Malaria and the development of pulmonary fibrosis

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Intriguing new evidence suggests that early pulmonary fibrosis is associated with exposure to air pollutants http://ow.ly/FDor30gAYzS

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Sorry for the bait-and-switch. This is not a review about the role of parasitic infections and lung scarring. Instead, the manuscript by Sack *et al.* [1] in this issue of the *European Respiratory Journal* gives us the opportunity to consider the relationship between air pollution, or "bad air" (the literal translation of the contracted Italian words *mala aria*), and the development of, and progression from, early stages of pulmonary fibrosis.

Major sources of outdoor air pollution include primary emissions generated from motor vehicles, power plants and forest fires, as well emissions resulting from industrial, residential and agricultural combustion. Sources of secondary outdoor pollution include gases and particulates generated by the interaction between primary emissions and the atmosphere. Air pollution can similarly occur from indoor emissions generated by tobacco smoke and from the burning of solid fuels often compounded by poor ventilation [2]. Examples of primary air pollutants include suspended particulate matter (PM), nitrogen oxides (NO_x) and sulfur oxides (SO_x), while examples of secondary pollutants include ozone (O_3) and sulfuric acid (H_2SO_4). Particulate matter is often classified as coarse dust particles (PM_{10}) and fine particulates ($PM_{2.5}$) [3]. Measures of NO_x exposure in general, and nitrogen dioxide (NO_2) exposure in particular, are frequently used as surrogates for exposure to the myriad of traffic related emissions [4], while O_3 is a secondary pollutant whose correlation with primary pollutants can be more variable.

In addition to the growing scientific consensus on the adverse outcomes associated with air pollution exposure experienced by those with cardiovascular disease [5] and with obstructive respiratory diseases such as asthma and chronic obstructive pulmonary disease [6–8], studies have also demonstrated that air pollution exposure may result in adverse outcomes in patients with pulmonary fibrosis [9–11]. In longitudinally followed cohorts of patients with idiopathic pulmonary fibrosis (IPF), increased short-term exposures to higher levels of O_3 exposure has consistently been associated with increased rates of acute exacerbations, while findings for NO_2 have been discordant between studies [9, 10]. Positive associations between increased particulate matter (PM_{10} and $PM_{2.5}$) exposure and important IPF outcomes, such as an accelerated decline in forced vital capacity and an increased rate of mortality, have also been demonstrated

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but the results are variable between studies [10, 11]. In total these findings suggest that outdoor air pollution in general, and perhaps higher levels of ozone (or factors closely related to ozone exposure) in particular, may lead to disease progression and acute exacerbations in IPF patients.

Could bad air also lead to the early development of pulmonary fibrosis? It is worth noting that over 40 years ago exposure to indoor air pollution was suggested to be a cause of pulmonary fibrosis in a resource poor setting [12]. Before evaluating this question, it is important to briefly review the literature on the development of early pulmonary fibrosis. Germ line genetic mutations (*i.e.* genetic factors passed down from our parents) substantially increase the risk of developing IPF [13, 14], a disorder that generally presents late in life. Late onset, and incomplete penetrance of genetic factors, suggests additional exposures probably contribute to IPF disease pathogenesis. Furthermore, because IPF is often defined by advanced fibrotic imaging findings [15], it is logical to presume that those at risk for developing clinically apparent IPF transition through a period where their imaging findings are more subtle, and their clinical syndrome is less apparent. Studies attempting to identify people with these more subtle imaging findings have assessed chest computed tomography (CT) scans of undiagnosed participants in research cohorts using both qualitative [16–27] and quantitative [28–33] imaging metrics. These studies have demonstrated that both qualitatively assessed interstitial lung abnormalities (ILA) and increased measures of quantitative metrics are more common than IPF is reported to be, and that research participants with these imaging abnormalities are also more likely to have genetic predictors noted in IPF patients [17, 20, 22, 33, 34], restrictive physiologic and exercise impairments [16–18, 27, 29, 33], radiologic progression (*e.g.* interval development of fibrosis in general, and IPF in particular) [20], accelerated lung function decline [20], and an increased risk for death [21, 27, 33]. In total these studies suggest that clinically apparent IPF may arise from a larger, but similarly genetically predisposed, group beginning to develop detectable imaging findings. The hunt is now on, to determine the additional factors that contribute to subclinical pulmonary fibrosis and the transition between subclinical and clinical disease.

