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Effects of smoking, gender and occupational exposure on the risk of severe pulmonary fibrosis: a population based case-control study

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ABSTRACT

Objectives: To estimate the effects of smoking, gender and occupational exposure on the risk of developing severe pulmonary fibrosis (PF), including dose-response and interaction effects.

Methods: National case-control study of 171 patients (cases) starting long-term oxygen therapy (LTOT) for PF in Sweden between February 1997 and April 2000, and 719 random control subjects from the general population. Of cases, 137 had probable idiopathic pulmonary fibrosis (IPF). The odds ratios (ORs) for smoking, gender, and occupational exposure were estimated using Mantel-Haenzel analysis and conditional logistic regression, controlling for age and year of diagnosis.

Results: The adverse effect of smoking was amplified by male gender and occupational exposure, OR 4.6 ([95% confidence interval] 2.1 – 10.3) for PF, and OR 3.0 (1.3 – 6.5) for IPF, compared to in non-exposed women. Higher cumulative smoking exposure was linearly associated with increased risks. Compared to smoking less than ten pack-years, smoking ≥ 20 pack-years was associated with increased risk of PF and IPF, OR 2.6 (1.4 – 4.9) and OR 2.5 (1.3 – 5.0), respectively.

Conclusion: Smoking has a dose-related association with increased risk of severe PF. Men with a history of smoking and occupational exposure is a particular risk group for developing severe pulmonary fibrosis.

ARTICLE SUMMARY

Article focus

- Smoking, male gender and occupational exposures are proposed risk factors for developing severe idiopathic pulmonary disease (IPF), but data on the interplay between these factors are limited.
- This study aims to estimate the effects of smoking, gender and occupational exposure on the risk of developing severe IPF, including interactions and dose-response effects.

Key messages

- Smoking has a dose-response association with increased risk of severe IPF.
- The adverse effect of smoking is strongly amplified by male gender and occupational exposure. This study identifies men with a history of smoking and occupational exposures as a particular risk group for developing severe IPF.

Strengths and limitations

- Population-based case-control study of subjects developing oxygen-dependent pulmonary in Sweden with randomly selected controls from the general population.
- Analysis of detailed exposure data, accounting for confounders and lag time between exposure and disease.
- As the underlying etiology may be difficult to ascertain in patients with oxygen-dependent pulmonary fibrosis, IPF was defined through review of national administrative register data and individual medical records.

BACKGROUND

Pulmonary fibrosis (PF) constitutes a range of conditions that are either secondary to diseases or factors, such as systemic inflammatory disease and drug therapies, or primary, of which the most common is idiopathic pulmonary fibrosis (IPF).[1]

IPF is a chronic, progressive, fibrosing interstitial lung disease with a high risk of rapid progression and mortality.[2] Median survival after diagnosis is approximately two years.[2] The incidence of IPF has increased over time, with marked regional differences suggesting the pathogenic role of various environmental and occupational exposures.[3]

The etiology of IPF remains unknown.[2] The majority of IPF patients are men with a history of current or past smoking.[2] Most case-control studies have suggested an association between smoking and an increased risk of IPF,[4-7] although one study reported no such association.[8] This inconsistency is most likely due to differences in study settings, the included covariates and, in some studies, the use of hospital patients as control subjects, which might have biased the smoking estimates.[4 7 9-11] Occupational exposures, including metal, stone and wood dust, have been linked to higher risks of developing IPF.[12]

It is unknown if there are interactions between smoking, gender and occupational exposure, and the risk of developing IPF. The only two studies which analyzed interactions reported a tendency towards an amplified IPF risk in patients with a history of smoking and occupational exposure, but the studies failed to establish statistically significant interactions.[6,13] Moreover, it is unclear if smoking really is an etiologic factor for IPF, as studies included low numbers of patients, and data on whether there is a dose-dependent relation between smoking and the risk of IPF are limited.

The aim of the present nationwide case-control study was therefore to estimate the associations between smoking, gender, occupational exposure, and the risk of developing severe pulmonary fibrosis.

METHODS

This was a national, register-based case-control study. Patients starting long-term oxygen therapy (LTOT) for PF between 1 February 1997 and 4 April 2000 in the national Swedevox register were eligible for inclusion as cases. The Swedevox register covers some 85% of all patients starting LTOT in Sweden.[13] Details of the study design and a previous analysis using the same data set have been published.[14] Data was collected through an extensive postal questionnaire on smoking, occupational exposure (including fibers, fumes, gas, mineral dust, organic dust, and vapours) and diagnosis of PF. The questionnaire has been described in detail elsewhere.[15] Smoking data included the year of starting smoking, date of stopping smoking, and the mean number of smoked cigarettes per day during each ten year period between ages 15 – 65 years, and the mean exposure after 65.[15] After the exclusion of patients who were incorrectly registered (n = 12; 5%) or did not respond to the questionnaire (n=58; 24%), 171 PF cases were included in the analysis.

Patients with probable idiopathic pulmonary fibrosis (IPF cases, n = 137) were identified through a review of each patient's medical record done independently by specialists in respiratory medicine (KN, TG).[14] IPF cases in the study included only patients without any identifiable or probable cause of PF (infection, pneumoconiosis, medications, irradiation, rheumatic or systemic inflammatory diseases etc.)[14]

Control subjects were selected as a random sample (n = 1000) from the general population of the same age range as the PF patients. Of the control subjects, 719 (72%) returned complete exposure data and were included in the analysis.

Ethics Statement

All participants gave their informed consent to participate. The study was approved by all the relevant ethics committees in Sweden, the Swedish National Board of Health and Welfare, and the Data Inspection Board.

Statistical Analysis

Cases and control subjects were categorized according to year of birth (1906 – 1923, 1924 – 1936 or 1937 – 1969) and cases according to year they received their PF diagnosis (1968–1986, 1987–1993 or 1994–1999). Control subjects were assigned a time point corresponding to the year patients received their PF diagnosis, using a method described previously.[14 15] First, control subjects within each birth year group were assigned a random diagnosis year group, weighted by the number of cases in each diagnosis year group. Then, the year of PF diagnosis of each control subject was set to the mid-year of the corresponding year of the patient group. Characteristics at baseline (the date the questionnaire was filled in) were presented using frequencies and percentages for categorical variables. Continuous data were presented using mean with standard deviation (SD) and median with range or interquartile range (IQR) for variables with normal and skewed distribution, respectively.

Smoking status and cumulative smoking exposure, calculated as pack years ([mean number of cigarettes per day] / 20 x [years of exposure]), were recorded up to 10 years prior to the date

of the PF diagnosis (a 10-year time lag), allowing time between smoke exposure and the development of oxygen-dependent PF.

Associations between smoking and the risk of developing oxygen-dependent PF and IPF, and the interactions between smoking, occupational exposure and gender were estimated and reported using Mantel-Haenzel analysis, controlling for year of birth, year of diagnosis and gender, as applicable. Interactions were also analyzed using conditional logistic regression, stratified for year of birth, year of diagnosis, gender, with adjustment for age and pack-years of smoking. All estimates were consistent between Mantel-Haenzel analysis and the conditional logistic models.

