Association Between Tuberculosis and Parkinson Disease
A Nationwide, Population-Based Cohort Study

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Abstract: Few studies have investigated the association between tuberculosis (TB) and Parkinson disease (PD). This nationwide, population-based, retrospective cohort study investigated the risk of PD in patients with TB.

We selected patients newly diagnosed with TB (International Classification of Diseases, Ninth Revision, Clinical Modification: 011) from 2000 to 2009 in the Taiwan National Health Insurance Database as the TB cohort. The comparison cohort (the non-TB cohort) was frequency matched to the TB cohort at a ratio of 4:1 by sex, age, and the index date. We analyzed the risks of PD by using Cox proportional hazard regression models.

A total of 121,951 patients with TB and 487,800 non-TB controls were enrolled in this study. The TB cohort had a 1.38-fold risk of PD compared with the non-TB cohort after adjustment for age, sex, and comorbidities (aHR, 95% CI: 1.30–1.46). The adjusted risk of PD in the TB and non-TB cohorts increased in subgroups regardless of age, sex, and comorbidities. Combined effect of TB and comorbidities on the risk of PD was significant in patients with TB who had diabetes (aHR: 2.26, 95% CI: 2.02–2.52), hypertension (aHR: 2.23, 95% CI: 2.04–2.44), head injury (aHR: 2.32, 95% CI: 1.95–2.77), chronic kidney disease (aHR: 2.02, 95% CI: 1.49–2.72), chronic obstructive pulmonary disease (aHR: 1.84, 95% CI: 1.66–2.05), depression (aHR: 4.66, 95% CI: 3.59–6.05), dementia (aHR: 3.70, 95% CI: 2.99–4.59), and stroke (aHR: 2.56, 95% CI: 2.28–2.87). The risk of PD was higher in a follow-up within 1 year (aHR: 1.78, 95% CI: 1.58–2.00) and decreased with the follow-up period in the TB cohort.

Patients with TB have an independently 1.38-fold risk of PD. The risk of PD decreased with the follow-up period in the TB cohort. Physicians should be aware of the risk of PD in patients with TB when treating such patients.

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INTRODUCTION

Tuberculosis (TB), a chronic infection caused by Mycobacterium tuberculosis, remains one of the most crucial public health issues worldwide. The World Health Organization Global Tuberculosis Report estimated that approximately 9.0 million people developed TB in 2013. TB is characterized by intracellular survival strategies of tubercle bacilli that result in chronic pulmonary inflammation and release of proinflammatory cytokines. In addition to pulmonary consequences such as bronchiectasis, pleural fibrosis, and chronic obstructive pulmonary disease (COPD), TB is also associated with non-pulmonary diseases including malignancy, ischemic stroke, acute coronary syndrome, chronic kidney disease (CKD), and depression.

Parkinson disease (PD) is a progressively neurodegenerative disorder characterized by both motor and nonmotor manifestations such as bradykinesia, resting tremor, rigidity, postural instability, autonomic dysfunction, neuropsychiatric symptoms, and sensory and sleep difficulties. The prevalence of PD increases from 2% in the general population to 5% in adults over 60 years of age, with a higher prevalence in people over 80 years of age. Epidemiologic studies have shown that diabetes, hypertension, head injury, CKD, COPD, depression, dementia, and stroke are associated with the PD.
Infectious diseases may contribute to PD development.²⁵–³² Acute parkinsonian has been reported in subjects infected with influenza virus.²⁶,²⁷ A case-control study has disclosed that PD is significantly related to several infections including mumps, scarlet fever, influenza, whooping cough, and herpes simplex.²⁸ Another nationwide population study has shown an association between central nervous system (CNS) infections and a higher future risk of PD.²⁹ Recently, a positive epidemiological association between hepatitis C virus infection and PD has been found.³⁰ Moreover, some studies have also demonstrated that *Helicobacter pylori*, a pathogen on the luminal surface of the gastric epithelium, correlates with high PD severity.³¹,³²

A large TB treatment trial conducted in the United States and Canada has shown a low mortality rate directly caused by TB³³. Because TB is representative of chronic infection,² we consider that systemic manifestations other than mortality, such as neurodegenerative diseases, should be a concern. Taiwan remains a TB-endemic area. In 2008, the TB incidence was 62 per 100,000 population, but the TB mortality was only 3.3 per 100,000 population.³⁴ Few studies have examined the association between TB and PD. Therefore, we conducted a nationwide, population-based cohort study to investigate whether TB increases the risk of PD.

