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ORIGINAL ARTICLE

Risk of Parkinson's Disease after a Diagnosis of Bacterial Pneumonia: A Nationwide Longitudinal Follow-up Study

Chih-Sung Liang[1,2], Fu-Chi Yang[3], Shih-Jen Tsai[4,5], Ya-Mei Bai[4,5], Chia-Kuang Tsai[3], Mu-Hong Chen[4,5]

[1]Department of Psychiatry, Beitou Branch, Tri-service General Hospital and School of Medicine, National Defense Medical Center, [2]Department of Psychiatry, Tri-service General Hospital and School of Medicine, National Defense Medical Center, [3]Department of Neurology, Tri-service General Hospital and School of Medicine, National Defense Medical Center, [4]Department of Psychiatry, Taipei Veterans General Hospital, [5]Department of Psychiatry, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

Background: Parkinson's disease (PD) is receiving increasing attention owing to the possibility of its immense burden on society in the future. The inconsistent findings of previous studies highlight that different pathogens and infection sites may have different effects on the risk of PD development. **Aim:** This study primarily investigates the risk assessment of future PD in relation to bacterial pneumonia caused by different bacterial species. **Methods:** We selected patients diagnosed with bacterial pneumonia and nonbacterial pneumonia control cohort from 1997 to 2012 in the Taiwan National Health Insurance Database and followed them until the end of 2013. A diagnosis of PD was identified during the follow-up period. Sensitivity analysis was performed to eliminate patients with prodromal PD. **Results:** Participants with bacterial pneumonia had a higher risk of developing PD than the nonbacterial pneumonia controls during the follow-up period (hazard ratio [HR] with 95% confidence interval: 3.00, 2.37–3.80). The subanalyses stratified by different pathogens showed that there were four pathogens (*Streptococcus*, *Staphylococcus*, *Klebsiella*, and *Mycoplasma*) associated with a higher risk of PD, with HRs ranging from 2.52 (*Staphylococcus*) to 3.96 (*Mycoplasma*). The results of sensitivity analyses demonstrate consistent findings, including after the elimination of the observation period over 3 or 5 years and the exclusion case recruitment before 2010 or 2008. **Conclusion:** This study demonstrates that patients with bacterial pneumonia have a 3.0-fold higher risk of developing PD than nonbacterial pneumonia controls. Moreover, different pathogens of bacterial pneumonia are correlated with varying risks of PD. More studies are warranted to elucidate the mechanism underlying the relationship between infectious pathogens of pneumonia and PD.

Key words: Bacterial pneumonia, Parkinson's disease, risk

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease characterized by motor and nonmotor symptoms, such as resting tremors, rigidity, bradykinesia, a loss of smell, autonomic dysfunction, and sleep disorders.[1] PD typically develops after the age of 60 years and can lead to disability.[2] The global population's age and life span have increased, and the number of PD patients is estimated to almost double from 6.9 million to approximately 14 million worldwide from 2015 to 2040 according to the Global Burden of Disease Study.[3] Therefore, this "PD Pandemic" is receiving increasing attention owing to the possibility of its immense burden on society in the future.

The underlying mechanisms and provoking factors for PD development are multifactorial, and further investigation is needed. Previous research has reported that a history of head

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Corresponding Author: Dr. Mu-Hong Chen, Department of Psychiatry, Taipei Veterans General Hospital, No. 201, Sec. Shihpai Road, Beitou District, Taipei, Taiwan 11217. Tel: +886-2-28344012; Fax: +886-2-28344012. E-mail: kremer7119@gmail.com
Dr. Chia-Kuang Tsai, Department of Neurology, Tri-service General Hospital and School of Medicine, National Defense Medical Center, No.325, Sec. 2, Chenggong Road, Neihu District, Taipei City, Taiwan.Tel: +886-2-87923311; Fax: +886-2-87927174. E-mail: jiakuang@mail.ndmctsgh.edu.tw