Associations were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was defined as a double-sided $p < 0.05$. Statistical analyses were performed using Stata version 11.1 (StataCorp LP; College Station, TX) and SAS version 9.2 (SAS Institute, Inc., Cary, NC).

RESULTS

We included 171 patients with PF, of whom 137 were classified as having IPF, and 719 control subjects. Baseline characteristics are shown in Table 1. Among PF cases, the rate of occupational exposure was higher in men than in women (80% vs. 52 %; $p < 0.001$). Men also had higher smoking exposure. Ten years before the PF diagnosis, 90 (84%) men were ever-smokers with a median 10 (IQR, 3 – 23) pack years, compared to 29 (45%) women with a median 8 (IQR, 3 – 15) pack years. A similar difference was seen for IPF cases.

There was a significant interaction between smoking, occupational exposure and gender, and the risk of oxygen-dependent PF (test of homogeneity, p = 0.028). The differences in effects were similar for IPF (Table 2). Men with current or past smoking and occupational exposure had markedly increased risk of PF, OR 4.6 (2.1 – 10.3), and IPF, OR 3.0 (1.3 – 6.5), compared to non-exposed women (Table 2). Adjustment for differences in pack years between men and women, in addition to the other covariates, did not affect the estimates.

There was a linear association between higher cumulative smoking exposure (up to ten years before diagnosis) and increased risk of PF and IPF, OR 1.03 (95% CI, 1.01 – 1.04) per pack year and OR 1.02 (95% CI, 1.01 – 1.04) per pack year, respectively. Compared to lower levels of smoking (1 – 9 pack years), heavy smoking (≥ 20 pack years) was associated with an increased risk of PF, OR 2.6 (95% CI, 1.4 – 4.9), and IPF, OR 2.5 (95% CI, 1.3 – 5.0), as shown in Table 3. Using a 5-year time lag for smoking exposure instead of 10 years resulted in similar estimates.

DISCUSSION

The main findings are that 1) smoking was a risk determinant in the development of oxygen-dependent pulmonary fibrosis and that this risk was amplified by male gender and occupational exposure; 2) the association with smoking was dose-dependent, which may support the theory of the causative role of smoking in the pathogenesis of severe pulmonary fibrosis.

Our findings are consistent with reports of increased risk of IPF associated with smoking [4-6 10 12 16] and occupational exposures.[4-7 9 12 14 16] A previous analysis using the present data set

showed that specific occupational factors associated with an increased risk of PF included exposure to birds and wood dust.[14] Studies of a possible dose-response correlation between smoking and IPF have shown conflicting results, with two studies indicating a dose-dependent effect[5 6] and one study showing no dose correlation .[17] The latter study, however, analyzed only smoking status and the current smoking dose (cigarettes per day) and not cumulative smoking exposure such as pack years.[17] The present study extends the previous observations by demonstrating that the association between smoking and severe pulmonary fibrosis is dose-dependent and is modified by gender and occupational exposure.

A strength of the present study is that it included cases from a population-based prospective register of patients starting LTOT in Sweden. Control subjects were randomly selected from the general population. Previous studies using control subjects in hospitals may have yielded biased estimates, as the risk of hospitalization is likely to be related to occupational factors and smoking.[4 7 9-11] We had detailed data on the temporality, dose and duration of smoking. In contrast with previous studies, only exposure data up to ten years before the year of the PF diagnosis was included in the analysis to avoid reverse causation and to allow for the time lag between exposure to risk factors and the manifestation of clinical disease.

A possible limitation is that the self-reported exposure data could be influenced by recall bias. The validity of the exposure classification is, however, supported by a high degree of consistency between reported employment histories and occupational exposure to specific agents.[14] Secondly, the association between smoking and starting LTOT could be affected by survivor bias, as smokers are likely to be at high risk of dying of other diseases, such as cancer and cardiovascular disease, before they can develop severe IPF. Also, stopping smoking is a mandatory criterion for starting LTOT. Both these potential biases would tend to lower the number of smokers starting LTOT and our findings might thus underestimate the association between smoking and oxygen-dependent PF. Thirdly, the IPF diagnosis could be

misclassified in some patients. The validity of the PF and IPF diagnoses was checked by a respiratory physician using medical records, including available radiographic and histologic data.[14] Among idiopathic interstitial pneumonias, IPF is the most common condition and it is associated with a high risk of progression to hypoxemic respiratory failure and death.[1 18] Thus, the prevalence of IPF is likely high in oxygen-dependent pulmonary fibrosis. We included the PF cohort in the analysis, as it may be difficult to obtain a specific diagnosis in patients with advanced pulmonary fibrosis at the clinic. Our results were consistent in both the PF and IPF groups, which supports the validity of the present findings.

Mechanisms governing the relationship between smoking, gender, occupational exposure, and the development of severe pulmonary fibrosis are unknown but likely involve complex interactions between different environmental factors in genetically predisposed individuals.[19] The adverse effect of smoking could in part be attributable to the development of concurrent emphysema, which has been shown to predict hypoxemia and a poor prognosis in IPF.[20]

For the clinician, this study identifies a group of male, heavy smokers with occupational exposure to harmful substances, who have a greatly increased risk of developing severe pulmonary fibrosis. In this group, interventions to help people reduce or stop smoking are a top priority.

In conclusion, smoking is associated with a dose-dependent increase in oxygen-dependent pulmonary fibrosis. The adverse effects of smoking are stronger in men and in people with occupational exposure.

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Author contributions: ME had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. Conception and design: KB, KN, GT, KT; Acquisition of data: TG, KB, KN, GT, KT; Analysis and interpretation of data: ME, TG, NM, KT; Drafting the article: ME, TG, KT; Revising it for important intellectual content and approval of the version to be published: ME, TG, KB, KN, GT, NM, KT.

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Conflicts of interest: No conflicts of interest exist for the authors.

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Data sharing statement: Analysis code is available from the corresponding author. No additional data is available.

References

1 American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 2002;165:277-304.

2 Raghu G, Collard HR, Egan JJ et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *American Journal of Respiratory and Critical Care Medicine* 2011;183:788-824.

3 Navaratnam V, Fleming KM, West J et al. The rising incidence of idiopathic pulmonary fibrosis in the U.K. *Thorax* 2011;66:462-7.

4 Iwai K, Mori T, Yamada N, Yamaguchi M, Hosoda Y. Idiopathic pulmonary fibrosis. Epidemiologic approaches to occupational exposure. *American Journal of Respiratory and Critical Care Medicine* 1994;150:670-5.

5 Hubbard R, Lewis S, Richards K, Johnston I, Britton J. Occupational exposure to metal or wood dust and aetiology of cryptogenic fibrosing alveolitis. *Lancet* 1996;347:284-9.

6 Baumgartner KB, Samet JM, Stidley CA, Colby TV, Waldron JA. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine* 1997;155:242-8.

7 Miyake Y, Sasaki S, Yokoyama T et al. Occupational and environmental factors and idiopathic pulmonary fibrosis in Japan. *The Annals of occupational hygiene* 2005;49:259-65.

8 Scott J, Johnston I, Britton J. What causes cryptogenic fibrosing alveolitis? A case-control study of environmental exposure to dust. *BMJ* 1990;301:1015-7.

