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Environmental and occupational exposures and the risk of idiopathic pulmonary fibrosis: A systematic review

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ABSTRACT. **Purpose.** ***Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive, fibrosing interstitial pneumonia. The recognition of the risk factors for IPF is mandatory for disease prevention. The aim of the present systematic review is to evaluate the association between occupational and environmental exposures and the risk of IPF.*** **Methods.** ***Original observational studies published before July 3rd (2020) were identified through electronic searches of the PubMed, Embase, Cochrane and Web of Science databases. To meet the inclusion criteria, studies had to describe the exposure assessment, and the diagnosis had to be based on clinical history, computed tomography (CT) and/or histology.*** **Results.** ***Eight studies met the inclusion criteria for the systematic review, including a total of 2084 patients. A quantitative meta-analysis could not be performed due to the heterogeneity of the studies. Smoking was associated with an increased risk of IPF, but there was no clear dose-response relationship for smoking years and pack-years consumption. Exposure to birds and occupational exposure to metal and organic dust at work were also associated with the risk of IPF.*** **Conclusions.** ***This systematic review revealed an association between smoking, exposures to birds and cat allergens and occupational exposures to metal, wood and organic dusts and the risk of IPF, although the findings were controversial among the studies. Further investigations should integrate genetic susceptibility analysis, dose-response relationships, and direct measures of exposure, performing adjustments for possible confounders.***

Key words: *Idiopathic pulmonary fibrosis, Environmental exposure, Occupational exposure, Risk factors, Systematic review.*

RIASSUNTO. Esposizione ambientale e lavorativa e rischio di fibrosi polmonari e idiopatica: una revisione sistematica della letteratura.
Introduzione. **La fibrosi polmonare idiopatica (IPF) è una forma specifica di polmonite interstiziale cronica, fibrosante, e progressiva. Il riconoscimento dei fattori di rischio dell'IFP è indispensabile ai fini della prevenzione della malattia. Lo scopo della presente revisione sistematica è quello di valutare l'associazione tra esposizione professionale e ambientale e il rischio di IPF.**
Metodi. **Attraverso la ricerca nei database elettronici PubMed, Embase, Cochrane e Web of Science sono stati identificati gli studi epidemiologici osservazionali originali, pubblicati fino al 3 luglio 2020, che riguardavano l'esposizione ad agenti inalanti e il rischio di IPF. Sono stati inclusi gli studi in cui era stata valutata l'esposizione ambientale e/o lavorativa e la diagnosi di IPF era stata fatta mediante anamnesi, tomografia computerizzata (CT) toracica e/o esame istologico.**
Risultati. **Otto studi hanno soddisfatto i criteri di inclusione per la revisione sistematica, per un totale di 2084 pazienti.**

Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause, limited to the lungs and defined by a histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP) (1, 2). IPF is characterized by an irreversible decline in lung function associated with an average life expectancy of approximately 3 years (3). IPF affects approximately 5 million people worldwide (4). Prevalence and incidence increase with age and are higher in men (2, 5, 6).

Several risk factors have been associated with the development of IPF, including advanced age, male sex, genetic factors, smoking and other environmental exposures (7-9). Cigarette smoking, especially more than 20 pack-years, was the strongest environmental risk factor associated with IPF (10). Exposure to stone, wood dust, metal dust, silica, textile dust, agriculture, farming, livestock and organic dust have also been suggested as risk factors (11-14). Observational data have implicated obstructive sleep apnea, air pollution and herpesvirus infections in the risk of interstitial lung diseases (11, 15-18). Gastroesophageal reflux may contribute to lung injury via microaspiration, although this association is more difficult to interpret given the high frequency of gastroesophageal reflux in the general population (19, 20).

There is no cure for IPF; nintedanib and pirfenidone can slow disease progression and extend life expectancy (21-23). The recognition of risk factors could help to promote preventive strategies for IPF. The aim of this systematic review was to evaluate the available evidence for the connection between occupational and environmental exposures and IPF.