**METHODS**

**Data Source**

Thirteen insurance programs were reorganized into the nationwide, single-payer Taiwan National Health Insurance (NHI) program in 1995, and the NHI program covered 99% of 23 million Taiwan residents in 2000. After the Taiwan NHI program was established, claims data were collected and compiled in a large, computerized database, the National Health Insurance Research Database (NHIRD). The claims data include registry for beneficiaries, registry for catastrophic illness, and registry for contracted medical facilities and are updated every year. The NHIRD is maintained and made accessible for scientific research purposes by the National Health Research Institutes, Taiwan. We used all inpatient files from 1 subset of the NHIRD to sample the study population. These specific subject datasets are including all the inpatient files of Taiwan residents from 1996 to 2011 (source: http://nhird.nhri.org.tw/en/Data_Subsets.html). The diseases in inpatient files are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

To ensure patient privacy, the original identification numbers are removed from NHIRD data before release for research purposes. This study was approved by the Ethics Review Board of China Medical University (CMUH104-REC2-115).

**Study Population**

This population-based retrospective cohort study investigated the association between the risk of PD (ICD-9-CM: 332) and TB (ICD-9-CM: 011). Figure 1 shows a flowchart of patient selection. There are 200,552 patients with TB diagnosis in this database from 1996 to 2011. The TB cohort comprised patients newly diagnosed with TB (n = 121,222) from 2000 to 2009, and then excluded TB patients with PD diagnosis date before the date of TB diagnosis (n = 3271) and missing information on sex.

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**FIGURE 1.** Flowchart presenting study subjects selection.
or age (n = 0). There are 121,951 TB patients enrolled in the TB cohort. The index date was defined as the date of TB diagnosis. For each TB case, we randomly selected 4 persons without medical claims for TB care, frequency matching with age (every 5-year span), and sex of individuals in the non-TB cohort in the same period. The index year of entry for a subject eligible for this study was the same year on which the individual was identified and included in the study cohort from the claims data. The exclusion criteria of non-TB cohort were the same as TB cohort. After the frequency matching method, the number of non-TB cohort is 487,800. Patients were followed up from the index date to PD diagnosis, withdrawal from the NHI program, or December 31, 2011.

We also considered confounding factors other than demographic factors; that is, the history of coexisting conditions such as diabetes (ICD-9-CM: 250), hypertension (ICD-9-CM: 401–405), head injury (ICD-9-CM: 310.2, 800, 801, 803, 804, 850, 851, 853, and 854), CKD (ICD-9-CM: 585), COPD (ICD-9-CM: 490–492, 494, and 496), depression (ICD-9-CM: 296.2, 296.3, 296.82, 300.4, and 311), dementia (ICD-9-CM: 290, 294.1, and 331.0), and stroke (ICD-9-CM: 430–438). Conditions diagnosed before the index date were considered as diabetes (ICD-9-CM: 250), hypertension (ICD-9-CM: 401–405), head injury (ICD-9-CM: 310.2, 800, 801, 803, 804, 850, 851, 853, and 854), CKD (ICD-9-CM: 585), COPD (ICD-9-CM: 490–492, 494, and 496), depression (ICD-9-CM: 296.2, 296.3, 296.82, 300.4, and 311), dementia (ICD-9-CM: 290, 294.1, and 331.0), and stroke (ICD-9-CM: 430–438). Conditions diagnosed before the index date were considered comorbidities.

Statistical Analyses

The SAS 9.4 software (SAS Institute, Cary, NC) was used for all data management and statistical analyses. The Student t test was used to analyze the difference in the continuous variable of age between both cohorts, and the results are presented as the mean and standard deviation (SD). The \( \chi^2 \) test was used to analyze the difference in categorical variables, including sex, age group, and comorbidity history, between the TB and non-TB cohorts. The cumulative incidences of PD were calculated for the study cohorts by using the following formula: dividing the number of PD events by the sum of follow-up years (per 1000 person-yr). The cumulative incidence curves of PD were created using the Kaplan–Meier method and tested for differences by using the log rank test. Poisson regression analysis was used to estimate the incidence rate ratio (IRR) of PD in the TB and non-TB cohorts.

