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Risk of Cerebrovascular Events in Pneumoconiosis Patients

A Population-based Study, 1996–2011

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Abstract: Pneumoconiosis is a parenchymal lung disease that develops through the inhalation of inorganic dust at work. Cerebrovascular and cardiovascular events are leading causes of mortality and adult disability worldwide. This retrospective cohort study investigated the association between pneumoconiosis, and cerebrovascular and cardiovascular events by using a nationwide population-based database in Taiwan.

The data analyzed in this study was retrieved from the Taiwan National Health Insurance Research Database. We selected 6940 patients with pneumoconiosis from the database as our study cohort. Another 27,760 patients without pneumoconiosis were selected and matched with those with pneumoconiosis according to age and sex as the comparison cohort. We used univariate and multivariate Cox proportional-hazard regression analyses to determine the association between pneumoconiosis and the risk of cerebrovascular and cardiovascular events after adjusting for medical comorbidities.

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After adjustment for age, sex, and comorbidities, the patients with pneumoconiosis exhibited a significantly higher incidence of ischemic stroke (hazard ratio [HR] 1.14, 95% confidence interval [CI] 1.05–1.24) than did those without pneumoconiosis. The incidence of hemorrhagic stroke was higher, but not significant, in the pneumoconiosis patients (HR 1.20, 95% CI 0.99–1.46). No statistically significant differences were observed between the pneumoconiosis and nonpneumoconiosis groups in acute coronary syndrome (HR 1.10, 95% CI 0.95–1.26).

The findings of this study reveal an association between pneumoconiosis and a higher risk of cerebrovascular events after adjustment for comorbidities. Healthcare providers should control the related risk factors for primary prevention of stroke in pneumoconiosis patients.

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Abbreviations: CIs = confidence intervals, HRs = hazard ratios, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHIRD = National Health Insurance Research Database, RR = relative risks.

INTRODUCTION

Chronic dust inhalation has been confirmed to increase cardiovascular morbidity and mortality by the American Heart Association.¹ Chronic dust exposure can result in decreased prothrombin time via a proinflammatory cytokine pathway, leading to reduced clotting times, intravascular thrombin formation, and accelerated arterial thrombosis.² Pneumoconiosis is an occupational lung disease primarily caused by exposure to inorganic dust that is retained in the lung parenchyma.³ It is characterized by the development of granulomatous and fibrotic changes in the lungs after the inhalation of inorganic substances such as crystalline silica, asbestos, and coal dust.⁴

Epidemiological studies have validated the increased risk of coronary heart disease associated with exposure to fine particulate matter in air.^{5,6} A study reported that long-term silica dust exposure was associated with an increased risk of death due to respiratory diseases, lung cancer, and cardiovascular disease.⁷ Nevertheless, the risk of cardiovascular diseases has yet to be studied thoroughly in patients with pneumoconiosis.

In addition to pulmonary and cardiovascular problems, the impact of pneumoconiosis is expected to be related with the development of cerebrovascular diseases. Nevertheless, studies on the association between pneumoconiosis and cerebrovascular disease are few and conflicting. One recent study reported that pneumoconiosis patients with chronic obstructive pulmonary disease (COPD) are at a higher risk of ischemic stroke.⁸ Another study reported increased stroke mortality in asbestos workers.⁹ By contrast, 1 study showed significantly lower mortality in pneumoconiosis patients with cerebrovascular disease.¹⁰

We hypothesize that pneumoconiosis is related to an elevated risk of cardiovascular and cerebrovascular diseases

because of the prothrombotic tendency caused by long-term dust exposure.^{9,10} We used representative datasets derived from the National Health Insurance (NHI) program of Taiwan to assess the relationship between cardiovascular and cerebrovascular diseases and pneumoconiosis, and the findings provide valuable information for preventive health care.