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injury, exposure to toxins, and genetic factors are associated with the onset of PD.[4] Several studies have tested the hypothesis that infectious diseases may increase the risk of PD through microglia-mediated neuroinflammation.[5-8] Nevertheless, previous studies addressing this issue have reported inconsistent findings. For example, Sasco and Paffenbarger reported that a history of measles infection was negatively associated with PD risk.[6] Fang *et al*. reported that central nervous system (CNS) infections, rather than sepsis, were correlated with a higher future risk of PD in a case–control study in Sweden.[7] Shen *et al*. reported that patients with tuberculosis infection had a 1.38-fold higher risk of PD in a nationwide cohort study.[5] However, Fiszer *et al*. reported a negative association between *Bordetella pertussis* infection and PD by analyzing serum levels of antibodies against the abovementioned pathogen in PD patients and age-matched controls.[9] These inconsistent findings highlight that different pathogens and infection sites may have different effects on the risk of PD development.

To evaluate this hypothesis, we conducted a cohort study to investigate the risk of PD development after a diagnosis of bacterial pneumonia using the National Health Insurance Research Database (NHIRD) in Taiwan. We hypothesized that different bacterial pneumonia pathogens would be associated with varying risks for PD. The results illuminated whether antibiotic therapy is associated with the development of PD.

MATERIALS AND METHODS

Data acquisition

The Taiwan National Health Insurance, a mandatory universal health insurance program, offers comprehensive medical care coverage to all Taiwanese residents (more than 23 million people). The NHIRD was audited and released by the Taiwan National Health Research Institute for scientific studies.[10,11] Comprehensive information on insured individuals, such as demographic data, clinical visit dates, disease diagnoses, inpatient procedures, and prescriptions, is included in the database. The insurance claim information of the individuals is anonymous to maintain privacy. The diagnostic codes used were based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The NHIRD has been used extensively in many Taiwanese epidemiological studies.[12-15] The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Taipei Veterans General Hospital (2018-07-016AC; approval date: July 23, 2021). Informed written consent was waived by the IRB.

Inclusion criteria for patients with bacterial pneumonia and the control group

We enrolled individuals in the study cohort if they were aged ≥20 years and had a diagnosis of bacterial pneumonia (ICD-9-CM codes: 481, 482, 483.0, 483.1) made by a board-certified physician in the inpatient dataset before enrollment between January 1, 1997, and December 31, 2012. Individuals in the study cohort were required to have no history of PD or related diseases (ICD-9-CM code: 332). The time of enrollment was defined as the discharge diagnosis time of bacterial pneumonia. We enrolled a control cohort who was randomly selected after eliminating those individuals with a diagnosis of any pneumonia (ICD-9-CM codes: 480, 481, 482, 483, 484, 485, 486) anytime in outpatient and inpatient datasets and with a prior diagnosis of PD or any related diseases before enrollment. The control cohort (1:10) was composed of age-, sex-, time-of-enrollment-, medical- and mental-comorbidity-, income-, and residence-matched individuals. A diagnosis of PD (ICD-9-CM code: 332.0) made by a board-certified neurologist was identified during the follow-up (from enrollment to December 31, 2013, or until death). Medical and mental comorbidities, including cerebrovascular diseases, traumatic brain injury, hypertension, dyslipidemia, diabetes mellitus, major depressive disorder, alcohol use disorder, and substance use disorder, were assessed. Furthermore, specific bacterial origins of pneumonias were identified based on specific ICD-9-CM codes: 481 and 482.3 for *Streptococcus*, 482.0 for *Klebsiella*, 482.1 for *Pseudomonas*, 482.2 for *Haemophilus*, 482.4 for *Staphylococcus*, and 483.0 for *Mycoplasma*. In Taiwan, hospital infectious disease specialists supervise the use of antibiotics in infectious diseases (including bacterial pneumonia) to reduce and control the risk of the development of antibiotic-resistant bacteria. Cultures of infectious pathogens are required to be performed in clinical practice. These clinical procedures ensured the diagnostic validity of bacterial pneumonias and their origins. In addition, the Charlson Comorbidity Index (CCI) and the numbers of all-cause clinical visits were obtained for the study and control cohorts. The CCI, consisting of 22 physical conditions, was assessed to determine the systemic health conditions of all enrolled individuals.[16] The number of all-cause clinical visits (the number of clinical visits for any cause per year) for the study and control cohorts was included as a variable to account for potential detection bias. Income level (levels 1–3/month: ≤15,840 New Taiwanese dollars [NTD] or 528 United States dollars [USD], 15,841–25,000 NTD or 528–833 USD, and ≥25,000 NTD or ≥833 USD) and urbanization level of residence (levels 1–5, most to least urbanized) were identified as proxies for healthcare availability in Taiwan.

