Comparing childhood asthma incidence in three neighbouring cities in Southwestern Ontario: a 25-year longitudinal cohort study

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Data sharing: The data set from this study is held securely in coded form at ICES. While data sharing-agreements prohibit ICES from making the data set publicly available, access can be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS.

Abstract

Background: Air pollution is a known trigger for exacerbations among individuals with asthma, but its role in the development of new onset asthma is unclear. We aimed to compare the rate of new asthma cases in Sarnia, a city with high pollution levels, to two neighbouring regions in Southwestern Ontario.

Methods: Using a population-based birth cohort design, and linked health administrative data, we compared the risk of incident asthma between children born in Lambton (Sarnia) versus Windsor and London-Middlesex from April 1, 1993 to March 31, 2008. We used Cox proportional-hazards models to adjust for year of birth, and air pollutant exposures as well as maternal, geographical, and socioeconomic factors.

Results: Among 114,427 children, the highest incidence of asthma was in Lambton at 30.3, followed by Windsor at 24.4 and London-Middlesex at 19.8 per 1,000 person years ($p<0.0001$). The risk of asthma adjusted for socioeconomic and perinatal factors was lower in Windsor (HR = 0.71; 95% CI: 0.67,0.74) and London-Middlesex (HR = 0.60; 95% CI: 0.58, 0.63) compared to Lambton. Inclusion of air pollutants attenuated this difference in Windsor (HR = 0.79; 95% CI: 0.62, 1.01), and London (HR = 0.89; 95% CI: 0.64, 1.24) such that asthma risk was no longer different compared to Lambton.

Interpretation: We identified a higher incidence of asthma among children born in Lambton (Sarnia) relative to two other regions in Southwestern Ontario. We suggest higher air pollution levels (particularly $PM_{2.5}$) in the first year of life in this region, may be contributory.

Introduction

Asthma is the most common chronic disease in children with a Canadian prevalence of 15% - 25% .[1] Asthma exacerbations reduce quality of life, and are a leading cause of emergency room visits and hospitalizations.[2] While there are numerous known risk factors for asthma exacerbations,[3-12] identifying new modifiable risk factors for its onset could lead to primary prevention.

There is a clear association reported in the literature between asthma exacerbations among individuals with previously diagnosed asthma and air pollution [13,1415-17] but less certainty as to whether air pollution may be involved in the pathophysiology of new onset asthma.[18-21] This association has been challenging to study due to inadequate attribution of air pollution exposure owing to population mobility, and difficulties differentiating between workplace and residential exposures. Furthermore, most research has focused on adults[22,23], but asthma likely develops during gestation or within the first year of life.[24,25] Systematic reviews of the relationship between incident asthma in children and air pollution exposure have been inconclusive.[26]

In the province of Ontario, Canada, a spatial analysis of asthma prevalence between 2002-2006 identified a cluster of high rates among children ages 10-14 in and around the city of Sarnia.[27] Sarnia, in Southwestern Ontario, is home to the “Chemical Valley”, which accounts for 40% of Canada’s chemical processing facilities[28,29]. This region has been recorded as having the worst air quality in our country, with measurements above the World Health Organization recommended limits.[30] In recent years, this region has received media and government attention

due revelations of unreported toxic emissions and high levels of morbidity as a result of exposure to pollutants.[18,31,32]

We aimed to clarify the link between air pollution exposure and incident asthma in Canadian children. Using a population-based birth cohort design, we compared the rate of new asthma cases in Sarnia, to two neighbouring regions in Southwestern Ontario. We also examined if the risk of incident asthma attenuated with decreasing air pollution levels in more recent years.

Methods

Overview

We conducted a longitudinal birth cohort study spanning 25 years (April 1, 1993 to March 31, 2018) using linked health administrative databases available at ICES. We compared the incidence of asthma in children born between April 1, 1993 to March 31, 2009 in three neighbouring urban regions in Southwestern Ontario. The reporting of this study follows the Reporting of Studies Conducted Using Observational Routinely Collected Health Data (RECORD) guidelines for observational studies.[33]

Data Sources

In the province of Ontario, Canada (population 13 million) more than 99% are eligible for government funded health insurance through the Ontario Health Insurance Plan (OHIP). The OHIP number was used to link individuals to multiple health administrative datasets including the OHIP dataset, which contains information on all physician outpatient visits; the Ontario Registered Persons Database, which provides basic demographic information; and the Canadian

Institute of Health Information discharge abstract database (CIHI-DAD), which details all hospital admissions. The MOMBABY dataset is derived from CIHI-DAD and includes a record of all mothers linked to their Ontario-born children. The Ontario Marginalization (ONMarg) index[34,35] is a geographically based marker of socioeconomic status, consisting of four dimensions: residential instability, material deprivation, dependency and ethnic concentration.

These health administrative datasets were further linked to the Ontario Ministry of Environment air quality data[36] and Environment Canada's National Air Pollution Surveillance data[37], two publicly available datasets that provide information on air pollution levels across the province. These datasets were linked using unique encoded identifiers and analyzed at ICES. (Table S1).

Participants

We included all live in-hospital births within the Lambton (Sarnia is the major urban centre) Windsor and London-Middlesex Local Health Integration Network (LHIN) sub-regions over a15 year accrual period (between April 1, 1993 and March 31, 2009). For much of the study period, since 2006, LHINs were the health authorities responsible for regional administration of healthcare services in Ontario.[38] The three sub-regions were chosen for comparison as they align with previously conducted studies,[39] each of their major cities (Sarnia, Windsor and London) are separated by ≤200 kilometers (km), and they have similar climate and socioeconomic exposures. However, these sub-regions differ in their air pollution levels due to the major industries present in each. (See Supplement)

We excluded births if they occurred outside these sub-regions, or if the mother lived in a different sub-region in the one year prior to delivery (to establish perinatal exposure). We excluded deliveries of multiple births and births prior to 37 weeks gestation as these are known risk factors for asthma.[40] We further excluded deliveries where the mother was less than 14 years of age or older than 50 years, and infants who died or did not reside in the region of birth for at least one year (to establish early life exposure).

