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Pneumoconiosis Increases the Risk of Peripheral Arterial Disease

A Nationwide Population-Based Study

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Abstract: This nationwide population-based retrospective cohort study was used to evaluate the association between pneumoconiosis and peripheral arterial disease (PAD).

We identified 3374 patients with pneumoconiosis from the catastrophic illness registry who were newly diagnosed from 2000 to 2005; 13,496 patients without pneumoconiosis from Longitudinal Health Insurance Database 2000 (LHID2000) were randomly frequency matched according to sex, age, and index year and used as a nonpneumoconiosis group. Multivariate Cox proportional hazards regression was used to calculate adjusted hazard ratios (HRs) of PAD in the pneumoconiosis group compared with the nonpneumoconiosis group.

The mean follow-up years were 7.44 years in the pneumoconiosis group and 8.17 years in the nonpneumoconiosis group. The incidence density rate of PAD was 1.25 times greater in the pneumoconiosis group than in the nonpneumoconiosis group (8.37 vs 6.70 per 1000 person-years). After adjusting for sex, age, and comorbidities, the adjusted HRs of PAD for the pneumoconiosis group were 1.30 (95% CI = 1.08–1.57), compared with the nonpneumoconiosis group. The combined impacts of patients with pneumoconiosis and diabetes, hyperlipidemia, hypertension, ischemic heart disease, chronic obstructive pulmonary disease, and asthma showed a significant by joint association with PAD risk compared with patients with no pneumoconiosis and no counterpart comorbidity.

Patients with pneumoconiosis have an independently higher risk of developing PAD. Physicians should include pneumoconiosis in evaluating PAD risk.

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Abbreviations: CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, LHID2000 = Longitudinal Health Insurance Database 2000, NHIRD = National Health Insurance Research Database, PAD = peripheral arterial disease.

INTRODUCTION

Pneumoconiosis is a group of occupational lung diseases associated with the inhalation of mineral dusts and reaction of lung tissue to them, which eventually induce irreversible lung damage.[1] The Global Burden of Disease Study disclosed that approximately 125,000 deaths per year resulted from pneumoconiosis as of 2010.[2] In the United States, pneumoconiosis resulted in 1000 to 2000 hospitalizations per year and accounted for 525 deaths in 2007.[3] The principal cause of pneumoconiosis is workplace exposure, mostly exposure to inorganic mineral particles such as coal dust, crystalline silica, and asbestos. Pathologic features of pneumoconiosis include focal collections of dust and reticulin around the small airways, fibrotic lesions exhibiting irregularly arranged collagen, and lesions of massive fibrosis.[4,5] An inflammatory cascade including direct oxidant effects, alveolar macrophages activation, and then alveolar epithelial cell damage is triggered through exposure.[4,6] Several cytokines, such as tumor necrosis factor-α, interleukin-1, platelet-derived growth factor, transforming growth factor-β, and interleukin-6, play crucial roles in recruiting inflammatory cells into the alveoli and producing this chronic inflammation.[6,7]

Peripheral arterial disease (PAD), which is caused by atherosclerosis and thromboembolic pathophysiologic processes that alter the arteries of the lower extremity, affects about 27 million individuals in Europe and North America.[8,9] The worldwide prevalence of PAD ranges from 2.35% to 12%.[8–14] PAD is underdiagnosed and undertreated but causes a considerable burden to health care systems.[15,16] The common risk factors associated with developing PAD are increased age,

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female sex, smoking, diabetes, and hyperlipidemia.[14,17–20] Diseases such as hypertension, ischemic heart disease (IHD), heart failure, stroke, chronic kidney disease (CKD), and chronic obstructive pulmonary disease (COPD) have been well established as playing major roles in the pathogenesis of PAD or its clinical manifestations.[20–26]

Multiple, independent pathways of evidence have pinpointed inflammation as a main regulatory process for atherosclerosis in various arterial beds, including that in PAD.[27,28] Pneumoconiosis commonly represents chronic inflammation, but previous studies on the association between pneumoconiosis and PAD have been few. We conducted a nationwide population-based cohort study to investigate whether pneumoconiosis increases the risk of PAD.

