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Occupational Exposures and Chronic Obstructive Pulmonary Disease

Causality Established, Time to Focus on Effect and Phenotypes

Chronic obstructive pulmonary disease (COPD) is complex and is the result, among susceptible hosts, of the interaction of repeated environmental injurious exposures and abnormal host defense or reparative mechanisms (1, 2). In addition to an intricate pathogenesis, a variable progression and disease expression (3) are responsible for difficulties in ascertaining causality at the individual level and hence in accurately determining to what extent the societal burden of disease is a result of one specific exposure, and designing appropriate preventive or mitigating interventions, to ameliorate the impact of the disease. The 2010 American Thoracic Statement on novel risk factors and the global burden of COPD described how, rightfully, cigarette smoking remains the main factor responsible for the development of COPD, but erroneously is still considered as the sole explanatory factor (4). The evidence summarized in the document, and in other communications in the years since its publication (5, 6), has resulted in general acceptance of a causal relationship between new risk factors and COPD, including occupational exposures in particular.

In this issue of the *Journal*, Paulin and colleagues (pp. 557–565), using data from well-characterized participants in the Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS), provide cross-sectional evidence of the association between job exposures and the risk of developing COPD, both in current and former smokers, with the resulting combined odds (odds ratio, 1.44; 95% confidence interval, 1.04–1.97) being of similar magnitude to other reports (7). It is appropriate to ask why, if, based on larger longitudinal studies, the scientific community has already accepted a causal relationship between job exposures and COPD, Paulin and colleagues' contribution should be considered relevant and influential enough to be reported in the same journal where it was stated, less than 3 years ago, that causality requirements have been fulfilled (8). There are many reasons researchers and practitioners should be interested in this area, and in the specific contributions of this report. Perhaps the clarity of the statistical analysis and the consistency of the findings with previous reports are not necessarily the main contribution, because it is not possible to ascertain causality in cross-sectional studies. In fact, many population-based longitudinal studies, with adequate follow-up periods, were needed for the pulmonary community to accept the link between work and COPD and to be able to estimate a population-attributable risk of around 15–20% (4, 9). Nonetheless, Paulin and colleagues have provided interesting insight and opened the door to new questions in the area. For example, they did not find significant differences in the association between COPD and job exposure history between men and women, which is a persistent question in occupational epidemiology, where a large proportion of the evidence is based on studies heavily populated by male participants (6). The efforts to include minorities and women in COPD research offer an opportunity for more detailed analyses based on sex and racial and ethnic differences, and the authors have taken advantage of this. They also not only used sex as a confounder but also tested interactions and presented stratified models by sex, as it has been recommended in occupational epidemiology, where there are differential rates of job exposure (10). The investigation also provides information on the association between relevant patient-centered outcomes in COPD (disease-specific and generic quality of life, dyspnea, healthcare use) and history of occupational exposure. Thus,

independent of smoking history and lung function, participants with COPD and occupational exposure had worse scores on the Saint George's Respiratory Questionnaire (4.5 points difference) and COPD Assessment Test (1.8 points difference), shorter walking distance in the 6-minute walking test (26 m difference), and higher odds (odds ratio, 1.53) of exacerbations requiring healthcare use. Again, with the exception of exacerbations, the contribution of a history of occupational exposures is as strong in men as in women. Controlling for other factors that usually run in parallel with a history of occupational exposures and COPD risk (i.e., smoking status, comorbidities, and income) did not change the strength of the findings. In summary, Paulin and colleagues confirm that a history of occupational exposure is associated not only with a higher odds of COPD but also with worse clinical markers of disease effect.

