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Risk of pneumothorax in pneumoconiosis patients in Taiwan: a retrospective cohort study

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ABSTRACT

Objectives This study was conducted to explore the association between pneumoconiosis and pneumothorax.
Design Retrospective cohort study.
Setting Nationwide population-based study using the Taiwan National Health Insurance Database.
Participants A total of 2333 pneumoconiosis patients were identified (1935 patients for propensity score (PS)-matched cohort) and matched to 23 330 control subjects by age and sex (7740 subjects for PS-matched cohort).
Primary and secondary outcome measures The incidence and the cumulative incidence of pneumothorax.
Results Both incidence and the cumulative incidence of pneumothorax were significantly higher in the pneumoconiosis patients as compared with the control subjects (p<0.0001). For multivariable Cox regression analysis adjusted for age, sex, residency, income level and other comorbidities, patients with pneumoconiosis exhibited a significantly higher risk of pneumothorax than those without pneumoconiosis (HR 3.05, 95% CI 2.18 to 4.28, p<0.0001). The male sex, heart disease, peripheral vascular disease, chronic pulmonary disease and connective tissue disease were risk factors for developing pneumothorax in pneumoconiosis patients.
Conclusions Our study revealed a higher risk of pneumothorax in pneumoconiosis patients and suggested potential risk factors in these patients. Clinicians should be aware about the risk of pneumothorax in pneumoconiosis patients.

Strengths and limitations of this study

- The nationwide population-based data could minimise the selection bias with a broad view of the real-world epidemiology.
- This long-term cohort study provides better evidence about the temporal trajectory for the association between pneumoconiosis and pneumothorax.
- The propensity-scored-matched model was applied to account for confounding factors.
- The risk factors for incident pneumothorax in pneumoconiosis patients were also disclosed in our study.
- This study was limited by the shortage of clinical information, such as smoking history, in the National Health Insurance database.

INTRODUCTION

Pneumoconiosis, one of the oldest occupational diseases, continues to disable the health of labourers to this day. Three kinds of dusts, including coal dust, crystalline silica and asbestos, are mainly responsible for this disease,[1] with the deposition of this (inhaled) inorganic dust causing irreversible fibrotic reaction in lung tissue through inflammatory cascades. Most patients develop respiratory symptoms, lung function impairment and chest radiologic abnormalities, and the disease may progress even after cessation of exposure.[2 3]

Pneumoconiosis, maintaining a relatively high incidence in recent years, is still prevalent worldwide.[4] Although it is thought to be preventable, endemic resurgence is still reported, even in developed countries.[5 6] According to the Global Burden of Disease study of 2017, approximately 528 000 cases were living with pneumoconiosis,[7] and 21 600 cases of global deaths were resulted from pneumoconiosis.[8] Despite of regulation control and health surveillance, medical care for pneumoconiosis patients is unneglectable. However, with limited treatment options for pneumoconiosis, management has focused merely on alleviating progression of the disease as well as the complications or comorbidities.

Pneumothorax has been considered as one of the major complications of pneumoconiosis as reported in different countries and industries.[4] Poorer outcome has been observed in patients of rapidly progressing pneumoconiosis who develop pneumothorax.[9] Pneumoconiosis might be a preexisting lung aetiology for secondary spontaneous pneumothorax[10 11]; however, the incidence of pneumothorax in pneumoconiosis patients is not well established, nor has its risk in pneumoconiosis patients been comprehensively compared with that of the general population. This nationwide population-based cohort study was, therefore, developed using the Taiwan National Health Insurance Research Database (NHIRD) to explore the association between pneumothorax and pneumoconiosis.

METHODS

Data sources

The Taiwan NHIRD, compiled and maintained by the Taiwan National Health Research Institute, is an administrative database containing reimbursement information from the Taiwan National Health Insurance (NHI) programme, which has enrolled more than 99% of Taiwan's population covering ambulatory care, hospital inpatient care, dental services and prescription drugs.[12] The dataset used for this study was the Longitudinal Health Insurance Database 2005, a cohort of 1 million subjects randomly sampled from the beneficiaries in the Taiwan NHI programme in 2005, which was considered a highly representative sample of Taiwan's general population.[13–16] The dataset contains information of subjects from the start of the NHI programme in March 1995 to the end of 2013.

Study cohorts

From the database, we selected patients with a diagnosis of pneumoconiosis (ICD-9-CM codes of 500–505) in at least one inpatient or two ambulatory claims (figure 1). The initial pneumoconiosis diagnosis date was the index date for the pneumoconiosis cohort. Patients were excluded if they had washout periods (from enrolment to the index date) or observation periods (from the index date to the end of follow-up) less than a year, were younger than 18 years or older than 90 years on the index date, or with diagnosis of pneumothorax before the index date. The ICD-9-CM codes of 512 was used for diagnosis of pneumothorax. For each pneumoconiosis patient, ten age-matched and sex-matched control subjects were randomly selected, considering the same exclusion criteria as the pneumoconiosis cohort, and given the same index date as their corresponding pneumoconiosis patient. All the subjects were followed from the index date to either being diagnosed with pneumothorax, end of the study period, withdrawal from the insurance programme or death. To calculate the Charlson Comorbidity Index score, the other comorbidities were also identified by diagnostic codes from the database.[17] Comorbidities were confirmed with presence of the corresponding diagnostic codes at least twice in the ambulatory database or at least once in the inpatient database before the index date[13]; then, the prevalence, incidence rate (IR) and the cumulative incidence of pneumothorax were compared between pneumoconiosis patients and control subjects.

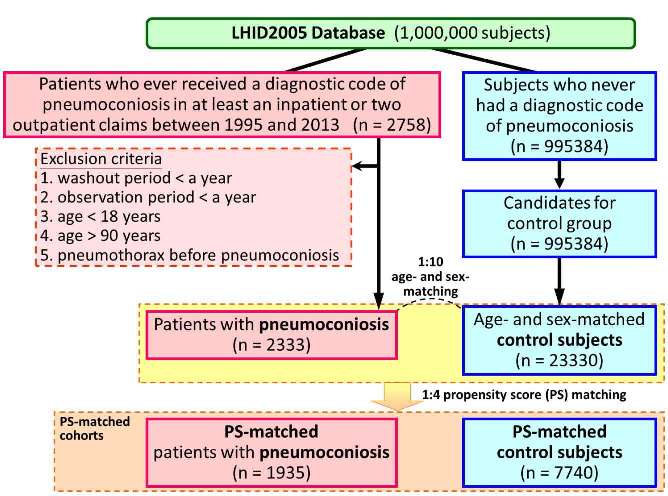

Figure 1 Algorithm for identifying the study population. LHID, Longitudinal Health Insurance Database; PS, propensity score.