Methods

The methods and the writing of this report are in accordance with the recommendations of the Meta-analysis of Observational Studies in Epidemiology Group and the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines, respectively (24, 25). The PubMed, Embase, Cochrane and Web of Science data-

Non è stato possibile eseguire una meta-analisi quantitativa a causa dell'eterogeneità degli studi. Il fumo di sigaretta è risultato associato ad un aumentato rischio di IPF, anche se non è emersa una relazione dose-risposta per quanto riguarda gli anni di esposizione al fumo e il numero di pacchetti di sigarette consumati per anno. Altri fattori di rischio sono risultati l'esposizione a volatili e l'esposizione a metalli e polveri organiche in ambito lavorativo.
Conclusioni. **Questa revisione sistematica ha evidenziato una possibile associazione tra IPF ed i seguenti fattori di rischio: fumo di sigaretta, esposizione a volatili e allergeni del gatto ed esposizione professionale a metalli, polveri organiche e di legno. Sono necessari ulteriori studi che comprendano il monitoraggio ambientale per misurare l'esposizione e per valutare il rapporto dose-risposta e l'interazione con possibili fattori confondenti. Infine sono necessari studi che approfondiscano la suscettibilità genetica e la sua interazione con fattori ambientali.**

Parole chiave: Fibrosi polmonare idiopatica, esposizione ambientale, esposizione lavorativa, fatori di rischio, revisione sistematica.

bases were used to search for published and original articles until 3rd July 2020. No language or geographical restrictions were imposed. The PubMed search strategy was based on an article that identified efficient PubMed search filters for the study of environmental determinants of diseases that could be potentially related to outdoor air pollution (26). These filters were combined with other proposed strings regarding occupational determinants (27). The more "sensitive" string was chosen based on the use of broader fields and additional coverage provided by other terms under study. Search strategies are described in the supplemental material (Table S1). Additional articles were also searched from the reference lists of relevant articles obtained. Duplicates were removed within EndNote.

The prespecification protocol included studies with case-control and cohort designs, with exposed and unexposed groups, that assessed the adult population, without gender, geographic and ethical restrictions, and with at least 50 subjects in each group. They had to analyze the association between occupational or environmental exposure and IPF and include descriptions of exposure assessment and a diagnosis based on clinical history, CT scan (UIP pattern) and/or histology. Studies had to exclude autoimmune diseases. The reported results had to allow the computation of a measure of association, such as relative risk (RR) or odds ratio (OR) and either report an effect estimate and 95% confidence interval (CI). Meta-analyses, review articles, letters to the editor, editorials, case series, case reports, cross-sectional studies, conference proceedings, conference abstracts, unpublished articles, articles that did not focus on the association of interest and those that included only silica or asbestos exposure were excluded. The Office of Health Assessment and Translation (OHAT) risk-of-bias tool was used to assess the credibility of the link between exposure and outcome (28, 29).

Results

The search strategies retrieved 971 references, 327 from PubMed, 498 from Embase, 15 from Cochrane and 216 from Web of Science (Figure 1). Of the 1056 studies obtained, 164 were removed within EndNote (duplications). One additional paper was identified from the refer-