To arrive at their conclusions, Paulin and colleagues used data from SPIROMICS, one of the contemporary COPD cohorts assembled as a result of a collaborative multicenter effort, with support from the National Institutes of Health. The intended goal of SPIROMICS, identifying new COPD subgroups and intermediate markers of disease progression (11), requires collecting very detailed clinical, historic, and imaging data from a large number of participants, allowing a more precise characterization of the study participants, to test innovative hypothesis about COPD outcomes and phenotypes. Data from the Study of the Genetic Epidemiology of COPD, another National Institutes of Health–funded effort (12) with similar inclusion criteria to SPIROMICS, have recently provided evidence of a higher burden of symptoms among patients with COPD with occupational exposures to dust and fumes and more severe emphysema, both in men and women, and on the associations with chronic bronchitis, even before developing COPD (13, 14). Asking occupational questions using these new cohorts, as Paulin and colleagues have done, represents important progress in occupational epidemiology. Again, these studies, although large, were not designed to be representative of the population, making difficult the ascertainment of causality. However, this limitation should not be a reason to doubt the validity and generalizability of the findings: If we have already accepted there is enough proof of cause and effect between job exposures and COPD, there is momentum to switch the focus toward outcomes, phenotypes, and mechanisms, using a road paved by other clinically oriented COPD research (15). The extraordinary array of data provided by contemporary cohorts of COPD opens a window to new research questions, as demonstrated by Paulin and colleagues. Gray areas in need of further exploration, which could be developed using these data, include the role of early small airway involvement, the differences in disease progression according to exposure history, clinical and imaging phenotypes of occupational COPD, sex differences, and genetic interactions as determinants of outcomes and disease (16–19).

Finally, the clinical implications of findings such as Paulin's and other recent investigations of the effect of occupational exposures on COPD go beyond the (obvious) role of exposure reduction. They remind us of the need to educate our workforce on the risks of tobacco smoke and that tobacco cessation is an additional preventive measure in this group. They also underscore the critical importance of adding questions about the occupational history, hopefully as a means of identifying patients with COPD at high risk for poor outcomes sooner. Unfortunately, even with the growing body of evidence, why do so many clinicians still think (erroneously) that COPD is solely tobacco-related? Perhaps the chronic problem of limited exposure during medical school, residency, and fellowship training in pulmonary medicine to the importance of occupational illnesses makes clinicians unlikely to take the time to elicit a proper occupational history (20) or to consider work a causal factor. Undoubtedly, there is a need to continuously reinforce education on this "other COPD," as the problem will likely only get worse: the emerging economies where tobacco use is still widespread are the same regions where industrialization is also growing and where interventions, both occupational and tobacco-related, are urgently needed (21). ■

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Scientific Evidence Supports Stronger Limits on Ozone

In 2007, 2010, and now again in 2015, the American Thoracic Society has recommended that the U.S. Environmental Protection Agency (EPA) adopt an 8-hour ozone national ambient air quality standard of 60 ppb to adequately protect public health (1, 2). Although the recommended standard endorsed by the American Thoracic Society has not changed during this time, the scientific evidence supporting this recommendation has significantly strengthened. The scientific evidence available 7 years ago justifying this recommendation has been supplemented by an even greater understanding of the health effects of ozone exposures, including infant respiratory problems, worse childhood asthma control, reduced lung function, and increased mortality in adults.

On November 25, 2014, the EPA proposed a standard in the range of 65–70 ppb, which is lower than the current standard of 75 ppb (the standard is defined as the annual fourth highest maximum daily 8-hour ozone average averaged over 3 years). Although we applaud the EPA for proposing a stricter standard, we believe the scientific evidence clearly calls for a standard of 60 ppb to protect human health. We are currently in the public comment period for the proposed ozone rule and urge the EPA to issue a more protective standard of 60 ppb. This is the second time the Obama Administration has reviewed the current ozone standard of 75 ppb. The previous administration established the current standard outside the range recommended by the Clean Air Science Advisory Committee of 60–70 ppb (3). In 2010, the Clean Air Science Advisory Committee reaffirmed its initial recommendation as part of an early reassessment of the ozone standard, an effort that was ultimately abandoned in 2011 (4). Because a new science assessment was not conducted as part of that review, the current review of the ozone standard is the first to consider new scientific evidence since 2006.

Since 2006, much more evidence has accumulated that ozone exposures in the range of 60–75 ppb have adverse physiologic effects across the entire age spectrum, from infants to older adults. Although there is also some evidence of health effects of ozone exposure below 60 ppb, the strongest evidence supports the conclusion that serious adverse health effects occur across all ages at levels above 60 ppb.

Highlights of this new body of evidence include a study of emergency department visits among children aged 0 to 4 years in Atlanta, Georgia, which found that each 30-ppb increase in the 3-day average of ozone was associated with an 8% higher risk of pneumonia and a 4% higher risk for upper respiratory infection (5). Several studies have demonstrated dose–response relationships between ozone exposure and childhood asthma admissions at exposure levels in the 60–80 ppb range (6–9). Similar associations have been found for adult admissions for asthma (9–11) and chronic obstructive pulmonary disease (12, 13). A population-based cohort study of generally healthy adults found that FEV_1 was 56 ml lower after days