Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE)

BACKGROUND

The growing scientific evidence for 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 might be warranted 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, that is, lower than current air quality guidelines and standards for Europe and the United States for $PM_{2.5}$, NO_2, and O_3. HEI convened an independent Special Review Panel to evaluate the studies' strengths and weaknesses. This Statement highlights results from the European study.

APPROACH

The ELAPSE study by Brunekreef and colleagues examined whether exposure to low concentrations of ambient air pollution is associated with adverse effects on human health in 22 European cohorts. The study focused on four pollutants — $PM_{2.5}$, BC, NO_2, and O_3 — and developed new exposure models that combined monitoring data, land use data, satellite observations, and dispersion models to estimate exposures for cohort participants throughout Europe.

What This Study Adds

- The ELAPSE study evaluated health outcomes related to variation in exposures to low ambient air pollution concentrations, below current international guidelines.

- Brunekreef and colleagues developed new exposure models for all of Europe at a spatial resolution of 100 m × 100 m for four pollutants, namely fine particulate matter ($PM_{2.5}$), black carbon (BC), nitrogen dioxide (NO_2), and ozone (O_3), as well as $PM_{2.5}$ particle composition.

- They used data from 11 European countries to analyze (1) a pooled cohort of 15 well-characterized cohorts and (2) seven large administrative cohorts individually, followed by a meta-analysis.

- For both approaches, they reported that exposure to $PM_{2.5}$, BC, and NO_2 was significantly associated with natural-cause, cardiovascular, respiratory, and lung cancer mortality. They also reported inverse associations between O_3 and all causes of death examined.

- The shape of the associations with natural-cause mortality showed steeper slopes at lower exposures, with no evidence of concentrations below which no associations were found for $PM_{2.5}$, BC, and NO_2.

- This study contributes important evidence of associations between long-term exposures to relatively low concentrations of ambient air pollution and several important health endpoints.

The study had the following objectives:

1. To estimate long-term average exposure to air pollution in seven large administrative cohorts and in a pooled cohort consisting of participants from 15 existing cohorts from the European Study of Cohorts for Air Pollution Effects (ESCAPE).

2. To investigate the shape of the concentration–response relationship between long-term exposure to these pollutants and four broad categories of health outcomes: (1) natural and cause-specific mortality, (2) coronary and cerebrovascular events, (3) lung cancer incidence, and (4) asthma and chronic obstructive pulmonary disease incidence.

3. To investigate variability of the concentration–response function across populations and different exposure assessment methods, the effect of different methods for addressing exposure measurement error, the role of co-occurring pollutants, and the effect of indirect approaches for confounder control.

4. To compare epidemiological effect estimates for those obtained using the ELAPSE $PM_{2.5}$ exposure model with those obtained using an exposure model developed through the Mortality–Air Pollution Associations in Low-Exposure Environments (MAPLE) study in Canada that was funded under the same RFA.

The ELAPSE study consists of two parallel sets of epidemiologic analyses. First, Brunekreef and colleagues created Europewide exposure models for all pollutants of interest with monitoring data from 2010 at a spatial resolution of 100 m × 100 m. They then assigned estimates of exposure to participants in two sets of cohorts:

- They analyzed a pooled cohort that included 15 conventional research cohorts (i.e., those for which individuals were invited to participate and to respond to questionnaires). Most of those cohorts are located in a region that included at least one large city and a surrounding smaller town. The key strength of the pooled cohort approach is the rich amount of individual-level information available for about 325,000 participants.

- They analyzed seven large administrative cohorts individually and then conducted a meta-analysis to produce overall results. The administrative cohorts were formed by linking census data, population registries, and death registries. The key strength of the administrative cohorts is their large sample size (about 28 million total) and national representativeness.

The investigators applied standard Cox proportional hazard models to describe associations between exposures to the pollutants and the health outcomes of interest. Briefly, all models included age, sex, calendar year of enrollment, and selected individual and area-level (i.e., neighborhood or community-level) information, with slight variations in model specification for the two approaches. The investigators conducted many sensitivity analyses to evaluate exposure specification, confounder control, and various concentration–response functions.

KEY RESULTS

The Europewide exposure models explained 51% to 66% of the variability in concentrations of $PM_{2.5}$, BC, NO_2, and O_3, with good spatial stability (across the full study area) and good temporal stability (throughout the study period). In 2010, almost all participants had annual average exposures below the European Union limit values for $PM_{2.5}$ (25 μg/m³) and NO_2 (40 μg/m³), and about 14% had exposures below the U.S. National Ambient Air Quality Standards for $PM_{2.5}$ (12 μg/m³). Participants in the pooled cohort were exposed on average to 15 μg/m³ $PM_{2.5}$, 1.5×10^{-5}/m BC, 25 μg/m³ (13 ppb) NO_2, and 67 μg/m³ (34 ppb) O_3. Among the administrative cohorts, mean concentrations of $PM_{2.5}$ ranged from 12 to 19 μg/m³, except for the Norwegian cohort (8 μg/m³).

In analyses with both sets of cohorts, Brunekreef and colleagues reported significant positive associations between $PM_{2.5}$, BC, and NO_2 and natural-cause (Statement Figure) cardiovascular, respiratory, and lung cancer mortality. They also reported inverse associations between O_3 and all causes of death examined. The estimated risks associated with exposure were generally greater in the pooled cohort than in the administrative cohorts.