METHODS

Data Source

The data used in this study were derived from the Taiwan National Health Insurance Research Database (NHIRD) provided by the Taiwan National Health Research Institutes (NHRI). The NHIRD files contain only deidentified secondary data, the need for informed consent from individual patients was waived. The NHI program was initiated in 1995 and covers over 99% of the 23.74 million residents of Taiwan.¹¹ In the NHI program, beneficiaries with any of the 30 categories of catastrophic illnesses including pneumoconiosis patients can apply for catastrophic illness certificates. The details of the Registry of Catastrophic Illness database were adequately described in previous studies.¹² In addition, we used a subdataset of the NHIRD that comprises records on 1 million randomly sampled beneficiaries enrolled in the NHI program in 2000 (Longitudinal Health Insurance Database 2000 [LHID2000]) and collected all information regarding these beneficiaries from 1996 to 2011. The LHID2000 represents approximately 5% of Taiwan's population. The NHRI has reported no significant differences in age, sex, and healthcare costs between the LHID2000 enrollees and all the other enrollees. This study was exempted by the Institutional Review Board of China Medical University in Central Taiwan (CMUH104-REC2-115).

Sampled Patients

This retrospective cohort study used data extracted from the Registry of Catastrophic Illness database and LHID2000 from 1996 to 2011. Patients who were newly diagnosed with pneumoconiosis (International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-9-CM 500, 501, 502, 503, and 505) between January 1, 2000 and December 31, 2011, from the Registry of Catastrophic Illness database, formed the pneumoconiosis cohort. The date of application of the catastrophic illness certificates in the approved patients with pneumoconiosis was considered the index date. Patients who experienced a cerebrovascular or cardiovascular event (ICD-9-CM 410–414, 430–438) before the index date, those who were younger than 20 years, or those for whom demographical information was incomplete were excluded from the study. For each patient with pneumoconiosis, we randomly selected 4 comparison patients from the LHID2000 to form a nonpneumoconiosis cohort; these patients did not have pneumoconiosis and were frequency-matched with the patient with pneumoconiosis according to the year of the index date, age (per 5 years), and sex. The aforementioned exclusion criteria were applied in selecting the nonpneumoconiosis cohort patients. In total, 6940 patients with pneumoconiosis and 27,760 comparison patients without pneumoconiosis were enrolled in this study.

Outcome Measurement and Comorbidities

The endpoint of the study was the development of a cerebrovascular or cardiovascular event (ICD-9-CM codes 410, 411, 430–438). The cerebrovascular and cardiovascular events were classified into 3 subtypes: ischemic stroke (ICD-9-

CM codes 433–438), hemorrhagic stroke (ICD-9-CM codes 430–432), and acute coronary syndrome (ACS; ICD-9-CM codes 410, 411). All patients were followed up from the index date to the endpoint, until withdrawal from the insurance program, or until December 31, 2011. Moreover, the baseline comorbidities in this study included diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM codes 272), congestive heart failure (ICD-9-CM 428), atrial fibrillation (ICD-9-CM codes 427.31), and COPD (ICD-9-CM 491, 492, 496).

Statistical Analysis

The Pearson chi-square test was used to examine the differences in the distributions of age, sex, and conventional risk factors for cerebrovascular and cardiovascular diseases, namely diabetes, hypertension, hyperlipidemia, congestive heart failure, atrial fibrillation, and COPD, between the pneumoconiosis and nonpneumoconiosis cohorts. The *t* test was used to determine the differences in the continuous variables between the cohorts. Subsequently, we estimated the cumulative incidence of cerebrovascular and cardiovascular events during the follow-up period by using the Kaplan–Meier method, and the differences between the cohorts were examined using the log-rank test. Univariate and multivariate Cox proportional-hazard regression analyses were performed to determine the association between pneumoconiosis and the risk of cerebrovascular and cardiovascular events, which is expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). The risk factors for cerebrovascular and cardiovascular events in the multivariate Cox models were age, sex, and comorbidities, namely diabetes, hypertension, hyperlipidemia, congestive heart failure, COPD, and atrial fibrillation. In addition, we performed a subgroup analysis by stratifying the cohorts according to sex, age, follow-up time, and the presence of comorbidities. The SAS software (Version 9.2 for Windows; SAS Institute Inc., Cary, NC) was used for data analyses. A *P* value of <0.05 was considered statistically significant.