9 Awadalla NJ, Hegazy A, Elmetwally RA, Wahby I. Occupational and environmental risk factors for idiopathic pulmonary fibrosis in Egypt: a multicenter case-control study. *Int J Occup Environ Med* 2012;3:107-16.

10 Garcia-Sancho Figueroa MC, Carrillo G, Perez-Padilla R et al. Risk factors for idiopathic pulmonary fibrosis in a Mexican population. A case-control study. *Respir Med* 2010;104:305-9.

11 Miyake Y, Sasaki S, Yokoyama T et al. Case-control study of medical history and idiopathic pulmonary fibrosis in Japan. *Respirology* 2005;10:504-9.

12 Taskar VS, Coultas DB. Is idiopathic pulmonary fibrosis an environmental disease? *Proceedings of the American Thoracic Society* 2006;3:293-8.

13 Strom K, Boe J. A national register for long-term oxygen therapy in chronic hypoxia: preliminary results. *Eur Respir J* 1988;1:952-8.

14 Gustafson T, Dahlman-Hoglund A, Nilsson K, Strom K, Tornling G, Toren K. Occupational exposure and severe pulmonary fibrosis. *Respir Med* 2007;101:2207-12.

15 Toren K, Jarvholm B, Brisman J, Hagberg S, Hermansson BA, Lillienberg L. Adult-onset asthma and occupational exposures. *Scand J Work Environ Health* 1999;25:430-5.

16 Baumgartner KB, Samet JM, Coultas DB et al. Occupational and environmental risk factors for idiopathic pulmonary fibrosis: a multicenter case-control study. Collaborating Centers. *Am J Epidemiol* 2000;152:307-15.

17 Gribbin J, Hubbard R, Smith C. Role of diabetes mellitus and gastro-oesophageal reflux in the aetiology of idiopathic pulmonary fibrosis. *Respir Med* 2009;103:927-31.

18 Bjoraker JA, Ryu JH, Edwin MK et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998;157:199-203.

19 Macneal K, Schwartz DA. The genetic and environmental causes of pulmonary fibrosis. *Proc Am Thorac Soc* 2012;9:120-5.

20 Mejia M, Carrillo G, Rojas-Serrano J et al. Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. *Chest* 2009;136:10-5.

TABLES

Table 1. Patient characteristics

Characteristic	PF cases (n = 171)	IPF cases (n = 137)	Controls (n = 719)
Age	73.7 ± 9.5	74.2 ± 9.8	64.3 ± 13.7
Males, n (%)	107 (63)	86 (63)	337 (47)
Never-smokers, n (%)	52 (30)	44 (32)	344 (48)
Ex-smokers, n (%)	114 (67)	89 (65)	251 (35)
Current smokers, n (%)	5 (3)	4 (3)	124 (17)
Smoking history up to 10 years before PF diagnosis, n (%)	119 (70)	93 (68)	375 (52)
1 – 9 pack years	29 (17)	22 (16)	176 (24)
10 – 19 pack years	34 (20)	27 (20)	91 (13)
≥ 20 pack years	36 (21)	27 (20)	62 (9)
Occupational exposure, n (%)	119 (70)	93 (68)	397 (55)

Data presented as mean ± standard deviation unless otherwise specified.

Abbreviations: IPF, idiopathic pulmonary fibrosis; PF, pulmonary fibrosis.

Table 2. Effect of smoking on the adjusted risk of pulmonary fibrosis, according to gender and occupational exposure

	PF Odds ratio (95% CI)		IPF Odds ratio (95% CI)	
	Women	**Men**	**Women**	**Men**
No occupational exposure	1.10 (0.50 – 2.42)	1.97 (0.64 – 6.13)	1.12 (0. 49 – 2.59)	1.44 (0.43 – 4.83)
Occupational exposure	1.10 (0.52 – 2.34)	4.63 (2.08 – 10.33)	1.32 (0.58 – 3.03)	2.96 (1.34 – 6.52)

Odds ratios (95% confidence interval) for the effect of smoking vs. no smoking on the risk of developing PF and IPF, estimated using Mantel Haenzel analysis controlled for year of birth and year of diagnosis. Smoking was defined as the presence of ever-smoking earlier than 10 years before the diagnosis.

Abbreviations: CI, confidence interval; IPF, idiopathic pulmonary fibrosis; PF, pulmonary fibrosis.

Table 3. Dose-response effect of smoking on the risk of severe pulmonary fibrosis

Smoking, pack years*	PF OR (95% CI)	IPF OR (95% CI)
0	1	1
1 – 9	1.03 (0.62 – 1.70)	0.90 (0.52 – 1.57)
10 – 19	2.26 (1.35 – 3.80)	2.10 (1.20 – 3.68)
≥ 20	2.66 (1.56 – 4.55)	2.25 (1.26 – 4.02)

Odds ratios (ORs) for levels of smoking estimated using conditional logistic regression adjusted for age and stratified for year of birth, year of diagnosis, gender and occupational exposure.

* Pack years of smoking up to 10 years before the year of PF diagnosis.

Abbreviations: IPF, idiopathic pulmonary fibrosis; PF, pulmonary fibrosis.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes
Methods			
Study design	4	Present key elements of study design early in the paper	Yes
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes
Participants	6	*(*a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	Yes
		(*b*) For matched studies, give matching criteria and the number of controls per case	Yes
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes
Bias	9	Describe any efforts to address potential sources of bias	Yes
Study size	10	Explain how the study size was arrived at	Yes
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes
		(*b*) Describe any methods used to examine subgroups and interactions	Yes
		(*c*) Explain how missing data were addressed	Yes
		(*d*) If applicable, explain how matching of cases and controls was addressed	Yes
		(*e*) Describe any sensitivity analyses	Yes
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes
		(b) Give reasons for non-participation at each stage	Yes
		(c) Consider use of a flow diagram	Yes
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes
		(b) Indicate number of participants with missing data for each variable of interest	Yes
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	Yes
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Adjusted analysis presented, biased crude estimates will be added upon request from reviewers or editor.
		(*b*) Report category boundaries when continuous variables were categorized	Yes
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Yes
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes
Discussion			
Key results	18	Summarise key results with reference to study objectives	Yes
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Article focus

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- This study aims to estimate the effects of smoking, gender and occupational exposure on the risk of developing severe IPF, including interactions and dose-response effects.

Key messages

- Smoking has a dose-response association with increased risk of severe IPF.
- The adverse effect of smoking is strongly amplified by male gender and occupational exposure. This study identifies men with a history of smoking and occupational exposures as a particular risk group for developing severe IPF.

Strengths and limitations

- Population-based case-control study of subjects developing oxygen-dependent pulmonary in Sweden with randomly selected controls from the general population.
- Analysis of detailed exposure data, accounting for confounders and lag time between exposure and disease.
- As the underlying etiology may be difficult to ascertain in patients with oxygen-dependent pulmonary fibrosis, IPF was defined through review of national administrative register data and individual medical records.

