Université de Montréal

Industrial Air Pollutant Emissions and Respiratory Health Effects in Children

par Xiaohui Geng

Département de médecine sociale et préventive, École de Santé Publique
de l'Université de Montréal

Thèse présentée en vue de l'obtention du grade de Philosophiae Doctor (PhD)
en Santé publique, option Épidémiologie

Janvier, 2020

© Xiaohui Geng, 2020

Université de Montréal
Faculté des études supérieures et postdoctorales

Cette thèse intitulée:

Industrial Air Pollutant Emissions and Respiratory Health Effects in Children

Présentée par :
Xiaohui Geng

a été évaluée par un jury composé des personnes suivantes :
Helen Trottier, Présidente-rapporteure
Audrey Smargiassi, Directrice de recherche
Maryse Bouchard, Membre du jury
Cheryl Peters, Examinatrice externe

ABSTRACT

Asthma is a main chronic childhood disease. It has been associated with exposure to outdoor air pollutants from remote regional and traffic sources. Pollutant mixtures from industrial sources and their effects may not be the same as those from traffic and regional sources. Yet contrary to associations between pollutants from these sources and asthma in children, associations with community exposures to industrial air pollutant emissions have not been systematically assessed. Furthermore, although substantial reductions in industrial emissions of fine particles ($PM_{2.5}$) and sulphur dioxide (SO_2) have been noted in industrialized countries over the past decades, associations between the geographic and the temporal variations of industrial air pollutant emissions and the variation of asthma morbidity in children have been understudied.

In this dissertation, we aimed to investigate the association between asthma morbidity and industrial air pollutant emissions in children. We first assessed the association between exposure to industrial air pollutant emissions and asthma in children based on available evidence. We then assessed the associations between the spatial and the temporal variations in industrial air pollutant emissions and the spatial and temporal variations in asthma morbidity in Québec.

For the first objective, we searched bibliographic databases to identify studies on the association between children's exposure to air pollution from industrial point-sources and asthma-related outcomes, including: asthma, asthma-like symptoms, wheezing and bronchiolitis. Where possible, we performed random-effects meta-analyses of results. For the second and third objectives, we conducted spatial and temporal ecological analyses based on data for small geographic areas (n=1386) in the province of Québec. For the second objective, we related industrial emissions of $PM_{2.5}$ and SO_2 obtained from the National Pollutant Release Inventory and other variables such as regional levels of $PM_{2.5}$, median annual household income and the percentage of the population of children exposed to Environmental Tobacco Smoke (ETS) to the total count of asthma hospital admissions in children younger than 13 years of age per small area (data from the database MED-ÉCHO: Maintenance et exploitation des données pour l'étude de la clientèle hospitalière), for the years 2002 to 2011, with negative binomial General Additive Models. For the third objective, we related industrial emissions of $PM_{2.5}$ and SO_2, as well as

other environmental and sociodemographic variables mentioned above, to the yearly numbers of asthma onset cases in children aged <13 years from the database QICDSS (Québec Integrated Chronic Disease Surveillance system) over the years 2002 to 2011, with fixed effects negative binomial models (statistical models for panel data). In these models, regional $PM_{2.5}$ levels were from satellite data, the median income from the census, ETS was from a pan Canadian survey and traffic related air pollution was estimated with kilometers of major roads in small areas.

The systematic review highlighted that half of the selected published studies used a cross sectional study design, ecological binary proximity was the main exposure method used in 15 out of 36 articles, while asthma outcomes were diverse but mainly collected by questionnaires and healthcare services. The pooled odds ratios (ORs) from the meta-analysis from case-crossover studies with hospitalisation for asthma and bronchiolitis in children younger than 5 years old was 1.02 (95%CI: 0.96-1.08; I^2 = 56%) per 10 ppb increase in the daily mean concentration of SO_2; for $PM_{2.5}$, the pooled ORs was 1.02 (95%CI: 0.93-1.10; I^2 = 56%) per 10 $\mu g/m^3$ increase in the daily mean concentration. In cross-sectional studies on the prevalence of asthma and wheezing in children, pooled ORs in relation to residential proximity to industries were 1.98 (95%CI: 0.87-3.09; I^2 =71%) and 1.33 (95%CI: 0.86-1.79; I^2= 65%), respectively. Results of the spatial and temporal ecological analyses suggested that industrial emissions of $PM_{2.5}$ and SO_2 were not related to asthma morbidity. The relative risk (RR) for asthma hospital admissions from the multivariate spatial model was 1.0009, per increase of one ton of $PM_{2.5}$ (95%CI: 0.9982-1.0037); the RR for SO_2 per increase of one ton was 0.9999 (95%CI: 0.9997-1.0001). Additionally, the RR for new asthma onset cases in children from the multivariate temporal models were 0.99 per 1000 tons of SO_2 (95%CI: 0.99-1.00) and also 0.99 per 100 tons of $PM_{2.5}$ (95%CI: 0.98-1.00). Nonetheless, there was a 3.29% decrease in the rate of cases (95%CI: 2.44-4.14) per 1 ug/m^3 decrease in the regional $PM_{2.5}$ levels.

Overall, our results suggest that industrial air pollutant emissions have limited influence on asthma morbidity. This is in contrast with what would be expected based on the published literature that report effects of air pollution from sources other than industries. The results suggest that better exposure assessment and better study designs should be adopted in future

studies to assess the association between asthma morbidity and industrial air pollutant emissions in children.

Keywords: Air pollution, industries, childhood asthma, environmental and socioeconomic factors.

RÉSUMÉ

L'asthme est une des principales maladies chroniques de l'enfance. Elle a été associée à l'exposition aux polluants de l'air extérieur provenant de sources régionales éloignées et du trafic routier. Les mélanges de polluants provenant de sources industrielles et leurs effets peuvent ne pas être les mêmes que ceux provenant du trafic routier et de sources régionales. Pourtant, contrairement aux associations entre les polluants provenant de sources régionales et liées au trafic et l'asthme chez les enfants, les associations avec l'exposition des communautés aux émissions de polluants atmosphériques industriels n'ont pas été systématiquement évaluées. En outre, bien que des réductions substantielles des émissions industrielles de particules fines ($PM_{2.5}$) et de dioxyde de soufre (SO_2) aient été constatées dans les pays industrialisés au cours des dernières décennies, les associations entre les variations géographiques et temporelles des émissions industrielles de polluants atmosphériques et la variation de la morbidité de l'asthme chez les enfants ont été sous-étudiées.

Dans cette thèse, nous avons étudié l'association entre la morbidité liée à l'asthme et les émissions de polluants atmosphériques industriels chez les enfants. Nous avons d'abord évalué l'association entre l'exposition aux émissions industrielles de polluants atmosphériques et l'asthme chez les enfants sur la base des écrits scientifiques. Nous avons ensuite évalué les associations entre les variations spatiales et temporelles des émissions industrielles de polluants atmosphériques et la variation spatiale de la morbidité liée à l'asthme au Québec.

Pour le premier objectif, nous avons consulté des bases de données bibliographiques afin d'identifier les études sur l'association entre l'exposition des enfants à la pollution atmosphérique provenant de sources industrielles et l'asthme, en incluant les symptômes d'asthme, la respiration sifflante et la bronchiolite. Lorsque possible, nous avons effectué des méta-analyses des résultats avec effets aléatoires. Pour le deuxième et le troisième objectifs, nous avons effectué des analyses écologiques spatiales et temporelles à partir de données pour de petites zones géographiques (n=1386) dans la province de Québec. Pour le deuxième objectif, nous avons mis en relation les émissions industrielles de $PM_{2.5}$ et de SO_2 obtenues à partir de l'Inventaire national des rejets de polluants et d'autres variables telles que les niveaux régionaux

de $PM_{2.5}$, le revenu annuel médian des ménages et le pourcentage de la population d'enfants exposés à la fumée de tabac secondaire (FTS) avec le nombre total d'admissions à l'hôpital pour asthme chez les enfants de moins de 13 ans par petite région (données de la base MED-ÉCHO: Maintenance et exploitation des données pour l'étude de la clientèle hospitalière), pour les années 2002 à 2011, avec des modèles binomiaux négatifs additifs généralisés. Pour le troisième objectif, nous avons mis en relation les émissions industrielles de $PM_{2.5}$ et de SO_2, ainsi que les autres variables environnementales et sociodémographiques mentionnées ci-dessus, avec le nombre annuel de nouveaux cas d'asthme chez les enfants âgés de <13 ans de la base de données SISMACQ (Système intégré de surveillance des maladies chroniques du Québec) pour les années 2002 à 2011, avec des modèles binomiaux négatifs à effets fixes (modèles statistiques pour les données de panel). Dans ces modèles, les niveaux régionaux de $PM_{2.5}$ provenaient de données satellitaires, le revenu médian du recensement, la FTS d'une enquête pancanadienne et la pollution atmosphérique liée au trafic a été estimée avec les kilomètres de routes principales dans de petites zones.

La revue systématique a montré que la moitié des études publiées sélectionnées utilisaient un devis d'étude transversal, que la proximité binaire écologique était la principale méthode d'exposition utilisée dans 15 des 36 articles, tandis que les résultats de l'asthme étaient divers mais principalement recueillis par questionnaires et à partir des services de santé. Les rapports de cotes (RC) combinés de la méta-analyse des études cas-croisés avec hospitalisation pour asthme et bronchiolite chez les enfants de moins de 5 ans étaient de 1.02 (IC95% : 0.96-1.08; I2 = 56%) par 10 ppb d'augmentation de la concentration moyenne quotidienne de SO_2 ; pour les $PM_{2,5}$, les RC combinés étaient de 1.02 (IC95% : 0.93-1.10; I2 = 56%) par 10 µg/m3 d'augmentation de la concentration moyenne quotidienne. Dans les études transversales sur la prévalence de l'asthme et la respiration sifflante chez les enfants, les RCs combinés, pour la proximité résidentielle à des industries étaient respectivement de 1.98 (IC95% : 0.87-3,09; I2 = 71%) et 1.33 (IC95% : 0.86-1.79; I2 = 65%). Les résultats des analyses écologiques spatiales et temporelles ont suggéré que les émissions industrielles de $PM_{2.5}$ et de SO_2 n'étaient pas liées à la morbidité liée à l'asthme. Le risque relatif (RR) pour les admissions à l'hôpital pour l'asthme selon le modèle spatial multivarié était de 1.0009, par augmentation d'une tonne de $PM_{2.5}$ (95%IC : 0.9982-1.0037); le RR pour le SO_2 par augmentation d'une tonne était de 0.9999

(95%IC: 0.9997-1.0001). En outre, le RR pour les nouveaux cas d'asthme chez les enfants à partir des modèles temporels multivariés était de 0.99 pour 1000 tonnes de SO_2 (95%IC : 0.99-1.00) et également de 0.99 pour 100 tonnes de $PM_{2.5}$ (95%CI : 0.98-1.00). Néanmoins, on a constaté une diminution de 3.29 % du taux de cas d'asthme (95%CI : 2.44-4.14) pour chaque diminution de 1 ug/m3 des niveaux régionaux de $PM_{2.5}$.

Dans l'ensemble, nos résultats suggèrent que les émissions industrielles de polluants atmosphériques ont une influence limitée sur la morbidité liée à l''asthme. Ceci contraste avec ce à quoi on pourrait s'attendre sur la base de la littérature publiée qui fait état des effets de la pollution atmosphérique provenant de sources autres que les industries. Les résultats suggèrent qu'une meilleure évaluation de l'exposition et de meilleurs devis d'études devraient être adoptés dans les études futures pour évaluer l'association entre la morbidité liée à l'asthme et les émissions industrielles de polluants atmosphériques chez les enfants.

Mots clés: Pollution de l'air, industries, asthme infantile, facteurs environnementaux et socioéconomiques.

TABLE OF CONTENTS

LIST OF TABLES

Chapter 3.1

Chapter 3.2

Chapter 3.3

LIST OF FIGURES

Chapter 3.1

Appendix

Chapter 3.2

Figure 1. Map of residuals of asthma hospitalization rates in children 0-12 years from the model with a constant only, by CLSCs & CTs in Québec during the years 2002-2011. The absolute values of residuals of asthma hospital admissions rates are transformed to values between zero and one, with a division by the maximum residual rate value per area (CTs/CLSCs).

Figure 2. Maps of absolute residuals of asthma hospitalization rates in children 0-12 years by CLSCs & CTs in Québec during the years 2002-2011 of univariate model with A) median income as independent variable. B) coordinate as independent variable.

Appendix

Figure A. Map of geographic sectors (CT and CLSC)

Figure B. A) Pearson and B) Spearman correlations between predictors.

Figure C. Relationships between rate of asthma hospital admission and predictors: A) Univariate models, B) Multivariate models with industrial emission (PM2.5&SO2), C) Multivariate models with coordinate (x, y) & industrial emission (PM2.5&SO2).

Figure D. The calculation of variogram of spatial autocorrelation of different models. A) Empty model, B) Without coordinate & with industrial ($PM_{2.5}$&SO_2), C) With coordinate & with industrial ($PM_{2.5}$&SO_2).

Chapter 3.3

Figure 1. Time trend of percentage of annual rates of variables from 2002 to 2011, averaged for all areas.

Appendix

Figure B. A) Pearson and B) Spearman correlations of annual predictor variables for small areas (CT/CLSC).

LIST OF ABBREVIATIONS

AHD: administrative health data

ATS-DLD: American Thoracic Society and the Division of Lung Diseases

BC: black carbon

CCHS: Canadian Community Health Survey

CDC: Centers for Disease control and prevention

CI: confidence interval

CLSCs: centre local de services communautaires

CO: carbon monoxide

CTs: census tracts

DAs: dissemination areas

DMTI: Digital Mapping Technologies Inc.

ECRHS: European Community Respiratory Health Survey

EBM: Evidence-Based Medicine

ED: Emergency department

EPA: United Stated Environmental Protection Agency

ER: emergency room

ERV: emergency room visit

ETS: environmental tobacco smoke

FIPA: Fichier d'inscription des personnes assurées

GAM: generalized additive models

HIRD: the HealthCore Integrated Research Database

HR: hazard ratio

ICD: International Classification of Disease

IDW: inverse distance weighted

INSPQ: Institut national de santé publique du Québec

IQR: interquartile range

ISAAC: The International Study of Asthma and Allergies in Childhood

LISA: Local Indicator of Spatial Autocorrelation

MED-ÉCHO: Maintenance et exploitation des données pour l'étude de la clientèle hospitalière

NDVI: standardized difference vegetation index

NO_2: nitrogen dioxide

NO_X: nitrogen oxide

NPRI: National Pollutant Release Inventory

O_3: ozone

ORs: odds ratios

PCs: postal codes

PCCF: postal code conversion file

PHAC: the Public Health Agency of Canada

PM: particulate matters

$PM_{2.5}$: particulate matters with diameter less or equal to 2.5 μm

PM_{10}: particulate matters with diameter less or equal to 10 μm

PR: prevalence ratio

QICDSS: Québec Integrated Chronic Disease Surveillance system

REML: Restricted Maximum Likelihood

RH: relative humidity

RR: relative risk/risk ratio

SD: standard deviation

SES: socioeconomic status

SEP: socioeconomic position

SHS: second hand smoke

SO_2: sulfate dioxide

SOx: sulphur oxides

SOB: shortness of breath

Ta: near-surface air temperature

TRI: toxics related inventory program

TSP: total suspended particulates

UK: the United Kingdoms

VOC: volatile organic compounds

WHO: World Health Organization

ACKNOWLEDGEMENTS

I would first like to thank my supervisor, Dr. Audrey Smargiassi, who helped me to form the objectives, and provided me with financial support and academic advice during my study. I am grateful for your time and guidance when revising this dissertation, for sharing your expertise and experience.

I would also like to thank my co-authors from the Public Health Department in Montréal and the National Institute of Public Health of Québec for their help and involvement. Thank you, Stéphane Buteau, for your precious contribution on the systematic review paper. I would like to thank Michel Fournier for all the hours spent providing statistical support and for always being available. I thank Sophie Goudreau for preparing all the hospital admission data, and geographic frameworks. I also would like to thank Philip Gamache for the preparation of the asthma onset data.

Finally, I would like to thank my family for their invaluable support. Especially, William Knowles, my husband who travelled across Canadian and American borders to provide financial and emotional support. I would also like to thank my mom who came over from China to help me with my new born daughter, so I could continually work on my projects.

CHAPTER 1. INTRODUCTION

1.1 Introduction

Epidemiological studies on both long-term and short-term exposures to ambient air pollutants have reported associations with asthma in children, a subgroup of the population particularly vulnerable for physiological reasons (Subbarao et al. 2009a). Most studies on the effects of air pollution have been performed in urban areas and focused either on regional air pollutants like fine particles ($PM_{2.5}$) or on traffic-related air pollutants like nitrogen oxides (NOx).

Certain industries such as those related to resource extraction and smelting are important emitters of air pollutants like $PM_{2.5}$ and NOx and contribute to both local and regional air pollutant concentrations. In addition to $PM_{2.5}$ and NOx, major industries like refineries, power plants and smelters are important emitters of sulfur dioxide (SO_2) (Environnement et Lutte Contre les Changements Climatiques 2011). Human clinical, epidemiological and animal toxicological studies have also indicated that short term exposure to SO_2 could induce asthma-like problems such as bronchoconstriction and decrease of lung functions, which could lead to Emergency Room (ER) visits and hospitalizations (EPA 2017).

In Québec, the industrial sector (e.g. aluminum industries, non-ferrous metals industries, etc), emitted nearly 81.2% of SO_2, as well as produced 39.1% of $PM_{2.5}$ in 2008 (Environnement et Lutte Contre les Changements Climatiques 2011; more recent data are not available). In locations where specific industries are main contributors to local air pollution, pollution mixture and particulate composition can be characteristic of these point sources and differ from non industrial areas (EPA 2019; Seagrave et al. 2006). Thus in industrial areas or in proximity to

industries, health effects of air pollutants may differ from those in non industrial areas, due to these differences in pollution mixtures and particulate composition.

This dissertation focuses on the association between industrial air pollutant emissions and asthma outcomes in children. This thesis includes a Background section, a Methods section, a Results chapter, and a Discussion. The Background section presents information on asthma and asthma-like symptoms and its risk factors including air pollutants, but health risks of industrial air pollution are presented in the Results section. The Results section includes, in addition to a literature review (Geng et al. 2019) investigating the associations between industrial air pollution and asthma and asthma-like symptoms, two articles on the spatio-temporal varaitions in industrial air pollutant emissions and asthma morbidity (asthma onset and asthma hospital admissions) in children in Québec, Canada.

1.2 Background

1.2.1 Asthma morbidity

1.2.1.1 Description of asthma

Asthma is defined as a chronic disorder attacking all the age groups, especially children. The main symptoms of asthma are the recurrences of breathlessness and wheezing at various frequencies, and the physiological characteristic of asthma is the inflammation of the airways in the lungs. (WHO 2020).

Asthma onset is defined through clinical diagnosis, and the diagnosis of asthma is the first step of asthma management (NIH 2007). Due to the similarity between asthma and other respiratory conditions, asthma can be difficult to diagnose properly (Ontario Ministry of Health and Long-Term Care 2000). Therefore, asthma diagnosis is a complex process, and it generally combines the medical history and physical examination including pulmonary function testing (spirometry) (NIH 2007). Pulmonary function testing is the most important indicator for asthma diagnosis in children aged five or older since it is an objective assessment. Differential diagnoses of asthma are recommended in case of confusion, namely in children under age 5, due to the infeasibility of pulmonary function testing (NIH 2007).

In asthma cases, asthma exacerbations are defined as "acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, and chest tightness, or some combination of these symptoms, characterized by decreases in expiratory airflow and objective measures of lung function (spirometry and peak flow). Severe exacerbations, i.e. asthma attacks, can lead to emergency room (ER) visits or hospitalizations (NIH 2007).

1.2.1.2 Geographic variation of asthma morbidity in children

Published information on asthma morbidity and its geographic variation pertains to various types of data on asthma and asthma-like symptom prevalence (current or ever), incidence and exacerbations, based on questionnaires (e.g. have you ever been diagnosed by a doctor as having asthma; wheeze in last 12 months) or medico-administrative data (e.g. algorithm to identify new cases based on health services used for asthma), from different regions, with diverse socio-

economic contexts (Mallol et al. 2013, Mahboub et al. 2012, PHAC 2018, Ouédraogo et al. 2018).

Due to dramatic increases in asthma morbidity in children in western and developing countries, the International Study of Asthma and Allergies in Childhood was initiated in 1991 to investigate asthma, rhinitis and eczema in children (ISAAC 2017). The first phase of the ISAAC study documented variations in asthma morbidity in 56 countries worldwide using standardized questionnaires in two age groups of children (13-14 and 6-7 years). Between countries, the variation of the prevalence of current asthma-like symptoms (e.g. wheeze in the last 12 months) was as high as 15-fold. Subsequently, Lai et al. (2009) reported global variations in the prevalence and severity of asthma symptoms based on the ISAAC Phase Three surveys in children aged 13-14 years in 97 countries, and in children aged 6-7 years in 61 countries between 2000 and 2003. The prevalence of asthma-like symptoms (wheeze in the past 12 months) was lowest in regions of China and India in age groups of 13-14 years and 6-7 years respectively (Tibet, 13-14 years old: 0.8%; Jodhpur, 6-7 years old: 2.4%); and the highest values of 32.6% and 37.6 % were found in New Zealand (Wellington) in the age group 13-14 years old, and in Costa Rica in the age groups 6-7 years old, respectively (Lai et al. 2009). Lai reported that the prevalence of current wheeze was higher in high income countries (Lai et al. 2009). In contrast to the prevalence of current asthma-like symptoms which was reported as higher in "Westernized" countries, higher prevalence rates of severe asthma symptoms were reported in low income countries (Lai et al. 2009). The Global Asthma Report (2018) highlighted similar trends for asthma mortality (associated with severe symptoms).

There is limited information on asthma incidence and its geographic variation in children. Even in Canada, information on its geographic variation is not available for children. However, age standardized incidence rates varied in Canada from 722.3 cases per 100,000 individuals to 262.5 cases per 100,000 individuals between provinces and territories for the year 2011-2012.

1.2.1.3 Temporal variation of asthma morbidity

Besides spatial variations in asthma morbidity, there also appears to be large temporal inter-annual variations and intra-annual variations (seasonal). Published information on the temporal variation of asthma morbidity has also used various types of data on asthma (e.g. Questionnaires on ever or current asthma and symptoms, administrative health data), from different regions, with diverse socio-economic contexts. Some studies showed that the trends of asthma prevalence and incidence were increasing in some regions or countries, nevertheless, some studies showed that the trends were decreasing or stabilizing in other regions or countries over the past few decades (Pearce et al. 2007, The Global Asthma Report 2018).

To investigate the time trend of asthma and asthma-like symptoms, the ISAAC study Phase One was repeated with the Phase Three surveys, and reported that the changes in current asthma, current asthma-like symptoms and asthma severity were small (Pearce et al. 2007). Worldwide, the current asthma-like symptoms increased on average by 0.06% per year in the 13-14 years age group, and by 0.13% per year in the 6-7 years age group, respectively. However, different regions showed different patterns of time trends in asthma and asthma-like symptom prevalence. For example, in English language countries, current asthma-like symptom prevalence declined (-0.51 and -0.09%) in both age groups (6-7 and 13-14 years); however, an increase in children

reporting to have had asthma at some time in their lives (ever asthma) was also reported (respectively 0.28% per year and 0.18% per year in the two age groups) (Pearce et al. 2007).

The Global Asthma Network (2018) also drew a global picture of asthma time trends among children of high-income countries in terms of self-reported prevalence, hospital admission rates and mortality rates for asthma. During the period of 1955-2010, self-reported asthma per 100 children consistently increased from 4 to 15; the asthma admissions per 1000 children increased from 1 to 7.3 during the period of 1955-1988, then declined sharply from 7.3 to 2 during the period of 1988-2010; asthma mortality per 1,000,000 children increased from 2.2 in 1955 to 7.2 in 1967, and then mostly declined in the following years, till the mortality rate was 1.9 per 1,000,000 in 2010 (The Global Asthma Report 2018).

On a national level, studies have also investigated the time trend of asthma morbidity in children. The Public Health Agency of Canada (2018) reported, based on medico-administrative data, that in the 1-9 age group, the prevalence of asthma was highest (13.8%) in 2002-2003 and 2003-2004 and then declined from 13.8% to 10.4% through to 2011-2012. In the age group of 10-19 years old, the prevalence of asthma consistently increased from 9.4% to 19.3% over the period of 2000-2001 to 2011-2012. (PHAC 2018). Although not only pertaining to children, the time trend of age-standardized prevalence of diagnosed active asthma among Canadians (based on medico-administrative data), was generally declining during this period with the highest prevalence value of 2.8 in 2000-2001, and the lowest prevalence value of 2.3 in 2011-2012 (PHAC 2018). In Canada, between 2000-2001 and 2011-2012, the incidence rates of diagnosed asthma among Canadian in age groups 1-9 years and 10-19 years also declined from 2472.9 and

944.1 per 100,000 population to 1730.5 and 467.4 per 100,000 population, respectively (PHAC 2018).

Besides inter-annual time trends in asthma morbidity, intra-annual time trends (seasonal) also exist. In the province of Ontario, for example, for the period of 2003 to 2013, Larsen et al. (2016) reported that rates of asthma emergency department (ED) visits in children (highest in age groups of 0-4 years and 5-9 years) were highest in September; ED visits may include new asthma cases, but also severe exacerbations of prevalent cases. An American retrospective observational cohort study, based on the HealthCore Integrated Research Database (HIRD) between January 1st 2007 and December 31st 2010 investigating seasonal variations of asthma exacerbations, also reported that in children of 6-17 years, the rate of asthma exacerbations peaked in mid-fall, and the fall peak was particularly pronounced in October/November (Gerhardsson de Verdier et al. 2017).

1.2.2 Determinants of asthma morbidity

1.2.2.1 Introduction

Among respiratory health outcomes, asthma is a major concern due to the enormous burden on health care usage, and economic cost (Ehteshami-Afshar et al. 2016). To reduce the overall burden of asthma, the prevention of asthma onset and control of asthma exacerbations are important. To reach this goal, it is essential to identify the causes or risk factors of asthma incidence and exacerbations.

Observational epidemiological studies on individuals identified non-modifiable factors, such as genetic and host factors, and modifiable risk factors, such as socioeconomic and environmental factors, as determinants related to asthma onset (Subbarao et al. 2009b). According to Subbarao et al. (2009a), indoor and outdoor air pollution are the most important environmental factors associated with asthma onset in children. Environmental and socioeconomic conditions have also been identified as main risk factors for asthma exacerbations (Kopel et al. 2014, Kanchongkittiphon et al. 2015, Orellano et al. 2017, Weichenthal et al. 2016).

Although genetic factors may be main risk factors for asthma in children, these factors are generally non-modifiable. Therefore, the section that follows focuses on the impacts of nongenetic risk factors, such as socioeconomic status (SES) factors like income, and environmental factors like environmental tobacco smoke (ETS) (e.g. second hand smoke), outdoor air pollution, and also vegetation, and walkability, which can influence air pollution exposures. Such factors can be modified through behavioral changes (e.g. smokers producing ETS), policy making and implementation of regulations.

1.2.2.2 Socioeconomic Status (SES)

SES is an important public health determinant. To date, individual or household income and education have been the most used indicators for SES (Darin-Mattsson et al. 2017), while some regional complex deprivation indices were developed such as Pampalon deprivation index in Québec, Canada (Pampalon et al. 2014).

Many studies have reported correlations between SES and asthma (prevalence, incidence and exacerbations) (Uphoff et al. 2015, Gupta et al. 2018). Uphoff et al. (2015) reviewed 183 selected articles, and reported that the adjusted odds ratio for the prevalence of asthma for people of the lowest SES compared with the highest SES was 1.11 (95% CI, 1.09-1.14). Although this review study did not separate asthma in children and adults, the result was mainly drawn based on children since the majority of the selected articles were for children.

There are also studies that reported associations between SES and asthma incidence. A cohort study conducted in Sweden, for example, provided evidence that children born from lower income families had a higher risk of asthma onset in the first year of life; the hazard ratio (HR) was respectively, 1.19 (95% CI 1.09-1.31) for asthma incidence (defined as >=1 asthma diagnosis), and 1.17 (95% CI 1.08-1.26) for asthma incidence (defined as >=2 medications) by comparing to the highest parental income level (Gong et al. 2014). Moreover, this study reported that children born with lower educated parents had a higher risk of asthma onset regardless of age, compared to children born with college-educated parents; the HRs for inpatients (asthma hospital admissions) and outpatients (outpatient department and specialist visits) diagnosis were respectively 2.07 (95% CI, 1.61-2.65) and 1.32 (95% CI, 1.18-1.47) in children born with the lowest parental education (Gong et al. 2014). Another study performed in Australia that adopted a longitudinal method reported that children who chronically lived in low-income environments from birth, had a higher risk to develop persistent asthma; the association between low family income and asthma was OR=2.21 (95% CI, 1.17, 4.17) versus “never low income” (Kozyrskyj et al. 2010).

Even in Canada, a newly published Canadian cohort study using a material deprivation index (based on high school graduation, lone parent families, government transfers, unemployment, low income, and homes needing major repairs), as an SES indicator, reported an adjusted association (HR=1.11, 95% CI, 1.09-1.13) between high birth neighborhood deprivation and asthma incidence versus low birth neighborhood deprivation (Simons et al. 2019).

SES is not only a risk factor for asthma incidence; asthma exacerbations have also been related to SES. In their study, Simons et al. (2019) reported that children with high neighborhood deprivation in any year of life were more likely to encounter a healthcare visit for asthma than those with low neighborhood deprivation (OR=1.03; 95% CI, 1.02-1.05).

Many studies have also shown that in asthmatic children, poor asthma control, based on symptoms from questionnaires or based on health services use, is more noticeable in children of low SES (Kopel et al. 2014, Ungar et al. 2011). According to Kopel et al. (2014), asthmatic children in impoverished areas and inner-cities have poorer control, due to poor access to primary care and maintenance medications.

SES is also a major concern as a covariate when analysing associations with environmental risk factors, since it is related to both asthma onset and exacerbations and to environmental exposures according to previous studies (Disano et al. 2010, Almqvist et al. 2005). For example, SES is related to ETS and traffic-related air pollution (Hiscock et al. 2012).

1.2.2.3 Indoor air pollution

Indoor air pollution has been associated with asthma morbidity (WHO 2019b). According to the World Health Organization (WHO), 2018, the sources of indoor air pollution vary with economic conditions and geographic locations. (WHO 2019b). Around 3 billion people living in low and middle-income countries use solid fuels on open fires or traditional stoves to cook and heat their homes, which produce high levels of indoor health damaging air pollutants (e.g. $PM_{2.5}$ and carbon oxide (CO)) due to insufficient burning process. Studies have correlated these indoor air pollutants with asthma morbidity in children (Thacher et al. 2013, Forno et al. 2015, Schei et al. 2004, Lowe et al. 2017).