RESULTS

Because the pneumoconiosis and nonpneumoconiosis cohorts were frequency-matched according to age and sex, no significant differences were observed in these 2 variables between the groups (Table 1). In the pneumoconiosis cohort, 80.8% patients were aged >60 years, and 88.2% were men. The mean age of the patients in the pneumoconiosis and the nonpneumoconiosis cohorts was 66.0 (± 7.40) and 65.5 (± 7.93) years, respectively. The pneumoconiosis cohort patients exhibited higher comorbidity rates for diabetes, hyperlipidemia, congestive heart failure, and COPD than did the nonpneumoconiosis cohort patients (all *P* values <0.01). Figure 1 presents the cumulative incidence of cerebrovascular and cardiovascular events in both cohorts, indicating that the incidence curve of the pneumoconiosis cohort was significantly higher than that of the nonpneumoconiosis cohort (log-rank test *P* < 0.001). During the mean follow-up duration of 7.92 years for the pneumoconiosis cohort and 8.57 years for the nonpneumoconiosis cohort, the overall incidence of cerebrovascular and cardiovascular events (per 1000 person-years) was 23.6 and 21.2, yielding an adjusted HR of 1.14 (95% CI 1.07–1.22) (Table 2). After adjustment for age, sex, and comorbidities, patients with pneumoconiosis exhibited a 1.15-fold higher risk of stroke than did those without pneumoconiosis (95% CI 1.07–1.24). In the multivariate Cox models, the HR for ischemic stroke in the

TABLE 1. Characteristics of Patients With Pneumoconiosis and Matched Patients Without Pneumoconiosis

	Pneumoconiosis				P
	Yes (n = 6940)		No (n = 27,760)		
	n	%	n	%	
Age, y					0.99
≤59	1336	(19.3)	5349	(19.3)	
60–69	3690	(53.2)	14755	(53.2)	
≥70	1914	(27.6)	7656	(27.6)	
Mean (SD)*	66.0	(7.40)	65.5	(7.93)	<0.001
Sex					0.99
Female	822	(11.8)	3288	(11.8)	
Male	6118	(88.2)	24472	(88.2)	
Comorbidity					
Diabetes	345	(4.97)	1791	(6.45)	<0.001
Hypertension	2392	(34.5)	9532	(34.3)	0.84
Hyperlipidemia	793	(11.4)	3792	(13.7)	<0.001
Atrial fibrillation	30	(0.43)	94	(0.34)	0.24
Congestive heart failure	122	(1.76)	219	(0.79)	<0.001
COPD	3512	(50.6)	2439	(8.79)	<0.001

Chi-square test.
* *t* test.

pneumoconiosis cohort was 1.14 (95% CI 1.05–1.24). The overall incidence of ACS was not significantly higher in the pneumoconiosis cohort than in the nonpneumoconiosis cohort (5.37 vs 4.79 per 1000 person-years), with the adjusted HR being 1.10 (95% CI 0.95–1.26). The incidence of cerebrovascular and cardiovascular events was higher in men than in women in both cohorts (Table 3). In the sex-specific pneumoconiosis and nonpneumoconiosis cohorts, the relative risk of stroke was significantly higher in men (adjusted HR 1.14, 95% CI 1.06–1.23). Moreover, the risk of cerebrovascular and cardiovascular events increased with age in both cohorts. In the age-specific pneumoconiosis and nonpneumoconiosis cohorts, the adjusted HRs of cerebrovascular and cardiovascular

events were significant for patients aged 60–69 years (adjusted HR 1.18, 95% CI 1.07–1.29).