Statistical analysis

The categorical variables were described with frequencies and percentages, and the continuous variables were expressed with means and SD, while baseline characteristics were compared between groups by Pearson's χ^2 test (for categorical variables) or Student's t-test (for continuous variables). The IR of pneumothorax was calculated as all new cases of pneumothorax during the study period divided by the number of the total person-years, while the IR ratios (IRRs) were estimated by comparing the IRs of pneumothorax in pneumoconiosis patients and control subjects. The 95% CIs for the IRRs were estimated by Poisson regression. The adjusted IRRs were calculated by multivariable analyses after adjusting for age, sex, residency, income level and the presence of other comorbidities.[13–16] The Kaplan-Meier method and log-rank test were used to calculate and compare the cumulative incidences of pneumothorax. With adjustment of the same covariates as in Poisson regression, multivariable Cox proportional hazards regression analyses were performed to further assess the effect of pneumoconiosis with the results presented in HRs. Stratified analyses were also performed for Poisson and Cox regression in subgroups of covariates.

Multivariable Cox proportional hazards regression analysis was also used to investigate the risk factor for incident pneumothorax. In addition to the maximal models, reduced multivariable models were developed with backward variable selection method, keeping only variables with p<0.05 from the maximal model.

To account for confounding factors, sex, age, year of the index date, residency, income level and comorbidities were included in a logistic regression model with pneumoconiosis as the dependent variable to determine a propensity score (PS). By selecting four PS-matched control subjects for each pneumoconiosis patient, PS-matched cohorts were extracted from the original cohorts.

Extraction and computation of data, data linkage, processing and sampling, and statistical analyses were performed using SAS system (V.9.4 for Windows, SAS Institute). The statistical significance level was set at a two-sided p<0.05.

Patient and public involvement

Data collection was performed from records in the database. There was no increased burden to patients in this study. Results were disseminated alongside increasing awareness in timely caring for pneumoconiosis patients.

RESULTS

In total, 2333 pneumoconiosis patients from the database were identified and matched with 23 330 control subjects by age and sex (figure 1), with table 1 showing

Table 1 Baseline characteristics of the study population

	All subjects	Pneumoconiosis	Control	P value
N	25 663	2333	23 330	
Sex, n (%)				
Female	7447 (29)	677 (29)	6770 (29)	
Male	18 216 (71)	1656 (71)	16 560 (71)	
Age (year), mean±SD	57.4±15.3	57.4±15.3	57.4±15.3	
Age (year), n (%)				
≤65	17 314 (67)	1574 (67)	15 740 (67)	
>65	8349 (33)	759 (33)	7590 (33)	
Residency, n (%)				<0.0001
Northern Taiwan	7778 (30)	1152 (49)	6626 (28)	
Other areas	17 885 (70)	1181 (51)	16 704 (72)	
Monthly income (NT$), median (IQR)	19 200 (1007–21 900)	19 200 (0–21 900)	19 200 (1007–21 900)	<0.0001
Monthly income (NT$), n (%)				0.4691
≤24 000	20 111 (78)	1842 (79)	18 269 (78)	
>24 000	5552 (22)	491 (21)	5061 (22)	
CCI score, mean±SD	0.7±1.4	0.8±1.5	0.7±1.4	<0.0001
CCI score, n (%)				<0.0001
=0	17 740 (69)	1408 (60)	16 332 (70)	
=1	3777 (15)	459 (20)	3318 (14)	
≥2	4146 (16)	466 (20)	3680 (16)	
Underlying diseases, n (%)				
Heart disease	692 (3)	79 (3)	613 (3)	0.0310
Myocardial infarction	224 (1)	16 (1)	208 (1)	0.3084
Congestive heart failure	505 (2)	63 (3)	442 (2)	0.0075
Peripheral vascular disease	188 (1)	18 (1)	170 (1)	0.8169
Major neurological disorder	1814 (7)	152 (7)	1662 (7)	0.2741
Cerebral vascular disease	1725 (7)	146 (6)	1579 (7)	0.3482
Dementia	176 (1)	12 (1)	164 (1)	0.2926
Hemiplegia	202 (1)	21 (1)	181 (1)	0.5171
Chronic pulmonary disease	3544 (14)	619 (27)	2925 (13)	<0.0001
Connective tissue disease	220 (1)	17 (1)	203 (1)	0.4798
Peptic ulcer disease	2782 (11)	276 (12)	2506 (11)	0.1068
Liver disease	1731 (7)	162 (7)	1569 (7)	0.6881
Diabetes mellitus	1765 (7)	143 (6)	1622 (7)	0.1342
Renal disease	583 (2)	46 (2)	537 (2)	0.3077
Cancer	809 (3)	113 (5)	696 (3)	<0.0001

NT$, New Taiwan Dollar; CCI, Charlson Comorbidity Index; .

the baseline characteristics of the study population. Patients with pneumoconiosis had more comorbidities than the control subjects, particularly in terms of heart diseases, chronic pulmonary diseases and cancers.

The IR of pneumothorax was significantly higher in pneumoconiosis patients as compared with the subjects in the control cohort (1.7 vs 0.5 per 1000 patient-years; adjusted IRR 3.0, 95% CI 2.7 to 3.3) (table 2). The increased pneumothorax risk related to pneumoconiosis is shown in all strata as stratified by baseline characteristics (table 2). Pneumoconiosis patients, compared with the control subjects, had a significantly higher cumulative incidence of pneumothorax (p<0.0001) (figure 2A). Stratified analyses revealed that these patients had significantly higher cumulative incidences of pneumothorax than control subjects in female, male, younger and elder subjects (figure 2B–E).

On multivariable Cox regression analysis, pneumoconiosis was an independent risk factor contributing to incident pneumothorax (adjusted HR 3.06, 95% CI 2.18 to 4.28), p<0.0001) (online supplemental table S1). Stratified analyses showed that pneumoconiosis was associated with a higher risk for the development of pneumothorax in all strata (online supplemental figure S1).

Multivariable Cox regression analyses were also used to identify the factors contributing to the development of pneumothorax in the pneumoconiosis patients (table 3). After backward variable selection, it was found that the male sex, heart disease, peripheral vascular disease, chronic pulmonary disease and connective tissue disease were independent risk factors for incidents of pneumothorax in pneumoconiosis patients.

