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


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 COrhorte Fibrose (COF), 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 PM2.5 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 PM2.5 (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 PM2.5 on overall mortality.

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.1–3 The natural history of IPF has not been fully elucidated and remains unpredictable.4–6 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 present sudden and unexplained deterioration of the disease, described as acute exacerbation (AE).4–6 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,2 microaspiration10 and viral infections.11 AEs are responsible for high mortality, accounting for about 21%–40% of all deaths of patients with IPF.9–10 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.12–14 Although IPF is a disease of unknown aetiology, a number of potential environmental risk factors have been identified, such as cigarette smoking,14 and exposure to metal and wood dusts.15–17 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...
chronic obstructive pulmonary disease (COPD). COPD exacerbations and respiratory-related mortality. Recently, using data from a South Korean IPF cohort, Johansson et al 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. 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 (PM₂.₅) and may therefore have missed an important issue. Indeed, PM₁₀ can penetrate the bronchi, whereas PM₂.₅ 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 (PM₂.₅), 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 FIlbrose (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.

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, (3) 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 PM₂.₅ 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 PM₂.₅ 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 Johansson et al. 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).

**Statistical analysis**

Comparisons were performed using Student’s t-test and χ² 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. 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. The model was also adjusted for risk factors of exacerbation described in the literature, including smoking status and baseline FVC%pred and DLco%pred.
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.

Statistical analysis was performed using R software V3.0.1, 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 disease; SLB, surgical lung biopsy; TLC, total lung capacity.

**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 PM_{10} 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 AE 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 \(^{17}\) 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 of 1.47 (95% CI 1.13 to 1.92) per 10 µg/m\(^3\) (p=0.005). No association was observed between AE and NO\(_2\), PM\(_{10}\) 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 NO\(_2\), O\(_3\), PM\(_{10}\) or PM\(_{2.5}\) (table 3).

**Short-term effect of air pollution on AE**

AE events were significantly associated with a higher mean concentration of O\(_3\) during the exposure period, with an HR of 1.47 (95% CI 1.13 to 1.92) per 10 µg/m\(^3\) (p=0.005). No association was observed between AE and NO\(_2\), PM\(_{10}\) and PM\(_{2.5}\) (table 2).

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

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Increase</th>
<th>HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(_3)</td>
<td>10 µg/m(^3)</td>
<td>1.47 (1.13 to 1.92)</td>
<td>0.005</td>
</tr>
<tr>
<td>NO(_2)</td>
<td>10 µg/m(^3)</td>
<td>0.92 (0.68 to 1.24)</td>
<td>0.584</td>
</tr>
<tr>
<td>PM(_{10})</td>
<td>10 µg/m(^3)</td>
<td>0.80 (0.52 to 1.27)</td>
<td>0.347</td>
</tr>
<tr>
<td>PM(_{2.5})</td>
<td>10 µg/m(^3)</td>
<td>1.29 (0.65 to 2.57)</td>
<td>0.463</td>
</tr>
</tbody>
</table>

Cox proportional hazards model adjusted on season, FVC% predicted at baseline, DLco% predicted and smoking status. NO\(_2\), nitrogen dioxide; O\(_3\), ozone; PM\(_{10}\), and PM\(_{2.5}\) particles with a 50% cut-off aerodynamic diameter of 10 µm and 2.5 µm.

