Determinants of the magnitude and shape of the associations between long-term PM$_{2.5}$ exposure and mortality: harmonized analyses in three large cohort studies in Canada, United States and Europe

HEI Annual Conference
June 27, 2022
Jie Chen on behalf of the ELAPSE, MAPLE and Harvard teams
Background

• A causal relationship between long-term fine PM (PM$_{2.5}$) exposure and all-cause mortality (2019 ISA, US EPA), indicating population health benefits of reductions in PM$_{2.5}$ concentrations;

• Evaluating the benefits of reductions in concentrations depends upon understanding both the magnitude of the PM$_{2.5}$ mortality risk and the shape of this relationship;

• Positive associations generally reported with varying magnitude across studies

• Heterogeneity related to study population, level of PM$_{2.5}$ exposure, composition PM$_{2.5}$ mixture, exposure assessment, statistical models...

• Little systematic evaluation of these factors
Estimating the Effects of Exposure to Low Levels of Air Pollution – HEI studies

Geographical areas

PI: Michael Brauer, U British Columbia (~ 10 million)
PI: Francesca Dominici, Harvard (~ 60 million)
PI: Bert Brunekreef, Utrecht University (~28 million)

Average PM$_{2.5}$ levels:
- 15 µg/m$^3$ (Europe)
- 11 µg/m$^3$ (US)
- 7 µg/m$^3$ (Canada)

Current PM$_{2.5}$ Standards:
- US 12 µg/m$^3$
- Europe 25 µg/m$^3$
- WHO AQG 5 µg/m$^3$
Mortality and Morbidity Effects of Long-Term Exposure to Low-Level PM$_{2.5}$, BC, NO$_2$, and O$_3$: An Analysis of European Cohorts in the ELAPSE Project


Assessing Adverse Health Effects of Long-Term Exposure to Low Levels of Ambient Air Pollution: Implementation of Causal Inference Methods

Francesca Dominici, Antonella Zanobetti, Joel Schwartz, Danielle Braun, Ben Sabath, and Xiao Wu

Mortality–Air Pollution Associations in Low-Exposure Environments (MAPLE): Phase 1

Michael Brauer, Jeffrey R. Brook, Tanya Christidis, Yen Chu, Dan L. Crouse, Anders Erickson, Perry Hystad, Chi Li, Randall V. Martin, Jun Meng, Amanda J. Pappin, Lauren L. Pinault, Michael Tjepekema, Aaron van Donkelaar, Scott Weichenthal, and Richard T. Burnett
Cox proportional hazard ratios of mortality per 5µg/m³ increase of PM$_{2.5}$

<table>
<thead>
<tr>
<th>Study populations</th>
<th>Exposure</th>
<th>Outcome</th>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAPLE</td>
<td>“stacked” 1991, 1996, 2001 CanCHEC ages &gt; 25 yrs</td>
<td>1×1 km</td>
<td>Natural mortality</td>
</tr>
<tr>
<td>Medicare</td>
<td>Medicare enrollees from 2000 to 2016 ages &gt; 65 yrs</td>
<td>1×1 km</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>ELAPSE</td>
<td>Seven administrative cohort participants ages &gt; 30 yrs</td>
<td>100×100 m</td>
<td>Natural mortality</td>
</tr>
</tbody>
</table>
Aim

• To investigate and discuss the impact of determinants on the associations between long-term PM$_{2.5}$ exposure and mortality, by performing harmonized analyses across three large studies in Canada (MAPLE), the United States (Medicare) and Europe (ELAPSE).
### Methods: harmonized analysis

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<td>1×1 km</td>
<td>Natural mortality</td>
<td></td>
</tr>
<tr>
<td>Medicare Medicare enrollees from 2000 to 2016 ages ≥ 65 yrs</td>
<td>1×1 km</td>
<td>All-cause mortality</td>
<td>Limited available at individual level</td>
</tr>
<tr>
<td>ELAPSE Seven administrative cohort participants ages &gt; 30 yrs</td>
<td>100×100 m</td>
<td>Natural mortality</td>
<td></td>
</tr>
<tr>
<td>Harmonized Participants ages ≥ 65 yrs</td>
<td>1×1 km MAPLE method</td>
<td>All-cause mortality</td>
<td>Common covariate models</td>
</tr>
</tbody>
</table>

