Risk factors for pneumonia among patients with Parkinson’s disease: a Taiwan nationwide population-based study

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Objective: Pneumonia is the leading cause of death in patients with Parkinson’s disease (PD). However, few studies have been performed to explore the risk factors for pneumonia development in patients with PD.

Methods: We conducted a nationwide population-based cohort study of patients with PD to identify the risk factors for these patients developing pneumonia. Participants with newly diagnosed PD between 2000 and 2009 were enrolled from the 2000–2010 National Health Insurance Research Database in Taiwan. We compared patients with PD with an incidence of hospitalization with pneumonia vs those without, and Cox proportional hazard models were used to estimate the risk of pneumonia.

Results: Of the 2,001 enrolled patients (mean follow-up duration 5.8 years, range: 2.7–14.7 years), 381 (19.0%) had an incidence of hospitalization with pneumonia during the study period. Multivariate Cox proportional hazards analysis identified older age group (≥80 years of age, hazard ratio [HR] = 3.15 [95% confidence interval 2.32–4.28]), male sex (HR = 1.59 [1.29–1.96]), certain geographic regions (northern, HR = 1.36 [1.04–1.78], southern and eastern, HR = 1.40 [1.05–1.88]), rural areas (HR = 1.34 [1.05–1.72]), chronic heart failure (HR = 1.53 [1.02–2.29]), and chronic kidney disease (HR = 1.39 [1.03–1.90]) as risk factors for hospitalization with pneumonia in patients with PD. However, treatment for dental caries was a protective factor (HR = 0.80 [0.64–0.99]).

Conclusion: The results of this study highlight risk factors that are associated with hospitalization with pneumonia, and, for the first time, suggest a link between treated dental caries and a diminished risk of hospitalization with pneumonia in patients with PD.

Keywords: pneumonia, Parkinson’s disease, dental caries, chronic heart failure, chronic kidney disease

Introduction

Parkinson’s disease (PD) is a common neurodegenerative disorder characterized by bradykinesia, rigidity, resting tremor, and postural instability.1,2 With progression of the disease, the response to levodopa decreases and various problems that are less dopa responsive (or dopa resistant) develop, such as cognitive dysfunction and speech and swallowing problems.3,4 Studies have documented a very high prevalence of oropharyngeal dysphagia in patients with PD,5 which predisposes to aspiration pneumonia. Pneumonia in turn is a major reason for hospitalization of patients with PD and it is the leading cause of mortality in patients with PD (in one prospective study accounting for 64% of deaths).6,7

Pneumonia is a very common infectious disease and is one of the ten leading causes of death in the world.8 Several risk factors for pneumonia in the general population,
including chronic pulmonary disease, chronic heart failure, diabetes, chronic liver disease, chronic kidney disease, cochlear implants, cerebrospinal fluid shunts, splenic dysfunction, and HIV/AIDS, have been recognized.\textsuperscript{9,12} In PD, aspiration pneumonia is thought to be a multifactorial event, and aspiration alone is insufficient to cause pneumonia. Other important factors include alterations in the bacterial flora of the oropharynx, as well as impaired pulmonary clearance and host resistance.

To our knowledge, however, there have been no population-based studies exploring the risk factors for pneumonia in patients with PD. Thus, we conducted a cohort study of patients with PD to identify the risk factors associated with pneumonia using a nationwide longitudinal population-based database.

**Methods**

**Data source**

Data for this study were derived from the 2000–2010 National Health Insurance Research Database (NHIRD), developed and managed by the Taiwan National Health Insurance Program for research purposes. The Taiwan National Health Insurance Program, since its introduction in 1995, has provided approximately 99% of Taiwan residents with comprehensive and universal health care.\textsuperscript{13} We used one of the subsets of the NHIRD, composed of 1 million randomly selected subjects (constituting nearly 5% of the total Taiwan population) drawn in 2000. The NHIRD includes data on patients’ demographic characteristics, diagnoses, and prescription claims (medication types, prescription dates, dosage, and duration supplied). The study was approved by the Institutional Review Board at Kaohsiung Medical University Hospital, and informed consent was waived by the Institutional Review Board because the data obtained from the NHIRD have been de-identified.