To control the confounding risk factors, the adjusted hazard ratios (aHRs) and 95% confidence intervals (95% CIs) were estimated using multivariable Cox proportional hazard models when the crude hazard ratios (crude HRs) of PD was achieved the statistically significant effect in particularly risk factor. \( P \) values <0.05 indicated significance for 2-sided tests.

RESULTS

Table 1 shows a comparison of demographics and comorbidities between the TB and non-TB cohorts. The cohorts had a similar mean age (63 y; SD, 19.4) and similar sex ratios (men, 71.9%) after frequency matching. The TB cohort had a higher prevalence of comorbidities than the non-TB cohort did.

Table 2 shows the risk of PD in each different risk factor. These risk factors were selected for adjustment because they presented the statistically significant effect in PD, including sex, age groups (age <65-year old; age ≥65-year old), TB, diabetes, hypertension, head injury, CKD, COPD, depression, dementia, and stroke (crude HR \( P \) value <0.001). After adjusted by multivariable Cox proportional hazard models, the aHR of PD was higher 1.25-fold in women than in men. The risk of PD got increased with age (aHR = 11.1, 95% CI: 10.2–12.1 for ≥65-year old). The risk of PD was great than subject without particularly comorbidity, for example: diabetes patient had 1.15-fold risk of PD than non-diabetes patient (95% CI: 1.08-1.23). By the end of the follow-up period, the cumulative incidence of PD was higher in the TB cohort than in the non-TB cohort (log rank test \( P \) value <0.0001, Figure 2).

### Table 1. Comparison of Demographics and Comorbidity Between TB and Non-TB

|                | No (N = 487,800) | Yes (N = 121,951) |        |
|----------------|------------------|-------------------|--------|
|                 | n                | %                 | n      | %     |        |
| Sex            |                  |                   |        |       |        |
| Women          | 137,272          | 28.1              | 34,318 | 28.1  | 0.99   |
| Men            | 350,528          | 71.9              | 87,633 | 71.9  |        |
| Age, y         |                  |                   |        |       | 0.99   |
| <65            | 207,896          | 42.6              | 51,974 | 42.6  |        |
| ≥65            | 279,904          | 57.4              | 69,977 | 57.4  |        |
| Mean (SD)*     | 63.6 (19.4)      |                   | 63.7 (19.4) | 0.02 |
| Comorbidity    |                  |                   |        |       |        |
| Diabetes       | 39,545           | 8.11              | 22,044 | 18.1  | <0.0001|
| Hypertension   | 81,672           | 16.7              | 31,643 | 25.9  | <0.0001|
| Head injury    | 17,776           | 3.64              | 8507   | 6.98  | <0.0001|
| CKD            | 5573             | 1.14              | 4311   | 3.54  | <0.0001|
| COPD           | 29,100           | 5.97              | 23,699 | 19.4  | <0.0001|
| Depression     | 3129             | 0.64              | 1964   | 1.61  | <0.0001|
| Dementia       | 4532             | 0.93              | 3162   | 2.59  | <0.0001|
| Stroke         | 38,226           | 7.84              | 17,435 | 14.3  | <0.0001|

CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, SD = standard deviation.

\( \chi^2 \) test.

Student t test.
Table 3 illustrates that the incidence rate of PD was higher in the TB cohort (2.83 per 1000 person-yr) than in the non-TB cohort (2.38 per 1000 person-yr), and the IRR of PD was 1.19-fold (95% CI: 1.17–1.22) higher in the TB cohort than in the non-TB cohort. After adjustment for age, sex, and all comorbidities, patients with TB had a 1.38-fold increased risk of PD compared with the people without TB (aHR: 1.38, 95% CI: 1.30–1.46). Sex-stratified analysis showed that the risk of PD was higher in men with TB than in men without TB (aHR: 1.34, 95% CI: 1.25–1.44) and higher in women with TB than in women without TB (aHR: 1.48, 95% CI: 1.31–1.66). The age-specific incidence of PD increased with age in both cohorts, with the highest incidence in patients with TB aged older than 65 years (5.76 per 1000 person-yr). Age-stratified analysis showed a higher risk of PD in patients with TB than in people without TB for ages <65 years (aHR: 1.69, 95% CI: 1.40–2.03) and ≥65 years (aHR: 1.22, 95% CI: 1.14–1.30). Compared with patients in the non-TB cohort without comorbidity, the risk of PD was higher in those in the TB cohort without comorbidity (aHR: 1.33, 95% CI: 1.21–1.47). Patients in the TB cohort with comorbidity had a 1.32-fold higher risk of PD (95% CI: 1.22–1.42) compared with those in the non-TB cohort with comorbidity.

