Other limitations to the clinical message are the use of young pigs that are more resistant to hypotension, as suggested by the absence of mortality in this study. The results may be different in older comorbid animals or an older clinical population with chronic hypertension, for instance. This study confirms that in hemorrhagic shock adding norepinephrine to fluid resuscitation does not threaten the renal microcirculation or renal function. ■

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# Small Airway Anatomy: An Indicator of Pollution Susceptibility in Adults?

It is well accepted that long-term exposure to higher amounts of air pollution impairs lung function in adults and accelerates the rate of lung function decline (1, 2). Ambient pollution exposure may also increase risk of developing chronic obstructive pulmonary disease (COPD), even among never-smokers (3). However, few individual-level traits have been identified that modify the long-term effects of air pollution on adult respiratory health, particularly at low pollutant concentrations just above recently revised World Health Organization air quality guidelines (4). In this issue of the *Journal*, Bourbeau and colleagues (pp. 44–55) sought to address this need (5). The authors evaluated dysanapsis, a mismatch of airway tree caliber to lung parenchyma size, as a potential indicator of pollution susceptibility, building on emerging evidence implicating airway abnormalities and impaired lung growth as risk factors for COPD (6). The authors found that long-term exposure to particulate matter ⩽2.5 μm in aerodynamic diameter ($PM_{2.5}$) and nitrogen dioxide ($NO_2$) were each associated with lower lung function. Among those in the lowest quartile of radiographic airway-to-lung ratio, the associations of $PM_{2.5}$ with lung function and odds of COPD were greater.



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The authors present a cross-sectional study of 1,452 adults recruited from the CanCOLD (Canadian Obstructive Lung Disease) study, which drew from nine Canadian cities between 2009 and 2015. Participants completed postbronchodilator spirometry, which defined the primary outcomes of $FEV_1$, FVC, $FEV_1$-to-FVC ratio, and COPD (defined as $FEV_1$-to-FVC ratio of less than 0.70). Long-term exposure to ambient $PM_{2.5}$ and $NO_2$ before baseline assessment was assigned by residential postal code using validated regression models informed by satellite imagery and land-use data. In adjusted models, each interquartile range increment of 2.4 $\mu g/m^3$ of average $PM_{2.5}$ and 9.2 ppb of average $NO_2$ was associated with a −101.7 ml (95% confidence interval, −166.2 to −37.2) and −115.0 ml (95% confidence interval, −196.5 to −33.4) difference in $FEV_1$, respectively. This study only examined lung function once and did not assess if pollution exposure was associated with change in lung function over time, which would have provided more compelling evidence of causality. Finer-scaled exposure estimates, using buffers of a few hundred meters around residential addresses, might have improved precision of these estimates by reducing exposure misclassification. Nonetheless, these associations of long-term $PM_{2.5}$ and $NO_2$ with lower lung function are consistent with a large body of research (2, 7, 8).

Dysanapsis was quantified from chest computed tomography scan images obtained at the same time as baseline lung function testing. The airway-to-lung ratio was calculated by dividing the geometric mean of airway lumen diameters at 19 standard anatomic locations by the cube root of total lung volume, with lower values indicating smaller airways relative to lung size (i.e., more dysanapsis). Although the authors found some suggestion of a difference in the lowest quartile of airway-to-lung ratio compared with the highest quartile for associations of $PM_{2.5}$ with both $FEV_1$ and odds of COPD, we would be hesitant to conclude this is definitive evidence of dysanapsis as an effect modifier. There was no significant effect modification when dysanapsis was considered as a continuous variable, and these quartiles are arbitrary cutoffs and not necessarily clinically relevant. The cross-sectional study design, with ascertainment of dysanapsis at the same time as lung function assessment, also limits inference around causality of dysanaptic lung growth as a modifier that makes the lungs more susceptible to air pollution exposure in adulthood. This limitation may be addressed in future longitudinal studies.

It is plausible that those with less than average airway caliber relative to lung size, whether because of dysanaptic airway growth or airway remodeling, could have elevated risks of airway injury from particle pollution exposure. Studies suggest airway morphology is a key determinant of particle deposition patterns in the lungs (9–11). Deposition may increase as airway size decreases, such that the effective dose of pollution to the airways may be higher at a given degree of ambient pollution among those with dysanapsis. In one of few studies to examine dysanapsis as a risk factor for pollution-related respiratory health effects, children and young adults with relatively small airway size, determined spirometrically as the ratio of maximum mid-expiratory flow to FVC, were found more likely to experience respiratory symptoms, especially wheeze, in association with wildfire smoke exposure (12). Cohort studies with long-term air pollution exposure estimates, repeated lung function measures, and chest imaging data could explore dysanapsis as a pollution-susceptibility trait over time. Future studies might also assess how previously reported associations of long-term air pollution exposure and other respiratory health outcomes, such as asthma incidence, lung cancer, and respiratory mortality, may be modified by spirometrically defined dysanapsis.