**Design and study population**

The PD cohort comprised patients who were newly diagnosed (between January 1, 2000 and December 31, 2009) based on the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic criteria (ICD-9-CM code 332). Patients were diagnosed by neurologists and received antiparkinsonian medication(s) (levodopa and decarboxylase inhibitor, entacapone, bромocриптине, pergolide, cabergoline, ropinirole, pramipexole, amantadine, or selegiline) with at least three consecutive outpatient clinic visits, which were characterized as regular follow up.\textsuperscript{14} Exclusion criteria were as follows: age <40 years; dementia, psychosis, or stroke before the diagnosis of PD (because of the potential for diagnostic confusion with dementia with Lewy bodies or vascular parkinsonism); and patients having a pneumonia-related diagnosis before PD diagnosis (Figure 1). We also identified patients with PD with dementia that occurred ≥1 year after the diagnosis of PD (termed PD dementia; ICD-9-CM codes 290, 294.1, 331.0).\textsuperscript{1}

**An incidence of hospitalization with pneumonia**

Cases were determined by claims for hospital admissions using the following pneumonia-related codes: principal diagnosis of pneumonia (codes 480 to 487.0) or principal diagnosis of acute respiratory failure (code 518.81) or septicemia (code 038) with pneumonia as a secondary diagnosis.\textsuperscript{15} All enrolled patients with PD were followed-up until one of the following events occurred: first-time pneumonia diagnosis, death, the end of follow-up in the medical records, or the end of 2010. The study flowchart is shown in Figure 1.

**Risk factors related to pneumonia**

We identified the inpatient and outpatient diagnosis files and prescription files of patients with PD before they were diagnosed with PD\textsuperscript{16} to ascertain their history of diabetes mellitus, alcoholism, chronic pulmonary disease, dental caries, periodontitis, osteoporosis, chronic heart failure, chronic kidney disease, rheumatoid arthritis, chronic liver disease, cancer, epilepsy, asplenia after operation, cerebrospinal fluid shunt, multiple sclerosis, sickle cell disease, celiac disease, and HIV/AIDS, using ICD-9-CM codes and/or anatomical therapeutic chemical classification system codes.\textsuperscript{9,14,17,18} Of note, we used the diagnosis of dental caries or periodontitis based on ICD-9-CM and anatomical therapeutic chemical codes and required at least three visits as a proxy for treated dental illness (Table S1).

**Statistical analysis**

The chi-square test and t-test were used to compare the demographic and clinical characteristics of patients with PD with, vs those without, pneumonia. The Kaplan–Meier method was used to estimate the probability of pneumonia. The Cox proportional hazards model was applied to analyze the effect of single and multiple covariates in predicting pneumonia development in patients with PD. All statistical analyses were performed with SAS Version 9.3 (SAS Institute, Cary, NC, USA). A P-value <0.05 was considered statistically significant.

**Results**

**Demographic and clinical characteristics of the study population**

After excluding subjects who did not meet the study criteria, a total of 2,001 patients with newly diagnosed
PD were identified. The mean duration of follow-up was 5.77 years ± (standard deviation) 3.1 years. Of the 2,001 patients with PD, 381 (19.0%) had an incidence of hospitalization with pneumonia, with a mean latency after PD diagnosis of 4.3 ± 2.6 years. Among the patients with PD in our study, several baseline characteristics were associated with the occurrence of pneumonia, including older age, male sex, geographic region of Taiwan (northern, southern, and eastern), lower income, fewer dental appointments, and also subsequent development of dementia (Table 1).