In this issue of the *European Respiratory Journal*, Sack *et al.* [1] present the first assessment of the associations between measures of air pollution and both qualitative and quantitative imaging metrics of subclinical pulmonary fibrosis in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort. Individual estimates of air pollutant exposures were generated from measurements obtained from community sources, as well as a sample of participant homes, using previously published spatio-temporal models that have been demonstrated to explain most of the variation in measurement of these pollutants [35, 36]. Qualitative ILA assessments were performed in 2671 MESA participants with full thoracic chest CT scans, and quantitative assessments included measures of the progression of high attenuation areas (HAAs, a quantitative metric of the percent of lung occupied by increased density measures) in 5495 MESA participants with serial cardiac chest CT scans separated by a follow-up period of nearly 6 years. Sack *et al.* [1] demonstrate, in models adjusting for important covariates, that the odds of having ILA in MESA participants increased by 77% for every 40 parts per billion increment in NO_x exposure over a 10-year period. A similar trend, of borderline statistical significance, was noted between 10-year estimates of NO_x exposure and increases in HAA measures over time. While there was no evidence for effect modification by sex, there was evidence for effect modification by race (with increased evidence for positive associations between NO_x, NO_2, and $PM_{2.5}$ and HAA progression in analyses limited to non-Hispanic white participants), and modest evidence for effect modification by tobacco use (with increased evidence for positive associations between NO_x, NO_2, and $PM_{2.5}$ and ILA, and surprisingly an inverse association between O_3 and ILA, in analyses limited to never-smokers).

The strengths of this study include the large, well-characterised cohort, the well-validated assessments of individual air pollution exposure measures, and demonstration of similar findings between NO_x exposure and two different measures suggestive of early pulmonary fibrosis development. The authors should be applauded for taking the first steps towards assessing the role that air pollution exposures might play in the early development of this debilitating lung disease. Replication of these findings in independent cohorts would provide greater confidence that air pollution exposure avoidance should be considered in groups at higher risk to develop pulmonary fibrosis.

Some limitations of these findings are also worth considering. It is currently challenging to know how to interpret discrepant findings between qualitative and quantitative metrics of subclinical stages of pulmonary fibrosis because, although these metrics are correlated, they are not interchangeable [37]. In addition, it is also becoming clear that even qualitative assessments of ILA can result in a heterogenous phenotype that can confound important findings of association. For example, apparent discrepancies between the associations of the *MUC5B* promoter polymorphism [22] (the genetic mutation most commonly associated with IPF [13, 14]) and ILA between whites and African-Americans are better explained by different contributions of ILA subtypes, such as a subpleural predominant pattern, in these populations, than by racial differences in the findings of association [22]. As expected, histopathologic

differences are also noted between ILA subtypes [38]. In short, not all findings currently characterised as ILA or that have increased measures of quantitative metrics are likely to represent the same clinical phenotype. This suggests that future studies should consider phenotypic refinements to determine the imaging characteristics that best portend subclinical pulmonary fibrosis and the risk for disease progression.

In conclusion, the study by Sack *et al.* [1] provides growing weight to the concern that increased exposure to air pollution might contribute to the development and progression of pulmonary fibrosis and suggests that environmental exposures could represent a potentially preventable contributor to disease pathogenesis.

The name malaria, derived from the Italian *mal aria* (or bad air) emanates from the beliefs of some ancient Romans who observed that the cyclical febrile illness was more common among those who lived near swamps and developed the disease by breathing the horrible fumes that came from them [39]. While "draining the swamp" has modern political connotations, it was initially a term used by the Romans to deal with the problem of malaria. While swamp drainage may have had the unintended consequence of reducing some mosquito breeding habitats, lack of a complete knowledge of malaria disease pathogenesis left the ancient Romans to deal with the ravages of malaria for many years to come. The lack of complete understanding of the medical and environmental consequences of unchecked air pollution and the current shift in US domestic policy away from combating the problems of air pollution [40] makes the findings of this work timely.

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