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Air Pollution Exposure
A Novel Environmental Risk Factor for Interstitial Lung Disease?

Kerri A. Johannson, MD; John R. Balmes, MD, FCCP; and Harold R. Collard, MD, FCCP

Air pollution exposure is a well-established risk factor for several adverse respiratory outcomes, including airways diseases and lung cancer. Few studies have investigated the relationship between air pollution and interstitial lung disease (ILD) despite many forms of ILD arising from environmental exposures. There are potential mechanisms by which air pollution could cause, exacerbate, or accelerate the progression of certain forms of ILD via pulmonary and systemic inflammation as well as oxidative stress. This article will review the current epidemiologic and translational data supporting the plausibility of this relationship and propose a new conceptual framework for characterizing novel environmental risk factors for these forms of lung disease.

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ABBREVIATIONS: ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; NO_2 = nitrogen dioxide; NOx = nitrogen oxides; O_3 = ozone; PM = particulate matter; ROS = reactive oxygen species; TGF-β = transforming growth factor-β

The interstitial lung diseases (ILDs) comprise a diverse group of entities primarily characterized by the proliferation and thickening of the pulmonary interstitium. Despite a wide range of etiologic processes, many share a common phenotype of irreversible lung fibrosis that, in some patients, leads to progressive hypoxemia, respiratory failure, and death. Inhaled environmental causes have been identified in several well-described forms of ILD, including hypersensitivity pneumonitis, asbestosis, and silicosis.

Ambient air pollution has received relatively little attention in the field of ILD but is known to contribute to a range of pulmonary and systemic diseases. Air pollution exposure is increasingly implicated in adverse health outcomes, including asthma, COPD, cardiovascular disease, and, most recently, lung cancer. We believe that a plausible argument can be made for a relationship between ambient air pollution and ILD. This article reviews the current clinical and biologic evidence linking air pollution exposure to the development and progression of ILD and proposes a new way of conceptualizing cumulative environmental risk factors in this patient population.

Air Pollution Overview

Ambient air pollution includes chemical, biologic, and particulate materials released

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AFFILIATIONS: From the Department of Medicine (Drs Johannson, Balmes, and Collard), University of California, San Francisco, San Francisco, CA; Division of Environmental Health Sciences (Drs Johannson and Balmes), School of Public Health, University of California, Berkeley, Berkeley, CA; and Department of Medicine (Dr Johannson), University of Calgary, Calgary, AB, Canada.

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CORRESPONDENCE TO: Kerri A. Johannson, MD, University of Calgary, 4448 Front St SE, Calgary, AB, T3M-1M4, Canada; e-mail: kerri.johannson@albertahealthservices.ca

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into the atmosphere. Of the six criteria air pollutants regulated by the US Environmental Protection Agency (particulate matter [PM], ozone [O_3], nitrogen dioxide [NO_2], sulfur dioxide, carbon monoxide, and lead), PM, ground-level O_3, and NO_2 have been most strongly associated with adverse respiratory outcomes.

PM is a uniquely complex mixture that may include solid particles, liquids, and vapors. Sources of PM include geologic sources (eg, sand, salt), metals, and fossil fuel combustion (eg, diesel exhaust particles, black carbon). PM is typically defined by size, such as PM $\leq$ 10 μm, $\leq$ 2.5 μm, or $\leq$ 0.1 μm in aerodynamic diameter (PM_{10}, $PM_{2.5}$, and $PM_{0.1}$, respectively), or more qualitatively as coarse, fine, and ultrafine. However, its toxicity varies depending on factors like particle weight and composition, as well as host factors determining the location and density of deposition in the respiratory tract.[1] PM toxicity can be further enhanced by exposure to other pollutants like NO_2 and O_3, with which it is frequently accompanied. PM exerts its effects directly from deposition in the respiratory tract and indirectly from triggering a local inflammatory response that can spread to the systemic circulation.

NO_2 is emitted whenever fossil fuels are combusted. It is a good marker of traffic-related air pollution and is an indicator for the larger group of nitrogen oxides (NOx). NOx combine with other compounds such as ammonia and moisture to form small particles capable of penetrating deep into the lung. Exposure to NO_2 induces a proinflammatory response in bronchial epithelial cells and can alter the distribution of leukocyte subsets in both blood and bronchoalveolar fluid.[2-4] NO_2 also reacts with volatile organic compounds, heat, and ultraviolet radiation to produce ground-level O_3.

Trophospheric O_3 exists within 10 km of the Earth's surface and is photochemically produced through the reactions of sunlight with other pollutants like volatile organic compounds and NOx. In both human and animal studies, O_3 has been found to induce airway hyperreactivity and airway inflammation, as well as to modify the cell-surface phenotypic expression of immunoregulatory proteins.[5-8]

Respiratory Health Effects of Air Pollution (Epidemiology)

Air pollution exposure has been linked extensively to respiratory-related morbidity, particularly with respect to airways disease. Increased exposure levels have been associated with poorly controlled asthma,[9,10] asthma hospitalizations,[11] impaired lung function growth,[12] COPD incidence,[13] and COPD exacerbations.[14] Proximity to a major road, as a proxy of traffic-related air pollution, was associated with elevated pulmonary and systemic markers of inflammation and an increased risk of bronchiolitis obliterans syndrome and death in a cohort of patients who had undergone lung transplantation.[15] Additionally, air pollution has been identified as a risk factor for pulmonary exacerbations in cystic fibrosis.[16-18] A large retrospective analysis identified an increased risk of respiratory-related mortality associated with elevations in chronic O_3 exposure.[19] Using individualized exposure estimates, NO_2 exposure has been associated with an increased risk of death from lung cancer.[20] Other population-based studies have demonstrated improved health outcomes subsequent to reduced air pollution levels, ranging from incident COPD to greater life expectancy.[21,22]

There has been a paucity of studies investigating air pollution and ILD despite many ILDs arising from inhalational exposures. Asbestosis and other pneumoconioses, hypersensitivity pneumonitis, chronic beryllium disease, and the smoking-related ILDs are all clearly linked to inhalational exposure to environmental agents. These agents range from toxic particulates and noxious gases to organic antigens, all of which are potentially modifiable in the patient's environment. Idiopathic pulmonary fibrosis (IPF) has been associated with industrial and production-based jobs as well as occupational metal and wood dust exposures, and it has been proposed that the male predominance of disease is attributable to the sex distribution in these occupations. The most well-established environmental risk factor for IPF is cigarette smoking, with smokers more likely to develop disease.[23] In a susceptible patient with underlying cumulative stress to the alveolar epithelium, cigarette smoking may accelerate fibrogenesis in the IPF lung via oxidative stress and other profibrotic signals inducing cellular senescence.[24-26] Additionally, the age-related predominance of IPF suggests a cumulative, time-dependent risk, consistent with a dose-response relationship. The biologic and chemical agents discussed share similarities to the ambient air pollutants. Like the antigens known to cause hypersensitivity pneumonitis, organic components of PM may trigger abnormal immune responses leading to inflammation, epithelial damage, and over time, fibrosis. Cigarette smoking exposes the lung to particulates of varying size and to volatile organic compounds, both components of air pollution.

There is a small but growing body of evidence investigating the relationship between air pollution exposure