**Comorbid physical conditions in enrolled patients with PD**

After excluding dementia, psychosis, and stroke, the most common comorbid physical diseases were dental caries (48.1% of enrolled patients), periodontitis (44.1%), chronic pulmonary disease (37.4%), diabetes mellitus (25.6%), and chronic liver disease (19.7%) (Table 2). Comorbidities with a low incidence were cancer (n=42), epilepsy (n=29), asplenia after operation (n=4), cerebrospinal fluid shunt (n=3), and multiple sclerosis (n=3). There were no patients with sickle cell disease, celiac disease, or HIV/AIDS.

**Risk factors for pneumonia in the PD cohort (univariate Cox proportional hazards analysis)**

A univariate Cox proportional hazards analysis showed that patients with PD with chronic pulmonary disease, dental caries, chronic heart failure, and chronic kidney disease were at increased risk of developing pneumonia (Table 2). Multivariate Cox proportional hazards analysis identified the following as risk factors for pneumonia (Table 3): older age (70–79 years: hazard ratio [HR] =2.12, 95% confidence interval [CI] 1.64–2.75, P<0.001; ≥80 years: HR =3.15, ...
95% CI 2.32–4.28, *P*<0.001; male sex (HR =1.59, 95% CI 1.29–1.96, *P*<0.001); geographic region of Taiwan (northern: HR =1.36, 95% CI 1.04–1.78, *P*=0.024; southern and eastern: HR =1.40, 95% CI 1.05–1.88, *P*=0.023); rural areas (HR =1.34, 95% CI 1.05–1.72, *P*=0.021); chronic heart failure (HR =1.53, 95% CI 1.02–2.29, *P*=0.042); and chronic kidney disease (HR =1.39, 95% CI 1.03–1.90, *P*=0.034).

However, treatment for dental caries was a protective factor (HR =0.80, 95% CI 0.64–0.99, *P*=0.036). Figure 2 shows the Kaplan–Meier analysis of the incidence of pneumonia in male and female patients with PD. Based on the analysis, we found similar patterns of pneumonia incidence in the male and female groups in the first 2 years after PD diagnosis; however, pneumonia incidence increased more rapidly in the male group during the follow-up period.

**Discussion**

To the best of our knowledge, this is the first study to identify risk factors for pneumonia in the PD population. This study used a nationwide population-based screening

### Table 1

| Patient characteristics | Patients with PD with pneumonia (n=381) | Patients with PD without pneumonia (n=1,620) | *P*-value |
|-------------------------|-----------------------------------------|---------------------------------------------|-----------|
| Age at enrolment, mean (SD), years | 74.78 (7.46) | 70.16 (9.17) | <0.001 |
| Age group, years, n (%) | | | |
| <70 | 90 (23.6) | 719 (44.4) | <0.001 |
| 70–79 | 200 (52.5) | 667 (41.2) | |
| ≥80 | 91 (23.9) | 234 (14.4) | |
| Sex, n (%) | | | <0.001 |
| Male | 231 (60.6) | 782 (48.3) | |
| Female | 150 (39.4) | 838 (51.7) | |
| Geographic region of Taiwan, n (%) | | | 0.015 |
| Central | 78 (20.5) | 448 (27.7) | |
| Northern | 188 (49.3) | 713 (44.0) | |
| Southern and Eastern | 115 (30.2) | 459 (28.3) | |
| Urban level, n (%) | | | 0.098 |
| Urban and suburban | 276 (72.4) | 1,103 (68.1) | |
| Rural | 105 (27.6) | 517 (31.9) | |
| Monthly income, NT$, n (%) | | | <0.001 |
| ≥30,000 | 18 (4.7) | 195 (12.0) | |
| <30,000 | 363 (95.3) | 1,425 (88.0) | |
| Dental attendance rate, n (%) | | | <0.001 |
| No | 210 (54.3) | 696 (42.9) | |
| Yes | 177 (45.7) | 927 (57.1) | |
| PD with dementia, n (%) | | | 0.001 |
| | 102 (26.4) | 264 (16.3) | |

*Note:* Dementia occurred at least 1 year after diagnosis of PD. | *Abbreviations:* PD, Parkinson disease; SD, standard deviation; NT$, new Taiwan dollar.