In contrast, solid fuel and open fires are not the sources of indoor air pollutants of main concern in developed countries. A review conducted by Kanchongkittiphon et al. (2015) based on studies from 69 selected articles (mainly for developed countries) summarized the relationships that exist between indoor environmental exposures and exacerbation of asthma. According to this review, 1) House dust mite allergens, cat allergens, cockroach allergens, and ETS have sufficient evidence for causation; 2) Dog allergens, fungi, dampness or dampness-related agents, and NO_2 from indoor combustion sources have sufficient evidence for association; 3) Domestic birds, formaldehyde (nonoccupational), and some fragrances have limited or suggestive evidence for association; 4) other indoor environmental exposure such as houseplants, pollen indoors, etc. have inadequate or insufficient evidence for association.

Regarding asthma development and indoor air pollution, the associations between dampness, mold, and dampness-related agents (e.g. microorganisms) have been investigated extensively.

A review study reported non-conclusive results on the development of asthma, while most studies reported that these pollutants were positively associated with asthma exacerbations as mentioned above (Mendell et al. 2011).

Among indoor environmental factors, ETS is, however, the main concern for asthma exacerbations and development in children (Subbarao et al. 2009a, Wang et al. 2015, Silvestri et al. 2015). Burke et al. (2012) performed a systematic review and meta-analysis on the relationship between prenatal and passive tobacco smoke exposure at different stages of childhood and incidence of asthma. The meta-analysis reported an overall ~20% increased risk of asthma onset for ETS exposure vs no exposure. The results from four sub-categories (prenatal maternal smoking, maternal smoking, paternal smoking, household smoking) were respectively: 1) OR=1.85 (95% CI, 1.35-2.53) in children aged <=2, and OR=1.23 (95% CI, 1.12-1.36) in children aged 5-18 years exposed to prenatal maternal smoking; 2) OR=1.20 (95% CI, 0.98-1.46) in children aged 5-18 years exposed to maternal smoking; 3) OR=1.34 (95% CI, 1.23-1.46) in children aged 3 to 4 years exposed to paternal smoking; 4) OR=1.21 (95% CI, 1.00-1.47) in children aged 3 to 4 years and OR=1.30 (95% CI, 1.04-1.62) in children aged 5 to 18 years exposed to household smoking (Burke et al. 2012).

According to Statistics Canada, in recent years, the exposure of children to ETS in the home has been reduced due to the declination of the prevalence of smoking and the increased restrictions on indoor smoking (Statistics Canada 2019). However, there are still significant numbers of children exposed to ETS (Statistics Canada 2019). According to Health Canada, in year 2011,

7.2% of Québec children younger than 12 years old were exposed to ETS at home, which was the highest in Canada (Health Canada 2012).

1.2.2.4 Outdoor air pollution

Main sources of outdoor air pollutants include road traffic, industrial emissions, agriculture and domestic consumption of fuels (EPA 2019a). Outdoor air pollution/ambient air pollution can be categorized as regional and local pollution. The American Meteorological Society defined regional air pollution as pollutants that "have been emitted from all sources in a region and have had time to mix, diffuse from their peak concentration, and undergo physical, chemical, and photochemical reactions. The size of a region usually incorporates one or more cities, and is on the order of 100 to 10 000 km^2". Local air pollution is related to local sources like road traffic and industries (American Meteorological Society 2018).

Particles and gases such as ozone (O_3) and oxides of sulphur and nitrogen (SO_x and NO_x) are defined as the main outdoor ambient air pollutants in Canada (Government of Canada 2017). Primary particles are directly from emissions sources (e.g. from industries); secondary particles are secondary products from different precursor gases such as sulphates, nitrates, and ammonia. These precursor gases go through a series of chemical and physical reactions to form different particulate matters (EPA 2019b). Therefore, secondary particles are made of diverse chemical substances including water soluble ions, trace metals, elemental and organic carbon and organic compounds (Yin et al. 2008). Moreover, particles are classified into different categories ($PM_{10,}$ $PM_{2.5,}$ and ultrafine particles) according to the diameter of the particles: Respectively, PM_{10} have a median diameter of 10 µm; $PM_{2.5}$ have a median diameter of 2.5 µm; "Ultrafine particles"

have a diameter smaller than 0.1 micrometers (EPA 2019b). These particles can be from different sources. In general, roadways and industries are the main sources of PM_{10} (EPA 2019b). Ultrafine particulate matter is mainly from combustion; the largest sources of ultrafine particle mass are fuel combustion from motor vehicles and stationary sources, as well as some miscellaneous processes like charbroiling, petroleum refining, and waste burning (EPA 2019b). As for NO_x, SO_x, and O_3, road traffic and industries produce NO_x, and subsequently, NO_2 forms from reactions with ground-level O_3, and $PM_{2.5}$ (EPA 2019d); Ground level O_3 is a secondary product of other air pollutants such as NO_x and volatile organic compounds (VOC) in the presence of sunlight (EPA 2019c). SO_x are mainly from industries like power plants, smelters and refineries and industrial activities like hydrocarbon extraction (EPA 2019e);

In some areas, industrial activities can be important sources of local atmospheric pollution. Furthermore, ambient air pollution in industrial areas may different from ambient air pollution in general urban areas. Seagrave and colleagues emphasized that local outdoor air pollution affected by industrial emissions may substantially differ to that of urban settings in terms of concentrations and composition, which could lead to differential effects (Seagrave et al. 2006). For example, in Montréal East, an industrial area of the island that housed refineries and a number of other industries in past decades, higher levels of SO_2 and benzene have been reported, compared to the urban core of the city (RSQA 2007). Particulate composition and size have also been reported to differ between urban and industrial settings. For example, Taiwo et al. (2014) showed that the $PM_{2.5}/PM_{10}$ ratio was higher in urban than in industrial areas, due to higher levels of coarse particles in industrial areas. The presence of secondary aerosols was also higher in urban than in industrial areas; elemental compositions of particles also differed between sites

(Taiwo et al. 2014). In terms of the composition of $PM_{2.5}$, the study conducted by Kundu et al. (2014) for example, indicated that the city of Davenport, which was heavily industrialized, had worse air quality than other locations, and the main air pollutant was $PM_{2.5}$ composed of higher levels of trace metals (e.g. Fe, Zn and, Pb).

Both long term and short-term exposures to ambient air pollutants have been associated with respiratory health effects like asthma onset and exacerbation in children (EPA 2019). Most studies on the effects of air pollutants have been performed in urban areas and focused either on regional air pollutants like $PM_{2.5}$ or on traffic-related air pollutants like NO_x (Tetreault et al. 2016, EPA 2019a, EPA 2019c).

Regarding asthma exacerbations, a systematic review based on 22 selected articles using a case-crossover observational design showed that in children (aged 0 to 18 years), outdoor air pollutant exposure (NO_2, SO_2, $PM_{2.5}$) was related to severe asthma exacerbations (per increase in 10 ug/m3, OR for NO_2=1.040, 95% CI, 1.001-1.081; OR for SO_2=1.047, 95% CI, 1.009-1.086; OR for $PM_{2.5}$=1.022 (95% CI, 1.000-1.045) (Orellano et al. 2017). Severe exacerbations were based on ER visits and/or hospital admissions. Several epidemiological time series analyses have also reported positive associations between daily ambient air pollution (mainly $PM_{2.5}$ and NO_2 levels) and increases in the number of ER visits and hospitalizations for respiratory causes in children. For example, in Ontario, Canada, Weichenthal et al. (2016) reported that an interquartile (5.92 ug/m^3) increase in the 3-day mean of $PM_{2.5}$ levels was related to a 7.2% (95% CI, 4.2-10) increase in ER visits for asthma in children younger then 9 years (Weichenthal et al. 2016). Meanwhile, Samoli et al. (2011) reported that a same day increase in PM_{10} (of 10 ug/m^3)

was associated with a daily percent increase of 2.54 (95% CI, 0.06-5.08) in asthma hospital admissions in children aged 0-14 years in Athens (Samoli et al. 2011). Besides severe exacerbations based on such medico-administrative data, studies on symptoms from questionnaires also suggest that exposure to pollutants such as $PM_{2.5}$ and NO_2 exacerbates asthma (Dales et al. 2009, Weinmayr et al. 2010, Rodriguez-Villamizar et al. 2015).

Long-term adverse respiratory health effects of $PM_{2.5}$ and NOx in urban areas, such as the onset of asthma and the decrease in lung function have also been documented (Tetreault et al. 2016; EPA 2019b; EPA 2019d). While the role of air pollution in the development of asthma is still unclear, findings from a recent systematic review and meta-analysis by Khreis et al. (2017) suggests that childhood exposure to traffic-related air pollutants may contribute to the development of childhood asthma. Khreis et al. (2017) reported positive associations between exposure to black carbon (BC), NO_2, NOx, $PM_{2.5}$ and PM_{10} and asthma development in children (1.08, 95% CI, 1.03-1.14 per 0.5×10^{-5} m^{-1} increase in BC; 1.05, 95%CI, 1.02-1.07 per 4 $\mu g/m^3$ increase in NO_2;, 1.48, 95%CI, 0.89-2.45 per 30 $\mu g/m^3$ increase in NOx; 1.03, 95%CI, 1.01-1.05 per 1 $\mu g/m^3$ increase in $PM_{2.5}$; 1.05, 95%CI, 1.02-1.08 per 2 $\mu g/m^3$ increase in PM_{10}).

Studies have also assessed associations between pollutants from industries and asthma onset and exacerbation (based on asthma diagnosis and asthma-like symptom prevalence and incidence), and varied results have been observed. Yet these associations between community exposures to industrial air pollutant emissions and asthma morbidity in children have not been systematically assessed. We present a systematic review of these studies in Chapter 3.

1.2.2.5 Susceptibility of children to indoor and outdoor air pollution

Studies have shown that children are the most susceptible population to effects of air pollution on asthma. Children's physiological characteristics, and their daily living environment, as well as daily activities could make them particularly susceptible to environmental risk factors of asthma (WHO 2008). Physiologically, the growth and development of the respiratory system continue from birth. Compared to adults, children have physiological characteristics such as underdeveloped pulmonary alveoli and capillaries, narrow airways, high resting metabolic rate and rate of oxygen consumption per unit body weight (Moya et al. 2004). Indoor air pollution (e.g. ETS) and outdoor air pollution (e.g. particulates and ozone) during these growth periods can have adverse consequences on both structure and function of the lung (Dietert et al. 2000). Physically, children have lower breathing zones comparing to adults due to smaller sizes. For example, the indoor concentration of airborne pesticide following pesticide applications are always highest closest to the floor, where children live (Gurunathan et al. 1998). Young children would be particularly affected by indoor air pollutants since they spend most time at home (WHO 2019b). Furthermore, children older than 5 years old are more physically active, and spend more time outdoors than adults, which may increase their exposure to outdoor pollutants (Moya et al. 2004). Children also typically experience a greater exposure to outdoor air pollution as compared to adults because of their higher respiratory volume relative to their body mass (Gilliland et al. 1999, Dixon et al. 2002, Schwartz et al. 2004, Bateson et al. 2008, Goldizen et al. 2016). Different age groups of children could also have different effects of exposure due to other differences in their daily activities. For example, studies have shown that high ozone levels decreased the growth in lung function in year-round athletic children and increased asthma onset in children who participated in three or more sports (McConnell et al. 2002).

1.2.2.6 Other determinants

Neighborhood vegetation and walkability can also influence susceptibility of children to air pollution and their subsequent effects on asthma morbidity. Indeed, some studies suggest that neighborhood walkability may encourage the practice of physical activity which in turn may increase outdoor pollution exposure. However, inconsistent results exist regarding the impact of walkable neighborhood on air pollution exposure and asthma outcomes (McConnell et al. 2002, Simons et al. 2017).

Furthermore, atmospheric pollutants may be removed by urban trees and other vegetation (e.g. through dry deposition), but vegetation (e.g. pollen) could be an underling factor of seasonal asthma exacerbations. Therefore, not all studies consistently support the positive impact of urban vegetation as exposure to allergenic vegetation may contribute to asthma exacerbations (Setälä et al. 2013). Lambert et al. (2017) conducted a systematic review and meta-analysis to assess the association between residential greenness and asthma in children and adolescents, and summarized that the selected studies reported inconsistent effects (a protective effect, a detrimental effect, or no associations) of residential greenness on asthma morbidity (asthma-like symptoms or diagnosed asthma). Moreover, in this review study, the meta-analysis based on studies adopting similar measures of residential greenness showed no significant overall association between residential greenness and asthma morbidity. However, this result was not convincing given the high heterogeneity (Lambert et al. 2017). Another review study performed by Hartley et al. (2020) based on published articles since 2017 on the association between greenness and asthma morbidity also reported that the relationship between greenness and asthma morbidity is inconsistent, and further research is needed.

1.2.3 Determinants of spatio-temporal variation in asthma morbidity

Besides individual epidemiological observational studies on the various asthma risk factors, ecological studies have also been performed to document factors associated with the geographic and temporal variations of asthma. Nonetheless, factors that explain the large spatial variations in asthma (incidence, prevalence and symptoms) have been overlooked as most studies have focused on individual risk factors and asthma outcomes (Uphoff et al. 2015, Kanchongkittiphon et al. 2015, Wang et al. 2015, Orellano et al. 2017).

1.2.3.1 Determinants of spatial variations in asthma morbidity

The geographic variation in socioeconomic factors has most often been assessed in relation to the geographic variation in asthma outcomes in ecological studies and most studies reported negative relations. Recently Beck et al. (2013) reported a significant variation in asthma hospital admission rates in children among American neighborhoods of a county, with the highest admission rate in one neighborhood, 88 times greater than the lowest one. In this study, the dependent variable (admission rate) was strongly associated with a few neighborhood-level markers of SES such as the neighborhood's percentage of individuals below the poverty line, the percentage of households without access to care, and the percentage of vacant homes (Beck et al. 2013). A recent Canadian study also reported associations between a number of socioeconomic factors (material deprivation, rurality, family physician/general physicians per 10,000 persons) and asthma morbidity from spatial regression models (Ouédraogo et al. 2018). In this study, rurality was negatively associated with asthma prevalence and rates of physician

visits, but positively associated with rates of ER visits (respective RR=0.708, 95% CI, 0.636-0.795; RR = 0.630, 95% CI, 0.504–0.758; RR = 1.818, 95% CI, 1.194–2.858) (Ouédraogo et al. 2018). Meanwhile, hospitalization and ER visit rates were higher in materially deprived areas, compared to areas with low material deprivation (RR = 1.559, 95% CI: 1.358–1.737; RR = 1.259, 95% CI: 1.143– 1.374) (Ouédraogo et al. 2018).

Ecological studies also explored associations between environmental factors and asthma outcomes in children but results are less conclusive. Using the ISAAC Phase One surveys Asher et al. (2010) studied multiple environmental factors (e.g. pollen, air pollution, etc.) but found that most were only marginally associated with the geographic variation of the prevalence of childhood asthma. Anderson et al. (2010) also reported, based on the ISAAC Phase One data, that ambient particulate pollution (PM_{10}) was not associated with the world-wide prevalence of asthma in children. The large scale of this ecological study suggested that the international variation in childhood asthma prevalence could not be explained by community levels of ambient particulate matter (Anderson et al. 2010). However more recently, Ayres-Sampaio et al. (2014) reported that some environmental factors were related to the geographic variation in asthma outcomes. They studied near-surface air temperature (Ta), relative humidity (RH), vegetation density (Normalized Difference Vegetation Index (NDVI)), and space-time estimates of nitrogen dioxide (NO_2) and PM_{10} (Ayres-Sampaio et al. 2014). They reported correlations between these variables and asthma admission rates (per 1000 inhabitants), that were also higher in urbanized areas than in moderate and low urbanized areas (Ta=0.600, $p<0.001$; RH=-0.449, $p<0.01$; NDVI=-0.439, $p<0.01$; NO_2=0.466, $p<0.001$; PM_{10}=0.265). Nonetheless, associations between environmental factors such as traffic-related NO_2 and asthma outcomes in children

have also recently been reported inconclusive and to vary by outcome (Ouédraogo et al. 2018); furthermore few studies have reported geographic variations in asthma outcomes with geographic variations in industrial emissions (Alwahaibi et Zekal 2016; Aylin et al. 2001).

1.2.3.2 Determinants of temporal variations in asthma morbidity

There are many risk factors associated with asthma morbidity (e.g. incidence, prevalence, exacerbations) that may also explain temporal variations. While genetic changes are unlikely, changes in socioeconomic and environmental factors may explain changes over time. In the province of Québec (Canada), such as many other parts of the world, tobacco smoking dramatically declined in the past decades (Statistics Canada 2019a). Air pollution contributed by industrial emissions decreased as well along the shutdown or higher level of emission control of major industries such as with the shut down of petrochemical and refinery plants in Québec (RSQA 2007). Common indicators of SES such as educational level or/and income, have increased yearly over the past 10 years in Québec (Statistics Canada 2019b). Yet to our knowledge, there are very few studies worldwide that have assessed the benefit of pollutant reduction and increase in SES.

Nonetheless, approaches such as difference-in-difference and fixed effects models can be very useful to assess how changes in socioeconomic and environmental factors have influenced trends in asthma morbidity. Such approaches, although rare, have been used to assess impacts of changes in pollutant levels on mortality or birth outcomes (not on asthma). For example, Correia et al. (2013) investigated the association between yearly county-specific average $PM_{2.5}$

and yearly county-specific life expectancy using first-difference linear regression models in 545 US counties of the US for the period 2000 to 2007. They found that there was a negative association between the change of $PM_{2.5}$ and the change of life expectancy (for every 10 μg/m3 decline in $PM_{2.5}$ levels, there was a significant increase in life expectancy of 0.35 years), while changes in all available socioeconomic and demographic variables as well as smoking prevalence proxy variables were controlled as confounding variables (Correia et al. 2013). Moreover, this study reported that the decrease of $PM_{2.5}$ had more pronounced positive effects on the change of life expectancy (e.g. an increased life expectancy of 0.95 was associated with a 10 $\mu g/m^3$ reduction in $PM_{2.5}$) in counties with proportion of urban residences >=90%. To explore the effect of the closure of coal and oil power plants in California on preterm birth among populations living in proximity (within 20 km), Casey et al. (2018) adopted a difference-in-difference method to estimate their association, and reported that there were reductions in the probability of preterm birth within exposed pregnant women (within 5 km and 5-10 km) compared to unexposed women living 10-20 km away after the closure of eight oil and coal power plants, and the values of the decrease in the proportion of preterm birth were respectively -0.019 (95% CI, -0.031, -0.008) at a distance of 0-5 km and -0.015 (95% CI, -0.024, -0.007) between 5-10 km. One advantage of these approaches is that, in assessing within-region long-term temporal changes in both exposure to air pollution and in population health outcomes, the potential bias due to unmeasured constant confounding factors is reduced. These approaches have not been reported to study the temporal trends in asthma morbidity. Yet difference-in-difference and fixed effects modeling may be useful approaches to assess the influence of industrial air pollutant emission changes or changes in levels of air pollutants in Canada over time, on the onset or exacerbation of childhood asthma.

1.2.4 Summary of evidence

Asthma is associated with many risk factors including indoor air pollution (e.g. mould, ETS), outdoor air pollution (PM2.5, NO2) and SES. While associations between regional air pollutants and traffic related pollutants and asthma morbidity have been reviewed, the associations between community exposures to industrial air pollutant emissions in children on asthma have not been systematically assessed. Yet air pollutants from industrial emissions may differ from regional air pollution and traffic-related air pollution in terms of pollutants mixture and composition of particulate matters, and their effects may not be the same as pollutants from traffic and regional sources. Secondly, many individual observational studies have reported associations between environmental and socioeconomic risk factors and childhood asthma morbidity, however, few assessed factors associated with spatial patterns considering multiple environmental variables including industrial emissions. Furthermore, although industries are major emitters of $PM_{2.5}$ and SO_2, and influence local air pollutant levels, the association between the geographic variation of industrial air pollutant emissions and the variation of childhood asthma morbidity has been understudied. Finally, while substantial industrial air pollutant emission reductions have been noted in industrialized countries (Dominici et al. 2014), no study has been performed to investigate the health benefit in childhood asthma of such reductions.

To address these knowledge gaps, we proposed the following objectives.

1.3 Objectives

1.3.1 General objective

To assess the association between industrial air pollutant emissions and asthma morbidity in children.

In this thesis, asthma morbidity includes asthma prevalence, incidence (new onset cases) and exacerbations, based on questionnaires (e.g. asthma-like symptoms, doctor diagnosed asthma) or on medico-administrative data (e.g. ED visits or hospital admissions, and algorithms based on both to define disease onset).

1.3.2 Specific objectives

Objective 1: To assess the association between exposure to industrial air pollutant emissions and asthma in children based on available evidence.

Objective 2: To assess the spatial variation of asthma hospital admissions in children that is explained by industrial pollution and other environmental and socioeconomic factors in Québec.

Objective 3: To assess the relationship between the time trend of industrial emissions and other environmental and socioeconomic factors and the time trend of asthma onset in children in small areas of Quebec.

.

CHAPTER 2. METHODS

2.1 Methods of systematic review

2.1.1 Literature search

As detailed in chapter 3, section 3.1, we searched EmBase, MedLine, "EBM Reviews/Cochrane, and CINAHL (Cumulative Index to Nursing and Allied Health Literature) bibliographic databases based on a list of keywords determined by investigators by combining the concepts of air pollution, industries, respiratory outcomes, and children (see chapter 3, section 3.1 for the complete list of keywords). Moreover, we applied additional limits on searched articles as written in English and published between January 1, 2000 and September 6, 2017. Following this first search, search results were screened through titles and abstracts according to the defined criteria, and then, two investigators obtained the full-text of qualified papers to determine the articles to be included in the review. To complete the literature search, qualified papers were included through inspecting the reference list of selected articles and relevant reviews.

2.1.2 Selection criteria

As detailed in article (see chapter 3, section 3.1), we only selected studies that reported quantitative estimates of association between exposures to air pollution related to industrial sources and selected asthma-related respiratory outcomes in children, and articles with health results as asthma, asthma-like symptoms, wheezing and bronchiolitis. In this systematic review, the study population was determined as children aged 14 years old or younger, while a few studies that comprised some subjects older than 14 years were included. Moreover, we included

studies which estimated exposure with models (e.g. atmospheric dispersion models), as long as they clearly indicated that the air pollution exposure related to emissions of industrial point sources.

2.1.3 Extraction of the data

Four investigators (XG, RL, SB and AS) were involved in the data extraction process. A list of information to be extracted from the selected articles was detailed in chapter 3, section 3.1.

2.1.4 Method of analysis

To apply meta-analysis on selected articles, several groups were carefully formed based on the concept of homogeneity (see chapter 3, section 3.1 for details), and each group included minimum three selected studies. A few random effects meta-analysis were performed, and the I^2 statistic was used to measure heterogeneity among studies. However, funnel plots were not drawn, the quality of included studies was not assessed, and a meta-regression analysis was not performed in this systematic review. See chapter 3, section 3.1 for more explanation.

2.2 Methods for spatial and temporal analyses (articles 2 and 3)

2.2.1 Study designs, study population, and unit of analysis

We adopted an ecological study design for both spatial and temporal analyses (see chapter 3, section 3.2 & section 3.3), while temporal analysis included three cross sectional data collections.

For articles 2 and 3 (see chapter 3, sections 3.2, section 3.3), the study populations were children population aged 0-14 years old residing in Québec based on 2006 census year. For both articles, geographic units of census tracts (CTs) and Centre Local de Services Communautaires (CLSCs) were used as units of analysis. See chapter 3, section 3.2 and section 3.3 for details.

2.2.2 Health outcome

In spatial analyses, the number of asthma hospital admissions of children aged 12 years old or younger, for the period of 2002-2011, was computed per CTs/CLSCs (of 2006). The data source for asthma hospital admissions was the database MED-ÉCHO (Maintenance et exploitation des données pour l'étude de la clientèle hospitalière). In temporal analyses, the annual new cases of asthma in children aged 12 years old or younger, for the period of 2002-2011, was computed per CTs/CLSCs (of 2006) using the Québec Integrated Chronic Disease Surveillance system of the Québec Institute of Public Health (INSPQ). See chapter 3, section 3.2, section 3,3 for details.

2.2.3 Predictors

The values of predictor variables were calculated for the geographic delineation of CTs/CLSCs of the 2006 census. Both spatial analysis and temporal analyses had the following predictors: household income, regional $PM_{2.5}$ levels, industrial air pollutant emissions ($PM_{2.5}$&SO_2), and ETS. However, temporal analyses did not include predictors (traffic related air pollution, walkability, vegetation) considered in spatial analysis. Due to lack of data, we assumed that these three risk factors did not change during our study period.

Median Income— In both spatial and temporal analyses, we estimated SES by the median household income per CTs/CLSCs. Different calculation methods are presented in chapter 3, section 3.2, section 3.3 for the.

Regional PM2.5 levels— Bi-yearly levels of $PM_{2.5}$ (in $\mu g/m^3$) estimated with satellite images and ground data were downloaded from a free website (http://fizz.phys.dal.ca/~atmos/martin/) for the years 2001 to 2012, and then yearly values of background $PM_{2.5}$ per geographic units were calculated (see chapter 3, section3.2, section 3.3 for details). In spatial analyses, $PM_{2.5}$ levels per CTs/CLSCs were the average of the values of yearly values of all $PM_{2.5}$ levels within the CTs/CLSCs for the period of 2002-2011. In temporal analysis, annual $PM_{2.5}$ levels were the estimated yearly values of $PM_{2.5}$ level within the CTs/CLSCs from 2002 to 2011.

Industrial air pollutant emissions—We used emissions reported to the National Pollutant Release Inventory (NPRI) emission data (Government of Canada 2017) for the years of 2002 to

2011 to calculate average industrial emissions of $PM_{2.5}$ and sulfur dioxide (SO_2) (in tons) within CTs/CLSCs in spatial analysis, and to calculate yearly industrial emissions of $PM_{2.5}$ and SO_2 (in tons) within CTs/CLSCs in temporal analysis, respectively. Chapter 3 (section 3.2, section 3.3) presents details.

ETS —In both spatial and temporal analyses, we used data on older than 12 years old non-smokers exposed to ETS from the Canadian Community Health Survey (CCHS) per health regions, to estimate exposure to ETS in the population of children aged 0 to 12 years per CTs/CLSCs per health regions across Québec. There was a total of 18 health regions in Québec (Statistics Canada 2016). We used the proportions of exposure of the 15 regions (three regions do not have data available), and averaged over ten years, attributing the regional values to CTs/CLSCs in the spatial analyses. We used the yearly proportions of exposure for the 15 regions and attributed the regional values to the CTs/CLSCs in temporal analyses. See chapter 3, section 3.2, section 3.3 for details.

The following three predictors were only analyzed in spatial analyses:

Traffic related air pollution — This independent variable was estimated by the km of major roads within CTs/CLSCs (see chapter 3, section 3.2 for details).

Vegetation & Walkability—we used the walkability indicator established by the Institut national de santé publique du Québec (INSPQ) to calculate walkability per CTs/CLSCs. The

standardized difference vegetation index (NDVI) was used as a vegetation index per CTs/CLSCs. See chapter 3, section 3.2, section 3.3 for details.

2.2.4 Statistical methods

Spatial analyses

As described in chapter 3, section 3.2, we removed outliers and some missing values from the total CTs/CLSCs dataset. Meanwhile, divisions with fewer than five cases for the 2002-2011 period were filled with count of 2.5 due to confidentiality (see chapter 3, section 3.2 for details).

For spatial analyses, we adopted an advanced non-linear statistic model--generalized additive models (GAM) to analyze the associations between independent variables and the dependent vaiable (count of asthma hospital admissions in children). Moreover, we used negative binomial models with penalized regression splines as smooth function in the GAM model. More information in terms of model selection process are presented in chapter 3, section 3.2.

Step by step, we run a series of models composed of an empty model, a few univariate models, and several multivariate models (see chapter 3, section 3.2 for more information). In all models, the population of children aged 0-14 years per geographic unit in 2006 was used as the offset in the statistical analyses. Moreover, Moran's I was calculated as global spatial autocorrelation indicator, and Local Indicator of Spatial Autocorrelation (LISA) analysis was conducted to detect locations of clusters. See chapter 3, section 3.2 for details.

Temporal analyses

For temporal analyses, missing data and outliers were removed from the original dataset of 13980 observations for the study period of 2002-2011. Similar to spatial analyses, annual values of observations per CTs/CLSCs equal or fewer than five asthma onset cases were replaced by values of 2.5. More details are presented in chapter 3, section 3.2.

Univariate and multivariate fixed effects negative binomial models were run separately to assess associations between the independent variables (the time trend of predictors-- income, regional $PM_{2.5}$ levels, industrial air pollution emissions ($PM_{2.5}$&SO_2), ETS) and the dependent variable (the time trend of count of asthma onset in children nested within geographic units). Same as spatial analyses, the populations of children aged 0-14 years per geographical areas were used as offsets (see chapter 3, section 3.2 for details).

CHAPTER 3. RESULTS

3.1 Article 1: Review of the effect of air pollution exposure from industrial point sources on asthma-related effects in childhood

Xiaohui Geng[1], Stephane Buteau[2], Remi Labelle[3], Audrey Smargiassi[4]

Status of paper and contributions of co-authors

This article is published in Environmental Epidemiology, volume 3(6):e077.

The contributions of authors on this paper are as follows:

1. Xiaohui Geng is the doctoral Candidate, Xiaohui Geng conceptualised the paper with her director, gathered the published literature, prepared the first draft of the paper and co-write the final version with Stephane Buteau. Xiaohui Geng also developed the statistical programs and performed the analyses.
2. Stephane Buteau is the co first author of this systematic review article. He contributed to the wrting of the paper.
3. Remi Labelle is the coauthor of this systemtic review article. He conducted the first search of databases and created the first version of the tables.
4. Audrey Smargiassi is the thesis Supervisor. She conceptualized the study with the student, and oversaw the work. She provided valuable input and feedback on the writing of this paper.

3.1.1 Abstract

Background: We reviewed epidemiological studies of the association between exposure to air pollution from industries and asthma-related outcomes in childhood.

Methods: We searched bibliographic databases and reference lists of relevant papers to identify studies examining the association between children's exposure to air pollution from industrial point-sources and asthma-related outcomes, including asthma, asthma-like symptoms, wheezing and bronchiolitis. We extracted key characteristics of each study and when appropriate we performed a random-effects meta-analysis of results and quantified heterogeneity (I^2).

Results: 36 studies were included. Meta-analysis was generally not possible and limited to a few studies because of substantial variation across design characteristics and methodologies. In case-crossover studies using administrative health data, pooled odds ratio (OR) of hospitalisation for asthma and bronchiolitis in children <5 years were 1.02 (95% CI: 0.96, 1.08; I^2 = 56%) and 1.01 (95% CI: 0.97, 1.05; I^2 = 64%) per 10 ppb increase in the daily mean and hourly maximum concentration of SO_2, respectively. For $PM_{2.5}$, pooled ORs were 1.02 (95% CI: 0.93, 1.10; I^2 = 56%) and 1.01 (95% CI: 0.98, 1.03 I^2 = 33%) per 10 μg/m^3 increment in the daily mean and hourly maximum concentration. In cross-sectional studies using questionnaires, pooled ORs for the prevalence of asthma and wheezing in relation to residential proximity to industry were 1.98 (95% CI: 0.87, 3.09; I^2 =71%) and 1.33 (95% CI: 0.86, 1.79; I^2= 65%), respectively.

