A deeper dive into the evidence for some of the selected health outcomes

*Moderated by Jeff Brook, University of Toronto and HEI Research Committee*

<table>
<thead>
<tr>
<th>Health Outcome</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth outcomes</td>
<td>Danielle Vienneau, Swiss Tropical and Public Health Institute</td>
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<tr>
<td>Respiratory</td>
<td>Audrey Smargiassi, University of Montreal</td>
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<tr>
<td>Neurodegenerative</td>
<td>Jennifer Weuve, Boston University</td>
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</tbody>
</table>
Selected birth outcomes:

Fetal growth and growth restriction
  - Term low birth weight (TLBW)
  - Term birth weight (TBW)
  - Small for gestational age (SGA)

Length of gestation
  - Preterm birth

86 studies included:

- Cohort design
- Whole pregnancy window
- In North America & Europe
- Birth registry data
- High traffic specificity
TRAP and term low birth weight (TLBW)

- Strongest for PM$_{2.5}$
- NO$_x$ and EC weaker, NO$_2$ null
- NO$_2$ stronger high vs. moderate traffic specificity
- Regional differences: stronger NO$_2$, EC and PM$_{2.5}$ for Western Europe
- Some studies with monotonic exposure-response function

Summary:
- Meta-analysis: *moderate confidence* in presence of an association
- Consistent:
  - studies not included in meta-analyses

Increments: 10 $\mu$g/m$^3$ for NO$_2$, 20 $\mu$g/m$^3$ for NO$_x$, 1 mg/m$^3$ for CO, 1 $\mu$g/m$^3$ for EC, 10 $\mu$g/m$^3$ for PM$_{10}$ and 5 $\mu$g/m$^3$ for PM$_{2.5}$
Consistent association of PM for growth restriction

**PM$_{2.5}$ and term LBW**

- **Relative Risk**
  - Weight: 1.11
  - RR: 1.03 (95%-CI: 0.91, 1.16)

- **PM$_{10}$ and SGA**
  - **Random effects model**
    - Heterogeneity: $I^2 = 0\%$, $Q = 0.76$
  - **Relative Risk**
    - Weight: 1.09
    - RR: 1.04 (95%-CI: 1.03, 1.16)

- **PM$_{2.5}$ and term BW**

- **PM$_{10}$ and SGA**

- **Mean Difference**
  - Heterogeneity: $I^2 = 77\%$, $Q = 99.0936$, $p < 0.01$
TRAP and preterm birth

- Null associations for all pollutants
- Individual studies have effect estimates above and below unity
- Third trimester effect for NO$_2$
- 3 traffic-PM$_{2.5}$ studies showed associations (i.e. PM from primary traffic emissions)

Summary:
- Meta-analysis: low confidence in presence of an association
- Supporting association:
  - 3 traffic-PM studies
  - distance to roadway

Increments: 10 µg/m$^3$ for NO$_2$, 10 µg/m$^3$ for NO, 20 µg/m$^3$ for NO$_x$, 1 µg/m$^3$ for EC and 5 µg/m$^3$ for PM$_{2.5}$
## Confidence assessment

<table>
<thead>
<tr>
<th>Health Outcome</th>
<th>NO$_2$ (per 10 µg/m$^3$)</th>
<th>NO$_x$ (per 20 µg/m$^3$)</th>
<th>EC (per 1 µg/m$^3$)</th>
<th>PM$_{2.5}$ (per 5 µg/m$^3$)</th>
<th>Overall Assessment of Confidence in Association with TRAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term low birth weight</td>
<td>1.01 (0.99; 1.03)</td>
<td>1.02 (1.01; 1.03)</td>
<td>1.01 (0.99; 1.04)</td>
<td>1.11 (1.03; 1.20)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Term birth weight</td>
<td>−3.2 (−11.0; 4.6)</td>
<td>−3.4 (−11.7; 4.8)</td>
<td>−2.6 (−6.1; 0.9)</td>
<td>−17.3 (−33.2; −1.5)</td>
<td>Low</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>1.00 (0.98; 1.02)</td>
<td>Fewer than three studies</td>
<td>1.02 (0.92; 1.14)</td>
<td>1.09 (1.04; 1.14)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.00 (0.96; 1.04)</td>
<td>1.03 (0.90; 1.17)</td>
<td>1.02 (0.97; 1.07)</td>
<td>0.99 (0.90; 1.09)</td>
<td>Low</td>
</tr>
</tbody>
</table>

