributions:**

13
14 351 Choi HG composed the manuscript, Lim JS provided neurologists' perspectives, Lee YK

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16 352 reviewed the result, and Sim S and Kim M designed and supervised the study.
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20
21 354 **Data sharing**

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23 355 The data used for this study are available from the Korea National Health Insurance Sharing

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25 356 Service (<https://nhiss.nhis.or.kr>) subject to their requirements and fees.
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3 418 **Figure legend**
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5 419 **Fig. 1** A schematic illustration of the participant selection process that was used in the present
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8 420 study. Of the 1,125,691 total participants, 4,169 with Parkinson's disease (PD) were selected.
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10 421 Participants with PD were matched 1:4 with a control group comprising individuals not
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12 422 diagnosed with PD. Ultimately, 3,510 participants with PD and 14,040 control participants
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14 423 were included.
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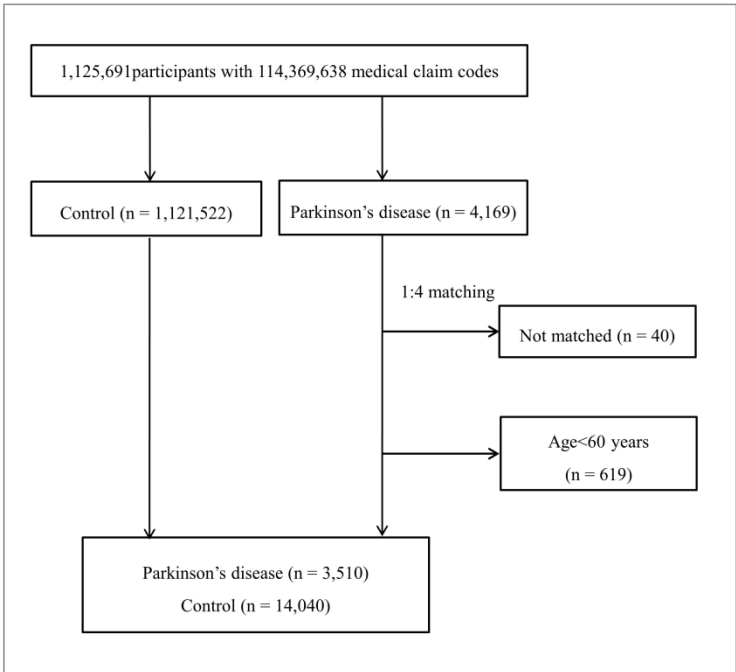


Figure 1

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
Helminthiasis	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 mesothelial 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

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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 disorders 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 mental disorders	F00-F09	29	46
Mental and behavioral disorders due to psychoactive substance use	F10-F19	2	3
Schizophrenia, schizotypal and delusional disorders	F20-F29	2	0
Mood[affective] disorders	F30-F39	0	0
Neurotic, stress-related and somatoform disorders	F40-F48	0	0
Behavioral syndromes associated with physiological disturbances and	F50-F59	0	0
	F60-F69	0	0
	F70-F79	0	0
	F80-F89	0	0
	F90-F98	0	0
	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 capillaries	I70-I79	2	13