BACKGROUND

Pulmonary fibrosis (PF) constitutes a range of conditions that are either secondary to diseases or factors, such as systemic inflammatory disease and drug therapies, or primary, of which the most common is idiopathic pulmonary fibrosis (IPF).[1]

IPF is a chronic, progressive, fibrosing interstitial lung disease with a high risk of rapid progression and mortality.[2] Median survival after diagnosis is approximately two years.[2] The incidence of IPF has increased over time, with marked regional differences suggesting the pathogenic role of various environmental and occupational exposures.[3]

The etiology of IPF remains unknown.[2] The majority of IPF patients are men with a history of current or past smoking.[2] Most case-control studies have suggested an association between smoking and an increased risk of IPF,[4-7] although one study reported no such association.[8] This inconsistency is most likely due to differences in study settings, the included covariates and, in some studies, the use of hospital patients as control subjects, which might have biased the smoking estimates.[4 7 9-11] Occupational exposures, including metal, stone and wood dust, have been linked to higher risks of developing IPF.[12]

It is unknown if there are interactions between smoking, gender, and occupational exposure, and the risk of developing IPF. The only two studies which analyzed interactions reported a tendency towards an amplified IPF risk in patients with a history of smoking and occupational exposure, but the studies failed to establish statistically significant interactions.[6,13] Moreover, it is unclear if smoking really is an etiologic factor for IPF, as studies included low numbers of patients, and data on whether there is a dose-dependent relation between smoking and the risk of IPF are limited.

The aim of the present nationwide case-control study was therefore to estimate the associations between smoking, gender, occupational exposure, and the risk of developing severe pulmonary fibrosis.

METHODS

This was a national, register-based case-control study. Patients starting long-term oxygen therapy (LTOT) for PF between 1 February 1997 and 4 April 2000 in the national Swedevox register were eligible for inclusion as cases. The Swedevox register covers some 85% of all patients starting LTOT in Sweden.[13] Details of the study design and a previous analysis using the same data set have been published.[14] Data was collected through an extensive postal questionnaire on smoking, occupational exposure (including fibers, fumes, gas, mineral dust, organic dust, and vapours) and diagnosis of PF. The questionnaire has been described in detail elsewhere.[15] Smoking data included the year of starting smoking, date of stopping smoking, and the mean number of smoked cigarettes per day during each ten year period between ages 15 – 65 years, and the mean exposure after age 65.[15] Occupational data included the presence, start year, stop year and intensity (hours per week) for any occupational exposure, and exposure to birds (both at work and at home), metal dust, and wood dust. Occupational exposure was defined as any exposure ten or more years before the date of the PF diagnosis, allowing for a ten year lag-time between exposures and developing the disease.

After the exclusion of patients who were incorrectly registered (n = 12; 5%) or did not respond to the questionnaire (n=58; 24%), 171 PF cases were included in the analysis.

Patients with probable idiopathic pulmonary fibrosis (IPF cases, n = 137) were identified through a review of each patient's medical record done independently by specialists in respiratory medicine (KN, TG).[14] High-resolution computed tomography (HRCT) was performed in 41% of PF patients, CT in an additional 10%, and trans-bronchial and open lung biopsy was performed in 6%, respectively. The IPF cohort excluded patients with an identifiable or probable cause of PF: rheumatic or systemic inflammatory diseases (20% of PF cases), pneumoconiosis (6%), medications or irradiation (2%).[14]

Control subjects were selected as a random sample (n = 1000) from the general population of the same age range as the PF patients. Of the control subjects, 719 (72%) returned complete exposure data and were included in the analysis.

Ethics Statement

All participants gave their informed consent to participate. The study was approved by all the relevant ethics committees in Sweden, the Swedish National Board of Health and Welfare, and the Data Inspection Board.

Statistical Analysis

Cases and control subjects were categorized according to year of birth (1906 – 1923, 1924 – 1936 or 1937 – 1969) and cases according to year they received their PF diagnosis (1968–1986, 1987–1993 or 1994–1999). Control subjects were assigned a time point corresponding to the year patients received their PF diagnosis, using a method described previously.[14 15] First, control subjects within each birth year group were assigned a random diagnosis year group, weighted by the number of cases in each diagnosis year group. Then, the year of PF

diagnosis of each control subject was set to the mid-year of the corresponding year of the patient group. Characteristics at baseline (the date the questionnaire was filled in) were presented using frequencies and percentages for categorical variables. Continuous data were presented using mean with standard deviation (SD) and median with range or interquartile range (IQR) for variables with normal and skewed distribution, respectively.

Smoking status and cumulative smoking exposure, calculated as pack years ([mean number of cigarettes per day] / 20 x [years of exposure]), were recorded up to 10 years prior to the date of the PF diagnosis (a 10-year time lag), allowing time between smoke exposure and the development of oxygen-dependent PF.

Associations between smoking and the risk of developing oxygen-dependent PF and IPF, and the interactions between smoking, occupational exposure and gender were estimated and reported using Mantel-Haenzel analysis, controlling for year of birth, year of diagnosis and gender, as applicable. Interactions were also analyzed using conditional logistic regression, stratified for year of birth, year of diagnosis, gender, with adjustment for age and pack-years of smoking. All estimates were consistent between Mantel-Haenzel analysis and the conditional logistic models.

Associations were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was defined as a double-sided $p < 0.05$. Statistical analyses were performed using Stata version 11.1 (StataCorp LP; College Station, TX) and SAS version 9.2 (SAS Institute, Inc., Cary, NC).

RESULTS

We included 171 patients with PF, of whom 137 were classified as having IPF, and 719 control subjects. Baseline characteristics are shown in Table 1. Among PF cases, the rate of any occupational exposure was higher in men than in women (80% vs. 52 %; $p < 0.001$). Men also had higher smoking exposure. Ten years before the PF diagnosis, 90 (84%) men were ever-smokers with a median 10 (IQR, 3 – 23) pack years, compared to 29 (45%) women with a median 8 (IQR, 3 – 15) pack years. A similar difference was seen for IPF cases.

Interactions

There was a significant interaction between smoking, occupational exposure and gender, and the risk of developing oxygen-dependent PF (test of homogeneity, $p = 0.028$). The interaction was similar in the IPF cohort (Table 2). Men with current or past smoking and occupational exposure had markedly increased risk of PF, OR 4.6 (2.1 – 10.3), and IPF, OR 3.0 (1.3 – 6.5), compared to non-exposed women (Table 2). Adjustment for differences in pack years between men and women, in addition to the other covariates, did not affect the estimates.

Dose-response effect

There was a linear association between higher cumulative smoking exposure (up to ten years before diagnosis) and increased risk of PF and IPF, OR 1.03 (95% CI, 1.01 – 1.04) per pack year and OR 1.02 (95% CI, 1.01 – 1.04) per pack year, respectively. Compared to lower levels of smoking (1 – 9 pack years), heavy smoking (≥ 20 pack years) was associated with an increased risk of PF, OR 2.6 (95% CI, 1.4 – 4.9), and IPF, OR 2.5 (95% CI, 1.3 – 5.0), as shown in Table 3. Using a 5-year time lag for smoking exposure instead of 10 years resulted in similar estimates.