The adjusted HR for cerebrovascular and cardiovascular events slightly increased with the follow-up duration, and the pneumoconiosis cohort was associated with a higher risk of cerebrovascular and cardiovascular events than the nonpneumoconiosis cohort in a follow-up period >1 years. Table 4 summarizes the results of the univariate and multivariate Cox proportional-hazard regression analyses regarding the association between pneumoconiosis, and cerebrovascular and cardiovascular events. The risk of cerebrovascular and cardiovascular events increased 1.14-fold (95% CI 1.07–1.22) with age (every 1 year) and in male patients (adjusted HR 1.52, 95% CI 1.40–1.66). The risk of cerebrovascular and cardiovascular events was higher in patients with comorbidities such as diabetes (adjusted HR 1.55, 95% CI 1.41–1.70), hypertension (adjusted HR 1.85, 95% CI 1.75–1.94), and atrial fibrillation (adjusted HR 1.71, 95% CI 1.22–2.42). Table 5 illustrates the cumulative effects of pneumoconiosis and diabetes, hypertension, and hyperlipidemia on the risk of cerebrovascular and cardiovascular events. A higher risk of cerebrovascular and cardiovascular events was observed in patients with both pneumoconiosis and diabetes (adjusted HR 2.26, 95% CI 1.83–2.77), both pneumoconiosis and hypertension (adjusted HR 2.16, 95% CI 1.97–2.36), or both pneumoconiosis and atrial fibrillation (adjusted HR 2.02, 95% CI 1.01–4.04) than in those without pneumoconiosis, diabetes, hypertension, and atrial fibrillation.

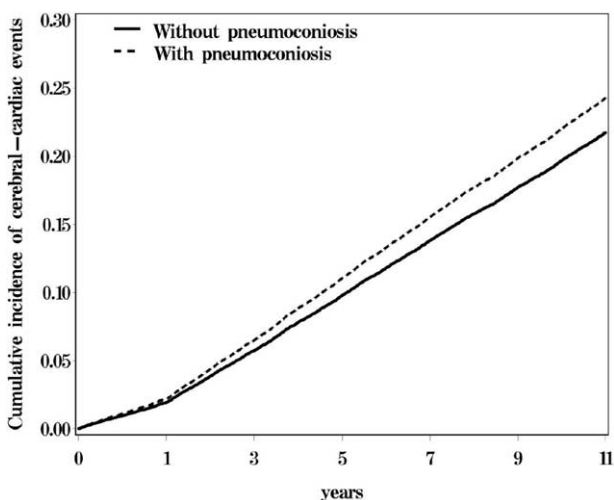


FIGURE 1. Cumulative incidence of cerebrovascular and cardiovascular events in patients with and without pneumoconiosis.

DISCUSSION

The present study demonstrated that pneumoconiosis was associated with an increased risk of cerebrovascular and cardiovascular events compared with that of the control group after adjustment for age, sex, and medical comorbidities. Patients with pneumoconiosis exhibited a significantly higher incidence

TABLE 2. Incidence and Hazard Ratio of Cerebral-cardiac Events Between Patients With Pneumoconiosis and Without Pneumoconiosis

Outcome	Pneumoconiosis						Crude HR [‡] (95% CI)	Adjusted HR [§] (95% CI)
	Yes			No				
	Event	PY	Rate [†]	Event	PY	Rate [†]		
Cerebral-cardiac events	1286	54576	23.6	5016	236602	21.2	1.12 (1.05, 1.19) ^{***}	1.14 (1.07, 1.22) ^{***}
Stroke	1058		19.4	4154		17.6	1.11 (1.04, 1.18) ^{**}	1.15 (1.07, 1.24) ^{***}
Ischemic stroke	906		16.6	3547		15.0	1.11 (1.03, 1.19) ^{**}	1.14 (1.05, 1.24) ^{**}
Hemorrhagic stroke	152		2.79	607		2.57	1.09 (0.91, 1.30)	1.20 (0.99, 1.46)
ACS	293		5.37	1133		4.79	1.12 (0.99, 1.28)	1.10 (0.95, 1.26)

ACS = acute coronary syndrome, CI = confidence interval, HR = hazard ratio, PY = person-years.

[†] Rate, incidence rate per 1000 person-years.

[‡] Crude HR, relative hazard ratio.