Conclusions: This review showed substantial heterogeneity across study designs and methods. Meta-analysis results suggested no evidence of an association for short-term asthma-related effects and an indication for long-term effects, but heterogeneity between results as well as

limitations in terms of design and exposure assessment preclude drawing definite conclusions. Further well-conducted studies making use of a longitudinal design and of refined exposure assessment methods are needed to improve risk estimates.

---

[1] Doctoral Candidate, Département de santé environnementale et santé au travail, École de santé publique, Université de Montréal, Canada; Centre de recherche en santé publique de Université de Montréal.

[2.]Co-first author, Institut National de Santé Publique du Québec.

[3] Co-author, Département de santé environnementale et santé au travail, Université de Montréal;

[4]. Thesis Supervisor, Département de santé environnementale et santé au travail, École de santé publique, Université de Montréal, Canada; Centre de recherche en santé publique de Université de Montréal, Institut National de Santé Publique du Québec.

WHAT THIS STUDY ADDS

This study is the first to review and summarize findings of epidemiological studies of the association between exposure to air pollution from industries and asthma-related outcomes in childhood. This study identifies substantial heterogeneity across design and results of selected studies. As well, many studies had important limitations that make causal inference difficult. This review stresses the importance that further well-conducted studies in terms of design and methods, particularly to assess exposure, are needed to improve risk estimates. Harmonization of methods may improve comparability across studies for future meta-analysis and help to shed light on putative agents and drivers of heterogeneity.

3.1.2 Introduction

There is considerable evidence that an increase in ambient air pollution is associated with both acute and chronic respiratory health outcomes.[1,2] Children are a subgroup of particular interest; early life and childhood are likely critical exposure windows because of the immaturity of the immune system and the potential for developmental disruption.[3-6] Children also typically experience a greater exposure to outdoor air pollution as compared to adults because of their higher respiratory volume relative to their body mass and because they tend to be more active and spend more time outdoors.[3-6]

Several epidemiological studies have reported positive associations between ambient air pollution and increase in the number of emergency department visits and hospitalizations for respiratory causes in children.[7-13] Others suggest that outdoor air pollution may exacerbate acute respiratory infections in children, exacerbate respiratory and asthma symptoms as well as acute changes in lung function in children.[14-17] While past evidence on the contribution of air pollution in the development of asthma have been mixed [18,19], findings from the most recent and comprehensive systematic review and meta-analysis on the subject support that childhood exposures to air pollutants, particularly traffic-related, is associated with the development of the disease in childhood[20].

Although air pollution studies on the respiratory outcomes in children have mostly focused on ambient urban and traffic-related air pollutants [13,16,20-22], industrial emissions may importantly contribute to ambient air pollution experienced by some local populations. Ambient air pollution affected by industrial point-source emissions may differ to that of urban settings in terms of

concentrations and composition, possibly yielding to differential toxicity [23]. We sought to investigate the effect of air pollution from industrial point sources on asthma in childhood. We performed a structured review of epidemiological studies of the associations between children's exposure to air pollution from industrial point sources and the following outcomes: asthma, asthma-like symptoms, wheezing and bronchiolitis. Specific objectives included providing a detailed description of characteristics of the selected studies, of estimates of association and, when appropriate, summarize estimates of effect using a meta-analysis of results.

3.1.3 Methods

3.1.3.1 Literature search

We searched EmBase, MedLine, "EBM Reviews/Cochrane, and CINAHL (Cumulative Index to Nursing and Allied Health Literature) bibliographic databases using a combination of keywords representing the following concepts: 1) air pollution; 2) industries; 3) respiratory outcomes; 4) children. More details about the search, including the complete list of keywords, is presented in Appendix A.

Our search was restricted to articles written in English published between January 1, 2000 and September 6, 2017. Our strategy consisted of screening all titles and abstracts to assess their eligibility according to the criteria listed below. We then obtained the full-text of papers meeting our selection criteria. In the next stage we underwent full-text read of selected articles to determine whether they should be included in the review. We completed our literature search manually through inspection of the reference list of selected articles and relevant reviews. All

the process was performed by two investigators (XG and RL) and in case of discrepancy a third investigator (AS or SB) was consulted to reach a consensus.

3.1.3.2. Selection criteria

Our review was restricted to studies that reported quantitative estimates of association (thus excluding studies that reported only a p-value, as this statistic provides no information about the magnitude of the effect) between exposures to air pollution related to industrial sources and selected asthma-related respiratory outcomes in children. Specifically, selected outcomes were asthma, asthma-like symptoms, wheezing and bronchiolitis. Wheezing and bronchiolitis were included as they produce clinical symptoms that may be similar to those of asthma and difficult to distinguish, especially in children 5 years and younger.[24]

In terms of the study population, consistently with in another review of childhood asthma and wheezing [25] the age range of interest was children aged 14 years old and younger; thus we excluded studies not reporting effects for participants 14 years and younger. However, we did retain a very few studies that reported findings for a group of participants that were mostly overlapping with our age group of interest, but also included some older participants as long as there were not adults (i.e., 18 years or older). (For example, in one study[26] the age range was 6-15 years, with 88% of participants aged 6-11 years; thus this study was included.)

We excluded studies in which the exposure investigated was not assessed during the aforementioned age range of interest, thus excluding studies examining the effects of prenatal air pollution exposures. Studies that reported associations for concentrations of air pollutants

measured at monitoring sites or using personal monitoring were excluded if it was not clearly specified that the study population was living in close proximity or in areas affected by emissions from industrial point sources. Studies in which the exposure was estimated by models, such as atmospheric dispersion models, were included if it was made clear that the air pollution exposure related to emissions of industrial point sources.

3.1.3.3. Extraction of the data

Data extraction from the selected articles was performed independently by at least two investigators (from XG, RL, SB). In case of discrepancies between the extracted information, another investigator (AS) reviewed the paper to reach consensus. Information extracted included: publication year, study design, location, sample size and age of study subjects, type of industries, method of exposure assessment, type of outcome and method of characterization, statistical analysis method, metric of exposure and effect size estimates, as well as covariates used for adjustments. When associations were reported for different age groups, we extracted the stratified results rather than for combined age groups. In instances where results were reported for the same outcome, metric of exposure and population in more than one paper, we extracted the results from the latest publications (for PM_{10} : [28] vs [29]; for residential proximity: [30] vs [29]) or which reported the primary results [31], whereas another paper reported sensitivity analyses [32].

3.1.3.4. Method of analysis

With the aim to summarize effects of exposure to air pollution from industries on asthma-related outcomes by mean of a meta-analysis of results, we carefully considered a number of study

design characteristics to determine whether study results can be pooled. Notably, we considered the type of outcomes, distinguishing prevalence from incidence, effects resulting from short term exposures from those of long term exposures, and whether the outcome was assessed from questionnaire or from administrative health data. Although we had no restriction in terms of study design, this was carefully considered to determine if studies could combined in a meta-analysis of results, as the parameters of the association being estimated may differ depending on the design used.[33] The exposure assessment methods used in the selected studies (e.g., defining exposure as living within a municipality with an industry *vs* within 2 or 10 km of the industry) as well as the functional representation of the exposure variable in the statistical analysis (e.g., categorizing residential proximity to industry *vs* treating it on its native scale as a continuous variable) were also of particular concern. These differences may yield to measures of associations that are not quantitatively comparable or that cannot be expressed uniformly across studies.

We performed a meta-analysis of results when at least three studies were deemed to be comparable according to the outcome investigated, the outcome and exposure assessment methods, and the exposure metric used in the analysis. Meta-estimates of association were calculated where appropriate using random-effects models[34], thus assuming that true effect size varies across studies. In instance where the air pollutant concentration (treated as continuous) was used as the metric of exposure, then effect size estimates and pooled estimates were expressed in terms of 10-unit increment in the air pollutant concentrations in order to facilitate comparisons. We quantified heterogeneity among estimates using the I^2 statistic, representing the percentage of the total variability explained by differences between studies rather than

sampling error.[35] As rules of thumb, an I^2 value of 25%, 50% and 75% are often used to characterize low, moderate and high heterogeneity. In presence of high heterogeneity, no definite conclusion should be drawn from the pooled effect estimate, even if a random-effects model is used. We did not perform meta-regression analysis to investigate specific factors contributing to heterogeneity because of the limited number of studies included in each meta-analysis.

3.1.4 Results

3.1.4.1 Selection of studies

Figure 1 shows the selection of studies included in this review. Our initial bibliographic search yielded 308 peer-reviewed articles. Three additional studies[36-38] were identified throughout the inspection of the references of the articles selected and one study[39] by the authors was also included. 111 articles underwent full-text review, whereas one article[40] could not be retrieved. 39 articles fulfilled our inclusion criteria. This includes one study[41] that we retained although the outcome investigated was hospitalisation for asthma, bronchiolitis, bronchitis and pneumonia, as it was reported in text that sensitivity analyses restricted to asthma yielded similar results. We included five studies that reported estimates of association not strictly for children aged 0-14 years; specifically these were reported for 0-15 years [43,44], 5-15 years [45], 6-15 years [26], and <17 years old [27]. We identified two studies for which multiple papers were published; more precisely, there were two articles[31,42] (another[32] was excluded as it was a sensitivity analysis) on the Viadana study and three articles[28-30] on the opencast coal mining study in England. These multiple papers were all retained for this review but considered as a single

citation; therefore, this review included a total of 39 published articles from 36 unique studies.

3.1.4.2 Characteristics of the selected studies

Study settings and population

Table 1 summarizes the main characteristics of the selected studies, according to the geographic locations (Appendix Table B1 includes more information about the exposure metrics and covariates). Most studies were conducted in North America (n=12), followed in decreasing order by Europe (n=10), Latin America and the Caribbean (n=5), Middle East countries (n=4), East, South and Southeast Asia (n=3), and southern Africa (n=2).

The age range varied substantially across studies; some focused strictly on younger children aged less than 5 years [36,37,46-52], others on children 5 years and older [26,45,53-59], whereas some studies included both younger and older children[29-31,41-43,60-63]. In one study[54] the exact age range was unclear; the methods section states that the study population is children aged 11 to 14 years, but estimates of association are reported for children with mean age of 6.65 years (standard deviation: 0.69 years).

Study design and outcome assessment

In terms of the outcome, it should be noted that we reported in Table 1 only information about the selected asthma related-outcomes, but other respiratory outcomes were investigated in the selected studies. In the 20 studies[26,28-31,42,43,45,51,53,55-59,62-69] that assessed respiratory outcomes through questionnaires (including diaries, questionnaire survey or interviews), the outcome frequently investigated were the prevalence of asthma (n=16) and of wheezing (n=14).

Questionnaires were generally derived from standardized ones, notably the International Study of Asthma and Allergies in Childhood (ISAAC). In 18 studies using a questionnaire, a cross-sectional design was used to investigate the effects of long-term exposure to air pollution from industries on asthma-related outcomes. The remaining two studies were longitudinal; one short term panel investigating short term effects[57] and one with a longer follow up investigating long term effects[51]. In addition, in the opencast coal mining study in England both a cross-sectional and panel study analysis was used to investigate long and short term effects, respectively.[28-30] Specifically, lifetime and period (2 and 12 months) prevalence of asthma, wheezing and asthma-related symptoms were obtained from a questionnaire, whereas short term effects were assessed from a daily diary of respiratory symptoms collected over 6 weeks during which daily PM_{10} was concurrently measured. General Practitioner consultation records were also obtained in that study but this was not considered in the review because reasons for consultations were not reported specifically for asthma.

In 16 studies asthma-related outcomes were assessed from administrative health data (i.e., general practitioner consultation records, hospital discharges and emergency department visits). Four studies[37,47,50,52] investigated the effects of short-term exposure to air pollution from industries on asthma-related outcomes. In these four studies a case-crossover design was used and the outcome investigated was hospitalization for asthma[50,52], and, hospitalization for asthma or bronchiolitis[37,47]. In the remaining 12 studies using health administrative data, long-term effects were investigated using different type of study designs, including cohort (n=3 [39,48,70]), nested case-control (n=3 [27,36,49]), ecological (n=3 [44,46,60]), case-control study (n=1 [41]), longitudinal (n=1 [54]) and cross-sectional (n=1 [61]). Notably, one cohort study was a natural

experiment, investigating the incidence of wheezing before and after the closure of a factory among birth cohorts living in close proximity and further away from the factory.[48] Relationship between exposure to industrial point sources and childhood asthma onset was investigated in one nested case-control[36] and in one population-based birth cohort study[39].

Exposure assessment

In terms of the methods used to assess children's exposure to air pollution from industries, there was substantial variation across the selected studies. In 15 studies the proximity of the residence (or school (e.g., [66]) to the point source, generally treated as ecological and binary, was used as a proxy measure for long-term exposure to industrial air pollution emissions. However, varying criteria were also used to define the categories of exposure; in some studies the exposure was defined by the city or municipality of residence (or school) (such exposure assessment was referred to as "area-based" in Table 1), whereas in others it was determined according to residing within a specific distance from the industry. In the latter studies, different cut-off values, ranging from ~400 meters (quarter mile) [44] to 20 km [61], were used to distinguish children exposed to those unexposed to emissions from the industry. In some other studies the distance between the industrial air pollution point source and the child's residence treated as a continuous variable was used as the metric of exposure.[27,39,46,68] In the Viadana study, one of the surrogate measures used for exposure was based on the distance from home and school to the closest chipboard industries, weighted to account for the time spent at each location.[31,32,42] In addition, a three-category variable, defined as the number (i.e., none, one, two) of wood factories within 2 km from home and school, was used.

Although in most studies measurements of air pollutants concentrations were available, these were mostly used for descriptive purposes. Specifically, ten studies used measurements from fixed-site monitors as the metric of exposure. Pollutants investigated were sulphur dioxide (SO_2) [37,47,50,52,56,57,64,65], particles with median diameter of less than 10 μm (PM_{10}) [28,29,56,57], or of less than 2.5 μm ($PM_{2.5}$) [37,47,50,57], total suspended particles[55] and nitrogen dioxide (NO_2) [47]. In the only study[67] that made use of personal monitoring PM_{10} were collected for 24 hours and metals in filters were measured, including Mn, Ni, Fe, Cr and Zn. Dispersion modelling was used to estimate exposure to ambient concentration of SO_2 [52,64] and total suspended particulate matter [55] from industrial point sources. In another study ambient $PM_{2.5}$ concentration from the industry was estimated using positive matrix factorization.[57]

In other studies, varying metrics of exposure were constructed using information about emissions of industrial point sources, distance to the industry and meteorological data. Specifically, metrics used to assess exposure of children included tons of air pollutants emitted by industries nearby the residence [39], percentage of hours that the child's residence was downwind of the industry[37,50], indicators of exposure combining data on emissions and residential proximity to industries [36], emissions and percent time that the child's residence was downwind of the industrie[47], emissions corrected for the residential proximity and wind direction [39], as well as residential proximity corrected for wind direction and wind speed[68].

3.1.4.3 Associations between exposure to emissions of industries and selected asthma-related outcomes

In the next sections we present findings of studies included in this review, according to the outcome assessment methods and the metric of exposure used. Specifically, we have analysed separately studies in which the outcome was assessed from administrative health data from those using a questionnaire. In view of the varying outcomes investigated and metrics of exposure used, many studies were not comparable to each other; thus a meta-analysis of results was possible in a few instances and included a limited number of studies.

3.1.4.3.1 Studies using administrative health data

Main findings from all studies making use of administrative health data are reported in the Appendix Table B2. The findings were organized according to the type of exposure metrics and of outcome.

Association to air pollutant concentrations

Four short-term effects studies used ambient air pollutant concentrations as the metric of exposure to pollutants from main industrial emitters to investigate the association with hospitalisation for asthma or bronchiolitis in childhood.[37,47,50,52] All of these studies assessed exposures using measurements at fixed-site monitors, but in addition Smargiassi et al.[52] used dispersion modeling. Associations for SO_2 and $PM_{2.5}$ from these studies were pooled in a meta-analysis of results. Figure 2 and 3 present forest plot showing estimates from individual primary studies together with pooled estimates and heterogeneity as measured by the I^2.

For SO_2 (Figure 2), the meta-analyses presented in Figure 2 include findings from Smargiassi et al.[52] estimated from dispersion modeling rather than measurements from fixed-site, as this method likely provide the better estimates of exposure. Pooled odds ratios of hospitalisation for asthma or bronchiolitis were 1.02 (95% CI: 0.96, 1.08) and 1.01 (95% CI: 0.97, 1.05) for a 10 ppb increase in same-day daily mean and hourly maximum concentrations of SO_2, respectively. In both instances, heterogeneity was considerable (I^2 = 56 and 64%, respectively). When considering findings from Smargiassi et al.[52] derived from fixed-site monitors rather than dispersion modeling (Appendix Figure B1 and B2), pooled odds ratios were 1.00 (95% CI: 0.95, 1.05) and 1.00 (95% CI: 0.97, 1.03), whereas heterogeneity was reduced (I^2 ranging between 34 and 38%).

For $PM_{2.5}$ (Fig. 3), pooled odds ratios were 1.02 (95% CI: 0.93, 1.10) and 1.01 (95% CI: 0.98, 1.03) for a 10 $\mu g/m^3$ increase in the 24-hour daily mean and hourly maximum concentration. Heterogeneity across results was moderate (I^2 = 56% and 32%).

In addition, ambient NO_2 was investigated in one study [47]; positive association with hospitalisation for asthma or bronchiolitis was reported for the daily mean (OR per 7.4 ppb = 1.09; 95% CI: 0.65, 1.82) and hourly maximum concentration (OR per 14.6 ppb = 1.15; 95% CI: 0.64, 2.06), but confidence intervals were fairly large and included the null.

Association to residential proximity

In six studies residential proximity to major but varied industries such as powers plants and smelters was treated as categorical (either binary or 3-level variables).[41,44,54,60,70] All of these

studies reported statistically significant associations between residential proximity and health service used for asthma, including hospitalisation, emergency department visits and clinical visits. A population-based birth cohort study found that the risk of asthma onset in children's living within 7.5 km of a major industrial air pollutant emitter (defined as emitting more than 100 tons per year of either $PM_{2.5}$ or SO_2) was significantly greater than in those living further than 7.5 km, whereas within 7.5 km every one kilometer increase was associated with a 2.2% (95% CI: 1.0, 3.3%) decrease in the hazard of asthma onset.[39] In the other studies that treated the distance to the industry as a continuous variable, every 1 km decrease was found to increase the risk of hospitalisation for asthma by 7% (95% CI: -2, 18%)[46] and of asthma-related medical visits by 69% (95% CI: 50, 91%)[27].

A meta-analysis of results was not possible because the number of studies investigating a similar outcome and using a similar metric of exposure was insufficient.

Association to tons emitted and wind exposure

In the two case-crossover studies[37,50] that considered as the metric of exposure the percentage of daily time that the child's residence was downwind of the point-source (in this case a smelter), associations were found with hospitalisation for asthma or bronchiolitis.[37,50] More precisely, Lewin et al.[50] found a positive association in children aged 2-4 years (OR per 29% increment: 1.27; 95% CI: 1.03, 1.56), but no association in those aged less than 2 years (OR per 21% increment: 1.00; 95% CI: 0.84, 1.20). As well, one cross-sectional study used a binary indicator of exposure based on wind direction from an industrial park housing various heavy industries, and found association with the prevalence of asthma (OR: 1.95; 95% CI: 1.01, 3.76).[61]

Three studies, one of short-term[47] and two of long-term effects[49], used a metric of exposure combining tons emitted and distances. Brand et al.[47] found no association for hospitalisation for asthma or bronchiolitis and daily exposure to air emissions from pulp mills, oil refineries and metal smelters, using a case-crossover analysis. Using a nested case control design, Karr et al.[49] found a positive association between hospitalisation and emergency department visits for asthma or bronchiolitis (OR: 1.10; 95% CI: 1.06, 1.13) and the proximity-weighted sum of total regulated air pollutant emissions during the first year of life. In a population-based birth cohort study of long-term effects, childhood asthma onset was associated with the yearly tons emitted by industries weighted by the percentage of time downwind and the inverse distance.[39]

Association to other metrics of exposure

Using a natural-experimental design, Cara et al.[48] found that the closing of a iron, steel and coke factory was associated with a significant decrease in the occurrence of wheezing among cohorts of children aged less than 2 years old.

3.1.4.3.2 Studies using questionnaire

Results of associations from all studies making using a questionnaire (or a diary) to assess the outcome are presented in Appendix Table B3. Studies were organized according to the type of exposure metrics and the type of outcome.

Association to air pollutant concentration

We identified six studies investigating the association between the selected respiratory outcomes

and air pollutant concentrations. A meta-analysis of results was not possible because of substantial differences across study design, outcome investigated and exposure assessment methods.

For $PM_{10,}$ long-term effects were investigated in two cross-sectional studies[56,67], whereas short-term effects were investigated in two panel studies [28,57]. Notably, in one cross-sectional study, 24-hour personal PM_{10} exposure was found to be associated with lifetime asthma and asthma medication use in past 12 months; for an interquartile range (IQR) (38 g/m^3), risk ratios (RR) were 1.12 (95% CI: 1.00, 1.21) and 1.21, (95% CI: 1.09, 1.35), respectively).[67] In contrast, panel studies found no association between asthma reliever use and 24-hour daily mean PM_{10} exposure from fixed-site monitors at lag 0 and 1 day[28], and for 1 to 7 days averaging window of exposure[57].

Prieto-Parra et al.[57] investigated wheezing and reliever use in association to exposure to ambient $PM_{2.5}$ as well as ambient $PM_{2.5}$ attributable to the copper smelter. For ambient $PM_{2.5}$ they found stronger association for longer exposure; specifically associations where positive for 5- and 7-day averaging concentration (e.g., for wheezing and 7-day average exposure, RR per IQR (18.0 $\mu g/m^3$) = 1.60; 95% CI: 1.15, 2.26), whereas for 1-and 3-day averaging concentration associations were null. These findings were not consistent with those for $PM_{2.5}$ attributable to the copper smelter, as for this metric associations were negative and mostly comprising the null. Hruba et al.[55] found positive associations between annual total suspended particulate matter concentrations from dispersion modeling and the lifetime prevalence of asthma, and wheezing.

For SO_2, asthma prevalence was found to be associated with exposure during the first year of life in one study[65]. The two short-term effect studies investigating respiratory symptoms found no association. Specifically, one was a panel study[57] investigating the effects daily exposures related to emissions of a copper smelter, whereas the other[56] was a cross-sectional study contrasting children from a highly industrialised compared to a non-industrialised area, and using their 8-month average SO_2 exposure at school.

Association to residential proximity

In 12 studies, exposure was based on residential proximity to various types of industries including petro-chemical, chipboard and cement plants treated as binary covariate. From these, six studies [42,43,45,53,56,59] reported positive statistically significant association with at least one of the selected outcomes. We pooled results from the 5 studies reporting an odds ratio for the association between residential proximity to industries and the lifetime prevalence of asthma and wheezing.

For asthma (Fig. 4), the pooled odds ratio was 1.98 (95% CI: 0.87, 3.09), but heterogeneity across study results was substantial (I^2 = 71%). Much larger effect was reported in the two studies.[53,63] When removing these two studies (one on steel iron coke plant [53] and the other unspecified [63]), the pooled odds ratio was 1.85 (95% CI: 0.78, 2.93), and heterogeneity remained substantial (I^2 = 79%) (see Appendix Fig. B3 for the forest plot).

For wheezing (Fig. 5), the pooled odds ratio was 1.33 (95% CI: 0.86, 1.79; I^2 = 65%). However, two studies included in this meta-analysis used a definition of wheezing that is not entirely

consistent with the others. Specifically, in one study[56] wheezing was defined as chest sounding wheezy or whistling on most days and nights, whereas in the other study[59] the occurrence of wheezing was limited to the past 12 months. When removing these two studies the pooled OR was 1.29 (95% CI: 0.50, 2.08; $I^2 = 58\%$) (see Appendix Fig. B4 for the forest plot).

Other studies making use of indicators of exposure based on residential proximity included one cross-sectional study that found no association between the prevalence of asthma and asthma-like symptoms and the weighted average of minimum distances of each child's home and school from the chipboard industries.[31] In another study, exposure was represented by the percentage of a 250 meters buffer from the child's residence that was within 0.80 km of an unspecified industrial point source.[51] In this study, positive association (OR: 1.30; 95% CI: 0.98, 1.52) was found between proximity to air pollution industrial point sources and parental reporting of asthma diagnosis, but not of wheezing.[51]

Association to wind and other related metrics of exposure

In one cross-sectional study a binary indicator of exposure based on wind direction from a petrochemical plant was used, and increased risk of prevalence of wheezing was reported (OR: 2.01; 95% CI: 1.01, 4.01).[62] White et al. found that distance weighted for wind direction and wind speed, but not simple distance from the refinery, was positively associated with asthma-related symptom prevalences.[68]

3.1.5 Discussion

We reviewed and summarized 36 studies investigating the association between exposure to air pollution from industrial point source and asthma-related outcomes in childhood. Although individual studies mostly reported positive associations, there was some mixed results and our meta-analyses did not provide strong evidence about the effect of exposure to air pollution from industries on asthma outcomes in childhood. Specifically, pooled effect estimates from case-crossover studies using administrative health data suggest no effect of daily exposure to SO_2 and $PM_{2.5}$ on hospitalisation for asthma and bronchiolitis in younger children (<5 years). Findings from cross-sectional studies using questionnaires suggest that residential proximity to industry may be associated with the prevalence of asthma (pooled OR: 1.98; 95% CI: 0.87, 3.09) and wheezing (pooled OR: 1.33; 95% CI: 0.86, 1.79), but heterogeneity across results was considerable (I^2 = 71% and 65%).

While some previous reviews of the association between air pollution and asthma have focused on urban and traffic-related air pollution [15,18-20,71,72], this review is the first to focus on the effects of air pollution from industrial point sources. Despite that our quantitative analysis did not provide strong evidence of an association, we consider that this should not be interpreted as air pollution emitted by industries have no effect on asthma-related outcome in children. The body of evidence from epidemiological studies strongly support the association between ambient air pollution and asthma exacerbation as well as asthma onset in childhood; therefore it is very difficult to envision that emissions from industries would not contribute to such adverse respiratory effects. Rather, we consider that the mixed associations from primary studies as well as the lack of evidence from our meta-analyses are due to important limitations that we discuss

below.

Notably, although we did not exclude studies based on quality assessment, we consider that many of the selected studies were not of high quality. Particularly, almost half of the studies used a cross-sectional design. This type of design provides a snapshot of the outcome and exposure at a specific point in time; therefore, prevalence can be measured but not incidence.[73] The lack of information about temporality is an important limitation to infer causality.

The exposure assessment, which is a critical component of air pollution studies, was a major limitation in many of the selected studies. Assessing the contribution of point sources to air pollution experienced by individuals is challenging. Point source characteristics, including the amount of emissions, stack height and plume properties, as well as other parameters influencing dispersion in the atmosphere such as meteorological conditions (e.g., wind speed and direction) and topography are among factors determining the contribution of point sources to ambient air pollution.[74] Most studies that account for wind data have found positive association.[27,37,39,50,62,68] Especially, findings from White et al.[68] showed that in adding wind adjustments (speed, direction, and proportion of time blown) to the distance may make an appreciable difference to the inference of association between point source emissions exposure and respiratory symptoms. However, in many studies (n=15) the exposure was treated as binary based on the community of residence or using an arbitrarily cut-off distance, thus neglecting to account for factors influencing the spatial dispersion of emissions, such as wind direction. Furthermore, the exposure was time-invariant, thus assuming that the current residential location is an adequate proxy of the children long-term (or historical) exposure. Such exposure assessment is subject to

substantial exposure misclassification, making it difficult to ascertain whether the observed associations were indeed attributable to air pollution and to what extent emissions from industrial point sources contributed to the observed effects. If misclassification in exposure were non-differential, this would bias effect estimates toward the null and could explain some of the mixed results. For the investigation of the short-term effects, the use of personal monitoring is typically recommended to better quantify the exposure of participants to air pollution, as it allows to account for mobility and time-activity patterns. However, distinguishing the contribution of industries from that of other sources remains very challenging, particularly for air pollutant emitted by multiple sources such as PM. In the only study that made use of personal monitoring, which was limited by a cross-sectional design, the contribution of PM attributable to industries was not determined.[67] Alternatively, atmospheric dispersion modeling making use of reliable and sufficient data accounting for characteristics of point source, meteorological conditions and topography, can provide spatiotemporally refined estimates of exposure (both short and long term) to industrial emissions at participants' residence as compared to fixed-site monitoring.[75,76] For short-term exposure to SO_2, stronger association with hospitalization for asthma and bronchiolitis was found when using dispersion modeling as compared to measurements at fixed-site monitors.[52] Fixed-site monitors may not be specifically located to capture the influence of industrial point source emissions. The ability of a fixed-site monitoring station to represent the exposure of individuals will depend on its location, particularly in terms of distance to the point source and wind direction, and will likely be limited to individuals residing in very close proximity to the station. Additionally, the use of dispersion modeling can be refined when combined with other air pollution estimates, such as background regional ambient concentrations of air pollutant from satellite-based or land use regression models.[76]

However, because emissions data are rarely available on daily basis, the variation of estimates of pollution from dispersion modeling may be limited to the use of meteorological factors (e.g., wind direction and speed) when investigating the short-term effects of air pollution exposure. Another limitation of this review relates to the substantial variation across study design and characteristics that made pooling findings generally not possible. These variations likely contributed to the statistical heterogeneity (reflected by the I^2 statistic) observed in the meta-analyses conducted, which make interpretation of findings challenging. Particularly, the exposure assessment was a main source of heterogeneity, as a variety of exposure metrics were used. In studies in which the outcome was collected from a questionnaire, many used a binary indicator of exposure based on residential proximity to industries; however, varying distances or definitions were used across studies limiting our ability to compare results across studies. In addition to being subject to important exposure misclassification, such qualitative indicators of exposure do not allow to account for the quantitative magnitude and type of exposure in the analysis, making impossible to derive an exposure-response functions that would support causality.

The fact that studies were conducted in different countries of the world, where ambient air pollution concentration and emission standards may also substantially differ, is likely another source of heterogeneity. In addition, studies covered a wide range of industrial activities, emitting complex mixtures of pollutants that likely vary in composition and toxicity. Evidence from toxicological, controlled human exposure and epidemiological studies suggest that adverse health effects of particulate matter likely depend on the size, composition and solubility of the particulate matter.[2] This was our motivation for extracting information about the types of

industrial source, but it was not possible to consider this in our meta-analysis because of the very few number of studies included and the relatively large variety of industrial activities. To address possible drivers of heterogeneity, putative agents and differential toxicity by type of point source, a greater standardization of future study design and methods may be desirable, including greater harmonization of methods and definitions for the outcome and for the exposure, as well as harmonization of confounders included in the analysis. However, because the air pollution mixture may importantly differ across geographical location and depending on the type of industry, any evidence base as defined by non-heterogeneous meta-analysis may be difficult to achieve. In our meta-analysis of case-crossover studies of the association between air pollutants and hospitalisation for asthma and bronchiolitis, statistical heterogeneity was substantial despite all studies[37,47,50,52] used a similar design, were conducted in Canada, among children of similar age, using similar methods of exposure and outcome assessment, and of statistical analysis. This inherent heterogeneity implies that evidence may have to rely on findings from a very limited number of studies rather than meta-analyses, thus stressing the importance of having high quality and well-conducted studies.