Exposures

Our primary exposure of interest was the geographic area of birth, namely, the LHIN sub-regions of Lambton, Windsor and London-Middlesex. This was determined using the child's postal code at birth (Table S2).

Secondary exposures included i) the fiscal year in which child was born as this would reflect ambient pollutant (and other) exposures present both in-utero and in the first year of life during the critical period for asthma susceptibility, and ii) ambient air pollutant concentrations (used as a proxy for air pollution exposure). Exposure measures for nitrogen dioxide (NO_2), ozone (O_3) and particulate matter 2.5 micrometers or smaller ($PM_{2.5}$) were assigned to each child based on their forward sortation area or city region of birth. Additional covariates reported to be associated with risk of childhood asthma were also included (see Supplement).

Outcomes

Our primary outcome was the physician-diagnosed incidence of asthma as identified using the Ontario Asthma Surveillance Information System (OASIS). OASIS has a sensitivity of 89% and specificity of 72% to detect asthma in children, and has been widely used to evaluate asthma rates and related health care burden in Ontario.[1,4,41-44] Children were followed for a maximum of 10 years to capture the majority of childhood asthma cases[45]. Our secondary outcome was persistent asthma beyond age 6. (see Supplement).

Statistical analysis

We compared baseline cohort characteristics between regions using one-way ANOVA and Chi square tests as appropriate. We constructed Kaplan Meier curves to examine the 10-year incidence of asthma, and compared regions using the log-rank test. Individuals were censored at the age of 10 or death. We used adjusted Cox proportional-hazards models to assess the relative difference in risk of asthma by age 10 in the three sub-regions, with Lambton as the reference. We adjusted models for maternal age, maternal asthma, sex, rural geography, neighbourhood material deprivation, neighbourhood ethnic concentration, caesarian section delivery, and fiscal year of birth. Due to recent declining pollution levels, we tested for an interaction between the sub-regions and year of birth using the log-likelihood ratio test, and if significant, reported results in four-year groupings (fiscal years 1993-1996, 1997-2000, 2001-2004, 2005-2008). For our secondary outcome, a second adjusted Cox proportional-hazards model was developed to examine the risk of persistent asthma.

To compare the risk of incident asthma attributable to NO_2, O_3, SO_2, or $PM_{2.5}$, four pre-defined sensitivity models were developed as above, but each with the additional inclusion of one pollutant exposure. In a final analysis, all pollutants were included the same model. Results are expressed as hazard ratios (HR) and 95% confidence intervals (CI). All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC), and we interpreted 2-tailed P-values <0.05 as statistically significant.

Ethics approval

This study was approved by the Children's Hospital of Eastern Ontario research ethics board.

Results

We identified 2,112,270 children who were born in hospital in Ontario between the fiscal years of 1993 to 2008. After excluding those born outside of the regions of interest and following exclusions for data integrity, a total of 114,427 children were retained (Figure 1), with 16,758 (14.6%) born in Lambton, 34,962 (30.6%) born in Windsor and 62,707 (54.8%) born in London-Middlesex.

The most notable differences in baseline population characteristics (Table 1) were the proportion of rurality, which was highest in Lambton at 27.2% of the population, and neighbourhood-level characteristics such as income quintile distribution, with evidence of lower socioeconomic status in Windsor, along with higher levels of ethnic concentration and material deprivation.

Air pollutant levels at birth differed between regions, with the highest NO_2 concentration seen in Windsor (34.9 parts per billion (ppb) ± 3.9), and the highest O_3 (41.8 ppb ± 1.9), $PM_{2.5}$ (23.6 ppb ± 2.8) and SO_2 (8.8 ppb ± 1.8) levels seen in Lambton. Air pollutant levels generally decreased over the study period, although levels of O_3 remained stable (Supplementary Figures 1A-1D).

The overall cumulative incidence of asthma by age 10 years was 22.6 per 1,000 person years, with the highest incidence in Lambton at 30.3, followed by Windsor at 24.4 and lowest in London-Middlesex at 19.8 per 1,000 person years ($p<0.0001$) (Figure 2).

We identified a significant interaction by birth year ($p<0.001$) (Table 2), although unadjusted and adjusted hazard ratios remained significant across the years, with risk estimates attenuated over time. The lowest risk of asthma persisted in London-Middlesex (adjusted HR in 2005-2008 birth years = 0.65, 95% CI: 0.60, 0.71), followed by Windsor (adjusted HR in 2005-2008 birth years = 0.67, 95% CI: 0.61, 0.74), compared to Lambton.

In our secondary analysis, we found that the adjusted risk of persistent asthma was still lowest in London-Middlesex (HR = 0.62, 95% CI: 0.59, 0.65), followed by Windsor (HR = 0.76, 95% CI: 0.72, 0.80), compared to Lambton (Table S3).

In sensitivity analyses the hierarchy of adjusted asthma risk between sub-regions was preserved, though the magnitude of the difference in asthma risk was reduced with the sequential addition of individual air pollutants, with the greatest risk reduction noted after the addition of PM2.5.

When combining all four air pollutants, the difference in adjusted asthma risk was further reduced and no longer significantly different between regions (Table 3).

Interpretation

In this population-based study comparing three cities in Southwestern Ontario with varied levels of air pollution over 25 years, we observed a significantly lower cumulative incidence of asthma in London-Middlesex and Windsor compared to Lambton (Sarnia). This difference was present after adjusting for multiple confounders associated with asthma risk, such as sex, socioeconomic factors and urban versus rural setting. While the risk of asthma reduced in more recent years, the hierarchy of adjusted asthma risk between sub-regions was preserved and remained significant. These findings remained robust when we examined for persistent asthma beyond the age of six. The difference in asthma risk estimates were most reduced with the addition of $PM_{2.5}$ and were no longer significant when all four air pollutants were included in the model.