To better account for confounding factors, another set of analyses were performed using PS-matched cohorts, including 1935 pneumoconiosis patients and 7740 control subjects (online supplemental table S2). In the PS-matched cohorts, no significant differences in the baseline characteristics between pneumoconiosis patients and the control subjects were noted. Pneumoconiosis patients had significantly higher IR of pneumothorax than the controls (1.5 vs 0.5 per 1000 patient-years; IRR 3.1, 95% CI 2.7 to 3.6), and stratified analyses showed similar findings except in the female subjects (online supplemental table S3). The cumulative incidences of pneumothorax were significantly higher in pneumoconiosis patients than in the control subjects in the whole PS-matched cohorts, as well as in stratified analyses of the male, younger and older subjects (online supplemental figure S2). In stratified analysis of female subjects, both pneumoconiosis patients and control subjects had very low cumulative incidence of pneumothorax, which showed no significant difference. Cox regression analysis showed that pneumoconiosis was a risk factor for pneumothorax (HR 3.10, 95% CI 2.01 to 4.77, p<0.0001) (online supplemental figure S3). Stratified analyses showed similar results, but the effect of pneumoconiosis on pneumothorax was not found in female subjects.

DISCUSSION

This is the first long-term nationwide population-based cohort study to comprehensively explore the associations between pneumoconiosis and pneumothorax. Both incidence and cumulative incidence of pneumothorax were significantly higher in pneumoconiosis patients than in those without pneumoconiosis. In multivariable Cox regression analysis, pneumoconiosis was an independent risk factor for developing pneumothorax after adjusting for age, sex, residency, income levels and other comorbidities. The PS-matched cohort showed similar results in all strata except for female subjects.

Secondary spontaneous pneumothorax has been discussed mostly concerning silicosis. A study observing 50 silicosis patients in India reported a 44% incident rate of pneumothorax, mainly with unilateral involvement.[18] A significant association between secondary spontaneous pneumothorax and bullae in acute and accelerated silicosis was found in stone workers in Iran.[19] The association between silica exposure and emphysema has been noted.[20] The effect of inflammatory response products on the elastic fibres of the alveolar walls and the coalescence of peri-nodular emphysematous regions were considered to cause the formation of blebs.[19 21 22] An uneven expansion of the lung due to increased elastic recoil and collapse of adjacent regions following massive fibrosis develops the pressure gradient subsequently to facilitate rupture of the blebs.[22 23] Piezoelectricity, a phenomenon where crystals generate electronic charges with mechanical stress, might also play some role in the pathophysiology of developing pneumothorax in silicosis due to the free oxygen radicals on the silica crystal surface.[18 24] For other types of pneumoconiosis sharing the traits of inflammatory and fibrotic response, bullae and emphysema are also commonly observed in secondary spontaneous pneumothorax in a progressive state of coal workers' pneumoconiosis[25]; an association between emphysema and asbestosis has also been suggested by epidemiological study of constructors in Canada and Finland.[26 27] A similar mechanism for silicosis to develop pneumothorax might be applied to most pneumoconiosis patients, though future studies are obligated to investigate the association of pneumothorax in different types of pneumoconiosis.

In this study, the association between pneumoconiosis and pneumothorax in female was not significant, which might be attributed to the small sample size of female subjects. Consistent with other studies investigating the association between pneumothorax and pneumoconiosis, the numbers of female patients were small because dust-exposed occupations are mostly taken by males. An increased prevalence of secondary spontaneous pneumothorax has been reported in silicosis with smoking patients.[18 24 28] In the literature, most patients of pneumoconiosis reported as

Table 2 Incidence rate of pneumothorax (PTX) after the index date in each group

	Pneumoconiosis				Control					
	N	**PTX**	**PY**	**IR**	**N**	**PTX**	**PY**	**IR**	**Crude IRR (95% CI)**	**Adjusted IRR (95% CI)**
Whole study population	2333	48	28 906.0	1.7	23 330	154	296 269.3	0.5	3.2 (2.9 to 3.5)***	3.0 (2.7 to 3.3)***
Stratified analyses										
Sex										
Female	677	4	9371.7	0.4	6770	13	94 447.9	0.1	3.1 (2.5 to 3.9)***	2.9 (2.3 to 3.6)***
Male	1656	44	19 534.3	2.3	16 560	141	201 821.4	0.7	3.2 (2.9 to 3.6)***	3.0 (2.7 to 3.4)***
Age										
≤50	1574	29	20 898.8	1.4	15 740	71	213 707.7	0.3	4.2 (3.7 to 4.7)***	3.6 (3.2 to 4.1)***
>50	759	19	8007.3	2.4	7590	83	82 561.6	1.0	2.4 (2.0 to 2.8)***	2.4 (2.0 to 2.9)***
Residents in										
Northern Taiwan	1152	24	15 188.1	1.6	6626	26	91 560.5	0.3	5.6 (4.7 to 6.5)***	4.8 (4.0 to 5.6)***
Other areas	1181	24	13 718.0	1.7	16 704	128	204 708.8	0.6	2.8 (2.4 to 3.2)***	2.4 (2.1 to 2.7)***
Monthly income										
≤NT$24 000	1842	39	22 460.8	1.7	18 269	139	228 973.3	0.6	2.9 (2.6 to 3.2)***	2.8 (2.5 to 3.1)***
>NT$24 000	491	9	6445.3	1.4	5061	15	67 296.1	0.2	6.3 (5.1 to 7.6)***	5.1 (4.2 to 6.3)***
Comorbidity										
No (CCI score=0)	1408	20	19 582.1	1.0	16 332	86	225 549.3	0.4	2.7 (2.3 to 3.1)***	2.7 (2.4 to 3.1)***
Yes (CCI score ≥1)	925	28	9324.0	3.0	6998	68	70 720.0	1.0	3.1 (2.7 to 3.7)***	3.2 (2.8 to 3.8)***

The adjusted IRRs were calculated by multivariable analyses adjusting for sex, age, residency, income level and the presence of various comorbidities (except for the variable used for stratification).
***P<0.0001.
CCI, Charlson Comorbidity Index; IR, incident rate; IRR, incidence rate ratio; ;NT$, New Taiwan Dollar; PY, total patient-years.