**Table 3**  Association of cumulative air pollution exposure and disease progression

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Increase</th>
<th>HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(_3)</td>
<td>10 µg/m(^3)</td>
<td>1.06 (0.74 to 1.54)</td>
<td>0.72</td>
</tr>
<tr>
<td>NO(_2)</td>
<td>10 µg/m(^3)</td>
<td>1.09 (0.85 to 1.40)</td>
<td>0.52</td>
</tr>
<tr>
<td>PM(_{10})</td>
<td>10 µg/m(^3)</td>
<td>1.03 (0.51 to 2.08)</td>
<td>0.92</td>
</tr>
<tr>
<td>PM(_{2.5})</td>
<td>10 µg/m(^3)</td>
<td>1.89 (0.68 to 5.23)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Cox proportional hazards model adjusted on age, FVC% predicted at base line and DLco% predicted at baseline. NO\(_2\), nitrogen dioxide; O\(_3\), ozone; PM\(_{10}\), 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 PM$_{10}$ 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 PM$_{10}$ (WHO recommends not exceeding an annual concentration of 20 µg/m$^3$ for PM$_{10}$ and 10 µg/m$^3$ for PM$_{2.5}$). Adjusting for age, smoking status, FVC and DLco, the HR for PM$_{10}$ and PM$_{2.5}$ cumulative exposure was 2.01 (95% CI 1.07 to 3.77) per 10 µg/m$^3$ and 7.93 (95% CI 2.93 to 21.33) per 10 µg/m$^3$, respectively. Noteworthy, the South Korean study, conducted in a longitudinal IPF cohort in Seoul, failed to find a link between the mean exposure to PM$_{10}$ 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 PM$_{10}$ 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 PM$_{2.5}$ 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 PM$_{10}$ 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 erosion 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 PM$_{10}$ and PM$_{2.5}$ is associated with cardiopulmonary mortality, consistent with our finding that cumulative exposure to PM$_{10}$ 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 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 PM$_{10}$ and PM$_{2.5}$ is associated with cardiopulmonary mortality, consistent with our finding that cumulative exposure to PM$_{10}$ and PM$_{2.5}$ increases the risk of death in patients with IPF.

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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 affects the external validity of the study. 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.

Last, the exclusion of cases living in areas where measurements were not available may have excluded more rural regions.

**Table 4** Association of cumulative air pollution exposure and mortality

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Increase</th>
<th>HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>O$_3$</td>
<td>10 µg/m$^3$</td>
<td>0.89 (0.66 to 1.18)</td>
<td>0.43</td>
</tr>
<tr>
<td>NO$_2$</td>
<td>10 µg/m$^3$</td>
<td>1.01 (0.79 to 1.29)</td>
<td>0.90</td>
</tr>
<tr>
<td>PM$_{10}$</td>
<td>10 µg/m$^3$</td>
<td>2.01 (1.07 to 3.77)</td>
<td>0.03</td>
</tr>
<tr>
<td>PM$_{2.5}$</td>
<td>10 µg/m$^3$</td>
<td>7.93 (2.93 to 21.33)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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

NO$_2$, nitrogen dioxide; O$_3$, ozone; PM$_{10}$ and PM$_{2.5}$ particles with a 50% cut-off aerodynamic diameter of 10 µm and 2.5 µm.
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%±20.2% vs 46.4±15.9%, p<0.01), but their FVC was similar (87.6%±22.9% vs 75.2%±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 PM$_{10}$ and PM$_{2.5}$ on overall mortality. These results, which are in line with WHO recommendations to reduce pollutant emissions, 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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Acknowledgements
The authors would like to thank Professor Vittinghoff for his advice on statistical analysis and all Air Quality Regional Agencies for providing us with air pollution data.

Contributors
(1) Substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work; (2) drafting the work or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors meet all four criteria for authorship (LS, HH, VC, SS, MD, ZC, Di-B, BC, JC, BW, AT, BM, GP, SM-A, SG-D, AN, SD, VG, AG, KI, RB, MW, DV and IA-MI).

Funding
Chancellerie des Universités de Paris (Legs Poix, grant #637), PHRC (grant # AOR 07076) and the Medical Research Foundation.

Competing interests
HH reports other from Intermune, other from Roche, other from Boehringer-Ingelheim, other from Sanofi, during the conduct of the study; other from Centocor; outside the submitted work, DV reports personal fees from Intermune, personal fees from Roche, personal fees from Boehringer Ingelheim, personal fees from Intermune, Roche, Boehringer Ingelheim, outside the submitted work. Dr AG reports grants and personal fees from Boehringer Ingelheim, personal fees from Roche, outside the submitted work. GP reports personal fees from Actelion, Bayer, Boehringer Ingelheim, GSK, Roche, outside the submitted work. VC reports personal fees from Actelion, Bayer, Biogen Idec, Boehringer Ingelheim, Gilead, GSK, MSD, Novartis, Pfizer, Roche/Intermune, Sanofi, grants from Actelion, Boehringer Ingelheim, GSK, Pfizer and Roche and personal fees from Boehringer Ingelheim, outside the submitted work. All other authors have no competing interests to declare.

Ethics approval
Ethics Committee (Comité de Protection des Personnes Ile-de-France) and by the French data protection authority (CNIL: 908198).

Provenance and peer review
Not commissioned; externally peer reviewed.

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Interstitial lung disease


