Is chronic exposure to air pollutants a risk factor for the development of idiopathic pulmonary fibrosis?

Valérie Siroux[1] and Bruno Crestani[2,3,4]

Affiliations: [1]Univ. Grenoble Alpes, Inserm, CNRS, Intitute for Advanced Biosciences, Team of environmental epidemiology applied to reproduction and respiratory health, Grenoble, France. [2]Université Paris Diderot – Paris 7, Sorbonne Paris Cité, Paris, France. [3]Inserm U1152, Laboratoire d'Excellence Inflamex, Paris, France. [4]Assistance Publique-Hôpitaux de Paris, Hôpital Bichat, Service de Pneumologie A, Département Hospitalo-Universitaire FIRE, Paris, France.

Correspondence: Valérie Siroux, Institut pour l'Avancée des Biosciences, Centre de Recherche UGA / Inserm U 1209 / CNRS UMR 5309, Equipe d'épidémiologie environnementale, Site Santé - Allée des Alpes, 38700 La Tronche, France. E-mail: Valerie.siroux@univ-grenoble-alpes.fr

@ERSpublications
For the first time, a role of air pollution in the development of idiopathic pulmonary fibrosis is suggested http://ow.ly/EH2V30hBapf

Cite this article as: Siroux V, Crestani B. Is chronic exposure to air pollutants a risk factor for the development of idiopathic pulmonary fibrosis?. *Eur Respir J* 2018; 51: 1702663 [https://doi.org/10.1183/13993003.02663-2017].

The recent *Lancet* Commission on Pollution and Health emphasises the considerable health burden attributable to environmental pollution, including air, water, soil, heavy metal and chemical pollution, and occupational exposure [1]. All forms of pollution were responsible for an estimated 9 million deaths in 2015, and air pollution, including both household and ambient air pollution, was responsible for the largest part, with an estimate of 6.5 million deaths [1, 2]. In 2016, air pollution was among the first five risk factors in terms of attributable disability-adjusted life-years at the global level [3]. Noteworthy, these estimates are probably underestimates as they account for the well-established associations between air pollution and disease and do not include unknown or emerging, but still unquantified, health effects of air pollutants.

In this issue of the *European Respiratory Journal*, Conti *et al.* [4] provide evidence for such emerging health effects of air pollution by investigating, for the first time, the association between chronic exposure to ambient air pollutants (nitrogen dioxide (NO_2), particulate matter with an aerodynamic diameter <10 µm (PM_{10}) and ozone) and the incidence of idiopathic pulmonary fibrosis (IPF). They identified IPF incident cases in Lombardy, Northern Italy, from the healthcare administrative database and modelled the association between area-specific IPF incidence rate and average concentrations of air pollutants. The results suggest a deleterious effect of NO_2 on IPF incidence, with association often marginally significant, and did not find evidence of any effect of PM_{10} and ozone.

The authors should be commended for their efforts in merging various existing data sources to investigate, for the first time, the role of air pollution on the development of IPF. However, no study is totally perfect, and the results warrant a cautious interpretation given some issues. Regarding the study design, this is an

Received: Dec 20 2017 | Accepted: Dec 21 2017

Conflict of interest: V. Siroux reports honoraria for speaking from TEVA, AstraZeneca and Novartis, all outside the submitted work. B. Crestani reports honoraria for speaking from Aventis, Boehringer Ingelheim, MedImmune and Roche; research grants from CARDIF, LVL, MedImmune and Roche; congress travel support from Boehringer Ingelheim, AstraZeneca, MedImmune and Roche, all outside the submitted work.

ecological study using the community as the unit of observation; therefore, the results are based on geographical correlations between disease incidence and concentration of air pollutants. This approach has inherent methodological limitations, in particular poor control of confounding. For example, as acknowledged by the authors, the model was not adjusted for smoking, although this is a major risk factor for the development of IPF [5]. Exposure assessment is the major challenge of environmental epidemiology applied to air pollution. In this study, air pollution was estimated using different approaches across the pollutants, possibly resulting in differential exposure measurement error across the pollutants, which might partly explain the association identified with NO_2 but not with PM_{10}. With regards to the definition of the outcome, the accuracy of the IPF incidence based on ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) diagnosis codes is subject to the quality of this coding. It is challenging to accurately identify IPF patients from administrative records without access to patient-level test results (*e.g.* computed tomography scan findings). For example, among the IPF patients identified by ICD-9-CM diagnosis codes and/or procedure codes in one study, only 65.4% had visits to pulmonologists on or after diagnosis, and very few (1.9%) underwent surgical lung biopsy to confirm the diagnosis [6]. In addition, diagnosis is often delayed; some patients with IPF may be symptomatic for more than 5 years before diagnosis [7].

