

ORIGINAL ARTICLE

Role of atmospheric pollution on the natural history of idiopathic pulmonary fibrosis

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ABSTRACT

Introduction Idiopathic pulmonary fibrosis (IPF) has an unpredictable course corresponding to various profiles: stability, physiological disease progression and rapid decline. A minority of patients experience acute exacerbations (AEs). A recent study suggested that ozone and nitrogen dioxide might contribute to the occurrence of AE. We hypothesised that outdoor air pollution might influence the natural history of IPF.

Methods Patients were selected from the French cohort COhorte Fibrose (COFI), a national multicentre longitudinal prospective cohort of IPF (n=192). Air pollutant levels were assigned to each patient from the air quality monitoring station closest to the patient's geocoded residence. Cox proportional hazards model was used to evaluate the impact of air pollution on AE, disease progression and death.

Results Onset of AEs was significantly associated with an increased mean level of ozone in the six preceding weeks, with an HR of 1.47 (95% CI 1.13 to 1.92) per 10 µg/m³ (p=0.005). Cumulative levels of exposure to particulate matter PM₁₀ and PM_{2.5} were above WHO recommendations in 34% and 100% of patients, respectively. Mortality was significantly associated with increased levels of exposure to PM₁₀ (HR=2.01, 95% CI 1.07 to 3.77) per 10 µg/m³ (p=0.03), and PM_{2.5} (HR=7.93, 95% CI 2.93 to 21.33) per 10 µg/m³ (p<0.001).

Conclusion This study suggests that air pollution has a negative impact on IPF outcomes, corroborating the role of ozone on AEs and establishing, for the first time, the potential role of long-term exposure to PM₁₀ and PM_{2.5} on overall mortality.

Key messages**What is the key question?**

- ▶ Does outdoor air pollution influence the natural history of idiopathic pulmonary fibrosis (IPF)?

What is the bottom line?

- ▶ The occurrence of acute exacerbations is significantly associated with an increased mean level of ozone, and long-term exposure to elevated levels of PM₁₀ and PM_{2.5} is a risk factor for mortality in patients with IPF.

Why read on?

- ▶ This is the first study to assess the effect of air pollution on the entire natural history of IPF and more specifically the impact of PM_{2.5}.

present sudden and unexplained deterioration of the disease, described as acute exacerbation (AE).⁴

AE is defined as worsening of dyspnoea in the previous 30 days, combined with the emergence of new parenchymal opacities on high-resolution CT (HRCT), including diffuse ground glass attenuation or consolidations. Potential causes of abrupt respiratory deterioration, such as infection, congestive heart failure or pulmonary embolism, must be ruled out.^{7–9} Several triggers have been described, including surgical lung biopsy,⁷ microaspiration¹⁰ and viral infections.¹¹ AEs are responsible for high mortality, accounting for about 21%–40% of all deaths of patients with IPF.^{9 12 13} Disease progression of IPF is usually defined by at least 10% decrease of the predicted value for forced vital capacity (FVC%pred) or at least 15% decrease of the predicted value for diffusing capacity of the lung for carbon monoxide (DLco%pred) from baseline values, respectively.⁵

Although IPF is a disease of unknown aetiology, a number of potential environmental risk factors have been identified, such as cigarette smoking¹⁴ and exposure to metal and wood dusts.¹⁵

The impact of air pollution has now been clearly established in various airway diseases. It has been associated with poorly controlled asthma,¹⁶ altered lung function growth,¹⁷ increased incidence of

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is the most common and most severe form of idiopathic interstitial pneumonia, with few treatment options and a median survival after diagnosis between 24 and 36 months.^{1–4} The natural history of IPF has not been fully elucidated and remains unpredictable.^{5 6} While the majority of patients experience slow and gradual progression on pulmonary function tests (PFTs), some remain relatively stable and others experience rapid decline. A minority of patients



