Long-Term Exposure to Ozone and Cardiopulmonary Mortality: Epidemiology Strikes Again

For many years ozone was the most studied air pollutant, primarily because it caused acute, mostly respiratory, symptoms during "smog" episodes in Southern California that generated considerable public concern. In 1966, California enacted regulations requiring smog controls on cars to limit emissions that promoted the formation of ozone, before the Clean Air Act of 1970 led to the establishment of the U.S. Environmental Protection Agency (EPA). The Clean Air Act mandated the EPA to set National Ambient Air Quality Standards (NAAQS) to control the levels of pollutants that are considered harmful to public health based on a review of the scientific literature. Ozone was one of the initial so-called "criteria" pollutants for which NAAQS were promulgated, but these standards were based solely on adverse health effects related to short-term exposures. Over time, as accumulating evidence indicated that acute respiratory effects (airway inflammation and lung function decrements) occurred in people at lower and lower exposure concentrations, the NAAQS for ozone has been periodically modified, but the standard has always been a short-term standard and is currently 70 ppb over an 8-hour averaging time.

The evidence for adverse health effects as a consequence of long-term exposure to ozone is much less robust than the evidence for effects of short-term exposures. The criteria pollutant for which there is strong evidence that long-term exposure is associated with a risk of premature mortality is particulate matter $\leqslant 10$ μm in aerodynamic diameter ($PM_{2.5}$) (1). That said, there is an increasing body of studies that report an increased risk of cardiopulmonary mortality in association with long-term exposure to ozone. Perhaps the first important study to report a mortality effect with long-term exposure was conducted by Jerrett and colleagues using data from the large ($n = 448{,}850$) American Cancer Society Cancer Prevention Study II (CPS-II) (2). The authors found a significant increase in the risk of death from respiratory causes associated with increased annual ozone concentrations. They were not able, however, to detect an effect of ozone on the risk of death from cardiovascular causes when they adjusted their analysis for concentrations of $PM_{2.5}$. Subsequently, the analysis of this cohort was updated with a longer follow-up period and improved exposure estimates (3). The updated analysis confirmed the association of long-term ozone exposure with an increased risk of death owing to respiratory causes, but it also found an association with cardiovascular mortality that remained significant in a two-pollutant model that included $PM_{2.5}$.

In this issue of the *Journal*, Lim and colleagues (pp. 1022–1031) report the results of another large study of long-term ozone and cause-specific mortality (4). The authors prospectively studied 548,780 participants in the NIH-AARP Diet and Health Study over 17 years of follow-up and found that the long-term annual average concentration of ozone was significantly associated with deaths due to cardiovascular disease (per 10 ppb; hazard ratio [HR], 1.03; 95% confidence interval [CI], 1.01–1.06), ischemic heart disease (HR, 1.06; 95% CI, 1.02–1.09), respiratory disease (HR, 1.04; 95% CI, 1.00–1.09), and chronic obstructive pulmonary disease (HR, 1.09; 95% CI, 1.03–1.15) in single-pollutant models. In models adjusting for coexposure to $PM_{2.5}$ and NO_2, these associations remained significant. The authors also found a significantly elevated respiratory disease mortality risk associated with long-term ozone exposure for NIH-AARP participants living in locations with warmer climates.

The interaction with higher temperature is not really a surprise, as ozone concentrations increase as temperatures rise (5). Ozone is generated from motor vehicle emissions and other sources by photochemistry, so urban areas with warm, sunny afternoon weather after the morning rush hour (e.g., Denver, Houston, Las Vegas, Los Angeles, Philadelphia, Phoenix, Salt Lake City, and Washington-Baltimore) typically have the highest ozone concentrations (6). High temperature has an independent effect on mortality (7), but when these exposures occur together, the risk greatly increases. At least 35,000 deaths were attributed to a severe heat wave in Europe in August 2003 that was complicated by high ozone levels (8). With increasing global warming, coexposures to high heat and ozone will be occurring with greater frequency and longer duration (9).