### Table 2

| Comorbidities, n (%) | Patients with PD with pneumonia (n=381) | Patients with PD without pneumonia (n=1,620) | *P*-value | Crude HR (95% CI) | *P*-value | Adjusted HR (95% CI) | *P*-value |
|----------------------|-----------------------------------------|---------------------------------------------|-----------|-----------------|-----------|---------------------|-----------|
| Diabetes mellitus    | 90 (23.6) | 423 (26.1) | 0.317 | 1.20 (0.95–1.53) | 0.125 | 1.10 (0.86–1.40) | 0.438 |
| Alcoholism           | 37 (9.7) | 150 (9.3) | 0.785 | 1.35 (0.96–1.89) | 0.087 | 1.24 (0.88–1.75) | 0.229 |
| Chronic pulmonary disease | 145 (38.3) | 603 (37.2) | 0.690 | 1.41 (1.14–1.73) | 0.001 | 1.14 (0.92–1.41) | 0.231 |
| Dental caries        | 141 (37.0) | 822 (50.7) | <0.001 | 0.76 (0.61–0.93) | 0.008 | 0.80 (0.64–0.99) | 0.036 |
| Periodontis          | 134 (35.2) | 748 (46.2) | <0.001 | 0.83 (0.67–1.02) | 0.077 | 0.89 (0.69–1.14) | 0.339 |
| Osteoporosis         | 63 (16.5) | 321 (19.8) | 0.144 | 1.10 (0.84–1.44) | 0.499 | 1.12 (0.84–1.49) | 0.430 |
| Chronic heart failure | 26 (3.8) | 75 (4.6) | 0.078 | 1.95 (1.31–2.91) | 0.001 | 1.53 (1.02–2.29) | 0.042 |
| Chronic kidney disease | 48 (12.6) | 180 (11.1) | 0.411 | 1.60 (1.18–2.17) | 0.002 | 1.39 (1.03–1.90) | 0.034 |
| Rheumatoid arthritis | 18 (4.7) | 72 (4.4) | 0.812 | 1.31 (0.82–2.11) | 0.260 | 1.26 (0.78–2.04) | 0.339 |
| Chronic liver disease | 51 (13.4) | 343 (21.2) | 0.001 | 0.83 (0.62–1.21) | 0.215 | 0.77 (0.57–1.05) | 0.100 |

*Note:* *A* adjusted for age group, sex, geographic region, level of urbanization, monthly income, PD with dementia, and comorbidities including chronic pulmonary disease, dental caries, chronic heart failure, and chronic kidney disease. | *Abbreviations:* PD, Parkinson’s disease; HR, hazard ratio; CI, confidence interval.
of patients with PD to estimate the risk of hospitalization with pneumonia in Taiwan. A total of 2,001 patients with new-onset PD between 2000 and 2010 were identified in our cohort analysis. Overall, our study found that older age, male sex, geographic region of Taiwan, rural areas, chronic heart failure, and chronic kidney disease were independent risk factors for pneumonia among patients with PD. However, treatment for dental caries was a protective factor.

In general, the incidence of pneumonia in the general population increases with age, and is higher in males than in females. The demographics of our PD population in terms of age and sex were similar to those of the general population in these studies. Male patients with PD had a higher risk (HR = 1.59) of developing pneumonia (after adjusting for other confounding factors) than female patients. Although male vulnerability to pneumonia has long been recognized, and the consistency and magnitude of these differences between the sexes are particularly impressive in patients with interstitial pneumonia or ventilator-associated pneumonia, the underlying mechanisms responsible for this phenomenon are still unclear. Our study found that the incidence of pneumonia among patients with PD was lower in central Taiwan and urbanized/suburbanized regions. The results suggest that environmental factors may play a role in pneumonia risk in the PD population, and one possible reason may be a relative lack of access to health care resources. There is some literature reporting geographic differences in pneumonia incidence.

