penetrance is immeasurably more challenging. The advent of parallelizable techniques, such as MPRA, goes a considerable distance toward enabling investigators to weigh the subtle influence of SNPs in specific contexts. Indeed, MPRA could be further parallelized to weigh the influence of various SNPs across different exposures, such as culturing transfected 16HBE with and without cigarette smoke extract. Aggregated with chromatin immunoprecipitation sequencing, 3C, and CRISPR for validation, a relatively exhaustive list of molecular interactions can be assayed, making the future brighter for molecular cryptographers by making the functional genetics less enigmatic. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Could the Air You Breathe Increase Your Risk of Developing Acute Respiratory Distress Syndrome?

Since the Industrial Revolution, products of combustion have entered the atmosphere at increasing rates, with profound effects on the air we breathe. Early major air pollution events that caused

Supported by a Merit Review Grant from the Department of Veterans Affairs and by grants from the NHLBI to the PETAL Network and to SPIROMICS II.

Originally Published in Press as DOI: 10.1164/rccm.201808-1513ED on August 22, 2018

dramatic spikes in mortality attracted attention to the adverse health effects of air pollution. Subsequent research resulted in national standards for air quality, identifying levels of individual pollutants deemed unhealthy for susceptible groups or for the population at large. Heavy air pollution exposure is a specific risk factor for all-cause mortality and for a number of specific cardiovascular and respiratory events. Recently, important studies have extended the range of air pollutant exposure associated with adverse health outcomes, demonstrating significant direct

relationships between both long-term (1) and short-term (2) pollutant levels and mortality, even at levels of pollutants previously considered safe.

In many instances, air pollution exposure exerts adverse health effects by modulating preexisting illness. For instance, exposure to particulate matter less than 2.5 μm in aerodynamic diameter ($\text{PM}_{2.5}$) is associated with increased rates of acute coronary events in individuals with preexisting coronary artery disease (3). Similarly, air pollution episodes often trigger exacerbations of airway diseases (4) or increase the severity of illness in individuals with community-acquired pneumonia (5). In this issue of the *Journal*, Reilly and colleagues (pp. 62–70) report the results of a prospective study identifying a strong relationship between exposure to several pollutants (sulfur dioxide, nitrogen dioxide, ozone, carbon monoxide, and $\text{PM}_{2.5}$) and the risk of developing acute respiratory distress syndrome (ARDS) after trauma (6). The major associations were with longer term exposure (3 yr). It is particularly noteworthy that this cohort was exposed to levels of pollution at or below current U.S. Environmental Protection Agency (EPA) standards. Although those developing ARDS were more severely injured, the contribution of air pollutant exposure remained significant in multivariate analyses controlling for severity of illness and other known risks for ARDS. In the logistic regression analysis, the odds ratio for comparison of the 75th and 25th percentiles for $\text{PM}_{2.5}$ was 3.58 (95% confidence interval, 2.40–5.34), with similar values for the other pollutants, demonstrating the importance of this contribution. Prior work from some of the same investigators using a cohort in Tennessee identified an association between low-level ozone exposure and ARDS, which was most significant in patients with trauma (7). These observations strongly suggest a relationship between trauma and chronic air pollutant exposure in determining individual risk for ARDS. It adds to the group of environmental exposures, including cigarette smoke (8) and chronic alcohol use (9), that constitutes risks for ARDS.

This study does not provide specific information delineating the mechanism by which pollutants increase risk of ARDS. Animal studies indicate that dysfunction of alveolar epithelial cells or pulmonary capillary endothelial cells can induce acute lung injury (10); other studies demonstrate that air pollutants can target these same cells (4). Similarly, dysregulated inflammation, oxidative stress, and coagulation abnormalities are pathways commonly linked to ARDS that are also activated by pollutant exposure. In prospective studies of healthy adults, improvement in air quality in Beijing at the time of the 2008 Olympics was associated with significant decreases in a broad range of measures of oxidative stress and inflammation (11, 12). Thus, the suggestion that air pollution exposure may increase risk for ARDS has biological plausibility.

This study stimulates important but unanswered questions. ARDS is a heterogeneous condition. Although the organ physiology may be similar, trauma, nonpulmonary sepsis, and pneumonia are predisposing factors that lead to ARDS by pathways that may differ widely and have different trajectories of disease (13). This heterogeneity is an important consideration with respect to environmental exposures that increase risk for ARDS. For instance, cigarette smoke exposure appears to

increase risk of ARDS in those with nonpulmonary sepsis, but not in those with pneumonia (8). The report by Reilly and colleagues is focused on trauma patients; whether their findings can be extended to those at risk for ARDS in other settings is an open question. Similarly, multiple different pollutants were found to have independent associations with risk for ARDS. It is not known whether each of these pollutants acts by the same mechanism, if there might be synergistic effects, and whether the pollutants measured are simply surrogates for other, unidentified, factors. Although the most prominent pollutant effects were with chronic rather than acute exposure, it is not known whether duration or cumulative dose is the key factor. One major question is whether the pollution effect on risk of ARDS after trauma is also associated with adverse effects on survival. It is a limitation that this report does not include survival data.