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4	Diseases of veins, lymphatic vessels and lymph nodes, NEC	I80-I89	0	0
5	Other and unspecified disorders of the circulatory system	I95-I99	0	0
6				
7	Respiratory disease	J00-J99		
8	Acute upper respiratory infections	J00-J06	0	0
9	Influenza and pneumonia	J09-J18	48	105
10	Other acute lower respiratory infections	J20-J22	0	0
11	Other diseases of upper respiratory tract	J30-J39	0	0
12	Chronic lower respiratory diseases	J40-J47	31	106
13	Lung diseases due to external agents	J60-J70	13	20
14	Other respiratory diseases principally affecting the interstitium	J80-J84	3	11
15	Suppurative and necrotic conditions of lower respiratory tract	J85-J86	1	1
16	Other diseases of pleura	J90-J94	0	0
17	Other diseases of the respiratory system	J95-J99	1	5
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19	Digestive disease	K00-K93		
20	Diseases of oral cavity, salivary glands and jaws	K00-K14	0	0
21	Diseases of oesophagus, stomach and duodenum	K20-K31	3	12
22	Disease of appendix	K35-K38	0	0
23	Hernia	K40-K46	0	0
24	Noninfective enteritis and colitis	K50-K52	1	0
25	Other diseases of intestines	K55-K64	7	12
26	Diseases of peritoneum	K65-K67	0	2
27	Diseases of liver	K70-K77	10	35
28	Disorders of gallbladder, biliary tract and pancreas	K80-K87	4	21
29	Other diseases of the digestive system	K90-K93	5	6
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31	Muscular disease	M00-M99		
32	Infectious arthropathies	M00-M03	0	0
33	Inflammatory polyarthropathies	M05-M14	2	3
34	Arthrosis	M15-M19	0	0
35	Other joint disorders	M20-M25	0	0
36	Systemic connective tissue disorder	M30-M36	0	1
37	Deformin dorsopathies	M40-M43	0	0
38	Spondylopathies	M45-M49	1	0
39	Other dorsopathies	M50-M54	0	1
40	Disorders of muscles	M60-M63	0	2
41	Disorders of synovium and tendon	M65-M68	0	0
42	Other soft tissue disorders	M70-M79	0	1
43	Disorders of bone density and structure	M80-M85	5	6
44	Other osteopathies	M86-M90	0	1
45	Chondropathies	M91-M94	0	0
46	Other disorders of the musculoskeletal system and connective tissue	M95-M99	0	0
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48	Genitourinary disease	N00-N99		
49	Glomerular diseases	N00-N08	0	0
50	Renal tubulo-interstitial diseases	N10-N16	2	4
51	Renal failure	N17-N19	18	38
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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 the genitourinary system	N99	0	0
Abnormal finding	R00-R99		
Symptoms and signs involving the circulatory and respiratory 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 the 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 unspecified part of trunk, limb or body region	T08-T14	3	8
Effects of foreign body entering through natural orifice	T15-T19	6	2
Burns and corrosions of external body surface, 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 unspecified 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 substances 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 injuries, 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

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

	Item No	Recommendation	Page No.
2 3 4 5 6 7 8 9	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
10 Introduction			
11 12 13	2	Background/ rationale	4–5
14	3	Objectives	5
15 Methods			
16 17	4	Study design	6
18 19 20	5	Setting	6
21 22 23 24	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
25		(b) For matched studies, give matching criteria and number of exposed and unexposed	7
26 27	7	Variables	8
28 29 30 31	8*	Data sources/ measurement	8–9
32	9	Bias	9
33	10	Study size	N/A
34 35 36	11	Quantitative variables	9
37 38 39 40 41 42 43 44	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
45 Results			
46 47 48 49 50 51 52 53	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
54 55 56 57 58	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
59	15*	Outcome data	9–12
60	16	Main results	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>.

BMJ Open

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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Primary Subject Heading:	Epidemiology
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Manuscripts

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3 **1 Mortality and cause of death in South Korean patients with Parkinson's disease: A**
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5 **2 longitudinal follow-up study using a national sample cohort**
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10 4 Hyo Geun Choi, MD, PhD^{1,2}, Jae-Sung Lim, MD³, Young Kyung Lee, MD, PhD⁴, Songyong
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3 37 **Mortality and cause of death in South Korean patients with Parkinson's disease: A**
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5 38 **longitudinal follow-up study using a national sample cohort**
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9
10 40 **ABSTRACT**
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12 41 *Objective:* The incidence rate of Parkinson's disease (PD) is growing rapidly owing to the
13
14 42 aging population. We investigated the mortality rates and causes of death in South Korean
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16
17 43 patients with PD.

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19 44 *Design:* We investigated a national cohort using the nationwide insurance database.
20

21 45 *Setting:* Korean Health Insurance Review and Assessment Service - National Sample Cohort.
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23
24 46 *Participants:* We included 3,510 participants ≥ 60 years of age who were diagnosed with PD
25
26 47 between 2002 and 2013, as well as 14,040 matched controls.
27