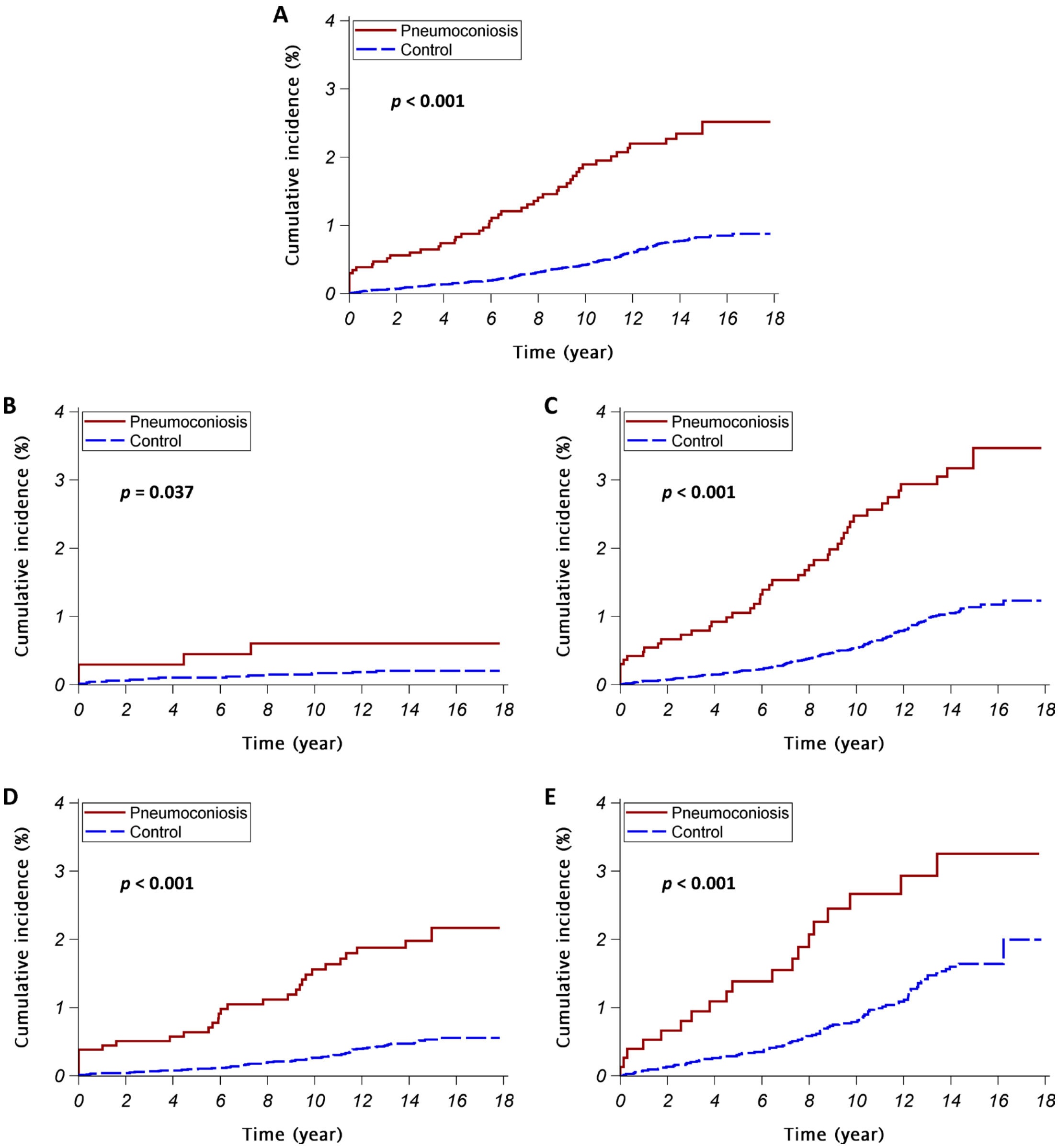

Figure 2 The cumulative incidences of pneumothorax. The red continuous lines and blue dashed lines show the cumulative incidence of pneumothorax for the pneumoconiosis patients and the control subjects, respectively. (A) All study subjects; (B) female subjects; (C) male subjects; (D) subjects aged ≤65 years; (E) subjects aged >65 years.

developing pneumothorax had a smoking history (online supplemental table S4). In Taiwan, the prevalence of smoking is markedly lower in females than males, and this could explain why the risk of pneumothorax was increased in female pneumoconiosis patients in our study. However, silicosis per se, in the absence of smoking, might contribute to the development of emphysema, a common underlying cause for secondary spontaneous pneumothorax.[19 26] Without a smoking history recorded in the NHI database, the effect of smoking on the risk of development of pneumothorax in pneumoconiosis patients remains undetermined.

In the current study, being male, having heart disease, peripheral vascular disease, chronic pulmonary disease and connective tissue disease were found as independent risk factors for developing pneumothorax in pneumoconiosis patients. As a major risk factor for pneumothorax, smoking might be an important confounder because the smoking prevalence is much higher in men and smoking is associated with various systemic diseases, including heart disease, peripheral vascular disease and chronic pulmonary disease. Further study adjusting for smoking history is required to evaluate the confounding effect of smoking; nevertheless, it is still clinically valuable to identify the pneumoconiosis patients at higher risk of development of pneumothorax as shown in the current studies.

Secondary pneumothorax in silicosis has often featured with localised pneumothorax due to pleural adhesion, shortly progressing to respiratory failure due to poor

Table 3 Multivariable Cox regression analysis of the factors contributing to pneumothorax in the pneumoconiosis patients

Variables	Maximal model	Reduced model
Male vs female	4.71 (1.67 to 13.3)**	4.84 (1.73 to 13.57)**
Age >65 vs ≤65	1.15 (0.60 to 2.24)	
Residency (Northern Taiwan vs other areas)	1.07 (0.59 to 1.94)	
Higher income (>NT$24 000) vs lower income (≤NT$24 000)	0.87 (0.40 to 1.90)	
Presence of underlying diseases		
Heart disease	3.94 (1.50 to 10.36)**	3.78 (1.52 to 9.42)**
Peripheral vascular disease	11.31 (2.48 to 51.53)**	6.76 (1.59 to 28.77)**
Major neurological disorder	1.32 (0.48 to 3.58)	
Chronic pulmonary disease	2.11 (1.12 to 3.96)*	2.22 (1.20 to 4.09)*
Connective tissue disease	7.65 (1.73 to 33.94)**	7.40 (1.75 to 31.24)**
Peptic ulcer disease	1.13 (0.47 to 2.70)	
Liver disease	1.26 (0.48 to 3.35)	
Diabetes mellitus	0.15 (0.02 to 1.22)	
Renal disease	1.25 (0.27 to 5.82)	
Cancer	1.47 (0.42 to 5.22)	

