Online Supplement

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

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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].

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Table S1. Descriptive statistics of air pollution measures and Pearson correlation coefficients across time periods.

				NO_2 (ppb)						$PM_{2.5}$ ($\mu g/m^3$)					
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
NO_2 (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						
$PM_{2.5}$ ($\mu g/m^3$)															
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

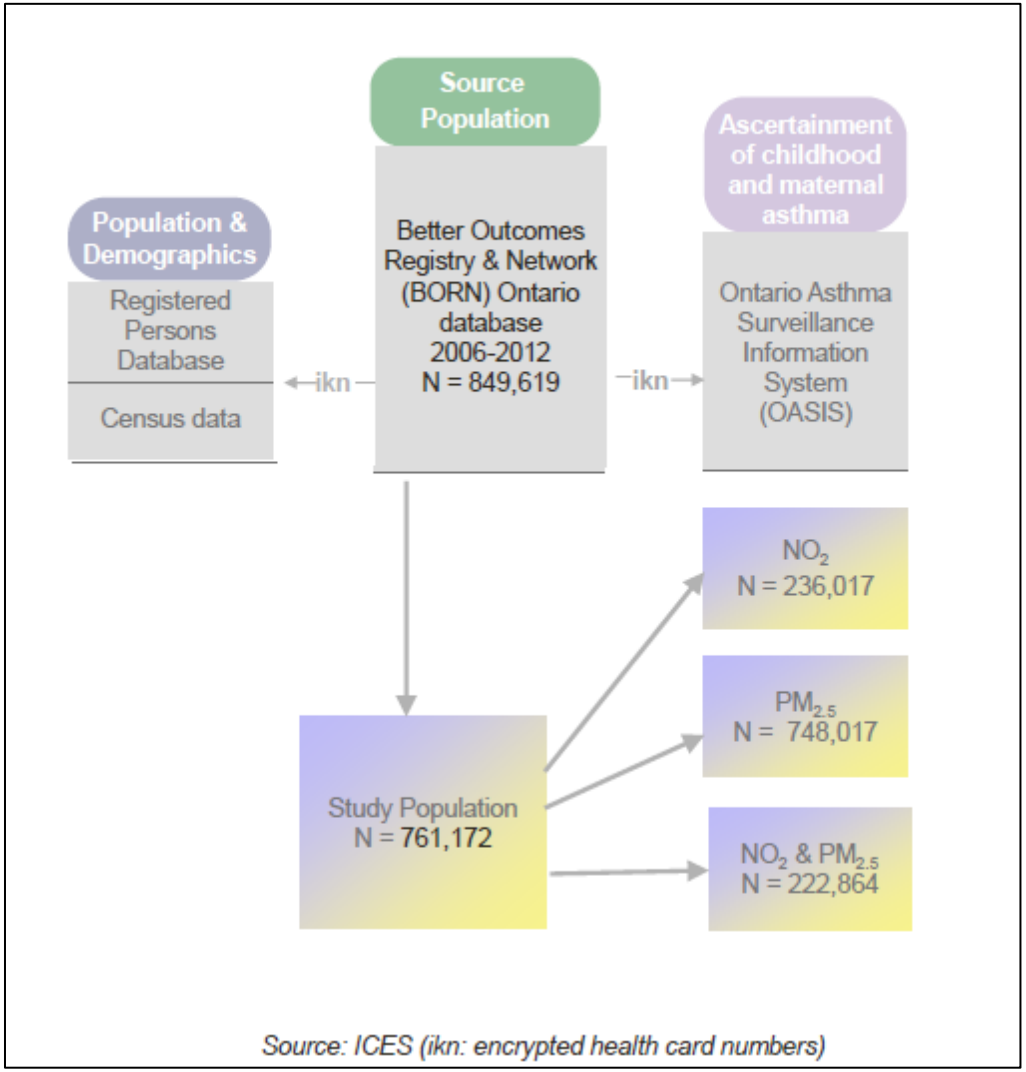
Table S2. Hazard ratios (HR) and 95% confidence intervals (95% CI) for the associations between NO_2 (per IQR) and $PM_{2.5}$ (per IQR) in one- and two-pollutant models over specific periods and childhood asthma risk.

Exposure period	Obs. cases	NO_2		$PM_{2.5}$	
		One pollutant model[a] HR (95% CI)	Two pollutant model[b] HR (95% CI)	One pollutant model[a] HR (95% CI)	Two pollutant model[b] HR (95% CI)
1st 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)
2nd 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)
3rd 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.



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 $PM_{2.5}$ and NO_2.

Figure S2. Concentration-response curves (blue solid line) and 95% confidence intervals (grey shaded area) for the associations between NO_2 (a) and $PM_{2.5}$ (b) over the entire pregnancy and childhood asthma risk.