Legend

- high
- moderate
- low
- Very low

Modified OHAT assessment: confidence in quality of the body of evidence
A deeper dive into the evidence for some of the selected health outcomes

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</table>
# Description of studies

<table>
<thead>
<tr>
<th>Health Outcome Category</th>
<th>Number of studies</th>
<th>Cohort - control</th>
<th>Case-control</th>
<th>Cross-sectional</th>
<th>Pub. before 2008</th>
<th>Exposure assessment method</th>
<th>High traffic specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory effects - children</td>
<td>118</td>
<td>50 (42%)</td>
<td>17 (14%)</td>
<td>51 (45%)</td>
<td>35 (30%)</td>
<td>Monitoring (&lt;5km)</td>
<td>22 (19%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LUR Modeling</td>
<td>41 (35%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dispersion/CTM</td>
<td>17 (14%)</td>
</tr>
<tr>
<td>Respiratory effects – adults</td>
<td>50</td>
<td>19 (38%)</td>
<td>7 (14%)</td>
<td>24 (48%)</td>
<td>11 (22%)</td>
<td>Monitoring (&lt;5km)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LUR Modeling</td>
<td>15 (30%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dispersion/CTM</td>
<td>15 (30%)</td>
</tr>
</tbody>
</table>

Studies excluded if no control for inter-regional contrasts; Preference given to the earliest exposures (most estimates for exposure during pregnancy, at birth, or for the first year of life);

**Most studies:**
- from Europe / North America;
- controlled for lifestyle characteristics (ex. parental or individual smoking) except those based on administrative data (but control for area level SES);
Meta-analysis of associations between TRAP and asthma onset in children

- Many cohorts based on questionnaires but minimal changes when removing such studies at moderate RoB
- Most estimates positive but some negative contributing to heterogeneity
- Smaller estimates from administrative cohorts, all from North America

Increments used: 10 µg/m³ for NO₂, 20 µg/m³ for NOₓ, 1 µg/m³ for EC and 5 µg/m³ for PM₂.₅
Meta-analysis of associations between TRAP and ALRI in children

- Cross-sectional and cohort studies based on questionnaires or administrative data
- Different infections considered
- Most estimates positive but some negative contributing to heterogeneity

Increments used: 10 µg/m³ for NO₂ and 1 µg/m³ for EC
Associations between NO$_2$ and **asthma onset** in adults: meta-analysis

- Mainly cohort studies (n=6/7)
Overall confidence in the evidence for an association between long-term exposure to TRAP and respiratory outcomes

<table>
<thead>
<tr>
<th></th>
<th>Narrative assessment</th>
<th>Confidence assessment of the body of evidence (modified OHAT)</th>
<th>Overall assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma onset</td>
<td>Moderate</td>
<td>High</td>
<td>Moderate to high</td>
</tr>
<tr>
<td>Asthma ever</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Active asthma</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>ALRI</td>
<td>High</td>
<td>Moderate</td>
<td>Moderate to high</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma onset</td>
<td>High</td>
<td>Moderate</td>
<td>Moderate to high</td>
</tr>
<tr>
<td>ALRI</td>
<td>Low</td>
<td>Very low</td>
<td>Very low to low</td>
</tr>
<tr>
<td>COPD</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

- Mixed results from indirect traffic with asthma outcomes in children
- Limited information on associations with asthma exacerbations in children (n=6 with TRAP all positive estimates; no meta-analysis)
- Limited information and low confidence on associations in adults with asthma ever (n=5), active asthma (n=4) or exacerbations of COPD and asthma, with positive, negative and null findings

Aspects not covered in the modified OHAT assessment: number and size of the evidence base; strength (magnitude) of the association; different pollutants and indirect traffic measures.
A deeper dive into the evidence for some of the selected health outcomes

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Mortality        Gerard Hoek, Utrecht University
Neurodevelopmental Sharon Sagiv, University of California - Berkeley
Neurodegenerative Jennifer Weuve, Boston University
### Substantial increase in published studies