Measures of airway anatomy, determined by chest imaging or other methods, potentially could have clinical utility by identifying individuals at risk of future COPD and/or lung function impairment, who may particularly benefit from air quality interventions before lung disease develops. Although CT imaging may not be a useful screening measure in younger adults because of prohibitive costs and radiation risks, other potential screening measures of airway dysanapsis, including maximum mid-expiratory flow-to-FVC ratio or volumetric lung function testing, may be feasible. Long-term air purifier use is an intervention that could be offered to children and adults who are determined to be at higher risk of air pollution health effects. Air purification has been shown to reduce $PM_{2.5}$ concentrations in the indoor air, and recent evidence suggests that it improves respiratory symptoms in asthma and COPD (13, 14).

In this cross-sectional study, long-term pollution exposure was associated with lower lung function at amounts within current air quality guidelines in the United States and Canada but above the latest World Health Organization air quality guidelines. These findings underscore the need for policies to reduce emissions and individual-level strategies to reduce pollution exposure and promote respiratory health. This study suggests that adults with small airways relative to lung size may experience greater respiratory effects, including risk of COPD, in association with long-term exposure to particulate matter pollution. We hope this study will inspire future avenues of investigation of airway anatomy as a marker of pollution susceptibility. ■

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# Genetic Association Study Advances Idiopathic Pulmonary Fibrosis Pathophysiology and Health Equity

Idiopathic pulmonary fibrosis (IPF) is a devastating lung disease that, despite the advent of antifibrotic agents, urgently needs additional research to discover new pathobiology to unearth novel therapeutic pathways. Human genetics support for drug targets increases the chance that related drugs will be approved as novel therapies (1). IPF susceptibility is partially attributable to genetics, with ∼20% of all IPF cases being familial (two or more IPF cases noted in a family) and with common genetic variants explaining ∼30% or more of the risk of sporadic IPF (2). Genome-wide association studies (GWASs) offer an unbiased approach to identify population-level common genetic variants associated with IPF, and the most recent IPF GWAS reported a total of 14 genetic regions associated with IPF, including novel associations at three loci including a variant (rs78238620) near *KIF15* (kinesin family member 15) (3). Although GWASs are a powerful tool for the robust association of genetic variation with disease, the majority of GWAS associations fall in noncoding regions of the genome, making translation of genetic associations to disease-causing genes and disease-relevant biologic function difficult. By contrast, studies of nonsynonymous (i.e., associated with a change in protein structure) rare genetic variants allow for the direct assignment of a genetic association with a putative causal gene. Genetic studies of familial and sporadic IPF using targeted sequencing of candidate regions as well as whole-exome sequencing have identified IPF-associated rare genetic variants in surfactant protein genes and telomere-related genes, including *TERT*, *TERC*, *RTEL1*, *PARN*, and others (4–6).

In this issue of *Journal*, Zhang and colleagues (pp. 56–69) report the largest-to-date IPF genetic association analysis of rare deleterious protein-coding genetic variants (7). The authors used whole-exome and whole-genome sequencing of international multiple-ancestry familial and sporadic IPF cohorts with ∼3,250 total IPF cases included in the overall meta-analysis. In addition to replicating prior rare deleterious variant IPF associations in the telomere-related genes *TERT*, *PARN*, and *RTEL1*, the authors for the first time reported an excess number of rare deleterious *KIF15* variants in IPF cases compared with controls. The enrichment of rare deleterious *KIF15* variants in IPF cases is interesting considering the above-mentioned common variant IPF GWAS locus near *KIF15* (3). The IPF GWAS locus near *KIF15* had yet to be convincingly mapped to a causative gene. Finding rare variants of large effect in a gene near a common variant GWAS locus is not typical and significantly advances our knowledge of the pathobiology of IPF. *KIF15* is in the kinesin family and participates in the bipolar spindle assembly, which is essential to cell division (8). Zhang and colleagues performed functional studies demonstrating that decreased KIF15 protein expression reduced proliferation of lymphoblastoid cells heterozygous for the *KIF15* common variant rs78238620. Furthermore, the authors analyzed publicly available human lung single-cell RNA-sequencing data to demonstrate that *KIF15* gene expression is present in replicating epithelial and resident immune cells in the lungs. Together, these findings provide baseline functional evidence of common and rare genetic variants in and around *KIF15* perturbing a telomerase-independent pathway germane to the pathobiology of IPF.

The manuscript by Zhang and colleagues represents a significant advance in the study of genetic susceptibility to IPF; however, it also presents an opportunity to highlight the



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