Online Supplement

Effect modification of perinatal exposure to air pollution and childhood asthma incidence

Éric Lavigne, Marc-André Bélair, Daniel Rodriguez Duque, Minh T. Do, David M. Stieb, Perry Hystad, Aaron van Donkelaar, Randall V. Martin, Eric Crighton, Hong Chen, Richard T. Burnett, Scott Weichenthal, Paul J. Villeneuve, Teresa To, Jeffrey R. Brook, Markey Johnson, Sabit Cakmak, Abdool S. Yasseen, and Mark Walker

a Air Health Science Division, Health Canada, Ottawa, Ontario, Canada
b School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Ottawa, Ontario, Canada
c Institute for Clinical Evaluative Sciences, Ottawa, Ontario, Canada
d Surveillance and Epidemiology Division, Public Health Agency of Canada, Ottawa, Ontario, Canada
e Population Studies Division, Health Canada, Vancouver, British Columbia, Canada
f College of Public Health and Human Sciences, Oregon State University, Corvallis, Oregon, USA
g Department of Physics and Atmospheric Science, Dalhousie University, Halifax, Nova Scotia, Canada
h Department of Sociology, University of New Brunswick, Fredericton, New Brunswick, Canada
i Department of Geography, Environment and Geomatics, University of Ottawa, Ottawa, Ontario, Canada
j Public Health Ontario, Toronto, Ontario, Canada
k Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
l Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada
m Population Studies Division, Health Canada, Ottawa, Ontario, Canada
n Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada
o Department of Health Sciences, Carleton University, Ottawa, Ontario, Canada
p Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, Ontario, Canada
q Air Quality Research Division, Environment Canada, Downsview, Ontario, Canada
r Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
s Better Outcomes Registry and Network Ontario, Ottawa, Ontario, Canada
t Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada
u Department of Obstetrics and Gynecology, University of Ottawa, Ottawa, Ontario, Canada

Corresponding author’s contact details
Eric Lavigne, PhD, Air Health Science Division, Health Canada
269 Laurier Avenue West, Mail stop 4903B, Ottawa, Ontario, Canada, K1A 0K9
Telephone: 613-948-3686; E-mail: eric.lavigne@hc-sc.gc.ca
**Study design population & design**

Information on maternal residential location(s) based on residential postal code(s) was geo-coded using the Postal Code Conversion File Plus (PCCF+) to obtain Statistics Canada’s standard geographic identifiers and dissemination area (DA) information. The encrypted unique identifier (also referred to the IKN) was used to link health administrative data at the Institute for Clinical Evaluative Sciences (ICES) in Ontario, Canada (see Figure S1). In urban areas, the 6-digit postal code generally represents one side of a city block or a large apartment complex while it usually represents a larger area in rural areas. We also used an indicator for urban/rural place of residence. In Canada, a six-character alphanumeric string forms part of a postal address. The second digit specifies if the postal code is in an urban or rural area. A zero indicates a rural region. Therefore, postal codes were considered rural if the second character was zero. There were 268,489 postal codes in urban areas and 1,122 postal codes in rural areas. This translated into 687,338 mother-infant pairs in urban areas and 73,834 mother-infant pairs in rural areas. Pregnancies with postal codes of residence outside Ontario (i.e. less than 1% of all pregnancies) were excluded from the analysis. We also excluded subjects without a valid health card number for data linkage, missing date of birth, sex, 6-digit postal code value and/or exposure estimates. Those who were excluded from the study due to these reasons exhibited similar sociodemographic factors to those measured in this study (data not shown).

**Childhood asthma ascertainment**

A previously validated case definition of asthma was used to identify individuals with asthma and included those who have had at least two primary care visit claims for asthma in two consecutive years and/or at least one hospitalization for asthma [1]. This definition has been shown to have 89% sensitivity and 72% specificity in children (aged 0-17 years). This case definition has been previously used [2-4]. All datasets were housed at the Institute for Clinical Evaluative Sciences (ICES; www.ices.on.ca), where individual-level data were anonymized and linkage between datasets was achieved using encrypted health card numbers as unique identifiers.