28 48 *Interventions:* None
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31 49 *Primary and secondary outcome measures:* A stratified Cox proportional hazards model was
32
33 50 used to evaluate patients with PD who were matched 1:4 with non-PD control subjects
34
35 51 adjusted for age, sex, income, and region of residence. The causes of death were grouped into
36
37 52 12 classifications.
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40 53 *Results:* The adjusted hazard ratio (HR) for mortality in the PD group was 2.09 (95%
41
42 54 confidence interval [CI] = 1.94–2.24, $P < 0.001$). Subgroup analysis according to age (<70
43
44 55 years, 70–79 years, and ≥ 80 years) and sex revealed that patients with PD showed higher
45
46 56 adjusted HRs for mortality across all subgroups. Mortalities caused by metabolic, mental,
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48 57 neurologic, circulatory, respiratory, and genitourinary diseases, as well as trauma, were more
49
50 58 common in the PD group than in the control group, with the highest odds ratio observed in
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52 59 patients with neurologic disease.
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56 60 *Conclusions:* We demonstrated that PD in South Korean patients ≥ 60 years of age was
57
58 61 associated with increased mortality in both sexes regardless of age.
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Key words: Parkinson's disease, mortality, Korean

65 **Strengths and limitations of this study**

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

76 **INTRODUCTION**

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

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3 86 Even though PD is associated with increased mortality in general, previous studies show
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5 87 inconsistent data, with mortality rates ranging from 0.80 to 3.50 [2]. Some studies performed
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7 88 in the post-levodopa era even reported “super-normal” survival rather than increased
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10 89 mortality among PD patients [2]. Furthermore, the causes of death in patients with PD remain
11
12 90 unclear [7]. The heterogeneity observed in studies of mortality as related to PD could be
13
14 91 caused by the variable methodology and patient selection criteria. Different studies tend to be
15
16 92 hospital-, pharmaceutical trial- or community-based, and thus yield results that are not very
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18 93 representative of the general population [6].
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21 94 According to the Global Burden of Disease, Injuries, and Risk Factors Study of 2016,
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23 95 the death rate, prevalence, and disability-adjusted life-years of patients with PD varied
24
25 96 depending on ethnicity and/or geography [5]. Among high-income Asia Pacific countries,
26
27 97 South Korea showed the highest percentage change in age-standardized mortality rates
28
29 98 between 1990 and 2016 (24.6%) compared to Brunei (17.9%), Japan (10.2%), and Singapore
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31 99 (11.3%), even though the percentage change in the age-standardized rates of prevalence
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33 100 during the same time period (21.0%) was similar to that of Japan (21.3%) [5]. Thus, analyses
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35 101 focused on a particular ethnic/geographic group is important to estimate the social burden of
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37 102 PD and the patient management plan in each country. However, a large cohort-based
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39 103 investigation of PD-related mortality rates and causes of death in South Korea has never been
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41 104 performed.
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46 105 To better understand the natural courses and prognoses of patients with PD, and to
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48 106 provide valuable information on planning the distribution of health resources, we investigated
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50 107 the mortality rates and causes of death in patients with PD using a representative PD
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52 108 population in South Korea. We performed a large-scale longitudinal follow-up study, with a
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54 109 maximum follow-up duration of 12 years, using national cohort data.
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111 MATERIALS AND METHODS

112 Patient and Public Involvement

113 No patient involved.

114

115 Study Population and Data Collection

116 The ethics committee of Hallym University approved the use of these data (approval number
117 2014-I148). The requirement for written informed consent was waived by the Institutional
118 Review Board.

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

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3 135 Because all Korean citizens are recognized by a 13-digit resident registration number
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5 136 from birth to death, exact population statistics can be determined using this database. It is
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7 137 mandatory for all Koreans to enroll in the NHIS. All Korean hospitals and clinics use the 13-
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9 138 digit resident registration number to record individual patients in the medical insurance
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11 139 system. Therefore, the risk of overlapping medical records is minimal, even if a patient
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13 140 relocates to another geographical region. Moreover, all medical treatments in Korea can be
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15 141 tracked without exception using the HIRA system. In Korea, a notice of death must legally be
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17 142 delivered to an administrative entity before a funeral can be held. Causes and dates of death
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19 143 are recorded by medical doctors on death certificates.
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26 145 **Participant Selection**