Subtypes of occupational exposure

The effect of occupational exposure seemed to be mediated partly through exposure to birds and wood dust. The risk of PF was increased by exposure to birds (OR 1.9; 95% CI, 1.0 – 3.7) and wood dust (OR 1.7; 95% CI, 1.0 – 3.0), controlling for age, gender, year of diagnosis, and smoking. There were no evidence of effects of inorganic dust (OR 1.3; 95% CI, 0.8 – 2.0) or metal dust (OR 1.1; 95% CI, 0.6 – 1.8). There were signs of interactions with smoking and gender for exposure to birds ($p = 0.021$) and wood dust ($p = 0.023$), respectively. Estimates were similar for the IPF cohort, except for a lower effect of bird exposure (OR 1.3; 95% CI, 0.6 – 2.8).

DISCUSSION

The main findings are that 1) smoking was a risk determinant in the development of oxygen-dependent pulmonary fibrosis and that this risk was amplified by male gender and occupational exposure; 2) the association with smoking was dose-dependent, which may support the theory of the causative role of smoking in the pathogenesis of severe pulmonary fibrosis.

Our findings are consistent with reports of increased risk of IPF associated with smoking [4-6 10 12 16] and occupational exposures.[4-7 9 12 14 16] A previous analysis using the present data set showed that specific occupational factors associated with an increased risk of PF included exposure to birds and wood dust.[14] Studies of a possible dose-response correlation between smoking and IPF have shown conflicting results, with two studies indicating a dose-dependent

effect[5 6] and one study showing no dose correlation.[17] The latter study, however, analyzed only smoking status and the current smoking dose (cigarettes per day) and not cumulative smoking exposure such as pack years.[17] The present study extends the previous observations by demonstrating that the association between smoking and severe pulmonary fibrosis is dose-dependent and is modified by gender and occupational exposure.

A strength of the present study is that it included cases from a population-based prospective register of patients starting LTOT in Sweden. Control subjects were randomly selected from the general population. Previous studies using control subjects in hospitals may have yielded biased estimates, as the risk of hospitalization is likely to be related to occupational factors and smoking.[4 7 9-11] We had detailed data on the temporality, dose and duration of smoking. In contrast with previous studies, only exposure data up to ten years before the year of the PF diagnosis was included in the analysis to avoid reverse causation and to allow for the time lag between exposure to risk factors and the manifestation of clinical disease.

A possible limitation is that the self-reported exposure data could be influenced by recall bias. The validity of the exposure classification was, however, supported by a high degree of consistency between reported employment histories and occupational exposure to specific agents.[14] Second, the association between smoking and starting LTOT could be affected by survivor bias, as smokers are likely to be at high risk of dying of other smoke-related disease, such as cancer and cardiovascular disease, before they can develop severe IPF. Also, stopping smoking is a mandatory criterion for starting LTOT. Both these potential biases would tend to lower the number of smokers starting LTOT and to underestimate the association between smoking and oxygen-dependent PF. Third, the IPF diagnosis could be misclassified in some patients, especially as the cohort was collected prior to the publication of main consensus definition of IPF.[1] The validity of the PF and IPF diagnoses was checked by respiratory physicians using medical records, including available radiographic and histologic data.[14]

Among idiopathic interstitial pneumonias, IPF is the most common condition and it is associated with a high risk of progression to hypoxemic respiratory failure and death.[1 18] Thus, the prevalence of IPF is likely high in oxygen-dependent pulmonary fibrosis. It is possible that we included patients with combined PF and emphysema, which may be present in up to one third of IPF patients.[19] Concurrent emphysema may constitute a smoking-related comorbidity or a distinct IPF phenotype,[19] and could explain, at least partly, the association between smoking, male gender, and the development of severe IPF in the present study. We included the PF cohort in the analysis, as it may be difficult to obtain a specific diagnosis in patients with advanced pulmonary fibrosis in the clinic. Findings were similar in the PF and IPF cohorts, which supports the validity of the analysis. Using national population based cases and controls, the present findings likely have high applicability to severe PF in Swedish clinical practice. The validity to other settings may be lower owing to differences in socio-demographics factors, health care organization, and pattern of exposure.

Mechanisms governing the relationship between smoking, gender, occupational exposure, and the development of severe pulmonary fibrosis are unknown but likely involve complex interactions between different environmental factors in genetically predisposed individuals.[20] The adverse effect of smoking could in part be attributable to the development of concurrent emphysema, which has been associated with hypoxemia and earlier death in IPF.[21]

For the clinician, this study identifies a group of male, heavy smokers with occupational exposure to harmful substances, who have a greatly increased risk of developing severe pulmonary fibrosis. In this group, interventions to help people reduce or stop smoking are a top priority.

In conclusion, smoking is associated with a dose-dependent increase in oxygen-dependent pulmonary fibrosis. The adverse effects of smoking are stronger in men and in people with occupational exposure.

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Author contributions: ME had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. Conception and design: KB, KN, GT, KT; Acquisition of data: TG, KB, KN, GT, KT; Analysis and interpretation of data: ME, TG, NM, KT; Drafting the article: ME, TG, KT; Revising it for important intellectual content and approval of the version to be published: ME, TG, KB, KN, GT, NM, KT.

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Data sharing statement: Analysis code is available from the corresponding author.

References

1 American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 2002;165:277-304.

2 Raghu G, Collard HR, Egan JJ et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *American Journal of Respiratory and Critical Care Medicine* 2011;183:788-824.

3 Navaratnam V, Fleming KM, West J et al. The rising incidence of idiopathic pulmonary fibrosis in the U.K. *Thorax* 2011;66:462-7.

4 Iwai K, Mori T, Yamadaa N, Yamaguchi M, et al. Idiopathic pulmonary fibrosis. Epidemiologic approaches to occupational exposure. *American Journal of Respiratory and Critical Care Medicine* 1994;150:670-5.

5 Hubbard R, Lewis S, Richards K, et al. Occupational exposure to metal or wood dust and aetiology of cryptogenic fibrosing alveolitis. *Lancet* 1996;347:284-9.

6 Baumgartner KB, Samet JM, Stidley CA, Colby TV, Waldron JA. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine* 1997;155:242-8.

7 Miyake Y, Sasaki S, Yokoyama T et al. Occupational and environmental factors and idiopathic pulmonary fibrosis in Japan. *The Annals of occupational hygiene* 2005;49:259-65.

8 Scott J, Johnston I, Britton J. What causes cryptogenic fibrosing alveolitis? A case-control study of environmental exposure to dust. *BMJ* 1990;301:1015-7.

9 Awadalla NJ, Hegazy A, Elmetwally RA, et al. Occupational and environmental risk factors for idiopathic pulmonary fibrosis in Egypt: a multicenter case-control study. *Int J Occup Environ Med* 2012;3:107-16.

10 Garcia-Sancho Figueroa MC, Carrillo G, Perez-Padilla R et al. Risk factors for idiopathic pulmonary fibrosis in a Mexican population. A case-control study. *Respir Med* 2010;104:305-9.

11 Miyake Y, Sasaki S, Yokoyama T et al. Case-control study of medical history and idiopathic pulmonary fibrosis in Japan. *Respirology* 2005;10:504-9.

12 Taskar VS, Coultas DB. Is idiopathic pulmonary fibrosis an environmental disease? *Proceedings of the American Thoracic Society* 2006;3:293-8.

13 Strom K, Boe J. A national register for long-term oxygen therapy in chronic hypoxia: preliminary results. *Eur Respir J* 1988;1:952-8.