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chronic obstructive pulmonary disease (COPD),¹⁸ COPD exacerbations¹⁹ and respiratory-related mortality.²⁰ Recently, using data from a South Korean IPF cohort, Johannson *et al.*²¹ showed a significant association between AE and increased urban background levels of ozone (O₃) and nitrogen dioxide (NO₂) close to the residential addresses in the previous 6 weeks.²¹ However, these findings have not yet been validated in another cohort, although the type and degree of pollution are known to vary considerably throughout the world. In addition, the study assessed the role of coarse particulate matter (PM₁₀) but not that of fine and ultrafine particulate matter (PM_{2.5}) and may therefore have missed an important issue. Indeed, PM₁₀ can penetrate the bronchi, whereas PM_{2.5} can reach the pulmonary alveoli, which could be particularly relevant in the natural history of IPF.

We hypothesised that outdoor air pollution could influence the natural history of IPF and investigated the impact of major urban air pollutants, namely NO₂, O₃, PM with an aerodynamic diameter of 10 mm (PM₁₀) and 2.5 mm (PM_{2.5}), on AE, disease progression and death in a national longitudinal prospective cohort in France.

PATIENTS AND METHODS

Source population

Patients were selected from the French cohort COhorte Fibrose (COFI), a national multicentre prospective study on the natural history of IPF. The primary endpoint of the COFI study was to determine the factors associated with progression-free survival by focusing on several events, including disease progression, AE and death. The recruitment period extended from December 2007 to December 2010, with 5-year follow-up. Patients included in the cohort were required to have a diagnosis of incident IPF less than 9 months before inclusion, according to the American Thoracic Society/European Respiratory Society consensus criteria.³

Patients were followed every 3 months. Health events were defined as follows:

- ▶ AE: (1) worsening dyspnoea ≤ 1 month, (2) decrease in arterial oxygen tension (or pressure) PaO₂ >10 mm Hg compared with the results of the previous scheduled visit, (3) new opacities on HRCT (ground glass attenuation or consolidations) and (4) exclusion of other causes of worsening.
- ▶ Disease progression: (1) absolute decrease in FVC >10%pred or absolute decrease in DLco >15%pred compared with baseline values, (2) within >6 months and (3) exclusion of other causes of worsening.

Study population

From the COFI cohort, we excluded patients for whom the residential address or air pollution exposure measurements were unavailable, and those with no clinical follow-up. Baseline characteristics and the date of diagnosis of AE, disease progression and death were collected prospectively, from December 2007 to December 2014.

For the purposes of the study, three health events were considered in successive analyses. The occurrence of an event did not result in excluding the patient for a potential following event. For example, a patient may initially show a disease progression and thereafter an AE or die in further follow-up. However, a patient who presented an AE as the first event could not develop a disease progression, as an AE is ultimately the equivalent of a rapid progression. We modelled the three events separately

because we assumed that the exposure period was different for AE, disease progression and death.

First, we considered patients who experienced an AE at some point during the study period (cases). Each of these cases was compared with all other patients from the cohort at risk at the date of the event, who had not yet experienced an AE and who did not experience an AE during the 6 weeks following the date of the case event (pooled controls). For patients who experienced more than one AE, only the first event was included in the analysis.

Similarly, we compared patients with disease progression to the other patients.

Lastly, we compared the exposures of patients who died from any cause to those of the other patients.

All patients enrolled in the COFI cohort provided their informed consent, and the study was approved by the local ethics committee (*Comité de Protection des Personnes Ile-de-France*) and by the French data protection authority (CNIL: 908198).

Air pollution data

French Regional Air Quality Agencies (Airparif, ATMO Picardie, ATMO Champagne Ardenne, Lig'Air, Air Rhone-Alpes, Airbreizh, ORAMIP, respectively) provided the hourly concentrations of NO₂, O₃, PM₁₀ and PM_{2.5} from rural and traffic ambient air monitoring stations, during the study period (from December 2007 to December 2014). Air pollutants levels obtained from the air quality monitoring station closest to the patient's residential address were assigned to each patient. The distance between the monitoring station and the patient's residential address was identified by the Google Map Distance Calculator after having geocoded the patient's address.