The adjusted HR with 95% CI are presented.
Reduced multivariable models was developed with backward variable selection method, keeping only variables with p<0.05, from the maximal model.
*p<0.05; **p<0.01.
NT$, New Taiwan Dollar.

respiratory functional status with a small amount of pneumothorax, and combined with persistent air leak or refractory pneumothorax.[25] A recurrence rate of spontaneous pneumothorax, as high as 48%, has also been revealed in China in a clinical analysis of 350 pneumoconiosis patients.[29] The decline in forced expiratory volume in the first second and forced vital capacity values in spirometry were found associated with the occurrence of pneumothorax in rapidly formed silicosis.[9] As compared with nature stone-associated silicosis, a higher incidence of spontaneous pneumothorax has also been reported in artificial stone-associated silicosis (16.7% vs 1.6%, p<0.05), as well as a more accelerated loss of pulmonary function.[30]

Although the association of spirometry impairment and developing pneumothorax in other types of pneumoconiosis is unclear, a pulmonary function test might be considered during regular follow-up to predict the (poor) outcome. Few studies have focused on management of secondary spontaneous pneumothorax in pneumoconiosis patients. Secondary spontaneous pneumothorax often occurs in the late course of pneumoconiosis along with poor physical and respiratory status, when surgical management is usually contraindicated.[31] Chemical pleurodesis may be required after chest tube drainage for a persistent air leak or refractory pneumothorax.[32] Bronchial occlusion with endobronchial Watanabe spigots has also been reported to stop or reduce air leaks effectively.[33] If surgical intervention is applicable, an absorbable polyglycolic acid patch as a reinforcement or repair material might be helpful to reduce postoperative air leakage for refractory pneumothorax due to silicosis.[34]

With the nationwide, population-based data, this cohort study minimised selection bias and provided a broad view of real-world epidemiology, and with its long follow-up period, has provided better evidence about the temporal trajectory for the association between pneumoconiosis and pneumothorax. However, it is limited by the shortage of clinical information in the NHI database, as potentially important risk factors for pneumothorax such as smoking history, body mass index and family history were unavailable. In the current study, efforts were made to minimise the effect of these confounders by multivariable regression analyses adjusting for baseline characteristics and comorbidities as well as by PS matching. In addition, without information of chest radiography and occupational history, the accuracy of identifying patients with diagnostic codes could not be assessed. Information concerning exposure of dust types, intensity and tenure was also unavailable for more detailed analysis. Future studies with more detailed clinical information are warranted to disclose the effects of these factors.

CONCLUSION

This large nationwide population-based cohort study confirmed that patients of pneumoconiosis had significantly higher risk of developing pneumothorax compared with matched control subjects without pneumoconiosis.

Clinicians should be aware of the risk of pneumothorax in such patients, especially in males with heart disease, peripheral vascular disease, chronic pulmonary disease and connective tissue disease.

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Competing interests None declared.

Patient consent for publication Not applicable.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement This study is based on data from the National Health Insurance Research Database provided by the National Health Insurance Administration, Ministry of Health and Welfare, and managed by the National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of the National Health Insurance Administration, Ministry of Health and Welfare or National Health Research Institutes (NHRI). Due to legal and ethical restrictions, researchers should contact NHRI (https://nhird.nhri.org.tw/) for access of the data after approval by the Institutional Review Board. No data are directly available. This study is based on data from the National Health Insurance Research Database provided by the National Health Insurance Administration, Ministry of Health and Welfare and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of National Health Insurance Administration, Ministry of Health and Welfare or National Health Research Institutes (NHRI). Due to legal and ethical restrictions, researchers should contact NHRI (http://nhird.nhri.org.tw/index.htm) for access of the data after approved by institutional review board.

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Original Article

The risk of pneumothorax in pneumoconiosis patients in Taiwan: a retrospective cohort study

Supplemental Material

Running title: Pneumothorax in Pneumoconiosis Patients

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Table S1. Multivariable Cox regression analysis of the factors contributing to pneumothorax in the study population.

Variables	HR [95% CI]	*P* value
Pneumoconiosis patients *vs.* Control subjects	3.05 [2.18-4.27]	<0.0001
Male *vs.* Female	4.46 [2.70-7.37]	<0.0001
Age > 65 *vs.* ≤65	1.59 [1.17-2.17]	0.0030
Residency (Northern Taiwan *vs.* Other areas)	0.74 [0.53-1.04]	0.0795
Higher income (>NT$24000) *vs.* lower income (≤NT$24000)	0.61 [0.39-0.96]	0.0324
Presence of underlying diseases:		
Heart disease	1.70 [0.93-3.10]	0.0868
Peripheral vascular disease	3.50 [1.39-8.80]	0.0078
Major neurological disorder	1.78 [1.15-2.75]	0.0098
Chronic pulmonary disease	2.42 [1.73-3.38]	<0.0001
Connective tissue disease	3.25 [1.31-8.07]	0.0111
Peptic ulcer disease	1.00 [0.65-1.55]	0.9876
Liver disease	1.31 [0.80-2.16]	0.2800
Diabetes mellitus	0.58 [0.31-1.10]	0.0931
Renal disease	1.21 [0.57-2.57]	0.6175
Cancer	1.30 [0.68-2.50]	0.4337

Abbreviation: NT$ = New Taiwan Dollar; HR = hazard ratio; CI = confidence interval.