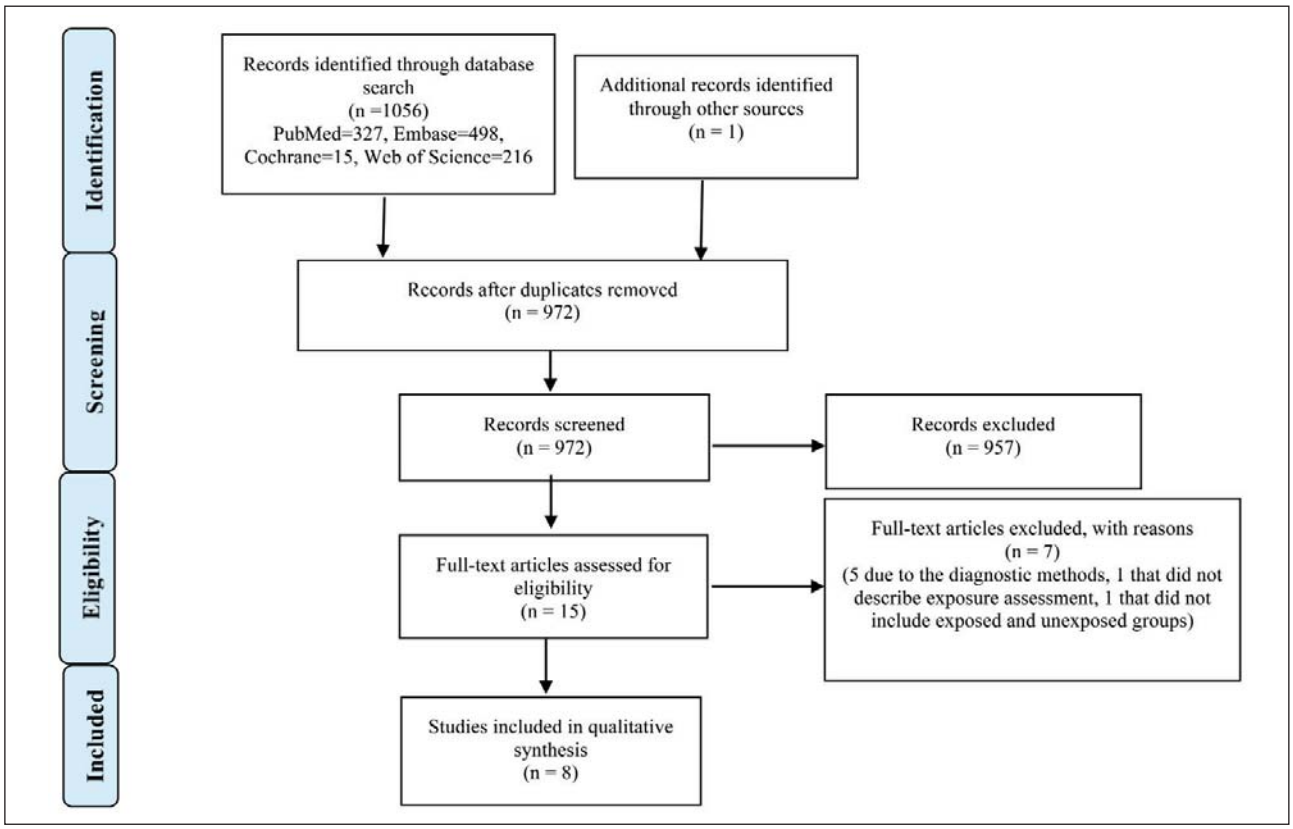

Figure 1. ***PRISMA flow diagram***

ence list of a relevant article. A total of 957 abstracts were not relevant to this review (basic science, genetics, research in animals, asbestosis). Other articles were excluded due to the study design (reviews, case series, conference abstracts, case reports). The 15 remaining articles were fully reviewed, after which 8 studies were deemed to meet the inclusion and exclusion criteria, including a total of 2084 patients. Eight studies were excluded: 5 due to the diagnostic method, one that did not describe exposure assessment (autopsy study, and another that did not include exposed and unexposed groups (30-36). Two selected studies evaluated different exposures in the same group of subjects (11, 37). All included studies used a case-control design. Due to heterogeneity and variation in study methodology, a formal meta-analysis for deriving summary statistics was not possible.

Study Characteristics and Results of Individual Studies

The characteristics of the studies included in the systematic review and the main results that found a positive association between environmental and occupational exposures and the risk of IPF are summarized qualitatively in Table I. Cases were selected from hospital databases, collaborating institutions or national registers. Comparability of the results among the studies was difficult due to the assessment of different exposures; thus, the results are described individually. Smoking and exposure to domestic animals were considered environmental exposures.

Paolocci and cols. evaluated the relationship between UIP patterns and occupational exposure in the Umbria region. The diagnosis was based on the UIP pattern observed on the CT scan. Exposure was defined by an occupation or an exposure lasting for at least five years and, for cases of IPF, starting five years or more before the diagnosis of the disease. As shown in Table I, subjects with any occupational exposures to agents known to cause UIP had an increased risk for UIP. Higher risk was observed in the metallurgical and steel industries, followed by exposure to metal dust or metal fumes. No association was found between wood industry or construction workers and subjects exposed to mineral dust, vapors, gas, and fumes (38).