METHODS

Data Source

Taiwan's National Health Insurance (NHI) program was implemented in 1995 and offers comprehensive medical coverage to all residents of Taiwan. The National Health Research Institute of the Ministry of Health and Welfare maintains and releases the National Health Insurance Research Database (NHIRD) for use in health service studies. Comprehensive information on insured NHI participants is included in the database, including patients' sex and date of birth, all records of clinical visits and hospitalizations, prescribed drugs and dosages, and diagnosed diseases. The diagnostic codes used are based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The NHIRD covers a highly representative sample of Taiwan's general population because the reimbursement policy is universal and operated by a single buyer, the government in Taiwan. All insurance claims should be scrutinized by medical reimbursement specialists and peer review.

In this study, we used data sets of the Registry for LHID2000 and Catastrophic Illness Patient Database. Every individual in Taiwan has a unique personal identification number. The anonymity of those insured is retained by cryptographically scrambling their personal data. All NHI data sets can be interlinked with the personal identification number of each individual. This study was approved by the Institutional Review Board of China Medical University in Central Taiwan (CMU-REC-101-012).

Population

We conducted a nationwide population-based cohort that included 2 groups. The case group was defined as newly diagnosed patients with pneumoconiosis (ICD-9-CM codes 500, 501, 502, 503, and 505) with a certificate of catastrophic illness between 2000 and 2005. In Taiwan, pneumoconiosis is one of 30 major categories of conditions recognized as catastrophic illnesses and covered under the NHI program. The application date of the catastrophic illness certificate was used as the index date. Patients with PAD before the index date and those with incomplete information (ie, age or sex) were excluded from this study. For each patient with pneumoconiosis, 4 study participants were randomly selected from the LHID2000 without a history of pneumoconiosis or PAD and frequency matched using a sex, 5-year age interval, and the year of the index date.

The demographic factors in this study included sex and age (in groups aged 20–64 and $\geq$ 65 years). We considered diabetes (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), hypertension (ICD-9-CM codes 401–405), IHD (ICD-9-CM codes 410–414), heart failure (ICD-9-CM code 428), stroke (ICD-9-CM codes 430–438), COPD (ICD-9-CM codes 490, 491, 495, and 496), and CKD (ICD-9-CM code 585) as comorbidities that could potentially confound the association between pneumoconiosis and PAD. Smoking is a risk factor for PAD, and smokers have an increased risk of IHD, stroke, COPD, and asthma. Because history of smoking was not available in the database of Taiwan NHI, adjustment of the data with smoking-related disorders such as stroke, IHD, COPD, and asthma (ICD-9-CM code 493) contributes to minimize confounding from the effect of smoking.[29]

PAD was diagnosed and coded (ICD-9-CM codes 440.0, 440.2, 440.3, 440.8, 440.9, 443, 444.0, 444.22, 444.8, 447.8, and 447.9) by the specialists according to the standard diagnosed criteria including typical symptoms/signs, laboratory data, and imaging findings. Occurrences of PAD were determined from NHIRD ambulatory and inpatient care records. All patients were observed from the index date to the PAD diagnosis date, withdrawal from the NHI program, or the end of 2011.

Statistical Analysis

Summary statistics are expressed as frequencies and percentages for categorical data and means $\pm$ standard deviations (SD) for continuous variables, as appropriate. Pearson χ^2 tests and Student t tests were used to compare categorical and continuous variables between patients with and without pneumoconiosis, respectively. Follow-up time in person-years was calculated for each person until PAD diagnosis, death, cancellation of follow-up, or completion of follow-up (December 31, 2011). Incidence density rates were calculated by dividing the number of participants newly diagnosed with PAD by the number of person-years for each group by sex, age, and comorbidity. A Kaplan–Meier analysis was used to calculate the cumulative incidence rates of PAD in the groups of participants with and without pneumoconiosis, and a log-rank test was employed to analyze differences between the survival curves. We performed a Cox proportional hazards analysis stratified by sex, age group, and comorbidity to examine the effect of pneumoconiosis when manually adjusting for sex, age, and comorbidity. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to quantify the risk of PAD. SAS Version 9.3 software (SAS Institute, Cary, NC) was used for data analyses; 2-sided tests were performed, and $P < .05$ was considered statistically significant.