Statistical analysis

For between-group comparisons, the F test was used for continuous variables, and Pearson's χ^2-test was used for

nominal variables. After adjusting for demographic data (age, sex, income, and residence), comorbidities (cerebrovascular diseases, traumatic brain injury, hypertension, dyslipidemia, diabetes mellitus, major depressive disorder, alcohol use disorder, and substance use disorder), the CCI score, and the number of all-cause clinical visits, Cox regression analysis was performed to investigate the risk of developing PD among patients with bacterial pneumonia and the control group. Subanalyses stratified by age group (<40 years vs. 40–59 years vs. ≥60 years) and specific bacterial origins of pneumonias (*Streptococcus*, *Klebsiella*, *Pseudomonas*, *Haemophilus*, *Staphylococcus*, *Mycoplasma*) were also conducted to further assess the relationship between bacterial pneumonia and subsequent PD risk. Furthermore, we examined the association of repeated bacterial pneumonia (≥3 vs. 2 vs. only one) with the risk of developing PD during the follow-up. Given the insidious onset of PD, two types of sensitivity analyses were performed to validate the results. In the "exclusion of observation period" model, the first 3 years or first 5 years of observation after bacterial pneumonia diagnoses were excluded, eliminating all cases of PD diagnosed within these 1st year following bacterial pneumonia diagnoses. In the "exclusion of enrollment period" model, only patients diagnosed with bacterial pneumonia before the dates January 1, 2010, or January 1, 2008, were included in the analysis; patients with bacterial pneumonia diagnosed after these time points were selectively excluded. Residual confounding was examined by an E-value. The E-value was defined as the minimum association strength in the risk ratio scale that an unmeasured confounder would need to have with both the exposure and outcome to fully account for a specific exposure–outcome association, conditional on the measured covariates.[17,18] A large E-value implies that considerable unmeasured confounding would be needed to explain away an effect estimate. A low E-value implies that little unmeasured confounding would be needed to explain away an effect estimate. Statistical significance was set at two-tailed $P \leq 0.05$. Data processing and statistical analyses were performed with SAS (version 9.1, SAS Institute, Cary, NC, USA).

RESULTS

Demographic characteristics and comorbidities of the study participants

This study recruited a total of 21,870 patients with bacterial pneumonia and 87,480 matched controls. Table 1 shows the comparisons of demographic characteristics and comorbidities between the bacterial pneumonia and nonbacterial pneumonia cohorts. The mean age was 65.35 ± 18.66 in patients with bacterial pneumonia and 65.29 ± 18.65 in controls. The proportion of men was 60.8% in both groups. Participants with bacterial pneumonia had higher CCI scores than controls (3.91 ± 2.69 vs. 2.91 ± 2.51, $P < 0.001$), a higher incidence of developing any PD-related disease (0.6% vs. 0.2%, $P < 0.001$), younger age at the diagnosis of any PD-related disease (74.84 ± 9.45 vs. 79.39 ± 8.45, $P < 0.001$), and a higher number of all-cause clinical visits per year (14.51 ± 18.94 vs. 13.84 ± 14.59, $P < 0.001$) [Table 1].