<table>
<thead>
<tr>
<th>Health outcome Category</th>
<th>Subcategory</th>
<th>Total number of studies</th>
<th>Total number of studies in meta-analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiometabolic outcomes</td>
<td>Ischemic Heart Disease</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Coronary events</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Stroke events</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Type 2 diabetes mellitus – incidence</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Type 2 diabetes mellitus - prevalence</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

- Evidence base dominated by studies from Europe and North America
- Most studies incidence studies (exception: Diabetes studies), exclusion of diseased individuals at baseline (in contrast to mortality chapter)
- Many studies not included in meta-analysis because only indirect traffic measures available or less than 3 per pollutant
- Where possible, stratified analyses according to fatality of outcome
Ischemic Heart Disease

- Clear null associations for gaseous pollutants NO$_2$ and NO$_x$
- Subgroup analyses showed stronger and more consistent estimates for fatal disease
- Several studies with monotonic exposure-response function
- Additional support for indirect traffic measures, PM$_{coarse}$ and PM nontailpipe indicators
- 4 out of 4 robust to noise adjustment

Increments used: 10 µg/m$^3$ for NO$_2$, 20 µg/m$^3$ for NO$_x$, 1 µg/m$^3$ for EC, 10 µg/m$^3$ for PM$_{10}$ and 5 µg/m$^3$ for PM$_{2.5}$
Stroke

- Clear null associations for gases NO$_2$ and NO$_x$
- Additional support for traffic-specific PM fractions
- Robust upon adjustment for noise (4 out of 4)

Increments used: 10 µg/m$^3$ for NO$_2$, 20 µg/m$^3$ for NO$_x$, 1 µg/m$^3$ for EC, 10 µg/m$^3$ for PM$_{10}$ and 5 µg/m$^3$ for PM$_{2.5}$.
Diabetes mellitus

- Indirect traffic measures (6 out of 7)
- Additional support for NO, UFP and traffic-specific PM fractions
- Robust upon adjustment for noise (4 out of 5)
- Studies with more extensive confounder control and outcome assessment with clinical exams yielded higher estimates and lower heterogeneity – upgrade in OHAT (1)

Increments used: 10 µg/m³ for NO₂, 20 µg/m³ for NOₓ, 1 µg/m³ for EC, 10 µg/m³ for PM₁₀ and 5 µg/m³ for PM₂.₅
# Overall assessment

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<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Coronary events</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Stroke events</td>
<td>Moderate</td>
<td>Low</td>
<td>Low to moderate</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

- Generally stronger effects for fatal disease – in line with high ratings for cause-specific mortality outcomes (circulatory and ischemic heart disease)
- Exclusion of nonfatal (sub)clinical precursor conditions and short-term studies
- Repeated search conducted in 2022 for stroke and diabetes strengthens conclusions of moderate evidence
- Need for more toxicological / mechanistic evidence for nitrogen oxides and cardiometabolic disease
A deeper dive into the evidence for some of the selected health outcomes

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</table>
Many more studies on mortality than in 2010 HEI review