Nevertheless, although more research is needed before drawing a causal relationship between air pollution and the development of IPF, this study provides the first evidence on the chronic effects of air pollution on the incidence of IPF and converges with previous work identifying air pollution as a risk factor for acute exacerbation and lung function decline in IPF patients [8–10]. These findings expand recent results from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, which reported that higher exposure to oxides of nitrogen and NO_2 increased risk of interstitial lung abnormalities and the 6-year progression of high attenuation areas, two measurements of subclinical interstitial lung disease [11]. From a broader point of view, this study adds to the literature showing association between air pollution exposure and the development of chronic lung diseases such as asthma [12], chronic obstructive pulmonary disease [13] or lung cancer [14]. It remains largely unknown whether some subjects are more sensitive to the effects of air pollution on the development of chronic lung disease, for example given some specific genetic background, as suggested for genes involved in the antioxidant pathway [15], or exposure to other environmental factors possibly interacting with air pollution, as suspected for aeroallergens [16].

Importantly, Conti *et al.* [4] identified a potential modifiable risk factor for the development of IPF, a chronic and progressive disease with a very poor prognosis [17]. The two drugs already available for IPF treatment (nintedanib and pirfenidone) slow the progression of the disease and most probably improve survival [18, 19], but IPF still cannot be cured. Prevention of IPF is thus highly desirable. Our current understanding of the pathophysiology of pulmonary fibrosis is that alveolar epithelial cell injury drives abnormal repair with recruitment of mesenchymal cells to the lung leading to accumulation of extracellular matrix and destruction of the normal architecture of the lung [20]. Exogenous factors (such as air pollutants, drugs or viruses) or endogenous factors (such as an altered microbiome) [21] may contribute to alveolar epithelial cell injury, and thus fibrosis development, in individuals susceptible to fibrosis due to genetic predisposition [22, 23] and ageing [20] (figure 1). Exposure to some environmental factors may participate in this process, such as smoking, and occupational exposure to metal, asbestos

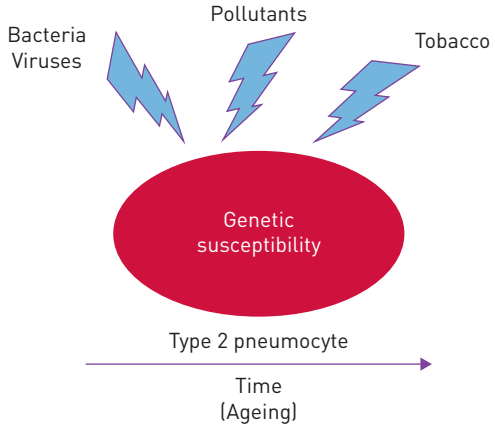

FIGURE 1 A schematic model of idiopathic pulmonary fibrosis pathogenesis. Type 2 pneumocytes, susceptible to injury due to genetic susceptibility and ageing, drive the fibrotic process. Environmental pollutants, bacteria, viruses and tobacco smoke may act as a trigger of the disease in a genetically susceptible individual. Ageing is a key driver of the disease.

[24], wood dust or farming [25]. The data we have, from this study and others, suggests that air pollution, *via* oxidative stress, inflammation and telomere shortening, might promote lung fibrosis, trigger acute exacerbation or accelerate progression of interstitial lung diseases. Overall, controlling air pollution has the potential to decrease IPF incidence, slow lung function decline and prevent IPF exacerbation. Of course, preventing exposure to tobacco smoke is also a major leverage to improve the health of populations.

In conclusion, if the term idiopathic means the cause is not known, cumulative evidence suggests that some environmental factors increase the risk of development of IPF. Air pollution appears to be a common risk factor for the development of various chronic lung diseases, rare or frequent, in children and in adults. If the use of air filters can be discussed as a way to reduce the burden of air pollution in selected patients with chronic lung diseases [26, 27], the only way to limit the impact of air pollution on the development of chronic disease is to improve our air quality. This study emphasises the importance of clean air for lung health and advocates for better air quality on a broad population basis.