Risk of acquiring Parkinson's disease among participants with bacterial pneumonia

By the end of the follow-up period, Figure 1 presents a probability of PD-free Kaplan–Meier survival over time in patients with bacterial pneumonia compared to a control group. The difference in survival curves between the two groups is statistically significant ($P < 0.001$), indicating a potential link between bacterial pneumonia and an increased risk of PD development.

After adjusting for demographic characteristics, comorbidities, the CCI score, and the number of all-cause clinical visits, participants with bacterial pneumonia had a higher risk of developing PD than the nonbacterial pneumonia controls during the follow-up period (40–59 years: reported as hazard ratio [HR] with 95% confidence interval [CI]: 2.86, 1.33–6.13; ≥60 years: 2.91, 2.26–3.74; total: 3.00, 2.37–3.80) [Table 2]. The subanalyses stratified by different pathogens showed that there were four pathogens (*Streptococcus*, *Staphylococcus*, *Klebsiella*, and *Mycoplasma*) associated with a higher risk of PD, with HRs ranging from 2.52 (*Staphylococcus*) to 3.96 (*Mycoplasma*). For the subgroup analyses by age, there was a higher risk of PD in 40–59-year-old patients having bacterial pneumonia caused by *Streptococcus* (HR 4.94 vs. 3.59) and *Staphylococcus* (HR 5.22 vs. 2.34) than in ≥60-year-old patients; nevertheless, such a correlation was not observed for *Klebsiella*. A positive association between *Klebsiella* and *Mycoplasma* infection and an increased risk of PD development existed in ≥60-year-old participants (HR 2.87 and 4.63, respectively).

Number of bacterial pneumonia hospitalizations and risk of Parkinson's disease

We further investigated the number of hospitalizations for bacterial pneumonia and the risk of PD. As shown in Table 3, there was a similar crude risk of PD in patients with between 1 and ≥3 hospitalizations due to bacterial pneumonia (HR 3.28–3.59). After fully adjusting for demographic data, comorbidities, the CCI score, and the number of all-cause clinical visits, participants with one hospitalization had the highest risk of PD (3.64, 95% CI 2.84–4.68), followed by participants with ≥3 hospitalizations (2.20, 95% CI 1.25–3.89), in comparison with those without bacterial pneumonia.

Table 1: Demographic data and incidence of Parkinson's disease among patients with bacterial pneumonia and control group

	Patients with bacterial pneumonia (*n*=21,870), *n* (%)	Controls (*n*=87,480), *n* (%)	*P*
Age at enrollment (years), SD	65.35 (18.66)	65.29 (18.65)	0.656
Male	13,294 (60.8)	53,176 (60.8)	1.000
Bacterial origins			
Any origin	21,870 (100.0)		
Streptococcus	2780 (12.7)		
Staphylococcus	2154 (9.8)		
Pseudomonas	5007 (22.9)		
Klebsiella	5205 (23.8)		
Hemophilus	1450 (6.6)		
Mycoplasma	1798 (8.2)		
Numbers of hospitalization due to bacterial pneumonia			
1	16,417 (75.1)		
≥2	3187 (14.6)		
≥3	2266 (10.3)		
PD-related comorbidities			
Cerebrovascular diseases	6238 (28.5)	24,952 (28.5)	1.000
Traumatic brain injury	1201 (5.5)	4904 (5.5)	0.999
Hypertension	12,757 (58.3)	51,028 (58.3)	1.000
Dyslipidemia	4742 (21.7)	18,968 (21.7)	1.000
Diabetes mellitus	6995 (32.0)	27,980 (32.0)	1.000
Major depressive disorder	301 (1.4)	1204 (1.4)	0.997
Alcohol use disorder	1277 (5.8)	5108 (5.8)	0.999
Substance use disorder	606 (2.8)	2424 (2.8)	0.998
CCI score (SD)	3.91 (2.69)	2.91 (2.51)	<0.001
Level of urbanization			
1 (most urban)	6688 (30.6)	26,752 (30.6)	1.000
2	4071 (18.6)	16,284 (18.6)	
3 (most rural)	11,111 (50.8)	44,444 (50.8)	
Income-related insured amount (NTD/month)			
≤15,840	11,639 (53.2)	46,556 (53.2)	1.000
15,841~25,000	8260 (37.8)	33,040 (37.8)	
≥25,001	1971 (9.0)	7884 (9.0)	
Incidence of any PD	130 (0.6)	172 (0.2)	<0.001
Age at diagnosis of any PD (years), SD	74.84 (9.45)	79.39 (8.45)	<0.001
Duration between enrollment and event (years), SD	4.40 (4.19)	5.84 (4.43)	0.004
All-cause clinical visits (times per year), SD	14.51 (18.94)	13.84 (14.59)	<0.001

