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Air Pollution as a Risk for Death from Infectious Respiratory Disease

In this issue of the *Journal*, Liu and colleagues (pp. 1429–1439) have contributed to our understanding of how ubiquitous air pollutants associate with death from lower respiratory tract infections (1). Their findings could have important implications for protecting society from future pandemics and for reducing mortality from infections in susceptible groups.

The study is part of the "Effects of Low-Level Air Pollution: A Study in Europe" (ELAPSE) project, sponsored by the Health Effects Institute, Boston, Massachusetts, from its program on effects of low-level exposure to air pollution. Led by the venerable Professor Bert Brunekreef, Utrecht University, the Netherlands, investigators of ELAPSE studied numerous health outcomes, with a focus on low-level exposures (2). Interest in low-level exposure arises for several reasons. First, many high-income countries have succeeded in regulating air pollutants to substantially lower ambient levels over the past 40–50 years, which often increases marginal cost of further reductions. This raises the bar for demonstrating that benefits outweigh the costs of new regulations. Second, several mortality studies have indicated a supralinear concentration-response curve, whereby effects of air pollution are larger at lower levels than at higher ones (3). Third, recent revisions to the World Health Organization Air Quality Guidelines dramatically reduced limit values for most common air pollutants, with the implication that health gains would accrue at even lower levels (4). Although the balance of evidence supports this conclusion, many questions remain about susceptible groups, outcomes most affected, specific pollutant levels, and the shape of concentration-response curves (i.e., linear or supralinear).

Liu and colleagues (1) pooled eight cohorts from several regions of Europe, notably with three cohorts from Nordic countries with lower exposures than in other parts of Europe. They sought specifically to investigate the association between deaths from respiratory infections and four common air pollutants: nitrogen dioxide (NO_2), black carbon (BC), fine particulate matter with aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$), and ozone (O_3). The study sample consisted of 325,367 participants with 682 deaths from pneumonia, 712 deaths from pneumonia and influenza combined, and 695 from acute lower respiratory infections (ALRI) over a 19.5-year follow-up. Researchers used a hybrid land use regression model that fused *in situ* pollutant observations with information on traffic, land use, and broader spatial patterns based on satellite observations to estimate ambient pollution concentrations.

The study produced several confirmatory and novel findings. The authors confirmed an association between common air pollutants and death from pneumonia and ALRI. They found that NO_2 and BC had positive associations with borderline significance. Results for pneumonia and ALRI were similar in size. The relatively small number of deaths despite the large sample size may have reduced statistical power, leading to this result. Moreover, exposure models for pollutants had modest predictive power (i.e., $R^2 = 59\%$ for NO_2 and 54% for BC). Hence, exposure measurement error could have biased effects toward the null. Although confirmatory on NO_2, this is the first study to report on BC, which is also a short-lived, climate-forcing pollutant (5) that, if limited, would have the dual benefit of reducing present health effects and slowing future climate change.

The investigators report novel findings on effect modification by obesity status, smoking, and employment status. Pathologies underlying obesity likely relate to chronic oxidative stress and inflammation. Obese people, therefore, have increased systemic oxidative stress and weakened oxidant defense (6). One key pathway of air pollution health effects is through oxidative stress, particularly in the vasculature. Similar effect modification exists with cardiovascular death and disease (6), but this is the first report of obesity modifying pollution effects on deaths from respiratory infections.

The causative role of smoking as a risk for heightened infectious respiratory disease is well established, as is the link between smoking and deaths from respiratory disease (7). Cigarette smoke and ambient air pollution share many similar constituents. Therefore, it is not surprising that smoking amplifies the association between air pollution and death from respiratory infections.

The employment finding raises interesting questions. The authors conjecture that employed individuals might have a greater chance of being exposed to infections in transit and at the workplace than those who were unemployed, which is possible. They lacked the data in this study to examine different occupational classes, but future research should investigate whether this modification arises from specific occupations. Nascent research on coronavirus disease

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(COVID-19) reports higher mortality risks in the farming, construction, material moving, production, and transportation sectors (8), all of which would likely have higher exposures to ambient or workplace air pollution. Understanding the air pollution–occupational nexus will be challenging (9) but could be critical for protecting workers from deadly infections.

They found that $PM_{2.5}$ and O_3 were not associated with mortality and had insignificantly protective effects, which conflicts with other major studies. $PM_{2.5}$ exhibited an inverted U-shaped concentration-response curve, with indications of positive linear effects for levels below 15 $\mu g/m^3$ and similarly negative effects for levels above 15 $\mu g/m^3$. A large portion of $PM_{2.5}$ mass results from secondary formation (10), leading to smoother variations over space than pollutants such as NO_2 and BC (11), which have fine-scale variation around sources such as roadways. Geographically smaller, higher exposure domains of the cohort may have lacked sufficient variability in $PM_{2.5}$ exposures to derive stable and reliable effect estimates, leading to this biologically implausible result.

As a secondary pollutant, O_3 also exhibits broader regional patterns, and because of the complex photochemistry involved (12), it might not have been well predicted by the European-wide exposure models trained on ground-level observations. When the authors tested the association with a 3D Eulerian model capable of incorporating atmospheric chemistry, they found positive associations between O_3 and death from respiratory infections; hazard ratio = 1.29 (95% confidence interval, 0.98–1.70). Thus, the perplexing negative association observed in their primary analysis might have resulted from the inability of the hybrid exposure model to accurately predict in regions with complex topography and atmospheric chemistry.

Looking to the future, the COVID-19 pandemic, a disease that can lead to deadly pneumonia, has emphasized the importance of understanding risk factors for respiratory infections. Globally, other respiratory infections also remain a major mortality risk (7). Both facts underscore the salience of high-quality studies such as Liu and colleagues (1) that investigate links between deaths from respiratory infections and air pollution at low levels. ■

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