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28 146 From among 1,125,691 individuals with 114,369,638 medical claim codes, we included
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30 147 participants who visited a clinic or hospital for PD-related reasons between 2002 and 2013 (n
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32 = 4,169). PD was categorized using ICD-10 codes (Parkinson's disease: G20). For accurate
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34 148 diagnoses, we only selected participants who visited outpatient clinics, were hospitalized, or
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36 149 both at least twice because of PD. The control participants were extracted from 1,121,522
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38 150 participants who had no diagnoses of PD between 2002 and 2013.
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42 152 Participants with PD were matched 1:4 with the control group. The matches were
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44 153 adjusted for age group, sex, income, region of residence, and medical histories of
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46 154 hypertension, diabetes mellitus, and dyslipidemia. We set the index date as that of the first
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48 155 visit to a clinic or a hospital for PD during the study period in the PD group; participants
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50 156 from the control group were also followed from the same index date as their matched
51
52 157 counterparts with PD. To prevent selection bias, participants in the control group were sorted
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54 158 using a random number, and were then selected in descending order. It was assumed that the
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56 159 matched control participants were involved at the same time of each matched PD participant;
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3 160 therefore, participants in the control group who died before the time of involvement of the
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5 161 matched PD participant were excluded. Forty PD participants for whom we could not identify
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7 162 a sufficient number of matching participants were also excluded, as were 619 participants
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9 163 who were diagnosed with PD while under the age of 60 years since the prevalence of PD is
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11 164 relatively low in younger individuals [9]. Ultimately 3,510 PD participants matched 1:4 with
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13 165 14,040 control participants were included (Fig. 1).
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19 167 **Variables**

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21 168 Age groups were classified by 5-year intervals into 6 age groups: 60–64, 65–69, 70–74, 75–
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23 169 79, 80–84, and 85+ years old. The income groups were initially divided into 41 classes (1
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25 170 health aid class, 20 self-employment health insurance classes, and 20 employment health
26
27 171 insurance classes). These groups were re-categorized into 11 classes (class 1 [lowest income]
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29 172 to class 11 [highest income]). Regions of residence were divided into 16 areas according to
30
31 173 the administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu,
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33 174 Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk,
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35 175 Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.
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40 176 The causes of death were classified according to the Korean standard classification of
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42 177 diseases, developed by the World Health Organization based on the ICD, into 12
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44 178 classifications: (i) Infection (certain infections and parasitic diseases, A00–B99); (ii)
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46 179 Neoplasm (neoplasms, C00–D48); (iii) Metabolic disease (endocrine, nutritional, and
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48 180 metabolic diseases, E00–E90); (iv) Mental disease (mental and behavioural disorders, F00–
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50 181 F99); (v) Neurologic disease (diseases of the nervous system, G00–G99); (vi) Circulatory
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52 182 disease (diseases of the circulatory system, I00–I99); (vii) Respiratory disease (diseases of
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54 183 the respiratory system, J00–J99); (viii) Digestive disease (diseases of the digestive system,
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56 184 K00–K93); (ix) Muscular disease (diseases of the musculoskeletal system and connective
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3 185 tissue, M00–M99); (x) Genitourinary disease (diseases of the genitourinary system, N00–
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5 186 N99); (xi) Abnormal finding (symptoms, signs and abnormal clinical and laboratory findings
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7 187 ‘not elsewhere classified’, R00–R99); and (xii) Trauma (injury, poisoning, and certain other
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9 188 consequences of external causes, S00–T98). We also added 1 more category: (xiii) Others
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11 189 (diseases of the blood and blood-forming organs and certain disorders involving the immune
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13 190 mechanism, D50–D89; diseases of the skin and subcutaneous tissue, L00–L99). The Charlson
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15 191 comorbidity index was used for 17 comorbidities as a continuous variable (0 [no
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17 192 comorbidity] through 29 [multiple comorbidities]) [10].
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24 194 **Statistical Analyses.**

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26 195 The chi-square or Fisher’s exact test was used to compare the general characteristics of
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28 196 participants in the PD and control groups, as well as to compare their mortality rates
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30 197 according to the cause of death. The false discovery rate was used to adjust for incorrect
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32 198 rejections of the null hypothesis.
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35 199 To determine hazard ratios (HRs) for mortality as a function of PD, a stratified Cox-
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37 200 proportional hazards model, both crude (simple) and adjusted for the Charlson comorbidity
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39 201 index, was used. Age, sex, income, and region of residence were stratified. Two-tailed P-
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41 202 values less than 0.05 were considered significant. Statistical analyses were conducted using
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43 203 the SPSS software, version 21.0 (IBM, Armonk, NY, USA).
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49 205 **RESULTS**

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51 206 The mean follow-up duration was 49.6 months (standard deviation [SD] = 37.3 months) in
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53 207 the PD group and 57.3 (SD = 40.6) months in the matched control group.
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208 Age, sex, income level, and region of residence were matched between the PD and control
 209 groups (Table 1). The mortality rate was significantly higher in the PD group than that in the
 210 control group (34.6% [1,214/3,510] and 19.0% [2,661/14,040], respectively, $P < 0.001$).

