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Air Pollution and Respiratory Infection: An Emerging and Troubling Association

Evidence that inhalation of combustion-derived material increases vulnerability to airway infection dates back to at least the 1952 London smog, in which coal smoke was temporarily trapped over the city. The subsequent landmark paper published a year later in the *Lancet* by Logan (1) reported that, during the smog, deaths from pneumonia increased threefold, with the very young and the elderly particularly at risk. Notifications for pneumonia also increased 1.4-fold during the smog event itself, and 2.4- to 2.7-fold in the subsequent 2 weeks compared with the corresponding weekly average during 1947–1951. Indeed, Bell and colleagues (2) recently estimated that pneumonia was a significant cause of the 12,000 excess deaths resulting from acute and persisting effects of exposure to the 1952 London smog. Since then, the types of combustion sources associated with increased risk for pneumonia have expanded. For example, in Vietnam, a population-based survey found a 1.5-fold (95% confidence interval [CI], 1.25-fold to 1.92-fold) increased risk for pneumonia in young children exposed to environmental tobacco smoke, with 28% of childhood pneumonia attributable to environmental tobacco smoke (3); more recently, a meta-analysis of 10 European birth cohorts found a 1.3-fold (95% CI, 1.02-fold to 1.65-fold) increase in risk for pneumonia in young children with long-term exposure to traffic-related nitrogen dioxide (per 10 $\mu g/m^3$ NO_2), and 1.8-fold (95% CI, 1.0-fold to 3.09-fold) increase for particulate matter less than 10 microns in aerodynamic diameter (per 10 $\mu g/m^3$ PM_{10}) (4).

With consistent effects reported between air pollution and pneumonia, it is puzzling why the evidence base for a link (or its absence) to more common respiratory infections has been, to date, relatively limited. As globally, acute lower respiratory infection (ALRI) remains one of the leading causes of morbidity and mortality in children younger than 5 years (5), the article in this issue of the *Journal* by Horne and colleagues (pp. 759–766) (6), focusing on the association between short-term changes in air pollution and risk for ALRIs, is therefore particularly welcome. Similar to the pattern of pneumonia diagnoses during and after the London smog, Horne and colleagues (6) found that for children younger than 2 years, the risk for an encounter with a healthcare provider with an ALRI was increased during a week with elevated $PM_{2.5}$, and that this increased risk persisted for 3 weeks after the event, a pattern that probably is similar for older children. An association between exposure and increased ALRI risk was also found in the subgroup of young children with proven respiratory syncytial virus (RSV) infection, which is an important analysis, as globally, in 2015, 33 million episodes of ALRI that were a result of RSV infection resulted in 3 million hospital admissions and 60,000 in-hospital deaths in children younger than 5 years (7).

What more do we need to know about the association between air pollution and respiratory infection? On one hand, we now have sufficient data on the adverse health effects of air pollution throughout the life course, so that healthcare professionals should advocate further immediate rapid reductions in fossil fuel emissions to protect population health. On the other hand, these new troubling data on the association between air pollution and respiratory infections in children may resonate with the public, and thereby goad policy makers into more action. Certainly, it would be helpful to see the association between short-term increases in PM and ALRI replicated in other countries, together with exploration of the independent effect of increased long-term exposure from living near heavily used roads. Mechanistically, it would be helpful to understand whether it is the complex pollutant mix or one or two individual pollutants that impair host defense to viral infection. For bacterial pneumonia, this mechanistic evidence is emerging. For example, urban PM increases the expression of platelet-activating factor receptor on airway epithelial cells *in vitro*, which pneumococci subsequently co-opt to increase adhesion to PM-exposed cells (8). For human rhinovirus (RV) infection, exposure of primary human nasal epithelial cells to NO_2 *in vitro* increases the expression of the RV entry receptor intercellular adhesion molecule-1 (9). However, the effect of either PM or NO_2 on RSV infection of airway cells remains unclear. In one of the few studies performed to date, Becker and Soukop (10) reported a rather

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confusing picture of increased RSV internalization by airway epithelial cells exposed to 0.5 ppm NO_2 for 60 minutes, but decreased RSV internalization in cells exposed to 1.5 ppm NO_2. The study of Horne and colleagues (6) should therefore stimulate researchers to revisit RSV and pollutant interactions *in vitro* and, if possible, to model the effect of individual pollutants on the emerging area of the role of viral respiratory tract infection in increasing risk for clinically severe bacterial infections (11). ■

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Predicting Outcome in Idiopathic Pulmonary Fibrosis Using Automated Computed Tomography Analysis

The prevalence of idiopathic pulmonary fibrosis (IPF) is increasing worldwide and there has been increased interest in developing efficacious drug therapies for this terminal disease (1). Currently, there is debate as to what is the most valid endpoint to be used in clinical trials, although the current consensus is that using a 10% decline in FVC as the primary measure of outcome in IPF is indicative of clinically significant disease progression (2, 3). In addition, the unpredictable and variable rate of decline of patients with diagnosed IPF makes it very challenging to select patients for a given drug trial and to compare results across different study populations. Characterization of indicators suggesting a poor prognosis at baseline in IPF is essential to guide optimal management and in drug trial settings, to allow for cohort enrichment to identify patients who are likely to experience increased clinical events, thereby reducing sample sizes and reducing the prohibitive costs (4–7).

In this issue of the *Journal*, Jacob and colleagues (pp. 767–776) highlight the importance of identifying novel and more efficient biomarkers for predicting the progression of IPF, as well as the need to develop tools for more effective selection of subjects for clinical trials (8). The authors should be congratulated for their invaluable contribution to this topic. The very well designed study and excellently crafted manuscript demonstrate the complexity of this field and emphasize new methods and approaches for biomarker discovery with the potential to stratify patients and potentially reduce the size and thus the cost of clinical trials. The authors highlight the importance of using novel computer-based image analysis algorithms, which have all been shown to be predictive of survival and FVC changes (9–11). In this paper, they offer a first look into the analytic validation of the vessel-related structure (VRS) score as a biomarker to predict survival and identify subjects who are most likely to progress in the short term. They suggest that VRS scores may in fact reduce the number of subjects required in a clinical trial, based on power calculations they analyzed. This is an attractive concept, but it requires careful consideration of the assertion.

A power calculation is based on the effect size, type 1 error, and type 2 error. The effect size in a two-group *t* test with equal variances is based on the ratio of the difference of the mean to an SD (12, 13). The authors set the three differences of FVC means at 30 ml, 48 ml, and 60 ml, which correspond to 25%, 40%, and 50%

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