Table 4 shows the combined effect of TB and comorbidities on the risk of PD in relation to a reference group without TB and comorbidities. Most comorbidities without TB diagnosis were presented higher risk of PD such as diabetes (aHR: 1.47, 95% CI: 1.37–1.58), hypertension (aHR: 1.55, 95% CI: 1.47–1.63), CKD (aHR: 1.76, 95% CI: 1.48–2.10), depression (aHR: 2.89, 95% CI: 2.43–3.45), dementia (aHR: 2.78, 95% CI: 2.41–3.20), and stroke (aHR: 1.84, 95% CI: 1.72–1.96). We observed the greatest risk of PD occurrence than reference group in TB with coexistent comorbidity such as TB with diabetes (aHR: 2.26, 95% CI: 2.02–2.52), hypertension (aHR: 2.23, 95% CI: 2.04–2.44), head injury (aHR: 2.32, 95% CI: 1.95–2.77), CKD (aHR: 2.02, 95% CI: 1.49–2.72), COPD (aHR: 1.84, 95% CI: 1.66–2.05), depression (aHR: 4.66, 95% CI: 3.59–6.05), dementia (aHR: 3.70, 95% CI: 2.99–4.59), and stroke (aHR: 2.56, 95% CI: 2.28–2.87), respectively.

### TABLE 2. Adjusted Hazard Ratio of Parkinson Disease in Different Risk Factors

| Variables            | Event | Crude HR (95% CI) | aHR (95% CI) |
|----------------------|-------|------------------|--------------|
| **Tuberculosis (TB)**|       |                  |              |
| No                   | 6961  | 1.00             | 1.00         |
| Yes                  | 1396  | 1.19 (1.13–1.26) | 1.27 (1.20–1.35) |
| **Sex**              |       |                  |              |
| Women                | 1931  | 1.00             | 1.00         |
| Men                  | 6426  | 1.36 (1.29–1.43) | 1.25 (1.19–1.31) |
| **Age groups, y**    |       |                  |              |
| <65                  | 610   | 1.00             | 1.00         |
| ≥65                  | 7747  | 12.8 (11.7–13.9) | 11.1 (10.2–12.1) |
| **Comorbidity, types**|      |                  |              |
| Diabetes             |       |                  |              |
| No                   | 7179  | 1.00             | 1.00         |
| Yes                  | 1178  | 2.16 (2.03–2.30) | 1.15 (1.08–1.23) |
| Hypertension         |       |                  |              |
| No                   | 5810  | 1.00             | 1.00         |
| Yes                  | 2547  | 2.91 (2.77–3.05) | 1.34 (1.27–1.42) |
| Head injury          |       |                  |              |
| No                   | 7916  | 1.00             | 1.00         |
| Yes                  | 441   | 1.52 (1.38–1.67) | 1.15 (1.04–1.27) |
| CKD                  |       |                  |              |
| No                   | 8188  | 1.00             | 1.00         |
| Yes                  | 169   | 2.53 (2.17–2.95) | 1.31 (1.12–1.53) |
| COPD                 |       |                  |              |
| No                   | 7315  | 1.00             | 1.00         |
| Yes                  | 1042  | 2.58 (2.41–2.75) | 1.14 (1.06–1.22) |
| Depression           |       |                  |              |
| No                   | 8173  | 1.00             | 1.00         |
| Yes                  | 184   | 4.02 (3.47–4.65) | 2.02 (1.73–2.35) |
| Dementia             |       |                  |              |
| No                   | 8069  | 1.00             | 1.00         |
| Yes                  | 288   | 6.71 (5.96–7.55) | 2.42 (2.13–2.74) |
| Stroke               |       |                  |              |
| No                   | 6944  | 1.00             | 1.00         |
| Yes                  | 1413  | 3.31 (3.13–3.51) | 1.49 (1.39–1.59) |

aHR = adjusted hazard ratio.

