Multi-pollutant analyses in MAPLE, Medicare and ELAPSE cohorts

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Jie Chen on behalf of the ELAPSE, MAPLE and Harvard teams
Background

Most air pollution epidemiological studies have focused on single-pollutant research

Limitations of single pollutant models

• Not clear whether the observed association reflects the effect of the analyzed pollutant
• Not characterizing the complexity of the exposures and their health impacts
Multi-pollutant approaches estimate:

- the independent effect of a single pollutant in the presence of other pollutants

Challenges in interpretation:

- Highly correlated pollutants
- Differential measurement error – the lowest ME show the most consistent association
- Pollutants treated symmetrically despite the hierarchical natural
- Inclusion of multiple pollutants supported by biologic mechanism (e.g., toxicology)

This presentation:

- Share experience in interpreting results from multi-pollutant analyses
• Stacked CanCHEC (1991, 1996, 2001); N = 7.1 million
• The Canadian Community Health Survey (CCHS); N = 0.54 million
• Age ≥25 y at baseline, censored at 89 y
• Follow-up until end of 2016
• Non-accidental mortality

• PM$_{2.5}$, annual average, 1x1km resolution
• O$_3$, warm season
• O$_x$, combined oxidant capacity of O$_3$ and NO$_2$

$$O_x = \frac{((1.07 \times NO_2) + (2.075 \times O_3))}{3.145}$$
# Associations between PM$_{2.5}$ and non-accidental mortality

<table>
<thead>
<tr>
<th></th>
<th>N deaths</th>
<th>Single-pollutant model</th>
<th>Two-pollutant model adjusting for O$_3$</th>
<th>Two-pollutant model adjusting for O$_x$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stacked CanCHEC</td>
<td>1,253,300</td>
<td>1.084 (1.073, 1.096)</td>
<td>1.039 (1.027, 1.051)</td>
<td>1.022 (1.010, 1.035)</td>
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<td>CCHS with behavior</td>
<td>50,100</td>
<td>1.086 (1.021, 1.155)</td>
<td>1.016 (0.948, 1.089)</td>
<td>0.995 (0.924, 1.071)</td>
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HR per 10 µg/m$^3$ PM$_{2.5}$
Stratified PM$_{2.5}$ by terciles of O$_3$ or O$_x$

Stacked CanCHEC

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<td>Lowest</td>
<td>1.091 (1.065, 1.118)</td>
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<td>Middle</td>
<td>1.041 (1.020, 1.062)</td>
<td>1.006 (0.985, 1.027)</td>
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<td>Highest</td>
<td>1.099 (1.078, 1.120)</td>
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• The strongest association observed in areas with higher oxidant gases

• The observed impact of oxidant gases on associations for PM$_{2.5}$ concentrations likely reflects spatial variations in atmospheric processes/sources that can impact the toxicity of overall air pollution mixtures (e.g., particle aging/oxidation of organic components) and not a direct biological impact of the oxidant gases themselves
• Pooling eight ESCAPE cohorts and the Danish Nurse Cohort (N = 325,367)
• Large administrative cohorts from seven countries in Europe (N = 28 million)
• Age ≥30 y at baseline
• Non-accidental mortality

• Annual average of PM$_{2.5}$, NO$_2$, BC and warm season O$_3$ at 100x100 m resolution, year 2010
• Two-pollutant linear models for all combinations of PM$_{2.5}$, NO$_2$, BC and O$_3$
Air pollution and non-accidental mortality in the **pooled cohort**