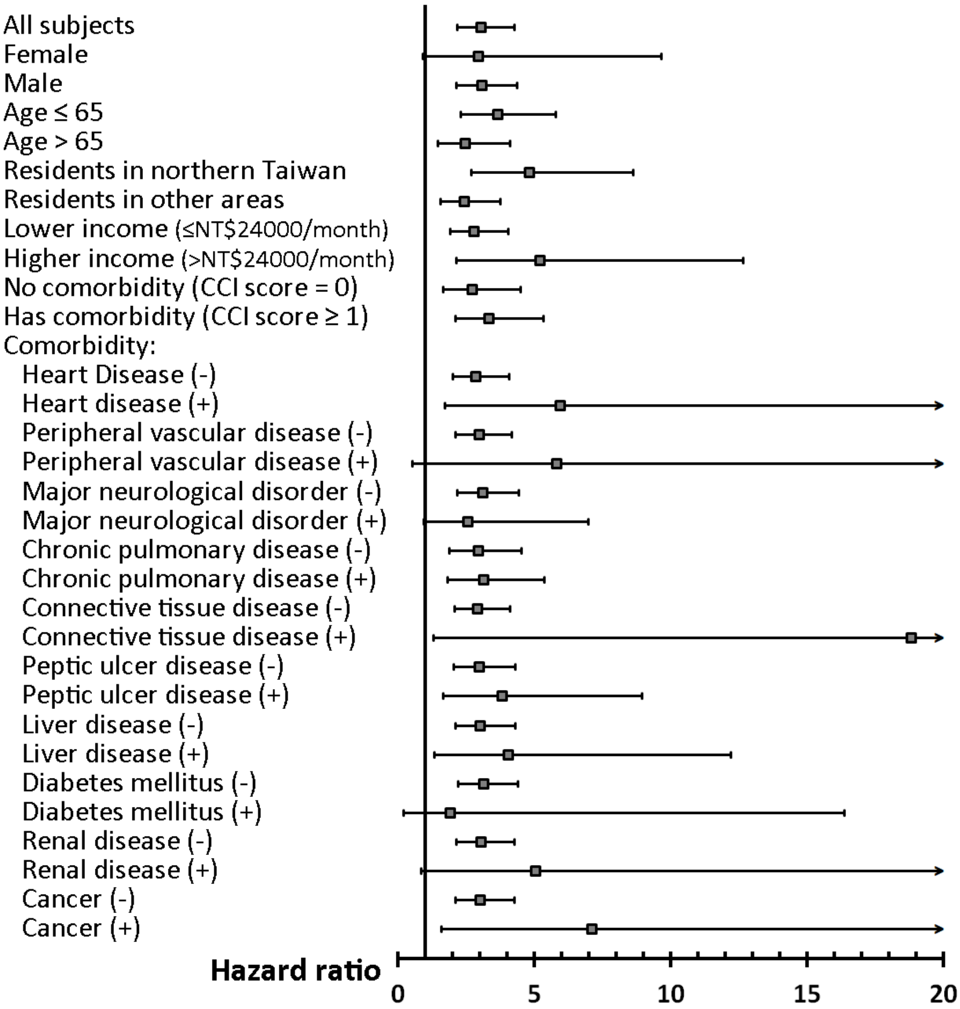

Figure S1. Stratified analyses of multivariable Cox regression analyses assessing the effect of pneumoconiosis on incident pneumothorax.

The results are presented with adjusted HRs (95% CI) of pneumoconiosis, which are adjusted for sex, age, residency, income level, and the presence of various comorbidities (except for the variable used for stratification).

*Abbreviations: CCI = Charlson Comorbidity Index; HR = hazard ratio; CI = confidence interval.

Table S2. Baseline characteristics of the propensity score (PS)-matched cohorts.

	All subjects	Pneumoconiosis	Control	P value
N	9675	1935	7740	
Sex, n (%)				
Female	2800 (29%)	560 (29%)	2240 (29%)	
Male	6875 (71%)	1375 (71%)	5500 (71%)	
Age (year), mean ± SD	56.7 ± 15.6	56.7 ± 15.6	56.7 ± 15.6	
Age (year), n (%)				
≤ 65	6622 (68%)	1323 (68%)	5299 (68%)	
> 65	3053 (32%)	612 (32%)	2441 (32%)	
Residency, n (%)				>0.99
Northern Taiwan	4315 (45%)	863 (45%)	3452 (45%)	
Other areas	5360 (55%)	1072 (55%)	4288 (55%)	
Monthly income (NT$), median (IQR)	19200 (0-21900)	19200 (0-21900)	19200 (0-21900)	0.5137
Monthly income (NT$), n (%)				0.3931
≤ 24000	7596 (79%)	1533 (79%)	6063 (78%)	
> 24000	2079 (21%)	402 (21%)	1677 (22%)	
CCI score, mean ± SD	0.5 ± 1	0.5 ± 1.1	0.5 ± 1	0.3092
CCI score, n (%)				0.5506
= 0	7038 (73%)	1389 (72%)	5649 (73%)	
= 1	1423 (15%)	292 (15%)	1131 (15%)	
≥ 2	1214 (13%)	254 (13%)	960 (12%)	
Underlying diseases, n (%)				
Heart disease	176 (2%)	42 (2%)	134 (2%)	0.1959
Myocardial infarction	49 (1%)	11 (1%)	38 (0%)	0.6674
Congestive heart failure	137 (1%)	31 (2%)	106 (1%)	0.4387
Peripheral vascular disease	42 (0%)	10 (1%)	32 (0%)	0.5362
Major neurological disorder	491 (5%)	96 (5%)	395 (5%)	0.7989
Cerebral Vascular disease	477 (5%)	96 (5%)	381 (5%)	0.9438
Dementia	24 (0%)	4 (0%)	20 (0%)	0.6827
Hemiplegia	41 (0%)	8 (0%)	33 (0%)	0.9376
Chronic pulmonary disease	1532 (16%)	306 (16%)	1226 (16%)	0.9778
Connective tissue disease	43 (0%)	7 (0%)	36 (0%)	0.5410
Peptic ulcer disease	874 (9%)	190 (10%)	684 (9%)	0.1778
Liver disease	512 (5%)	108 (6%)	404 (5%)	0.5249
Diabetes mellitus	458 (5%)	89 (5%)	369 (5%)	0.7557
Renal disease	120 (1%)	28 (1%)	92 (1%)	0.3583
Cancer	139 (1%)	31 (2%)	108 (1%)	0.4943

Abbreviation: NT$ = New Taiwan Dollar; CCI = Charlson Comorbidity Index; SD = standard deviation; IQR = interquartile range.

Table S3. Incidence rate of pneumothorax (PTX) after the index date in each propensity score (PS)-matched cohort.