* Multiple analysis including age groups (age <65-year old, age ≥65-year old), sex, and comorbidities.

† P < 0.001.
Table 5 presents the risk of PD in patients with TB stratified by the follow-up period. The aHR was calculated according to the follow-up period from the index date to the date of PD diagnosis. We observed that the aHR was 1.78-fold (95% CI: 1.58–2.00) higher in the TB cohort than in the non-TB cohort for a follow-up period within 1 year. Compared with the non-TB cohort, the aHR of PD was 1.35 (95% CI: 1.24–1.47) in the TB cohort for a follow-up duration of 1 to 5 years. The aHR of PD decreased with the follow-up period in the TB cohort.

**DISCUSSION**

This is the first nationwide, population-based cohort study to investigate the association between TB and PD. After adjustment for sex, age, and comorbidities, a Cox proportional hazard model showed that patients with TB had a 1.38-fold higher risk of PD compared with the general population.

We observed that patients with TB had a significantly higher PD incidence than did those without TB, regardless of sex, age, and comorbidities (Table 3). These findings strengthened the observation that TB influences PD independently. The role of infection in PD is associated with loss of dopaminergic neurons in the substantia nigra pars compacta and the widespread presence of α-synuclein aggregates. Viruses, the influenza virus in particular, can enter the substantia nigra and cause cell death directly. In addition, viral infections may initiate a cytokine “storm” in the brain, with sequelae including the activation of microglia and apoptosis of neurons. The brain is protected by the blood–brain barrier; therefore, CNS infections are more likely to have neurological consequences than peripheral infections. However, increasing evidence indicates that neuroinflammation may be caused by non-CNS infections. The association between *H. pylori* and PD highlights that gastrointestinal tract represents a vulnerable area through which pathogens can induce CNS neuroinflammation. TB, a common chronic infection of the lung known to induce proinflammatory responses, may also play a key role in the pathogenesis of PD.

In addition to neuroinflammation, there may be other mechanisms that explain this observation. The parkin protein, an ubiquitin ligase in the innate defense mechanism, plays a key role in ubiquitin-mediated autophagy against invading *M. tuberculosis*. PARK2 mutations in humans are well-known risk factors for PD, and some polymorphisms in the regulatory region of PARK2 result in reduced expression of the parkin protein. Therefore, mutations in PARK2, which imply an impaired innate defense mechanism against *M. tuberculosis*, may lead to increased susceptibility to PD.

We observed that the risk of PD decreased with the follow-up period in the TB cohort (Table 5). A similar correlation has never been found between infections and PD in previous studies. Two possible explanations are proposed for this observation. First, the national guidelines for TB diagnosis and treatment may influence the risk of PD. Second, the inflammatory response induced by TB may suppress immune response against PD pathogen.
treatment have been developed by the Taiwan Centers for Disease Control (CDC) in the past decade.42 Taiwan has also implemented the World Health Organization recommended strategy of the Directly Observed Treatment, Short Course program.42 Under these policies, the treatment success rate among new smear-positive cases reported in 2009 after 12 months of follow-up was 87%.34 The reduction in the risk of PD with the follow-up period in our study may indicate that the successful treatment of TB not only cures TB but also subsequently reduces the risk of PD.

Second, first-line medications for TB include rifampicin, isoniazid, pyrazinamide, and ethambutol.43 Among these medications, rifampicin has a cytoprotective role under a variety of experimental, non-TB conditions.44 It suppresses the formation of α-synuclein aggregates, alleviates mitochondrial oxidative stress, and reduces microglial activation, thereby improving neuron survival under inflammatory conditions.44 Although additional research is required, rifampicin may be used not only to treat M. tuberculosis but also to prevent development of PD for subjects with active TB.