RESULTS

We identified 3374 patients with pneumoconiosis from 2000 to 2005 and assigned them to the pneumoconiosis group and frequency matched 13496 participants without pneumoconiosis by sex and age and assigned them to the nonpneumoconiosis group. The distribution of sex and age were similar in both groups. Patients with pneumoconiosis had a lower prevalence of diabetes and a higher prevalence of IHD, heart failure, asthma, and COPD than those of patients without pneumoconiosis (Table 1). The mean follow-up years were 7.44 (SD = 3.59 years) in the pneumoconiosis group and 8.17 (SD = 3.16 years) in the nonpneumoconiosis group.

Patients with pneumoconiosis had a higher risk of PAD than those of patients without pneumoconiosis (adjusted HR = 1.30, 95% CI = 1.08–1.57) in the multivariate Cox model (Table 2). Furthermore, each 1-year increment in age had an

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TABLE 1. Baseline Demographic Factors and Comorbidity of Study Participants According to Pneumoconiosis Status

Variables	Nonpneumoconiosis N = 13496 n	%	Pneumoconiosis N = 3374 n	%	*P* Value
Sex					0.99
Female	2448	18.14	612	18.174	
Male	11048	81.86	2762	81.86	
Age, y					0.99
20–64	5616	41.61	1404	41.61	
≥ 65	7880	58.39	1970	58.39	
Mean (SD)	66.54	(8.34)	66.88	(7.86)	0.03
Comorbidity					
Diabetes	2197	16.28	460	13.63	<0.001
Hyperlipidemia	2946	21.83	690	20.45	0.09
Hypertension	6541	48.47	1652	48.96	0.62
IHD	3339	24.74	960	28.45	<0.001
Heart failure	514	3.81	231	6.85	<0.001
Stroke	782	5.79	215	6.37	0.22
COPD	732	5.42	2080	61.65	<0.001
Asthma	1009	7.48	1023	30.32	<0.001
CKD	268	1.99	58	1.72	0.35

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

increased risk of PAD (adjusted HR = 1.03, 95% CI = 1.02–1.04). Patients with diabetes, hyperlipidemia, hypertension, or IHD had a significantly higher risk of PAD than did those without these diseases (adjusted HR = 1.38, 95% CI = 1.17–1.62; 1.26, 1.08–1.46; 1.28, 1.11–1.49; and 1.38, 1.19–1.60, respectively).

Figure 1 presents the cumulative-incidence curves of PAD according to pneumoconiosis status. We used the log-rank test to compare the cumulative incidence of PAD in the 2 groups, determining that the cumulative incidence of PAD was significantly higher in patients with pneumoconiosis than in those without pneumoconiosis ($P < .01$).

Table 3 shows the incidence density rates and HRs of PAD according to pneumoconiosis status stratified by demographic factors and comorbidity. Patients with pneumoconiosis had a higher incidence of PAD than did those without pneumoconiosis (8.37 vs 6.70 per 1000 person-years). Sex-specific analysis indicated that the incidence density rates of PAD in females and males with pneumoconiosis were 9.94 and 7.95 per 1000 person-years, respectively; these rates were higher than those in patients without pneumoconiosis (7.74 and 6.42 per 1000 person-years, respectively). In addition, males in the pneumoconiosis group showed a 1.36-fold (adjusted HR = 1.36, 95% CI = 1.09–1.70) higher risk of PAD than those of males in the nonpneumoconiosis group. Compared with patients without pneumoconiosis, patients with pneumoconiosis had a higher adjusted HR of PAD in aged 20 to 64 years (adjusted HR = 1.59, 95% CI = 1.16–2.18). In individuals without comorbidity and in the subgroup without diabetes, hyperlipidemia, hypertension, IHD, heart failure, stroke, or CKD, patients with pneumoconiosis were more likely to have PAD than those without pneumoconiosis (adjusted HR = 1.73, 95% CI = 1.15–2.60; 1.33, 1.07–1.64; 1.34, 1.07–1.67; 1.66, 1.24–2.22; 1.52, 1.21–1.92; 1.32, 1.08–1.60; 1.36, 1.12–1.65; and 1.30, 1.08–1.58, respectively). In individuals with asthma, patients with pneumoconiosis were more likely to have PAD than no pneumoconiosis patients (adjusted HR = 1.67, 95% CI = 1.02–2.71) (Table 3).