	Pneumoconiosis				Control				IRR [95% CI]
	N	PTX	PY	IR	N	PTX	PY	IR	
All PS-matched subjects	1935	36	24639.4	1.5	7740	48	101849.3	0.5	3.1 [2.7-3.6]***
Stratified analyses									
Sex									
Female	560	1	8115.7	0.1	2240	5	32460.7	0.2	0.8 [0.5-1.2]
Male	1375	35	16523.7	2.1	5500	43	69388.6	0.6	3.4 [2.9-4.0]***
Age									
≤ 50	1323	22	18000.0	1.2	5299	25	74282.3	0.3	3.6 [3.1-4.3]***
> 50	612	14	6639.4	2.1	2441	23	27567.0	0.8	2.5 [2.0-3.2]***
Residents in									
Northern Taiwan	863	12	11836.9	1.0	3452	11	48460.0	0.2	4.5 [3.6-5.6]***
Other areas	1072	24	12802.5	1.9	4288	37	53389.2	0.7	2.7 [2.2-3.3]***
Monthly income									
≤ NT$24000	1533	29	19155.5	1.5	6063	45	78417.2	0.6	2.6 [2.3-3.1]***
> NT$24000	402	7	5483.9	1.3	1677	3	23432.0	0.1	10.0 [6.9-14.4]***
Comorbidity									
No (CCI score = 0)	1389	19	19330.8	1.0	5649	27	80127.9	0.3	2.9 [2.5-3.5]***
Yes (CCI score ≥ 1)	546	17	5308.6	3.2	2091	21	21721.4	1.0	3.3 [2.6-4.3]***

***p<0.0001

Abbreviation: NT$ = New Taiwan Dollar; CCI = Charlson Comorbidity Index;
N = number of patients; PTX = pneumothorax (number of patients);
PY = total patient-years;
IR = incident rate, as expressed as PTX incidence per 1000 patient-years;
IRR = incidence rate ratio; CI = confidence interval.

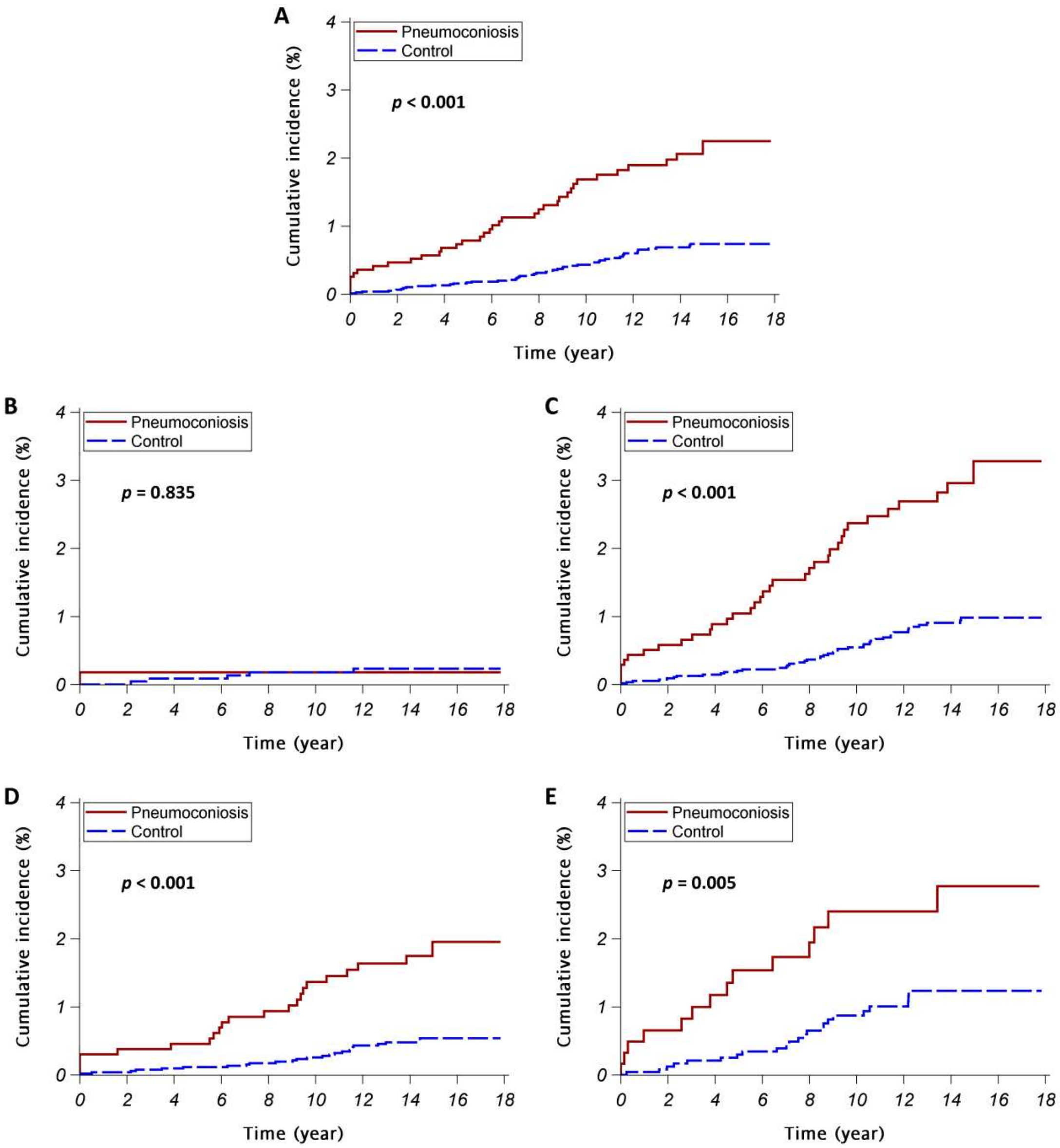

Figure S2. The cumulative incidences of pneumothorax in the propensity score (PS)-matched cohorts.

The red continuous lines and blue dashed lines show the cumulative incidence of pneumothorax for the pneumoconiosis patients and the control subjects respectively.
(a) all study subjects;
(b) female subjects; (c) male subjects;
(d) subjects aged ≤65 years; (e) subjects aged >65 years.