This study has several limitations. First, the NHIRD lacks information on patient behaviors and crucial PD risk factors, such as smoking, obesity or BMI, alcoholism, exercise, occupation, and dietary habits. Second, several relevant clinical variables, such as laboratory data, imaging results, and culture reports, were unavailable in our study; therefore, we could not

| Variable            | Diabetes | No | No | 448,255 | 6106 | 1.00 | 0.3833 |
|---------------------|----------|----|----|---------|------|------|-------|
| Tuberculosis (TB)   | No       | No | No | 39,545  | 855  | 1.47 (1.37–1.58) |       |
|                     | Yes      | No | Yes| 99,907  | 1073 | 1.44 (1.35–1.54) |       |
|                     | Yes      | Yes| Yes| 22,044  | 323  | 2.26 (2.02–2.52) |       |
| Hypertension        | No       | No | No | 406,128 | 4937 | 1.00 | 0.8072 |
|                     | Yes      | Yes| Yes| 81,672  | 2024 | 1.55 (1.47–1.63) |       |
|                     | Yes      | No | No | 90,308  | 873  | 1.46 (1.36–1.57) |       |
|                     | Yes      | Yes| Yes| 31,643  | 523  | 2.23 (2.04–2.44) |       |
| Head injury         | No       | No | No | 470,024 | 6646 | 1.00 | 0.0357 |
|                     | Yes      | No | Yes| 17,776  | 315  | 1.25 (1.12–1.40) |       |
|                     | Yes      | No | No | 113,444 | 1270 | 1.47 (1.39–1.57) |       |
|                     | Yes      | Yes| Yes| 8507    | 126  | 2.32 (1.95–2.77) |       |
| CKD                 | No       | No | No | 482,227 | 6835 | 1.00 | 0.1208 |
|                     | Yes      | No | Yes| 5573    | 126  | 1.76 (1.48–2.10) |       |
|                     | Yes      | Yes| Yes| 117,640 | 1353 | 1.51 (1.43–1.60) |       |
|                     | Yes      | Yes| Yes| 4311    | 43   | 2.02 (1.49–2.72) |       |
| COPD                | No       | No | No | 458,700 | 6297 | 1.00 | 0.6092 |
|                     | Yes      | No | Yes| 29,100  | 664  | 1.23 (1.13–1.33) |       |
|                     | Yes      | No | No | 98,252  | 1018 | 1.45 (1.35–1.55) |       |
|                     | Yes      | Yes| Yes| 23,699  | 378  | 1.84 (1.66–2.05) |       |
| Depression          | No       | No | No | 484,671 | 6834 | 1.00 | 0.6199 |
|                     | Yes      | No | Yes| 3129    | 127  | 2.89 (2.43–3.45) |       |
|                     | Yes      | No | No | 119,987 | 1339 | 1.49 (1.40–1.58) |       |
|                     | Yes      | Yes| Yes| 1964    | 57   | 4.66 (3.59–6.05) |       |
| Dementia            | No       | No | No | 483,268 | 6758 | 1.00 | 0.4253 |
|                     | Yes      | No | Yes| 4532    | 203  | 2.78 (2.41–3.20) |       |
|                     | Yes      | No | No | 118,789 | 1311 | 1.48 (1.40–1.57) |       |
|                     | Yes      | Yes| Yes| 3162    | 85   | 3.70 (2.99–4.59) |       |
| Stroke              | No       | No | No | 449,574 | 5857 | 1.00 | 0.4379 |
|                     | Yes      | No | Yes| 38226   | 1104 | 1.84 (1.72–1.96) |       |
|                     | Yes      | No | No | 104,516 | 1087 | 1.47 (1.38–1.57) |       |
|                     | Yes      | Yes| Yes| 17,435  | 309  | 2.56 (2.28–2.87) |       |

aHR = adjusted hazard ratio.

* Model adjusted for age and sex.

† P value for interaction.

† P < 0.001.
assess the severity of TB and chronic inflammation in patients. Third, the diagnosis of PD was based on clinical presentation, because neuroimaging findings are not available in the NHIRD. Finally, the evidence obtained from a retrospective cohort study generally has lower statistical quality than that obtained from randomized trials, because of potential biases related to adjustment for confounding variables. Bias resulting from unknown confounders might have affected the results despite our meticulous study design and control for confounding factors.

In conclusion, this study demonstrated that patients with TB exhibited a 1.38-fold higher risk of PD compared with the general population by using a nationwide, population-based database containing a high number of TB cases. The risk of PD decreased with the follow-up period in the TB cohort. Physicians should be aware of the risk of PD in patients with TB and should provide adequate treatment to such patients to prevent PD development.

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