In this review, a large number of the cross-sectional studies used questionnaire surveys to assess respiratory symptoms and doctor-diagnosed respiratory outcomes. Although studies mostly used standardized questionnaires, these are subject to recall bias; we may suspect that people living in proximity to industries will have a tendency to over-report, thus yielding to overestimated effect size. In addition, standardized questionnaires, including the ISAAC and the ATS, are subjected to between-country and between-language variation that have been shown to influence the results and may limit comparison of findings across studies.[77,78] Administrative

health data using ICD codes is also not free of possible outcome misclassification, but this method appears less prone to biases as compared to questionnaire. However, administrative health data is influenced by healthcare access, which is an issue in several countries worldwide. This may be an additional source of heterogeneity in this review.

Although our review focus on children, age groups varied across studies and this may also be a source of uncertainty and heterogeneity. The diagnosis of asthma is particularly difficult in children younger than 5 years old due to developmental limitations, which may lead outcome misclassification, particularly if this diagnosis is from emergency room visits.[79] Age is a risk factor for asthma and possibly an effect modifier of the association with air pollution from industries; however this could not be addressed in this review because too few studies were comparable.

3.1.6 Conclusions and Recommendations

This review highlighted substantial heterogeneity across study design and methods, limiting the conduct of a meta-analysis to a few instances and including very few studies. Results from meta-analyses suggested no evidence for short-term asthma-related effects, whereas for long-term effects there was an indication of an association; however, limitations in terms of design (i.e., cross-sectional) and exposure assessment (i.e., binary exposure based on residential proximity) preclude drawing definite conclusions. Further high quality and well-conducted studies are needed to improve our understanding of the effects of industrial air pollution emissions on asthma and other respiratory outcomes. Specific recommendations include the use of a

longitudinal study design, of methods of outcome assessment beyond reporting of doctor-diagnosis (e.g. using prescribed medication from prescription registry and/or diagnosis codes), of refined exposure assessment methods (e.g. atmospheric dispersion modeling) that capture local influence of point sources and that may allow distinguishing the contribution of industries from that of other sources, of continuous rather than categorical exposure analysis and, the inclusion of all important confounders in the analyses.

3.1.7 Reference

1. US EPA. Final Report: Integrated Science Assessment (ISA) for Sulfur Oxides – Health Criteria. Washington, DC: U.S. Environmental Protection Agency, 2008.

2. US EPA. Final Report: Integrated Science Assessment for Particulate Matter. Washington, DC, 2009.

3. Bateson TF, Schwartz J. Children's Response to Air Pollutants. *Journal of Toxicology and Environmental Health, Part A* 2007; **71**(3): 238-43.

4. Dixon JK. Kids need clean air: air pollution and children's health. *Family & community health* 2002; **24**(4): 9-26.

5. Gilliland FD, McConnell R, Peters J, Gong H. A theoretical basis for investigating ambient air pollution and children's respiratory health. *Environmental Health Perspectives* 1999; **107 Suppl 3**: 403-7.

6. Schwartz J. Air pollution and children's health. *Pediatrics* 2004; **113**(4 Suppl): 1037-43.

7. Delfino RJ, Wu J, Tjoa T, Gullesserian SK, Nickerson B, Gillen DL. Asthma morbidity and ambient air pollution: effect modification by residential traffic-related air pollution. *Epidemiology (Cambridge, Mass)* 2014; **25**(1): 48-57.

8. Lavigne E, Villeneuve PJ, Cakmak S. Air pollution and emergency department visits for asthma in Windsor, Canada. *Canadian journal of public health = Revue canadienne de sante publique* 2012; **103**(1): 4-8.

9. Samoli E, Nastos PT, Paliatsos AG, Katsouyanni K, Priftis KN. Acute effects of air pollution on pediatric asthma exacerbation: evidence of association and effect modification. *Environmental Research* 2011; **111**(3): 418-24.

10. Strickland MJ, Darrow LA, Klein M, et al. Short-term associations between ambient air pollutants and pediatric asthma emergency department visits. *American Journal of Respiratory and Critical Care Medicine* 2010; **182**(3): 307-16.

11. Weichenthal SA, Lavigne E, Evans GJ, Godri Pollitt KJ, Burnett RT. Fine Particulate Matter and Emergency Room Visits for Respiratory Illness. Effect Modification by Oxidative Potential. *American Journal of Respiratory and Critical Care Medicine* 2016; **194**(5): 577-86.

12. Zheng X-y, Ding H, Jiang L-n, et al. Association between Air Pollutants and Asthma Emergency Room Visits and Hospital Admissions in Time Series Studies: A Systematic Review and Meta-Analysis. *PloS one* 2015; **10**(9): e0138146.

13. Lim H, Kwon HJ, Lim JA, et al. Short-term Effect of Fine Particulate Matter on Children's Hospital Admissions and Emergency Department Visits for Asthma: A Systematic Review and Meta-analysis. *Journal of preventive medicine and public health = Yebang Uihakhoe chi* 2016; **49**(4): 205-19.

14. Dales R, Chen L, Frescura AM, Liu L, Villeneuve PJ. Acute effects of outdoor air pollution on forced expiratory volume in 1 s: a panel study of schoolchildren with asthma. *The European Respiratory Journal* 2009; **34**(2): 316-23.

15. Orellano P, Quaranta N, Reynoso J, Balbi B, Vasquez J. Effect of outdoor air pollution on asthma exacerbations in children and adults: Systematic review and multilevel meta-analysis. *PloS one* 2017; **12**(3): e0174050.

16. Rodriguez-Villamizar LA, Magico A, Osornio-Vargas A, Rowe BH. The effects of outdoor air pollution on the respiratory health of Canadian children: A systematic review of epidemiological studies. *Can Respir J* 2015; **22**(5): 282-92.

17. Weinmayr G, Romeo E, De Sario M, Weiland SK, Forastiere F. Short-term effects of PM10 and NO2 on respiratory health among children with asthma or asthma-like symptoms: a systematic review and meta-analysis. *Environmental Health Perspectives* 2010; **118**(4): 449-57.

18. Guarnieri M, Balmes JR. Outdoor air pollution and asthma. *Lancet* 2014; **383**(9928): 1581-92.

19. Koenig JQ. Air pollution and asthma. *The Journal of allergy and clinical immunology* 1999; **104**(4 Pt 1): 717-22.

20. Khreis H, Kelly C, Tate J, Parslow R, Lucas K, Nieuwenhuijsen M. Exposure to traffic-related air pollution and risk of development of childhood asthma: A systematic review and meta-analysis. *Environment international* 2017; **100**: 1-31.

21. Holguin F. Traffic, Outdoor Air Pollution, and Asthma. *Immunology and allergy clinics of North America* 2008; **28**(3): 577-88.

22. Zhang S, Li G, Tian L, Guo Q, Pan X. Short-term exposure to air pollution and morbidity of COPD and asthma in East Asian area: A systematic review and meta-analysis. *Environmental Research* 2016; **148**: 15-23.

23. Seagrave J, McDonald JD, Bedrick E, et al. Lung toxicity of ambient particulate matter from southeastern U.S. sites with different contributing sources: relationships between composition and effects. *Environmental Health Perspectives* 2006; **114**(9): 1387-93.

24. Pedersen SE, Hurd SS, Lemanske RF, et al. Global strategy for the diagnosis and management of asthma in children 5 years and younger. *Pediatric pulmonology* 2011; **46**(1): 1-17.

25. Hehua Z, Qing C, Shanyan G, Qijun W, Yuhong Z. The impact of prenatal exposure to air pollution on childhood wheezing and asthma: A systematic review. *Environmental Research* 2017; **159**: 519-30.

26. Herrera R, Radon K, von Ehrenstein OS, Cifuentes S, Munoz DM, Berger U. Proximity to mining industry and respiratory diseases in children in a community in Northern Chile: A cross-sectional study. *Environmental health : a global access science source* 2016; **15**(1): 66.

27. Loyo-Berrios NI, Irizarry R, Hennessey JG, Tao XG, Matanoski G. Air pollution sources and childhood asthma attacks in Catano, Puerto Rico. *American journal of epidemiology* 2007; **165**(8): 927-35.

28. Howel D, Darnell R, Pless-Mulloli T. Children's Respiratory Health and Daily Particulate Levels in 10 Nonurban Communities. *YENRS Environmental Research* 2001; **87**(1): 1-9.

29. Pless-Mulloli T, Howel D, King A, et al. Living near opencast coal mining sites and children's respiratory health. *Occup Environ Med* 2000; **57**(3): 145-51.

30. Pless-Mulloli T, Howel D, Prince H. Prevalence of asthma and other respiratory symptoms in children living near and away from opencast coal mining sites. *International journal of epidemiology* 2001; **30**(3): 556-63.

31. Rava M, Marcon A, Girardi P, et al. Proximity to wood factories and hospitalizations for respiratory diseases in children. *The Science of the total environment* 2011; **410-411**: 80-6.

32. Rava M, Crainicianu C, Marcon A, et al. Proximity to wood industries and respiratory symptoms in children: a sensitivity analysis. *Environment international* 2012; **38**(1): 37-44.

33. Buteau S, Goldberg MS. Methodological issues related to pooling results from panel studies of heart rate variability and its association with ambient air pollution. *Environmental Research* 2015; **140**: 462-5.

34. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials* 1986; **7**(3): 177-88.

35. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Bmj* 2003; **327**(7414): 557-60.

36. Clark NA, Demers PA, Karr CJ, et al. Effect of early life exposure to air pollution on development of childhood asthma. *Environ Health Perspect* 2010; **118**(2): 284-90.

37. Labelle R, Brand A, Buteau S, Smargiassi A. Hospitalizations for Respiratory Problems and Exposure to Industrial Emissions in Children. *Environment and Pollution* 2015; **4**(2): 77-85.

38. Portnov BA, Dubnov J, Barchana M. On ecological fallacy, assessment errors stemming from misguided variable selection, and the effect of aggregation on the outcome of

epidemiological study. *Journal Of Exposure Science And Environmental Epidemiology* 2006; **17**: 106.

39. Buteau S, Doucet M, Tétreault L-F, et al. A population-based birth cohort study of the association between childhood-onset asthma and exposure to industrial air pollutant emissions. *Environment international* 2018; **121**(Pt 1): 23-30.

40. Biesiada M, Zejda JE, Skiba M. Air pollution and acute respiratory diseases in children: regression analysis of morbidity data. *Int J Occup Med Environ Health* 2000; **13**(2): 113-20.

41. Nirel R, Maimon N, Fireman E, Agami S, Eyal A, Peretz A. Respiratory hospitalizations of children living near a hazardous industrial site adjusted for prevalent dust: a case-control study. *International journal of hygiene and environmental health* 2015; **218**(2): 273-9.

42. de Marco R, Marcon A, Rava M, et al. Proximity to chipboard industries increases the risk of respiratory and irritation symptoms in children: the Viadana study. *The Science of the total environment* 2010; **408**(3): 511-7.

43. Awasthi S, Tripathi P, Prasad R. Environmental risk factors for asthma in Lucknow: A case–control study. *Clinical Epidemiology and Global Health* 2013; **1**(3): 115-23.

44. Maantay J. Asthma and air pollution in the Bronx: methodological and data considerations in using GIS for environmental justice and health research. *Health & place* 2007; **13**(1): 32-56.

45. Kobrossi R, Nuwayhid I, Sibai AM, El-Fadel M, Khogali M. Respiratory health effects of industrial air pollution on children in North Lebanon. *International journal of environmental health research* 2002; **12**(3): 205-20.

46. Aylin P, Bottle A, Wakefield J, Jarup L, Elliott P. Proximity to coke works and hospital admissions for respiratory and cardiovascular disease in England and Wales. *Thorax* 2001; **56**(3): 228-33.

47. Brand A, McLean KE, Henderson SB, et al. Respiratory hospital admissions in young children living near metal smelters, pulp mills and oil refineries in two Canadian provinces. *Environment international* 2016; **94**: 24-32.

48. Cara AC, Buntinx F, Van den Akker M, Dinant GJ, Manolovici C. Industrial air pollution and children's respiratory health: a natural experiment in Calarasi. *The European journal of general practice* 2007; **13**(3): 135-43.

49. Karr CJ, Demers PA, Koehoorn MW, Lencar CC, Tamburic L, Brauer M. Influence of ambient air pollutant sources on clinical encounters for infant bronchiolitis. *American Journal of Respiratory and Critical Care Medicine* 2009; **180**(10): 995-1001.

50. Lewin A, Buteau S, Brand A, Kosatsky T, Smargiassi A. Short-term risk of hospitalization for asthma or bronchiolitis in children living near an aluminum smelter. *Journal of exposure science & environmental epidemiology* 2013; **23**(5): 474-80.

51. Patel MM, Quinn JW, Jung KH, et al. Traffic density and stationary sources of air pollution associated with wheeze, asthma, and immunoglobulin E from birth to age 5 years among New York City children. *Environmental Research* 2011; **111**(8): 1222-9.

52. Smargiassi A, Kosatsky T, Hicks J, et al. Risk of asthmatic episodes in children exposed to sulfur dioxide stack emissions from a refinery point source in Montreal, Canada. *Environ Health Perspect* 2009; **117**(4): 653-9.

53. Cara AC, Degryse J, van den Akker M, Dinant GJ, Manolovici C, Buntinx F. Impact of early childhood air pollution on respiratory status of school children. *The European journal of general practice* 2010; **16**(3): 133-8.

54. Chiang TY, Yuan TH, Shie RH, Chen CF, Chan CC. Increased incidence of allergic rhinitis, bronchitis and asthma, in children living near a petrochemical complex with SO2 pollution. *Environment international* 2016; **96**: 1-7.

55. Hruba F, Fabianova E, Koppova K, Vandenberg JJ. Childhood respiratory symptoms, hospital admissions, and long-term exposure to airborne particulate matter. *Journal of exposure analysis and environmental epidemiology* 2001; **11**(1): 33-40.

56. Naidoo RN, Robins TG, Batterman S, Mentz G, Jack C. Ambient pollution and respiratory outcomes among schoolchildren in Durban, South Africa. *SAJCH : the South African journal of child health* 2013; **7**(4): 127-34.

57. Prieto-Parra L, Yohannessen K, Brea C, Vidal D, Ubilla CA, Ruiz-Rudolph P. Air pollution, PM 2.5 composition, source factors, and respiratory symptoms in asthmatic and nonasthmatic children in Santiago, Chile. *Environment international* 2017; **101**: 190-200.

58. Rovira E, Cuadras A, Aguilar X, et al. Asthma, respiratory symptoms and lung function in children living near a petrochemical site. *Environ Res* 2014; **133**: 156-63.

59. Wichmann FA, M¸ller A, Busi LE, et al. Increased asthma and respiratory symptoms in children exposed to petrochemical pollution. *YMAI The Journal of Allergy and Clinical Immunology* 2009; **123**(3): 632-8.

60. Alwahaibi A, Zeka A. Respiratory and allergic health effects in a young population in proximity of a major industrial park in Oman. *Journal of epidemiology and community health* 2016; **70**(2): 174-80.

61. Karakis I, Kordysh E, Lahav T, et al. Life prevalence of upper respiratory tract diseases and asthma among children residing in rural area near a regional industrial park: cross-sectional study. *Rural and remote health* 2009; **9**(3): 1092.

62. Lopes de Moraes AC, Ignotti E, Netto PA, Jacobson LSV, Castro H, Hacon SS. Wheezing in children and adolescents living next to a petrochemical plant in Rio Grande do Norte, Brazil. *Jornal de pediatria* 2010; **86**(4): 337-44.

63. Ripabelli G, Tamburro M, Sammarco ML, de Laurentiis G, Bianco A. Asthma prevalence and risk factors among children and adolescents living around an industrial area: a cross-sectional study. *BMC public health* 2013; **13**(1): 1038.

64. Deger L, Plante C, Jacques L, et al. Active and uncontrolled asthma among children exposed to air stack emissions of sulphur dioxide from petroleum refineries in Montreal, Quebec: a cross-sectional study. *Canadian respiratory journal : journal of the Canadian Thoracic Society* 2012; **19**(2): 97-102.

65. Deng Q, Lu C, Norback D, et al. Early life exposure to ambient air pollution and childhood asthma in China. *Environ Res* 2015; **143**(Pt A): 83-92.

66. Mirabelli MC, Wing S. Proximity to pulp and paper mills and wheezing symptoms among adolescents in North Carolina. *Environ Res* 2006; **102**(1): 96-100.

67. Rosa MJ, Benedetti C, Peli M, et al. Association between personal exposure to ambient metals and respiratory disease in Italian adolescents: a cross-sectional study. *BMC Pulm Med* 2016; **16**(1): 6.

68. White N, teWaterNaude J, van der Walt A, Ravenscroft G, Roberts W, Ehrlich R. Meteorologically estimated exposure but not distance predicts asthma symptoms in

schoolchildren in the environs of a petrochemical refinery: a cross-sectional study. Environmental health : a global access science source 2009; 8: 45.

69. Rusconi F, Catelan D, Accetta G, et al. Asthma symptoms, lung function, and markers of oxidative stress and inflammation in children exposed to oil refinery pollution. The Journal of asthma : official journal of the Association for the Care of Asthma 2011; 48(1): 84-90.

70. Liu X, Lessner L, Carpenter DO. Association between Residential Proximity to Fuel-Fired Power Plants and Hospitalization Rate for Respiratory Diseases. *Environmental Health Perspectives* 2012; **120**(6): 807-10.

71. Bowatte G, Lodge C, Lowe AJ, et al. The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization: a systematic review and a meta-analysis of birth cohort studies. *Allergy* 2015; **70**(3): 245-56.

72. Lau N, Norman A, Smith MJ, Sarkar A, Gao Z. Association between Traffic Related Air Pollution and the Development of Asthma Phenotypes in Children: A Systematic Review. *International Journal of Chronic Diseases* 2018; **2018**: 1-12.

73. Rothman KJ, Greenland S, Lash TL. Modern epidemiology; 2008.

74. Hertel O, Goodsite ME. Chapter 1 Urban Air Pollution Climates throughout the World. Air Quality in Urban Environments: The Royal Society of Chemistry; 2009: 1-22.

75. Cora MG, Hung Y-T. Air dispersion modeling: A tool for environmental evaluation and improvement. *Environ Qual Manage* 2003; **12**(3): 75-86.

76. Hodgson S, Nieuwenhuijsen MJ, Colvile R, Jarup L. Assessment of exposure to mercury from industrial emissions: comparing "distance as a proxy" and dispersion modelling approaches. *Occupational and Environmental Medicine* 2007; **64**(6): 380-8.

77. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet (London, England)* 1998; **351**(9111): 1225-32.

78. Osterman JW, Armstrong BG, Ledoux E, Sloan M, Ernst P. Comparison of French and English versions of the American Thoracic Society respiratory questionnaire in a bilingual working population. *International journal of epidemiology* 1991; **20**(1): 138-43.

79. Plante C, Goudreau S, Jacques L, Tessier F. Agreement between survey data and Régie de l'assurance maladie du Québec (RAMQ) data with respect to the diagnosis of asthma and medical services use for asthma in children. *Chronic diseases and injuries in Canada* 2014; **34**(4): 256-62.

3.1.8 Tables and figures

Table 1. Main characteristics of the studies included in the review.

Reference	Location	Design	Age (sample size)	Health data source	Outcome	Type of effect	Exposure metrics	Exposure type	Type of industry
North America									
Smargiassi et al., 2009 [52]	Montreal (Canada)	Case-crossover	2-4 yrs, (n = 263 hosp; 1,579 ERV)	AHD	• Hosp for asthma • ERV for asthma	Short term	• SO2 (dispersion model) • SO2 (fixed-site)	• Continuous • Continuous	Refineries
Deger et al., 2012 [64]	Montreal (Canada)	Cross-sectional	0.5-12 yrs, (n = 842)	Quest.	• Asthma ever • Wheezing in past 12 mo. • Asthma attack in past 12 mo. • Asthma medication use in past 12 mo. • Current wheeze (≥3 times per week)	Long term	• SO2 (dispersion model)	• Continuous	Refineries
Lewin et al., 2013 [50]	Shawinigan (Canada)	Case-crossover	0-4 yrs, (n = 396 hosp)	AHD	• Hosp for asthma	Short term	• PM2.5, SO2 (fixed-site) • Wind direction (continuous)	• Continuous	Aluminum smelter
Labelle et, al. 2015 [37]	Saguenay (Canada)	Case-crossover	0-4 yrs, (n = 1006 hosp)	AHD	• Hosp for asthma and bronchiolitis	Short term	• PM2.5, SO2 (fixed-site) • Wind direction	• Continuous	Aluminum smelter
Buteau et al., 2018 [39]	Province of Québec (Canada)	Cohort	0-9 yrs, (n = 722,667)	AHD	• Asthma onset	Long term	• PM2.5, SO2 emissions • Distance • PM2.5, SO2 emissions, weighted for distance and wind direction	• Continuous	All
Brand et al., 2016 [47]	Province of Quebec and British Columbia (Canada)	Case-crossover	2-4 yrs, (n = 2868)	AHD	• Hosp for asthma and bronchiolitis	Short term	• PM2.5, NO2, SO2 emissions, weighted for wind direction • PM2.5, SO2, NO2 (fixed-site)	• Continuous	Pulp mills, metal smelters and oil refineries
Clark et al., 2010 [36]	Southwestern British Columbia (Canada)	Nested case-control	3-4 yrs, (n = 37,401)	AHD	• Asthma onset	Long term	• Emissions, weighted for distance	• Continuous	All
Karr et al., 2009 [49]	Georgia Air Basin, British Columbia (Canada)	Nested case-control	2-12 mo., (n = 68,803)	AHD	• Outpatient visit or hosp for bronchiolitis	Long term	• Emissions, weighted for distance	• Continuous	All

Liu et al., 2012 [70]	New-York State (excluding New York city) (USA)	Cohort	<10 yrs, (n = 21,524,390 person-yrs)	AHD	• Hosp for asthma	Long term	• Distance	• Binary (area-based)	Fuel-fired power plant, electric generators, and hazardous waste site.
Maantay et al., 2007 [44]	Bronx, New York City (USA)	Ecological	0-15 yrs, (n = 20,764 hosp)	AHD	• Hosp for asthma	Long term	• Distance	• Binary (1/4 mile cut-off)	All
Patel et al., 2011 [51]	Northern Manhattan and the South Bronx (USA)	Longitudinal	0-5 yrs, (n = 593)	Quest.	• Asthma in past 12 mo. • Wheezing in past 12 mo.	Long term	• Percentage of residential buffer area within 0.80 km of an industrial facility	• Continuous	N/S
Mirabelli and Wing, 2006 [66]	North Carolina (USA)	Cross-sectional	12-14 yrs, (n = 64,432)	Quest.	• Wheezing in past 12 mo.	Long term	• Distance to school • Odor • Distance and odor	• 3-level categorical • Binary • Binary	Pulp and paper mill
Latin America and the Caribbean									
Loyo-Berrios et al., 2007 [27]	Catano (Puerto Rico)	Nested case-control	<17 yrs (n = 6282)	AHD	• Asthma-related medical visits	Long term	• Distance • Distance, adjusted for wind direction	• Continuous • Continuous	Rum distillery, electric power plants, petroleum refineries, sewage incinerator and treatment plants, cement plants.
Wichmann et al., 2009 [59]	La Plata (Argentina)	Cross-sectional	6-12 yrs, (n = 1212)	Quest.	• Asthma ever (doctor-diagnosed) • No. of asthma exacerbations in past 12 mo. • Wheezing	Long term	• Distance	• Binary (area-based)	Petrochemical complex
Lopes de Moraes et al., 2010 [62]	Guamaré (Brazil)	Cross-sectional	0-14 yrs, (n = 209)	Quest.	• Asthma ever • Wheezing ever ; • Wheezing in past 12 mo. ; • No. of wheezing attacks in past 12 mo.; • Sleep disturbance by wheezing in past 12 mo. • Speech limiting wheezing in past 12 mo.	Long term	• Distance and wind direction	• Binary (<5 km, downwind)	Petrochemical complex
Herrera et al., 2016 [26]	Northen Chile (Chile)	Cross-sectional	6-15 yrs, (n = 288)	Quest.	• Asthma (doctor diagnosed or taking asthma medications in past 12 mo.)	Long term	Distance	• Binary (cut-off : 1st quartile)	Opencast mining sites (gold and copper).

Prieto-Parra et al., 2017 [57]	Santiago (Chile)	Panel (12 weeks follow-up)	6-14 yrs, (n = 174)	Quest., daily diary	• Wheezing • Medication for asthma crisis	Short-term	• PM2.5, PM10, PM2.5-10, CO, NO2, SO2, O3 (fixed-site) • PM2.5 composition • PM2.5 sources contribution (positive matric factorization)	• Continuous • Continuous • Continuous	Copper smelter
Europe									
Pless-Mulloli et al., 2000; Pless-Mulloli et al., 2001; Howel et al. 2001. [28, 29, 30]	Northern England (United Kingdom)	Cross-sectional	1-11 yrs, (n = 3216)	Quest.	Lifetime prevalence: • Wheeze • Asthma Period prevalence (past 12 mo.): • >12 Wheezing in past 12 mo. • Woken child at night in past 12 mo. • Limited speech in past 12 mo. • Occurred on exercise in past 12 mo.	Long term	• Distance	• Binary (area-based)	Opencast coal mining sites
Pless-Mulloli et al., 2000; Pless-Mulloli et al., 2001; Howel et al. 2001.[28, 29, 30]	Northern England (United Kingdom)	Panel	1-11 yrs, (n = 244)	Daily diary	Daily prevalence and incidence of respiratory symptoms: • Wheeze • Asthma reliever use	Short-term	• PM10 (fixed-site)	• Continuous	Opencast coal mining sites
Aylin et al., 2001 [46]	England and Wales (United Kingdom)	Ecological	0-4 yrs, (n = approx. 43,932)	AHD	• ERV for asthma	Long term	• Distance	• Continuous	Coke works
Ripabelli et al., 2013 [63]	Termoli (Italy)	Cross-sectional	0.5-14 yrs, (n = 95)	Quest.	• Asthma ever	Long term	• Distance	• Binary (area-based)	N/S
Rosa et al., 2016 [67]	Brescia (Italy)	Cross-sectional	11-14 yrs, (n = 280)	Quest.	• Asthma ever • Asthma medication use in past 12 mo. • Wheezing in the past 12 mo.	Long term	• PM10, Mn, Ni, Cr, Fe, Zn, (personal monitoring)	• Continuous	Ferroalloy plants
Rusconi et al., 2011 [69]	Sarroch and Brucei (Italy)	Cross-sectional	6-14 yrs, (n = 489)	Quest.	• Wheezing symptoms in past 12 mo.	Long term	• Distance	• Binary (area-based	Petrochemical refinery and liquid fuel gasification plants.
Rava et al., 2011; Rava et al., 2012; De Marco et al.,	Viadana District (Italy)	Cross-sectional	3-14 yrs, (n = 3854)	Quest.	• Doctor-diagnosed asthma ever • Asthma-like symptoms in past 12 mo. • Asthma-like symptoms score (sums of symptoms by subjects) • asthma severity index	Long term	• Distance to school and home	• 3-level categorical	Chipboard industries

2010. [31, 32, 42,]									
Rovira et al., 2014 [58]	Tarragona (Spain)	Cross-sectional	6-7 yrs (n = 2672); 13-14 yrs (n = 2524)	Quest.	• Wheezing ever • Wheezing in past 12 mo. • Wheezing with exercise in past 12 mo. • Severe wheezing • Asthma ever	Long term	• Distance	• Binary (area-based)	Oil refinery, chemical industries, petrochemical plants, incinerators, two power plants.
Hruba et al., 2001 [55]	Banska Bystrica (Slovakia)	Cross-sectional	7-11 yrs, (n = 667)	Quest.	• Asthma ever (doctor-diagnosed) • Hospital admission ever for asthma or bronchitis or pneumonia. • Wheeze ever	Long term	• TSP (dispersion model)	• Continuous	Wood processing facility, cement plant, pharmaceutical company.
Cara et al., 2007 [48]	Calarasi and Roseti (Romania)	Cohort	<2 yrs (n= 851)	AHD	• Wheezing (doctor-diagnosed)	Long term	• Distance • Before vs after factory closure	• Binary (area-based)	Iron, steel and coke factory
Cara et al., 2010 [53]	Calarasi and Roseti (Romania)	Cross-sectional	7-10 yrs, (n = 519)	Quest.	• Asthma ever (doctor-diagnosed) • Wheezing ever • Wheezing in past 12 mo. • No. of wheezing attacks in past 12 mo. • Sleep disturbance by wheezing in past 12 mo. • Speech limiting wheezing in past 12 mo. • Exercise related wheezing in past 12 mo.	Long term	• Distance • Before vs after factory closure	• Binary (area-based)	Iron, steel, and coke factory
Middle East									
Alwahaibi et al., 2016 [60]	Province of Sohar and Liwa (Oman)	Ecological	≤ 1 yr (n = 7998), 1-14 yrs (n = 12,148)	AHD	• Medical clinics visits for asthma	Long term	• Distance	• 3-level categorical	Petrochemical industrial complex, iron smelter
Kobrossi et al., 2002 [45]	Districts of Koura, Batroun and Jbeil (Lebanon)	Cross-sectional	5-15 yrs, (n = 486)	Quest.	• Wheezing • Wheezing after physical exercise	Long term	• Distance	• Binary (area-based)	Four cement factories, one lime and plaster factory, one asbestos-cement factory, and two fertilizer factories
Nirel et al., 2015 [41]	Neot Hovav (Israel)	Case-control	0-14 yrs, (n = 6666)	AHD	• Hosp for asthma	Long term	• Distance • Relative direction of the residence from the industry	• 3-level categorical • 4-level categorical	Hazardous waste treatment

Karakis et al., 2009 [61]	Negev (Isreal)	Cross-sectional	0-14 yrs, (n = 550)	AHD	• Asthma life prevalence (from medical clinics visits for asthma)	Long term	• Distance • Wind direction	• Binary (20-km cut-off) • Binary	Chemical, pharmaco-chemical and heavy industries, industrial hazardous waste disposal site and an incinerator.
East, South and Southeast Asia									
Deng et al., 2015 [65]	Changsha (China)	Cross-sectional	3-6 yrs, (n = 2490)	Quest.	• Asthma ever (doctor-diagnosed)	Long term	• SO2 at kindergartens (IDW from fixed-site).	• Continuous	All
Awasthi et al., 2013 [43]	Lucknow (India)	Case-control	≤15 yrs, (n = 348)	Quest.	• Asthma symptoms from clinic record	Long term	• Distance	• Binary (1.5-km cut-off)	Smoke emitting industries
Chiang et al., 2016 [54]	Taiwan	Longitudinal	11-14 yrs [a], (n = 587)	AHD	• Outpatient visit or hosp for asthma	Long term	• Distance	• Binary (10-km cut-off)	Petrochemical complex
Southern Africa									
Naidoo et al., 2013 [56]	South Durban (South Africa)	Cross-sectional	9-12 yrs, (n= 423)	Quest.	• Asthma ever (doctor-diagnosed) • Wheezing • Wheezing with shortness of breath • Persistent asthma	Long term	• Distance	• Binary (area-based)	N/S
White et al., 2009 [68]	Cape Town (South Africa)	Cross-sectional	11-14 yrs, (n = 2361)	Quest.	Prevalence of recent, frequent, and ever: [b] • Wheeze at rest • Waking with wheezing at night • Wheezing after exercise • Distressing wheeze at rest • Need to bring inhaler to school	Long term	• Distance • Distance, weighted for wind speed, wind direction	• Continuous • Continuous	Petrochemical refinery

Abbreviations: AHD, Administrative health data; CI, confidence interval; ERV, emergency room visit; HR, hazard ratio; mo, month; IDW, inverse-distance weighting; N/S, not specified; NO2, nitrogen dioxide; PM2.5, particulate matter of median diameter of less than 2.5 µm, PM10, particulate matter of median diameter of less than 10 µm; Quest., questionnaire; SES, socio-economic status; SHS, secondhand smoke; SO2, sulfur dioxide; TSP, total suspended particles; yr, year.