Mean exposure was calculated by determining the average of all hourly concentrations of NO₂, O₃, PM₁₀ and PM_{2.5} during the exposure period of each IPF event. The exposure period was defined as 6 weeks preceding the date of AE, based on the study by Johannson *et al.*²¹ Based on the assumption that long-term pollution exposure had an impact on disease progression or death, the exposure period was defined as the entire period from inclusion to the date of the event or censoring. Cumulative exposure was expressed as the average concentration of each pollutant during the exposure period.

Air pollution data were divided into two 6-month seasonal periods (warm season, from May to October, and cool season, from November to April).²²

Statistical analysis

Comparisons were performed using Student's t-test and χ^2 test, as appropriate.

Patients were followed from inclusion until death or lung transplantation or until December 2014. Transplant patients were considered as alive at the date of transplantation. A Cox proportional hazards model was used to evaluate the short-term impact of air pollution on AEs of IPF.²³ The event of interest was the first AE. For each pollutant, we compared the mean concentration observed during the exposure period, corresponding to 6 weeks before AE. All patients at risk were used as pooled controls for each case. The model was adjusted for warm and cool seasons, as the air pollution composition can vary according to meteorological influences.²⁴ The model was also adjusted for risk factors of exacerbation described in from the literature, including smoking status and baseline FVC%pred and DLco%pred.

Table 1 Baseline characteristics of patients

Characteristics	No acute exacerbation n=152	Acute exacerbation n=40	p Value
Age (years)	67.9±11.2	68.0±8.2	0.95
BMI	27.5±4.3	27.7±4.5	0.89
Males	118 (77.6)	30 (75)	0.72
Smokers			
Never	36 (23.7)	13 (32.5)	
Former	11 (7.2)	2 (5.0)	0.58
Current	96 (63.2)	24 (60.0)	
TLC% predicted	69.9±16.0	64.7±13.0	0.06
FVC % predicted	76.8±20.3	73.4±15.1	0.33
DLco % predicted	47.6±16.5	42.2±13.0	0.05
FEV ₁ % predicted	81.5±21.5	78.1±16.2	0.41
Prednisone*	60 (39.4)	16(40)	0.95
SLB	51 (33.8)	19(47)	0.13
GORD	60 (39.4)	19 (31.7)	0.40
Death	73 (48)	36 (90.0)	<0.001

Data are presented as mean±SD or n (%).

*Prednisone use at inclusion or within the first 6 months after inclusion.

BMI, body mass index; DLco, diffusing capacity of the lung for carbon monoxide; FEV, forced expiratory volume; FVC, forced vital capacity; GORD, gastro-oesophageal reflux disease; SLB, surgical lung biopsy; TLC, total lung capacity.

A Cox proportional hazards model was conducted to estimate the impact of cumulative air pollution on disease progression. Cumulative exposure was calculated over the entire period from inclusion to the date of the event or censoring. The model was adjusted for age. The same methodology was used to study the impact of cumulative exposure on mortality. The model was adjusted for age, smoking status, and baseline FVC%pred and DLco%pred.

Statistic analysis was performed using R software V.3.0.1, and statistical significance was defined as a p value <0.05.

RESULTS

Of the 245 patients included in COFI, 25 patients with missing residential address, 10 patients with missing air pollution data, 11 patients with no clinical follow-up and 7 patients living more than 30 km from the monitoring station were excluded. Among the 192 patients with IPF selected, 40 experienced at least one episode of AE during follow-up (34.7±22.3 months). About one-half of the population experienced disease progression, as defined on PFTs (n=90), and the majority of patients died (n=109), and 17 patients were transplanted.

As expected, patients with AE had more impaired DLco (p=0.05) and higher rate of death (p<0.001). No significant difference was observed between groups in terms of age at inclusion, sex ratio, smoking status, FVC, gastro-oesophageal reflux and corticosteroid therapy (table 1).