Our results suggest that children in Sarnia have an increased risk of developing asthma which might be due to higher levels of air pollutants in this region. In our sample of over 100,000 children born in Southwestern Ontario over a 16-year period, we identified higher levels of $PM_{2.5}$ and SO_2 present in the first year of life for children born and living in the Lambton LHIN sub-region (with includes Sarnia). We also found that the decline in the risk of asthma in more recent years paralleled the concurrent decrease in air pollution.

Our results are similar to the few other studies that have explored and also identified a relationship between asthma incidence and air pollution exposure in children[15,16]. However, the natural experimental design of our study strengthens these previous observations by demonstrating an increased risk of asthma in comparison to regions (i.e. control cohorts) with lower air pollution levels. A recent study of children in California demonstrated reductions in asthma incidence concurrent with a reduction in air pollution[46] suggesting there may be a dose-response effect. While this previous study relied on patient/parent report of an asthma diagnosis (which may be unreliable), our study used a more valid physician-diagnosis of asthma for the outcome, and similarly showed reductions in asthma incidence as ambient air pollution levels have fallen in recent years. Reduced air pollution may not be the only reason for recent decreasing asthma incidence as lower rates of public smoking and increases in protective factors such as breast feeding may have also contributed. However, in our analyses that adjusted for all four air pollutant exposures in combination, the difference in asthma risk between regions was completely removed, lending further support to the likelihood of air pollution being an important mechanism in childhood asthma incidence.

Recent literature has focused on the effect of traffic-related air pollution on asthma development,[47-49,50] as the measured effects of industry related pollutants have been inconsistent in previous studies, perhaps due to inaccuracies in assignment of pollution exposure.[51,52,53] In our study we were able to sequentially analyze the difference in asthma risk between regions attributable to each individual type of air pollutant, and found that adjustment for exposure to NO_2 and O_3, compounds present in the atmosphere primarily due to air traffic pollution, only modestly reduced this difference. Adjustment for $PM_{2.5}$ significantly attenuated the difference in

asthma risk between London-Middlesex or Windsor versus Lambton, suggesting it may be the most contributory air pollutant to explain differences in asthma risk in this region. Although $PM_{2.5}$ and SO_2 are present in traffic-related air pollution, the largest sources in Sarnia are from petrochemical processing and smelting, where major industrial processes can be found. In this study, adjustment for SO_2 did not attenuate the difference in asthma risk. This may be due to the differences in exposure assignment; SO_2 exposure was obtained at a larger geographic level (city/region) and thus, this measure may be less accurate than the other pollutant exposures which were obtained at the smaller (neighbourhood) level.

A few recent studies have linked fine particulate matter ($PM_{2.5}$)[46] to new onset asthma both in the USA and globally. Within Canada, Buteau et al. examined the incidence of asthma in relation to proximity to industrial air pollution emitters in a population-based birth cohort, and found that the hazard of asthma incidence was proportional to increasing exposure to $PM_{2.5}$ and SO_2.[19] A cohort study by Clark et al, similarly demonstrated that the incidence of asthma in preschool children was proportional to the distance from industrial emitters within a 10 km radius of the child's residence at birth and during the first year of life.[18] These previous studies, despite their limited follow up duration and lack of adjustment for traffic-related air pollutants, support our current study.

Limitations

There are a number of strengths to this study including its population-based design, long observation period, and large sample size. One of the potential limitations is that our study design did not allow for individual measures of air pollution exposure; however, this lack of

individual measurement should have been addressed in our natural study design which allowed comparison of asthma incidence with otherwise comparable geographic regions with significantly lower overall ambient pollution levels. We were also limited in our ability to account for some potential unmeasured contributors to asthma risk, (e.g. environmental tobacco smoke, maternal breast-feeding, or allergen exposure), however our novel use of linked health administrative databases allowed us to account for others, such as socioeconomic status, and certain birth and perinatal risk factors.

Conclusions

We identified a higher incidence of asthma among children born in the Lambton (Sarnia) sub-LHIN region relative to two other regions in Southwestern Ontario. We observed that $PM_{2.5}$, an industrial pollutant found at highest levels in the Lambton sub-LHIN region may be contributing to this higher asthma risk. This study suggests that limiting early exposure to air pollution may be a strategy for primary prevention of asthma and could be confirmed in future studies.

