Prenatal Air Pollution and Child Lung Function: The Impossible Search for a Vulnerable Trimester

Numerous studies have demonstrated an association between ambient air pollution and reduced lung function in childhood (1). However, there is a lack of consensus regarding the most vulnerable exposure windows. In this issue of the *Journal*, Cai and colleagues (pp. 112–123) sought to answer this question (2). The authors present a prospective cohort study of more than 5,000 children in England, examining associations between exposures to particulate matter <10 μm in diameter (PM_{10}) during each pregnancy trimester, infancy, and childhood with lung function at ages 8 and 15 years. Higher levels of PM_{10}, particularly from road traffic, during pregnancy and childhood were associated with lower lung function at age 8 years. Average PM_{10} from road traffic was highly correlated among trimesters, precluding an assessment of trimester-specific associations. However, total PM_{10} from all sources during the third trimester was associated with lower age 8-years FVC, even after mutual adjustment for other trimester and postnatal exposure averages. At age 15 years, these associations reversed direction and prenatal PM_{10} was associated with higher lung function, though not after multiple test corrections. The authors conclude that prenatal and early-life exposure to traffic-related PM impairs lung function in childhood. Major strengths of this study are its very large size with detailed characterization and longitudinal follow-up of children from prebirth to adolescence, and the evaluation of PM_{10} coming from traffic versus nontraffic sources.

The cohort was born almost 30 years ago (1991–1992), at a time when ambient PM_{10} levels were generally higher than they are today in England and the United States. In the United States, emissions reductions have led to an almost 30% decrease in average PM_{10} levels since 1990 (3). Because the cohort was born in the early 1990s, the authors could not examine fine $PM_{2.5}$ because $PM_{2.5}$ was not monitored in the study area in the 1990s. PM_{10} is often referred to as "respirable" particles because particles in this size range are inhalable. Of these, the larger particles (2.5–10 μm) such as sand, dust, and pollen generally deposit in the nasopharynx. The smaller particles (<2.5 μm) include fuel combustion products like traffic-related soot and sulfate aerosol, and deposit throughout the respiratory tract, including the alveolar spaces (4). $PM_{2.5}$ is a better indicator of combustion-related pollution, whereas PM_{10} is less specific and potentially less toxic.

Although some studies suggest that long-term $PM_{2.5}$ exposure has a greater effect on lung function compared with PM_{10} (5), numerous studies have found that PM_{10} is also associated with worse lung function in children and adults (6, 7). In this study, investigators overcame limitations of their exposure data by applying advanced modeling methods to estimate PM_{10} from major road sources, incorporating data on traffic flows, tailpipe emission rates, and meteorological variables. Their main finding that traffic-related PM is associated with lower childhood lung function is consistent with a large body of evidence demonstrating that pollution from traffic sources is particularly harmful to child respiratory health.

The authors go to great lengths to identify "sensitive time periods" during the prenatal period and early childhood when PM exposure may be particularly harmful. Lung development starts in the first trimester and continues after birth, and so it is conceivable that maternal exposure to toxic pollutants could affect lung development. In animal toxicology, prenatal plus early postnatal exposure to $PM_{2.5}$ from motor vehicle sources has been found to impair lung growth (8), although little (if any) mechanistic research has focused on vulnerable periods during gestation. On the other hand, identifying an especially sensitive trimester has been of great interest in epidemiologic research, with inconclusive results (1, 9, 10). This question may be unanswerable with observational data because a trimester lasts 3 months and is therefore a snapshot of pollution exposure that aligns perfectly with season. Although statistical models adjust for season, if the differences in exposure are determined almost entirely by season, then statistical tools may not fully distinguish between effects of birth season versus trimester-specific PM exposure on lung function. This is an important issue with an outcome like lung function, which is affected by seasonal exposures like viruses and allergens.

The authors found that modeled PM_{10} from traffic sources was highly correlated across trimesters and therefore they could not contrast the effects of traffic-related pollution by trimester. This is not surprising, because traffic has little seasonal variability. On the other hand, fuel combustion for heating and cooling can vary a lot by season. Although the authors found some suggestion of a greater effect of third-trimester PM_{10} on FVC at age 8 years, we would be hesitant to conclude that this is convincing evidence of an especially vulnerable trimester. Newer, more flexible statistical methods have been developed to examine vulnerable windows during pregnancy, such as Bayesian distributed lag interaction models to identify weeks of gestation rather than specific trimesters, and these could be applied toward this question (11, 12). Nonetheless, this study's finding that children with higher prenatal exposure to PM_{10} had lower lung function at age 8 years is likely robust to seasonal confounding because the entire pregnancy spans most of a calendar year.

Paradoxically, the investigators also found a pattern of positive associations between prenatal PM_{10}, especially from traffic, and lung function at age 15 years. Similarly, PM_{10} during the first trimester was associated with greater lung function growth from age 8 to 15 years. The authors hypothesize that this may be due to catch-up growth following improved air quality during this time. Others have found stronger associations of recent (e.g., prior year) pollution exposure with child or adolescent lung function than early-life exposures, suggesting the effects of early-life PM exposures may reverse (1, 13). Several studies, most notably the Children's Health Study in California, have found more rapid lung function growth following improvement in air quality (14).

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Evaluating the effects of air quality improvements on lung function trajectories will address an important policy-relevant question: are the harmful effects of early-life traffic pollution exposure on lung function reversible if air quality is subsequently improved? ■

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Mary B. Rice, M.D., M.P.H.
Stephen A. Mein, M.D.
Department of Medicine
Beth Israel Deaconess Medical Center
Boston, Massachusetts

ORCID IDs: 0000-0003-2538-391X (M.B.R.); 0000-0002-6567-1564 (S.A.M.).

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Home Nitric Oxide Therapy for COVID-19

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a range of cardiopulmonary and vascular complications, ranging from upper respiratory tract symptoms to severe acute respiratory distress syndrome (ARDS), as well as shock, acute kidney injury, and thromboembolic complications (1, 2). Although SARS-CoV-2 initially infects the upper respiratory tract epithelia, some of the most serious complications of the disease appear to arise through vascular inflammation and injury.

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Although further mechanistic and epidemiological studies are needed, case reports, imaging studies, and autopsy series have suggested the possibility that the SARS-CoV-2 virus, once in the lower respiratory tract, may directly infect endothelial cells, leading to a cascade of consequences including vasoplegia, vascular thromboses, pulmonary edema, endothelial sloughing, and abnormal regulation of pulmonary perfusion (2, 3). Regardless of the mechanisms, it is clear that patients often develop severe respiratory failure with hypoxemia that may be refractory to oxygen supplementation and often requires invasive mechanical ventilation. Because of the rapidity with which the virus spread, many healthcare systems were stressed by the sudden increase in coronavirus disease (COVID-19) cases, with the accompanying increased need for hospital beds, ICU beds, ventilators, and even oxygen. A high percentage of mechanically ventilated patients develop multi-organ failure syndrome, characterized by pressor-dependent shock and a high associated mortality. Even those who survive with the assistance of mechanical ventilation may require prolonged hospitalizations (4). These concerted adverse sequalae of SARS-CoV-2 infection create major strains on health care system resources.