The cumulative exposure levels for the overall population were 19.46 (±3.25) µg/m³ for PM₁₀ and 26.23 (±3.43) µg/m³ for PM_{2.5}; 34% and 100% of patients had exposure levels above the WHO recommendations for PM₁₀ and PM_{2.5}, respectively.

Short-term effect of air pollution on AE

AE events were significantly associated with a higher mean concentration of O₃ during the exposure period, with an HR

Table 2 Short-term effect of air pollution on acute exacerbations

Exposure	Increase	HR (95% CI)	p Value
O ₃	10 µg/m ³	1.47 (1.13 to 1.92)	0.005
NO ₂	10 µg/m ³	0.92 (0.68 to 1.24)	0.584
PM ₁₀	10 µg/m ³	0.80 (0.52 to 1.27)	0.347
PM _{2.5}	10 µg/m ³	1.29 (0.65 to 2.57)	0.463

Cox proportional hazards model adjusted on season, FVC% predicted at baseline, DLco% predicted at baseline and smoking status.

NO₂, nitrogen dioxide; O₃, ozone; PM₁₀ and PM_{2.5}, particles with a 50% cut-off aerodynamic diameter of 10 µm and 2.5 µm.

of 1.47 (95% CI 1.13 to 1.92) per 10 µg/m³ (p=0.005). No association was observed between AE and NO₂, PM₁₀ and PM_{2.5} (table 2).

Long-term effect of cumulative air pollution exposure on disease progression

Disease progression was not associated with increased cumulative concentrations of NO₂, O₃, PM₁₀ or PM_{2.5} (table 3).

Long-term effect of cumulative air pollution exposure on mortality

Mortality was significantly associated with increased cumulative exposure to PM₁₀ with an HR of 2.01 (95% CI 1.07 to 3.77) per 10 µg/m³ (p=0.03) and to PM_{2.5} with a HR of 7.93 (95% CI 2.93 to 21.33) per 10 µg/m³ (p<0.001).

No association was observed between IPF mortality and NO₂ or O₃ (table 4).

DISCUSSION

This is the first study to assess the effect of air pollution on the natural history of IPF and more specifically the impact of PM_{2.5}. Our results confirm that short-term exposure to increased levels of ozone is a risk factor for AE and demonstrate, for the first time, that long-term exposure to elevated levels of PM₁₀ and PM_{2.5} is a risk factor for mortality in patients with IPF.

A recent publication proposed potential mechanisms by which air pollution, via oxidative stress, inflammation and telomere shortening, might trigger AEs or accelerate progression of interstitial lung diseases, in genetically susceptible individuals.²⁵ In the present study, analysis of the impact of air pollution on the natural history of IPF could not be restricted to a same exposure period for each event. We chose a 6-week exposure period for AE, as reported in the study by Johannson *et al*, in order to allow for a potential lag-time from pollutant exposure to onset of symptoms. We also hypothesised that disease progression and death could be associated with major long-term exposure to pollution, and therefore also focused on cumulative exposure

Table 3 Association of cumulative air pollution exposure and disease progression

Exposure	Increase	HR (95% CI)	p Value
O ₃	10 µg/m ³	1.06 (0.74 to 1.54)	0.72
NO ₂	10 µg/m ³	1.09 (0.85 to 1.40)	0.52
PM ₁₀	10 µg/m ³	1.03 (0.51 to 2.08)	0.92
PM _{2.5}	10 µg/m ³	1.89 (0.68 to 5.23)	0.22

Cox proportional hazards model adjusted on age, FVC% predicted at base line and DLco% predicted at baseline.

NO₂, nitrogen dioxide; O₃, ozone; PM₁₀ and PM_{2.5}, particles with a 50% cut-off aerodynamic diameter of 10 µm and 2.5 µm.