TABLE 2. Univariate and Multivariate Analyses for Predicting Peripheral Arterial Disease Risk

Variables	Univariate HR (95% CI)	Multivariate† HR (95% CI)
Pneumoconiosis		
No	1.00	1.00
Yes	1.25 (1.07–1.45)**	1.30 (1.08–1.57)**
Sex		
Female	1.00	1.00
Male	0.82 (0.70–0.95)**	0.91 (0.78–1.06)
Age (each increment year)	1.04 (1.03–1.05)***	1.03 (1.02–1.04)***
Comorbidity		
Diabetes		
No	1.00	1.00
Yes	1.75 (1.50–2.04)***	1.38 (1.17–1.62)***
Hyperlipidemia		
No	1.00	1.00
Yes	1.62 (1.41–1.85)***	1.26 (1.08–1.46)***
Hypertension		
No	1.00	1.00
Yes	1.77 (1.56–2.02)***	1.28 (1.11–1.49)**
IHD		
No	1.00	1.00
Yes	1.87 (1.64–2.13)***	1.38 (1.19–1.60)***
Heart failure		
No	1.00	1.00
Yes	1.70 (1.29–2.24)***	1.08 (0.81–1.44)
Stroke		
No	1.00	1.00
Yes	1.29 (0.98–1.70)	0.93 (0.71–1.24)
COPD		
No	1.00	1.00
Yes	1.18 (0.99–1.41)	0.88 (0.71–1.10)
Asthma		
No	1.00	1.00
Yes	1.32 (1.09–1.59)**	1.08 (0.88–1.33)
CKD		
No	1.00	1.00
Yes	1.91 (1.29–2.82)**	1.37 (0.93–2.04)

CI = confidence interval, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, IHD = ischemic heart disease.

† Multivariable analysis including pneumoconiosis, sex, age, diabetes, hyperlipidemia, hypertension, ischemic heart disease, heart failure, stroke, chronic obstructive pulmonary disease, asthma, and chronic kidney disease.

** $P < 0.01$.

*** $P < 0.001$.

Table 4 shows the combined effect of pneumoconiosis and the comorbidities of diabetes, hyperlipidemia, hypertension, IHD, heart failure, stroke, COPD, asthma, and CKD on the risk of PAD in relation to the referent group of no pneumoconiosis and no comorbidities. We observed a greater magnitude

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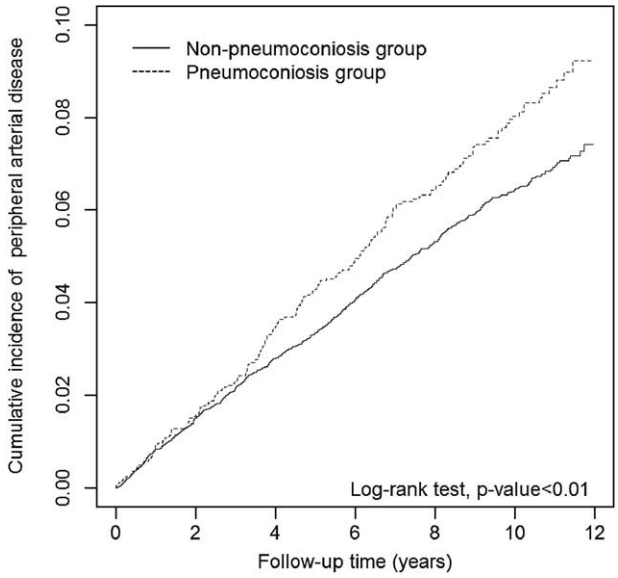

FIGURE 1. Cumulative incidence curves of peripheral arterial disease for pneumoconiosis and no pneumoconiosis groups.

of HRs of PAD for patients with pneumoconiosis and diabetes, hyperlipidemia, hypertension, IHD, COPD, and asthma compared with patients with no pneumoconiosis and no counterpart comorbidity (adjusted HR = 2.00, 95% CI = 1.44–2.78; 1.74, 1.32–2.31; 1.81, 1.45–2.26; 1.67, 1.29–2.15; 1.25, 1.04–1.52; and 1.42, 1.09–1.83, respectively).