**Maternal asthma maternal atopy ascertainment**

We used a previously validated case definition to identify pregnant women with physician-diagnosed asthma [5]. The case definition consists of one asthma hospitalization or two outpatient physician visits within a two year period. This yielded 84% sensitivity and 76% specificity in adults participating in a validity study when they were compared to a clinical reference standard. The date of the earliest asthma hospitalization or outpatient visit was used to determine the asthma diagnosis date. This case definition has been used in previous studies in Canada [6-8]. We identified maternal atopy based on two outpatient physician visits (i.e. any of the following diagnoses: maternal asthma identified as ICD-10 code J45, maternal atopic dermatitis identified as ICD-10 code L20, and maternal allergic rhinoconjunctivitis identified as ICD-10 codes J30 and H10) within a two year period.

**Exposure assessment to ambient air pollutants**

We assigned air pollution exposure estimates to the geographical coordinates representing the centroid of each subject’s residential 6-digit postal codes. Exposure to PM$_{2.5}$ during pregnancy,
during the first year of life and during childhood were assigned based on satellite-derived estimates of monthly surfaces at a 1 × 1 km resolution available across North America from 2006 to 2012. Childhood exposure was assigned on a cumulative basis (i.e. from birth until diagnosis of asthma, end of follow-up or death). Satellite estimates were developed following van Donkelaar et al. (2015) using a 1 km optimal estimation (OE) aerosol optical depth (AOD) satellite retrieval that was related to PM$_{2.5}$ with a chemical transport model, which was further adjusted with ground-based PM$_{2.5}$ monitors using a geographically weighted regression (GWR) to account for regional bias across North America [9,10]. Data were also assigned based on trimester-specific periods of exposure and were averaged to obtain estimates for the entire pregnancy.

Prenatal exposure to ambient NO$_2$ was estimated by using a national Land Use Regression (LUR) model developed with data from National Air Pollution Surveillance (NAPS; http://www.ec.gc.ca/rnspa-naps/) monitoring data, 2005–2011 satellite NO$_2$ estimates, road lengths within 10 km, area of industrial land use within 2 km, and mean summer rainfall [11,12]. To capture fine-scale variations in vehicle emissions, kernel density functions describing densities of roadways were incorporated into the LUR model predictions. This model explained 73% of the variation in annual 2006 NO$_2$ NAPS measurements with a root mean square error of 2.9 parts per billion (ppb). The resulting LUR NO$_2$ surface was available for each year of the study period. Because the national NO$_2$ surface only provided annual values, we applied a temporal adjustment to the LUR NO$_2$ model. This allowed us to map NO$_2$ values more precisely to gestational periods in order to examine effects by trimester, as well as evaluating effects for childhood exposures. This was done by first generating a scaling factor by calculating a ratio of monthly mean NO$_2$ concentration for each monitor in the province of Ontario to annual values for year 2006 LUR model estimate at each monitor location. Estimates of monthly average ambient concentrations of NO$_2$ were obtained from the NAPS network maintained by Environment Canada which collects NO$_2$ levels through 46 automated fixed-site monitoring stations in the province of Ontario. We then created a scaling surface for each day of the study period by spatially interpolating the scaling factors. We applied an inverse distance weighting (IDW) spatial interpolation to 6-character postal code locations that were within 25km of a NAPS station to create the scaling surface. These daily scaling surfaces were then applied to the yearly LUR estimates to create the daily NO$_2$ surfaces [13]. These were then used to estimate exposure to NO$_2$ over pregnancy, by trimesters, during the first year of life and for the cumulative childhood exposure.

