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Invited Perspective: The NO_2 and Mortality Dilemma Solved? Almost There!

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Particulate matter (PM) [both with an aerodynamic diameter of ≤10 μm (PM_{10}) and of ≤2.5 μm ($PM_{2.5}$)] is a well-established cause of adverse health effects. A clear link of short- and long-term PM exposure with mortality and morbidity from cardiovascular and respiratory disease has been shown and is supported by experimental evidence (U.S. EPA 2019). Multiple epidemiological studies have also showed a relationship between nitrogen dioxide (NO_2) and morbidity and mortality, but questions remain about the causal nature of these associations. For the past two decades researchers have tried to elucidate whether the NO_2 effects are due to the gas per se or whether they are simply a surrogate for exposure to emissions from vehicles and, therefore, a marker for spatial variation in the urban air pollution mixture (Seaton and Dennekamp 2003; WHO Regional Office for Europe 2013; COMEAP 2018; Stieb et al. 2021). The uncertainty is due to strong correlations between NO_2 and other combustion-derived air pollutants that vary within and between urban areas and over time, such as $PM_{2.5}$, black carbon, ultrafine particles, and gaseous copollutants (Brunekreef et al. 2021). This debate not only questions the weight of the evidence regarding NO_2-associated health effects but also leads to divergent conclusions regarding safe levels.

In this issue of *Environmental Health Perspectives*, Qian et al. (2021) present a new epidemiological study supporting a direct link between NO_2 and mortality. Their analysis is a large (comprising >13 million Medicare beneficiaries >65 years of age), retrospective, registry-based study in the southeastern United States. The authors were able to obtain estimates of daily NO_2 concentrations at a 1×1 km resolution across the contiguous United States from 2000 to 2016 using machine learning algorithms and multiple predictor variables. The study used a cohort design to evaluate the relationship between estimated annual mean NO_2 concentrations based on ZIP code of residence—and mortality. The authors observed that long-term exposure to NO_2 was associated with all-cause mortality [hazard ratio (HR) = 1.042; 95% confidence interval (CI): 1.040, 1.045] in single-pollutant models and HR = 1.047 (95% CI: 1.044, 1.049) in models adjusting for $PM_{2.5}$ and O_3, per 10-ppb increase in annual NO_2 concentrations. The relationship was linear across the entire exposure range (5th to 95th percentile: 5.25–27.10 pbb, median = 12.09 pbb), and the association was stronger among subjects who were White, female, and residents of urban areas. Distinguishing aspects of the study are *a*) its ability to confirm the independent effect of NO_2 after controlling for $PM_{2.5}$ and O_3, *b*) the evidence of linearity across the exposure distribution, and *c*) the extensive sensitivity analyses confirming the robustness of the results.

At least six systematic reviews have considered NO_2 and mortality since 2013 and estimated a statistically significant meta-analytic effect on all-cause (natural) mortality (Hoek et al. 2013; Faustini et al. 2014; Atkinson et al. 2018; Huangfu and Atkinson 2020; Huang et al. 2021; Stieb et al. 2021). The increased estimated risk was confirmed after removing studies with a potential risk of bias due to confounding [HR = 1.047 (95% CI: 1.023, 1.072) based on 32 studies] (Stieb et al. 2021), a value remarkably similar to the effect estimate detected in the new study (Qian et al. 2021). Positive associations also have been detected for mortality from cardiovascular disease, ischemic heart disease, lung cancer, and respiratory disease in the same studies. This evidence is further supported by a large New Zealand cohort in which NO_2 at very low mean estimated exposure levels (7.5 $\mu g/m^3$, ~4.0 pbb as annual mean) was strongly associated with mortality even after adjusting for $PM_{2.5}$ (Hales et al. 2021). The same conclusions were reached in two just-published reports from the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) project considering both a pooled cohort of 15 conventional research cohorts (Strak et al. 2021) and 7 administrative cohorts encompassing more than 28 million individuals (Brunekreef et al. 2021). In these investigations, a linear exposure–response was detected starting from a very low exposure level as in the Quin et al. (2021) study. It is important to note that all the studies together span at least three decades and took place in multiple cities and continents; consequently, combustion-related air pollution mixtures were quite different between study populations. Therefore, even if other important copollutants of NO_2 were not assessed in these settings, it is unlikely that the observed associations of NO_2 and mortality are solely attributable to one of those copollutants.

There are limitations to the study, primarily that the exposure characterization may have been too coarse to address the actual spatial variation of NO_2, which can have steep gradients close to sources such as roadways. In addition, the control for O_3 and $PM_{2.5}$ may have not been sufficient given that NO_2 may be an indicator of other traffic-related air pollutants (e.g., ultrafine particles, unmeasured gaseous pollutants, black carbon, trace metals). Exposure assessment is a critical issue in environmental epidemiology, and simulation work by Butland et al. (2020) has indicated that misclassification of NO_2 exposure assessment can produce a substantial bias toward the null.

Although there is evidence of direct NO_2 respiratory effects on bronchial reactivity in patients with asthma since the 1980s (Bylin et al. 1985; Strand et al. 1997), and a novel controlled human exposure experiment has clearly indicated that NO_2 from diesel exhaust enhances allergen sensitization (Wooding et al. 2019; Bosson et al. 2019), it should be noted that there is limited experimental evidence (controlled human exposure and animal

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toxicology studies) for an independent biological NO_2 response that might result in the observed mortality impacts (U.S. EPA 2016). The U.S. Environmental Protection Agency (U.S. EPA 2016) report indicated that the following evidence was available in 2016: "some, but not entirely consistent, findings from experimental studies for early, nonspecific effects with the potential to lead to heart disease or diabetes: dyslipidemia in rats with long-term NO_2 exposure, increases in markers of inflammation and oxidative stress in plasma of humans and heart tissue of rats with short-term NO_2 exposure." Research in this area has remained scarce to date, but repeated high NO_2 exposure in Wistar rats has induced impaired cardiac mitochondrial function, reactive oxygen species formation, and coronary endothelial dysfunction (Karoui et al. 2020), indicating a specific contribution of NO_2 to cardiovascular damage.

In conclusion, long-term exposure to NO_2 is associated with mortality even at concentrations well below the European Union limit values ($40\,\mu g/m^3$, ~ 21 ppb), U.S. EPA National Ambient Air Quality Standards (53 pbb, $\sim 103\,\mu g/m^3$), and World Health Organization (WHO) Air Quality Guidelines (AQGs) published in 2006 (WHO Regional Office for Europe 2006) ($40\,\mu g/m^3$). It is clear that the standards are not adequate to protect public health and they need to be urgently revised. The publication in September 2021 of the updated WHO AQGs (WHO 2021), indicating $10\,\mu g/m^3$ (~ 5.1 pbb) as the guideline value for annual NO_2 concentration, emphasizes this and is the first step toward a radical change.

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