A Korean study included cases diagnosed using chest CT, transbronchial lung biopsy and video-assisted thoracoscopic lung biopsy. Hospital-based controls were enrolled to match each patient, including patients with *Mycobacterium tuberculosis* infection, community-acquired bacterial or viral infection, pneumothorax, and pleurisy. Subjects exposed to potentially hazardous materials for > 1 year were considered exposed. Exposure to metal dust and to any occupational hazardous materials for more than one year were significantly associated with the risk of IPF. After adjustment for smoking history, environmental and military exposures, no association was observed between the risk of IPF and exposure to wood dust, silica, and asbestos fibers (39).

Kim and cols. assessed risk factors for chronic fibrosing idiopathic interstitial pneumonia (FIIP), including IPF and idiopathic nonspecific interstitial pneumonia (INSIP). The diagnosis was performed with surgical lung biopsy or an high-resolution computed tomography. An exposure ≥ 10 hours per week was defined as an occupational exposure. In the subgroup analysis between the IPF and INSIP groups, agriculture was associated with an increased risk for IPF. No association was found with metal exposure, machinery-related trades, building construction, demolition, agriculture, carpentry or woodworking, textile making/repair or leather processing. After logistic regression adjustment for age and smoking, an increased risk of IPF was observed with exposure to stone/sand/silica and insecticide/pesticides, but no association was found with exposure to wood dust, organic dust, welding fumes or metal dust (40).

A Swedish study assessed the interaction between smoking, gender, occupational exposure, and the risk of severe pulmonary fibrosis (PF) in patients who had started long-term oxygen therapy. Exposure was defined as any exposure 10 or more years before the date of the PF diagnosis. Men with current or past smoking and occupational exposure had greater risk of IPF than nonexposed women. Heavy smoking (≥ 20 pack-years) was associated with an increased risk for severe IPF, but no evidence of the effects of inorganic dust or metal dust and exposure to birds in this study on IPF risk was noted (41).

An Egyptian multicenter hospital-based study included IPF patients diagnosed through clinical history, clinical examination, and chest HRCT. Occupational agents were defined as present if the subject reported > 10 hours of exposure per week. For male workers, exposures to wood dust and wood preservatives increased the risk of IPF, as well as occupational exposures in chemical and petrochemical industries, carpentry and wood working. Environmental exposure to birds and cats increased the risk of IPF development in both genders. Among female workers, an increased risk of IPF was observed for farming, animal rearing occupational exposures to animal feeds, products and exposure to insecticides and pesticides. There was no association between the risk of IPF and occupational exposure to metal dust, metal fumes, solvents, stone, clay, glass, concrete and textile dust or environmental exposure to mold and dogs (42).

A Japanese study included IPF patients diagnosed within 2 years and hospitalized controls with acute bacterial pneumonia or outpatients with common colds. The diagnosis of IPF was based on clinical history, clinical examination, and HRCT of the chest. Exposure was assessed through self-administered questionnaires; occupational agents were defined as present if the subject reported ≥ 10 hours of exposure per week. Exposure to any dust was associated with an increased risk for IPF, with a higher risk linked to metal exposure. No association was observed with exposure to pesticides, solvents, stone, sand, chalk, coal, asbestos or wood, nor for workers in construction, farming, fishing, or forestry. Smokers with a consumption from 20 to 39.9 pack-years had a higher risk, but there was no dose-response association with cumulative consumption of cigarettes. No association was found with exposure to mold and indoor domestic pets (birds, cats, dogs, and hamsters) (43).