This study has important strengths. It was a prospective assessment of 996 trauma patients, 24% of whom developed ARDS. There was appropriate severity indexing, tracking of subjects after enrollment, and case definition. The analyses incorporated consideration of other important variables including demographics, surrogates for socioeconomic status, and cigarette/alcohol use. The authors estimated individual patient exposures based on the network of EPA monitors, with geocoding to each patient's residence and modeled values integrating input from multiple nearby monitors. The overall density of monitors in the area surrounding the study site was relatively high. They also performed reasonable sensitivity analyses that suggest that limiting the analysis to those residing closer to monitors did not change the conclusions.

Although the authors are to be commended for modeling exposure at the level of individual residence, they recognize that this model provides a limited estimate of actual individual exposure, which is influenced by time out of doors, work location and activity, and characteristics of the individual home. It is impressive that there are strong associations with ARDS risk at this level of granularity. However, air pollution varies widely across the country, with differences in the mixtures of criteria pollutants and additional unmeasured factors, such as toxic gases. In addition, $\text{PM}_{2.5}$ particles may have different chemical composition. The relative contributions of sulfate, nitrate, and organic carbon within particles vary considerably, resulting in different biological effects (14).

This new report adds to the compelling body of scientific evidence about the importance of pollution at levels below those established in EPA regulations. ARDS confers an enormous burden of morbidity and mortality. Many of the recognized risk factors for ARDS are intrinsic patient features that are not amenable to change. In contrast, air pollution exposure may be an important risk factor that is potentially actionable both at the level of the individual and across society. As we contemplate the regulatory burden of reducing pollutants in the air we breathe, it is crucial to recognize the additional health care costs that are associated with even low-to-moderate levels of pollution. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Respiratory Phenotypes during Childhood and Early-Life Exposures

It is widely accepted that childhood asthma is not a single disease but a heterogeneous condition with multiple dimensions that involve atopy or allergic sensitization, poor lung function, airway responsiveness, and a variety of symptoms. For the most common symptom, wheezing, a number of distinct patterns of early childhood wheezing have been identified and consolidated by using data-driven approaches (1). Similarly, distinct patterns of allergic sensitization (2) and lung function (3) based on data from several birth cohorts have recently been reported.

In this issue of the *Journal*, Bacharier and colleagues (pp. 71–82) combine distinct trajectories of wheezing and allergic sensitization together with pulmonary function measures in a single model using data from 442 participants from the URECA (Urban Environment and Childhood Asthma) birth cohort, a well-followed, high-risk population (4).

The study identified five respiratory phenotypes from birth to 7 years, differentiated mainly by patterns of wheezing and allergic sensitization: low wheeze/low atopy, low wheeze/high atopy, transient wheeze/low atopy, high wheeze/low atopy, and high wheeze/high atopy. Differences in lung function variables were less pronounced, with the greatest impairment in lung function seen in the two high-wheeze phenotypes. Phenotype-specific crude

associations with potentially modifiable early-life environmental exposures were also reported.

In a pioneering study that involved categorizing 826 children with wheeze data collected at 3 and 6 years of age, Martinez and colleagues (5) reported four mutually exclusive wheezing phenotypes: no wheezing, transient early wheezing, late-onset wheezing, and persistent wheezing. This finding was confirmed in several independent cohort studies (6, 7) and later extended using data-driven approaches to include more intermediate phenotypes (1, 8–12). In some of these studies, phenotype-specific associations with atopy and lower lung function were reported (8, 10). Furthermore, several different phenotypes of atopic sensitization that differ in their relation to asthma presence and severity have been identified throughout childhood in different population-based birth cohorts (2, 13).

It has been reported that different phenotypes of childhood wheezing have different environmental associations (5, 11, 14), and similarly, different phenotypes of allergic sensitization differ in their environmental risk factors (15). Although the effect of most environmental factors is likely to vary across subjects with different genetic predispositions, the underlying mechanisms that drive gene–environment interactions remain uncertain.

One of the strongest points of the study presented by Bacharier and colleagues is that the authors were able to incorporate deep phenotyping, with wheezing reports being