Table 4 Association of cumulative air pollution exposure and mortality

Exposure	Increase	HR (95% CI)	p Value
O ₃	10 µg/m ³	0.89 (0.66 to 1.18)	0.43
NO ₂	10 µg/m ³	1.01 (0.79 to 1.29)	0.90
PM ₁₀	10 µg/m ³	2.01 (1.07 to 3.77)	0.03
PM _{2.5}	10 µg/m ³	7.93 (2.93 to 21.33)	<0.001

Cox proportional hazards model adjusted on age, FVC% predicted at base line and DLco% predicted at base line and smoking status.

NO₂, nitrogen dioxide; O₃, ozone; PM₁₀ and PM_{2.5}, particles with a 50% cut-off aerodynamic diameter of 10 µm and 2.5 µm.

to air pollutants over the entire period from IPF diagnosis to the date of the event or censoring.

The major original result of this study is the relationship between long-term cumulative exposure to elevated levels of PM₁₀ and PM_{2.5} and the risk of mortality in patients with IPF. All patients were exposed to PM_{2.5} concentrations higher than the WHO recommendations, and 34% patients were exposed to higher than recommended PM₁₀ (WHO recommends not exceeding an annual concentration of 20 µg/m³ for PM₁₀ and 10 µg/m³ for PM_{2.5}²⁶). Adjusting for age, smoking status, FVC and DLco, the HR for PM₁₀ and PM_{2.5} cumulative exposure was 2.01 (95% CI 1.07 to 3.77) per 10 µg/m³ and 7.93 (95% CI 2.93 to 21.33) per 10 µg/m³, respectively. Noteworthy, the South Korean study, conducted in a longitudinal IPF cohort in Seoul, failed to find a link between the mean exposure to PM₁₀ over the entire follow-up period and mortality (HR=0.96, 95% CI (0.84 to 1.08), p=0.4794, results kindly provided by Johannson *et al*) and it does not mention the exposure to PM_{2.5}. These discrepant findings for PM₁₀ might be explained by differences in the exposure estimates between the two studies because of a different density of monitoring stations in France and Korea, or by the fact that the levels of PM₁₀ vary less in Korea. Most of our patients lived in Greater Parisian agglomeration (n=133) where the number of monitoring stations is high (70 stations spread over a 100 km radius around Paris). Moreover, the positive association found for both PM₁₀ and PM_{2.5} strengthens the probable role of fine particles on IPF mortality.

Fine particles are deposited deeply in the respiratory tract. PM components have the ability to trigger and/or enhance free radical reactions in cells and tissues. Prolonged exposure to PM induces oxidative stress and telomere erosion²⁷ and inflammation that become systemic, mechanisms underlying the development of chronic diseases and mortality. Thus, PM are responsible for both short-term and long-term health effects. Several cohort studies have demonstrated that long-term exposure to PM₁₀ and PM_{2.5} is associated with cardiopulmonary mortality,^{28 29} consistent with our finding that cumulative exposure to PM₁₀ and PM_{2.5} increases the risk of death in patients with IPF.

Ozone is formed in the atmosphere by photochemical reactions in the presence of light and precursor pollutants. Ozone is known to induce airway hyper-reactivity and airway inflammation^{30 31} and increase the risk of exacerbation in asthma.^{16 32}

Our results concerning the short-term effects of pollution on AEs are in agreement with those reported by Johannson *et al* showing an association between AE and increases in mean level, maximum level and number of exceedances above accepted standards of ozone (HR=1.57, 95% CI 1.09–2.24; HR=1.42, 95% CI 1.11 to 1.82; and HR=1.51, 95% CI: 1.17 to 1.94, respectively).²¹ If we express our results as in the Korean study, a lower risk was observed in our study with an HR of 1.039

(95% CI 1.012 to 1.067, p=0.005), after adjustments for season, smoking status, and baseline FVC and DLco. This lower risk can be explained by several differences in terms of exposure levels, geographical zones, adjustment factors and genetic/ethnic aspects. Having said that, such consistent results obtained despite the relatively small sample size of these two studies (compared with the large populations usually included in air pollution studies) strongly support our findings.