Table 3 Risk factors for pneumonia – multivariate Cox proportional hazards analysis

| Risk factors                      | Adjusted HR (95% CI) | P-value | Female (n=988) | Adjusted HR (95% CI) | P-value | Male (n=1,022) | Adjusted HR (95% CI) | P-value |
|-----------------------------------|-----------------------|---------|----------------|----------------------|---------|----------------|----------------------|---------|
| Age group, years                  |                       |         |                |                      |         |                |                      |         |
| <70                               | 1.00                  | –       | 1.00           | –                    | –       | 1.00           | –                    | –       |
| 70–79                             | 2.12                  | (1.64–2.75) | <0.001 | 2.69                  | (1.78–4.05) | <0.001 | 1.80                  | (1.28–2.52) | 0.001 |
| ≥80                               | 3.15                  | (2.32–4.28) | <0.001 | 4.18                  | (2.56–6.84) | <0.001 | 2.57                  | (1.74–3.81) | <0.001 |
| Sex                               |                       |         |                |                      |         |                |                      |         |
| Female                            | 1.00                  | –       | –              | –                    | –       | –              | –                    | –       |
| Male                              | 1.59                  | (1.29–1.96) | <0.001 | –                    | –       | –              | –                    | –       |
| Geographic region of Taiwan       |                       |         |                |                      |         |                |                      |         |
| Central                           | 1.00                  | –       | 1.00           | –                    | –       | 1.00           | –                    | –       |
| Northern                          | 1.36                  | (1.04–1.78) | 0.024 | 1.42                  | (0.90–2.24) | 0.135 | 1.33                  | (0.95–1.86) | 0.096 |
| Southern and Eastern              | 1.40                  | (1.05–1.88) | 0.023 | 1.49                  | (0.92–2.43) | 0.105 | 1.34                  | (0.92–1.93) | 0.126 |
| Urban level                       |                       |         |                |                      |         |                |                      |         |
| Urban and suburban                | 1.00                  | –       | 1.00           | –                    | –       | 1.00           | –                    | –       |
| Rural                             | 1.34                  | (1.05–1.72) | 0.021 | 1.43                  | (0.96–2.14) | 0.078 | 1.33                  | (0.96–1.85) | 0.083 |
| Monthly income, NT$                |                       |         |                |                      |         |                |                      |         |
| ≥30,000                           | 1.00                  | –       | –              | –                    | –       | 1.00           | –                    | –       |
| <30,000                           | 1.50                  | (0.91–2.46) | 0.114 | 1.83                  | (0.45–7.52) | 0.400 | 1.57                  | (0.91–2.71) | 0.108 |
| PD with dementia$                  |                       |         |                |                      |         |                |                      |         |
| No                                | 1.00                  | –       | 1.00           | –                    | –       | 1.00           | –                    | –       |
| Yes                               | 1.39                  | (0.92–2.10) | 0.114 | 1.51                  | (0.73–3.12) | 0.264 | 1.31                  | (0.79–2.17) | 0.290 |
| Comorbidities                     |                       |         |                |                      |         |                |                      |         |
| Chronic pulmonary disease         | 1.14                  | (0.92–1.41) | 0.231 | 1.20                  | (0.84–1.71) | 0.313 | 1.15                  | (0.88–1.52) | 0.307 |
| Dental caries                     | 0.80                  | (0.64–0.99) | 0.036 | 0.90                  | (0.64–1.27) | 0.548 | 0.74                  | (0.56–0.97) | 0.029 |
| Chronic heart failure             | 1.53                  | (1.02–2.29) | 0.042 | 2.22                  | (1.23–2.98) | 0.008 | 1.14                  | (0.64–2.03) | 0.649 |
| Chronic kidney disease            | 1.39                  | (1.03–1.90) | 0.034 | 1.03                  | (0.58–1.80) | 0.931 | 1.65                  | (1.13–2.39) | 0.009 |

Note: Dementia occurred at least 1 year after diagnosis of PD.
Abbreviations: PD, Parkinson’s disease; HR, hazard ratio; CI, confidence interval; NT$, new Taiwan dollar.