SD=Standard deviation; NTD=New Taiwan dollar; CCI=Charlson comorbidity index; PD=Parkinson's disease

Sensitivity analyses

We used sensitivity analyses to exclude misclassification bias [Table 4]. The results of sensitivity analyses suggested that participants with bacterial pneumonia were associated with an increased risk of subsequently acquiring PD later in life, including after the elimination of the observation period over 3 years (HR 2.27, 95% CI 1.65–3.13) or over 5 years (HR 2.20, 95% CI 1.51–3.20) and after the elimination of patient recruitment before 2010 (HR 4.60, 95% CI 2.96–3.86) or 2008 (HR 5.48, 95% CI 4.03–7.44).

Table 2: Risk of developing Parkinson's disease among patients with bacterial pneumonia and controls

	Risk of PD, HR (95% CI)			
	<40 years	40~59 years	≥60 years	Total, HR (95% CI)
Bacterial pneumonia (presence vs. absence); E	NA	**2.86 (1.33–6.13); 5.17 (1.99–NA)**	**2.91 (2.26–3.74); 5.27 (3.95–NA)**	**3.00 (2.37–3.80); 5.45 (4.17–NA)**
Stratified by bacterial origins (presence vs. absence)				
Streptococcus; E	NA	**4.94 (1.46–16.64); 9.35 (2.28–NA)**	**3.59 (2.25–5.75); 6.64 (3.93–NA)**	**3.79 (2.46–5.85); 7.04 (4.36–NA)**
Staphylococcus; E	NA	**5.22 (1.14–23.93); 9.91 (1.54–NA)**	**2.34 (1.18–4.62); 4.11 (1.54–NA)**	**2.52 (1.35–4.69); 4.48 (2.04–NA)**
Pseudomonas; E	NA	2.32 (0.49–10.94); NA	1.07 (0.58–1.97); NA	1.17 (0.67–2.06); NA
Klebsiella; E	NA	1.96 (0.47–8.18); NA	**2.87 (1.95–4.23); 5.19 (3.31–NA)**	**2.79 (1.93–4.05); 5.02 (3.27–NA)**
Hemophilus; E	NA	NA	1.73 (0.79–3.81); NA	1.65 (0.76–3.59); NA
Mycoplasma; E	NA	NA	**4.63 (1.88–11.42); 8.73 (3.17–NA)**	**3.96 (1.61–9.75); 7.38 (2.60–NA)**

Bold type indicates the statistical significance (P<0.05). Adjusted by demographic data, comorbidities, CCI score, and all-cause clinical visits. CI=Confidence interval; HR=Hazard ratio; NA=Not available; CCI=Charlson comorbidity index; PD=Parkinson's disease