DISCUSSION

This is the first nationwide population-based cohort study to investigate the associations between pneumoconiosis and PAD. After adjustments for sex, age, diabetes, hyperlipidemia, hypertension, IHD, heart failure, stroke, COPD, asthma, and CKD, a Cox proportional hazard model showed that patients with pneumoconiosis had a 1.30-fold higher risk of developing PAD compared with those without pneumoconiosis.

Although the patients with pneumoconiosis in this study exhibited a difference in prevalence of comorbidities associated with PAD development (such as diabetes, IHD, heart failure, and COPD) than did the comparison cohort, pneumoconiosis remained an independent factor in multivariate Cox analyses for predicting PAD risk. In addition to pneumoconiosis, our data also indicate that increased age, diabetes, hyperlipidemia, hypertension, and IHD are independent risk factors for PAD, which was compatible with the current consensus regarding risk factors for PAD.[17–26] Comparably, we found that patients with pneumoconiosis had a significantly higher PAD incidence than did those without pneumoconiosis in the subgroup of male sex, younger than 65 years, and no comorbidity (Table 3). These findings were contrary to the current consensus but strengthened the observation that pneumoconiosis influences PAD independently.

Most previous studies on pneumoconiosis have focused on its pulmonary manifestations such as interstitial lung disease, pulmonary fibrosis, and COPD.[5] Vascular injury associated with pneumoconiosis has been less frequently described. Lee et al evaluated the coronary artery calcification (which correlated with the degree of atherosclerosis) of 76 patients exposed to inorganic dusts by using multidetector computed tomography, which disclosed that patients with pneumoconiosis had a higher frequency in the calcified group than in the noncalcified group.[30] An inverse relationship was found between restrictive lung disease and atherosclerosis risk in workers exposed to inorganic dust.[31] Additional research is urgent to determine the inflammatory response of pneumoconiosis and its role in the course of atherosclerosis and PAD development.

Thromboembolic processes may also be involved in the development of PAD caused by pneumoconiosis. In an animal model, intratracheally instilled silica particles enhanced pulmonary macrophage-neutrophil cross-talk, released neutrophil elastase into the blood circulation, triggered activation of circulating platelets, and then initiated thrombotic events on damaged peripheral vasculature.[32] Pulmonary inflammation induced by carbon nanotubes translated rapid and transient activation of platelets into P-selectin-mediated systemic inflammation, eliciting in turn prothrombotic risk.[33] Our data indicate that male sex, younger than 65 years, and no comorbidity were associated with higher PAD incidence when comparing the pneumoconiosis and nonpneumoconiosis cohorts. Although older participants may have experienced longer occupational exposure with the accumulated effects of chronic inflammation, young male participants without comorbidity may have experienced greater workloads and more occupational exposures within the follow-up period. We propose the hypothesis that acute or subacute thromboembolic events coexist with the atherosclerosis to develop PAD in patients with pneumoconiosis.

The risk of developing PAD for patients afflicted with pneumoconiosis and diabetes, hyperlipidemia, hypertension, IHD, or COPD was higher than for those without pneumoconiosis and their corresponding comorbidities. However, we observed that only patients with pneumoconiosis who exhibited diabetes, hyperlipidemia, hypertension, or COPD had significantly increased multiplicative risks of PAD. The increased effect on multiplicative risk of PAD in patients with pneumoconiosis who exhibited IHD was equivocal. Otherwise, CKD and stroke, though nonspecific, were found to reduce the effect of increasing risk of PAD for patients with pneumoconiosis (Table 4). IHD, stroke, CKD, and PAD have similar pathophysiological implications for arteries; thus, antiplatelet therapy is universal for daily prevention. A previous study showed that atherosclerotic risk factors were less intensively treated among PAD patients than among IHD patients.[13] Providing adequate care for patients with pneumoconiosis with these comorbidities may be crucial in preventing further development of PAD.