211

212 **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*

213

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

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

216

217 The crude and adjusted HRs for mortality in the PD group were 2.29 (95% CI = 2.13–2.45,
 218 $P < 0.001$) and 2.09 (95% CI = 1.94–2.24, $P < 0.001$), respectively (Table 2). When
 219 categorizing patients according to age (<70 years, 70–79 years and ≥ 80 years) and sex, PD
 220 patients in all the subgroups showed higher crude and adjusted HRs for mortality than did the
 221 control patients.

222 **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	

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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.

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3 227 HR, hazard ratio; CI, confidence interval.
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8 229 Analysis of mortality rates according to the cause of death revealed an odds ratio (OR) for
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10 230 overall mortality of 2.26 (95% CI = 2.08–2.45, $P < 0.001$) in the PD group (Table 3); the
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12 231 detailed data are presented in Supplementary Table 1. Mortalities caused by metabolic
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14 232 disease, mental diseases, neurologic disease, circulatory disease, respiratory disease,
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16 233 genitourinary disease and trauma were higher in the PD group than in the control group (the
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18 234 false discovery rate-adjusted P-value was <0.05 for each). The OR for mortality was highest
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20 235 for neurologic disease (20.87, 95% CI = 16.05–27.14, $P < 0.001$); among these neurologic
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22 236 diseases, extrapyramidal and movement disorders were the most common (294/328, 89.6%).
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24 237 Mortalities caused by infection, neoplasm, digestive disease, muscular disease, and other
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26 238 causes were not significantly different between the PD and control groups.
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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				Odd ratio (95% CI)	P-value
	Parkinson's disease (total n = 3,510)		Control (total n = 14,040)			
	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*

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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

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

243 †%, calculated as the proportion of the number of deaths among all participants with/without mortality.

244 ‡%, calculated as the proportion of the number of deaths among participants with mortality.

245 CI, confidence interval.

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246 DISCUSSION

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

264 Our subgroup analyses showed that patients with PD had higher mortality rates across all
265 age groups and in both sexes. Previous studies have produced similar data, demonstrating that
266 PD is a risk factor for increased mortality regardless of age and sex [11, 12]. The adjusted
267 HRs were relatively high in patients with PD aged <70 years (2.77 in men and 3.32 in
268 women) but were relatively low in patients with PD aged 70–79 years (2.07 in men and 2.22
269 in women) and even lower in patients with PD aged >80 years (1.47 in men and 1.73 in
270 women). This phenomenon could be attributed to the death rates themselves increasing in