Figure 2 Kaplan–Meier analysis for incidence of pneumonia in patients with PD by sex.
Abbreviation: PD, Parkinson’s disease.
in the pediatric population, but this has not previously been observed in the PD population.\textsuperscript{21,24}

Our study showed that chronic heart failure and chronic kidney disease are both independent predictive factors for pneumonia in patients with PD. Of all the comorbidities in this study, chronic heart failure had the largest magnitude as a risk factor for pneumonia (HR = 1.53) (and particularly in females aged \(\geq 80\) years old – Table S2), which is comparable to the twofold increased risk of pneumonia in the general population.\textsuperscript{25,26} Chronic kidney disease was associated with an increased risk of pneumonia among patients with PD in our study, similar to that in the general population, and this risk was particularly seen in older male patients.\textsuperscript{31,20} Although chronic pulmonary disease is recognized as an important risk factor for pneumonia in the general population,\textsuperscript{28} for reasons that are unclear, this did not emerge as a risk factor in our study.

Of interest, we found that patients with PD who had received treatment for dental caries suffered less from pneumonia (especially in males aged \(< 70\) years old) (Table S3). Poor oral health, including dental caries and periodontal diseases, is commonly observed in patients with PD, even in the early stages of the disease.\textsuperscript{27–29} The high prevalence of impaired swallowing, periodontal diseases, and caries may lead to a greater risk of aspiration pneumonia.\textsuperscript{30–33} Maintenance of good oral hygiene and control of oral biofilm formation in the elderly reduce the number of potential respiratory pathogens in the oral secretions, which in turn reduces the risk of pneumonia.\textsuperscript{34} Our findings suggest that patients with PD who received treatment for dental caries may have better oral health and a reduced risk of pneumonia than those who did not. Although we cannot determine based on the available data whether there were differences in dysphagia between the two groups, we believe our results highlight the potential importance of good oral health in reducing morbidity and mortality in patients with PD. In brief, patients with PD had similar risk factors for pneumonia hospitalization when compared to general population. Our study found that chronic heart failure, chronic kidney disease, and dental caries were more significant risk factors for pneumonia hospitalization among patients with PD.

The main strength of our study is that it provides information from a nationwide population-based cohort with a large sample size, and the results may provide a good representation of ethnic Chinese patients with PD. To increase the accuracy of the diagnosis of PD, the study population was obtained by linking an ambulatory care expenditures database (neurologists and ICD-9-CM code) and a prescription claims database (medical treatment for PD). Moreover, covariates, including common underlying diseases (especially dental illness), were taken into consideration. Nevertheless, there are some limitations in our study that deserve comment. First, the study was retrospective. We did not have the opportunity to review all the medical charts of patients from the de-identified National Institutes of Health database. Second, although we analyzed national health care records from a database of 1 million randomly selected subjects, there were still relatively few PD cases to allow us to make a more precise estimation of total PD populations in Taiwan. Third, information on other risk factors contributing to pneumonia, such as the severity of comorbidities, lifestyle factors, such as smoking and alcohol consumption, and biochemistry data were unavailable for retrieval from the database. Other lifestyle-related pneumonia risk factors, including contact with children and nutritional status, were not included in the study. Finally, it was difficult to distinguish between aspiration pneumonia and infectious pneumonia from the details available in the database.

**Conclusion**

Identification of risk factors for hospitalization with pneumonia among patients with PD in Taiwan has highlighted chronic heart failure, chronic kidney disease, and oral hygiene as being associated with an increased risk of pneumonia. In particular, older female patients with PD with chronic heart failure and older male patients with PD with chronic kidney disease had a significantly higher risk of pneumonia. In contrast, male patients with PD had a diminished risk of pneumonia if dental caries were treated previously. Early recognition and prompt management of comorbid physical diseases/risk factors in patients with PD may help to reduce the risk of hospitalization with pneumonia, and thus, the burden of the disease.

