

Ⓜ Air Pollution Contributes to Asthma Deaths

The idea that air pollution can kill is not new. After all, 12,000 people died in the Great London Smog of 1952 (1), and it is well documented that air pollution can increase mortality associated with several diseases (2, 3). Yet, there have been almost no studies focused specifically on asthma mortality and short-term exposure to air pollution.

Initially, this may sound surprising, as asthma is one of the most common respiratory diseases and numerous studies have demonstrated associations between short-term air pollution exposures and asthma symptoms and exacerbations (4, 5). However, because asthma deaths are relatively rare, it has been difficult to specifically study the associations between asthma mortality and air pollution. In this issue of the *Journal*, Liu and colleagues (pp. 24–32) provide a detailed review of the relatively few studies on this topic (6) (see Table E1 in the online supplement of their work). To date, only one other study has examined the effects of short-term air pollution on asthma mortality (7); however, the sample size in that study was small, and there was at most one asthma death per day during the study period.

Liu and colleagues took advantage of the large population of China's Hubei province (58.9 million people) and the high temporal and spatial variability in air pollution to conduct this novel study to assess the role of short-term air pollution in asthma mortality. Over a 5.5-year period (2013–2018), the team identified 7,358 asthma death cases from over 1.7 million deaths of Hubei residents. After excluding individuals with incomplete address information and those who did not reside within 50 km of an air pollution monitor, the authors included 4,454 cases in the main data analyses, resulting in an average of at least two asthma death cases per day. Unfortunately, the authors do not report the distribution of the daily asthma death rate over their study period.

Liu and colleagues document an 11% increase in asthma deaths per interquartile range increase in nitrogen dioxide (NO₂) concentration averaged over the 3 days before death occurred. Similarly, the authors demonstrate that after a 3-day lag exposure, an interquartile range increase in the concentration of PM_{2.5} (particulate matter less than or equal to 2.5 μm in aerodynamic diameter) and ozone (O₃) was associated with a 7% and 9% increase in asthma deaths, respectively. These pollutants have been linked with inducing and enhancing airway inflammation and hyperresponsiveness and oxidative

stress (8, 9). There were no significant associations with sulfur dioxide, carbon monoxide, or PM₁₀.

In addition to the large population size, this study's strengths include the wide coverage of air pollution monitors in the region. The exposure assessment included daily measurements for all six pollutants at 57 government-controlled air-quality monitoring stations. The authors estimated exposures for the day of death and the control days by calculating the inverse distance weighted average of the concentrations from all of the monitoring stations within 50 km of the home address. This extensive network of air-quality monitoring stations captured air pollutant concentrations that ranged over two orders of magnitude for most pollutants over the 5-year period and a wide range of weather conditions. The authors used several cross-validation techniques and explored multiple lag days. One of the remarkable findings is that there appears to be no threshold, as the associations are linear. Multiple pollutant models also did not significantly change the associations between PM_{2.5}, O₃, and NO₂ exposures and asthma mortality.

A limitation of this exposure assessment technique is the buffer size. Approximately 40% of the death cases were not included in the analyses because the subjects lived more than 50 km away from an air pollution monitor. Not much information is provided about why so many of the subjects lived outside of the monitoring network. It is possible that these individuals lived in rural areas of the province, and perhaps their deaths would be less likely to be associated with air pollution. It is also possible that their air pollution exposures are representative of the cases included, and they just happened to not be near a monitoring station. The latter is probably more likely, as the study seems to include a wide range of air pollution concentrations, and a sensitivity analysis using only those monitors within 25 km of the subjects' addresses did not change the results substantially.

Another strength of this study is the time-stratified case-crossover study design, in which each subject serves as his or her own control (10). This design is used to investigate transient effects of an intermittent exposure, such as air pollution, on an acute outcome, such as death. Because the cases and the control subjects are the same person, there may be less confounding by other variables. Liu and colleagues assigned three to four control days to each case. These control days were matched to be the same year, month, and day of the week as the day the death. Although this helps control for potential confounding by day of the week, long-term trend, and seasonality, it is odd that the control days included days after the asthma death, as the person being considered had already expired and was clearly not exposed. It would be interesting to see if the authors would obtain the same findings if they chose control days for the 4 weeks preceding the individual's death rather than just by the calendar month during which it occurred.

As Liu and colleagues clearly state in their report, the generalizability of their results is limited primarily to the specific

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study area, and in particular these findings may not be applicable to areas with much lower air pollution exposures. It is important to note that although the median air pollution levels in this study are high compared with levels in the United States and Western Europe, almost half of the world's population is exposed to comparable or higher levels of ambient air pollution (11).

Although asthma mortality has decreased over time, rates have been relatively stable since the 1980s and remain significant despite advances in the management and care of patients with this disease (12). Worldwide, over 250,000 people still die of asthma annually (13). Asthma deaths have been attributed to several risk factors, with majority considered to be preventable and mostly dealing with the management of asthma (14). Liu and colleagues' article is important because it is the first report of an association between asthma mortality and short-term air pollution exposure in a large population. Thus, it is possible that reducing air pollution could have a significant effect on reducing asthma mortality worldwide. ■

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Corporate Memory and Rediscovering the Wheel

Although there is a generally accepted concept that inflammation plays a role in the pathophysiology of chronic obstructive lung diseases, the complexity and compartmentalization of the inflammation present many challenges to clinicians, scientists, and the pharmaceutical industry. Bronchiectasis is a condition in which the damage caused is largely bronchial and the relevant inflammation is readily accessible through studies of expectorated

sputum, which is often colonized by bacteria that drive the local inflammatory response.

With the advent of computed tomography and its widespread use, recognition of permanently dilated airways (the pathological hallmark of bronchiectasis) show not only a wide variation in pathological types and distributions but also a marked prevalence in patients with an underlying diagnosis of smoking-related chronic obstructive pulmonary disease (COPD) (1). So does this represent a parphenomenon or a specific trait for treatment? In some cases the bronchiectasis is limited to minor tubular changes and thus is clinically quiescent, whereas in others it is widespread and varicose in nature, leading to clinically important features that are more consistent with a classical primary diagnosis of bronchiectasis. Indeed, in the past, such a diagnosis was considered more likely in nonsmokers (and therefore believed to exclude

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