HEALTH EFFECTS INSTITUTE

STATEMENT

Synopsis of Research Report 211

Assessing Adverse Health Effects of Long-Term Exposure to Low Levels of Ambient Air Pollution

BACKGROUND

The growing scientific evidence reporting effects of air pollution on health at concentrations below current air quality standards and the large burden of disease attributed to air pollution suggest that more stringent air quality standards and guidelines will likely be considered in the future. To improve our understanding of exposure–response functions for mortality and morbidity at low concentrations of $PM_{2.5}$, NO_2, O_3, and other ambient air pollutants, HEI issued RFA 14-3, *Assessing Health Effects of Long-Term Exposure to Low Levels of Ambient Air Pollution*. Three studies based in the United States, Canada, and Europe were funded that used state-of-the-art exposure methods and large cohorts in high-income countries where ambient concentrations are generally low (i.e., lower than current air quality guidelines and standards for Europe and the United States). HEI convened an independent Low-Exposure Epidemiology Studies Review Panel to evaluate the studies' strengths and weaknesses. This Statement highlights results from the study in the United States.

What This Study Adds

- This study evaluated the risk of mortality associated with exposure to low ambient air pollution concentrations in a cohort of 68.5 million older Americans.
- The investigators developed annual exposure models for fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) at a spatial resolution of 1 km × 1 km for the years 2000 to 2016 covering the contiguous United States.
- They presented results from three newly developed causal inference approaches and from two traditional regression approaches.
- The investigators reported increased risks of all-cause mortality of 6% to 8% per 10-µg/m^3 increase in $PM_{2.5}$ across the five approaches, with larger effect estimates in a low exposure subcohort.
- The consistency of the associations across methods provides stronger support than past studies for what is likely a causal effect between long-term exposure to $PM_{2.5}$ and mortality.

APPROACH

Dominici and colleagues aimed to address some of the knowledge gaps related to health effects of long-term exposures to low concentrations of air pollution using a cohort of 68.5 million older Americans enrolled in the U.S. Medicare program. Their approach included modeling spatial and temporal patterns of ambient air pollution, developing cutting-edge causal inference statistical models, describing risks to mortality associated with exposures in a very large dataset, and making the methods and data available to the wider scientific community. The study had four broad aims:

1. **Exposure Prediction and Data Linkage** Estimate long-term exposures to concentrations of ambient $PM_{2.5}$, O_3, and NO_2 at 1 km × 1 km spatial resolution for the contiguous United States in 2000–2016.
2. **Causal Inference Methods for Exposure–Response Functions** Develop a new causal inference framework to estimate a nonlinear exposure–response function, adjust for measured and unmeasured confounders, and detect effect modification in the presence of multiple exposures.
3. **Evidence of Adverse Health Effects** Apply methods developed in Aim 2, along with traditional regression approaches, to estimate all-cause mortality by year and zip code associated with long-term exposure to ambient air pollution for cohort participants. Individual-level data included the date of death (if appli-

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. Francesca Dominici at the Harvard T.H. Chan School of Public Health, Boston, Massachusetts, and colleagues. The complete report, *Assessing Adverse Health Effects of Long-Term Exposure to Low Levels of Ambient Air Pollution: Implementation of Causal Inference Methods*, © 2022 Health Effects Institute, can be obtained from HEI or our website (see last page).

cable), age at year of Medicare entry, calendar year of entry, sex, race, ethnicity, zip code of residence, and Medicaid eligibility.

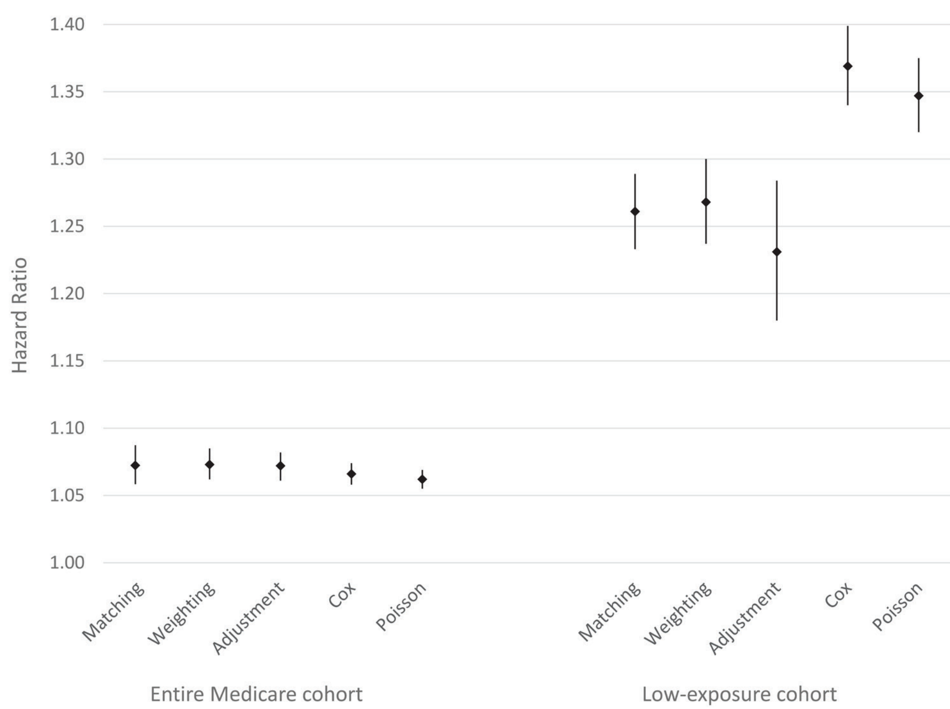
4. **Tools for Data Access and Reproducibility** Develop approaches for data sharing, record linkage, and statistical software to foster transparency and reproducibility of the work.