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Table 1. Cohort Description

	Lambton LHIN sub-region *n =16,758*	Windsor LHIN sub-region *n =34,962*	London-Middlesex LHIN sub-region *n =62,707*	*P*-Value
Maternal characteristics at delivery date				
Age, yr, mean ± SD	27.94 ± 5.37	28.30 ± 5.47	29.11 ± 5.44	**<.001**
Age group, yr, N (%)				
15-29	10,203 (60.9%)	20,261 (58.0%)	31,930 (50.9%)	**<.001**
30-39	6,285 (37.5%)	14,029 (40.1%)	29,366 (46.8%)	
40-49	270 (1.6%)	672 (1.9%)	1,411 (2.3%)	
Rural geography, N (%)	4,557 (27.2%)	15 (0.0%)	3,264 (5.2%)	**<.001**
Income quintile				
1 - lowest	3,918 (23.4%)	10,971 (31.4%)	14,272 (22.8%)	**<.001**
2	3,408 (20.3%)	9,105 (26.0%)	13,397 (21.4%)	
3	3,394 (20.3%)	7,551 (21.6%)	12,723 (20.3%)	
4	3,406 (20.3%)	4,083 (11.7%)	12,277 (19.6%)	
5 - highest	2,509 (15.0%)	3,200 (9.2%)	9,887 (15.8%)	
missing	123 (0.7%)	52 (0.1%)	151 (0.2%)	
Residential instability, N (%)				
1 – least instability	2,391 (14.3%)	2,810 (8.0%)	9,436 (15.0%)	**<.001**
2	3,483 (20.8%)	4,783 (13.7%)	11,554 (18.4%)	
3	4,533 (27.0%)	6,985 (20.0%)	11,834 (18.9%)	
4	3,681 (22.0%)	11,184 (32.0%)	13,382 (21.3%)	
5 – most instability	2,670 (15.9%)	9,200 (26.3%)	16,501 (26.3%)	
Material deprivation, N (%)				
1 - least deprived	2,541 (15.2%)	3,993 (11.4%)	11,889 (19.0%)	**<.001**
2	3,319 (19.8%)	6,411 (18.3%)	10,960 (17.5%)	
3	3,400 (20.3%)	5,455 (15.6%)	13,039 (20.8%)	
4	3,114 (18.6%)	6,975 (20.0%)	13,119 (20.9%)	
5 – most deprived	4,384 (26.2%)	12,128 (34.7%)	13,700 (21.8%)	
Dependency, N (%)				
1 - lowest	1,543 (9.2%)	5,591 (16.0%)	15,393 (24.5%)	**<.001**
2	2,934 (17.5%)	7,869 (22.5%)	16,275 (26.0%)	
3	3,575 (21.3%)	7,872 (22.5%)	14,897 (23.8%)	
4	4,277 (25.5%)	8,810 (25.2%)	9,438 (15.1%)	
5 - highest	4,429 (26.4%)	4,820 (13.8%)	6,704 (10.7%)	
Ethnic concentration, N (%)				
1 - lowest	6,903 (41.2%)	3,509 (10.0%)	9,437 (15.0%)	**<.001**
2	4,688 (28.0%)	4,400 (12.6%)	11,755 (18.7%)	
3	3,435 (20.5%)	6,268 (17.9%)	17,248 (27.5%)	
4	1,553 (9.3%)	10,080 (28.8%)	15,731 (25.1%)	
5 - highest	179 (1.1%)	10,705 (30.6%)	8,536 (13.6%)	
Newborn characteristics				
Female, N (%)	8,224 (49.1%)	16,982 (48.6%)	30,543 (48.7%)	0.562
Low birth weight/preterm, N (%)	1,445 (8.6%)	3,104 (8.9%)	5,533 (8.8%)	0.622
Mean NO_2** (ppb), mean ± SD	28.4 ± 4.8	34.9 ± 3.9	28.5 ± 4.2	**<.001**
Mean O3** (ppb), mean ± SD	41.8 ± 1.9	39.6 ± 2.6	40.3 ± 2.0	**<.001**
Mean $PM_{2.5}$** (ppb), mean ± SD	23.6 ± 2.8	21.3 ± 1.5	17.74 ± 1.6	**<.001**

Mean SO_2** (ppb), mean ± SD	8.8 ± 1.8	6.6 ± 1.7	2.75 ± 0.9	**<.001**

* Low birth weight or preterm refers to infants born with low birth weight <2500 grams, small for gestational age, intrauterine growth restriction or preterm gestation <37 weeks. All diagnostic codes are detailed in Table S1

** NO_2 and O_3 data were available between 1996 – 2009; $PM_{2.5}$ data were available between 2003-2009; SO_2 data were available between 1993 – 2009. Pollution values were based on annual summaries, and assigned to children at the time (i.e. year) of birth and location of birth (i.e. residential FSAs or city of birth depending on the source of data).

NO_2 = nitrogen dioxide, O_3 = ozone, $PM_{2.5}$ = fine particulate matter, SO_2 = sulfur dioxide, SD = standard deviation, ppb = parts per billion

Table 2. Cox proportional-hazards estimates for the development of asthma by age 10 years

Birth (fiscal) years		HR (95% CI)	
		Unadjusted	Adjusted*
1993-1996	Lambton	REF	REF
	Windsor	0.68 (0.64-0.73)	0.6 (0.56-0.65)
	London-Middlesex	0.57 (0.54-0.61)	0.54 (0.51-0.58)
1997-2000	Lambton	REF	REF
	Windsor	0.84 (0.77-0.9)	0.77 (0.71-0.84)
	London-Middlesex	0.63 (0.59-0.68)	0.61 (0.56-0.66)
2001-2004	Lambton	REF	REF
	Windsor	0.9 (0.83-0.97)	0.8 (0.73-0.88)
	London-Middlesex	0.69 (0.64-0.75)	0.65 (0.6-0.71)
2005-2008	Lambton	REF	REF
	Windsor	0.85 (0.78-0.92)	0.67 (0.61-0.74)
	London-Middlesex	0.77 (0.71-0.83)	0.65 (0.6-0.71)
1993-2008 (all years)	Lambton	REF	REF
	Windsor	0.81 (0.78-0.84)	0.7 (0.67-0.73)
	London-Middlesex	0.66 (0.63-0.68)	0.61 (0.58-0.63)

*Adjusted for maternal age, maternal asthma, sex, rural geography, neighbourhood material deprivation, neighbourhood ethnic concentration, caesarian section delivery, fiscal year.
HR: Hazard Ratio; CI: Confidence Interval

Table 3. Association of individual air pollution exposures on adjusted Cox proportional hazards estimates for development of asthma by age 10 years

		HR (95% CI)
		Adjusted*
Model A: NO_2	Lambton	REF
	Windsor	0.72 (0.67-0.77)
	London-Middlesex	0.63 (0.60-0.66)
Model B: O_3	Lambton	REF
	Windsor	0.73 (0.69-0.77)
	London-Middlesex	0.62 (0.59-0.65)
Model C: SO_2	Lambton	REF
	Windsor	0.72 (0.68-0.75)
	London-Middlesex	0.64 (0.59-0.69)
Model D: $PM_{2.5}$	Lambton	REF
	Windsor	0.75 (0.69-0.82)
	London-Middlesex	0.71 (0.63-0.81)
Model E: all pollutants combined	Lambton	REF
	Windsor	0.79 (0.62-1.01)
	London-Middlesex	0.89 (0.64-1.24)

*Adjusted for maternal age, maternal asthma, sex, rural geography, neighbourhood material deprivation, neighbourhood ethnic concentration, caesarian section delivery, fiscal year.
HR: Hazard Ratio; CI: Confidence Interval
Cohorts are restricted to children with no missing pollution exposures (i.e. models A, B: N = 92,809; model C: N = 114,427; model D, E: N = 44,737).