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3 271 both the control and PD groups as individuals age, which dilutes the impact of PD on the
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5 272 mortality rate of older individuals. A previous literature review by Ishihara et al. on the
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7 273 estimated life expectancies of UK and European individuals with PD showed that, as the age
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9 274 of PD onset increased, the standardized mortality ratio dropped gradually from 7.3 in men
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11 275 and 6.7 in women in their twenties to 2.5 in both men and in women in their nineties [11].
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14 276 However, this finding may be controversial, as a systematic review and meta-analysis by
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16 277 Macleod et al. found that, in 15 of 17 studies, older age either at onset or recruitment was
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18 278 associated with increased mortality [12]. This discrepancy could be related to the differing
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20 279 ethnicities of subjects in these studies, as well as the involved countries' economic statuses,
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22 280 study populations, and research methods. The differences in adjusted HRs between men and
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24 281 women were not notable in any of the age groups.
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28 282 In our study, patients with PD died more frequently of certain diseases and of trauma
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30 283 than their counterparts in the control population. Neurologic diseases (particularly
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32 284 extrapyramidal and movement disorders) were the most common causes of death, implying
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34 285 that PD features themselves were most responsible for death among PD patients in South
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36 286 Korea. Such studies of the outcomes of PD patients are scarce. In a study of mortality among
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38 287 211 levodopa-treated patients with PD in the United Kingdom, Morgan et al. showed that the
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40 288 most common cause of death was PD itself (52.6%) [3]. They interpreted this to indicate that,
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42 289 even though levodopa might improve motor symptoms such as tremor, bradykinesia, and
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44 290 rigidity, it did not slow disease progression [13]. As the PD progressed, levodopa-resistant
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46 291 motor symptoms (speech/swallowing impairment, gait, and balance problems) and nonmotor
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48 292 symptoms (autonomic dysfunction, mood disorders, cognitive impairment, sleep disorders,
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50 293 and psychosis) become more prevalent and may contribute to the increased morbidity and
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52 294 mortality [14]. Although our study cohort was not necessarily confined to levodopa-treated
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54 295 subjects, it is highly likely that a significant proportion of our patients were being treated with
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3 296 levodopa, as we only selected patients who were treated ≥ 2 times for PD. Our findings are
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5 297 different from those of other groups that described pneumonia to be the most common cause
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7 298 of death in PD patients [15-18]. The most likely explanation for this difference could be the
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10 299 varying methods of patient recruitment: we recruited our subjects based on their PD treatment
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12 300 history regardless of whether they were hospitalized; therefore, the cause of death among our
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14 301 patients; i.e., neurologic disease that may have included PD itself, may also reflect patients
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16 302 having died of other (perhaps natural) causes while afflicted with PD. However, the causes of
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18 303 death in hospitalized or nursing home-bound PD patients may have had a greater likelihood
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20 304 of being reported as pneumonia because of their orthostatic lability. Furthermore, our
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22 305 indication that PD-group patients did not necessarily die of pneumonia is true insofar as being
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24 306 compared to the control group, and is not a general statement, since we calculated the ORs of
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26 307 the cause of mortality. The significance of other causes of death such as cancer and
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28 308 circulation-impeding ischemic heart disease remain controversial [1, 2, 15-19]; the ORs for
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30 309 these conditions were not significant in our study. Nevertheless, our most important findings
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32 310 include (i) the overall death rate was higher in the PD group than that in the control group,
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34 311 and (ii) metabolic disease, mental diseases, neurologic disease, circulatory disease,
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36 312 respiratory disease, genitourinary disease, and trauma are common causes of death in PD
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38 313 patients in addition to PD itself. Our findings ought to be valuable for PD patient caregivers
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40 314 in both hospital and community settings.

