Yet Again, Air Pollution Impacts Lung Health

Cora S. Sack[1,2] and Christopher H. Goss[1,3]

[1]Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of Washington–Seattle, Seattle, Washington; [2]Department of Environmental and Occupational Health Sciences, Department of Medicine, University of Washington–Seattle, Seattle, Washington; and [3]Division of Pediatric Pulmonology, Department of Pediatrics, University of Washington, Seattle, Washington

Viral bronchiolitis remains one of the leading causes of child mortality worldwide, responsible for between 66,000 to 199,000 deaths per year. Disease manifestation represents the complex interplay between host-specific characteristics, pathogen attributes, and environmental risk factors (1). There is growing evidence that exposure to air pollution may be one contributing cause. Inhalation of pollutants results in oxidative stress that alters the lung's inflammatory response and ability to effectively clear pathogens. Because children have narrower airways, a higher ventilatory rate, and immature immune system, they may be a particularly susceptible population (2).

Several epidemiologic studies have demonstrated an association between air pollution exposure and bronchiolitis. Karr and colleagues (3) found that lifetime exposure to traffic-derived, wood smoke, and industrial point source pollution was associated with increased odds of bronchiolitis in British Columbia, Canada. In contrast, Ségala and colleagues (4) found that acute exposure to particulate matter (PM) less than 10 μm in diameter (PM_{10}), black smoke, sulfur dioxide (SO_2), and nitrogen dioxide (NO_2) was associated with increased consultations and hospitalizations for bronchiolitis in Paris, France. In a prospective cohort study, Pino and colleagues (5) found that short-term exposures to PM less than 2.5 μm ($PM_{2.5}$) was associated with a diagnosis of wheezy bronchitis in Santiago, Chile. The majority of these studies have been in urban areas where the principle components of air pollutants were by-products of fossil fuel combustion.

In this issue of the *AnnalsATS*, Yitshak-Sade and colleagues (pp. 1796–1802) present a case–cross-over study from southern Israel that adds significantly to this literature (6). In contrast to other studies, the authors have selected an area exposed to high levels of pollutants with significant contributions from nonanthropogenic sources—mainly dust storms composed of crustal matter. In addition, they have selected a unique population comprised of 80% urban Jews and 20% Bedouin-Arabs. By leveraging the case–cross-over study design, they can study this diverse population, controlling for many potential confounders and investigating several different periods of exposure.

The study includes all infants, aged 0–2 years, admitted to Soroka University Medical Center in southern Israel with an *International Classification of Diseases, Ninth Revision* diagnosis of bronchiolitis between 2003 and 2013. The authors focus their analysis on four measurements of air quality: PM_{10}, $PM_{2.5}$, NO_2, and SO_2. Exposures to PM are estimated from residential address using a combination of daily satellite-derived observations and land use regression. NO_2 and SO_2 measurements are obtained from a central monitoring site located in the largest city in the region. The authors define the case period as the hospitalization day, or the moving average lagged exposure of 0–1, 0–4, and 0–7 days. Each case is referenced against a control period in the subject, selected on the days of the week from the same month of the same year. This time-stratified approach has been shown to reduce confounding by seasonal and other temporal patterns in pollution (7). They use conditional logistic regression adjusted for temperature to examine the association between concentrations of air pollution and bronchiolitis.

The authors find that increases in weekly pollutant concentration are associated with an increased odds of hospitalization for bronchiolitis. Specifically, per increase in interquartile range of average daily concentration of PM_{10}, $PM_{2.5}$, and NO_2 1 week before admission, the odds of hospitalization for bronchiolitis increased by 6% (95% confidence interval [CI] = 2–9%), 4% (95% CI = 2–6%), and 36% (95% CI = 12–65%), respectively. This 0- to 7-day time frame is similar to the susceptibility period that Pino and colleagues (5) found in Santiago, Chile. Although the effect size is small, it is quantitatively similar to that reported in other epidemiologic studies in more urban areas. When considered in the context of the large population exposed, the adverse health consequences are sizable.

One of the more interesting aspects of the study is the suggestion of effect modification based on stratified analyses. The authors found statistical evidence of an increased association between air pollution and bronchiolitis in boys compared with girls. This mirrors the sex difference found

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Correspondence and requests for reprints should be addressed to Cora S. Sack, M.D., Occupational Medicine, Pulmonary and Critical Care Medicine, University of Washington Medical Center, Campus Box 356522, 1959 N.E. Pacific, Seattle, WA 98195. E-mail: cssack@u.washington.edu

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in the incidence of severe bronchiolitis and other childhood respiratory viral infections. The underlying mechanism for this disparity is uncertain, but may be related to difference in lung and airway development between the sexes (1).

The authors also found that effect estimates were higher in Bedouin–Arabs compared with Jews. Although intriguing, interpretation of these results is difficult, as there was no statistical evidence of effect modification. The authors postulate that this may be attributable to the high number of Bedouin-Arabs living in temporary living structures, with increased infiltration of outdoor air pollutants. Poor air quality may be further compounded by indoor air pollutants from cook stoves and burning of biomass fuels. Unfortunately, the authors did not have access to type of housing in their data, so they were unable to further refine their hypothesis.

One of the major strengths of this study was the case–cross-over design that allowed the authors to control for a wide range of variables, such as sex, age, and socioeconomic factors. However, it is important to recognize the limitations of this study design. First, it does not account for time-varying characteristics that may be closely linked to bronchiolitis. For example, household crowding and environmental tobacco smoke exposure may be significantly different in case versus control periods. Because these variables should not be strongly associated with ambient air pollutant exposures, it is likely that these unmeasured variables may attenuate results, and bias toward the null. Second, it is important to accurately characterize the temporal onset of the outcome for this analysis. Nearly 20% of the population had been prescribed steroids 10 days before their hospital admission, implying that many participants were symptomatic before their admission. By classifying the case period as 0–7 days before hospitalization, the authors may miss the critical time window in many study participants. This distinction effects the interpretation of whether exposure to air pollution enhances susceptibility to infection or, rather, worsens disease severity.

In addition to these considerations, this is an observational study with errors in exposure measurement, outcome misclassification, and an inability to infer causation. Cases of bronchiolitis were ascertained retrospectively from *International Classification of Diseases, Ninth Revision* codes rather than clinical diagnoses, and may include pneumonia, croup, or other respiratory infections. Although the authors used sophisticated models of air pollutants, exact home addresses were not available for the majority of study subjects. Furthermore, assigning exposure based on residence does not accurately reflect pollutant exposure in the participants' microenvironment.

Despite these limitations, the conclusions from this study are compelling and show a consistent association between acute exposure to pollution and the odds of hospitalization for bronchiolitis. These findings add significantly to prior literature, and highlight the role of air pollution in respiratory tract infections. More studies are needed to determine susceptible populations and further our understanding of the complex interaction that mediates these effects. ■

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