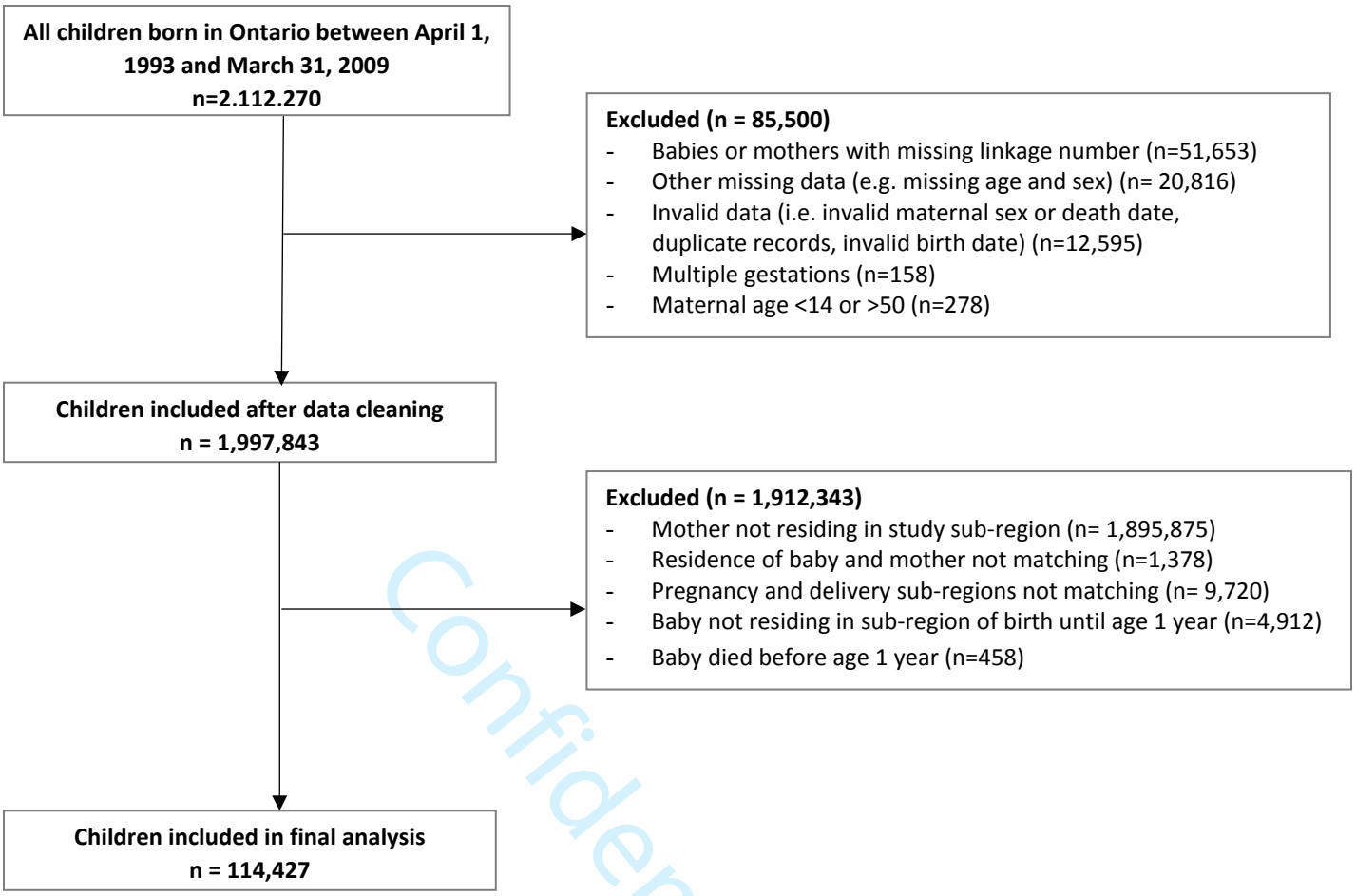


Figure 1. Cohort Inclusion/Exclusions Flow Chart

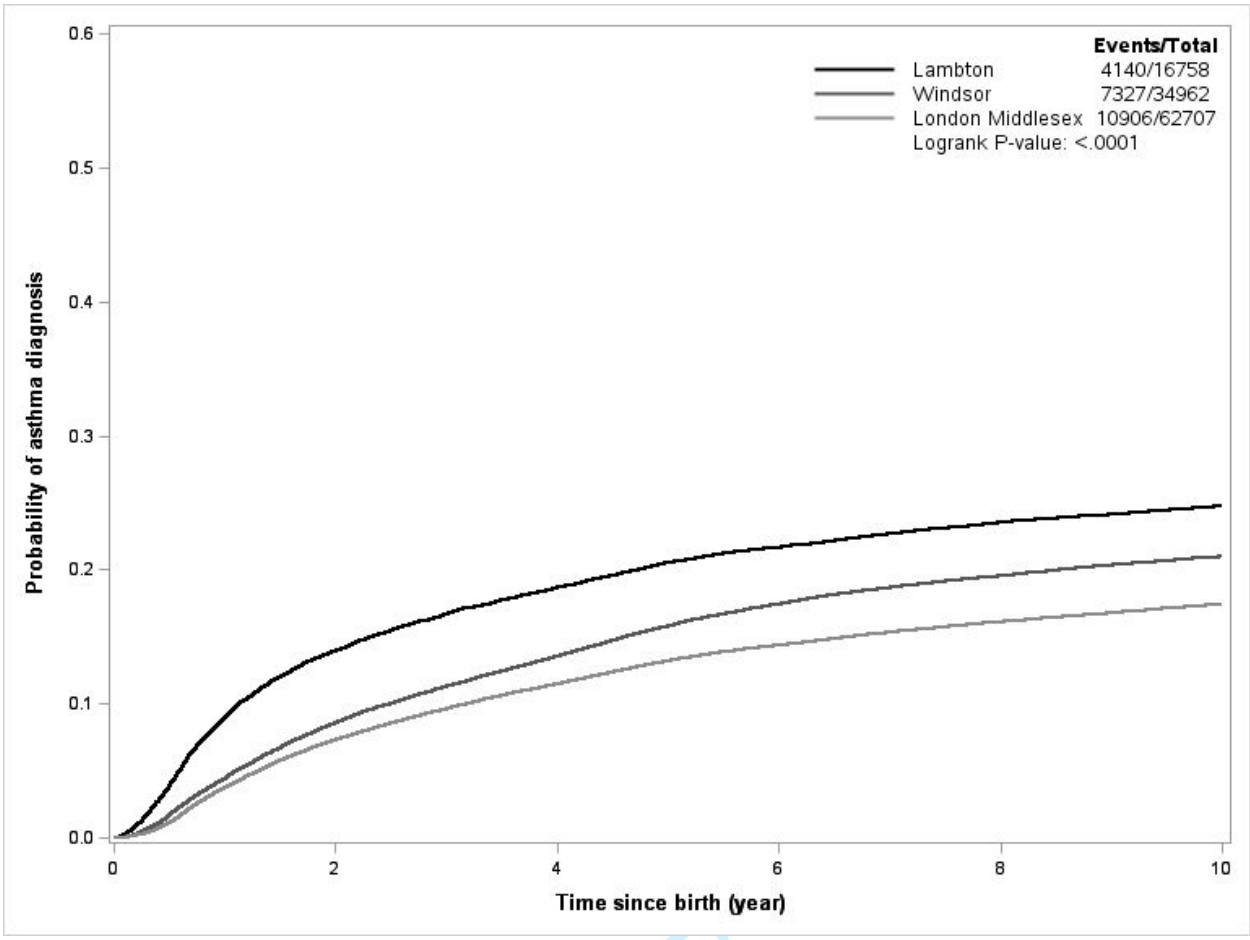


Figure 2. Probability of developing asthma by region of birth, censored at age 10 years

Online Supplementary Materials

Methods (supplemental)

Study Setting

A key difference between Sarnia, Windsor and London, Ontario, the three major urban centres within the study sub-regions of interest, is the major industry present in each. While Sarnia is a Canadian hub for petrochemical processing, the major industries in Windsor include automobile assembly plants, and scrap metal recycling. Windsor has high exposure to transboundary air and water pollution from Ohio, Illinois and, Michigan, and is also immediately downwind of major steel mills in Detroit, and 100 km down river from Sarnia. The city of London-Middlesex is the home of many branches of industry, corporate offices, medical and educational facilities. It is also a manufacturing, distribution and financial center, with less emphasis on manufacturing in the last few decades.

Secondary exposures

While NO_2 and O_3 are known to be markers of traffic related air pollution, SO_2, though also found in traffic related air pollution, is often used as a marker of industry related air pollution.[51] There are various sources for $PM_{2.5}$ including residential fireplace and wood stoves, pollen, industrial processes, as well as traffic.[52] ** NO_2 and O_3 data were available between 1996 – 2009; $PM_{2.5}$ data were available between 2003-2009; SO_2 data were available between 1993 – 2009.

Additional Covariates

Information on additional covariates that have been previously shown to be associated with risk of childhood asthma were also collected at the time of the child's birth including: sex, rural (community size <10,000 persons) versus urban location of residence, neighbourhood income quintile (approximated by linking the child's postal code at birth to the nearest Canadian census information), ONMarg index (with each of its four dimensions included separately in the multivariable logistic regression model), maternal age, maternal history of asthma, maternal diabetes, caesarian versus vaginal delivery, and preterm or low birthweight.

Secondary outcomes

Our secondary outcome, persistent asthma, was defined as those children with incident asthma who continued to have a subsequent health care encounter (outpatient visit or hospitalization) for asthma after the age of six years, or who newly developed asthma after the age of six years. This secondary outcome was explored due to the likelihood of asthma symptoms persisting in to adulthood in these children and specific definitions were chosen as per previous studies on phenotyping of asthma in children.[56]