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42 315 An interesting observation was that the proportion of female patients with PD was
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44 316 higher than that of their male counterparts (Table 1). No studies have investigated the
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46 317 sex ratio of patients with PD in Korea to date, so we had no records to compare our
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48 318 results to. However, this observation should be interpreted considering the prevalence
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50 319 of PD among each of the sexes in Korea, the prevalence of PD in different age groups,
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52 320 and the different life expectancies of men and women in Korea. A recent large-scale
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3 321 study utilizing the National Health Insurance Service-National Sample Cohort Database
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5 322 by Lee et al. found that the prevalence of PD in Korea was slightly higher among women
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7 323 (47.4 per 100,000 population) than among men (35.4 per 100,000 population) in 2004;
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9 324 these rates gradually increased to 167.3 and 117.7 per 100,000 population,
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11 325 respectively, in 2013 [20]. Lee et al.'s study also found that the prevalence of PD
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13 326 dramatically increased with age; the PD rates in 2004 were 8.1 and 310.9 per 100,000
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15 327 population among 40–49- and ≥ 80 -year-old subjects, respectively, and had risen to 20.9
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17 328 and 1,226.3 per 100,000 population, respectively, in 2013. The proportion of
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19 329 individuals in our overall cohort who had PD was different from those in the
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21 330 abovementioned studies because, as stated in Materials and Methods, we used different
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23 331 criteria in selecting PD patients to ensure their actual diagnosis with the disease.
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25 332 Moreover, the life expectancy of men in Korea is shorter than that of women (74.65 vs.
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27 333 81.48 years, respectively, in 2004 and 80.01 vs. 86.04 years, respectively, in 2017) [21].
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29 334 Shin et al. reported that the rates of death among individuals ≥ 80 years of age were
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31 335 29.5% for men and 58.0% for women [22].
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38 336 Taken together, we can speculate that the relatively high proportion of women in
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40 337 both the general and PD patient populations in Korea (particularly older age groups,
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42 338 which have a higher prevalence of PD and longer life expectancy) could have resulted in
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44 339 a higher proportion of women with the disease than men. This reasoning is supported
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46 340 by the relatively high number of patients with PD in the older age groups as shown in
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48 341 Tables 1 and 2. Our results not only confirm that there were relatively high numbers of
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50 342 patients with PD in the 80–84- and ≥ 85 -year age groups, but also show that the male-
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52 343 to-female ratio among patients with PD who are < 70 years was higher than that in
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54 344 patients 70–79 years; those ≥ 80 years showed the lowest male-to-female ratio. Further
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3 345 studies regarding the male/female proportions among patients with PD in different age groups
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5 346 would be helpful to clarify these patterns.
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8 347 A limitation of our study was that we were unable to determine the severity of PD. In the
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10 348 same context, we did not stratify patients by their hospitalization histories, disease durations,
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12 349 or the presence of mental illness, which may have skewed the mortality data. Furthermore,
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14 350 some confounding factors that can influence mortality, such as smoking status, alcohol
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16 351 consumption, and obesity, were not adjusted for [23-25]. Another limitation of our study was
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18 352 that the cause of death may not have encompassed all the different types of illnesses and
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20 353 complications that contributed to the death of a patient with PD. We retrieved the causes of
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22 354 death from death certificates, which only list a single condition. This may have resulted in the
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24 355 underestimation of other illnesses that contributed the death of the patient. Nevertheless, the
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26 356 cause of death reported on a death certificate was the most probable from among the multiple
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28 357 illnesses that may have contributed to the death of the patient; hence, our data ought to be
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30 358 representative in this regard.
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35 359 Despite these limitations, our data are nevertheless robust because we used a
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37 360 representative, large-scale sample from a cohort database comprising over 1 million subjects
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39 361 over a 12-year follow-up period. Another strength of our study is that our approach
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41 362 minimized the risk of recall bias or missing information, as the dataset was based on claims
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43 363 made to the compulsory HIRA nationwide health insurance system. We chose matched
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45 364 controls adjusted for the potential confounding factors of age, sex, income, and region of
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47 365 residence. Our subjects' comorbidity data were consistent with those of previous
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49 366 epidemiologic studies in the Korean population, which was further evidence of our study's
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51 367 reliability [26,27].
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3 369 **CONCLUSION**
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5 370 We performed the largest study on the risk of mortality in South Korean PD patients
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7 371 with clearly defined inclusion criteria. We found that PD increased the risk of mortality
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9 372 regardless of age and sex. Common causes of death in patients with PD included metabolic,
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11 373 mental, neurologic, circulatory, respiratory, and genitourinary diseases as well as trauma; the
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13 374 highest OR observed was for neurologic disease.
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19 376 **Acknowledgments**
20

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22
23 378 the National Research Foundation (NRF) of Korea.
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28 380 **Conflict of Interest**
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30 381 The authors do not have any conflict of interest to disclose.
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33 382
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35 383 **Author contributions:**
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37 384 Choi HG composed the manuscript, Lim JS provided neurologists' perspectives, Lee YK
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39 385 reviewed the result, and Sim S and Kim M designed and supervised the study.
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44 387 **Data sharing**
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46 388 The data used for this study are available from the Korea National Health Insurance Sharing
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48 389 Service (<https://nhiss.nhis.or.kr>) subject to their requirements and fees.
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3 461 **Figure legend**
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5 462 **Fig. 1** A schematic illustration of the participant selection process that was used in the present
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8 463 study. Of the 1,125,691 total participants, 4,169 with Parkinson's disease (PD) were selected.
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10 464 Participants with PD were matched 1:4 with a control group comprising individuals not
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12 465 diagnosed with PD. Ultimately, 3,510 participants with PD and 14,040 control participants
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15 466 were included.
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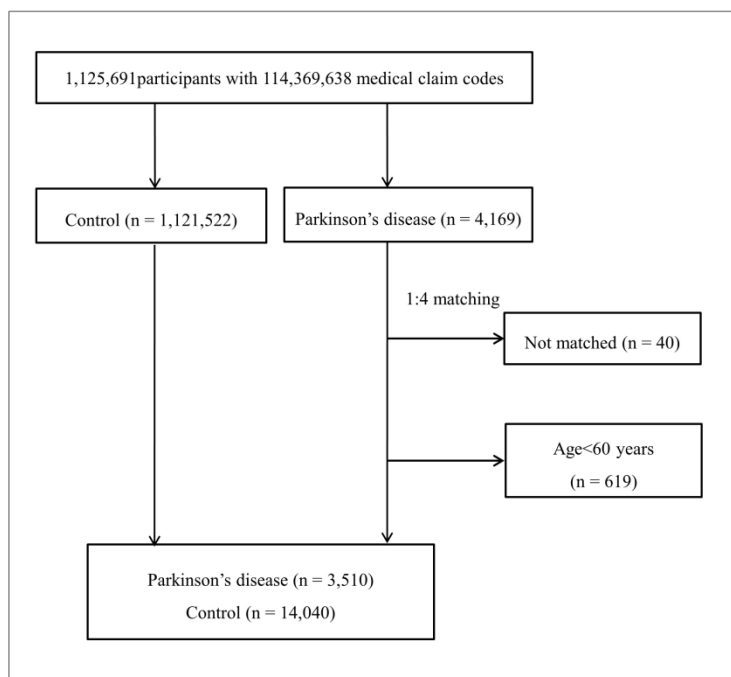


