Air pollution exposure and interstitial lung diseases: have we identified all the harmful environmental exposures?

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Interstitial lung disease encompasses a heterogeneous group of disorders characterised by excessive deposition of collagen within the extracellular matrix and thickening of the pulmonary interstitium. Many interstitial lung diseases are linked with known environmental exposures including tobacco smoke (idiopathic pulmonary fibrosis), inhaled dust, mould or other irritants (hypersensitivity pneumonitis) and occupational exposures (ie, silicosis, asbestosis).[1] However, the role of potentially relevant environmental exposures is difficult to establish due to the long latency period of these disorders (eg, 40–50 years for asbestosis). In a recent advance in the detection of early stage interstitial lung disease, interstitial lung abnormalities (ILA)—radiological abnormalities on chest CT—have been postulated as an indicator of subclinical interstitial lung disease,[2] opening the door to further discoveries. Exposure to traffic-related air pollution has been postulated as being another potential risk factor. The proposed mechanism of action for this effect is pulmonary and systemic inflammation, oxidative stress and dysregulated fibrogenesis.[3]

In 2016, outdoor air pollution was responsible for >3 million premature deaths,[4] and it is estimated that 91% of the world's population lives in places where air pollution exceeds the limits stipulated by WHO guidelines.[5] Exposure to air pollution has been linked to many conditions, including cardiovascular disease, obesity and neurological disorders, as well as an increase in the incidence of respiratory disorders and related mortality.[4] The American Lung Association recently emphasised that high levels of air pollution could be priming an epidemic of chronic respiratory diseases, such as COPD.[6] In the field of interstitial lung disease, however, air pollution has received very little attention to date.[7–10]

In *Thorax*, Rice *et al*[11] have shown, for the first time, that long-term exposure to elemental carbon (EC), a marker of traffic pollution, may increase the risk of the development and progression of ILA. Using a subsample of the well-known Framingham Heart Study (2618 subjects), Rice *et al* estimated exposure to ambient EC, fine particulate matter ($PM_{2.5}$) and ozone (O_3) over the 5 years (2004–2008) before each subject underwent a chest CT scan (2008–2010). They studied ILA progression in 1846 of the subjects in this subsample who had previously completed a cardiac CT (between 2002 and 2015). Air pollution levels in the Framingham population are very low compared with previous studies: the median residential levels of $PM_{2.5}$ ($9.9 \pm 1.3\,\mu g/m^3$) are close to the WHO threshold of $10\,\mu g/m^3$ and much lower than levels reported by other authors, such as Sack *et al*[7] ($16.5 \pm 2.8\,\mu g/m^3$) and Sesé *et al*[10] ($26.2 \pm 3.4\,\mu g/m^3$). This study by Rice *et al* is particularly pertinent because understanding the health impacts of low levels of exposure is a current research priority.[12]

The authors of the study found that an IQR difference in 5-year EC exposure of $0.14\,\mu g/m^3$ was associated with a 1.27 times greater odds of ILA and a 1.33 times greater odds of ILA progression. Interestingly, the increased odds of ILA was very similar to that reported by Sack *et al*[7] in the MESA study for 10-year exposure to NO_X (1.21; 95% CI 1.02 to 1.43 per IQR increase). The new study adds to the current evidence supporting the role of long-term exposure to air pollution, even at low levels, in the development and progression of interstitial lung diseases, highlighting the need for more detailed studies on the role of particle subtypes to better understand specific toxicity, starting with EC.[13]

The main strength of this study is the expert evaluation of ILA progression on repeated imaging. A previous study assessed repeated measurements of high-attenuation areas on cardiac CT scans, but this is an automated measure of unclear clinical significance.[7] Also, CT scans in the present study were evaluated by three readers, including radiologists and pulmonologists, blinded to previous radiological assessments and the participant's information, and using a sequential reading method with good agreement between CT scans scored by at least two readers.[14] Another strength is that the results remain robust on adjustment for important confounders (eg, pack years and primary occupation) and after sensitivity analyses (eg, including a category for indeterminate CT scans or excluding those who moved).