Table S1. Database descriptions

Database	Description
Ontario Health Insurance Plan (OHIP) Claims History Database	The OHIP claims database contains information on inpatient and outpatient services provided to Ontario residents eligible for the province's publicly funded health insurance system by fee-for-service health care practitioners (primarily physicians) and "shadow billings" for those paid through non-fee-for-service payment plans. Billing codes on the claims (OHIP fee codes) identify the care provider, their area of specialization and the type and location of service. OHIP billing claims also contain a 3-digit diagnosis code - the main reason for the service - captured using a modified version of the ICD, 8th revision coding system. OHIP claims are well completed, but the validity of the diagnosis coding is highly variable.[1]
OHIP Registered Persons Database (RPDB)	The OHIP RPDB provides basic demographic information (age, sex, location of residence, date of birth, and date of death for deceased individuals) for those issued an Ontario health insurance number. The RPDB also indicates the time periods for which an individual was eligible to receive publicly funded health insurance benefits and the best known postal code for each registrant on July 1st of each year.
Discharge Abstract Database (DAD)	The DAD is compiled by the Canadian Institute for Health Information (CIHI) and contains administrative, clinical (diagnoses and procedures/interventions), demographic, and administrative information for all admissions to acute care hospitals in Ontario. At ICES, consecutive DAD records are linked together to form 'episodes of care' among the hospitals to which patients have been transferred after their initial admission. Prior to April 1, 2002, diagnoses (up to 16 on a given DAD record) are captured using the International Statistical Classification of Diseases, Injuries, and Causes of Death, 9th Revision (ICD-9) coding system and procedures (up to 10 on a given DAD record) are captured using the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP) coding system. Following April 1, 2002, diagnoses (up to 25 on a given DAD record) are captured using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada (ICD-10-CA) coding system and interventions (up to 20 on a given DAD record) are captured using the Canadian Classification of Health Interventions (CCI) coding system. In a hospital medical record reabstraction study of 14,500 hospital discharges from 18 hospital sites between April 2002 and March 2004, DAD records were demonstrated to have excellent agreement (over 99%) for nonmedical information such as demographic and administrative data. Regarding diagnoses, median agreement between the original DAD records