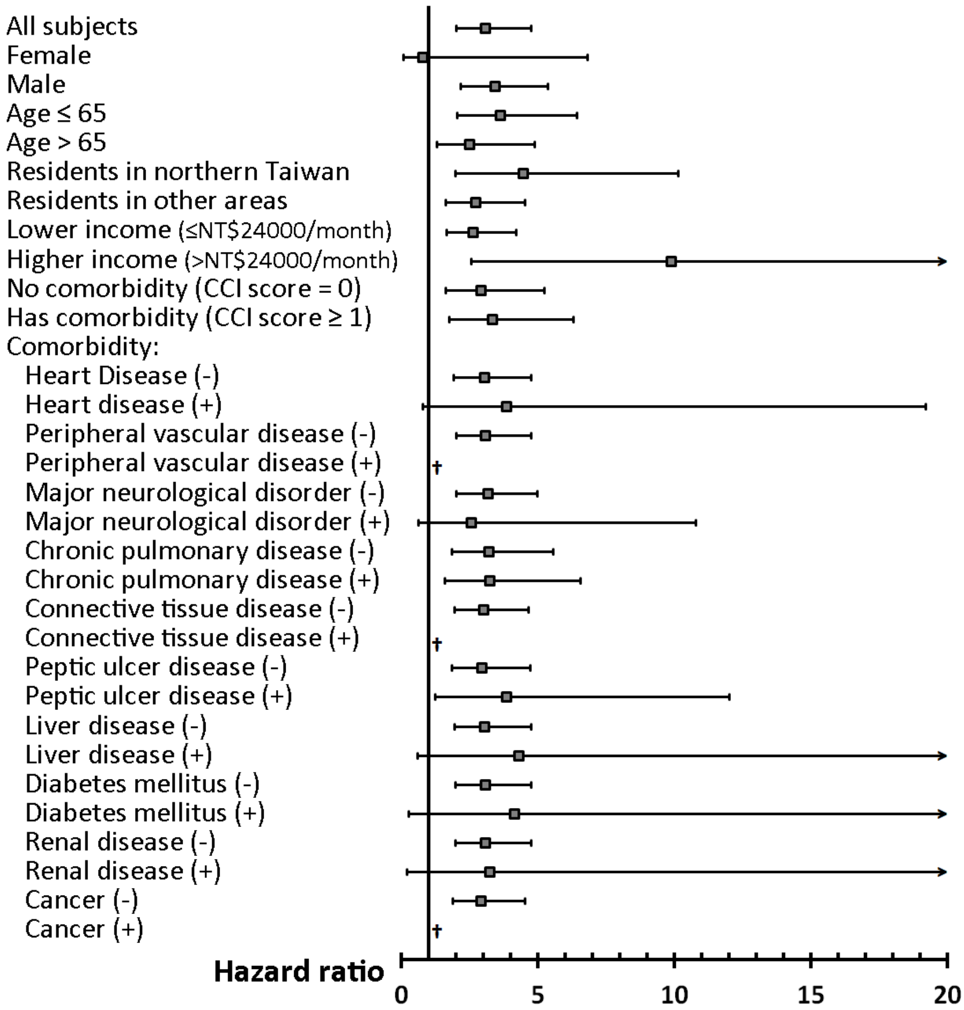

Figure S3. Stratified analyses of univariate Cox regression analyses assessing the effect of pneumoconiosis on incident pneumothorax in the propensity score (PS)-matched cohorts.

The results are presented with HRs (95% CI) of pneumoconiosis.

*Abbreviations: CCI = Charlson Comorbidity Index; HR = hazard ratio; CI = confidence interval.

†: Due to small sample size, hazard ratio cannot be estimated.

Table S4. Pneumoconiosis cases with pneumothorax reported from different countries and industries, available with patients' data.

Country	Author (year)	Occupation	Case number	Age	sex	Exposure dust	Exposure duration	Smoking
Indonesia	Amanda G (2016)[1]	builder	1	39	M	silica	18	Y
India	Natarajan AS (1992) [2]	silica flour mill worker	1	28	M	silica	7	N
	Gupta KB (2006) [3]	stone cutting	1	26	M	silica	3	Y
	Fotedar S (2010) [4]	stone cutting	1	24	M	silica	4	N
	Bairagya T (2012) [5]	stone cutting	1	21	M	silica	4	Y
	Srivastava GN (2014) [6]	stone crusher	1	28	M	silica	1	N
	Mishra P (2014) [7]	well driller	1	33	M	silica	10	N
	Dixit R (2015) [8]	stone crusher	1	35	M	silica	2	N
	Sharma RK (2017)[9]	Stone mining	20 (50)	—	M(45), F(5)*	silica	10 (5-15)*	Y(30)*
	Bairwa MK (2019) [10]	stone crusher & cutting	20	38.6 (26-65)	M	silica	13.7 (5-24)	Y(15)
	Meena MK (2020) [11]	stone mining	22 (50)	38.70 (10.17) *	—	silica	13.8 (4.8)*	Y(38)*
Iran	Mohebbi I (2007) [12]	stone grinding	7 (21)	26.43 (5.85)	M*	silica	2.14 (1)	N*
Japan	Hasejima N (1995) [13]	beryllium-copper wire drawing	1	24	M	beryllium	—	—
	Handa T (2009) [14]	—	2 (10)	33 (24-40) *	M(4), F(6)*	beryllium	5.84 (1-10.4)*	—
	Kobashi Y (2003) [15]	—	1	46	M	silica	13	—
	Kurihara T (2014) [16]	—	1	71	M	asbestos	—	—
Brazil	Moreira MA (2010) [17]	saws and knives sharpener	1	27	M	Hard metal	8	Y
Turkey	Fidan F (2005) [18]	welding	1	23	M	Hard metal	8	Y
	Sahbaz S (2007) [19]	denim, sandblasting	2	Case 1: 23 Case 2: 25	M	silica	Case 1: 3 Case 2: 1.5	Case 1: Y Case 2: —
	Aydin Y (2010) [20]	—	2 (5)	18.6 (16-22)*	M*	silica	—	Y *
Belgium	Demoulin AS (2009) [21]	metal sandblasting	1	26	M	silica	5	Y
South Africa	Oni T (2015) [22]	gold miner	1	59	M	silica	16.5	Y
Korea	Yang HS (2014) [23]	glass blending	1	57	M	silica	20	Y
Morocco	Elidrissi AM (2016) [24]	well-digger	2 (54)	50 (34-82)*	M	silica	12.9*	Y(36)*
China	Zhang DH (2003) [25]	gem worker	5 (47)	—	—	silica	4.67(1.17)*	—
	Wu N (2020)[26]	Artificial Stone Natural stone	3 (18) 1 (63)	36.1 (9.6)* 52.8 (8.6)*	M* M(52), F(11)*	silica	6.4 (2.9)* 29.3 (11.7)*	Y(12)* Y(43)*
USA	Suratt PM (1977)[27]	tombstone sandblaster	4	36 (23-47)	M	silica	2.9 (1.6-5.3)	Y(4)
	Mindy J. (2002)[28]	Aluminum welder	1 (2)	43	M	Aluminum fume	24	Y

Cases are presented as pneumoconiosis with pneumothorax (total observation cases).
Age is presented as mean (SD or range); duration of exposure is presented in mean years (SD or range).
—, information not available or not stated; * data for all observed cases; Y( ), yes(case number); N, not used.

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