14 Gustafson T, Dahlman-Hoglund A, Nilsson K, et al. Occupational exposure and severe pulmonary fibrosis. *Respir Med* 2007;101:2207-12.

15 Toren K, Jarvholm B, Brisman J, et al. Adult-onset asthma and occupational exposures. *Scand J Work Environ Health* 1999;25:430-5.

16 Baumgartner KB, Samet JM, Coultas DB et al. Occupational and environmental risk factors for idiopathic pulmonary fibrosis: a multicenter case-control study. Collaborating Centers. *Am J Epidemiol* 2000;152:307-15.

17 Gribbin J, Hubbard R, Smith C. Role of diabetes mellitus and gastro-oesophageal reflux in the aetiology of idiopathic pulmonary fibrosis. *Respir Med* 2009;103:927-31.

18 Bjoraker JA, Ryu JH, Edwin MK et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998;157:199-203.

19 Cottin V. The impact of emphysema in pulmonary fibrosis. *European Respiratory Review* 2013;22:153-157.

20 Macneal K, Schwartz DA. The genetic and environmental causes of pulmonary fibrosis. *Proc Am Thorac Soc* 2012;9:120-5.

21 Mejia M, Carrillo G, Rojas-Serrano J et al. Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. *Chest* 2009;136:10-5.

TABLES

Table 1. Patient characteristics

Characteristic	PF cases (n = 171)	IPF cases (n = 137)	Controls (n = 719)
Age	73.7 ± 9.5	74.2 ± 9.8	64.3 ± 13.7
Males, n (%)	107 (63)	86 (63)	337 (47)
Never-smokers, n (%)	52 (30)	44 (32)	344 (48)
Ex-smokers, n (%)	114 (67)	89 (65)	251 (35)
Current smokers, n (%)	5 (3)	4 (3)	124 (17)
Smoking exposure, n (%) *	119 (70)	93 (68)	375 (52)
1 – 9 pack years	29 (17)	22 (16)	176 (24)
10 – 19 pack years	34 (20)	27 (20)	91 (13)
≥ 20 pack years	36 (21)	27 (20)	62 (9)
Occupational exposure, n (%) *	119 (70)	93 (68)	397 (55)
Birds	16 (9)	11 (8)	33 (5)
Inorganic dust	55 (32)	40 (29)	164 (23)

Metal dust	35 (20)	27 (19)	119 (17)
Organic dust	67 (39)	52 (38)	182 (25)
Wood dust	32 (18)	25 (18)	57 (8)

Data presented as mean ± standard deviation unless otherwise specified.

* Exposure earlier than 10 years before PF diagnosis (ten year lag time).

Abbreviations: IPF, idiopathic pulmonary fibrosis; PF, pulmonary fibrosis.

Table 2. Effect of smoking on the adjusted risk of pulmonary fibrosis, according to gender and occupational exposure

	PF Odds ratio (95% CI)		IPF Odds ratio (95% CI)	
	Women	**Men**	**Women**	**Men**
No occupational exposure	1.10 (0.50 – 2.42)	1.97 (0.64 – 6.13)	1.12 (0. 49 – 2.59)	1.44 (0.43 – 4.83)
Occupational exposure	1.10 (0.52 – 2.34)	4.63 (2.08 – 10.33)	1.32 (0.58 – 3.03)	2.96 (1.34 – 6.52)

Odds ratios (95% confidence interval) for the effect of smoking vs. no smoking on the risk of developing PF and IPF, estimated using Mantel Haenzel analysis controlled for year of birth and year of diagnosis. Smoking was defined as the presence of ever-smoking earlier than 10 years before the diagnosis.

Abbreviations: CI, confidence interval; IPF, idiopathic pulmonary fibrosis; PF, pulmonary fibrosis.

Table 3. Dose-response effect of smoking on the risk of severe pulmonary fibrosis

Smoking, pack years*	PF OR (95% CI)	IPF OR (95% CI)
0	1	1
1 – 9	1.03 (0.62 – 1.70)	0.90 (0.52 – 1.57)
10 – 19	2.26 (1.35 – 3.80)	2.10 (1.20 – 3.68)
≥ 20	2.66 (1.56 – 4.55)	2.25 (1.26 – 4.02)

Odds ratios (ORs) for levels of smoking estimated using conditional logistic regression adjusted for age and stratified for year of birth, year of diagnosis, gender and occupational exposure.

* Pack years of smoking up to 10 years before the year of PF diagnosis.

Abbreviations: IPF, idiopathic pulmonary fibrosis; PF, pulmonary fibrosis.

Effects of smoking, gender and occupational exposure on the risk of severe pulmonary fibrosis: a population based case-control study

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ABSTRACT

Objectives: To estimate the effects of smoking, gender and occupational exposure on the risk of developing severe pulmonary fibrosis (PF), including dose-response and interaction effects.

Methods: National case-control study of 171 patients (cases) starting long-term oxygen therapy (LTOT) for PF in Sweden between February 1997 and April 2000, and 719 random control subjects from the general population. Of cases, 137 had probable idiopathic pulmonary fibrosis (IPF). The odds ratios (ORs) for smoking, gender, and occupational exposure were estimated using Mantel-Haenzel analysis and conditional logistic regression, controlling for age and year of diagnosis.

Results: The adverse effect of smoking was amplified by male gender and occupational exposure, OR 4.6 ([95% confidence interval] 2.1 – 10.3) for PF, and OR 3.0 (1.3 – 6.5) for IPF, compared to in non-exposed women. Higher cumulative smoking exposure was linearly associated with increased risks. Compared to smoking less than ten pack-years, smoking ≥ 20 pack-years was associated with increased risk of PF and IPF, OR 2.6 (1.4 – 4.9) and OR 2.5 (1.3 – 5.0), respectively.

Conclusion: Smoking has a dose-related association with increased risk of severe PF. Men with a history of smoking and occupational exposure is a particular risk group for developing severe pulmonary fibrosis.

ARTICLE SUMMARY

Article focus

- Smoking, male gender and occupational exposures are proposed risk factors for developing severe idiopathic pulmonary disease (IPF), but data on the interplay between these factors are limited.
- This study aims to estimate the effects of smoking, gender and occupational exposure on the risk of developing severe IPF, including interactions and dose-response effects.

Key messages

- Smoking has a dose-response association with increased risk of severe IPF.
- The adverse effect of smoking is strongly amplified by male gender and occupational exposure. This study identifies men with a history of smoking and occupational exposures as a particular risk group for developing severe IPF.

Strengths and limitations

- Population-based case-control study of subjects developing oxygen-dependent pulmonary in Sweden with randomly selected controls from the general population.
- Analysis of detailed exposure data, accounting for confounders and lag time between exposure and disease.
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group, weighted by the number of cases in each diagnosis year group. Then, the year of PF diagnosis of each control subject was set to the mid-year of the corresponding year of the patient group. Characteristics at baseline (the date the questionnaire was filled in) were presented using frequencies and percentages for categorical variables. Continuous data were presented using mean with standard deviation (SD) and median with range or interquartile range (IQR) for variables with normal and skewed distribution, respectively.