	and the reabstracted records for the 50 most common most responsible diagnoses was 81% (Sensitivity 82%; Specificity 82%).[2] The corresponding median agreement for the 50 most frequently performed surgical procedures was 92% (sensitivity 95%, positive predictive value 91%).
ICES Mother-Baby Linked Database (MOMBABY)	The ICES MOMBABY Database links the DAD inpatient admission records of delivering mothers and their newborns. From 2002 onward, this linkage is performed deterministically using a maternal-newborn chart matching number. Prior to 2002, mothers were linked to their children by matching on the institutions they were admitted, their postal codes, and their admission/discharge dates.
Ontario Ministry of Environment air quality data	The Ontario Ministry of Environment has a network of 38 outdoor air monitoring stations providing hourly concentrations of pollutants including, ozone, nitrogen dioxide and fine particulate matter.
Environment Canada national air pollution surveillance data (NAPS)	The NAPS database provides long-term air quality data for the purpose of monitoring and assessing the quality of outdoor air across Canada. Currently there are 286 sites in 203 communities in every province and territory providing continuous measurement of sulphur dioxide, nitrogen dioxide, ozone, fine particulate matter and carbon monoxide.
Ontario Marginalization Index (ONMarg)	This is a neighbourhood level measure of socioeconomic status that comprises multiple factors that may adversely impact health. The four dimensions of the Ontario Marginalization Index are i) residential instability: includes measures of crowding, marital status, etc., ii) material deprivation: incorporates education, low income and unemployment, iii) dependency: measures the proportion of seniors or young children versus employed individuals and iv) ethnic concentration: reflects the proportion of visible minorities or recent immigrants.[3] Each dimension of the Ontario Marginalization Index is divided into quintiles (Quintile 1 = least amount of marginalization).[3]

1. Williams J, Young W. A summary of the quality of health care administrative databases in Canada. In: Goel V, Williams J, Anderson G, Blackstien-Hirsch P, Fooks C, Naylor C, editors. Patterns of Health Care in Ontario: The ICES Practice Atlas. 2nd Edition. Ottawa: Canadian Medical Association; 1996. 339-346.

2. Juurlink D, Preyra C, Croxford R, Chong A, Austin P, Tu J et al. Canadian Institute for Health Information Discharge Abstract Database: A Validation Study. 2006. Toronto, Institute for Clinical Evaluative Sciences. Ref Type: Report

3. Matheson FI, Dunn JR, Smith KL, Moineddin R, Glazier RH. Development of the Canadian Marginalization Index: a new tool for the study of inequality. *Canadian journal of public health Revue canadienne de sante publique.* 2012;103(8 Suppl 2):S12-16.

Table S2. Health administrative codes used to define exposure variables and outcomes

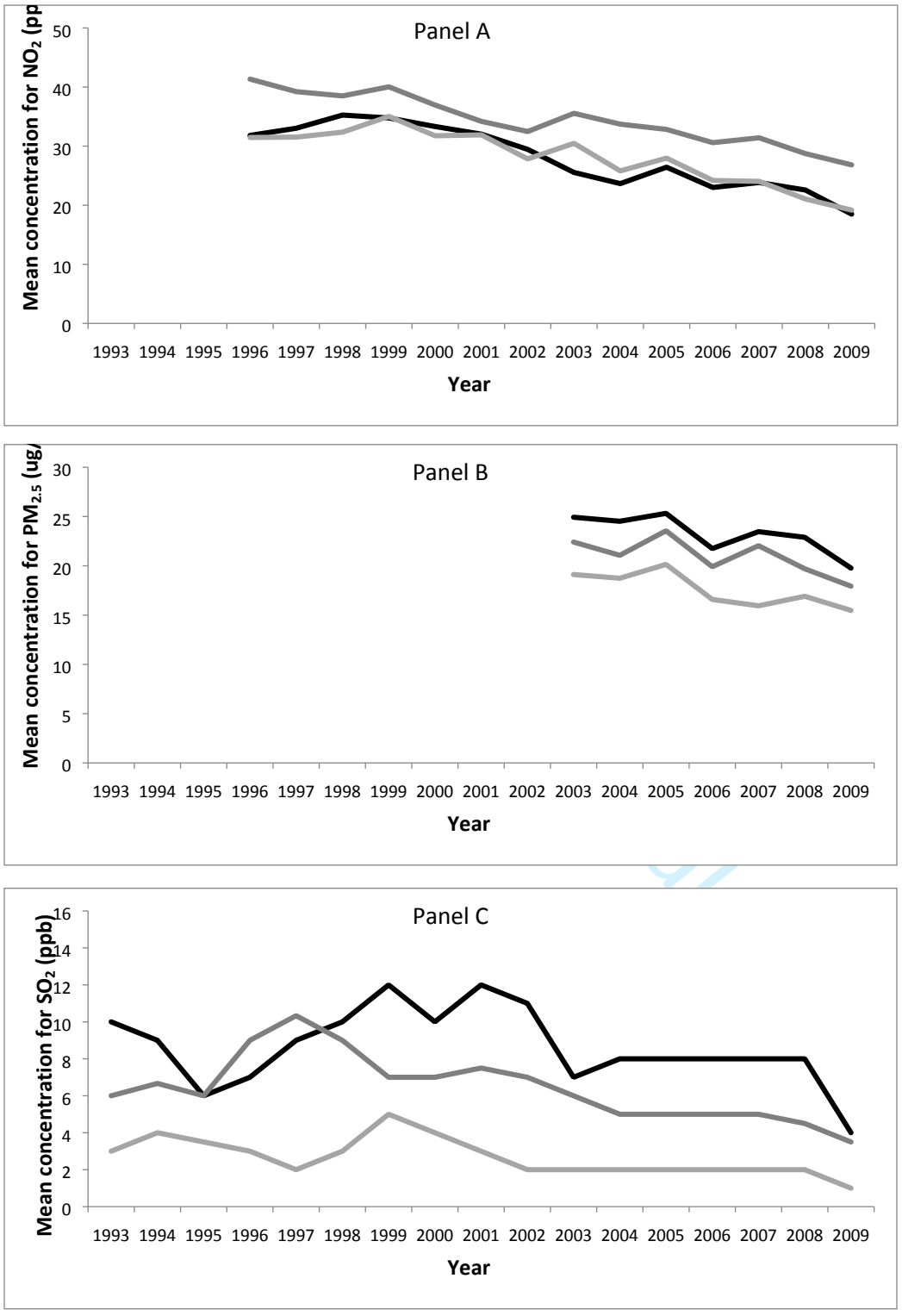
Variable	Database	Codes	Details
Live births	MOMBABY	B_date	
Local Health Integration Network (LHIN) sub-region	Registered Persons Database (RPDB)	PSTLCODE	Used postal code recorded on a child's OHIP registration at birth within Lambton, Windsor and London-Middlesex sub-regions
Asthma	Ontario Asthma Surveillance Information System (OASIS)	ICD9: 493 ICD10: J45, J46 OHIPdx: 493	One hospital admission with a most responsible diagnosis of asthma, or two outpatient physician visits for asthma within a two-year period
Air pollutant concentrations	Ontario Ministry of Environment Air Quality Data Environment Canada National Air Pollution Surveillance Data	Nitrogen dioxide Sulfur dioxide Particulate matter ≤2.5	