• 48 studies for all-cause (natural) and cause-specific mortality
• 31 studies for all-cause mortality
• Many cohort studies on air pollution not selected as not sufficiently traffic-specific (especially on PM$_{2.5}$ such as ACS, Medicare)
• Most selected were from Europe and North-America
• Studies with detailed lifestyle and very large population-based studies
Effect estimates cannot be directly compared across the different traffic-related pollutants because the selected increments do not necessarily represent the same contrast in exposure. The individual pollutants are considered as indicators of the TRAP mixture.
Meta-analysis NO$_2$ – All cause mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Name</th>
<th>Relative Risk</th>
<th>RR</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beelen et al. 2008</td>
<td>NLCS-AIR</td>
<td>1.03</td>
<td>1.00</td>
<td>1.05</td>
<td>9.8%</td>
</tr>
<tr>
<td>Carey et al. 2013</td>
<td>English National Cohort</td>
<td>1.02</td>
<td>1.00</td>
<td>1.04</td>
<td>10.8%</td>
</tr>
<tr>
<td>Cesaroni et al. 2013</td>
<td>Rome Longitudinal</td>
<td>1.03</td>
<td>1.02</td>
<td>1.04</td>
<td>12.2%</td>
</tr>
<tr>
<td>Yorifuji et al. 2013</td>
<td>Shizuoka Elderly</td>
<td>1.12</td>
<td>1.07</td>
<td>1.18</td>
<td>6.1%</td>
</tr>
<tr>
<td>Beelen et al. 2014</td>
<td>ESCAPE</td>
<td>1.01</td>
<td>0.99</td>
<td>1.03</td>
<td>10.6%</td>
</tr>
<tr>
<td>Crouse et al. 2015</td>
<td>1991 CanCHEC</td>
<td>1.05</td>
<td>1.04</td>
<td>1.07</td>
<td>11.3%</td>
</tr>
<tr>
<td>Nieuwenhuijsen et al. 2018</td>
<td>Barcelona Mega Cohort</td>
<td>1.02</td>
<td>1.00</td>
<td>1.04</td>
<td>10.6%</td>
</tr>
<tr>
<td>Yang et al. 2018</td>
<td>Hong Kong Elderly</td>
<td>1.00</td>
<td>0.99</td>
<td>1.01</td>
<td>11.7%</td>
</tr>
<tr>
<td>Dirgawati et al. 2019</td>
<td>HIMS</td>
<td>1.06</td>
<td>1.00</td>
<td>1.13</td>
<td>4.8%</td>
</tr>
<tr>
<td>Hanigan et al. 2019</td>
<td>45 and Up Study</td>
<td>1.06</td>
<td>0.97</td>
<td>1.16</td>
<td>2.9%</td>
</tr>
<tr>
<td>Hvidfeldt et al. 2019</td>
<td>DDCH</td>
<td>1.07</td>
<td>1.04</td>
<td>1.10</td>
<td>9.3%</td>
</tr>
</tbody>
</table>

Random effects model
- Prediction interval
- Heterogeneity: $I^2 = 83\%$, $\tau^2 = 0.0006$, $p < 0.01$

Relative Risk per 10 µg/m$^3$

$1.04 \ [1.01; 1.06], 100\%$
Narrative assessment: high confidence

- Consistent associations multiple pollutants
- Sizable number of well-conducted (large) cohort studies
- Generally adjusting for major covariates
- In different locations: confounding less likely as pollution and lifestyle / SES have different direction of association with exposure
- Robust to adjustment for noise
- Different research groups
- Support from studies on traffic intensity / distance to major roads
- Some support from studies not included in meta-analysis such as studies in patient populations
Modified OHAT assessment for TRAP and all-cause mortality

- Few downgrades (imprecision, Risk of bias)
- Upgrades for monotonic exposure response function (NO₂, PM₂.₅, NOₓ and PM₁₀) and consistency across regions (NO₂)

- PM₂.₅, NO₂, EC  high confidence
- NOₓ and PM₁₀    moderate confidence
- Cu, Fe          low confidence
- TRAP combined   high confidence
Conclusions

• High confidence in an association between TRAP and all-cause mortality
• Despite issues formal and narrative assessment broadly agreed
• Broadly agree with other assessment on PM$_{2.5}$ and NO$_2$ pollutants by WHO, IARC and EPA (Integrated Science Assessment)
• Policies reducing TRAP will deliver health benefits
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- **Neurodegenerative**  
  Jennifer Weuve, Boston University
Neurodevelopment

- Brain development across multiple dimensions of cognitive function, behavior

- 3 categories of outcomes selected for TRAP review
  - Cognitive function (intellectual function, attention, executive function)
  - Attention deficit hyperactivity disorder (ADHD)
  - Autism spectrum disorders (ASD)

- No formal meta-analysis/confidence assessment for these outcomes

- Rationale for inclusion as secondary outcome in HEI review
  - Rapid development in early life → period of heightened vulnerability to environmental insult (legacy chemicals: prenatal/early life lead, mercury → adverse neurodevelopment)
  - Rapid growth in literature (e.g., 174 publications on air pollution* & autism since 2010)

* Not restricted to TRAP
Cognitive function

• Poorer performance or slower development along a range of cognitive domains
  • general, verbal, and nonverbal IQ, learning, memory, language, visuospatial skills, visual-motor abilities, attention, and dimensions of executive function, including working memory and response inhibition

• 30 studies included (age at cognitive assessment: 1-20 years)
  • 18 different study populations; all but 1 study set in Europe and N. America
  • 14 prospective cohort studies, 5 cross-sectional studies, range n=176 to 9,482