[§] Adjusted HR, hazard ratio adjusted for age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, atrial fibrillation, congestive heart failure and COPD.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

of ischemic stroke (HR 1.14, 95% CI 1.07–1.22); moreover, the incidence of hemorrhagic stroke was higher, but not significant (HR 1.20, 95% CI 0.99–1.46). The risk of ACS was not significant in patients with pneumoconiosis. The risk of cerebrovascular and cardiovascular events was significantly increased in patients with concurrent diabetes, hypertension, and atrial fibrillation.

Several epidemiological studies have validated the increased risk of vascular events associated with exposure to

fine particulate matter in air.^{5,6,13} Air particulate matter has been associated with increased risks of coronary heart disease, stroke, arrhythmia, and exacerbation of heart failure in susceptible people.¹ The major mechanisms of inhalation-mediated vascular toxicity include activation of proinflammatory pathways and generation of reactive oxygen species.

Asbestosis is the most common form of pneumoconiotic disease. It is a chronic inflammatory disease caused by the inhalation and retention of asbestos in the lungs, causing

TABLE 3. Incidence and Hazard Ratio of Cerebral-cardiac Events Between Patients With Pneumoconiosis and Without Pneumoconiosis

Outcome	Pneumoconiosis						Crude HR [‡] (95% CI)	Adjusted HR [§] (95% CI)
	Yes			No				
	Event	PY	Rate [#]	Event	PY	Rate [†]		
Sex								
Female	134	7485	17.9	464	29834	15.6	1.15 (0.95, 1.40)	1.11 (0.90, 1.36)
Male	1152	47092	24.5	4552	206768	22.0	1.12 (1.05, 1.19) ^{***}	1.14 (1.06, 1.23) ^{***}
Age, y								
≤59	175	11659	15.0	609	51301	11.9	1.28 (1.08, 1.51) ^{**}	1.14 (0.93, 1.40)
60–69	727	31092	23.4	2682	132297	20.3	1.16 (1.07, 1.26) ^{***}	1.18 (1.07, 1.29) ^{***}
≥70	384	11826	32.5	1725	53004	32.5	1.00 (0.90, 1.12)	1.05 (0.93, 1.18)
Follow-up time, y								
≤1	132	6658	19.8	535	26994	19.8	1.00 (0.83, 1.21)	1.03 (0.84, 1.27)
>1	1154	47918	24.1	4481	209608	21.4	1.13 (1.06, 1.21) ^{***}	1.16 (1.08, 1.24) ^{***}

CI = confidence interval, HR = hazard ratio, PY = person-years.

[†] Rate, incidence rate per 1000 person-years.

[‡] Crude HR, relative hazard ratio.

[§] Adjusted HR, hazard ratio adjusted for age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, atrial fibrillation, congestive heart failure, and COPD.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

TABLE 4. Hazard Ratios of Cerebral-cardiac Events in Association With Age, Sex and Comorbidities in Univariable and Multivariable Cox Regression Models

Variables	Crude [†]		Adjusted [‡]	
	HR	(95% CI)	HR	(95% CI)
Pneumoconiosis	1.12	(1.05, 1.19) ^{***}	1.14	(1.07, 1.22) ^{***}
Age, y	1.05	(1.05, 1.05) ^{***}	1.04	(1.04, 1.05) ^{***}
Sex (female vs male)	1.40	(1.29, 1.53) ^{***}	1.52	(1.40, 1.66) ^{***}
Baseline comorbidities (yes vs no)				
Diabetes	1.92	(1.75, 2.09) ^{***}	1.55	(1.41, 1.70) ^{***}
Hypertension	2.10	(2.00, 2.21) ^{***}	1.85	(1.75, 1.94) ^{***}
Hyperlipidemia	1.31	(1.22, 1.40) ^{***}	1.06	(0.98, 1.13)
Atrial fibrillation	2.41	(1.72, 3.38) ^{***}	1.71	(1.22, 2.42) ^{**}
Congestive heart failure	1.59	(1.23, 2.06) ^{***}	0.97	(0.74, 1.26)
COPD	1.24	(1.16, 1.32) ^{***}	0.99	(0.92, 1.06)

CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio.