Baumgartner and cols. conducted a multicenter study in the US to evaluate the risk of IPF associated with cigarette

Table I. ***Study characteristics and synthesis of results that observed a positive association between occupational or environmental exposure and risk of IPF***

Reference/Location	Patients/Controls Population studied	Occupational or Environmental Exposure	OR (95% CI)
Paolocci, 2018 (38) Italy	60 patients/277 controls. Patients with unusual interstitial pneumonia (UIP) identified through medical records at the Section of Occupational Medicine, Respiratory diseases, and Toxicology of the University Hospital of Perugia. Controls were selected from a random sample among inhabitants of the same catchment area.	Any job at risk of UIP	4.14 (2.27-7.53)
		Metallurgical and steel industries	4.80 (1.50-15.33)
		Metal dust or metal fumes	3.8 (1.2-12.2)
		Farmers, vets and gardeners	2.73 (1.47-5.10)
		Organic dust	2.4 (1.3-4.3)
		Environmental tobacco smoke at work	2.2 (1.2-4.0)
Koo, 2017 (39) Korea	78 patients/78 controls. Patients newly diagnosed with IPF from in- and outpatient clinics of the department of respiratory medicine of four teaching hospitals in Seoul and Gyeonggi. Hospital-based controls were enrolled to match each patient from the same hospitals over the same period of time.	Metal dust	4.0 (1.34-11.97)
		Any exposure to occupational hazardous materials for > 1 year	3.67 (1.02-13.14)
		Type 2 diabetes	4.3 (1.9-9.8)
		Hardwood dust	2.5 (1.06-5.89)
Kim, 2017 (40) Korea	70 patients/70 controls. Patients with IPF and nonspecific interstitial pneumonia at a university hospital in South Korea. Controls were drawn from healthy subjects who were examined for an annual check-up at the health examination center.	Agriculture	4.5 (1.25-16.23)
		Insecticides/pesticides	4.45 (1.21-16.37)
		Stone/sand/silica	8.84 (1.07-73.49)
Ekström, 2014 (41) Sweden	137 patients/719 controls. Patients who had started a long-term oxygen therapy for pulmonary fibrosis (including IPF) in the Swedevox register. Controls were selected as a random sample from the general population.	Smoking 10-19 pack-years	2.10 (1.20 -3.68)
		Smoking >20 pack-years	2.25 (1.26-4.02)
		Men with current or past smoking and occupational exposure, compared to nonexposed women	2.96 (1.34-6.52)
Awadalla, 2012 (42) Egypt	201 patients/205 controls. All IPF cases admitted to the collaborating hospitals located in Cairo, Tanta, and Mansoura. One control subject was selected to match each patient in age (±3 years), sex, residence and smoking habits from patients admitted to the same wards, during the same period and treated from respiratory diseases other than interstitial pulmonary fibrosis.	Chemical/petrochemical (males)	6.47 (1.66-25.12
		Carpentry or woodworking (males)	2.56 (1.02-7.01)
		Wood dust, wood preservatives (males)	2.71 (1.01-7.37)
		Farming (females)	3.34 (1.17-10.12)
		Raising birds (females)	1.82 (1.03-3.85)
		Animal feeds, products, and dust (females)	1.78 (1.01-3.13)
		Insecticides/pesticides (females)	8.68 (1.04-72.17)
		Birds (males)	3.49 (1.49-8.19)
		Birds (females)	3.86 (1.95-7.62)
		Cats (females)	8.24 (1.8-37.70)
Miyake, 2005 (43) Japan	102 patients/59 controls. Patients aged 40 years or over who were within 2 years of having diagnosed with IPF among 21 collaborating hospitals and their 29 affiliated hospitals. Controls were selected from individuals (>40 years) who received treatment at the respiratory ward of the same hospitals.	Any dust	5.61 (2.12-17.89)
		Metal	9.55 (1.68-181.12)
		Pack-years of smoking (20.0-39.9 pack-years)	3.23 (1.01-10.84)
Baumgartner, 2000 (11) USA	248 patients/491 controls. Patients diagnosed at 16 collaborating institutions located in 15 states. Controls were recruited for each case by random digit dialing, with matching on age, sex, and geographic region.	Cigarette smoking	1.6 (1.1-2.4)
		Hairdressing	4.4 (1.2-16.3)
		Raising birds	4.7 (1.6-14.1)
		Stone cutting/polishing	3.9 (1.2-12.7)
		Vegetable/animal dust	4.7 (2.1-10.4)
		Livestock (≥ 5 ys)	3.3 (1.3-8.3)
		Raising birds (≥ 5 ys)	7.5 (2.0-28.6)
		Vegetable/animal dust (≥ 5 ys)	4.5 (1.9-10.8)
		Livestock	2.7 (1.3-5.5)
Baumgartner, 1997 (44) USA		Former smokers	1.9 (1.3-2.9)
		Ever cigarette smoking	1.59 (1.1-2.4)
		Smokers with 21 to 40 pack-year	2.26 (1.3-3.8)