[a] In the study by Chiang et al. (2016) [54], the methods section states that the study population was children aged 11 to 14 yrs; however some estimates of association are reported for children with mean age of 6.65 yrs (standard deviation: 0.69 yrs).

[b] In the study by White et al. (2009) [68], "recent" was defined as in the last 12 months, whereas "frequent" as at least monthly in the last 12 months.

[c] In the study by Howel et al. (2001)[28] and Pless-Mulloli et al. (2000)[29], a symptom was defined as incident if it had not been present on the previous day.

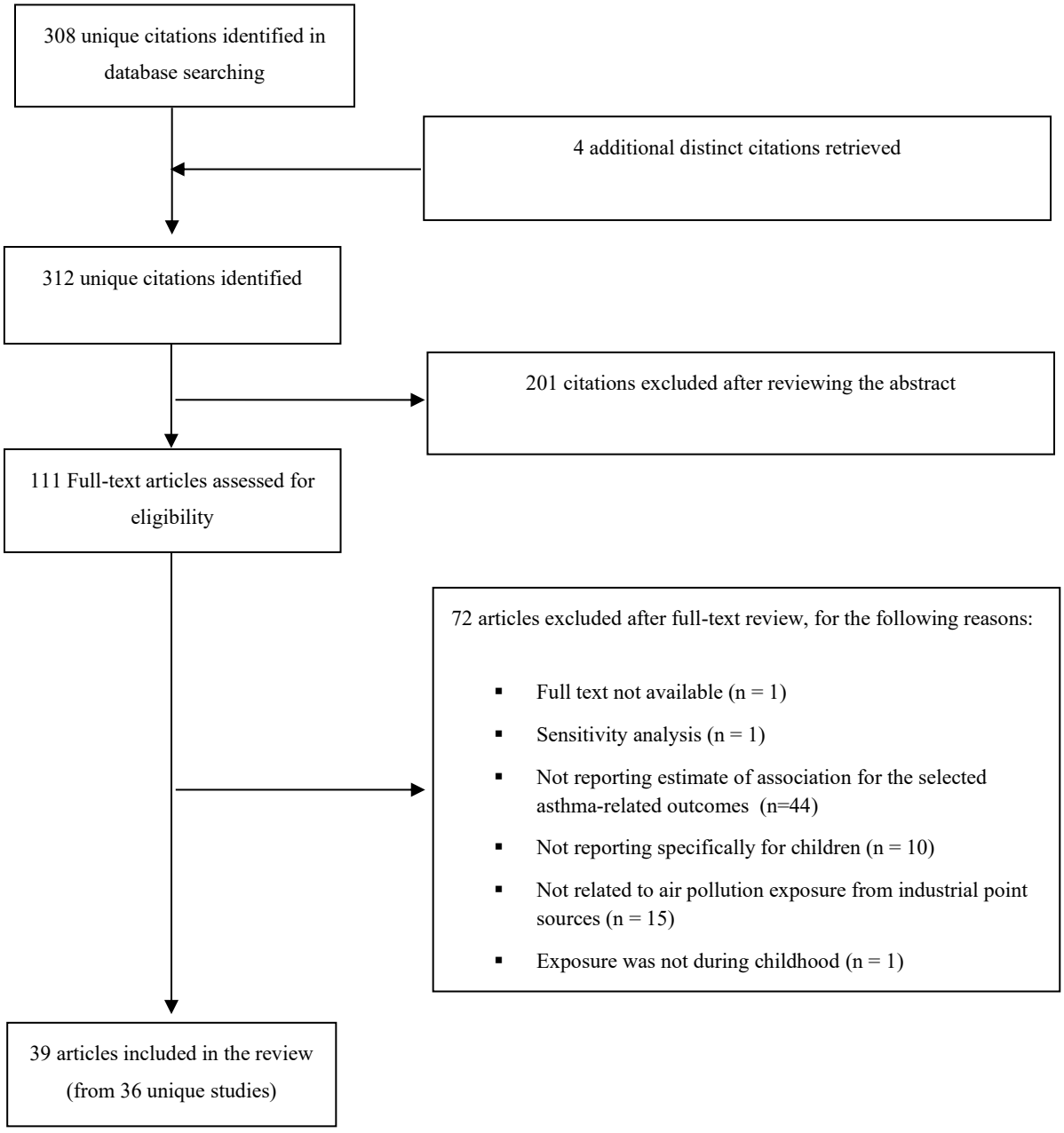
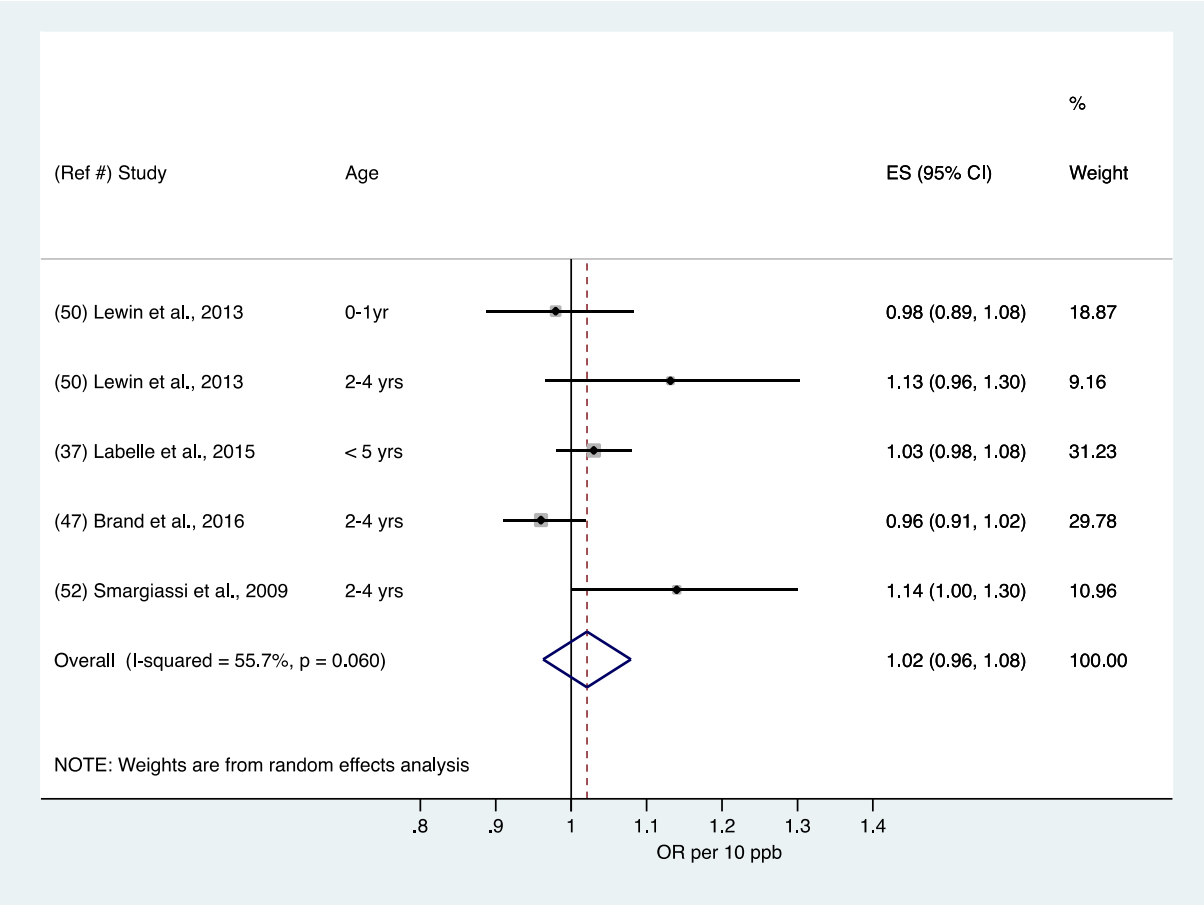


Figure 1: Flow chart presenting the selection of studies of the association between asthma-related outcomes and exposure to air pollution from industrial point sources.

A)


(Ref #) Study
Age
ES (95% CI)
%
Weight
(50) Lewin et al., 2013
0-1yr
0.98 (0.89, 1.08)
18.87
(50) Lewin et al., 2013
2-4 yrs
1.13 (0.96, 1.30)
9.16
(37) Labelle et al., 2015
< 5 yrs
1.03 (0.98, 1.08)
31.23
(47) Brand et al., 2016
2-4 yrs
0.96 (0.91, 1.02)
29.78
(52) Smargiassi et al., 2009
2-4 yrs
1.14 (1.00, 1.30)
10.96
Overall (I-squared = 55.7%, p = 0.060)
1.02 (0.96, 1.08)
100.00
NOTE: Weights are from random effects analysis
.8
.9
1
1.1
1.2
1.3
1.4
OR per 10 ppb

B)

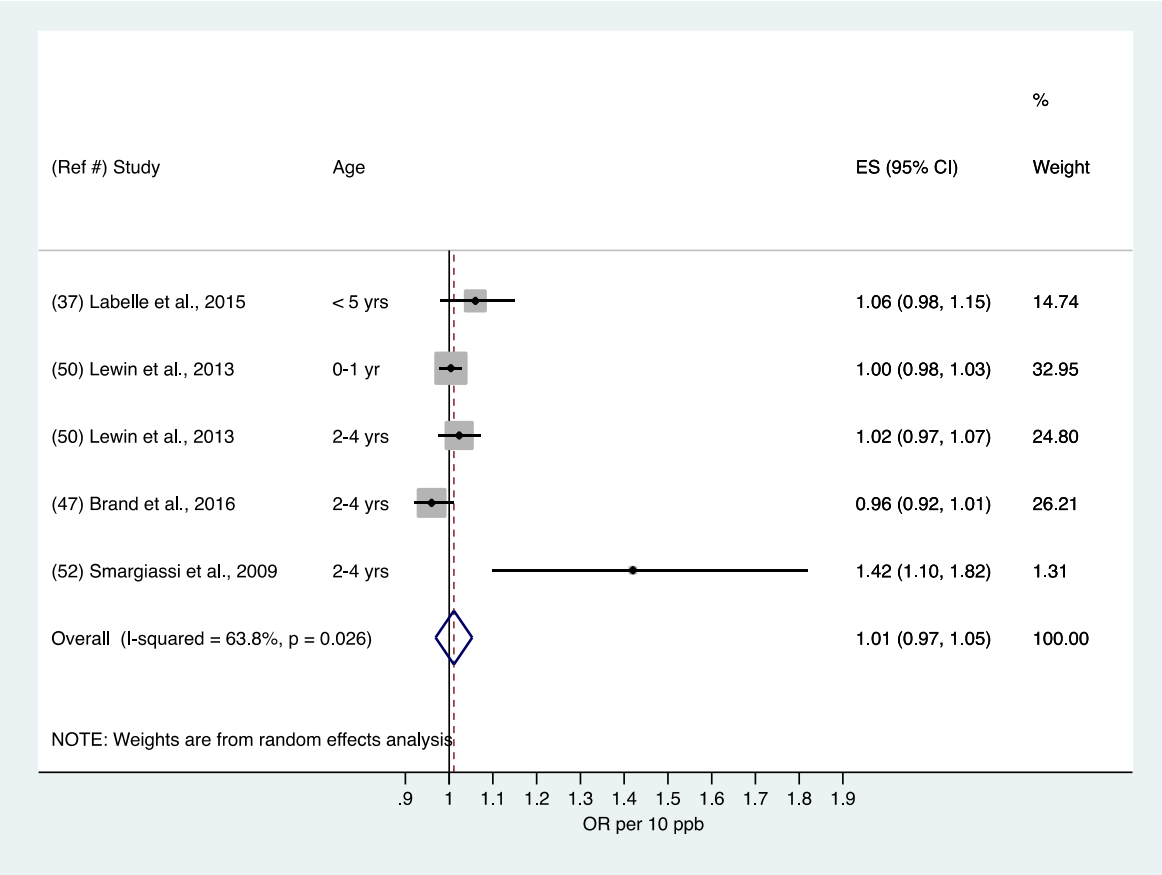


Figure 2. Forest plot of the association between hospitalization for asthma or bronchiolitis and A) same-day daily mean concentration of SO2, B) same-day hourly maximum concentration of SO2, from case-crossover studies using administrative health data. Effect size and 95% confidence intervals (CI) are expressed relative to a 10 ppb increase. Pooled estimates of effect size are indicated by black squares and 95% CI are represented by horizontal lines; size of black square around point estimate is proportional to weight in calculating pooled estimate.

A)

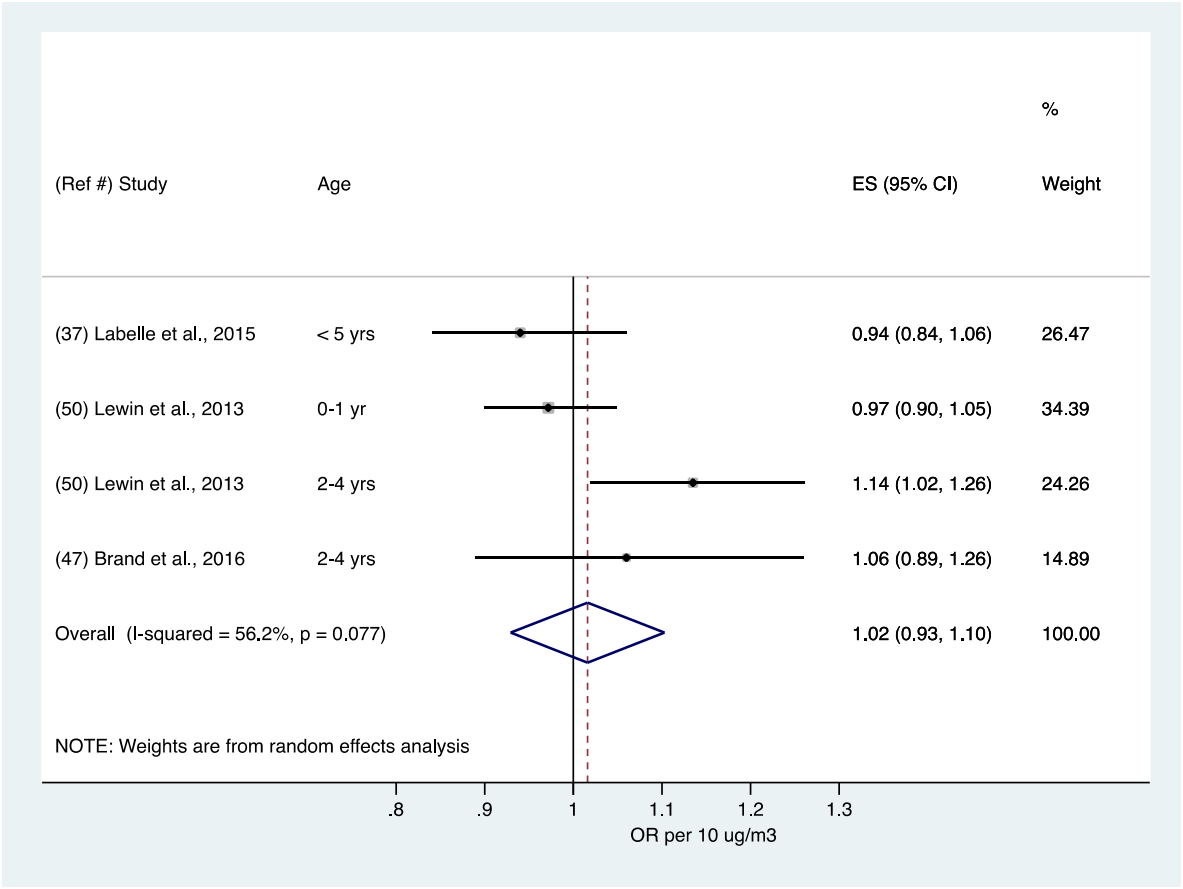


Figure 3. Forest plot of the association between hospitalization for asthma or bronchiolitis and A) same-day daily mean concentration of PM2.5

B)

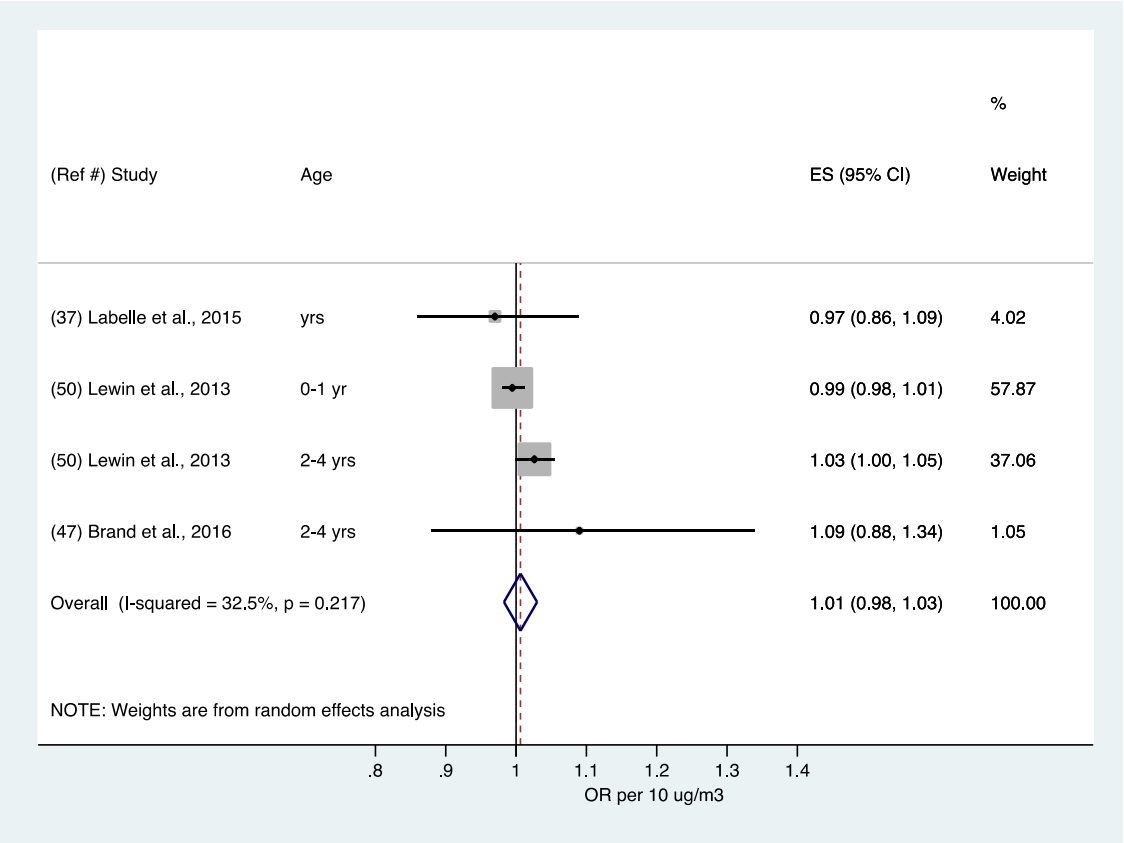


Figure 3 (continue) B) same-day hourly maximum concentration of PM2.5, from case-crossover studies using administrative health data. Odds ratios (OR) and 95% confidence intervals (CI) are expressed relative to a 10 μg/m^3 increase. Pooled random-effect estimate of ORs is indicated by vertical points of diamonds and 95% CI are represented by horizontal points. Black squares represent individual effect size of primary studies and the bars the 95% CI; size of black squares is proportional to weight in calculating random-effect summary estimate.

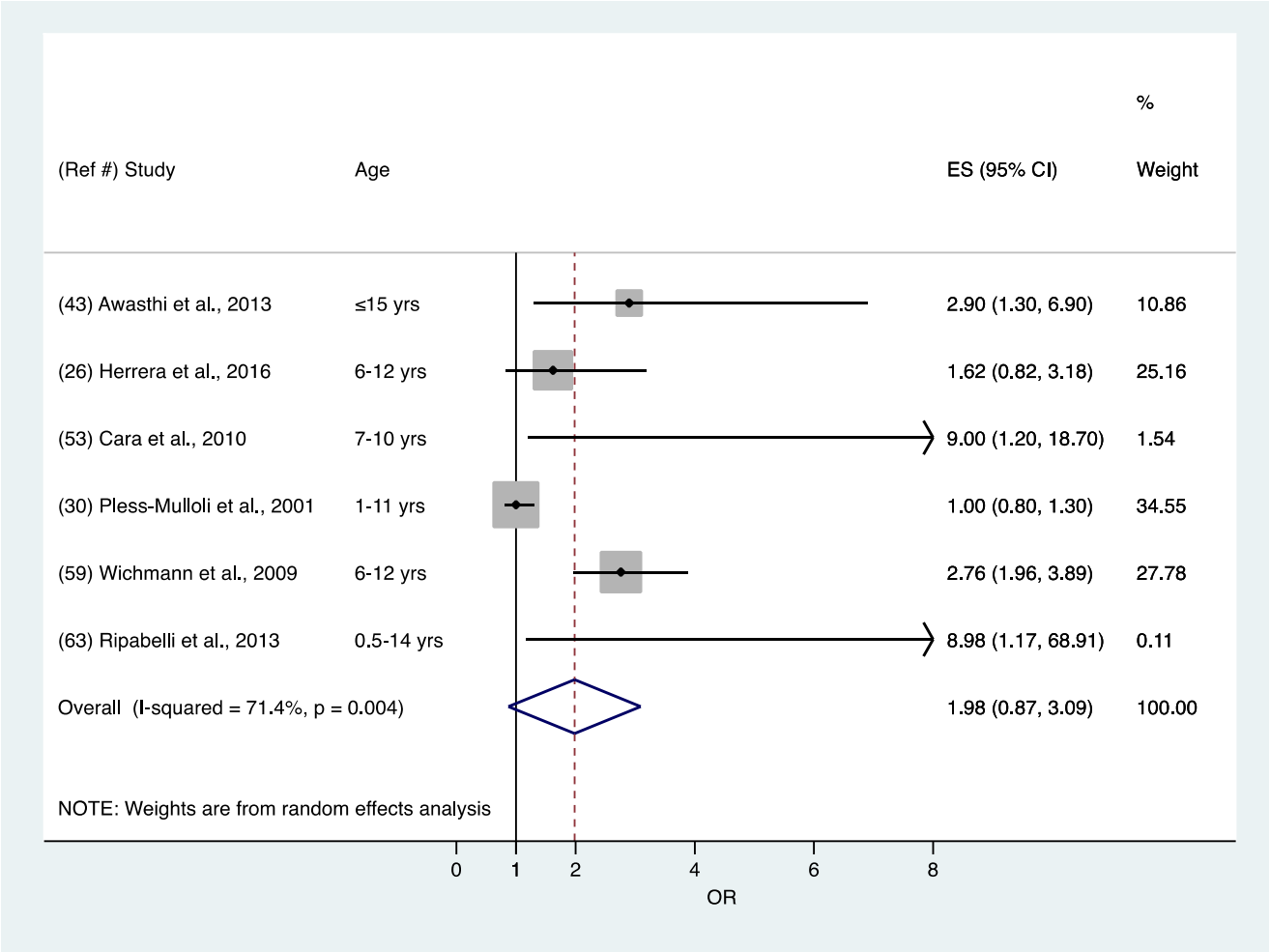


Figure 4. Forest plot of the association between residential proximity to industries and the prevalence of asthma, from cross-sectional studies using questionnaire. Pooled random-effect estimate of ORs is indicated by vertical points of diamonds and 95% CI are represented by horizontal points. Black squares represent individual effect size of primary studies and the bars the 95% CI; size of black squares is proportional to weight in calculating random-effect summary estimate. The arrows indicate that the confidence interval extends beyond the range of the value display.

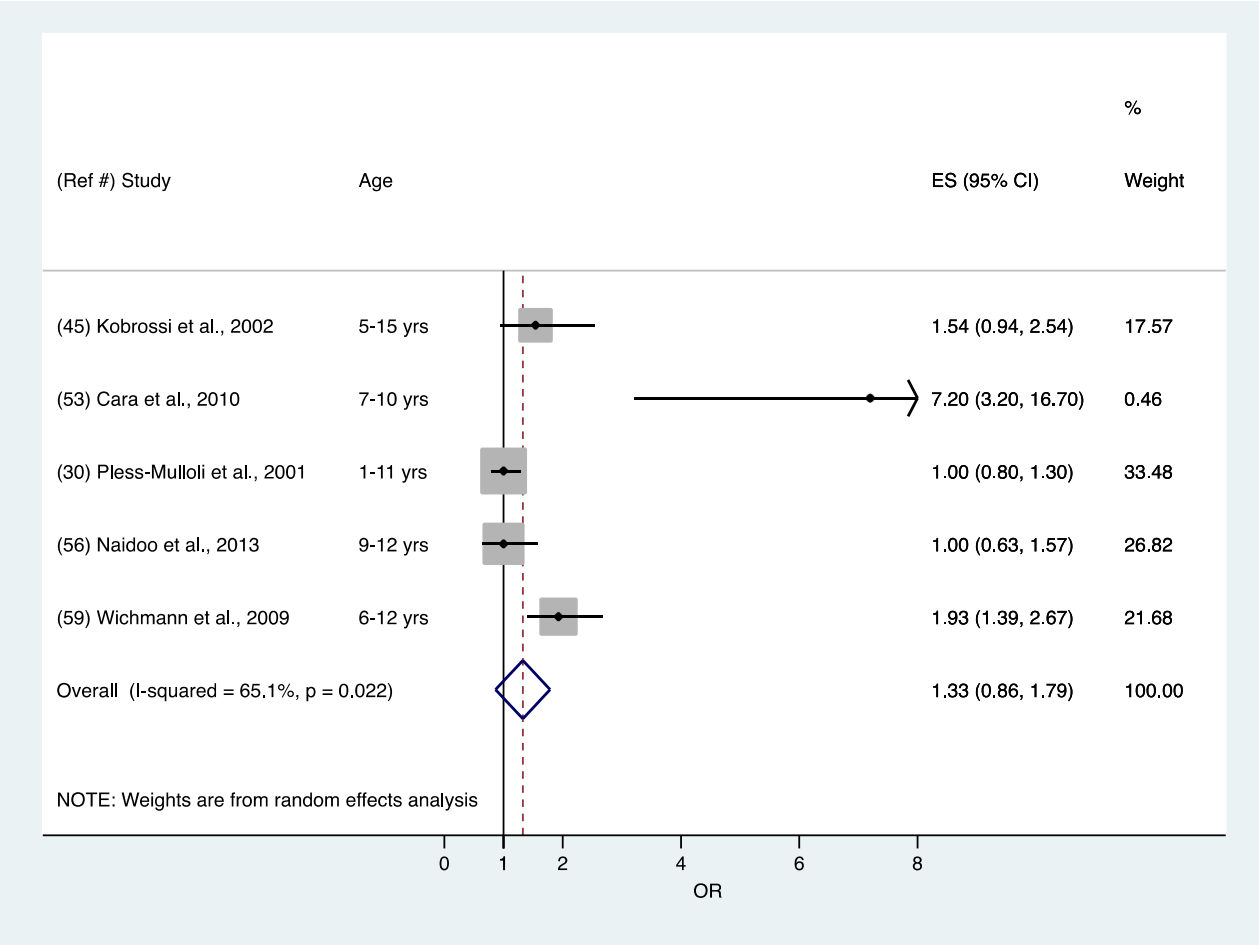


Figure 5. Forest plot of the association between residential proximity to industries and the prevalence of wheezing, from cross-sectional studies using questionnaire. Pooled random-effect estimate of ORs is indicated by vertical points of diamonds and 95% CI are represented by horizontal points. Black squares represent individual effect size of primary studies and the bars the 95% CI; size of black squares is proportional to weight in calculating random-effect summary estimate. The arrows indicate that the confidence interval extends beyond the range of the value display.

3.1.9 Appendix

Appendix A

Strategy and terms used searching bibliographic databases

We searched bibliographic databases using a combination of keywords targeting the following concepts: 1) Industries; 2) Air pollution; 3) Respiratory outcomes; 4) Children. The complete list of keywords is presented below:

Concept 1. Industries:

industr* OR industrial complex* OR coal min* OR smelter* OR refiner* OR power plant* OR wood industr* OR cement* OR paper mill* OR petrochemical OR chemical factor* OR coke work*

AND

Concept 2. Air Pollution :

air OR pollution OR pollutant* OR sulfur oxide OR sulfur dioxide OR nitrogen oxide OR nitrogen dioxide OR particle* OR particulate* OR emission

AND

Concept 3. Respiratory Outcomes:

respiratory OR infection* OR symptom* OR pulmonary OR bronchi* OR pneumoni* OR asthma OR lung function* OR allerg* OR consultation*

AND

Concept 4. Children

children OR infant OR preschooler OR adolescent

Appendix B

Additional results

Table B1. Description of the main characteristics of the selected studies, ordered by geographic region and country.

Reference	Location and period	Design	Children's age and sample size (or no. of events)	Type of outcome assessment	Asthma-related outcome	Type of industry	Exposure metrics	Covariates
North America								
Smargiassi et al., 2009	Montreal (Canada), 1996-2004	Case-crossover	2-4 yrs, n = 263 hospitalization; 1,579 emergency room visits	Administrative health data	• Hospitalization for asthma • Emergency department visits for asthma	Refineries	i) SO2 emissions from dispersion modeling ii) Ambient SO2 from fixed site monitors	Background air pollutant levels (daily mean concentrations of regional SO2, O3, NO2, and PM2.5), temperature, relative humidity
Deger et al., 2012	Montreal (Canada), 2006	Cross-sectional	0.5 - 12 yrs, n = 842	Questionnaire (ISAAC, ECHRS)	• Asthma ever • Wheezing in the past 12 months • Asthma attack in the past 12 months • Medication use against asthma in the past 12 months • Current wheeze at least 3 times per week.	Refineries	SO2 annual concentrations at the residence and school, estimated from dispersion modeling	Age, sex, family history of atopy, tobacco smoke exposure at home
Lewin et al., 2013	Shawinigan (Canada), 1999-2008	Case-crossover	0-4 yrs, n = 396 hospitalizations	Administrative health data	• Hospitalization for asthma	Aluminum smelter	i) The percentage of hours per day that the hospitalized child's residence was at downwind of the smelter. ii) SO2 and PM2.5 concentrations measured at a single fixed-site monitoring station	Average daily wind speed
Labelle et, al. 2015	Saguenay (Canada), 2001-2010	Case-crossover	0-4 yrs, n = 1 006 hospitalizations	Administrative health data	• Hospitalization for asthma and bronchiolitis	Industrial complex including a cast house, an alumina production plant, an iron smelter and a paper mill.	i) Daily mean and maximum concentrations of SO2 and PM2.5 at fixed monitoring stations. ii) Daily percentage of hours that a child's	Daily mean temperature, relative humidity, and average daily wind speed.