[†] Crude HR, relative hazard ratio.

[‡] Adjusted HR: multivariable analysis including age, sex and comorbidities of diabetes, hypertension, hyperlipidemia, atrial fibrillation, congestive heart failure, and COPD.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

fibrosis in the lungs. A large cohort study conducted in the United Kingdom evaluated asbestos workers from 1971 to 2005.⁹ The study reported 15,496 deaths among 98,117 workers followed up for 1,779,580 person-years. The standardized mortality ratio (SMR) for cerebrovascular disease was significantly increased (SMR 164, 95% CI 154–174). In addition, statistically significant positive associations were observed between the duration of exposure and stroke mortality. Another cohort study evaluated the mortality of asbestos workers during

a 15-year follow-up study conducted in South Carolina, United States.¹⁴ The mortality caused by cerebrovascular disease was significantly increased in white males (SMR 1.50, 95% CI 1.08–2.02). In addition, an increased risk of stroke had been reported in similar asbestos-exposed cohorts,^{15–17} but a large cohort study on Swedish male construction workers reported no association between exposure to inorganic dust, including asbestos, and the incidence of cerebrovascular diseases (Relative risks 0.97, 95% CI 0.88–1.07).¹⁸

TABLE 5. Cox Proportional-hazard Regression Analysis for the Risk of Cerebral-cardiac Events-associated Pneumoconiosis With Joint Effect of Comorbidity

Variables	N	Event, n	Adjusted HR [†] (95% CI)
Pneumoconiosis			
Diabetes			
No	25,838	4575	1 (Reference)
No	1762	441	1.88 (1.70, 2.07) ^{***}
Yes	6553	1194	1.12 (1.05, 1.19) ^{***}
Yes	342	92	2.26 (1.83, 2.77) ^{***}
Pneumoconiosis			
Hypertension			
No	18,171	2559	1 (Reference)
No	9429	2457	1.94 (1.83, 2.05) ^{***}
Yes	4530	684	1.14 (1.04, 1.24) ^{**}
Yes	2365	602	2.16 (1.97, 2.36) ^{***}
Pneumoconiosis			
Atrial fibrillation			
No	27,506	4990	1 (Reference)
No	94	26	1.95 (1.33, 2.87) ^{***}
Yes	6865	1278	1.11 (1.05, 1.18) ^{***}
Yes	30	8	2.02 (1.01, 4.04) [*]

CI = confidence interval, HR = hazard ratio.

[†] Adjusted HR: Adjusted for age and sex.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

A recent cohort study analyzed 1238 cases of pneumoconiosis and reported that 19.6% of pneumoconiosis patients developed ischemic stroke during 11 years of follow-up.⁸ After adjustment for comorbidities, patients with pneumoconiosis exhibited a higher incidence of ischemic stroke (HR 1.36, 95% CI 1.18–1.58). Pneumoconiosis patients are prone to developing COPD, which has been proven to increase the risk of stroke. However, the aforementioned cohort study revealed that patients with pneumoconiosis, but not COPD, still had a HR of 1.31 (95% CI 1.11–1.55) for ischemic stroke, indicating that pneumoconiosis is an independent risk factor for ischemic stroke. In addition to ischemic stroke, we evaluated the risk of hemorrhagic stroke and ACS in pneumoconiosis patients. Our study analyzed 6940 patients with pneumoconiosis, who exhibited a 1.14-fold higher risk of ischemic stroke (95% CI 1.05–1.23) than did those without pneumoconiosis. In addition, we evaluated the incidence of hemorrhagic stroke in pneumoconiosis patients. The risk of hemorrhagic stroke was higher, but not significant (HR 1.19, 95% CI 0.98–1.44). The hazard of developing ACS was not significant in both patients with and those without pneumoconiosis. Pneumoconiosis induces systemic chronic inflammation, which alters the hemodynamic status of the brain and triggers cerebral angiopathy that could partially explain the increase of ischemic stroke in our patients.^{19,20} However, the different results for cerebrovascular and cardiovascular events in pneumoconiosis patients are interesting and require further study.