References

1 Landrigan PJ, Fuller R, Acosta NJR, *et al.* The Lancet Commission on pollution and health. *Lancet* 2017; in press [https://doi.org/10.1016/S0140-6736(17)32345-0].
2 GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388: 1459–1544.
3 GBD 2016 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; 390: 1345–1422.
4 Conti S, Harari S, Caminati A, *et al.* The association between air pollution and the incidence of idiopathic pulmonary fibrosis in Northern Italy. *Eur Respir J* 2018; 51: 1700397.
5 Taskar VS, Coultas DB. Is idiopathic pulmonary fibrosis an environmental disease? *Proc Am Thorac Soc* 2006; 3: 293–298.
6 Collard HR, Chen SY, Yeh WS, *et al.* Health care utilization and costs of idiopathic pulmonary fibrosis in U.S. Medicare beneficiaries aged 65 years and older. *Ann Am Thorac Soc* 2015; 12: 981–987.
7 Hewson T, McKeever TM, Gibson JE, *et al.* Timing of onset of symptoms in people with idiopathic pulmonary fibrosis. *Thorax* 2017; in press [https://doi.org/10.1136/thoraxjnl-2017-210177].
8 Johannson KA, Vittinghoff E, Lee K, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis associated with air pollution exposure. *Eur Respir J* 2014; 43: 1124–1131.
9 Sese L, Nunes H, Cottin V, *et al.* Role of atmospheric pollution on the natural history of idiopathic pulmonary fibrosis. *Thorax* 2017; in press [https://doi.org/10.1136/thoraxjnl-2017-209967].
10 Winterbottom CJ, Shah RJ, Patterson KC, *et al.* Exposure to ambient particulate matter is associated with accelerated functional decline in idiopathic pulmonary fibrosis. *Chest* 2017; in press [https://doi.org/10.1016/j.chest.2017.07.034].
11 Sack C, Vedal S, Sheppard L, *et al.* Air pollution and subclinical interstitial lung disease: the Multi-Ethnic Study of Atherosclerosis (MESA) air-lung study. *Eur Respir J* 2017; 50: 1700559.
12 Jacquemin B, Siroux V, Sanchez M, *et al.* Ambient air pollution and adult asthma incidence in six European cohorts (ESCAPE). *Environ Health Perspect* 2015; 123: 613–621.
13 Andersen ZJ, Hvidberg M, Jensen SS, *et al.* Chronic obstructive pulmonary disease and long-term exposure to traffic-related air pollution: a cohort study. *Am J Respir Crit Care Med* 2011; 183: 455–461.
14 Chen G, Wan X, Yang G, *et al.* Traffic-related air pollution and lung cancer: a meta-analysis. *Thorac Cancer* 2015; 6: 307–318.
15 Bowatte G, Erbas B, Lodge CJ, *et al.* Traffic-related air pollution exposure over a 5-year period is associated with increased risk of asthma and poor lung function in middle age. *Eur Respir J* 2017; 50: 1602357.
16 Clifford RL, Jones MJ, MacIsaac JL, *et al.* Inhalation of diesel exhaust and allergen alters human bronchial epithelium DNA methylation. *J Allergy Clin Immunol* 2017; 139: 112–121.
17 Martinez FJ, Collard HR, Pardo A, *et al.* Idiopathic pulmonary fibrosis. *Nat Rev Dis Primers* 2017; 3: 17074.
18 Nathan SD, Albera C, Bradford WZ, *et al.* Effect of pirfenidone on mortality: pooled analyses and meta-analyses of clinical trials in idiopathic pulmonary fibrosis. *Lancet Respir Med* 2017; 5: 33–41.
19 Richeldi L, du Bois RM, Raghu G, *et al.* Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2071–2082.
20 Selman M, Pardo A. Revealing the pathogenic and aging-related mechanisms of the enigmatic idiopathic pulmonary fibrosis. An integral model. *Am J Respir Crit Care Med* 2014; 189: 1161–1172.
21 Molyneaux PL, Willis-Owen SAG, Cox MJ, *et al.* Host–microbial interactions in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2017; 195: 1640–1650.
22 Borie R, Tabeze L, Thabut G, *et al.* Prevalence and characteristics of TERT and TERC mutations in suspected genetic pulmonary fibrosis. *Eur Respir J* 2016; 48: 1721–1731.
23 Kropski JA, Blackwell TS, Loyd JE. The genetic basis of idiopathic pulmonary fibrosis. *Eur Respir J* 2015; 45: 1717–1727.
24 Gaensler EA, Jederlinic PJ, Churg A. Idiopathic pulmonary fibrosis in asbestos-exposed workers. *Am Rev Respir Dis* 1991; 144: 689–696.
25 Hubbard R. Occupational dust exposure and the aetiology of cryptogenic fibrosing alveolitis. *Eur Respir J* 2001; 18: Suppl. 32, 119s–121s.
26 Kaufman JD, Raghu G. Should we be concerned about air quality as a contributor to poor outcomes in lung transplant recipients? *Eur Respir J* 2017; 49: 1602369.
27 Johannson KA. Air pollution exposure and IPF: prevention when there is no cure. *Thorax* 2017; in press [https://doi.org/10.1136/thoraxjnl-2017-210808].