Reference	Location and period	Design	Children's age and sample size (or no. of events)	Type of outcome assessment	Asthma-related outcome	Type of industry	Exposure metrics	Covariates
							residence was downwind of the industry	
Buteau et al., 2018	Province of Québec (Canada), 2002-2011	Cohort	0-9 yrs, n = 722,667 (including 66,591 new cases of asthma)	Administrative health data	• Asthma onset	all industries reporting to the NPRI	i) Yearly number of tons of pollutant (PM2.5, SO2) emitted by industries within 2.5km of the residence; ii) Distance (in meters) between the residence and the closest industries emitting 100 tons of PM2.5 or SO2; iii) Yearly number of tons of pollutant (PM2.5, SO2) emitted by the closest major industries (100 tons/year), weighted by the inverse of the distance and percentage of time downwind.	Sex, material and social deprivation, calendar year, and unmeasured secondhand smoke (indirect adjustment).
Brand et al., 2016	Province of Quebec and of British Columbia (Canada), 2002-2010	Case-crossover	2-4 yrs, n = 2868 hospital admissions for wheezing diseases	Administrative health data	• Hospitalization for asthma and bronchiolitis	Pulp mills, metal smelters and oil refineries (from the NPRI)	i) air pollutant (PM2.5, SO2, and NO2) emissions by industries within 7.5km, weighted by the percentage of time downwind ii) Daily ambient PM2.5, SO2, NO2 at central fixed-site monitoring stations	Daily average temperature, relative humidity, and wind speed.

Reference	Location and period	Design	Children's age and sample size (or no. of events)	Type of outcome assessment	Asthma-related outcome	Type of industry	Exposure metrics	Covariates
Clark et al., 2010	Southwestern British Columbia (Canada), 1999-2003	Nested case-control	3-4 yrs, n = 37,401 (including 3,482 new cases of asthma)	Administrative health data	• Asthma onset	All types	Inverse distance-weighted summation of emissions from point sources within 10 km	Native status, breast-feeding, maternal smoking, income quintile, education quartile, maternal age, birth weight, gestational length and sex (strata)
Karr et al., 2009	Georgia Air Basin, British Columbia (Canada), 1999-2003	Nested case-control	2-12 months, n = 11,676 cases and 57,127 controls	Administrative health data	• Outpatient visit or hospitalization for bronchiolitis	All types	Proximity-weighted summation of emissions from point sources within 10 km of the residence	Sex, gestational age, first nation status, parity, maternal age, maternal smoking during pregnancy, maternal initiation of breastfeeding at birth, income, maternal education, and date of birth (matched).
Liu et al., 2012	New-York State (excluding New York city) (USA), 1993-2008	Cohort	<10 yrs, n =21,524,390 person-yrs	Administrative health data	• Hospitalization for asthma	Fuel-fired power plant, electric generators, and hazardous waste site.	Residential proximity (binary; children residing in a ZIP code with at least one fuel-fired power plant were exposed).	Sex, race/ethnicity, age, median household income, urban/rural.
Maantay et al., 2007	Bronx, New York City (USA), 1995-1999	Ecological	0-15 yrs, n = 20,764 asthma hospitalizations	Administrative health data	• Hospitalization for asthma	Facilities reporting to TRI and other major point sources	Residential proximity (binary; one-quarter mile cut-off)	Poverty, minority status
Patel et al., 2011	Northern Manhattan and the South Bronx (USA), 1998-2010	Longitudinal	0-5 yrs, n = 593	Questionnaire	• Current wheeze and doctor-diagnosed asthma	Not specified	Percentage of residential buffer area within 0.80 km of an industrial facility were considered as exposed.	Age, sex, ethnicity, presence of smokers in the home, annual house hold income, residential concentrations of cockroach and mouse allergen, four way intersection density and

Reference	Location and period	Design	Children's age and sample size (or no. of events)	Type of outcome assessment	Asthma-related outcome	Type of industry	Exposure metrics	Covariates
								percentage of building area designated for commercial use.
Mirabelli and Wing, 2006	North Carolina (USA), 1999-2000	Cross-sectional	12-14 yrs, n = 64,432	Questionnaire (ISAAC)	• Wheezing in past 12 months	Pulp and paper mill	i) School proximity (3 categories: 0-≤10 miles; >10-≤30 miles; >30 miles) ii) Odor reported (binary) iii) Distance and odor (binary: 0-≤10 and odor; >30 miles and no odor)	Sex, age, race, socioeconomic status, cigarette smoking, household cigarette smoke exposure, use of a gas kitchen stove at home
Latin America and the Caribbean								
Loyo-Berrios et al., 2007	Catano (Puerto Rico), 1997-2001	Nested case-control	<17 yrs n = 6282 (including 1382 cases)	Administrative health data	• Asthma-related medical visits	Industrial park, including rum distillery, electric power plants, petroleum refineries, sewage incinerator and treatment plants, cement plants.	i) Distance (continuous) to minor (<100 tons/year) and major>100 tons/year) industries ii) Distance (continuous)) to minor (<100 tons/year) and major>100 tons/year) industries, adjusted for same-day wind direction	cases and controls were matched on sex, age, insurance company, and event date
Wichmann et al., 2009	La Plata (Argentina), 2005-2006	Cross-sectional	6-12 yrs, n = 1212	Questionnaire (ISAAC)	• Asthma ever (doctor-diagnosed) • Asthma exacerbations in previous 12 months	Petrochemical complex	Residential proximity (binary; children living in neighborhoods next to the petrochemical complex were considered as exposed).	Age, sex, secondhand smoke, living close to busy roads or other non-petrochemical industries, time of residence in the study area, home environment, length of exclusive breast-feeding and family socioeconomic and demographic data

Reference	Location and period	Design	Children's age and sample size (or no. of events)	Type of outcome assessment	Asthma-related outcome	Type of industry	Exposure metrics	Covariates
Lopes de Moraes et al., 2010	Guamaré (Brazil), 2006	Cross-sectional	0-14 yrs, n = 209	Questionnaire (ISAAC)	• Wheezing ever ; • Wheezing in past 12 months ; • No. of wheezing attacks in past 12 months; • Sleep disturbance by wheezing in past 12 months • Speech limiting wheezing in past 12 months • Asthma ever	Petrochemical complex	Children living for at least 1 year in communities located within 5 km and downwind of petrochemical complex were considered as exposed.	Age, sex, race, family income, parental education, number of persons living in the house per room, water supply and disposition of household waste, presence or absence of farming activities, environmental tobacco smoke
Herrera et al., 2016	Northen Chile (Chile), 2009	Cross-Sectional	6-15 yrs, n = 288	Questionnaire (ISAAC)	• Asthma ever (doctor diagnosed or taking asthma medications in past 12 months)	Opencast mining sites (gold and copper).	Residential proximity to each mine separately and the average distance (binary; 1st quartile as the cut-off)	Parental history of atopic diseases, child's mother working, living with both parents
Prieto-Parra et al., 2017	Santiago (Chile), winter (May–September) of 2010-2011	Panel (12 weeks follow-up)	6-14 yrs, n = 174 (90 asthmatics and 84 non-asthmatics)	Questionnaire and daily diary	• Wheezing • Medication for asthma crisis	Copper smelter	i) Air pollutant concentration (PM2.5, PM10, PM2.5-10, CO, NO2, SO2, O3) measured one fixed site monitor ii) PM2.5 composition measured fixed site monitors iii) PM2.5 sources contribution estimated from positive matric factorization	Viruses (Influenza B, parainfluenza, respiratory syncytial virus, adenovirus), time variables (weekday, year), and meteorology (minimum temperature, relative humidity)
Europe or Central Asia								

Reference	Location and period	Design	Children's age and sample size (or no. of events)	Type of outcome assessment	Asthma-related outcome	Type of industry	Exposure metrics	Covariates
Pless-Mulloli et al., 2000; Pless-Mulloli et al., 2001; Howel et al. 2001.	Northern England (United Kingdom), 1996-1997	Cross-sectional	1-11 yrs, n = 3216	Questionnaire (ISAAC)	Lifetime prevalence: • Wheeze • Asthma Period prevalence (past 12 months): • >12 Wheezing in past 12 months • Woken child at night in past 12 months • Limited speech in past 12 months • Occurred on exercise in past 12 months	Opencast coal mining sites	Distance (binary; 5 communities near industries *vs* 5 referent communities further away)	Age, sex, community pairs, number of people in household, environmental tobacco smoke, presence of moulting pets, use of polluting fuel to heat or cook, quality of insulation, indicator of damp, housing tenure, unemployment, access to transport, family history of asthma, eczema/hay fever, propensity of parent to worry, population stability
Pless-Mulloli et al., 2000; Pless-Mulloli et al., 2001; Howel et al. 2001.	Northern England (United Kingdom), 1996-1997	Panel	1-11 yrs, n = 244	Daily diary	Daily prevalence and incidence of respiratory symptoms: • Wheeze • Asthma reliever use	Opencast coal mining sites	Daily PM10 concentration from fixed site monitors	Age, sex, community pairs, number of people in household, environmental tobacco smoke, presence of moulting pets, use of polluting fuel to heat or cook, quality of insulation, indicator of damp, housing tenure, unemployment, access to transport, family history of asthma, eczema/hay fever, propensity of parent to worry, population stability
Aylin et al., 2001	England and Wales (United Kingdom), 1992-1995	Time series	0-4 yrs, n = approx. 43,932	Administrative health data	• Emergency hospital admission for asthma	Coke works	Distance (continuous)	Age, sex, deprivation quintile, medical service provider

Reference	Location and period	Design	Children's age and sample size (or no. of events)	Type of outcome assessment	Asthma-related outcome	Type of industry	Exposure metrics	Covariates
Ripabelli et al., 2013	Termoli (Italy), 2008-2009	Cross-sectional	6 mo. - 14 yrs, n = 95	Questionnaire (ISAAC)	• Asthma	Not specified	Residential proximity (binary; living in Termoli (yes/no))	Age, gender
Rosa et al., 2016	Brescia (Italy), period not specified	Cross-sectional	11-14 yrs, n = 280	Questionnaire (ISAAC, ECRHS)	• Asthma • Asthma medication use in past 12 months • Wheezing in the past 12 months	Ferroalloy plants	PM10 and metals (Mn, Ni, Cr, Fe, Zn) concentrations measured for 24 hours using personal monitoring	Maternal asthma, child's sex, child's age and SES status
Rusconi et al., 2011	Sarroch and Brucei (Italy), 2006	Cross-sectional	6-14 yrs, n = 489	Questionnaire (ISAAC)	• Wheezing symptoms in past 12 months	Petrochemical high-complexity refinery and liquid fuel gasification plants.	Residential proximity (binary; Children living in Sarroch and Burcei were classified as exposed and unexposed, respectively)	Age, sex, active smoking, environmental tobacco smoke, parental education, distance to major road, respiratory infections in the last week, history of steroid prescriptions in the last 12 months, damp or mold in child's bedroom
De Marco et al., 2010; Rava et al., 2011; Rava et al., 2012	Viadana District (Italy), 2006	Cross-sectional	3-14 yrs, n = 3854	Questionnaire (ISAAC)	• doctor-diagnosed asthma • current asthma-like symptoms (in last 12 months) Asthma-like symptoms score (sums of symptoms by subjects) • asthma severity index	Chipboard industries	Residential and school proximity, 3-level categorical: Unexposed : no wood factories < 2 km from home and school; Low exposure : at least 1 low emission factory (but no chipboard industries) <2 km from home or school; High exposure: at least 1 chipboard industry <2 km from home or school.	Age, sex, nationality, residential area, frequency of heavy traffic, parental education, questionnaire complier (mother, father or others), compiler's environmental concern, environmental tobacco smoke, parents' smoking
Rovira et al., 2014	Tarragona (Spain), 2010	Cross-sectional	6-7 yrs (n = 2672) and 13-14 yrs (n = 2524)	Questionnaire (ISAAC)	• Wheezing ever • Wheezing in past 12 months • Wheezing with exercise in past 12 months	Oil refinery, chemical industries, petro-chemical plants, a municipal solid waste incinerator,	Residential proximity to petrochemical sites: Subjects residing in municipalities near two large petrochemical sites and those living in a city	Gender, length of residence in the town, parents' nationality, parental history of asthma, family affluence

Reference	Location and period	Design	Children's age and sample size (or no. of events)	Type of outcome assessment	Asthma-related outcome	Type of industry	Exposure metrics	Covariates
					• Severe wheezing • Asthma ever	a hazardous waste incinerator, and two power plants.	with medium vehicular traffic were cross-sectionally compared with children from an area with low vehicular traffic and without industry.	and passive and active smoking
Hruba et al., 2001	Banska Bystrica (Slovakia), 1996	Cross-Sectional	7-11 yrs, n = 667	Questionnaire (ISAAC)	• Asthma (doctor-diagnosed) • Hospital admission ever for asthma or bronchitis or pneumonia. • Wheeze ever	Wood processing facility, cement plant, pharmaceutical company.	TSP Annual average concentrations at the residence from industrial emissions, estimated from dispersion modeling, and treated as quartile in the analysis.	Age, sex, mother's education, number of smokers in house, moisture stain or molds in house, parental history of asthma or atopy
Cara et al., 2007	Calarasi and Roseti (Romania), 1994-2002	Cohort	<2 yrs n= 851	Administrative health data	• Wheezing (doctor-diagnosed)	Iron, steel and coke factory	Residential proximity (binary, community-based) to the industry and cohorts before vs after factory closure:	Environmental tobacco smoke, family history of allergy, at least 1 year of breastfeeding, presence of mould on the walls
Cara et al., 2010	Calarasi and Roseti (Romania), 1994-2002	Cross-sectional	7-10 yrs, n = 519	Questionnaire (ISAAC)	• Asthma ever (doctor-diagnosed) • Wheezing ever • Wheezing in past 12 months • No. of wheezing attacks in past 12 months • Sleep disturbance by wheezing in past 12 months • Speech limiting wheezing in past 12 months • Exercise related wheezing in past 12 months	Iron, steel, and coke factory	Residential proximity (binary, community-based) to the industry and cohorts before vs after factory closure.	Gender, birth cohort, environmental tobacco smoke, family history of allergy, at least six months of breastfeeding, the presence of mould in the house
Middle East								

Reference	Location and period	Design	Children's age and sample size (or no. of events)	Type of outcome assessment	Asthma-related outcome	Type of industry	Exposure metrics	Covariates
Alwahaibi et al., 2016	Province of Sohar and of Liwa (Oman), 2006-2010	Time series	≤ 1 yr (n = 7998), 1-14 yrs (n = 12,148)	Administrative health data	• Medical clinics visits for asthma	Petrochemical industrial complex, iron smelter	Residential proximity, 3-level categorical variable: - low/unexposed: ≥ 20 km from the refinery - moderate exposure: 5-10 km from the refinery - high exposure: ≤ 5 km from the refinery.	Age, gender, time trend, and SES.
Kobrossi et al., 2002	Districts of Koura, Batroun and Jbeil (Lebanon), 1999-2000	Cross-sectional	5-15 yrs, n = 486	Questionnaire (ATS)	• Wheezing • Wheezing after physical exercise	Four cement factories, one lime and plaster factory, one asbestos-cement factory, and two fertilizer factories	Residential proximity (binary; residents of Koura and Batroun are exposed; residents of Jbeil are unexposed)	Age, gender, parental education, income, type of residence, crowding index, dust level indoors, humidity index, frequency of heavy traffic, presence of carpets in bedrooms, use of polluting fuel to heat, school sector, number of classmates, frequency of exercise, number of persons sharing the child's bed, child allergies and eczema
Nirel et al., 2015	Neot Hovav (Israel), 2004-2009	Case-control	0-14 yrs, n = 6666 (3608 cases and 3058 controls)	Administrative health data	• Hospitalization for asthma	Hazardous waste treatment site	Residential proximity, (3-level categorical variable: low/unexposed : >20 km ; moderate exposure : 11–20 km ; high exposure : ≤10 km)	gender, area-level SES (low: ≤40th percentile for the study population, high: >40th percentile), urbanity and stratified by age group (0–1, 2–5, 6–14 yrs old)
Karakis et al, 2009	Negev (Isreal), 2002	Cross-sectional	0-14 yrs, n = 550	Administrative health data	• Asthma life prevalence (medical clinics visits for asthma)	Industrial park including chemical, pharmacochemical	i. Residential proximity (binary; using a 20 km cut-off)	Gender, parental origin, parental education, mother's marital status, child's birth history,

Reference	Location and period	Design	Children's age and sample size (or no. of events)	Type of outcome assessment	Asthma-related outcome	Type of industry	Exposure metrics	Covariates
						and heavy industries, industrial hazardous waste disposal site and an incinerator.	ii. Dominant wind direction was also considered as a binary indicator of exposure for those living within the 20 km buffer	pregnancy type, pregnancy complications, multiple gestation, mother's medication during pregnancy, mother's infectious diseases during pregnancy, delivery complications, environmental tobacco smoke, parents' hazardous occupational exposure, home pesticides use, pets, family history of asthma, number of people in household
East, South and Southeast Asia								
Deng et al., 2015	Changsha (China), 2011-2012	Cross-sectional	3-6 yrs, n = 2490	Questionnaire (ISAAC)	• Doctor-diagnosed asthma	All types	SO2 (continuous and quartiles) average concentration at kindergartens during 1st year of life, estimated from IDW of measurements at 7 monitoring stations.	Sex, age, birth weight, breast feeding, gestational age, and living area and covariates for parents were parental smoking during pregnancy, maternal age (the mother's age at the time of child's birth), parental atopy, and socio economic status.
Awasthi et al., 2013	Lucknow (India), 2007-2009	Case-control	≤15 yrs, n = 348 (211 cases, 137 controls)	Questionnaire	• Asthma symptoms from clinic record	Smoke emitting industries	Residential proximity (binary; living within 1.5 km of industrial area with emission of smoke)	Family type, birth order, motor vehicle air pollution, smoking status
Chiang et al., 2016 [a]	Taiwan, 1999-2010	Longitudinal	11-14 yrs, n = 587	Administrative health data	• Outpatient visit or hospitalization for asthma	Petrochemical complex	Residential proximity (binary; 10-km cut-off)	Age, sex, living near roads, passive smoking exposure, incense burning

Reference	Location and period	Design	Children's age and sample size (or no. of events)	Type of outcome assessment	Asthma-related outcome	Type of industry	Exposure metrics	Covariates
Southern Africa								
Naidoo et al., 2013	South Durban (South Africa), period not specified	Cross-sectional	9-12 yrs, n= 423	Questionnaire	• Doctor-diagnosed asthma • Wheezing • Wheezing with shortness of breath • Persistent asthma	Not specified	Children living in four communities in south Durban in close proximity to industrial area were considered as exposed and living in three communities in north Durban were considered as unexposed.	Age, gender, race/ethnicity, previous history of respiratory disease, education level of primary caregiver, smoker in the household, atopy status, annual household income.
White et al., 2009 [b]	Cape Town (South Africa), 2002	Cross-sectional	11-14 yrs, n = 2361	Questionnaire (ISAAC)	Prevalence of recent, frequent, and ever: • Wheeze at rest • Waking with wheezing at night • Wheezing after exercise • Distressing wheeze at rest • Need to bring inhaler to school	Petrochemical refinery	i) Distance (continuous) ii) Distance (continuous), weighted for wind speed, wind direction and proportion of the year blown	Family history of atopic disease, passive smoking, distance from a major road, sex.

Abbreviations: ATS, American Thoracic Society; CI, confidence interval; HR, hazard ratio; IDW, inverse-distance weighting; ISAAC, The International Study of Asthma and Allergies in Childhood; max., maximum; N/A, not applicable (as the metric of exposure is categorical); NPRI, National Pollutant release inventory (https://www.canada.ca/en/services/environment/pollution-waste-management/national-pollutant-release-inventory.html); NO2, nitrogen dioxide; OR, odds ratio; PM2.5, particulate matter of median diameter of less than 2.5 µm, PM10, particulate matter of median diameter of less than 10 µm; RR, risk ratio; SES, socio-economic status; SO2, sulfur dioxide; TRI, Toxics related inventory program (https://www.epa.gov/toxics-release-inventory-tri-program); TSP, total suspended particles; yr, year.

[a] In the study by Chiang et al. (2016), the methods section states that the study population was children aged 11 to 14 yrs; however some estimates of association are reported for children with mean age of 6.65 yrs (standard deviation: 0.69 yrs).

b In the study by White et al. (2009), recent was defied as in the last 12 months, whereas frequent was defined as at least monthly in the last 12 months.

c In the study by Howel et al. (2001) and Pless-Mulloli et al. (2000), a symptom was defined as incident if it had not been present on the previous day.

Table B2. Description studies making use of administrative health data in the investigation of the association between air pollution from industrial point source and asthma-related outcomes in childhood, ordered by metric of exposure and outcome.

Reference	Design	Outcomes	Age group (in years)	Type of industry	Exposure metric	Results			
						Increment	Effect	Mean	95% CI
Exposure metric: PM25 concentration									
Labelle et al. 2015	Case-crossover	Hospitalisation for asthma or bronchiolitis	<5	Aluminum smelter	PM2.5 (fixed site) - daily mean	4.3 µg/m^3	OR	0.94	0.84-1.06
Lewin et al., 2013[a]	Case-crossover	Hospitalisation for asthma or bronchiolitis	≤1	Aluminum smelter	PM2.5 (fixed site) - daily mean	14.3 µg/m^3	OR	0.96	0.86-1.07
Lewin et al., 2013[a]	Case-crossover	Hospitalisation for asthma or bronchiolitis	2-4	Aluminum smelter	PM2.5 (fixed site) - daily mean	15.7 µg/m^3	OR	1.22	1.03-1.44
Brand et al., 2016	Case-crossover	Hospitalisation for asthma or bronchiolitis	2-4	Pulp mills, metal smelters, oil refineries	PM2.5 (fixed site) - daily mean	5.8 µg/m^3	OR	1.06	0.89-1.26
Labelle et al., 2015	Case-crossover	Hospitalisation for asthma or bronchiolitis	< 5	Aluminum smelter	PM2.5 (fixed site) - daily hourly max.	10.0 µg/m^3	OR	0.97	0.86-1.09
Lewin et al., 2013[a]	Case-crossover	Hospitalisation for asthma or bronchiolitis	≤1	Aluminum smelter	PM2.5 (fixed site) - daily hourly max.	57.0 µg/m^3	OR	0.97	0.89-1.07
Lewin et al., 2013[a]	Case-crossover	Hospitalisation for asthma or bronchiolitis	2-4	Aluminum smelter	PM2.5 (fixed site) - daily hourly max.	57.5 µg/m^3	OR	1.16	0.99-1.36
Brand et al., 2016	Case-crossover	Hospitalisation for asthma or bronchiolitis	2-4	Pulp mills, metal smelters, oil refineries	PM2.5 (fixed site) - daily hourly max.	14.7 µg/m^3	OR	1.09	0.88-1.34
Exposure metric: SO2 concentration									
Lewin et al., 2013[a]	Case-crossover	Hospitalisation for asthma or bronchiolitis	0-1	Aluminum smelter	SO2 (fixed site) - daily mean	9.7 ppb	OR	0.98	0.89-1.08
Lewin et al., 2013[a]	Case-crossover	Hospitalisation for asthma or bronchiolitis	2-4	Aluminum smelter	SO2 (fixed site) - daily mean	8.4 ppb	OR	1.11	0.97-1.25
Labelle et al., 2015	Case-crossover	Hospitalisation for asthma or bronchiolitis	< 5	Aluminum smelter	SO2 (fixed site) - daily mean	9.2 ppb	OR	1.03	0.98-1.08
Brand et al., 2016	Case-crossover	Hospitalisation for asthma or bronchiolitis	2-4	Pulp mills, metal smelters, oil refineries	SO2 (fixed site) - daily mean	2.3 ppb	OR	0.96	0.91-1.02
Smargiassi et al., 2009	Case-crossover	Hospitalisation for asthma	2-4	Petrochemical refineries	SO2 (fixed site) - daily mean, lag 0	6.3 ppb	OR	0.91	0.67-1.23
Smargiassi et al., 2009	Case-crossover	Hospitalisation for asthma	2-4	Petrochemical refineries	SO2 (dispersion model) - daily mean, lag 0	4.3 ppb	OR	1.14	1.00-1.30
Smargiassi et al., 2009	Case-crossover	Hospitalisation for asthma	2-4	Petrochemical refineries	SO2 (fixed site) - daily mean, lag 1	6.3 ppb	OR	0.84	0.63-1.21
Smargiassi et al., 2009	Case-crossover	Hospitalisation for asthma	2-4	Petrochemical refineries	SO2 (dispersion model) - daily mean, lag 1	4.3 ppb	OR	1.03	0.91-1.16
Smargiassi et al., 2009	Case-crossover	Hospitalisation for asthma	2-4	Petrochemical refineries	SO2 (fixed site) - 5-day mean (lag 0 to lag 4)	4.4 ppb	OR	0.71	0.46-1.09
Smargiassi et al., 2009	Case-crossover	Hospitalisation for asthma	2-4	Petrochemical refineries	SO2 (dispersion model) - 5-day mean (lag 0 to lag 4)	3.6 ppb	OR	1.07	0.87-1.31

Reference	Design	Outcomes	Age group (in years)	Type of industry	Exposure metric	Results			
						Increment	Effect	Mean	95% CI
Labelle et al., 2015	Case-crossover	Hospitalisation for asthma or bronchiolitis	< 5	Aluminum smelter	SO2 (fixed site) - daily hourly max.	47.0 ppb	OR	1.06	0.98-1.15
Lewin et al., 2013[a]	Case-crossover	Hospitalisation for asthma or bronchiolitis	0-1	Aluminum smelter	SO2 (fixed site) - daily hourly max.	48.0 ppb	OR	1.02	0.90-1.15
Lewin et al., 2013[a]	Case-crossover	Hospitalisation for asthma or bronchiolitis	2-4	Aluminum smelter	SO2 (fixed site) - daily hourly max.	45.8 ppb	OR	1.11	0.89-1.38
Brand et al., 2016	Case-crossover	Hospitalisation for asthma or bronchiolitis	2-4	Pulp mills, metal smelters, oil refineries	SO2 (fixed site) - daily hourly max.	7.2 ppb	OR	0.96	0.92-1.01
Smargiassi et al., 2009	Case-crossover	Hospitalisation for asthma	2-4	Petrochemical refineries	SO2 (dispersion model) - daily hourly max., lag 0	31.2 ppb	OR	1.42	1.10-1.82
Smargiassi et al., 2009	Case-crossover	Hospitalisation for asthma	2-4	Petrochemical refineries	SO2 (dispersion model) - daily hourly max., lag 1	31.2 ppb	OR	1.01	0.79-1.29
Smargiassi et al., 2009	Case-crossover	Emergency department visits for asthma	2-4	Petrochemical refineries	SO2 (fixed site) - daily mean, lag 0	6.3 ppb	OR	1.04	0.94-1.16
Smargiassi et al., 2009	Case-crossover	Emergency department visits for asthma	2-4	Petrochemical refineries	SO2 (dispersion model) - daily mean, lag 0	4.3 ppb	OR	1.04	0.98-1.10
Smargiassi et al., 2009	Case-crossover	Emergency department visits for asthma	2-4	Petrochemical refineries	SO2 (fixed site) - daily mean, lag 1	6.3 ppb	OR	1.06	0.96-1.17
Smargiassi et al., 2009	Case-crossover	Emergency department visits for asthma	2-4	Petrochemical refineries	SO2 (dispersion model) - daily mean, lag 1	4.3 ppb	OR	1.05	1.00-1.12
Smargiassi et al., 2009	Case-crossover	Emergency department visits for asthma	2-4	Petrochemical refineries	SO2 (fixed site) - 5-day mean (i.e., lag 0 - lag 4)	4.4 ppb	OR	1.17	0.99-1.39
Smargiassi et al., 2009	Case-crossover	Emergency department visits for asthma	2-4	Petrochemical refineries	SO2 (fixed site) - daily hourly max., lag 0	11.9 ppb	OR	1.03	0.94-1.14
Smargiassi et al., 2009	Case-crossover	Emergency department visits for asthma	2-4	Petrochemical refineries	SO2 (dispersion model) - daily hourly max., lag 0	31.2 ppb	OR	1.10	1.00-1.22
Smargiassi et al., 2009	Case-crossover	Emergency department visits for asthma	2-4	Petrochemical refineries	SO2 (fixed site) - daily hourly max., lag 1	11.9 ppb	OR	0.95	0.86-1.06
Smargiassi et al., 2009	Case-crossover	Emergency department visits for asthma	2-4	Petrochemical refineries	SO2 (dispersion model) - daily hourly max., lag 1	31.2 ppb	OR	1.05	0.95-1.16
Smargiassi et al., 2009	Case-crossover	Emergency department visits for asthma	2-4	Petrochemical refineries	SO2 (fixed site) - 5-day mean (i.e., lag 0 - lag 4)	3.7 ppb	OR	0.969	0.73-1.29
Smargiassi et al., 2009	Case-crossover	Emergency department visits for asthma	2-4	Petrochemical refineries	SO2 (dispersion model) - 5-day mean (i.e., lag 0 - lag 4)	3.6 ppb	OR	1.04	0.94-1.14
Exposure metric: NO2 concentration									
Brand et al., 2016	Case-crossover	Hospitalisation for asthma or bronchiolitis	2-4	Pulp mills, metal smelters, oil refineries	NO2 (fixed site) - daily mean	7.4 ppb	OR	1.09	0.65-1.82
Brand et al., 2016	Case-crossover	Hospitalisation for asthma or bronchiolitis	2-4	Pulp mills, metal smelters, oil refineries	NO2 (fixed site) - daily hourly max.	14.6 ppb	OR	1.15	0.64-2.06
Exposure metric: Distance (categorical)									