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Interactions

There was a significant interaction between smoking, occupational exposure and gender, and the risk of developing oxygen-dependent PF (test of homogeneity, $p = 0.028$). The interaction~~differences in effects~~ was~~ere~~ similar ~~for~~ in the IPF cohort (Table 2). Men with current or past smoking and occupational exposure had markedly increased risk of PF, OR 4.6 (2.1 – 10.3), and IPF, OR 3.0 (1.3 – 6.5), compared to non-exposed women (Table 2). Adjustment for differences in pack years between men and women, in addition to the other covariates, did not affect the estimates.

Dose-response effect

There was a linear association between higher cumulative smoking exposure (up to ten years before diagnosis) and increased risk of PF and IPF, OR 1.03 (95% CI, 1.01 – 1.04) per pack year and OR 1.02 (95% CI, 1.01 – 1.04) per pack year, respectively. Compared to lower levels of smoking (1 – 9 pack years), heavy smoking (≥ 20 pack years) was associated with an increased risk of PF, OR 2.6 (95% CI, 1.4 – 4.9), and IPF, OR 2.5 (95% CI, 1.3 – 5.0), as

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shown in Table 3. Using a 5-year time lag for smoking exposure instead of 10 years resulted in similar estimates.

Subtypes of occupational exposure

The effect of occupational exposure seemed to be mediated partly through exposure to birds and wood dust. The risk of PF was increased by exposure to birds (OR 1.9; 95% CI, 1.0 – 3.7) and wood dust (OR 1.7; 95% CI, 1.0 – 3.0), controlling for age, gender, year of diagnosis, and smoking. There were no evidence of effects of inorganic dust (OR 1.3; 95% CI, 0.8 – 2.0) or metal dust (OR 1.1; 95% CI, 0.6 – 1.8). There were signs of interactions with smoking and gender for exposure to birds (p = 0.021) and wood dust (p = 0.023), respectively. Estimates were similar for the IPF cohort, except for a lower effect of bird exposure (OR 1.3; 95% CI, 0.6 – 2.8).

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DISCUSSION

The main findings are that 1) smoking was a risk determinant in the development of oxygen-dependent pulmonary fibrosis and that this risk was amplified by male gender and occupational exposure; 2) the association with smoking was dose-dependent, which may support the theory of the causative role of smoking in the pathogenesis of severe pulmonary fibrosis.

Our findings are consistent with reports of increased risk of IPF associated with smoking [4-6 10 12 16] and occupational exposures.[4-7 9 12 14 16] A previous analysis using the present data set

showed that specific occupational factors associated with an increased risk of PF included exposure to birds and wood dust.[14] Studies of a possible dose-response correlation between smoking and IPF have shown conflicting results, with two studies indicating a dose-dependent effect[5 6] and one study showing no dose ~~correlation .~~correlation.[17] The latter study, however, analyzed only smoking status and the current smoking dose (cigarettes per day) and not cumulative smoking exposure such as pack years.[17] The present study extends the previous observations by demonstrating that the association between smoking and severe pulmonary fibrosis is dose-dependent and is modified by gender and occupational exposure.

A strength of the present study is that it included cases from a population-based prospective register of patients starting LTOT in Sweden. Control subjects were randomly selected from the general population. Previous studies using control subjects in hospitals may have yielded biased estimates, as the risk of hospitalization is likely to be related to occupational factors and smoking.[4 7 9-11] We had detailed data on the temporality, dose and duration of smoking. In contrast with previous studies, only exposure data up to ten years before the year of the PF diagnosis was included in the analysis to avoid reverse causation and to allow for the time lag between exposure to risk factors and the manifestation of clinical disease.

A possible limitation is that the self-reported exposure data could be influenced by recall bias. The validity of the exposure classification ~~is~~was, however, supported by a high degree of consistency between reported employment histories and occupational exposure to specific agents.[14] Second~~ly~~, the association between smoking and starting LTOT could be affected by survivor bias, as smokers are likely to be at high risk of dying of other smoke-related disease~~s~~, such as cancer and cardiovascular disease, before they can develop severe IPF. Also, stopping smoking is a mandatory criterion for starting LTOT. Both these potential biases would tend to lower the number of smokers starting LTOT ~~and our findings might thus~~and to underestimate the association between smoking and oxygen-dependent PF. Third~~ly~~, the IPF diagnosis could

be misclassified in some patients, especially as the cohort was collected prior to the publication of main consensus definition of IPF.[1] The validity of the PF and IPF diagnoses was checked by ~~a~~ respiratory physicians using medical records, including available radiographic and histologic data.[14] Among idiopathic interstitial pneumonias, IPF is the most common condition and it is associated with a high risk of progression to hypoxemic respiratory failure and death.[1 18] Thus, the prevalence of IPF is likely high in oxygen-dependent pulmonary fibrosis. It is possible that we included patients with combined PF and emphysema, which may be present in up to one third of IPF patients.[19] Concurrent emphysema may constitute a smoking-related comorbidity or a distinct IPF phenotype,[19] and could explain, at least partly, the association between smoking, male gender, and the development of severe IPF in the present study. We included the PF cohort in the analysis, as it may be difficult to obtain a specific diagnosis in patients with advanced pulmonary fibrosis ~~at~~ in the clinic. ~~Our results~~Findings were similar ~~consistent~~ in ~~both~~ the PF and IPF ~~groups~~cohorts, which supports the validity of the ~~present~~ analysis~~findings~~. Using national population based cases and controls, the present findings likely have high applicability to severe PF in Swedish clinical practice. The validity to other settings may be lower owing to differences in socio-demographics factors, health care organization, and pattern of exposure.

Mechanisms governing the relationship between smoking, gender, occupational exposure, and the development of severe pulmonary fibrosis are unknown but likely involve complex interactions between different environmental factors in genetically predisposed individuals.[20] The adverse effect of smoking could in part be attributable to the development of concurrent emphysema, which has been associated ~~shown to predict~~with hypoxemia and ~~a~~ earlier death~~poor prognosis~~ in IPF.[21]

For the clinician, this study identifies a group of male, heavy smokers with occupational exposure to harmful substances, who have a greatly increased risk of developing severe

pulmonary fibrosis. In this group, interventions to help people reduce or stop smoking are a top priority.

In conclusion, smoking is associated with a dose-dependent increase in oxygen-dependent pulmonary fibrosis. The adverse effects of smoking are stronger in men and in people with occupational exposure.

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Data sharing statement: Analysis code is available from the corresponding author. No additional data is available.

References

1 American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 2002;165:277-304.

2 Raghu G, Collard HR, Egan JJ et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *American Journal of Respiratory and Critical Care Medicine* 2011;183:788-824.

3 Navaratnam V, Fleming KM, West J et al. The rising incidence of idiopathic pulmonary fibrosis in the U.K. *Thorax* 2011;66:462-7.

4 Iwai K, Mori T, Yamada N, Yamaguchi M, Hosoda Y. Idiopathic pulmonary fibrosis. Epidemiologic approaches to occupational exposure. *American Journal of Respiratory and Critical Care Medicine* 1994;150:670-5.

5 Hubbard R, Lewis S, Richards K, Johnston I, Britton J. Occupational exposure to metal or wood dust and aetiology of cryptogenic fibrosing alveolitis. *Lancet* 1996;347:284-9.

