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Response to "Comment on 'Invited Perspective: The NO_2 and Mortality Dilemma Solved? Almost There!'"

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We thank Dr. Paolo Crosignani for his comments on our perspective[1] and the opportunity to clarify our arguments. First, we stated that "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 [nitrogen dioxide] 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." This reasoning follows the recommendation to apply a triangulation from different approaches for evidence synthesis.[2] Here we explain how we reached our conclusion.

The systematic review conducted by Huangfu and Atkinson[3] for the update of the World Health Organization (WHO) Air Quality Guidelines[4] was based on 10 studies from Europe (high prevalence of diesel vehicles) and 11 studies from North America (low prevalence of diesel vehicles). They reported identical effect estimates for the two continents, namely 1.03 [95% confidence interval (CI): 1.02, 1.03] and 1.03 (95% CI: 1.01, 1.04) per $10\,\mu g/m^3$ NO_2, respectively. In addition, the latest report[5] from the large Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) project in Europe showed that adjusting for fine particulate matter ($PM_{2.5}$), black carbon, and ozone did not alter the effect estimate of NO_2 on mortality: single pollutant 1.044 (95% CI: 1.019, 1.069); with $PM_{2.5}$, 1.042 (95% CI: 1.020, 1.065); with black carbon, 1.041 (95% CIL 1.009, 1.073); and with ozone, 1.040 (95% CI: 1.012, 1.069). This evidence suggests that NO_2 is not merely an indicator of other pollutants from diesel exhaust.

Second, the evidence from mechanistic studies is indeed limited, but a number of recent studies link short-term and long-term ambient NO_2 concentrations to changes in pathophysiological function both in patients with cardiovascular disease[6,7] and in healthy adults.[8] These studies support the observed mortality associations. Given the overwhelming evidence from epidemiological studies on NO_2, the precautionary principle may call for action rather than another decade of research on the "dilemma."

Third, the combined evidence and the new WHO guidelines[4] clearly recommend a concerted approach toward the reduction of all criteria pollutants, including NO_2. We certainly do not propose regulating only NO_2 and nothing else.[9] With new evidence accumulating rapidly, we believe the WHO guidelines have immense potential to improve public health globally by regulating NO_2 and other pollutants jointly.

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