The diagnostic criteria of AE have changed over recent years. In the COFI cohort, we applied the criteria proposed by Akira *et al*, the criteria most widely used at the time of study initiation, whereas Johannson *et al* used those of Collard *et al* published in 2007. The primary difference between these sets of criteria is the requirement for invasive endotracheal aspirate or BAL to ascertain a diagnosis of ‘definite’ AE in Collard *et al* definition. Otherwise, acute deterioration was termed ‘suspected’ AE. In the COFI, a potential cause for acute deterioration was systematically investigated, including routine non-invasive tests for infectious organisms. However, as clinical evaluation was left to investigator’s judgement, only a minority of our patients underwent bronchoscopy. According to Collard *et al*’s definition, 32 patients (80%) had ‘suspected’ AE and eight patients (20%) had ‘definite’ AE, as compared with 31% and 69%, respectively, in the Korean study. This striking difference just reflects the heterogeneity of AE management between centres. Nevertheless, it should be underlined that, in an attempt to better fit into real life practice, exclusion of infection is no longer mandatory in the 2016 revised definition of AE.³³ Moreover, there is little clinical or biological support for distinguishing idiopathic from non-idiopathic respiratory events, so that the impact of AE definition between the French and Korean studies is unlikely.

NO₂ is a marker of traffic-related air pollution. Several studies in the literature have shown that high short-term exposure to NO₂ is responsible for exacerbations of COPD or asthma.^{16 34 35} Unlike Johannson *et al*, we did not find any association between AE and short-term NO₂ exposure, which is probably due to a lack of power, and possibly because the magnitude of traffic-related air pollution is higher in South Korea than in France (air pollution in the world: real time air quality index: <http://waqi.info/>). We did not find any association between disease progression of IPF and cumulative exposure to O₃, NO₂, PM₁₀ or PM_{2.5}. However, all HRs were greater than one, suggesting a possible low-risk link that have been missed due to insufficient power. Interestingly, Richards *et al* reported a correlation between ambient air pollution and longitudinal changes in pulmonary function of patients with IPF. In a longitudinal cohort of 325 patients, they found that short-term O₃ and SO₂ exposure were both significantly associated with DLco decline over time but not PM₁₀ exposure.³⁶

Our study has several limitations. Although it is a national multicentre cohort, the population is relatively small for this type of study, which could have prevented demonstration of the other impacts of air pollution. Second, our study is subject to exposure misclassification. The variable distance between the patient’s residence and the nearest air quality monitoring station may have led to underestimation or overestimation of real exposure. Moreover, exposure to air pollution at home or in the workplace, which has a recognised role in respiratory diseases, could not be taken into account. In addition, no information was available concerning temperature and relative humidity, and adjustments were based on 6-month seasonal periods. However, this method has already been used in several similar studies.²² Last, the exclusion of cases living in areas where measurements were not available may have excluded more rural regions.

However, there was no significant difference between the rates of AE (20.8% vs 20.0%, $p=1$) and death (56.8% vs 20.0%, $p=0.17$) between patients included and those not covered by a monitoring station. Similarly, the exclusion of cases lost to follow-up may have excluded healthiest or sickest patients not attending clinic visits. It is true that patients lost to follow-up had a significantly less altered DLco than the whole population included ($59.5\pm 20.2\%$ vs $46.4\pm 15.9\%$, $p=0.01$), but their FVC was similar ($87.6\pm 22.9\%$ vs $75.2\pm 23.5\%$, $p=0.19$). Excluding these patients may have induced a potential bias even though their number was small.

Conversely, one of the strengths of this study is the longitudinal and prospective nature of the cohort, limiting the event misclassification bias (AE, disease progression and death).

This study suggests that air pollution may affect IPF outcomes, corroborating the role of ozone on AE and establishing, for the first time, the potential role of long-term exposure to PM₁₀ and PM_{2.5} on overall mortality. These results, which are in line with WHO recommendations to reduce pollutant emissions,²⁶ require further investigation. In future studies, in order to improve exposure measurements, patients with IPF could be asked to wear a sensor all day long to more accurately quantify indoor and outdoor environmental air quality.

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