ICD = International Classification of Diseases, OHIP = Ontario Health Insurance Plan, MOMBABY = an ICES derived dataset that includes all mothers linked to their hospital-born children,

Table S3. Cox proportional hazards estimates for the development of persistent asthma

	HR (95% CI)	
	Unadjusted	**Adjusted***
Lambton		REF
Windsor	0.88 (0.84-0.93)	0.76 (0.72-0.80)
London-Middlesex	0.68 (0.65-0.71)	0.62 (0.59-0.65)

Persistent asthma = asthma diagnosis after age 6 and/or asthma diagnosis prior to age 6 and subsequent asthma health care encounter after age 6. Cohort N = 114,427; Number of events excluded = 7,593 children who did not have an asthma related health care encounter after the age of 6 years. Number of asthma events = 14,780.
*Adjusted for maternal age, maternal asthma, sex, rural geography, neighbourhood material deprivation, neighbourhood ethnic concentration, caesarian section delivery, fiscal year.
HR: Hazard Ratio; CI: Confidence Intervals


Panel A
Mean concentration for NO2 (pp
50
40
30
20
10
0
1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009
Year
Panel B
Mean concentration for PM2.5 (ug
30
25
20
15
10
5
0
1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009
Year
Panel C
Mean concentration for SO2 (ppb)
16
14
12
10
8
6
4
2
0
1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009
Year

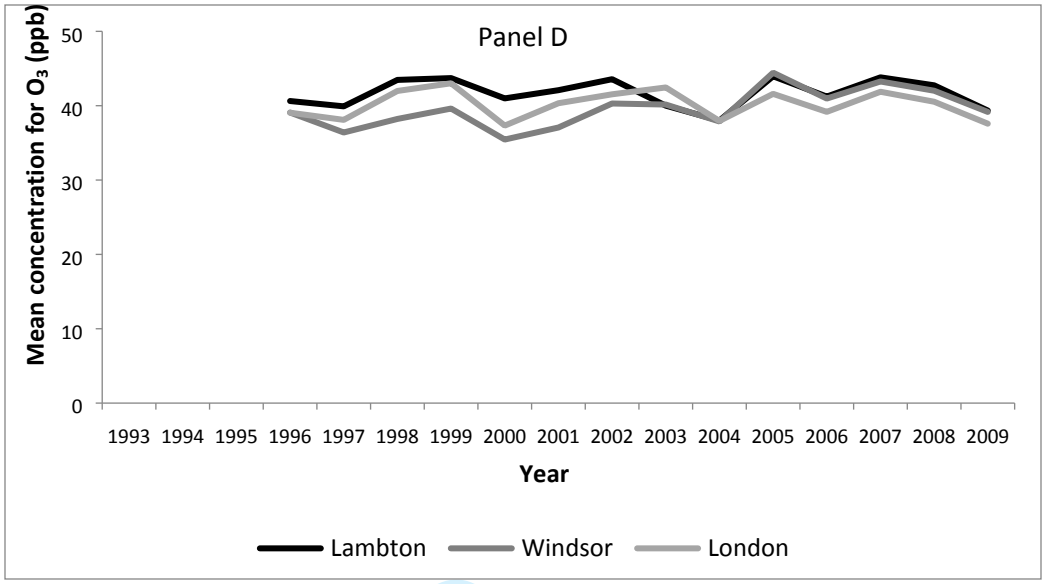


Figure S1. Mean air pollution concentrations for A) Nitrogen dioxide, NO_2, B) fine particulate matter, $PM_{2.5}$, C) Sulphur dioxide, SO_2, and D) Ozone, O_3 assigned to children at the time of birth and summarized by city.

Pollution values are based on annual summaries of pollution levels by forward sortation area (NO_2, $PM_{2.5}$, O_3) or city (SO_2). NO_2 and O_3 data were available between 1996 – 2009; $PM_{2.5}$ data were available between 2003-2009; SO_2 data were available between 1993 – 2009. ppb: part per billion; ug/m3: microgram per cubic meter