This study had several limitations. First, the NHIRD lacks information on patient behaviors and about certain critical cardiovascular risk factors such as smoking, obesity and BMI, alcoholism, exercise, and dietary habits. Second, we could not assess exposure periods and dust concentrations or the severity of pneumoconiosis (such as the extent of pulmonary fibrosis and decline of ventilator function) of the patients. These data are not contained in the NHIRD; thus, future studies are warranted. Third, it is difficult to do subgroup analyses because there are few cases in some of the following codes (ICD-9-CM codes: 501, 502, 503) (Supplementary Table, http://links.lww.com/MD/A285). Finally, an analysis of PAD prophylaxis patterns, a confounding factor that may have affected the outcome measurements, was infeasible in this study. The evidence derived from a retrospective cohort study is generally lower in statistical quality than that obtained from randomized trials because of potential biases related to adjustments for

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TABLE 3. Incidence Density Rates and Hazard Ratios of Peripheral Arterial Disease According to Pneumoconiosis Status Stratified by Demographic Factors and Comorbidity

	Pneumoconiosis							
	No			Yes			Compared to Nonpneumoconiosis Group	
Variables	Event No.	Person-Years	IR	Event No.	Person-Years	IR	Crude HR (95% CI)	Adjusted† HR (95% CI)
Overall	739	110315.36	6.70	210	25102.78	8.37	1.25 (1.07–1.45)**	1.30 (1.08–1.57)**
Sex								
Female	164	21181.48	7.74	52	5231.07	9.94	1.28 (0.94–1.75)	1.22 (0.85–1.74)
Male	575	89133.89	6.45	158	19871.70	7.95	1.23 (1.03–1.47)*	1.36 (1.09–1.70)**
Age, y								
20–64	246	50430.72	4.88	87	11400.42	7.63	1.57 (1.23–2.00)***	1.59 (1.16–2.18)**
≥ 65	493	59884.65	8.23	123	13702.36	8.98	1.09 (0.89–1.33)	1.13 (0.89–1.44)
Comorbidity‡								
No	166	45615.90	3.64	31	4410.13	7.03	1.89 (1.26–2.84)**	1.73 (1.15–2.60)**
Yes	573	64699.47	8.86	179	20692.65	8.65	0.98 (0.83–1.16)	1.01 (0.86–1.20)
Diabetes								
No	565	94339.50	5.99	172	22078.56	7.79	1.30 (1.10–1.54)**	1.33 (1.07–1.64)**
Yes	174	15975.87	10.89	38	3024.22	12.57	1.15 (0.81–1.63)	1.19 (0.78–1.82)
Hyperlipidemia								
No	502	86531.97	5.80	156	19824.70	7.87	1.36 (1.13–1.62)***	1.34 (1.07–1.67)*
Yes	237	23783.39	9.96	54	5278.08	10.23	1.02 (0.76–1.37)	1.20 (0.84–1.72)
Hypertension								
No	274	59554.64	4.60	100	13114.45	7.63	1.66 (1.32–2.09)***	1.66 (1.24–2.22)***
Yes	465	50760.73	9.16	110	11988.33	9.18	0.99 (0.81–1.23)	1.08 (0.84–1.39)
IHD								
No	456	84911.38	5.37	141	18123.38	7.78	1.45 (1.20–1.75)***	1.52 (1.21–1.92)***
Yes	283	25403.98	11.14	69	6979.40	9.89	0.88 (0.68–1.15)	0.96 (0.69–1.33)
Heart failure								
No	701	107099.52	6.55	194	23729.51	8.18	1.25 (1.06–1.46)**	1.32 (1.08–1.60)**
Yes	38	3215.85	11.82	16	1373.26	11.65	0.99 (0.55–1.77)	0.98 (0.45–2.16)
Stroke								
No	694	105598.19	6.57	202	23962.23	8.43	1.28 (1.10–1.50)**	1.36 (1.12–1.65)**
Yes	45	4717.17	9.54	8	1140.55	7.01	0.73 (0.35–1.55)	0.60 (0.24–1.46)
COPD								
No	706	105597.60	6.69	87	10654.31	8.17	1.23 (0.98–1.53)	1.22 (0.98–1.53)
Yes	33	4717.77	6.99	123	14448.47	8.51	1.22 (0.83–1.79)	1.40 (0.94–2.10)
Asthma								
No	678	103158.85	6.57	147	18481.30	7.95	1.21 (1.01–1.45)*	1.23 (0.99–1.51)
Yes	61	7156.51	8.52	63	6621.48	9.51	1.10 (0.78–1.57)	1.67 (1.02–2.71)*
CKD								
No	715	108720.32	6.58	208	24756.98	8.40	1.28 (1.09–1.49)**	1.30 (1.08–1.58)**
Yes	24	1595.04	15.05	2	345.80	5.78	0.38 (0.09–1.61)	0.84 (0.18–3.87)

CI = confidence interval, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, IHD = ischemic heart disease, IR = incidence density rate, per 1000 person-years.

