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Tuberculosis, Wildfires, and Case-crossover Studies: An Epidemiological Trifecta?

Tuberculosis is a leading cause of illness and death worldwide. Indeed, more than 1.7 billion people are thought to be infected with tuberculosis (1), with an estimated 10 million disease episodes and 1.5 million deaths in 2020 (2). Risk factors for tuberculosis include impaired immunity including HIV disease, birth in a tuberculosis endemic country, increased exposure to infected people through household contacts, living in crowded or poorly ventilated dwellings, or exposure to high-risk settings such as hospitals, prisons, nursing homes, and homeless shelters (3). In the United States, the highest burden of tuberculosis occurs among immigrants from endemic countries. Specifically, in 2021, the case rate for this group was 12.2 per 100,000 people compared with 2.4 per 100,000 people in the general population (3).

Environmental exposures have become increasingly recognized as important risk factors for tuberculosis. Currently, there is strong epidemiological evidence linking both occupational exposures to silica from mining (4) and tobacco smoking (5) with an increased risk of tuberculosis disease. Air pollution is a less well-studied risk factor with mounting evidence. One large cohort study in New Taipei City, Taiwan (6), consisting of 106,678 participants, found that higher ambient nitrogen dioxide (adjusted hazard ratio, 1.33 per 10 ppb; 95% confidence interval, 1.04–1.70) and nitrogen oxide (1.21 per 100 ppb; 95% confidence interval, 1.04–1.41) concentrations estimated using information from 16 monitoring stations were positively associated with the 418 cases of active tuberculosis (67% of which were culture-confirmed) registered over a 6.7-year (median) follow-up period but failed to find the same associations with either fine or coarse particulate matter, or for all pollutants when using land use regression (a statistical method commonly used to estimate spatial variation in air pollution concentrations for population exposure assessment).

A time series analysis in the city of Wulumuqi (population, 2.7 million), Xinjiang Uygur Autonomous Region, China, that analyzed 10,238 cases of pulmonary tuberculosis and monthly averages of multiple air pollutants ($PM_{2.5}$ [particulate matter that is <2.5 μm in size], PM_{10} [particulate matter that is <10 μm in size], SO_2, NO_2, CO, and O_3) adjusting for seasonality and other meteorological variables found positive associations between higher concentrations of all air pollutants and a higher number of tuberculosis cases (7). A recent meta-analysis involving 24 studies and 437,000 tuberculosis cases examined the role of ambient air pollution and tuberculosis disease and found that higher ambient concentrations of both fine and coarse particulate matter and SO_2 were all associated with a higher incidence of pulmonary tuberculosis (8). Most of the studies were either time series ($n = 10$), ecological analyses ($n = 5$), or cohort studies ($n = 5$), and the overall assessment by the authors about the quality of evidence was low. Moreover, the associations reported above do not necessarily mean causation. The link between household air pollution from biomass burning and tuberculosis is even less clear, with some studies showing positive relationships and others showing no relationship (9, 10).

In this issue of the *Journal*, Linde and colleagues (pp. 336–346) provide additional evidence of a link between air pollution from wildfire smoke and tuberculosis in California (11). They used a case-crossover study of 6,238 subjects aged 15 years or older diagnosed with active tuberculosis disease between 2014 and 2019 in eight California counties to determine if wildfire events, determined using $PM_{2.5}$ concentrations from more than 250 monitors of the California Air Resources Board statewide air monitor network and crosschecked against satellite maps of smoke plume boundaries using the National Oceanic and Atmospheric Administration Hazard Mapping System, could be associated with a higher risk of tuberculosis diagnosis. Specifically, they found that wildfire-associated $PM_{2.5}$ events were associated with 23% higher odds of tuberculosis diagnosis over a 6-month observation period.

Despite potential limitations related to the latency between the time window of wildfire smoke exposure and development of active tuberculosis, lack of control for time-varying confounders within the same individual, and inaccuracies in air pollution exposure assignments (which was limited to the participant's home address using inverse distance weighing estimation), the analysis conducted by Linde and colleagues provides further evidence of the potential role of air pollution in the development of tuberculosis. Moreover, it uses an epidemiological design that has become increasingly used to study the relationship between air pollution and other respiratory conditions, including asthma (a PubMed search yielded 58 studies when searching "asthma exacerbations" and "case-crossover") and chronic obstructive pulmonary disease exacerbations (26 studies when searching "chronic obstructive pulmonary disease exacerbations" and "case-crossover"). Indeed, the case-crossover

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design is a relatively recent epidemiological design that was introduced in 1991 to study the effects of a risk factor on a health outcome using only cases, controlling for potential confounding through matching (12). In this type of study design, however, matching is done using the same person at a different time rather than choosing a different person at the same time as is done in a conventional matched case-control study. Case-crossover studies were designed to answer questions like, "Was this outcome triggered by an exposure that happened just before?" (13). As a result, this type of design favors studies choosing outcomes that are abrupt in onset to avoid false positive associations and exposures that are transient in nature (e.g., a wildfire with an average duration of 37 d). Furthermore, case-crossover studies require a careful selection of the exposure time window to reliably answer the question; "would the exposed cases not have occurred at that time had they not been exposed immediately before?"

As tuberculosis has an average latency of 3–9 months to 2 years (14), one would therefore assume that a 6-month exposure window used by Linde and colleagues was reasonable, but longer time exposure windows of up to 2 years may be warranted as sensitivity analyses. Finally, it is important to recognize that the limitations of a case-crossover study lie in the type of question that it was designed to answer about exposures and outcomes. Nonetheless, the case-crossover study is a design that should be readily available in the epidemiological toolbox of modern respiratory scientists. ■

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