Reference	Design	Outcomes	Age group (in years)	Type of industry	Exposure metric	Results			
						Increment	Effect	Mean	95% CI
Alwahaibi et al., 2016	Cross-sectional	visits to health clinics for asthma	≤ 1	Petrochemical	Distance (≤10 km vs ≥20km)	N/A	RR	3.6	2.2-6.1
Alwahaibi et al., 2016	Cross-sectional	visits to health clinics for asthma	1-14	Petrochemical	Distance (≤10 km vs ≥20km)	N/A	RR	4.6	3.8-5.7
Alwahaibi et al., 2016	Cross-sectional	visits to health clinics for asthma follow-ups	≤ 1	Petrochemical	Distance (≤10 km vs ≥20km)	N/A	RR	4.4	1.9-10.1
Alwahaibi et al., 2016	Cross-sectional	visits to health clinics for asthma follow-ups	1-14	Petrochemical	Distance (≤10 km vs ≥20km)	N/A	RR	3.5	2.8-4.4
Liu et al., 2012	Cohort	Hospitalisation for asthma	< 10	Fuel-fired power plant	Distance (binary, living in a ZIP code that contained a fuel-fired power plant)	N/A	RR	1.01	0.91-1.12
Liu et al., 2012	Cohort	Hospitalisation for asthma	< 10	Hazardous waste site	Distance (binary, living in a ZIP code that contained a hazardous waste site)	N/A	RR	1.11	1.03-1.19
Liu et al., 2012	Cohort	Hospitalisation for asthma	< 10	Fuel-fired power plant and hazardous waste site	Distance (binary, living in a ZIP code that contained a fuel-fired power plant and a hazardous waste site)	N/A	RR	1.19	1.11-1.28
Maantay et al., 2007	Ecological	Hospitalisation for asthma	0-15	All industries reporting to the TRI	Distance (binary; cut-off: one-quarter mile radius)	N/A	OR	1.22	1.14-1.30
Maantay et al., 2007	Ecological	Hospitalisation for asthma	0-15	other major stationary point sources	Distance (binary; cut-off: one-quarter mile radius)	N/A	OR	1.23	1.16-1.30
Chiang et al., 2016	Longitudinal	Emergency department visits for asthma	Mean (SD) : 6.65 (0.69)	Petrochemical	Distance (binary; cut-off: 10km)	N/A	HR	1.60	1.03-2.48
Chiang et al., 2016	Longitudinal	Emergency department visits for asthma	Mean (SD) : 10.65 (0.69)	Petrochemical	Distance (binary; cut-off: 10km)	N/A	HR	1.28	0.89-1.83
Chiang et al., 2016	Longitudinal	Emergency department visits for asthma	Mean (SD) : 13.65 (0.69)	Petrochemical	Distance (binary; cut-off: 10km)	N/A	HR	1.29	0.91-1.83
Nirel et al., 2015[2]	Case-control	Hospitalisation for acute bronchitis, pneumonia, asthma, bronchitis	0-1	Industrial complex	Distance (≤10 km vs >20km)	N/A	OR	2.31	1.39-3.81
Nirel et al., 2015[b]	Case-control	Hospitalisation for acute bronchitis, pneumonia, asthma, bronchitis	2-5	Industrial complex	Distance (≤10 km vs >20 km)	N/A	OR	1.05	0.74-1.49
Nirel et al., 2015[b]	Case-control	Hospitalisation for acute bronchitis, pneumonia, asthma, bronchitis	6-14	Industrial complex	Distance (≤10 km vs >20 km)	N/A	OR	0.83	0.50-1.38
Nirel et al., 2015[b]	Case-control	Hospitalisation for acute bronchitis, pneumonia, asthma, bronchitis	0-1	Industrial complex	Distance (11-20 km vs >20 km)	N/A	OR	1.24	0.89-1.72
Nirel et al., 2015[b]	Case-control	Hospitalisation for acute bronchitis, pneumonia, asthma, bronchitis	2-5	Industrial complex	Distance (11-20 km vs >20km)	N/A	OR	0.97	0.75-1.26
Nirel et al., 2015[b]	Case-control	Hospitalisation for acute bronchitis, pneumonia, asthma, bronchitis	6-14	Industrial complex	Distance (11-20km vs >20km)	N/A	OR	1.04	0.73-1.48

Reference	Design	Outcomes	Age group (in years)	Type of industry	Exposure metric	Results			
						Increment	Effect	Mean	95% CI
Buteau et al., 2018	Cohort	Asthma onset	0-9	All major (≥100 tons) SO2 emitters from NPRI	Distance (binary; cut-off: 7.5km)	N/A	HR	1.09	1.07-1.11
Buteau et al., 2018	Cohort	Asthma onset	0-9	All major (≥100 tons) PM2.5 emitters from NPRI	Distance (binary; cut-off: 7.5km)	N/A	HR	1.03	1.00-1.05
Exposure metric: Distance (continuous)									
Aylin et al., 2001	Time series	Hospitalisation for asthma	0-4	Coke works	Distance (continuous, up to 7.5km)	1-km decrease	RR	1.07	0.98-1.18
Loyo-Berrios et al., 2007	Nested case-control	Asthma-related medical visits	<17	Major (≥100 tons) industrial point source	Distance (continuous)	1-km decrease	OR	1.69	1.50-1.91
Loyo-Berrios et al., 2007	Nested case-control	Asthma-related medical visits	<17	Minor (<100 tons) industrial point source	Distance (continuous)	1-km decrease	OR	1.95	1.51-2.53
Buteau et al., 2018	cohort	Asthma onset	0-9	Major (≥100 tons) SO2 emitters from NPRI	Distance (continuous, up to 7.5km)	1-km decrease	HR	1.02	1.01-1.03
Buteau et al., 2018	cohort	Asthma onset	0-9	Major (≥100 tons) PM2.5 emitters from NPRI	Distance (continuous, up to 7.5km)	1-km decrease	HR	1.00	0.99-1.01
Exposure metric: Wind direction (categorical)									
Karakis et al., 2009	Cross-sectional	Asthma prevalence from clinic records	0-14	Chemical factory	Wind direction (binary)	N/A	OR	1.95	1.01-3.76
Exposure metric: Wind direction (continuous)									
Lewin et al., 2013[a]	Case-crossover	Hospitalisation for asthma or bronchiolitis	0-1	Aluminum smelter	Percentage of hours downwind	29%	OR	1.00	0.84-1.20
Lewin et al., 2013[a]	Case-crossover	Hospitalisation for asthma or bronchiolitis	2-4	Aluminum smelter	Percentage of hours downwind	21%	OR	1.27	1.03-1.56
Labelle et al., 2015	Case-crossover	Hospitalisation for asthma or bronchiolitis	< 5	Aluminum smelter	Percentage of hours downwind	27%	OR	1.11	1.01-1.22
Exposure metric: Emissions									
Buteau et al., 2018	Cohort	Asthma onset	0-9	All PM2.5 emitters from NPRI	Tons of PM2.5 from all emitters within 2.5 km of the residence	13 tons	HR	1.002	1.001-1.003
Buteau et al., 2018	Cohort	Asthma onset	0-9	All SO2 emitters from NPRI	Tons of SO2 from all emitters within 2.5 km of the residence	327 tons	HR	1.003	1.003-1.005
Exposure metric: Emissions, adjusted for wind direction									
Brand et al., 2016	Case-crossover	Hospitalisation for asthma or bronchiolitis	2-4	Pulp mills, metal smelters, oil refineries	Tons of PM2.5 emitted, weighted for percentage of time downwind	0.15 tons/day	OR	1.03	0.99-1.06
Brand et al., 2016	Case-crossover	Hospitalisation for asthma or bronchiolitis	2-4	Pulp mills, metal smelters, oil refineries	Tons of SO2 emitted, weighted for percentage of time downwind	1.50 tons/day	OR	1.02	1.00-1.04
Brand et al., 2016	Case-crossover	Hospitalisation for asthma or bronchiolitis	2-4	Pulp mills, metal smelters, oil refineries	Tons of NO2 emitted, weighted for percentage of time downwind	0.40 tons/day	OR	0.99	0.88-1.11
Exposure metric: Distance, adjusted for wind direction									

Reference	Design	Outcomes	Age group (in years)	Type of industry	Exposure metric	Results			
						Increment	Effect	Mean	95% CI
Loyo-Berrios et al., 2007	Nested case-control	Asthma-related medical visits	< 17	Power plants	Distance, corrected for wind direction	1-km decrease	OR	1.12	1.03-1.22
Loyo-Berrios et al., 2007	Nested case-control	Asthma-related medical visits	< 17	Grain mills	Distance, corrected for wind direction	1-km decrease	OR	1.38	1.28-1.49
Loyo-Berrios et al., 2007	Nested case-control	Asthma-related medical visits	< 17	Petroleum refineries	Distance, corrected for wind direction	1-km decrease	OR	1.33	1.24-1.42
Loyo-Berrios et al., 2007	Nested case-control	Asthma-related medical visits	< 17	Asphalt plants	Distance, corrected for wind direction	1-km decrease	OR	1.39	1.29-1.50
Exposure metric: Emissions, corrected for distance									
Clark et al., 2010[c]	Nested case-control	Asthma onset	0-4	Industrial complex	Industrial point source score (from emissions and distance to point sources within 10 km, during 1st year of life)	30 points	OR	1.10	1.04-1.17
Karr et al., 2009[c]	Nested case-control	Hospitalisation and ER for bronchiolitis	2 mo -1yr	not specified	Industrial point source score (from emissions and distance to point sources within 10 km, during 1st year of life)	28 points	OR	1.10	1.06-1.13
Exposure metric: Emissions, corrected for distance and wind direction									
Buteau et al., 2018	Cohort	Asthma onset	0-9	All major (≥100 tons) PM2.5 emitters from NPRI	Wind and inverse-distance weighted emissions of closest major emitter	255 tons-km^{-1}	HR	Positive non-linear response function	
Buteau et al., 2018	Cohort	Asthma onset	0-9	All major (≥100 tons) SO2 emitters from NPRI	Wind and inverse-distance weighted emissions of closest major emitter	98 tons-km^{-1}	HR	1.004	1.003-1.006
Exposure metric: Before vs after closure of the industry									
Cara et al., 2007	Cohort	Wheezing, during first year of life	< 2	Iron, steel and coke factory	Cohort born after closure vs cohort ≥2 years old at time of the closure	N/A	OR	0.38	0.19-0.76
Cara et al., 2007	Cohort	Wheezing, during first 2 years of life	< 2	Iron, steel and coke factory	Cohort born after closure vs cohort ≥2 years old at time of the closure	N/A	OR	0.44	0.23-0.82

Abbreviations: CI, confidence interval; HR, hazard ratio; max., maximum; mo, month; N/A, not applicable (as the metric of exposure is categorical); NPRI, National Pollutant release inventory (Canada, https://www.canada.ca/en/services/environment/pollution-waste-management/national-pollutant-release-inventory.html); NO2, nitrogen dioxide; OR, odds ratio; PM2.5, particulate matter of median diameter of less than 2.5 µm, PM10, particulate matter of median diameter of less than 10 µm; RR, risk ratio, SO2, sulfur dioxide; TRI, Toxics related inventory program (USA, https://www.epa.gov/toxics-release-inventory-tri-program); yr, year.

[a] Results reported for Lewin et al. (2013) are those for children living within 7.5 km of the industries. For air pollutants, similar findings were reported when restricting to children living within 2.5 km of the point source. For wind direction, stronger mean effect estimates were obtained for children living within 2.5 km of the point source, however confidence intervals were wider due to reduced power (≤1 year, OR = 1.08 (95% CI: 0.76-1.53); 2-4 years, OR=1.45 (95% CI: 1.00-2.12)).

[b] Results reported by Nirel et al. (2015) are for hospitalisation for acute bronchitis, pneumonia, asthma, bronchitis; although not reported in the paper the authors mentioned in the text that similar results were obtained were restricting the analysis to asthma only.

[c] In the study by Karr et al., (2009) and Clark et al. (2010), the metric of exposure was an index value calculated as follow: each point source was assigned an index value base on its pollutant contribution (PM2.5, NOx, SOx, VOC) relative to other point sources in the region. Exposure at the children's postal code was determined using the inverse-distance weighted summations of emissions from point sources within 10 km.

[d] In the study by Smargiassi et al., (2009) two distinct monitoring stations were used to assess SO2 of two communities and associations were reported separately for these two communities. One of the communities is less affected by emissions (based on wind direction) and the monitoring station is located further away (median distance 5.6 km). Therefore, we decided to report findings for the community that is mostly exposed to emissions and for which the monitoring station likely provide a better estimate of people's exposure (median distance 1.6 km)

Table B3. Description studies making use of questionnaire or diary in the investigation of the association between air pollution from industrial point source and asthma-related outcomes in childhood, ordered by metric of exposure and outcome.

Study reference	Study design	Asthma-related outcome	Age group (years)	Type of industries	Metric of exposure	Results			
						Exposure increment	Effect	Mean	95% CI
Metric of exposure: PM25 concentration (continuous)									
Prieto-Parra et al., 2017	Panel	Wheezing	6-14	Copper smelter	PM2.5 (fixed site), 1-day average	18.0 µg/m^3	OR	1.01	0.85-1.23
Prieto-Parra et al., 2017	Panel	Wheezing	6-14	Copper smelter	PM2.5 (fixed site), 3-day average	18.0 µg/m^3	OR	1.05	0.85-1.30
Prieto-Parra et al., 2017	Panel	Wheezing	6-14	Copper smelter	PM2.5 (fixed site), 5-day average	18.0 µg/m^3	OR	1.25	1.04-1.70
Prieto-Parra et al., 2017	Panel	Wheezing	6-14	Copper smelter	PM2.5 (fixed site), 7-day average	18.0 µg/m^3	OR	1.60	1.15-2.26
Prieto-Parra et al., 2017	Panel	Reliever use	6-14	Copper smelter	PM2.5 (fixed site), 1-day average	18.0 µg/m^3	OR	0.93	0.83-1.06
Prieto-Parra et al., 2017	Panel	Reliever use	6-14	Copper smelter	PM2.5 (fixed site), 3-day average	18.0 µg/m^3	OR	0.92	0.80-1.07
Prieto-Parra et al., 2017	Panel	Reliever use	6-14	Copper smelter	PM2.5 (fixed site), 5-day average	18.0 µg/m^3	OR	0.93	0.79-1.08
Prieto-Parra et al., 2017	Panel	Reliever use	6-14	Copper smelter	PM2.5 (fixed site), 7-day average	18.0 µg/m^3	OR	0.95	0.79-1.13
Metric of exposure: ambient PM25 concentration from industrial emissions									
Prieto-Parra et al., 2017	Panel	Wheezing	6-14	Copper smelter	PM2.5 (fixed site), 1-day average	N/S	OR	0.85	0.71-0.99
Prieto-Parra et al., 2017	Panel	Wheezing	6-14	Copper smelter	PM2.5 (fixed site), 3-day average	N/S	OR	0.86	0.69-1.03
Prieto-Parra et al., 2017	Panel	Wheezing	6-14	Copper smelter	PM2.5 (fixed site), 5-day average	N/S	OR	0.89	0.70-1.11
Prieto-Parra et al., 2017	Panel	Wheezing	6-14	Copper smelter	PM2.5 (fixed site), 7-day average	N/S	OR	0.85	0.51-1.07
Prieto-Parra et al., 2017	Panel	Reliever use	6-14	Copper smelter	PM2.5 (fixed site), 1-day average	N/S	OR	0.97	0.89-1.08
Prieto-Parra et al., 2017	Panel	Reliever use	6-14	Copper smelter	PM2.5 (fixed site), 3-day average	N/S	OR	0.91	0.84-1.07
Prieto-Parra et al., 2017	Panel	Reliever use	6-14	Copper smelter	PM2.5 (fixed site), 5-day average	N/S	OR	0.88	0.80-1.07
Prieto-Parra et al., 2017	Panel	Reliever use	6-14	Copper smelter	PM2.5 (fixed site), 7-day average	N/S	OR	0.94	0.80-1.11
Metric of exposure: PM10 concentration									

Study reference	Study design	Asthma-related outcome	Age group (years)	Type of industries	Metric of exposure	Results			
						Exposure increment	Effect	Mean	95% CI
Rosa et al., 2016	Cross-sectional	Asthma	11-14	Ferroalloy activity	PM10 (personal monitoring), 24-h mean	38 µg/m^3	OR	1.12	1.00-1.21
Naidoo et al., 2013 [a]	Cross-sectional	Persistent asthma	9-12	N/S	PM10 (fixed site at school), 8-mo. Average	12.6 µg/m^3	OR	1.09	0.56-2.12
Pless-Mulloli et al., 2000; Howel et al., 2001 [C]	Panel	Wheezing (incidence) [b]	1-11	Opencast mining	PM10 (fixed site), 24-h mean lag 0	10.0 µg/m^3	OR	1.16	1.05-1.28
Pless-Mulloli et al., 2000; Howel et al., 2001 [C]	Panel	Wheezing (incidence) [b]	1-11	Opencast mining	PM10 (fixed site), 24-h mean lag 1	10.0 µg/m^3	OR	1.02	0.87-1.19
Pless-Mulloli et al., 2000; Howel et al., 2001 [C]	Panel	Wheezing (prevalence)	1-11	Opencast mining	PM10 (fixed site), 24-h mean lag 0	10.0 µg/m^3	OR	1.05	0.96-1.15
Pless-Mulloli et al., 2000; Howel et al., 2001 [C]	Cross-sectional	Wheezing (prevalence)	1-11	Opencast mining	PM10 (fixed site), 24-h mean lag 1	10.0 µg/m^3	OR	1.03	0.93-1.13
Naidoo et al., 2013 [a]	Cross-sectional	Wheezing	9-12	N/S	PM10 (fixed site at school), 8-mo. Average	12.6 µg/m^3	OR	1.27	0.75-2.15
Prieto-Parra et al., 2017	Panel	Wheezing	6-14	Copper smelter	PM10 (fixed site), daily mean	40.6 µg/m^3	OR	0.95	0.80-1.12
Prieto-Parra et al., 2017	Panel	Wheezing	6-14	Copper smelter	PM10 (fixed site), 3-day average	40.6 µg/m^3	OR	0.99	0.79-1.22
Prieto-Parra et al., 2017	Panel	Wheezing	6-14	Copper smelter	PM10 (fixed site), 5-day average	40.6 µg/m^3	OR	1.12	0.89-1.46
Prieto-Parra et al., 2017	Panel	Wheezing	6-14	Copper smelter	PM10 (fixed site), 7-day average	40.6 µg/m^3	OR	1.40	1.01-2.00
Naidoo et al., 2013 [a]	Cross-sectional	Wheezing with SOB	9-12	N/S	PM10 (fixed site at school), 8-mo. Average	12.6 µg/m^3	OR	0.98	0.88-1.10
Rosa et al., 2016	Cross-sectional	Wheezing in past 12 mo.	11-14	Ferroalloy activity	PM10 (personal monitoring), 24-h mean	38 µg/m^3	OR	0.58	0.28-1.21
Rosa et al., 2016	Cross-sectional	Asthma medication use, past 12 mo.	11-14	Ferroalloy activity	PM10 (personal monitoring), 24-h mean	38 µg/m^3	OR	1.21	1.09-1.35
Pless-Mulloli et al., 2000; Howel et al., 2001 [C]	Cross-sectional	Reliever use	1-11	Opencast mining	PM10 (fixed site), 24-h mean lag 0	10.0 µg/m^3	OR	1.00	0.94-1.06
Pless-Mulloli et al., 2000; Howel et al., 2001 [C]	Cross-sectional	Reliever use	1-11	Opencast mining	PM10 (fixed site), 24-h mean lag 1	10.0 µg/m^3	OR	1.01	0.94-1.07

Study reference	Study design	Asthma-related outcome	Age group (years)	Type of industries	Metric of exposure	Results			
						Exposure increment	Effect	Mean	95% CI
Prieto-Parra et al., 2017	Panel	Reliever use	6-14	Copper smelter	PM10 (fixed site), 1-day average	40.6 μg/m^3	OR	0.92	0.85-1.05
Prieto-Parra et al., 2017	Panel	Reliever use	6-14	Copper smelter	PM10 (fixed site), 3-day average	40.6 μg/m^3	OR	0.91	0.80-1.05
Prieto-Parra et al., 2017	Panel	Reliever use	6-14	Copper smelter	PM10 (fixed site), 5-day average	40.6 μg/m^3	OR	0.85	0.80-1.09
Prieto-Parra et al., 2017	Panel	Reliever use	6-14	Copper smelter	PM10 (fixed site), 7-day average	40.6 μg/m^3	OR	0.96	0.81-1.17
Metric of exposure: TSP concentration									
Hruba et al., 2001	Cross-sectional	Asthma	7-10	Wood industries	TSP (dispersion modeling), annual average	15.0 μg/m^3	OR	1.62	0.62-4.19
Hruba et al., 2001	Cross-sectional	Wheezing	7-10	Wood industries	TSP (dispersion modeling), annual average	15.0 μg/m^3	OR	1.24	0.68-2.28
Hruba et al., 2001	Cross-sectional	Hospital admission for asthma, bronchitis, or pneumonia	7-10	Wood industries	TSP (dispersion modeling), annual average	15.0 μg/m^3	OR	2.16	1.01-4.60
Metric of exposure: Metals concentration									
Rosa et al., 2016	Cross-sectional	Asthma	11-14	Ferroalloy activity	Mn from PM10 24-h personal monitoring	38 ng/m^3	OR	1.09	1.00-1.18
Rosa et al., 2016	Cross-sectional	Asthma	11-14	Ferroalloy activity	Ni from PM10 24-h personal monitoring	42 ng/m^3	OR	1.11	1.02-1.20
Rosa et al., 2016	Cross-sectional	Asthma	11-14	Ferroalloy activity	Fe from PM10 24-h personal monitoring	4 ng/m^3	OR	1.00	1.00-1.00
Rosa et al., 2016	Cross-sectional	Asthma	11-14	Ferroalloy activity	Cr from PM10 24-h personal monitoring	498 ng/m^3	OR	1.08	1.06-1.11
Rosa et al., 2016	Cross-sectional	Asthma	11-14	Ferroalloy activity	Zn from PM10 24-h personal monitoring	72 ng/m^3	OR	1.00	0.81-1.33
Rosa et al., 2016	Cross-sectional	Wheezing in past 12 mo.	11-14	Ferroalloy activity	Mn from PM10 24-h personal monitoring	38 ng/m^3	OR	1.09	0.92-1.29
Rosa et al., 2016	Cross-sectional	Wheezing in past 12 mo.	11-14	Ferroalloy activity	Ni from PM10 24-h personal monitoring	42 ng/m^3	OR	1.00	0.83-1.21
Rosa et al., 2016	Cross-sectional	Wheezing in past 12 mo.	11-14	Ferroalloy activity	Fe from PM10 24-h personal monitoring	4 ng/m^3	OR	1.00	0.99-1.00
Rosa et al., 2016	Cross-sectional	Wheezing in past 12 mo.	11-14	Ferroalloy activity	Cr from PM10 24-h personal monitoring	498 ng/m^3	OR	1.06	0.96-1.17
Rosa et al., 2016	Cross-sectional	Wheezing in past 12 mo.	11-14	Ferroalloy activity	Zn from PM10 24-h personal monitoring	72 ng/m^3	OR	0.75	0.36-1.65
Rosa et al., 2016	Cross-sectional	Asthma medication use past 12 mo.	11-14	Ferroalloy activity	Mn from PM10 24-h personal monitoring	38 ng/m^3	OR	1.13	1.00-1.23

Study reference	Study design	Asthma-related outcome	Age group (years)	Type of industries	Metric of exposure	Results			
						Exposure increment	Effect	Mean	95% CI
Rosa et al., 2016	Cross-sectional	Asthma medication use past 12 mo.	11-14	Ferroalloy activity	Ni from PM10 24-h personal monitoring	42 ng/m^3	OR	1.11	1.00-1.24
Rosa et al., 2016	Cross-sectional	Asthma medication use past 12 mo.	11-14	Ferroalloy activity	Fe from PM10 24-h personal monitoring	4 ng/m^3	OR	1.00	1.00-1.00
Rosa et al., 2016	Cross-sectional	Asthma medication use past 12 mo.	11-14	Ferroalloy activity	Cr from PM10 24-h personal monitoring	498 ng/m^3	OR	1.06	0.97-1.15
Rosa et al., 2016	Cross-sectional	Asthma medication use past 12 mo.	11-14	Ferroalloy activity	Zn from PM10 24-h personal monitoring	72 ng/m^3	OR	1.15	0.93-1.54
Metric of exposure: SO2 concentration									
Deng et al., 2015	Cross-sectional	Asthma	3-6	N/S	SO2 (IDW from fixed site monitors), average during 1st yr of life at kindergarten	50.0 ppb	OR	1.62	1.01-2.60
Naidoo et al., 2013 [a]	Cross-sectional	Persistent asthma	9-12	N/S	SO2 (fixed site at school), 8-mo. Average	6.7 ppb	OR	1.37	0.80-2.35
Naidoo et al., 2013 [a]	Cross-sectional	Wheezing	9-12	N/S	SO2 (fixed site at school), 8-mo. Average	6.7 ppb	OR	1.13	0.73-1.74
Prieto-Parra et al., 2017	Panel	Wheezing	6-14	Copper smelter	SO2 (fixed site), 1-day average	1 ppb	OR	0.92	0.80-1.09
Prieto-Parra et al., 2017	Panel	Wheezing	6-14	Copper smelter	SO2 (fixed site), 3-day average	1 ppb	OR	0.94	0.79-1.17
Prieto-Parra et al., 2017	Panel	Wheezing	6-14	Copper smelter	SO2 (fixed site), 5-day average	1 ppb	OR	1.00	0.80-1.31
Prieto-Parra et al., 2017	Panel	Wheezing	6-14	Copper smelter	SO2 (fixed site), 7-day average	1 ppb	OR	1.05	0.81-1.48
Naidoo et al., 2013 [a]	Cross-sectional	Wheezing with SOB	9-12	N/S	SO2 (fixed site at school), 8-mo. Average	6.7 ppb	OR	0.86	0.49-1.53
Prieto-Parra et al., 2017	Panel	Reliever use	6-14	Copper smelter	SO2 (fixed site), 1-day average	1 ppb	OR	0.96	0.90-1.05
Prieto-Parra et al., 2017	Panel	Reliever use	6-14	Copper smelter	SO2 (fixed site), 3-day average	1 ppb	OR	0.95	0.82-1.10
Prieto-Parra et al., 2017	Panel	Reliever use	6-14	Copper smelter	SO2 (fixed site), 5-day average	1 ppb	OR	0.97	0.82-1.13
Prieto-Parra et al., 2017	Panel	Reliever use	6-14	Copper smelter	SO2 (fixed site), 7-day average	1 ppb	OR	1.05	0.90-1.25
Metric of exposure: Distance (categorical)									
Awasthi et al., 2013	Case-control	Asthma	<=15	N/S	Distance (binary, cut-off: 1.5km)	N/A	OR	2.90	1.30-6.90
Herrera et al., 2016	Cross-sectional	Asthma	6-12	Opencast mining	Distance (binary, cut-off 1st quartile of distance)	N/A	OR	1.62	0.82-3.18

Study reference	Study design	Asthma-related outcome	Age group (years)	Type of industries	Metric of exposure	Results			
						Exposure increment	Effect	Mean	95% CI
Ripabelli et al., 2012	Cross-sectional	Asthma	0.5-14	N/S	Distance (binary, community-based)	N/A	OR	8.98	1.17-68.91
Cara et al., 2010	Cross-sectional	Asthma	7-10	Heavy industries	Distance (binary, community-based)	N/A	OR	9.00	1.20-18.70
Pless-Mulloli et al., 2000; 2001 [C]	Cross-sectional	Asthma	1-11	Opencast mining	Distance (binary, community-based)	N/A	OR	1.0	0.8-1.3
Wichmann et al., 2009	Cross-sectional	Asthma	6-12	Petrochemical	Distance (binary, community-based)	N/A	OR	2.76	1.96-3.89
Rovira et al., 2014	Cross-sectional	Asthma	6-7	Petrochemical	Distance (binary, community-based)	N/A	PR	1.01	0.67-2.75
Rovira et al., 2014	Cross-sectional	Asthma	13-14	Petrochemical	Distance (binary, community-based)	N/A	PR	0.90	0.70-1.95
Naidoo et al., 2013	Cross-sectional	Asthma	9-12	N/S	Distance (binary, community-based)	N/A	OR	1.14	0.75-1.74
Pless-Mulloli et al., 2000; 2001 [C]	Cross-sectional	Asthma in past 2 mo.	1-11	Opencast mining	Distance (binary, community-based)	N/A	OR	1.7	0.9-3.5
De Marco et al., 2010	Cross-sectional	Asthma-like symptoms	3-14	Wood industries	Distance (binary, cut-off: 2km)	N/A	OR	1.33	1.11-1.60
Pless-Mulloli et al., 2000; 2001 [C]	Cross-sectional	Asthma or wheezing in past 12 mo.	1-11	Opencast mining	Distance (binary, community-based)	N/A	OR	1.00	0.70-1.30
Wichmann et al., 2009	Cross-sectional	Asthma exacerbation in past 12 mo.	6-12	Petrochemical	Distance (binary, community-based)	N/A	OR	1.88	1.25-1.93
Naidoo et al., 2013	Cross-sectional	Wheezing with SOB	9-12	N/S	Distance (binary, community-based)	N/A	OR	1.12	1.01-1.24
Kobrossi et al., 2002	Cross-sectional	Wheezing	5-15	Industrial complex	Distance (binary, ≤ 3km vs. 4-7km)	N/A	OR	2.23	1.21-4.12
Kobrossi et al., 2002	Cross-sectional	Wheezing	5-15	Industrial complex	Distance (binary, ≤ 3km vs. in a community unexposed)	N/A	OR	1.54	0.94-2.54
Kobrossi et al., 2002	Cross-sectional	Wheezing	5-15	Industrial complex	Distance (binary, 4-7km vs. in a community unexposed)	N/A	OR	0.78	0.43-1.43
Cara et al., 2010	Cross-sectional	Wheezing	7-10	Heavy industries	Distance (binary, community-based)	N/A	OR	7.20	3.20-16.70
Pless-Mulloli et al., 2000; 2001 [C]	Cross-sectional	Wheezing	1-11	Opencast mining	Distance (binary, community-based)	N/A	OR	1.00	0.80-1.30
Naidoo et al., 2013	Cross-sectional	Wheezing	9-12	N/S	Distance (binary, community-based)	N/A	OR	1.00	0.63-1.57
Rovira et al., 2014	Cross-sectional	Wheezing	6-7	Petrochemical	Distance (binary, community-based)	N/A	PR	1.10	0.88-1.75
Rovira et al., 2014	Cross-sectional	Wheezing	13-14	Petrochemical	Distance (binary, community-based)	N/A	PR	0.95	0.80-1.49