• MODERATE confidence in presence of association with TRAP
  • NO₂, EC, PM₂.₅: approx. half of studies reported associations with cognitive function
    • both gestational and childhood exposure
    • mostly with general intelligence, attention, and working memory
  • null or scant evidence for NOₓ, PM₁₀&course, UFPs
  • mixed associations with indirect traffic measures (stronger for traffic density)
Attention deficit hyperactivity disorder (ADHD)

- ADHD diagnosis and related behaviors
  - inattention, hyperactivity, impulse control

- 8 studies included (age of ADHD assessment/diagnosis: 4 to 15 years)
  - 7 different study populations; all set in Europe and N. America
  - prospective cohorts except for 1 case-control study, range n=284 to 29,127

- LOW confidence in presence of association with TRAP
  - most studies reported null associations
  - small number of studies reported modest associations of childhood exposure to NO$_2$, EC, and PM$_{2.5}$ with ADHD behaviors
Autism Spectrum Disorders (ASD)

- ASD diagnosis and related behaviors
  - social cognition, restricted and repetitive behaviors
- 14 studies included (age at ASD assessment/diagnosis: 2 to 13)
  - 11 different study populations; most in Europe and N. America, also China, Israel
  - 7 case-control studies, 4 prospective cohorts, range n=430 to 126,402
  - all but 2 studies examined ASD diagnosis
- MODERATE TO HIGH confidence in presence of association with TRAP
  - $\text{NO}_2$: 4 of 5 studies reported higher ASD risk with gestational and early infancy exposure
  - $\text{PM}_{2.5}$: 3 of 4 studies reported higher ASD risk with exposure in first few years of life
  - null or mixed for other TRAP pollutants and indirect traffic
  - geographical heterogeneity in findings (+ N. America, Ø for Europe)
Discussion

• 49 studies representing 30 study populations included in review
• Confidence in presence of an association ranged from low (ADHD) to moderate/high (ASD)

• Limitations → directions for future study
  • Heterogeneity of outcomes, especially cognitive function → common set of endpoints
  • Sample sizes limited for many studies → larger studies, quantitative traits
  • Variable covariate inclusion → commons set of confounders
  • Critical window unclear (gestation, early life) → better identification of window of exposure, age at outcome assessment, biologic mechanisms

• Rapid growth in literature on air pollution and neurodevelopment
  • Formal meta-analysis/confidence assessment possible in the near future
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Outcomes, methods, rationale

• Neurodegenerative outcomes included
  • Dementia and related cognitive outcomes (function and decline)
  • Parkinson disease

• No formal meta-analysis/confidence assessment for these outcomes

• Rationale for assessing as secondary outcomes
  • Public health burden:
    54.7M with dementia (2019); 6.1M with Parkinson disease (2016)
  • Rapid growth in evidence base since 2010
Dementia and related cognitive outcomes: studies

15 studies in 10 cohorts
- N = 387 to >2 million
- Europe, N America
- Mostly cohort designs, some cross-sectional

TRAP measures used
- Density/distance
- EC, NO₂
- PM₂.₅, NOₓ
- PM₁₀
- PM_{coarse}
Dementia and related cognitive outcomes: findings

Association patterns

- Suggestively adverse
  - NO$_2$
  - NO$_x$

- Less consistent
  - PM$_{2.5}$
  - EC
  - Density / distance

- Inconsistent and sparse
  - PM$_{10}$
  - PM$_{coarse}$

Challenges

- Methodologic: selection bias, dementia misclassification in EMR
- Sparse numbers of specific pollutant-outcome pairs
- All associations with decline were null.

*Low to moderate confidence* in the presence of adverse association of TRAP with dementia-related outcomes
Parkinson disease: studies

6 studies in 5 cohorts
- N = 1290 to >2 million
- Europe, N America
- 3 cohort, 3 case-control

TRAP measures used
- NO₂
- PM₂.₅, NOₓ, PM₁₀, PMcoarse, density/distance
Parkinson disease: findings

Association patterns

Challenges

• Methodologic: selection bias, Parkinson misclassification, confounding by smoking
• Sparse numbers of specific pollutant-outcome pairs

Low confidence in the presence of adverse association of TRAP with Parkinson disease