<table>
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<tr>
<th>Pollutant</th>
<th>Single pollutant HR</th>
<th>HR adjusted for PM$_{2.5}$</th>
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<th>HR adjusted for BC</th>
<th>HR adjusted for O$_3$</th>
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<tr>
<td>PM$_{2.5}$</td>
<td>1.130 (1.106, 1.155)</td>
<td>NA</td>
<td>1.083 (1.054, 1.113)</td>
<td>1.092 (1.062, 1.123)</td>
<td>1.089 (1.061, 1.117)</td>
</tr>
<tr>
<td>NO$_2$</td>
<td>1.086 (1.070, 1.102)</td>
<td>1.050 (1.031, 1.070)</td>
<td>NA</td>
<td>1.074* (1.038, 1.112)</td>
<td>1.053 (1.032, 1.074)</td>
</tr>
<tr>
<td>BC</td>
<td>1.081 (1.065, 1.098)</td>
<td>1.039 (1.019, 1.060)</td>
<td>1.012* (0.977, 1.048)</td>
<td>NA</td>
<td>1.044 (1.024, 1.065)</td>
</tr>
<tr>
<td>O$_3$</td>
<td>0.896 (0.878, 0.914)</td>
<td>0.935 (0.913, 0.957)</td>
<td>0.940 (0.914, 0.966)</td>
<td>0.930 (0.906, 0.955)</td>
<td>NA</td>
</tr>
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N=325,367;
HR for increase in PM$_{2.5}$ – 5 µg/m$^3$, NO$_2$ – 10 µg/m$^3$, BC – 0.5×10$^{-5}$/m, O$_3$ – 10 µg/m$^3$
Air pollution and non-accidental mortality: meta-analysis of 7 administrative cohorts

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<td>1.053 (1.021, 1.085)</td>
<td>NA</td>
<td>1.003 (0.982, 1.025)</td>
<td>1.021 (0.997, 1.046)</td>
<td>1.031 (0.999, 1.064)</td>
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<td>NO$_2$</td>
<td>1.044 (1.019, 1.069)</td>
<td>1.042 (1.020, 1.065)</td>
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<td>BC</td>
<td>1.039 (1.018, 1.059)</td>
<td>1.030 (1.012, 1.049)</td>
<td>1.004* (0.985, 1.022)</td>
<td>NA</td>
<td>1.028 (1.005, 1.051)</td>
</tr>
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<td>O$_3$</td>
<td>0.953 (0.929, 0.979)</td>
<td>0.972 (0.947, 0.996)</td>
<td>0.987 (0.961, 1.014)</td>
<td>0.976 (0.948, 1.005)</td>
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N = 28,153,138;
HR for increase in PM$_{2.5}$ – 5 µg/m$^3$, NO$_2$ – 10 µg/m$^3$, BC – 0.5×10$^{-5}$/m, O$_3$ – 10 µg/m$^3$
• Associations observed not only for PM$_{2.5}$, but also NO$_2$

• PM$_{2.5}$ HR reduced with NO$_2$, cannot be interpreted as an artefact related to multi-collinearity (moderate correlation and the width of CI only modestly increased)

• The NO$_2$ association may reflect direct effects of NO$_2$ or correlated combustion-related particles such as ultrafine particles.

• The reduction of the PM$_{2.5}$ HR did not imply that particles had no effect, as adjustment for NO$_2$ also adjusted for particles from the sources shared with NO$_2$, including motorized traffic and other fossil fuel combustion sources.
Medicare

- Open cohort of Medicare enrollees (N = 68.5 million)
- Period 2000 – 2016
- Age ≥ 65 y
- All-cause mortality

- Annual PM$_{2.5}$, NO$_2$ and warm season O$_3$, 1 × 1 km grid, 2000 to 2016
Two-pollutant linear model (Di et al., NEJM, 2017)

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HR per 10 µg/m$^3$ PM$_{2.5}$ or per 10 ppb ozone
Causal exposure-response curve: air pollution and all-cause mortality (GPS matching)

(Dominici et al., HEI final report, under review)
### Summary

<table>
<thead>
<tr>
<th>Statistical methods</th>
<th>MAPLE</th>
<th>ELAPSE</th>
<th>Medicare</th>
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<tr>
<td>Linear two-pollutant</td>
<td>√</td>
<td>√</td>
<td>√</td>
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<td>Tercile analyses</td>
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<td>O$_x$</td>
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- Attenuated associations between PM$_{2.5}$ and mortality after adjusting for other pollutants
- Results should be interpreted with caution (e.g., spatial variation, emission sources, correlations)
Ongoing work related to multi-pollutant analyses

• Each team will apply multi-pollutant approaches applied by the other two teams
• The Harvard and ELAPSE teams will additionally assess $O_x$
• The Harvard and MAPLE teams will use the same $PM_{2.5}$ and $NO_2$ exposure surfaces; the ELAPSE team is not able to assign new exposures
Thanks for listening!