smoking and with occupational and environmental exposures in another analysis. The diagnosis of IPF was based on clinical history and, when available, on one or more of four types of information (open lung biopsy, transbronchial biopsy, bronchoalveolar lavage, and CT scan). A history of smoking at least once was associated with an increased risk of IPF. The risk was significantly elevated for former smokers, those who smoked cigarettes at least once and consumption from 21 to 40 pack-years but not for more than 40 pack-years. For smokers, the risk of developing IPF with smoking was higher for men and older participants (≥ 64 years of age) (44). Occupational history included all jobs of more than 6 months duration. After adjustment for age and smoking, occupational factors associated with increased risk of IPF were livestock, hairdressing, raising birds, stone cutting or polishing and exposure to vegetable dust/animal dust. No association was observed between the risk of IPF and occupational exposure to asbestos, fiberglass, insecticides, pesticides, solvents and talc; likewise, no association was observed with the following job activities: building, demolition, carpentry, woodworking, chemistry, petrochemistry, farming, insulation work, jewelry making, mining, painting and printing (45).

Risk of Bias

The risk of bias assessment is summarized in Table II. Methods of selection of subjects, controlling for confounders, exposure and outcome assessments differed significantly among the studies. Patients were drawn from major referral centers, possibly resulting in a sample of more severely affected cases. Some studies performed adjustments for age, gender, region (39, 42, 43), others for smoking (11, 38, 40, 42), but only two for clinical risk factors (38, 40). The family history of pulmonary fibrosis was assessed in only one study (38). Exposure was not assessed under the same method and time frame, and the dose-response relationship was not always assessed. Detection bias might arise due to the changes in definition, diagnostic criteria, and classification of idiopathic interstitial pneumonia. Updates were also performed during the conduction of the selected studies (2000, 2002, 2011 and 2018), and no study was included after the 2018 guidelines were issued. None of the articles reported a priori the study protocol, which might be a source of bias according to OHAT.

Discussion

This review qualitatively describes the results of eight systematically selected studies that evaluated the association between occupational and environmental exposures and the risk of IPF.

Regarding environmental exposure, most studies found a correlation between smoking and an increased risk of IPF. However, two studies did not observe a clear dose-response relationship for duration and pack-year consumption: there was an association for 20-39 pack-years but not for more than 40 pack-years consumption (37, 43). Smoking increased the risk of IPF when associated with different occupational exposures (37, 38). Domestic or occupational exposure to birds was associated with an increased risk of IPF in two studies (11, 42). An increased risk of IPF was observed with domestic exposure to cats but not to dogs and mold (42, 43). Exposure to organic material was associated with IPF risk in three studies (11, 38, 42). The interaction between exposure to

Table II. ***Risk of bias of the included studies in Environmental and occupational exposures and risk of idiopathic pulmonary fibrosis: A systematic review, according to OHAT***

Author, year (Reference)	Selection Bias	Confounding Bias	Attrition or Exclusion Bias	Detection Bias		Selective Reporting Bias	Other Sources of Bias
				Exposure Characterization	Outcome Assessment		
Paolocci, 2018 (38)	+	-	+	+	+ +	+	-
Koo, 2017 (39)	-	+	+	+	++	+	--
Kim, 2017 (40)	+	+	+	+	+	+	--
Ekström, 2014 (41)	-	-	+	+	-	+	-
Awadalla, 2012 (42)	-	+	+	-	++	+	--
Miyake, 2005 (43)	-	+	+	+	++	+	-
Baumgartner, 2000 (45)	-	+	+	+	+	+	+
Baumgartner, 1997 (44)	-	+	+	+	+	+	-

