Long-Term Exposure to Ozone and Small Airways: A Large Impact?

Ozone is perhaps the best studied air pollutant in terms of acute respiratory effects, and review of recent evidence confirms that short-term exposure is associated with acute decrements in lung function (1). In fact, the National Ambient Air Quality Standard for ozone promulgated by the U.S. Environmental Protection Agency is based primarily on evidence from multiple controlled human-exposure studies conducted over the past several decades showing acute decrements in lung function (2). Multihour ozone concentrations of 80 ppb or higher consistently produce significant decreases in FEV_1 and FVC in healthy adults that typically resolve within 24 hours (1, 2). Multiple epidemiological studies have also demonstrated acute decrements in spirometric lung function with real-world exposures during exercise (1–4). Despite the robust human experimental and epidemiological evidence of the acute effects of short-term ozone exposure on lung function, the evidence for chronic effects of long-term exposure to higher concentrations of ozone is relatively sparse and less clear. Such evidence by necessity must come from epidemiological studies.

Perhaps the best study of chronic exposure to air pollution on growth of lung function, the Children's Health Study conducted in southern California, revealed detrimental effects of annual average exposure to fine particulate matter (particulate matter ⩽2.5 μm in aerodynamic diameter) and nitrogen dioxide but surprisingly not to ozone (5). In contrast, a similar longitudinal study of children in Mexico City did demonstrate a significant detrimental effect of chronic exposure to ozone on growth of lung function (6). Other more recent studies have shown adverse effects of long-term exposure to ozone on lung function in children (7, 8).

Several studies in young adults have shown associations between lifetime cumulative exposure to ozone and decreased lung function parameters consistent with small airway obstruction. Two such studies involved college students in the United States, one involving Yale freshmen and 10-year average summer-season daily 1-hour maximum ozone concentrations in the region of their home residence (9) and the other involving University of California, Berkeley, freshmen from southern California (high ozone) and northern California (low ozone) (10). Both of these studies revealed an association with living in higher ozone regions before enrollment at students' respective schools and reduced lung function, including forced expiratory flow at 25–75% of FVC ($FEF_{25–75}$) and FEF at 75% of FVC (FEF_{75}).

Until recently, very few data were available on the potential effects of long-term ozone exposure on lung function in older adults. In this issue of the *Journal*, Niu and colleagues (pp. 450–458) report the results of one of the first studies to specifically address this data gap (11). This study from China has several strengths, including a sample size of more than 50,000 adults older than 20 years, reasonable ozone exposure assessment at the residential level, adjustment for coexposure to particulate matter ⩽2.5 μm in aerodynamic diameter ($PM_{2.5}$) and other covariates, good-quality spirometry enabling assessment of parameters associated with small airway obstruction, and appropriate sensitivity analyses, including adjustment for short-term exposure to ozone. The primary finding of interest is the association of the seasonal average residential ozone concentration of the previous warm season (May to October) and "small airway dysfunction," defined as decreased values of two of the three parameters FEF_{50}, FEF_{75}, and $FEF_{25–75}$. This finding is consistent with the results of the two U.S. college freshmen studies described above.

Niu and colleagues' study is not without limitations. First and foremost, like the U.S. college freshmen studies, it used a cross-sectional design that limits causal inference. The authors of the present study indicate that they will be following the study cohort in the future, and the results of a longitudinal analysis of ozone exposure on change in lung function will be of considerable interest. In addition, like most studies of air pollution health effects that rely on outdoor air concentrations, either measured or modeled, there is likely exposure misclassification given variable time study participants spend outdoors. That said, the exposure measurement error in Niu and colleagues' study is likely nondifferential and thus may bias the results toward the null.

An interesting secondary finding of Niu and colleagues' study is an enhanced effect of long-term ozone exposure on small airway obstruction among participants with chronic obstructive pulmonary disease. This finding is somewhat consistent with the results of a reasonably large cohort study conducted between 2000 and 2018 in six U.S. metropolitan regions showing that long-term exposure to ambient ozone was significantly associated with both increasing emphysema assessed quantitatively using computed tomography imaging and decreased FEV_1 (12).

In terms of biological plausibility, long-term exposure of infant rhesus monkeys to ozone has been shown to cause structural changes in small airway and lung development (13). Compared with control infants, ozone-exposed animals had fewer nonalveolarized airway generations, hyperplastic bronchiolar epithelium, and altered smooth muscle bundle orientation in terminal and respiratory bronchioles. The results of this rhesus monkey study support the findings of the U.S. college freshmen studies showing an association between long-term ozone exposure and spirometric parameters consistent with small airway obstruction in young adults. The results of Niu and colleagues' study suggest that these small airway effects persist later in adulthood. The clinical impact of these effects is not entirely clear, but the effect modification observed in individuals with chronic obstructive pulmonary disease may be an indicator of greater risk among those with preexisting respiratory conditions, consistent with recent evidence that small airway obstruction is a predictor of accelerated decline in FEV_1 (14). ■

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Inequity and the Interstitium: Pushing Back on Disparities in Fibrosing Lung Disease in the United States and Canada

If two patients, one poor and one wealthy, have the same fibrosing interstitial lung disease (fILD), could differential access to quality health care determine which one lives and which one dies? A study published in this issue of the *Journal* suggests that it may—but also that such inequity is not inevitable.

In a provocative analysis in this issue of the *Journal*, Goobie and colleagues (pp. 459–467) provide the first transnational comparison of outcomes among individuals with this serious progressive condition, which requires multidisciplinary evaluation, expensive therapies, and vigilant monitoring (1–3). They assessed the effects of patients' socioeconomic status (which they estimated based on a neighborhood-level metric of socioeconomic deprivation) on their outcomes, including mortality, lung transplantation, and lung function. Among U.S. patients with fILD, they identified a striking mortality gap: death rates were 51% higher for those living in the most deprived quartile of neighborhoods relative to those in the least deprived quartile (95% confidence interval, 1.17–1.95). No such disparity was present among Canadians with fILD. While lung transplant rates for all clinical conditions combined showed no consistent socioeconomic gradient in either nation, U.S. patients with idiopathic pulmonary fibrosis (IPF) residing in the most deprived quartile of neighborhoods were 64% less likely to have a lung transplant relative to those in the least deprived neighborhoods—a disparity that was not apparent among Canadians with IPF.

The study is not without limitations. Deprivation was assessed at the neighborhood (not the individual) level, and the type of deprivation score differed in the two nations. Apart from lung transplantation, no metrics of care utilization or quality were assessed. The U.S. cohort was drawn from a single tertiary referral center, with little racial/ethnic diversity, whereas the Canadian cohort was drawn

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