Traffic-related Air Pollution, Health, and Allergy: The Role of Nitrogen Dioxide

It is now well established that the adverse effects of air pollution are observed across all stages of the life course, from low birth weight, to increased respiratory and cardiovascular symptoms, to premature cardiopulmonary death (1). As the evidence base has advanced, an increasingly diverse range of systemic and metabolic endpoints as well as extrapulmonary complications have further been linked to air pollution exposure, as reviewed in the recent European Respiratory Society/American Thoracic Society policy statement (2). Throughout this literature, certainly since the mid-1990s, there has been an emphasis on fine particulate matter ($\leqslant$2.5 μm in aerodynamic diameter), which is derived from primary combustion sources. The working principle is thus established, not without some support, that it is the very small particles that we need to be most concerned about. However, somehow, along the way, the potential toxicity of copollutant gases and other volatile components has become neglected.

As individuals, we are clearly not exposed to a single pollutant in the real world; rather, we breathe in a cocktail of gases and compositionally heterogeneous solid and liquid particles in the air. Dissecting out which components drive specific adverse outcomes has been, and remains, one of the fundamental challenges in air pollution research. There has been some success with time series studies that have isolated components or source profiles within the particulate aerosol that are more strongly linked to respiratory and to cardiovascular endpoints than others (3–5), but in long-term studies, the high correlation between different pollutants has made it difficult to accurately quantify the contribution of primary combustion particles from copollutant gases, such as NO_2. When associations have been demonstrated with NO_2, it has become the default assumption that this is simply illustrating the source, reflecting the true underlying association with primary combustion and ultrafine particles. The picture is, however, not so clear-cut, with an increasing number of studies emerging demonstrating NO_2-induced health effects that are robust to adjustment to particulate matter $\leqslant$2.5 μm in aerodynamic diameter (6), and even in some studies to ultrafine particles exposures (7, 8). Epidemiological studies are fundamental to assess patterns in conditions and compositions of significance, yet their ability to fully resolve this issue is limited. Additional valuable information on component specific effects can be further deciphered though experimental exposure studies, in which the composition of the aerosol can be carefully manipulated and defined.

In this issue of the *Journal,* Wooding and colleagues (pp. 565–574), a Vancouver-based group of scientists, have studied the role of traffic-related air pollution on respiratory function and allergen responsiveness by means of controlled chamber exposure experiments in allergen-sensitized individuals (9). The notion that allergen reactions would be enhanced by diesel exhaust particles has previously been addressed in animal models (10, 11), but it was not until the pivotal paper by Diaz-Sanchez and colleagues that this was investigated in humans. By means of nasal instillation of allergen, in association with a diesel exhaust exposure, the authors demonstrated that exhaust particles enhanced both sensitization to neoallergen and the allergen response proper (12, 13).

In the present paper, the authors hypothesized that removing particles from the diesel exhaust aerosol would protect against allergen responses, with the counterfactual assumption being that the gaseous and volatile components would have little contribution to the adjuvant effect. Allergen-sensitized individuals with or without preexisting bronchial hyperresponsiveness were recruited and exposed in a fully randomized manner to allergen on three occasions, with preexposure to diesel exhaust, particle-filtered diesel exhaust, and filtered air. A double placebo exposure to filtered air and the saline diluent used for allergen challenges was also performed, with all exposures separated by a period of at least 4 weeks. All exposures lasted 2 hours, with the allergen challenge performed 1 hour after exposure. Airway responsiveness was evaluated 24 hours after the diesel exposure, using a methacholine challenge test. Spirometry was also examined preexposure, immediately following, and at various points up to 48 hours after exposure. Blood sampling for the assessment of systemic inflammation was also performed at set times pre- and postexposure.

Contrary to their hypothesis, removing particles using a high-efficiency particulate air filter and electrostatic precipitation to mimic catalytic particle traps used on diesel vehicles did not protect against the allergen-induced effects, despite 93% effectiveness in filtering particles. Diesel exhaust and allergen challenge enhanced bronchial hyperresponsiveness in subjects without preexisting bronchial hyperresponsiveness; however, filtering out the particles provided no protection. Instead, the lung function reduction in terms of FEV_1 was significantly higher when exposed to the particle-filtered diesel exhaust. The authors noted that the filtering reduced not only particles but also total volatile organic compounds and gases, with the exception of NO_2, which increased. This strongly implicates NO_2 associated with diesel exhaust as an important adjuvant factor enhancing allergen sensitization. This aligns with the older literature, again from human chamber studies, demonstrating the capacity of NO_2 to induce bronchial hyperresponsiveness and responses to inhaled allergen in patients

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with asthma (14, 15). These findings are pivotal, particularly in the light of sustaining discussions with regard to the role of ambient NO_2 concentrations on population health. It emphasizes the need to have strategies that not only reduce exhaust particulate but also scavenge NO_2, particularly within congested urban areas, where diesel vehicles make up a significant proportion of the fleet. ■

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Validation of Imaging Measures in Chronic Obstructive Pulmonary Disease

Imaging provides an amazing opportunity to glean *in vivo* insights into acute and chronic diseases. The imaging community has described many features that can be used to detect disease and stratify its severity, predict outcomes, and even assess disease progression. These typically begin with the identification of a novel structural aspect of an organ, obtaining a range of measures of that feature and then demonstrating that those measures remain statistically significantly associated with an outcome of interest despite exhaustive multivariable adjustment. These approaches are not wrong, but they are often accompanied, appropriately, by disclaimers in the limitations section of the discussion or even a modification of the name of the feature to communicate an appropriate degree of uncertainty as to what is actually being measured. Few of the imaging-based measures reported in the literature are backed by histopathology or knowledge of what is occurring on the microscopic level.

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