6 Baumgartner KB, Samet JM, Stidley CA, Colby TV, Waldron JA. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine* 1997;155:242-8.

7 Miyake Y, Sasaki S, Yokoyama T et al. Occupational and environmental factors and idiopathic pulmonary fibrosis in Japan. *The Annals of occupational hygiene* 2005;49:259-65.

8 Scott J, Johnston I, Britton J. What causes cryptogenic fibrosing alveolitis? A case-control study of environmental exposure to dust. *BMJ* 1990;301:1015-7.

9 Awadalla NJ, Hegazy A, Elmetwally RA, Wahby I. Occupational and environmental risk factors for idiopathic pulmonary fibrosis in Egypt: a multicenter case-control study. *Int J Occup Environ Med* 2012;3:107-16.

10 Garcia-Sancho Figueroa MC, Carrillo G, Perez-Padilla R et al. Risk factors for idiopathic pulmonary fibrosis in a Mexican population. A case-control study. *Respir Med* 2010;104:305-9.

11 Miyake Y, Sasaki S, Yokoyama T et al. Case-control study of medical history and idiopathic pulmonary fibrosis in Japan. *Respirology* 2005;10:504-9.

12 Taskar VS, Coultas DB. Is idiopathic pulmonary fibrosis an environmental disease? *Proceedings of the American Thoracic Society* 2006;3:293-8.

13 Strom K, Boe J. A national register for long-term oxygen therapy in chronic hypoxia: preliminary results. *Eur Respir J* 1988;1:952-8.

14 Gustafson T, Dahlman-Hoglund A, Nilsson K, Strom K, Tornling G, Toren K. Occupational exposure and severe pulmonary fibrosis. *Respir Med* 2007;101:2207-12.

15 Toren K, Jarvholm B, Brisman J, Hagberg S, Hermansson BA, Lillienberg L. Adult-onset asthma and occupational exposures. *Scand J Work Environ Health* 1999;25:430-5.

16 Baumgartner KB, Samet JM, Coultas DB et al. Occupational and environmental risk factors for idiopathic pulmonary fibrosis: a multicenter case-control study. Collaborating Centers. *Am J Epidemiol* 2000;152:307-15.

17 Gribbin J, Hubbard R, Smith C. Role of diabetes mellitus and gastro-oesophageal reflux in the aetiology of idiopathic pulmonary fibrosis. *Respir Med* 2009;103:927-31.

18 Bjoraker JA, Ryu JH, Edwin MK et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998;157:199-203.

19 Cottin V. The impact of emphysema in pulmonary fibrosis. *European Respiratory Review* 2013;22:153-157.

20 Macneal K, Schwartz DA. The genetic and environmental causes of pulmonary fibrosis. *Proc Am Thorac Soc* 2012;9:120-5.

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21 Mejia M, Carrillo G, Rojas-Serrano J et al. Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. *Chest* 2009;136:10-5.

TABLES

Table 1. Patient characteristics

Characteristic	**PF cases (n = 171)**	**IPF cases (n = 137)**	**Controls (n = 719)**
Age	73.7 ± 9.5	74.2 ± 9.8	64.3 ± 13.7
Males, n (%)	107 (63)	86 (63)	337 (47)
Never-smokers, n (%)	52 (30)	44 (32)	344 (48)
Ex-smokers, n (%)	114 (67)	89 (65)	251 (35)
Current smokers, n (%)	5 (3)	4 (3)	124 (17)
Smoking ~~history~~ exposure~~up to 10 years before PF diagnosis~~, n (%) *	119 (70)	93 (68)	375 (52)
1 – 9 pack years	29 (17)	22 (16)	176 (24)
10 – 19 pack years	34 (20)	27 (20)	91 (13)
≥ 20 pack years	36 (21)	27 (20)	62 (9)
Occupational exposure, n (%) *	119 (70)	93 (68)	397 (55)
Birds	16 (9)	11 (8)	33 (5)

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Inorganic dust	55 (32)	40 (29)	164 (23)
Metal dust	35 (20)	27 (19)	119 (17)
Organic dust	67 (39)	52 (38)	182 (25)
Wood dust	32 (18)	25 (18)	57 (8)

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Data presented as mean ± standard deviation unless otherwise specified.

* Exposure earlier than 10 years before PF diagnosis (ten year lag time).

Abbreviations: IPF, idiopathic pulmonary fibrosis; PF, pulmonary fibrosis.

Table 2. Effect of smoking on the adjusted risk of pulmonary fibrosis, according to gender and occupational exposure

	PF Odds ratio (95% CI)		IPF Odds ratio (95% CI)	
	Women	**Men**	**Women**	**Men**
No occupational exposure	1.10 (0.50 – 2.42)	1.97 (0.64 – 6.13)	1.12 (0. 49 – 2.59)	1.44 (0.43 – 4.83)
Occupational exposure	1.10 (0.52 – 2.34)	4.63 (2.08 – 10.33)	1.32 (0.58 – 3.03)	2.96 (1.34 – 6.52)

Odds ratios (95% confidence interval) for the effect of smoking vs. no smoking on the risk of developing PF and IPF, estimated using Mantel Haenzel analysis controlled for year of birth and year of diagnosis. Smoking was defined as the presence of ever-smoking earlier than 10 years before the diagnosis.

Abbreviations: CI, confidence interval; IPF, idiopathic pulmonary fibrosis; PF, pulmonary fibrosis.

Table 3. Dose-response effect of smoking on the risk of severe pulmonary fibrosis

Smoking, pack years*	PF OR (95% CI)	IPF OR (95% CI)
0	1	1
1 – 9	1.03 (0.62 – 1.70)	0.90 (0.52 – 1.57)
10 – 19	2.26 (1.35 – 3.80)	2.10 (1.20 – 3.68)
≥ 20	2.66 (1.56 – 4.55)	2.25 (1.26 – 4.02)

Odds ratios (ORs) for levels of smoking estimated using conditional logistic regression adjusted for age and stratified for year of birth, year of diagnosis, gender and occupational exposure.

* Pack years of smoking up to 10 years before the year of PF diagnosis.

Abbreviations: IPF, idiopathic pulmonary fibrosis; PF, pulmonary fibrosis.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes
Methods			
Study design	4	Present key elements of study design early in the paper	Yes
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	Yes
		(*b*) For matched studies, give matching criteria and the number of controls per case	Yes
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes
Bias	9	Describe any efforts to address potential sources of bias	Yes
Study size	10	Explain how the study size was arrived at	Yes
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes
		(*b*) Describe any methods used to examine subgroups and interactions	Yes
		(*c*) Explain how missing data were addressed	Yes
		(*d*) If applicable, explain how matching of cases and controls was addressed	Yes
		(*e*) Describe any sensitivity analyses	Yes
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes
		(b) Give reasons for non-participation at each stage	Yes
		(c) Consider use of a flow diagram	Yes
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes
		(b) Indicate number of participants with missing data for each variable of interest	Yes
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	Yes
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Adjusted analysis presented, biased crude estimates will be added upon request from reviewers or editor.
		(*b*) Report category boundaries when continuous variables were categorized	Yes
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Yes
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes
Discussion			
Key results	18	Summarise key results with reference to study objectives	Yes
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.