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**Disclosure**

The authors report no conflicts of interest in this work.

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## Supplementary materials

### Table S1 ICD-9-CM codes and ATC classification system codes used in this study

| Main diseases                              | ICD-9-CM codes |
|--------------------------------------------|----------------|
| Parkinson disease                          | 332            |
| Dementia                                   | 290, 294.1, 331.0 |
| Stroke                                     | 430–434, 436–438 |
| Psychoses                                  | 295, 297       |
| Pneumonia                                  | 480.0, 487.0   |
| Septicemia                                 | 038            |
| Acute respiratory failure                  | 518.81         |

**Comorbidities**

| Condition                                 | ICD-9-CM codes and ATC codes |
|-------------------------------------------|------------------------------|
| Diabetes mellitus                         | 249.XX–250.XX, 648.01, 648.02, 588.1, 357.2 |
| Alcoholism                                 | 291.XX, 303.0X, 303.9, 305.00–305.02, 571.0–571.5, 571.8–571.9, 980.0, 980.2, 980.3, 980.8, 980.9, 977.3, V11.3 |
| Chronic pulmonary disease                  | 416.8, 416.9, 490, 491–495, 496, 500–505, 506.4, 508.1 |
| Dental caries                              | 521.0, 521.1, 521.2, 521.3, 522.0, 522.1, 522.2, 522.3, 522.4, 522.5, 522.6, 522.7, 522.8, 522.9, 89001C–89005C, 89008C–89012C, 89101C–89105C, 89108C–89112C, 89006C, 90004C, 90005C, 90103C, 90104C, 90105C, 90016C, 90017C, 92013C, 92014C, 92015C, 92016C, 92055C |
| Periodontitis                              | 523.0, 523.1, 523.2, 523.3, 523.4, 523.5, 523.8, 523.9, 91001C, 91003C, 91004C, 91006C–91008C, 91104C, P4001C, P40002C, 91009B, 91010B, 92027C, 92033C, 92071C, 91011C, 91101C, 91012C, 91013C, 92014C, 92015C, 92016C, 92055C |
| Osteoporosis                               | 733.0X         |
| Chronic heart failure                      | 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4, 425.9, 428.4X |
| Chronic kidney disease                     | 581–583, 585–587 |
| Rheumatoid arthritis                       | 714.0, 714.1, 714.2, 714.30–714.33, 714.4 |
| Chronic liver disease                      | 571.40, 571.41, 571.49, 571.2, 571.5, 571.6, 572.2 |
| Cancers                                    | 140–208        |
| Epilepsy                                   | 345.XX, 649.40–649.44, 780.3 |
| Asplenia after operation                   | 414.2, 414.3, 415 |
| Cerebrospinal fluid shunt                  | 83049B         |
| Multiple sclerosis                          | 340            |
| Sickle cell or coeliac disease              | 282.60         |
| HIV/AIDS                                   | 042, 079.53, 795.71 |

**Drug categories**

| Drug name                                  | ATC codes |
|--------------------------------------------|-----------|
| Levodopa                                   | N04BA01   |
| Levodopa and decarboxylase inhibitor       | N04BA02   |
| Levodopa, decarboxylase inhibitor, and COMT inhibitor | N04BA03 |
| Entacapone                                  | N04BX02   |
| Bromocriptine mesylate                     | N04BC01   |
| Pergolide mesylate                         | N04BC02   |
| Cabergoline                                | N04BC06   |
| Ropinirole                                 | N04BC04   |
| Pramipexole                                | N04BC05   |
| Amantadine                                 | N04BB01   |
| Selegline                                  | N04BD01   |