A previous study evaluating the pathogenesis of pneumoconiosis suggested that alveolar macrophages play a pivotal role.²¹ Several studies have reported a major role of alveolar macrophages in particle clearance.^{20,21} Chronic exposure to mineral particles increases the number of alveolar macrophages in the lungs, and these macrophages ingest these particles.²² In the activation state, the macrophages release oxidants, cytokines, and growth factors. In addition to immune system cells, several lung cells (ie, fibroblasts, epithelial cells, and endothelial cells) can release secondary mediators including cytokines. Cytokines perform multiple functions in various biological events relevant to inflammation, metabolism, cell growth and differentiation, morphogenesis, fibrogenesis, and homeostasis.²³ Reportedly, pulmonary cytokines and relevant mediators might systemically activate inflammatory cascades in vessel walls, thereby resulting in the development of atherosclerosis.²⁴ Intracranial atherosclerotic disease is the most common cause of ischemic stroke.

In an animal study, long-term dust inhalation was associated with a reduced bleeding time, shortened prothrombin and partial thromboplastin times, increased levels of fibrinogen, and increased activity of factors II, VIII, and X, leading to reduced clotting times and accelerated arterial thrombosis.² This prothrombotic tendency was associated with an increase in the concentration of the prothrombotic cytokine interleukin (IL)-6 in bronchoalveolar fluid. In another animal study, dust exposure was related to an increase in plasminogen activator inhibitor-1 and a decrease in plasma tissue plasminogen activator, which can cause deficient fibrinolysis.²⁵

Aging is a major risk factor for cerebrovascular and cardiovascular events. Nevertheless, the present study showed that patients aged 60 to 69 years had a higher HR than that of patients older than 70 years. This is an interesting observation from our study, but no relevant reports have discussed the HR for pneumoconiosis in patients of different ages. The reason for this interesting finding should be evaluated by future studies.

The use of a large sample and nationwide population-based database to trace the development of cerebrovascular and cardiovascular events without loss to follow-up is the strength of the study. However, there are a few limitations in our study, which are as follows:

- (1) There were no individual data about the potential confounding risk factors of life activity/pattern/habit, body weight/length, and family history. Therefore, we had to use hypertension, diabetes, and hyperlipidemia to represent the variable of metabolic syndrome, and to use the COPD to represent smoking habits for analyzed adjustment in our study.
- (2) Because of possibly unmeasured or unknown confounders, an observational-epidemiologic cohort study is a lower methodological study design when compared with a randomized controlled study.
- (3) The NHI claims are originally used for insurance reimbursements, not for scientific research purposes. However, the insurance system has the strict peer review system by the experienced experts or physicians to double check the insurance claims. The data about the diagnoses in the NHIRD should be still reliable.
- (4) Nonavailability individual laboratory data, imaging finding, and pathologic result in the NHIRD may be the other study limitation.

Therefore, advanced population-based, unbiased, randomized controlled large trials are required to confirm our current findings before any definitive conclusions can be derived. Although statistical significance was observed in this study, we acknowledge that the clinical significance in this study might be moderate because of the marginally significant and low HR. The clinical significance of our findings should not be overemphasized. In clinical practice, healthcare professionals should not overlook other major risk factors of cerebrovascular events, such as hypertension, diabetes, and hyperlipidemia.

CONCLUSIONS

This nationwide survey demonstrated an association between pneumoconiosis and a higher risk of cerebrovascular events after adjustment for diabetes, hypertension, hyperlipidemia, atrial fibrillation, and related comorbidities. This information is critical for developing preventive strategies for cerebrovascular diseases. Clinicians should be aware of this phenomenon and implement strict control of other risk factors of cerebrovascular diseases, including diabetes, hypertension, hyperlipidemia, atrial fibrillation, and encourage lifestyle modifications including smoking cessation, weight reduction, diet control, limiting alcohol consumption, and increasing physical activity.

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