**• Statistical analysis:**

- **Linear association** – Cox proportional hazard models incorporating PM$_{2.5}$ as time-varying exposure. **Common covariate models specified** (next page)

- **Exposure-response relationships** – extended Shape-Constrained Health Impact Function (eSCHIF), which relates risk to concentration suitable for quantitative benefits analysis.
Methods: Common covariate models with increasing control of potential confounders

<table>
<thead>
<tr>
<th>Model</th>
<th>Individual-level covariates</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sex</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Follow-up year</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable representing Race/Ethnicity</th>
<th>Stacked CanCHEC</th>
<th>Medicare</th>
<th>Belgian</th>
<th>Danish</th>
<th>Dutch</th>
<th>Norwegian</th>
<th>Roman</th>
<th>Swiss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race/Ethnicity, visible minority status, indigenous identity</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable representing SES</th>
<th>Income</th>
<th>Medicaid eligibility</th>
<th>Education</th>
<th>Income</th>
<th>Income</th>
<th>Income</th>
<th>Education</th>
<th>Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite SES index</td>
<td>X</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>X</td>
<td>-</td>
<td>X</td>
<td>x</td>
</tr>
<tr>
<td>(Household) income</td>
<td>-</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>-</td>
</tr>
<tr>
<td>Median house value</td>
<td>-</td>
<td>x</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Residents in poverty (%)</td>
<td>-</td>
<td>x</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Residents that own their house (%)</td>
<td>-</td>
<td>x</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Education</td>
<td>-</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>-</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Unemployment rate</td>
<td>-</td>
<td>-</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Non-western ethnic rate</td>
<td>-</td>
<td>-</td>
<td>x</td>
<td>-</td>
<td>x</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>No. of regional indicators</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td>12</td>
<td>7</td>
<td>NA</td>
<td>7</td>
</tr>
</tbody>
</table>
RESULTS
HRs for PM$_{2.5}$ per 5 µg/m$^3$ from Harmonized Model 4 and Original studies
HRs for PM$_{2.5}$ per 5 µg/m$^3$ from Model 1 (minimally adjusted model) and Model 4 (main model)
HRs for PM$_{2.5}$ per 5 $\mu$g/m$^3$ from harmonized exposure assessment and the original exposures applied in Medicare and ELAPSE
HRs for PM$_{2.5}$ per 5 µg/m$^3$ in study populations aged 65+ and full populations in CanCHEC (aged 25+) and ELAPSE (aged 30+)
HRs for PM$_{2.5}$ per 5 µg/m$^3$ for mortality from all causes and natural causes
Shape of the PM$_{2.5}$-mortality exposure-response relationship
SUMMARY

• Applying a harmonized analytical approach marginally reduced the differences in the observed associations across studies; full harmonization was not possible.

• Age of the study population, confounders adjusted for, exposure assessment methodology applied all impacted the magnitude of the observed associations, but positive associations were observed in all cases;

• HRs increased in all three studies with more stringent covariate controls.

• Shape of the concentration-response relationship differed between cohorts, but generally showed associations down to the lowest observed levels.

• A combined eSCHIF suggested a near linear relationship that flattens out at higher concentrations.
Teams

Bert Brunekreef

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Göran Pershagen, Tom Bellander, Petter Ljungman (Karolinska Institutet, Sweden)
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Marie-Christine Boutron (French National Institute of Health and Medical Research)
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Zorana Andersen, Shuo Liu, Amar Mehta (University of Copenhagen, Denmark)
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Lauren L Pinault (Statistics Canada)
Michael Tjepkema (Statistics Canada)
Aaron van Donkelaar (Dalhousie University)
Crystal Weagle (Dalhousie University)
Scott Weichenthal (McGill University)
Poster session this afternoon!

1. Harmonized confounder model analyses
2. The shape of the PM$_{2.5}$-mortality exposure-response relationship
3. Harmonized causal inference analyses