**Abbreviations:** ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification; ATC, anatomical therapeutic chemical.
Table S2 Adjusted hazard ratio for pneumonia in the study population with PD stratified by age group and sex

| Variables                     | <70 years old group | 70-79 years old group | ≥80 years old group |
|-------------------------------|---------------------|-----------------------|--------------------|
|                               | No cases (%)        | Adjusted HR (95% CI)  | P-value            |
|                               | n=384               | 1.36 (0.76–2.44)      | 0.306              |
| Male                          | 17 (15.3)           | 0.27 (0.27–0.92)      | 0.71               |
| Chronic pulmonary disease     | 44 (21.2)           | 0.49 (0.27–0.92)      | 0.27               |
| Dental caries                 | 5 (17.2)            | 0.89 (0.35–2.22)      | 0.796              |
| Chronic heart failure         | 16 (8.4)            | 1.34 (0.46–3.91)      | 0.594              |
| Chronic kidney disease        | 10 (8.4)            | 1.70 (0.79–3.66)      | 0.179              |
| Female                        | n=425               | 0.76 (0.59–0.97)      | 0.045              |
| Chronic pulmonary disease     | 29 (17.3)           | 1.05 (0.60–1.65)      | 0.845              |
| Dental caries                 | 30 (16.3)           | 0.91 (0.28–1.45)      | 0.203              |
| Chronic heart failure         | 6 (24.0)            | 1.72 (0.73–4.06)      | 0.218              |
| Chronic kidney disease        | 11 (18.0)           | 1.23 (0.64–2.36)      | 0.533              |
|                             | 10 (8.4)            | 1.70 (0.79–3.66)      | 0.179              |
|                             | 29 (17.3)           | 1.05 (0.60–1.65)      | 0.845              |
|                             | 30 (16.3)           | 0.91 (0.28–1.45)      | 0.203              |
|                             | 6 (24.0)            | 1.72 (0.73–4.06)      | 0.218              |
|                             | 11 (18.0)           | 1.23 (0.64–2.36)      | 0.533              |

Notes: Adjusted age group, sex, geographic region of Taiwan, urban level, monthly income, severity of physical condition, PD with dementia, and comorbidities, including chronic pulmonary disease, dental caries, chronic heart failure, and chronic kidney disease.

Abbreviations: PD, Parkinson’s disease; HR, hazard ratio; CI, confidence interval.

Table S3 Adjusted hazard ratio for pneumonia in the study population with PD stratified by follow-up duration and sex

| Variable                    | Overall | Female | Male |
|-----------------------------|---------|--------|------|
|                             | <2 years | ≥2 years | <2 years | ≥2 years | <2 years | ≥2 years |
|                             | Adjusted HR (95% CI) | Adjusted HR (95% CI) | Adjusted HR (95% CI) | Adjusted HR (95% CI) | Adjusted HR (95% CI) | Adjusted HR (95% CI) |
| Dental caries               | 0.58 (0.37–0.89) | 0.76 (0.59–0.97) | 0.39 (0.16–0.90) | 1.00 (0.69–1.45) | 0.76 (0.44–1.32) | 0.62 (0.45–0.86) |
| Chronic heart failure       | 1.80 (0.87–3.75) | 1.35 (0.80–2.25) | 5.56 (0.97–31.83) | 2.56 (1.34–4.87) | 1.79 (0.77–4.16) | 0.64 (0.26–1.57) |
| Chronic kidney disease      | 0.87 (0.48–1.57) | 1.32 (0.91–1.92) | 0.47 (0.15–1.51) | 0.96 (0.49–1.87) | 1.01 (0.49–2.10) | 1.61 (1.02–2.56) |

Notes: Adjusted age group, sex, geographic region of Taiwan, urban level, monthly income, severity of physical condition, PD with dementia, and comorbidities, including chronic pulmonary disease, dental caries, chronic heart failure and chronic kidney disease.

Abbreviation: PD, Parkinson’s disease.