Risk of bias response options for individual itens:	
++	Definitely low risk of bias
+	Probably low risk of bias
-	Probably high risk of bias
--	Definitely high risk of bias
n/a	Not applicable

insecticides, pesticides, and agriculture was also shown to increase the risk of IPF (38, 40, 42). Livestock was associated with a higher risk for exposure for more than 5 years (11). Studies found different results regarding the association between IPF and metal dust (11, 38, 39, 41-43, 46). Metallurgical and steel industry occupations were associated with IPF risk (38). Men exposed to carpentry or woodworking hazards, such as wood dust or wood preservatives, were also associated with an IPF risk (42), but exposure to wood dust or woodworking was not associated in other studies (11, 38-40, 43). A meta-analysis presented as an abstract assessed the association between dust and IPF risk, including 32 risk estimates from 12 publications, totaling 1949 cases. An increased risk of IPF was associated with any dust exposure and individually with metal, wood and agricultural dust exposure (47). No study that evaluated the association between air pollution and the risk of IPF met the eligibility criteria for this review.

Comparability of the results among the studies was difficult due to different exposures and their assessments. Furthermore, the eight studies included in the final review were performed in six different countries, with significant exposure differences, because of economic, geographical, and cultural factors. Limitations were also derived from studies with case-control designs, which were subject to considerable bias. Patients were drawn from major referral centers, possibly resulting in a sample of more severely affected patients. Some articles included healthy controls (11, 37, 38, 40, 41), while others included hospitalized subjects (39, 42, 43). Only one study performed lung imaging from healthy control subjects to exclude interstitial disease (46). Most studies excluded subjects with possible occupational lung diseases (asbestosis and silicosis), lung irradiation, and current or previous use of medications known to cause lung fibrosis (11, 37, 38, 40, 43). However, others included exposure to asbestos in the assessment (11, 39, 43). End-stage chronic hypersensitivity pneumonitis (HP) may mimic IPF in patients exposed to birds (48). In addition, metalworking can also be associated with hypersensitivity pneumonitis due to the inhalation of bioaerosols with bacterial endotoxins present in fluids and emulsions (49, 50). Only Baumgartner and cols. performed serologic tests in subjects exposed to agents associated with HP to reduce the risk of misdiagnosis with IPF (44, 45). Most of the studies assessed exposure through self-reported questionnaires, which could be susceptible to recall bias. Different methods to assess exposure duration and intensity were used in each study, making it difficult to accurately compare them. Subjects might be exposed to more than one occupational or environmental factor. Studies that directly measured exposure in subjects (in blood, plasma, urine) were likely to have less measurement error and less risk of bias for exposure than studies relying on indirect measures.

The diagnosis of IPF remains a challenge due to the lack of pathognomonic findings. Bias may arise due to changes in definition, diagnostic criteria, and classification of idiopathic interstitial pneumonia. Potential gene and protein markers to discriminate IPF from other interstitial lung diseases have been identified (51). In the future, gene expression signatures may be helpful to diagnose IPF properly in dubious cases, and a better understanding of the underlying pathogenic mechanisms may also suggest new ways to improve treatments of the disease.

Conclusion

This systematic review revealed a positive association between environmental exposures (smoking, exposure to birds, cats) and occupational exposures to metal, wood and organic dusts and the risk of IPF. As IPF is an orphan disease, only through well-designed, multicentric prospective studies would it be feasible to properly assess this association. Further investigations should integrate genetic susceptibility analysis (through gene-environment interactions) and the dose-response relationship with direct measures of the exposure and adjust for possible confounders (age, smoking, gender, and geographic region).

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Compliance with ethical standards.

Conflict of interest Authors declare they have no conflicts of interest.

IPF new\Supplemental Material 3rd July.docx

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