The exposure model inputs included monitoring data from the U.S. EPA Air Quality System, satellite-derived aerosol optical depth, meteorological variables, land-use variables that represent local emissions and small-scale variations in concentrations (e.g., road density, elevation, and normalized difference vegetation index), and daily predictions from two chemical-transport models to simulate atmospheric components. The investigators assigned the predicted annual average exposures to cohort participants' residential zip code for each year of follow-up.

The causal inference approach used generalized propensity scores and attempted to mimic a randomized study. They applied three causal modeling approaches, namely matching, weighting, and adjustment. The propensity scores were estimated by modeling zip code–level exposures conditional on area-level risk factors, meteorological variables, and year and region. They also applied two traditional regression approaches, namely Cox and Poisson models. Throughout the study, they examined health effects for the entire cohort and for a subpopulation exposed to annual average $PM_{2.5}$ concentrations below or equal to 12 μg/m^3 during every year of follow-up (i.e., low exposure subcohort) in order to address the question of health effects below the current U.S. annual National Ambient Air Quality Standard for $PM_{2.5}$. They also performed additional analyses, using, for example, single- and multipollutant models.

KEY RESULTS

The investigators estimated that the mean $PM_{2.5}$ exposure for cohort participants was 9.8 μg/m^3, well below the current U.S. standard of 12 μg/m^3. The investigators reported consistent, statistically significant results for the five statistical approaches. Specifically, hazard ratios and 95% confidence intervals associated with a 10-μg/m^3 increase in $PM_{2.5}$ exposure were 1.07 (1.06, 1.07) for the Cox regression, 1.06 (1.06, 1.07) for the Poisson regression, 1.07 (1.05, 1.08) for general propensity score matching, 1.08 (1.07, 1.09) for score weighting, and 1.07 (1.06, 1.08) for score adjustment (see Statement Figure). The investigators found



Statement Figure. Associations between longer-term exposures to $PM_{2.5}$ and all-cause mortality among enrollees in the full Medicare cohort (left side) and low-exposure cohort (right side). Hazard ratios (calculated per 10-μg/m^3 increase in $PM_{2.5}$ exposure) and 95% confidence intervals were estimated using three causal inference approaches with generalized propensity scores (matching, weighting, and adjustment) and two traditional approaches (Cox and Poisson regression). (Source: Investigators' Report Figure 6).

notably larger effect estimates with the low-exposure subcohort. For example, with Cox regression, they reported a hazard ratio of 1.37 (1.34, 1.40).

In single-pollutant models, the investigators found evidence of increased risk of mortality associated with long-term $PM_{2.5}$ exposures across the range of annual average $PM_{2.5}$ concentrations between 2.8 and 17.2 μg/m^3, which included 98% of observations. The exposure–response function for $PM_{2.5}$ was almost linear at exposures below the current U.S. standard. They found evidence of a relationship between mortality and long-term NO_2 exposures at higher concentrations (associations at exposures below annual mean ≤53 ppb [approximately 100 μg/m^3] were nonlinear and statistically uncertain). Similarly, the exposure–response function for long-term O_3 exposures and mortality showed some evidence of increased risks at exposures higher than 45 ppb (approximately 88 μg/m^3), but the exposure–response function was almost flat at concentrations below that, showing no statistically significant effect. Generally, adjusting for the other two pollutants slightly attenuated the effects of $PM_{2.5}$ on mortality and slightly elevated the effects of NO_2 exposure; results for O_3 remained almost unchanged.

INTERPRETATION AND CONCLUSIONS

The HEI Low-Exposure Epidemiology Studies Review Panel concluded that this report presents a high-quality and thorough investigation into associations between risk of mortality and exposures to ambient air pollution in the United States. The finding of increased risks of all-cause mortality in the low exposure subcohort across the various analytical approaches increases the confidence that mortality is associated with long-term concentrations of $PM_{2.5}$ below the current U.S. standard. The investigators also reported adverse associations between O_3 and NO_2 with mortality, but not at the lowest concentrations.

The stronger effects reported in the low-exposure subgroup could be due in part to those in that group being more susceptible to the effects of exposure. For example, the low-exposure subcohort excluded participants in large areas of the Eastern United States and likely excluded most people in most major cities. Whereas the main analyses describe the risk for the elderly U.S. population as a whole, the low-exposure analyses to some extent describe the risk for those in smaller towns and rural areas (who tend to be of lower socioeconomic status, have poorer health behaviors, more limited access to health services, and have a higher prevalence of diabetes or other comorbidities that might also increase susceptibility to the effects of exposure).

Particularly strong aspects of this work included the use of an extremely large, national health cohort; relatively high-resolution annual mean exposure estimates for each year of follow-up; the development of novel approaches to causal modeling to assess the associations between air pollution exposure and mortality; and comparisons of results from these with results from traditional approaches. The evaluation of the nonlinearity in multipollutant models was an additional valuable contribution. The Panel appreciated that datasets and statistical codes have been made publicly available, thus facilitating transparency and reproducibility.

The Panel had concerns, however, about some of the approaches used, such as the quality of the exposure estimates in rural areas; the fact that all exposure estimates were aggregated to the zip code level of analysis; and the hybrid nature of the study design, which included covariates measured variously at the individual, zip code, and county level.

Ultimately, the major contribution of this study is that it found associations between exposure to low concentrations to $PM_{2.5}$ and mortality in a large cohort of older Americans, with larger effects at the lowest levels of exposure. The fact that the study produced findings using several different causal inference approaches that were generally consistent with each other and with those of previous studies strengthens confidence in the results.

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