**Exposure assessment to residential greenness**

Exposure to residential greenness was estimated using the satellite-derived Normalized Difference Vegetation Index (NDVI). The NDVI describes the density and coverage of green vegetation on the ground, and has been shown to be effective in estimating local patterns of greenness for epidemiologic analysis [14]. The NDVI ranges from -1 to 1, with greater positive
values indicating more greenness [15]. These data are available across Canada – excluding northern regions and territories – calculated as 16-day averages. We included observations only from the months of June, July, and August (when vegetation in Canada would be in full bloom) and calculated annual maximum values for the years 2006 to 2012. We assigned annual greenness estimates within 250 metres around the annual residential postal code centroids of each subject for each year from 2006 to 2012. Since the greenness measures were available annually, exposure during pregnancy was calculated as the weighted average of consecutive years, where weights were equal to the proportion of the pregnancy in each year. We used these estimates of exposure to greenness based on prior expert assessments of residential greenness exposure [14] and prior studies investigating exposure during pregnancy [16,17].

References

1. To T, Dell S, Dick PT, Cicutto L, Harris JK, MacLusky IB, Tassoudji M. Case verification of children with asthma in Ontario. Pediatr Allergy Immunol 2006; 17: 69-76.
2. Benchimol EI, Manuel DG, To T, Mack DR, Nguyen GC, Gommerman JL, Croitoru K, Mojaverian N, Wang X, Quach P, Guttman A. Asthma, type 1 and type 2 diabetes mellitus, and inflammatory bowel disease amongst South Asian immigrants to Canada and their children: a population-based cohort study. PLoS One 2015; 10: e0123599.
3. Cohen E, Yantzi N, Guan J, Lam K, Guttman A. Residential movement patterns of families of young children with chronic conditions in Ontario, Canada: a population-based cohort study. Int J Equity Health 2013; 12: 62-9276-12-62.
4. Stanojevic S, Shah B, Anand S, Sears M, Su J, Subbarao P. The burden of asthma among the South Asian and Chinese population residing in Ontario. Can Respir J 2014; 21: 346-350.
5. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying patients with physician-diagnosed asthma in health administrative databases. Can Respir J 2009; 16: 183-188.
6. Kendzerska T, Sadatsafavi M, Aaron SD, To TM, Lougheed MD, FitzGerald JM, Gershon AS. Canadian Respiratory Research Network. Concurrent physician-diagnosed asthma and chronic obstructive pulmonary disease: A population study of prevalence, incidence and mortality. PLoS One 2017; 12: e0173830.
7. Tetreault LF, Doucet M, Gamache P, Fournier M, Brand A, Kosatsky T, Smargiassi A. Childhood Exposure to Ambient Air Pollutants and the Onset of Asthma: An Administrative Cohort Study in Quebec. Environ Health Perspect 2016; 124: 1276-1282.
8. To T, Guan J, Zhu J, Lougheed MD, Kaplan A, Tamari I, Stanbrook MB, Simatovic J, Feldman L, Gershon AS. Quality of asthma care under different primary care models in Canada: a population-based study. BMC Fam Pract 2015; 16: 19-015-0232-y.
9. van Donkelaar A, Martin RV, Spurr RJ, Burnett RT. High-Resolution Satellite-Derived PM2.5 from Optimal Estimation and Geographically Weighted Regression over North America. Environ Sci Technol 2015; 49: 10482-10491.
10. Brunsdon C, Fotheringham AS, Charlton ME. Geographically Weighted Regression: A Method for Exploring Spatial Nonstationarity. Geogr Anal 1996; 28: 281-298.
11. Hystad P, Villeneuve PJ, Goldberg MS, Crouse DL, Johnson K, Canadian Cancer Registries Epidemiology Research Group. Exposure to traffic-related air pollution and the risk of
developing breast cancer among women in eight Canadian provinces: A case-control study. Environ Int 2015; 74: 240-248.

12. Hystad P, Setton E, Cervantes A, Poplawski K, Deschenes S, Brauer M, van Donkelaar A, Lamsal L, Martin R, Jerrett M, Demers P. Creating national air pollution models for population exposure assessment in Canada. Environ Health Perspect 2011; 119: 1123-1129.