Residential levels of air pollution in the Framingham cohort were estimated using a variety of validated spatiotemporal models of outdoor air pollution exposure with good performance (R^2 between 0.71 and 0.88). While these models are generally used in epidemiological studies because of their simplicity and cost-efficiency, they may not accurately reflect real long-term average personal exposure since they are usually based solely on the subject's home address and do not include other important determinants of personal exposure, such as the fraction of time spent at home and at work or the mode of transport used and time spent commuting. Furthermore, these models may introduce different levels of exposure measurement error, as already stated by the authors, due to their dependency on the number of measurement sites, the number of available predictors and the characteristics of the study area.[15] Future studies need to consider occupational address and indoor exposures (ie, gas cookers, fireplaces, woodstoves and so on) as well as other potential sources and determinants of personal exposure. Another important point with respect to the Framingham study is the low variability of air pollutant levels (ie, narrow IQRs: $0.14\,\mu g/m^3$ for EC), which may have obscured significant associations. Interestingly, Rice *et al* found associations only with EC and not with $PM_{2.5}$, O_3 or proximity to major roads. Previous studies have found an increased risk of interstitial lung diseases associated with exposure to NO_x,[7] NO_2,[8 9] $PM_{2.5}$[10] and O_3.[8 10] Although a good correlation exists between EC and $PM_{2.5}$ in the Framingham population, given the inconsistencies in air pollution indicators and the results of previous studies, these findings should be interpreted with caution.

Progressive imaging abnormalities have been associated with worse prognosis because patients with ILA progression have an accelerated rate of lung function decline and increased risk of death.[2] In the Framingham cohort, 6% of participants was classified as having ILA with progression (n~43) and 2% as having ILA without progression (n~14). A statistically significant OR was only observed between EC exposure and ILA with progression (1.33, 95% CI 1.00 to 1.77) but we need

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to consider that the odds of ILA without progression were very similar (1.32, 95% CI 0.82 to 2.13). For $PM_{2.5}$ exposure, the odds of ILA without progression (1.45, 95% CI 0.92 to 2.28) was even higher than the odds of ILA with progression (1.14, 95% CI 0.87 to 1.50). The low number of participants classified as ILA without progression may have hindered the observation of statistically significant associations. Further studies with repeated CT scans and a larger sample size are needed to confirm whether air pollution can affect ILA progression.

Smoking and occupational exposures have been clearly linked with interstitial lung diseases.[16] Rice *et al* consider these covariates as potential confounders. They also tested smoking as a potential effect modifier because previous research has found the effect of air pollution on ILA to be greater among never smokers[7]; in the present study, there is no evidence that smoking modifies the effect of exposure. Although occupational exposures clearly affect the outcomes, it is unclear to what extent they modify the individual's air pollution exposure levels. Treating occupation as an effect modifier would inform us whether the effect of air pollution on ILA differs across occupational groups. However, a more comprehensive approach is needed to better understand the complex relationship between all the different environmental exposures that intervene in the development of interstitial lung diseases (ie, synergies, antagonisms).

Environmental epidemiology has traditionally focused on the one-to-one relationship between environmental exposures and health related points; as Rice *et al* have done. In the last decade, the exposome approach has been proposed as a new paradigm to encompass the totality of environmental exposures from conception onwards, limiting the risk of selective reporting and the number of false-positive findings.[17 18] The application of the exposome approach in the field of respiratory medicine will improve our understanding of the risk factors and protective factors in complex, multifactorial, chronic pathologies such as interstitial lung diseases. To define the exposome in patients with interstitial lung diseases, we would have to assess the complete set of potential exposures (eg, air pollution, smoking, occupational hazards) at different time points throughout the lifespan in large population-based prospective cohorts.[3] This will allow us to fully elucidate the contribution of each environmental hazard and the most critical windows of exposure for disease onset.

This study by Rice *et al* reminds us that many challenges lie ahead. The recently published official ATS/ERS/JRS/ALAT clinical practice guideline for the diagnosis of idiopathic pulmonary fibrosis recommends taking a detailed history of environmental exposures at home, work and other places the patient visits frequently.[19] However, the guidelines do not include specific questions regarding air pollution exposure or recommendations on minimising exposure and avoiding strenuous activity on bad-air-quality days.[3] Future research should focus on understanding the implications of air pollution exposure on the natural history of interstitial lung disease.

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