Figure 1

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 mesothelial 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

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4	Benign neoplasms	D10-D36	1	2
5	Neoplasms of uncertain or unknown behaviour	D37-D48	6	6
6				
7	Metabolic disease	E00-E90		
8	Disorders of thyroid gland	E00-E07	1	0
9	Diabetes mellitus	E10-E14	71	154
10	Other disorders of glucose regulation and pancreatic internal secretion	E15-E16	0	0
11	Disorders of other endocrine glands	E20-E35	2	0
12	Malnutrition	E40-E46	0	1
13	Other nutritional deficiencies	E50-E64	1	0
14	Obesity and other hyperalimentation	E65-E68	0	0
15	Metabolic disorders	E70-E90	1	6
16				
17	Mental disease	F00-F99		
18				
19	Organic, including symptomatic	F00-F09	29	46
20	mental disorders	F10-F19	2	3
21	Mental and behavioral disorders	F20-F29	2	0
22	due to psychoactive substance use	F30-F39	0	0
23	Schizophrenia, schizotypal and	F40-F48	0	0
24	delusional disorders	F50-F59	0	0
25	Mood[affective] disorders	F60-F69	0	0
26	Neurotic, stress-related and	F70-F79	0	0
27	somatoform disorders	F80-F89	0	0
28	Behavioral syndromes associated	F90-F98	0	0
29	with physiological disturbances and	F99	0	0
30				
31	Neurologic disease	G00-G99		
32				
33	Inflammatory diseases of the central nervous system	G00-G09	1	1
34	Systemic atrophies primarily affecting the central nervous system	G10-G14	4	3
35	Extrapyramidal and movement disorders	G20-G26	294	7
36	Other degenerative diseases of the nervous system	G30-G32	22	51
37	Demyelinating diseases of the central nervous system	G35-G37	0	0
38	Episodic and paroxysmal disorders	G40-G47	1	4
39	Nerve, nerve root and plexus disorders	G50-G59	0	0
40	Polyneuropathies and other disorders of the peripheral nervous system	G60-G64	0	1
41	Diseases of myoneural junction and muscle	G70-G73	0	0
42	Cerebral palsy and other paralytic syndromes	G80-G83	1	1
43	Other disorders of the nervous system	G90-G99	5	1
44				
45	Circulatory disease	I00-I99		
46				
47	Acute rheumatic fever	I00-I02	0	0
48	Chronic rheumatic heart diseases	I05-I09	0	3
49	Hypertensive diseases	I10-I15	31	75
50	Ischemic heart diseases	I20-I25	54	148
51	Pulmonary heart disease and diseases of pulmonary circulation	I26-I28	1	5
52	Other forms of heart disease	I30-I52	39	102
53	Cerebrovascular diseases	I60-I69	150	359
54	Diseases of arteries, arterioles and capillaries	I70-I79	2	13
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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-interstitial 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 the genitourinary system	N99	0	0
Abnormal finding	R00-R99		
Symptoms and signs involving the circulatory and respiratory 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 the 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 unspecified part of trunk, limb or body region	T08-T14	3	8
Effects of foreign body entering through natural orifice	T15-T19	6	2
Burns and corrosions of external body surface, 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 unspecified 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 substances 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 injuries, 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>.