13. Bechle MJ, Millet DB, Marshall JD. National Spatiotemporal Exposure Surface for NO2: Monthly Scaling of a Satellite-Derived Land-Use Regression, 2000-2010. Environ Sci Technol 2015; 49: 12297-12305.

14. Rhew IC, Vander Stoep A, Kearney A, Smith NL, Dunbar MD. Validation of the normalized difference vegetation index as a measure of neighborhood greenness. Ann Epidemiol 2011; 21: 946-952.

15. Weier J, Herring D. Measuring Vegetation (NDVI & EVI). http://earthobservatory.nasa.gov/Features/MeasuringVegetation/, 2011.

16. Cusack L, Larkin A, Carozza S, Hystad P. Associations between residential greenness and birth outcomes across Texas. Environ Res 2017; 152: 88-95.

17. Hystad P, Davies HW, Frank L, Van Loon J, Gehring U, Tamburic L, Brauer M. Residential greenness and birth outcomes: evaluating the influence of spatially correlated built-environment factors. Environ Health Perspect 2014; 122: 1095-1102.
Table S1. Descriptive statistics of air pollution measures and Pearson correlation coefficients across time periods.

| Air pollutant      | Mean | SD  | IQR  | 1st trimester | 2nd trimester | 3rd trimester | Pregnancy average | Child’s 1st year | Childhood cumulative exposure | 1st trimester | 2nd trimester | 3rd trimester | Pregnancy average | Child’s 1st year | Childhood cumulative exposure |
|--------------------|------|-----|------|---------------|---------------|---------------|-------------------|------------------|-------------------------------|---------------|---------------|---------------|-------------------|------------------|-------------------------------|
| NO₂ (ppb)          |      |     |      |               |               |               |                   |                  |                               |               |               |               |                   |                  |                               |
| 1st trimester      | 13.2 | 7.8 | 9.6  | 1.00          |               |               |                   |                  |                               |               |               |               |                   |                  |                               |
| 2nd trimester      | 13.2 | 7.8 | 9.7  | 0.72          | 1.00          |               |                   |                  |                               |               |               |               |                   |                  |                               |
| 3rd trimester      | 13.1 | 7.8 | 9.5  | 0.51          | 0.69          | 1.00          |                   |                  |                               |               |               |               |                   |                  |                               |
| Pregnancy average  | 13.2 | 7.8 | 8.6  | 0.69          | 0.78          | 0.74          | 1.00              |                  |                               |               |               |               |                   |                  |                               |
| Child’s 1st year   | 13.1 | 7.8 | 8.9  | 0.51          | 0.56          | 0.55          | 0.62              | 1.00             |                               |               |               |               |                   |                  |                               |
| Childhood cumulative exposure | 13.0 | 7.8 | 8.9  | 0.48          | 0.51          | 0.56          | 0.59              | 0.63             | 1.00             |               |               |               |                   |                  |                               |
| PM₂.₅ (µg/m³)      |      |     |      |               |               |               |                   |                  |                               |               |               |               |                   |                  |                               |
| 1st trimester      | 7.3  | 3.0 | 4.1  | 0.31          | 0.35          | 0.43          | 0.43              | 0.40             | 0.32             | 1.00           |               |               |                   |                  |                               |
| 2nd trimester      | 7.3  | 3.0 | 3.9  | 0.33          | 0.33          | 0.35          | 0.39              | 0.39             | 0.35             | 0.64           | 1.00          |               |                   |                  |                               |
| 3rd trimester      | 7.3  | 3.0 | 3.8  | 0.40          | 0.36          | 0.33          | 0.42              | 0.40             | 0.39             | 0.62           | 0.63         | 1.00          |                   |                  |                               |
| Pregnancy average  | 7.3  | 3.0 | 3.7  | 0.43          | 0.43          | 0.46          | 0.49              | 0.49             | 0.47             | 0.66           | 0.65         | 0.69         | 1.00              |                  |                               |
| Child’s 1st year   | 7.3  | 3.0 | 3.7  | 0.39          | 0.41          | 0.40          | 0.43              | 0.42             | 0.44             | 0.59           | 0.62         | 0.71         | 0.72              | 1.00              |                               |
| Childhood cumulative exposure | 7.3  | 3.0 | 3.8  | 0.32          | 0.35          | 0.33          | 0.38              | 0.39             | 0.41             | 0.61           | 0.54         | 0.64         | 0.61              | 0.74              | 1.00              |