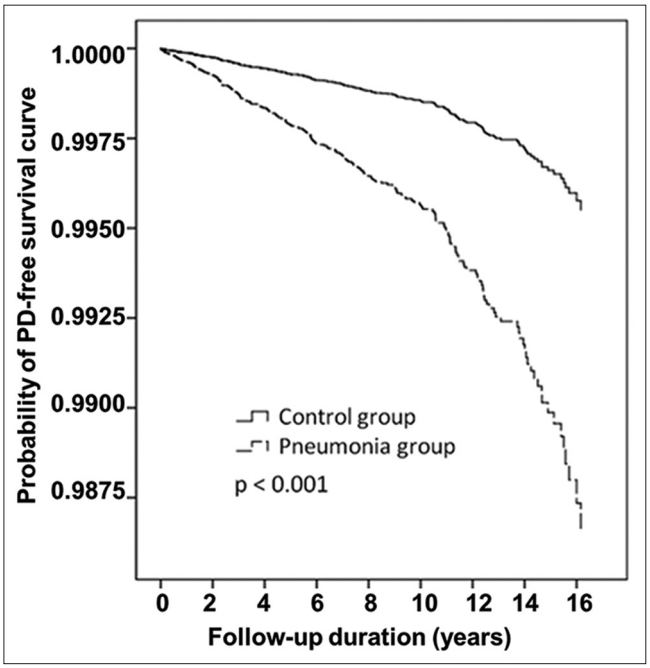

Figure 1: Parkinson's disease-free survival curve among patients with bacterial pneumonia and control group. PD = Parkinson's disease

DISCUSSION

This nationwide longitudinal follow-up study analyzed the risk of future PD in patients with bacterial pneumonia due to various pathogens, including *Streptococcus, Staphylococcus, Pseudomonas, Klebsiella, Haemophilus,* and *Mycoplasma*. We found that patients with pneumonia due to *Streptococcus*, *Staphylococcus*, *Klebsiella*, and *Mycoplasma* infection had a higher risk of PD in the following years; however, an increased risk of PD was not observed in patients with pneumonia due to *Pseudomonas* and *Haemophilus* infection. To the best of our knowledge, this is the first study reporting the risk of PD with different pneumonia pathogens.

Streptococcus, a Gram-positive and spherical bacterium, is one of the common pathogens affecting individuals worldwide. *Streptococcus* is also the major source of community-acquired bacterial pneumonia. However, *Streptococcus* infection can also lead to severe cases of meningitis and sepsis.[19] *Staphylococcus* is a Gram-positive bacterium that can trigger a variety of diseases varying in severity from minor infections, such as cellulitis, to life-endangering aggressive infections, such as endocarditis and pneumonia.[20] Among the many infection sites, the lungs are the most common site of *Staphylococcus* infections, which account for approximately 50,000 hospitalizations in the United States annually.[21,22] *Streptococcus* and *Staphylococcus* species infections have been proven to generate superantigens that cross-react with the major histocompatibility complex and T-cell receptors, causing the production of polyclonal T cells and cytokines.[23] Therefore, *Streptococcus* and *Staphylococcus* species infections may increase the onset of PD through immune effector cell-related neurotoxic syndrome or cytokine release syndrome-related brain disorder.[24]

Mycoplasma pneumoniae infections may cause not only lung injury but also extrapulmonary complications. CNS involvement is the most common site of involvement, followed by the respiratory system. It is estimated that approximately 7%

of patients hospitalized with *M. pneumoniae* infections have CNS symptoms, encompassing encephalitis, aseptic meningitis, and cerebellar ataxia.[25] Moreover, Tay *et al*. reported 2 cases of transient parkinsonism after *M. pneumoniae* infection.[26] These reports partially support the potential association between *M. pneumoniae* infection and PD. Currently, this is the first longitudinal study for which the results indicated a positive association between *M. pneumoniae* infections and PD.

Recently, Rozas *et al*. reported that PD patients have an increased abundance of opportunistic pathogens, including *Mycoplasma* and *Streptococcus* species, in their oral microbiota compared with controls.[27] Moreover, drooling, difficulty swallowing, and salivary pH are significant aspects correlated with a variety of microbiota compositions. This finding partially strengthens the potential mechanism by which already-diagnosed PD patients may have higher abundance of opportunistic pathogens in the oral microbiota.