The hazard ratios for natural-cause mortality remained elevated and significant for $PM_{2.5}$ even when the analyses were restricted to observations below 12 μg/m³. For NO_2, hazard ratios remained elevated and significant when analyses were restricted to observations below 20 μg/m³.

In the pooled cohort, the investigators found significant positive associations between $PM_{2.5}$, BC, and NO_2 and incidence of stroke, asthma, and COPD hospital admissions. Additionally, they reported significant associations between NO_2 and acute coronary heart disease and between $PM_{2.5}$ and lung cancer incidence.
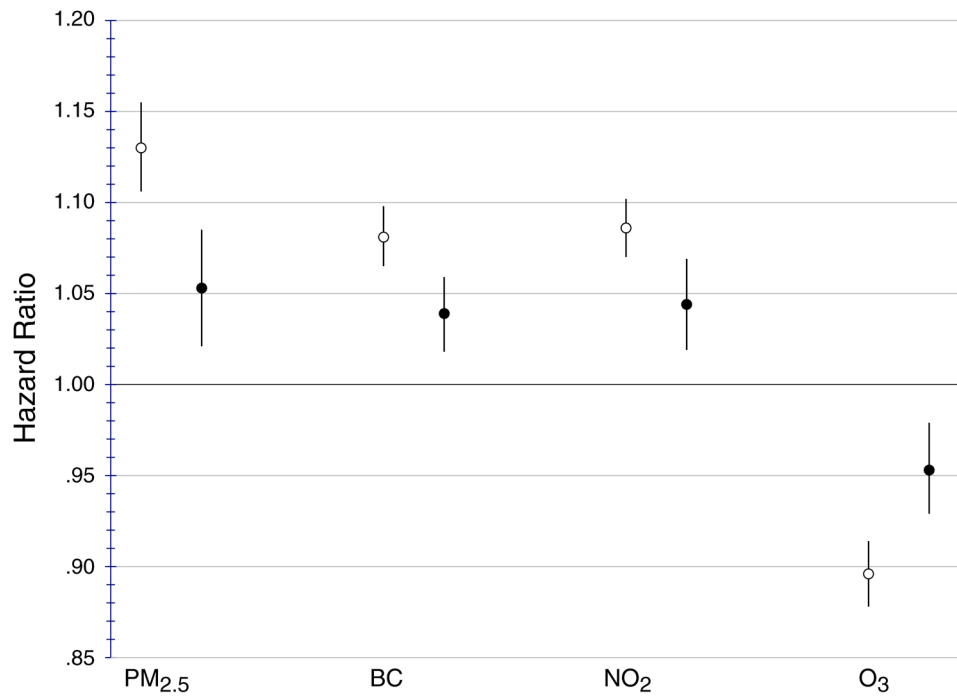
Statement Figure. Associations between air pollution and all-natural causes of death among participants in the pooled (white) and administrative (black) ELAPSE cohorts. Note that hazard ratios for the four pollutants were calculated over different concentration increments (see Tables 5 and 19 in the Investigators' Report).

In spline plots examining the shape of associations between exposure and natural-cause mortality, the investigators observed generally supralinear patterns (i.e., steeper slopes at lower exposures) with no evidence of concentrations below which no associations were found for $PM_{2.5}$, BC, and NO_2. That is, they found increased risks for mortality at even the lowest observed concentrations.

Lastly, in both sets of cohorts, the investigators reported comparable associations between mortality and exposures to $PM_{2.5}$ using the exposure estimates from the MAPLE study.

INTERPRETATION AND CONCLUSIONS

A key highlight of this study is the presentation of results from 11 European countries (pooled and individually), including heterogeneity in associations across countries. The creation of exposure models at 100 m × 100 m spatial resolution across Europe and analyses of associations between four pollutants and many important health endpoints, using two parallel cohort approaches, are all impressive achievements that provide important evidence for effects on health at low concentrations of exposures.

The analyses restricted to participants with the very lowest exposures provide further support that exposure to air pollution at low concentrations is associated with adverse health outcomes. However, it is important to acknowledge that these analyses were based on smaller numbers of cohorts that were less heterogeneous. The analysis at the lowest concentrations (below 10 μg/m³) in particular included data only from Norway and Stockholm. Thus, those findings might not be generalizable to the broader population.

Generally, the investigators have carefully explored several approaches to modeling concentration–response functions. However, the heterogeneity in the shapes of those functions for the administrative cohorts was not explained well (beyond acknowledging that the cohorts differed in mean exposures). On the other hand, the fact that the associations observed with the exposure model developed for the MAPLE study were similar to those observed with the exposure

model developed for ELAPSE corroborated the robustness of the associations. The near-consistent inverse associations between O_3 and the risk of the various health outcomes were unexpected and remained largely unexplained.

In summary, this study has provided important evidence of associations between long-term exposures to low concentrations of $PM_{2.5}$, BC, and NO_2 and various health outcomes, including mortality. Evidence for associations at the lowest concentrations remains limited because those analyses were based primarily on data from Norway and Stockholm. Continuing research on the effects of low concentrations of air pollutants in North America and Europe is expected to further inform the process of setting air quality standards in those and other global regions.