SD, standard deviation. IQR, interquartile range
Table S2. Hazard ratios (HR) and 95% confidence intervals (95% CI) for the associations between NO₂ (per IQR) and PM₂.₅ (per IQR) in one- and two-pollutant models over specific periods and childhood asthma risk.

| Exposure period                  | Obs. cases | NO₂          | PM₂.₅       |
|----------------------------------|------------|--------------|-------------|
|                                  |            | One pollutant model\(^a\) | Two pollutant model\(^b\) | One pollutant model\(^a\) | Two pollutant model\(^b\) |
|                                  |            | HR (95% CI)  | HR (95% CI) | HR (95% CI)  | HR (95% CI)  |
| 1\(^{st}\) trimester             | 28,201     | 1.02 (1.00 – 1.05) | 1.01 (0.99 – 1.04) | 1.00 (0.99 – 1.02) | 1.00 (0.98 – 1.02) |
| 2\(^{nd}\) trimester             | 27,621     | 1.06 (1.03 – 1.08) | 1.05 (1.02 – 1.07) | 1.07 (1.05 – 1.10) | 1.05 (1.03 – 1.07) |
| 3\(^{rd}\) trimester             | 27,104     | 0.98 (0.96 – 1.00) | 0.99 (0.96 – 1.01) | 1.01 (0.99 – 1.03) | 1.01 (0.98 – 1.03) |
| Entire pregnancy                 | 26,997     | 1.02 (0.99 – 1.05) | 1.01 (0.99 – 1.03) | 1.01 (0.98 – 1.04) | 1.00 (0.98 – 1.03) |
| First year of life               | 26,997     | 1.03 (1.00 – 1.06) | 1.01 (0.98 – 1.04) | 0.99 (0.98 – 1.01) | 1.00 (0.98 – 1.01) |
| Childhood cumulative exposure    | 26,105     | 1.00 (0.97 – 1.03) | 1.00 (0.97 – 1.03) | 1.00 (0.99 – 1.01) | 1.00 (0.98 – 1.01) |

\(^a\) Model adjusted for maternal age at delivery, infant sex, parity, breastfeeding status at the time of discharge, maternal smoking during pregnancy, maternal atopy, gestational age, birth weight, residential greenness exposure during pregnancy, dissemination area median family income, dissemination area proportion of population who are visible minority, dissemination area proportion of the adult female population aged 25-64 years old who completed postsecondary education, the average pregnancy exposure to the selected pollutant, the first year of life exposure to the selected pollutant and cumulative exposure after birth to the selected pollutant.

\(^b\) Includes all variables in the “one pollutant model” plus the other pollutant in the same exposure period.
Figure S1. Summary of administrative data linkages.

Source: ICES (ikn: encrypted health card numbers)
849,619 mother-infant pairs were linked to population & demographic databases and OASIS database using the unique ikn number. From 849,619 mother-infant pairs, 88,447 pairs were excluded due to postal codes of residence outside Ontario (i.e. less than 1% of all pregnancies), missing date of birth, sex, 6-digit postal code value and/or exposure estimates. A total of 222,864 participants could be assigned exposure estimates to both PM\textsubscript{2.5} and NO\textsubscript{2}.

**Figure S2.** Concentration-response curves (blue solid line) and 95% confidence intervals (grey shaded area) for the associations between NO\textsubscript{2} (a) and PM\textsubscript{2.5} (b) over the entire pregnancy and childhood asthma risk.