Klebsiella is a Gram-negative and rod-shaped bacterium featuring a polysaccharide-based capsule. *Klebsiella pneumoniae* instigates infections in various sites in humans, including the respiratory tract, liver, blood, and urinary tract.[28] *K. pneumoniae* infection triggers the upregulation of several inflammatory cytokines, such as interleukins (ILs), tumor necrosis factor-alpha, and interferon-γ, which may have an important role in the neurotoxic cascade, provoking neurodegeneration.[28] Currently, there are limited Gram-negative species reported to be associated with PD, such as *Borrelia burgdorferi*[29,30] and *Helicobacter pylori*.[31] This study is the first for which the results indicate that *K. pneumoniae* infection might be associated with the risk of PD, especially in populations aged more than 60 years.

In addition to the specific pathogen's pathophysiology, several common mechanisms might link infection to PD. First, infectious pathogens have been proven to provoke a significant response with the release of various inflammatory molecules, incorporating ILs, interferons, and tumor necrosis factors.[32] Neuroinflammation develops if the proinflammatory reaction overpowers the anti-inflammatory reaction that causes the breakdown of the blood–brain barrier, microglial activation, and eventually, cellular toxicity and neuronal death.[33] Second, alpha-synuclein is the major component of Lewy bodies and the pathological hallmark of PD. In particular, oligomerized alpha-synuclein, rather than fibrils, has been demonstrated to cause neurodegeneration due to its neurotoxicity.[34] Park *et al*. reported recombinant alpha-synuclein to have an antimicrobial effect on several bacterial and fungal strains by antimicrobial assays.[35] The findings of this study partially explain why the increase in oligomerized alpha-synuclein after infection may play a potential immunoprotective role.

There are some limitations of this study. First, some factors associated with PD, such as smoking, alcoholism, dietary habits, and individual lifestyle factors, are not available in the NHIRD. Therefore, we could not adjust for these confounding factors in this research. Second, additional studies are needed to verify the generalizability of our results because this survey was limited to the Han Chinese population in Taiwan. Different results may be found in other races and countries. Third, some PD patients with mild symptoms may not request primary health care, which might have led to an underestimation of the total population of PD patients. Finally, the enrollment of the control group without having any diagnosis of pneumonia and PD may have selection bias. Alternative selection methods, such as matching with a broader range of respiratory illnesses or using a general population control group, will be considered in future research.

Table 3: Numbers of hospitalization due to bacterial pneumonia and risk of Parkinson's disease

	Risk of PD, HR (95% CI)	
	Un-adjusted	Fully adjusted[#]
Control group	1 (reference)	1 (reference)
Numbers of hospitalization due to bacterial pneumonia		
1	**3.28 (2.56–4.20)**	**3.64 (2.84–4.68)**
≥2	**3.74 (2.33–6.00)**	1.06 (0.50–2.24)
≥3	**3.59 (2.04–6.31)**	**2.20 (1.25–3.89)**

[#]Adjusted by demographic data, comorbidities, CCI score, and all-cause clinical visits. Bold type indicates the statistical significance. HR=Hazard ratio; CI=Confidence interval; CCI=Charlson comorbidity index; PD=Parkinson's disease

CONCLUSION

Increasing evidence has revealed that bacterial infections

Table 4: Sensitivity analyses of developing Parkinson's disease among patients with bacterial pneumonia and controls

Bacterial pneumonia	Total	Exclusion of observation period		Exclusion of enrollment period	
		>3 years	>5 years	Enrollment year <2010	Enrollment year <2008
Presence	**3.00 (2.37–3.80)**	**2.27 (1.65–3.13)**	**2.20 (1.51–3.20)**	**4.60 (3.48–6.09)**	**5.48 (4.03–7.44)**
Absence	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)

Bold type indicates the statistical significance (P<0.05). Adjusted by demographic data, comorbidities, CCI score, and all-cause clinical visits. HR=Hazard ratio; CI=Confidence interval; CCI=Charlson comorbidity index

accelerate neurodegenerative development in PD. The findings of this study highlight that patients with bacterial pneumonia have a 3.0-fold higher risk of developing PD than nonbacterial pneumonia controls. Moreover, different pathogens of bacterial pneumonia are correlated with varying risks of PD. More studies are warranted to elucidate the mechanism underlying the relationship between infectious pathogens of pneumonia and PD.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

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