† Mutually adjusted for sex, age, and comorbidity in Cox proportional hazards regression.

‡ Patients with any one of diabetes, hyperlipidemia, hypertension, ischemic heart disease, heart failure, stroke, chronic obstructive pulmonary disease, asthma, and chronic kidney disease were classified as the comorbidity group.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

confounding variables. We have included hypertension, diabetes, and hyperlipidemia to adjust for the influence of BMI and obesity. To minimize the potential confounding effect of smoking, an alternative method to adjust for smoking-related diseases (including IHD, COPD, asthma, and stroke) in analysis was used, which was used in a previous study.[29] However, bias resulting from unknown confounders may have affected the results despite our meticulous study design and control measures for confounding factors.

In conclusion, this study demonstrated that the patients with pneumoconiosis exhibited a 1.30-fold risk of developing PAD compared with the general population by using a nationwide population-based database that contains a relatively high number of pneumoconiosis cases. In addition to the consensus

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TABLE 4. Interaction and Joint Effect Between Pneumoconiosis and Comorbidity in Association With Peripheral Arterial Disease in Study Population

Variables		HR† (95% CI)	p for interaction
Pneumoconiosis	Diabetes		0.63
No	No	1.00	
No	Yes	1.71 (1.44–2.03)***	
Yes	No	1.28 (1.08–1.52)**	
Yes	Yes	2.00 (1.44–2.78)***	
Pneumoconiosis	Hyperlipidemia		0.18
No	No	1.00	
No	Yes	1.68 (1.44–1.96)***	
Yes	No	1.34 (1.12–1.60)**	
Yes	Yes	1.74 (1.32–2.31)***	
Pneumoconiosis	Hypertension		0.01
No	No	1.00	
No	Yes	1.77 (1.52–2.06)***	
Yes	No	1.60 (1.27–2.02)***	
Yes	Yes	1.81 (1.45–2.26)***	
Pneumoconiosis	IHD		0.01
No	No	1.00	
No	Yes	1.84 (1.58–2.14)***	
Yes	No	1.43 (1.18–1.73)***	
Yes	Yes	1.67 (1.29–2.15)***	
Pneumoconiosis	Heart failure		0.60
No	No	1.00	
No	Yes	1.52 (1.09–2.11)*	
Yes	No	1.24 (1.06–1.45)**	
Yes	Yes	1.56 (0.95–2.56)	
Pneumoconiosis	Stroke		0.20
No	No	1.00	
No	Yes	1.27 (0.94–1.72)	
Yes	No	1.27 (1.09–1.48)**	
Yes	Yes	0.95 (0.47–1.90)	
Pneumoconiosis	COPD		0.28
No	No	1.00	
No	Yes	0.89 (0.62–1.26)	
Yes	No	1.20 (0.96–1.50)	
Yes	Yes	1.25 (1.04–1.52)*	
Pneumoconiosis	Asthma		0.58
No	No	1.00	
No	Yes	1.16 (0.89–1.51)	
Yes	No	1.19 (0.99–1.42)	
Yes	Yes	1.42 (1.09–1.83)**	
Pneumoconiosis	CKD		0.12
No	No	1.00	
No	Yes	2.05 (1.36–3.08)***	
Yes	No	1.26 (1.08–1.48)**	
Yes	Yes	0.82 (0.20–3.27)	

CI = confidence interval, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, IHD = ischemic heart disease.

† Model adjusted for sex and age.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

that the development of PAD is mainly associated with atherosclerosis, we propose the hypothesis that a coexistence of thromboembolic events may also aggravate the PAD risk in patients with pneumoconiosis. Physicians should consider the possibility of PAD when following up patients with pneumoconiosis and should include pneumoconiosis in evaluating PAD risk.

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