An increased risk of mortality due to cardiovascular causes has now been reported from two large and well-conducted prospective cohort studies that adjusted for multiple potentially confounding covariates (3, 4). Although residual confounding always remains a possibility in observational epidemiological studies, the quantitative levels of risk were remarkably similar in the two studies, with an HR of 1.03 in the NIH-AARP cohort, as noted above, and an HR of 1.03 (95% CI, 1.01–1.05) in the CPS-II cohort. It is difficult to dismiss these reported associations when considering regulatory policies to protect public health. Because a causal relationship between long-term $PM_{2.5}$ exposure and mortality has been recognized by the EPA, the NAAQS for $PM_{2.5}$ includes an annual standard (10). Lim and colleagues suggest that based on the findings of the NIH-AARP and CPS-II cohort studies, policies to reduce long-term exposures to ozone, such as the development of an annual ozone NAAQS in addition to the current 8-hour standard, should be considered.

The Clean Air Act specifically states that the EPA must address "air pollution which may reasonably be anticipated to endanger public health or welfare" when setting a NAAQS (11). The act also requires a review of the body of scientific literature by an independent panel when a NAAQS for a criteria pollutant is being considered. This panel, named the Clean Air Scientific Advisory Committee, is currently chaired by a statistician who does not support the use of observational epidemiology for environmental regulatory purposes, arguing that such studies can never prove causation because they do not adequately adjust for potential confounders such as weather and demographic and socioeconomic variables (12). Both Lim and colleagues' study published in this issue and Turner and colleagues' study published in 2016 (3) attempted to adjust for potential confounding covariates.

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More than a third of the nation's population lives in areas that exceed the current ozone standard (6). As healthcare providers and scientists, the members of the American Thoracic Society should urge the EPA to carefully consider the increasingly strong epidemiologic evidence that long-term exposure increases the risk of cardiopulmonary mortality when the agency next evaluates the current NAAQS for ozone. ■

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Remember Me? The Bone Marrow in Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a progressive, fibrosing disorder that is primarily confined to the lungs, in contrast to several other nonidiopathic forms such as those associated with connective tissue diseases. This does not exclude a participation of distant organs, in particular the bone marrow, in the development and/or progression of IPF. Despite early excitement of the potential for bone marrow–derived cells to give rise to structural cells of the lung (1–3), this concept of engraftment and differentiation has evolved into an understanding of the more plausible paracrine functions of bone marrow–derived cells in the host repair response to lung injury (4–6).

In this issue of the *Journal*, Nakashima and colleagues (pp. 1032–1044) (7) report exploring the hypothesis that low-level injury to the lung insufficient to cause fibrosis (the "first hit") leads to a priming of the bone marrow that results in a more robust fibrotic response to a second, more severe fibrogenic injury. With a series of elegant bone marrow chimeric studies in mice, the authors show that recipient mice subjected to bleomycin-induced lung injury develop worse fibrosis with donors previously subjected to a low-dose, nonfibrogenic lung injury. Further, their studies support a requirement for the immunomodulatory glycoprotein, B7-homolog 3 (B7H3, CD276) and the receptor for IL-33, ST2 (mouse homolog of the IL-1 receptor-like 1 gene), in mediating the priming effect on bleomycin-induced lung fibrosis. With corroborative *ex vivo* studies, the authors surmise that B7H3 exacerbates experimental lung fibrosis by activating (recruiting) a monocytic progenitor population in (from) the bone marrow and skewing of the immune response to a T-helper cell type 2 phenotype. The potential clinical relevance of these studies is supported by the observation that the soluble form of B7H3, sB7H3, is elevated in plasma of human subjects with IPF and in BAL fluid during acute exacerbations.

This innovative study provides conclusive evidence that changes in the bone marrow resulting from remote subclinical injury to a distant organ (the lung, in this case) may have a priming effect on the subsequent host response to injury in a mammalian model system. This concept of immunological memory has classically centered around antigen-specific memory in adaptive immune cells such T and

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