Study reference	Study design	Asthma-related outcome	Age group (years)	Type of industries	Metric of exposure	Results			
						Exposure increment	Effect	Mean	95% CI
Wichmann et al., 2009	Cross-sectional	Current wheezing	6-12	Petrochemical	Distance (binary, community-based)	N/A	OR	1.93	1.39-2.67
Pless-Mulloli et al., 2000 [C]	Cross-sectional	Wheezing in past 6 wk.	1-11	Opencast mining	Distance (binary, community-based)	N/A	OR	0.82	0.36-1.89
Cara et al., 2010	Cross-sectional	Wheezing in past 12 mo.	7-10	Heavy industries	Distance (binary, community-based)	N/A	OR	13.60	3.10-83.00
Rovira et al., 2014	Cross-sectional	Wheezing in past 12 mo.	6-7	Petrochemical	Distance (binary, community-based)	N/A	PR	0.95	0.76-2.01
Rovira et al., 2014	Cross-sectional	Wheezing in past 12 mo.	13-14	Petrochemical	Distance (binary, community-based)	N/A	PR	0.90	0.71-1.45
Pless-Mulloli et al., 2001 [C]	Cross-sectional	Wheezing in past 12 mo.	1-11	Opencast mining	Distance (binary, community-based)	N/A	OR	1.0	0.7-1.3
Rovira et al., 2014	Cross-sectional	Severe wheezing	13-14	Petrochemical	Distance (binary, community-based)	N/A	PR	2.51	0.73-5.00
Rovira et al., 2014	Cross-sectional	Severe wheezing	6-7	Petrochemical	Distance (binary, community-based)	N/A	PR	0.92	0.63-2.10
Kobrossi et al., 2002	Cross-sectional	Wheezing after physical exercise	5-15	Industrial complex	Distance (binary, ≤3km vs. 4-7km)	N/A	OR	0.76	0.28-2.08
Kobrossi et al., 2002	Cross-sectional	Wheezing after physical exercise	5-15	Industrial complex	Distance (binary, ≤ 3km vs. in a community unexposed)	N/A	OR	1.81	0.69-4.78
Kobrossi et al., 2002	Cross-sectional	Wheezing after physical exercise	5-15	Industrial complex	Distance (binary, 4-7km vs. in a community unexposed)	N/A	OR	2.30	0.78-6.75
Cara et al., 2010	Cross-sectional	Wheezing after physical exercise in past 12 mo.	7-10	Heavy industries	Distance (binary, community-based)	N/A	OR	6.60	1.40-42.20
Rovira et al., 2014	Cross-sectional	Wheezing after physical exercise in past 12 mo.	13-14	Petrochemical	Distance (binary, community-based)	N/A	PR	1.98	0.81-3.92
Rovira et al., 2014	Cross-sectional	Wheezing after physical exercise in past 12 mo.	6-7	Petrochemical	Distance (binary, community-based)	N/A	PR	0.98	0.82-1.75
Cara et al., 2010	Cross-sectional	1-3 Wheezing attacks in past 12 mo.	7-10	Heavy industries	Distance (binary, community-based)	N/A	OR	21.60	3.10-432.00
Pless-Mulloli et al., 2000; 2001 [C]	Cross-sectional	> 12 Wheezing attacks in past 12 mo.	1-11	Opencast mining	Distance (binary, community-based)	N/A	OR	0.5	0.2-0.9
Cara et al., 2010	Cross-sectional	Wheezing: Sleep disturbance, in past 12 mo.	7-10	Heavy industries	Distance (binary, community-based)	N/A	OR	8.40	1.90-52.60
Pless-Mulloli et al., 2000 [C]	Cross-sectional	Asthma attack: Woken child at night, in past 12 mo.	1-11	Opencast mining	Distance (binary, community-based)	N/A	OR	0.8	0.6-1.2
Pless-Mulloli et al., 2000 [C]	Cross-sectional	Asthma attack: Limited speech, in past 12 mo.	1-11	Opencast mining	Distance (binary, community-based)	N/A	OR	0.9	0.5-1.4
Pless-Mulloli et al., 2000 [C]	Cross-sectional	Asthma attack: Occurred on exercise, in past 12 mo.	1-11	Opencast mining	Distance (binary, community-based)	N/A	OR	1.01	0.7-1.5

Study reference	Study design	Asthma-related outcome	Age group (years)	Type of industries	Metric of exposure	Results			
						Exposure increment	Effect	Mean	95% CI
Pless-Mulloli et al., 2000 [C]	Cross-sectional	Asthma reliever use in past 6 wk.	1-11	Opencast mining	Distance (binary, community-based)	N/A	OR	1.00	0.3-2.9
Metric of exposure: Distance (continuous)									
Rava et al., 2011	Cross-sectional	Asthma	3-14	Wood industries	Weighted average of minimum distances of each child's home and school from the chipboard industries	2 km	RR	0.99	0.95-1.04
Rava et al., 2011	Cross-sectional	Asthma like symptoms, in past 12 mo.	3-14	Wood industries	Weighted average of minimum distances of each child's home and school from the chipboard industries	2 km	RR	0.98	0.97-0.99
Rava et al., 2011	Cross-sectional	Asthma severity index (based on symptoms), in past 12 mo.	3-14	Wood industries	Weighted average of minimum distances of each child's home and school from the chipboard industries	2 km	RR	0.97	0.95-0.99
White et al., 2009	Cross-sectional	Need to bring inhaler to school	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	1.6 km	OR	0.89	0.72 - 1.11
White et al., 2009	Cross-sectional	Ever wheeze at rest	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	1.6 km	OR	1.10	0.95 - 1.27
White et al., 2009	Cross-sectional	Wheezing at rest in past 12 mo.	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	1.6 km	OR	0.89	0.70 - 1.14
White et al., 2009	Cross-sectional	Wheezing at rest at least monthly in past 12 mo.	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	1.6 km	OR	0.93	0.71 - 1.21
White et al., 2009	Cross-sectional	Ever wake with wheezing at night	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	1.6 km	OR	1.11	0.97 - 1.28
White et al., 2009	Cross-sectional	Waking with wheezing at night in past 12 mo.	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	1.6 km	OR	0.95	0.74 - 1.24
White et al., 2009	Cross-sectional	Waking with wheezing at night, at least monthly in past 12 mo.	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	1.6 km	OR	1.08	0.86 - 1.37
White et al., 2009	Cross-sectional	Ever wheeze after exercise	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	1.6 km	OR	0.98	0.84 - 1.14
White et al., 2009	Cross-sectional	Wheezing after exercise in past 12 mo.	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	1.6 km	OR	0.83	0.64 - 1.08
White et al., 2009	Cross-sectional	Wheezing after exercise, at least monthly in past 12 mo.	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	1.6 km	OR	0.86	0.63 - 1.16
White et al., 2009	Cross-sectional	Ever distressing wheeze at rest	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	1.6 km	OR	1.02	0.86 - 1.20
White et al., 2009	Cross-sectional	Distressing wheeze at rest, in past 12 mo.	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	1.6 km	OR	0.97	0.72 - 1.30

Study reference	Study design	Asthma-related outcome	Age group (years)	Type of industries	Metric of exposure	Results			
						Exposure increment	Effect	Mean	95% CI
White et al., 2009	Cross-sectional	Distressing wheeze at rest, at least monthly in past 12 mo.	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	1.6 km	OR	0.95	0.67 - 1.35
Metric of exposure: Distance (% of residential buffer area within 0.8km of an industrial facility)									
Patel et al., 2011	Longitudinal	Asthma	0-5	N/S	% area <0.8km (continuous)	68.9%	OR	1.30	0.98-1.52
Patel et al., 2011	Longitudinal	Wheezing	0-5	N/S	% area <0.8km (continuous)	68.9%	OR	0.90	0.70-1.15
Metric of exposure: Wind direction (categorical)									
Lopes de Moraes et al., 2010	Cross-sectional	Wheezing, in past 12 mo.	0-14	Petrochemical	Wind direction (binary)	N/A	OR	2.01	1.01-4.01
Metric of exposure: Distance, weighted for wind direction and wind speed									
White et al., 2009	Cross-sectional	Need to bring inhaler to school	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	0.29 h/km^2	OR	1.22	1.06 - 1.40
White et al., 2009	Cross-sectional	Ever wheeze at rest	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	0.29 h/km^2	OR	1.15	1.04 - 1.28
White et al., 2009	Cross-sectional	Wheezing at rest in past 12 mo.	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	0.29 h/km^2	OR	1.12	0.94 - 1.34
White et al., 2009	Cross-sectional	Wheezing at rest at least monthly in the last 12 mo..	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	0.29 h/km^2	OR	1.27	1.05 - 1.54
White et al., 2009	Cross-sectional	Ever wake with wheezing at night	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	0.29 h/km^2	OR	1.03	0.93 - 1.14
White et al., 2009	Cross-sectional	Waking with wheezing at night in past 12 mo.	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	0.29 h/km^2	OR	1.33	1.06 - 1.66
White et al., 2009	Cross-sectional	Waking with wheezing at night, at least monthly in the last 12 mo.	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	0.29 h/km^2	OR	1.10	0.94 - 1.29
White et al., 2009	Cross-sectional	Ever wheeze after exercise	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	0.29 h/km^2	OR	1.08	0.97 - 1.21
White et al., 2009	Cross-sectional	Wheezing after exercise in past 12 mo.	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	0.29 h/km^2	OR	1.17	0.96 - 1.42
White et al., 2009	Cross-sectional	Wheezing after exercise, at least monthly in the last 12 mo.	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	0.29 h/km^2	OR	1.14	0.93 - 1.41
White et al., 2009	Cross-sectional	Ever distressing wheeze at rest	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	0.29 h/km^2	OR	1.08	0.96 - 1.21
White et al., 2009	Cross-sectional	Distressing wheeze at rest, in past 12 mo.	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	0.29 h/km^2	OR	1.16	0.93 - 1.43
White et al., 2009	Cross-sectional	Distressing wheeze at rest, at least monthly in the last 12 mo.	11-14	Petrochemical refinery	Distance, weighted for wind direction and wind speed	0.29 h/km^2	OR	1.26	0.98 - 1.62

Abbreviations: CI, confidence interval; h, h; HR, hazard ratio; IDW, inverse-distance weighting; IQR: interquartile range; km, kilometer; max., maximum; mo. month.; N/A, not applicable; NO2, nitrogen dioxide; N/S, not specified; OR, odds ratio; PM2.5, particulate matter of median diameter of less than 2.5 µm, PM10, particulate matter of median diameter of less than 10 µm; PR, prevalence ratio; RR, risk ratio, SO2, sulfur dioxide; SOB, shortness of breath; TSP, total suspended particulate; week, wk.; yr, year.

[a] In the paper by Naidoo et al. (2013), the exposure increment for PM10 and SO2 estimate associations are not reported. The exposure increment are interquartile range, corresponding to 12.6 $\mu g/m^3$ for PM10 and 6.7 ppb for SO2. (Naidoo, Personal Communication, 2019-04-16)

[b] In the study by Howel et al. (2001), a symptom was defined as incident if it had not been present on the previous day.

[c] In the study by Pless-Mulloli et al. (2000, 2001) and Howel et al. (2001), some results were reported separately by communities; in such instances we pooled results and we reported the pooled effect estimates for all communities.

(A)

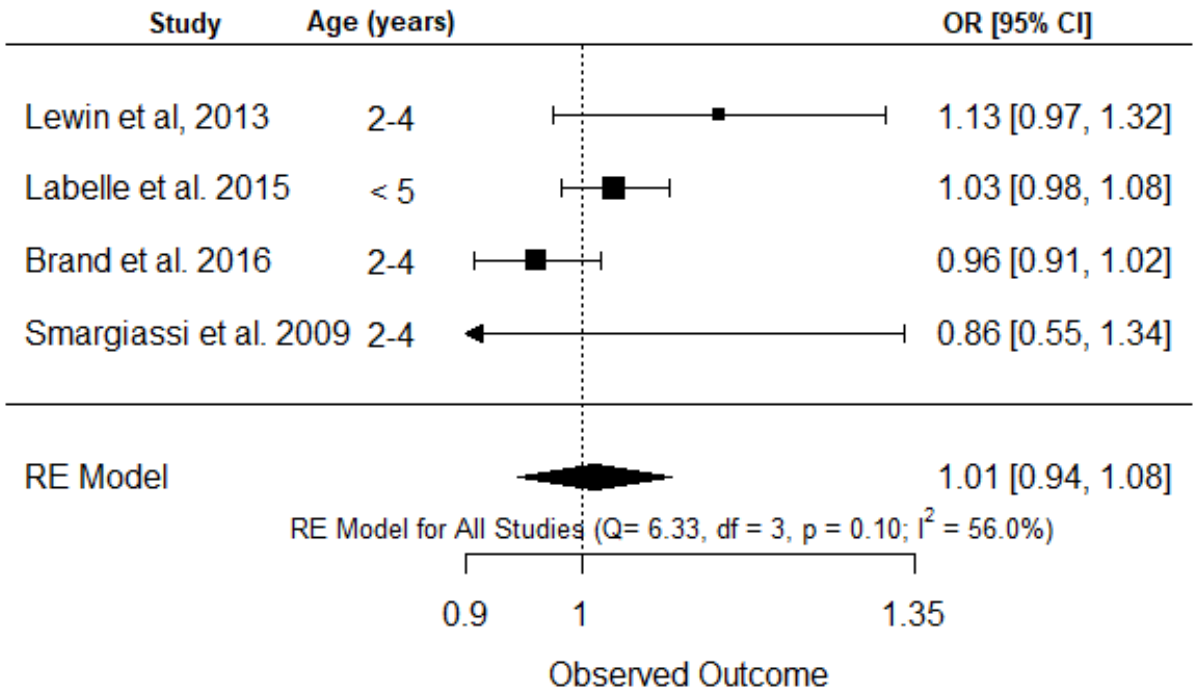


Figure B1. Forest plots of the association between hospitalization for asthma or bronchiolitis and same-day daily mean concentration of SO2, including results from Smargiassi et al. (2009) from fixed-site monitors. In the study by Smargiassi et al., (2009) two distinct monitoring stations were used to assess SO2 of two communities and associations were reported separately for these two communities. In (A) we included the effect when combining the two communities.

(B)

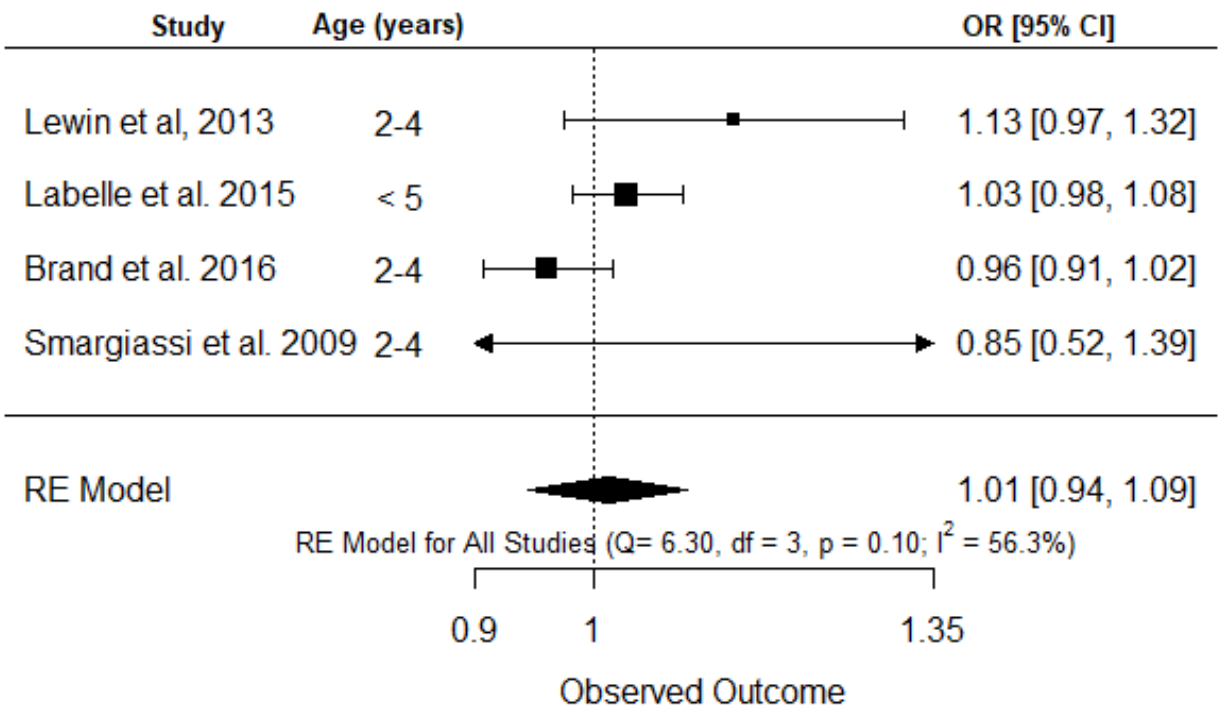


Figure B1 (continue). Whereas in (B) we included the results from the community that is mostly exposed to emissions and for which the monitoring station likely provide a better estimate of people's exposure (median distance 1.6 km). Effect size and 95% confidence intervals (CI) are expressed relative to a 10 ppb increase. Pooled estimates of effect size are indicated by black squares and 95% CI are represented by horizontal lines; size of black square around point estimate is proportional to weight in calculating pooled estimate.

(A)

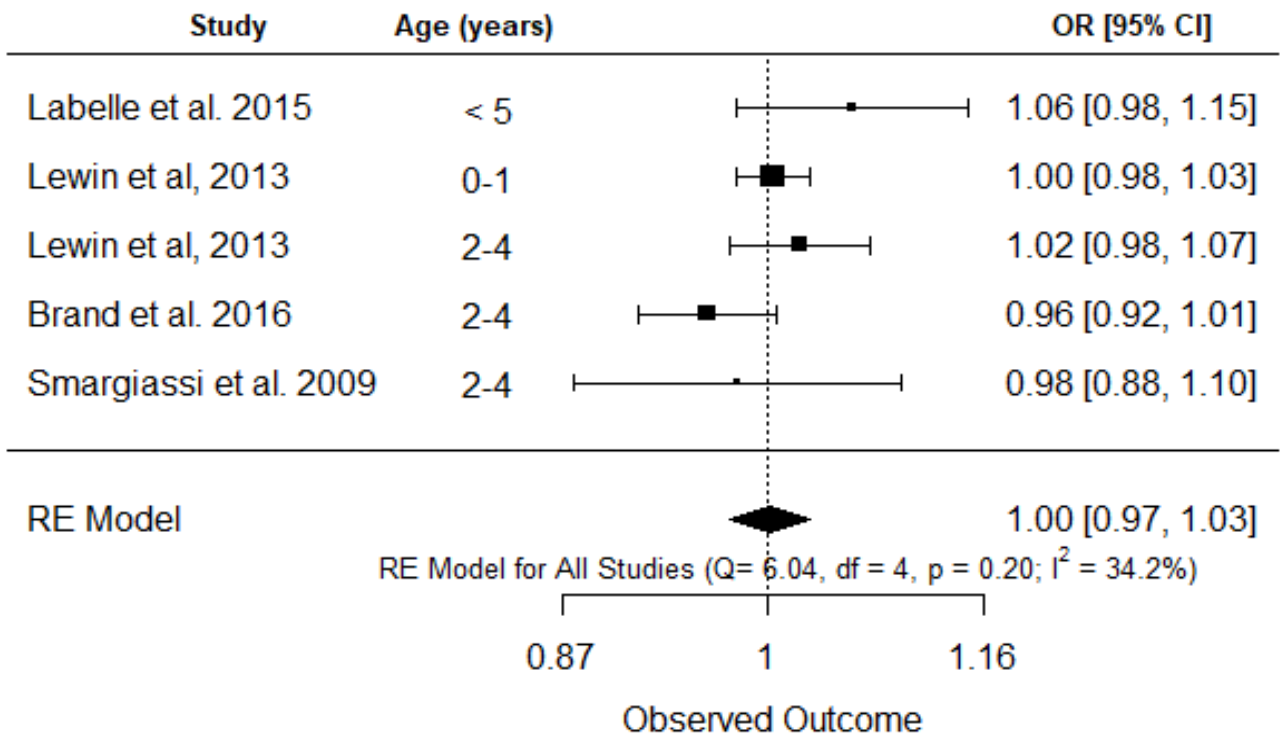


Figure B2. Forest plots of the association between hospitalization for asthma or bronchiolitis and same-day hourly maximum concentration of SO_2, including results from Smargiassi et al. (2009) from fixed-site monitors. In the study by Smargiassi et al., (2009) two distinct monitoring stations were used to assess SO_2 of two communities and associations were reported separately for these two communities. In (A) we included the effect when combining the two communities.

(B)

Figure B2 (continue). Whereas in (B) we included the results from the community that is mostly exposed to emissions and for which the monitoring station likely provide a better estimate of people's exposure (median distance 1.6 km). Effect size and 95% confidence intervals (CI) are expressed relative to a 10 ppb increase. Pooled estimates of effect size are indicated by black squares and 95% CI are represented by horizontal lines; size of black square around point estimate is proportional to weight in calculating pooled estimate.

3.2 Article 2: Predictors of the spatial variation of hospital admissions for asthma in children of Québec

Xiaohui Geng[1], Sophie Goudreau[2], Michel Fournier[2], Audrey Smargiassi[3]

Status of paper and contributions of co-authors

This article is not published.

The contributions of co-authors on this paper are as follows:

1. Xiaohui Geng is the doctoral Candidate, Xiaohui Geng conceptualized the paper with her director, developed the statistical programs and performed the analyses and prepared the draft paper.
2. Sophie Goudreau is the coauthor of this spatial analysis article. She provided the datasets of variables for the spatial analysis, and wrote the context of appendix A. Moreover, she provided review and feedback for the writing of this paper.
3. Michel Fournier is the coauthor of this spatial analysis article. He provided statistical consultation for Xiaohui Geng. Moreover, he provided review and feedback for the writing of this paper.
4. Audrey Smargiassi is the thesis Supervisor. She conceptualized the study with the student, coordinated the availability of datasets and statistical consultation and oversaw the work. She provided valuable input and feedback on the writing of this paper.

3.2.1 Abstract

Large spatial variations exist in rates of asthma morbidity in children, yet few studies have investigated the relationship between this variation and the spatial variations of multiple socio-environmental factors. To assess the association between the spatial variation in environmental and socioeconomic conditions and the spatial variation in asthma hospital admissions, we conducted an ecological study in children by small geographic areas in Québec, Canada. For 1386 geographic areas for the years 2002-2011 combined, we estimated the average median household income from the census, the average regional annual background of fine particulate levels ($PM_{2.5}$) from satellite and ground measurements, and the annual average industrial air pollutant emissions of $PM_{2.5}$ and sulfur dioxide (SO_2) from the National Pollutant Release Inventory. A vegetation index, based on satellite information, and a walkability index, based on land use information were also used. Environmental tobacco smoking information was retrieved from a large Canadian survey for 15 health regions encompassing the small areas. Traffic-related air pollution was estimated by kilometers of major roads. We used negative binomial General Additive Models with the population of children as offset to assess associations between these variables and hospital admissions for asthma for the years 2002-2011 combined. The multivariate model indicated that income and the geographic coordinates, also used in the model to capture spatial patterns, were the main variables associated with asthma hospital admissions. An increase of 23751$ in average median income (i.e. the interquartile range) was associated with a decrease of 25% (95%CI: 22%-28%) in asthma hospital admissions. The spatial variation in environmental factors was not related to the spatial variation in asthma hospital admission rates, except for km of major roads which presented a counterintuitive negative relationship.

Nonetheless, a large variation was explained by geographic coordinates representing unknown specific characteristics of the small areas that deserves further consideration.

---

[1] Doctoral Candidate, Département de santé environnementale et santé au travail, École de santé publique, Université de Montréal, Canada; Centre de recherche en santé publique de Université de Montréal.

[2.] Co-author, Direction régionale de santé publique de Montréal;

[3]. Thesis Supervisor, Département de santé environnementale et santé au travail, École de santé publique, Université de Montréal, Canada; Centre de recherche en santé publique de Université de Montréal, Institut National de Santé Publique du Québec.

3.2.2 Introduction

Asthma is the most common chronic disease of childhood in developed countries like Canada. Children younger than 13 years age have the highest incidence rate of asthma (Gershon et al. 2010, PHAC 2018). There is a large geographic variation in asthma morbidity (Ayres-Sampaio et al. 2014, Beck et al. 2013., Lai et al. 2009, Ouédraogo et al. 2018). Nonetheless, factors that explain this large spatial variation have been overlooked as most studies have assessed individual risk factors (Uphoff et al. 2015, Kanchongkittiphon et al. 2015, Wang et al. 2015, Orellano et al. 2017).

Studies that have assessed factors associated with the geographic variation in asthma outcomes are ecological and have focused on the influence of socioeconomic factors such as income; most studies have reported negative relationships (e.g. Beck et al. 2013; Ouédraogo et al. 2018). Ecological studies have also explored associations between environmental factors and asthma outcomes in children, but results are less conclusive. Based on the ISAAC Phase One surveys, Asher et al. (2010) and Anderon et al. (2010) reported that air pollutant levels were only marginally associated with the geographic variation in the prevalence of childhood asthma. On the contrary, other studies like Ayres-Sampaio et al. (2014), reported that in the most urban areas, the near-surface air temperature and nitrogen dioxide levels were positively related to asthma admission rates, while the vegetation index (NDVI) was negatively associated with asthma admission rates in children. The few studies that have assessed associations between industrial air pollutant emissions and rates of asthma outcomes considered different types of industries, and also reported contradictory results (Alwahaibi et Zekal 2016, Aylin et al. 2001). Moreover, most ecological studies only adopted simplified statistical analysis methods such as

Pearson correlations and linear regressions, and few of them (Ouédraogo et al. 2018) used more advanced statistical models to consider spatial correlations.

In this study, we investigated the association between the geographic variation of environmental and socioeconomic risk factors and the geographic variation of rates of asthma hospital admissions in children younger than 13 years of age in Québec, Canada for the years 2002-2011, using non-linear statistical modelling.

3.2.3 Materials and methods

Study design, study population, and unit of analysis

This is an ecological study performed for the province of Québec (Canada). The study population was children aged 0-12 in this province. We used the number of children aged 0-14 to estimate the number of children aged 0-12 because population numbers for children aged 0-12 was not available. For this study, the geographic units of analysis were census tracts (CT) in metropolitan areas or Centre Local de Services Communautaires (CLSC) territories outside metropolitan areas. Although the CTs only covers around 1.5 % of the province of Québec, 70.6% of the population lives in these areas. According to the rules of delineation of CTs, the area of CT is small and relatively stable, and should be as homogeneous as possible in terms of population size (Statistics Canada 2018). CLSC territories often have both urban and rural areas, so we created the CLSCs' geographic database by excluding urban areas. The CTs changed over the census years and we used the geographic delineation of census year 2006. The total area of CTs is much smaller than the total areas of CLSCs (see Figure A in appendix A). The population

of children aged 0 to 14 years per geographic units was calculated as the average of the population of children aged 0 to 14 years in census years 2001, 2006, and 2011. To perform this, we distributed the population of children aged 0 to 14 years of geographic areas in census years 2001 and 2011 according to geographic areas of 2006. The detailed computing process is explained in Appendix A.

Variables per CT/CLSC

Health outcome—cases of asthma hospital admissions

The total number of asthma hospital admissions of children aged 12 years old or younger, for the period of 2002-2011, was computed per CTs/CLSCs (of 2006).

The data source for asthma hospital admissions is the database MED-ÉCHO (Maintenance et exploitation des données pour l'étude de la clientèle hospitalière). The following International Classification of Disease (ICD) codes were used to identify asthma hospital admissions: ICD-9 493 or ICD-10-CA J45-46. Based on postal code conversion file of 2013 (PCCF), a spatial join was performed to assign all the residential postal codes (PCs) of hospitalized children to the corresponding census tracts (2006) or CLSCs.

Predictor variables

The values of predictor variables were calculated for the geographic delineation of CT/CLSCs of the 2006 census.

Median Income—The median household income per CTs/CLSCs was obtained averaging the dissemination area (DA) median household income within CTs/CLSCs from the 2001, 2006 and 2011 Canadian censuses (Statistic Canada 2018).

Regional $PM_{2.5}$ levels—We used yearly levels of particulate matter less than 2.5 µm ($PM_{2.5}$) (in $\mu g/m^3$) estimated with satellite images and ground data for the years 2001-2003 to 2010-2012 (Donkelaar et al. 2015); these levels were downloaded from the website (http://fizz.phys.dal.ca/~atmos/martin/). To correspond these ranges of years to the individual year of 2002-2011, we converted the range of years to the middle year (e.g. 2001-2003 as 2002, 2010-2012 as 2011). Annual $PM_{2.5}$ levels used represent the average of the values of all cells of 1 km x 1 km falling within the CTs/CLSCs from 2002 to 2011. Then, we obtained the $PM_{2.5}$ levels per CTs/CLSCs by averaging the estimated yearly values of $PM_{2.5}$ for the period of 2002-2011.

Traffic related air pollution— We used the 2010 DMTI (Digital Mapping Technologies Inc. 2019) to estimate the kilometers of major roads within CTs/CLSCs as an indicator of air pollutant emission from major roads.

Industrial air pollutant emissions—We calculated average industrial emissions of $PM_{2.5}$ and sulfur dioxide (SO_2) (in tons) within CTs/CLSCs using emissions reported to the National Pollutant Release Inventory (NPRI) emission data (Government of Canada 2017) for the years 2002 to 2011.

Environmental Tobacco Smoke (ETS) —We used data on non-smokers exposed to second hand smoke from three cycles (2003, 2007/2008, 2013/2014) of the Canadian Community Health Survey (CCHS) per health regions, to estimate exposure to ETS in the population of children aged 0 to 12 years per CTs/CLSCs across Québec (Statistics Canada 2016). The whole province of Québec is divided into 18 health regions embedding the CTs/CLSCs. There were no data available for three regions (Nord-du-Québec, Nunavik, and Terres-Cries-de-la-Baie-James). We calculated the average proportions of exposure for the 15 regions based on the three cycles of data and attributed the regional values to the CTs/CLSCs.

Vegetation & Walkability—We used the Institut national de santé publique du Québec (INSPQ) indicators on walkability and vegetation available for DAs. The walkability indicator is based on characteristics such as intersection density, mixture, land-use, residential density and destination density information (INSPQ 2019). The vegetation index used is the normalized difference vegetation index (NDVI) calculated from a 2006 Landsat image (INSPQ 2019). We averaged the values of these two indicators for DAs per CTs/CLSCs.

Statistical methods

First, among geographic units, divisions with numbers of asthma hospitalization fewer than five were replaced by 2.5 due to the concern of confidentiality, and then missing data (geographic units without population data or income information, and units without ETS information) were excluded. Moreover, due to extreme skewed distribution of variables, we removed values of all predictors greater than the 99 percentiles.

GAM modeling—We used negative binomial model with penalized regression splines (S) as smooth functions in generalized additive models (GAM) to analyze the associations between predictor variables described above and counts of asthma hospital admissions in children (Marra and Radice 2010). We used the MGCV package in R (Wood 2018). We used negative binomial models instead of Poisson models because Poisson models did not produce reliable results due to overdispersion.

Restricted Maximum Likelihood (REML) was adopted as smoothness selection criteria of GAM models. Smaller values of REML indicate better fit of GAM models. We first created models only with a constant, and then, univariate models (i.e. single predictor variables); one of the univariate models used the geographic coordinates of the centroid of the CTs/CLSCs as an independent variable to capture spatial trends. We then performed multivariate models with and without the coordinates of centroids of geographic units. In all models, the population of children aged 0-14 years per geographic unit in 2006 was used as the offset in the statistical analysis.

Global spatial autocorrelation indicator, Moran's I, was computed using queen's contiguity matrix (e.g. sharing any common boundaries) (Moran 1950). In addition, Local Indicator of Spatial Autocorrelation (LISA) analyses were conducted to detect the location of clusters of high/low rates, according to k-nearest neighbors (k=4) (Anselin 1995).

3.2.4 Results

First, among 1386 CTs/CLSCs divisions, we excluded missing data (34 geographic units without population data or income information, and 7 units without ETS information) from the 1386 divisions. After the removal of extreme data, the final complete dataset included 1248 CTs/CLSCs divisions. The percentage of eliminated data was less than 10% of the original dataset.

Descriptive characteristics of CLSCs & CTs in Québec during the year 2002-2011 are presented in Table 1. The rate of asthma hospital admissions per 1000 (total counts of asthma hospitalization for the 2002-2011 period/average annual population of children*1000 during the 2002-2011 period) in children aged 12 years old or younger has a wide range of 87.01 (1.35, 88.36). The ranges of industrial air pollutant emissions ($PM_{2.5}$/SO_2) are also wide, and the median values of these two predictors are zero, which indicate that the majority of geographic units has no industrial air pollutant emissions. The maximum values presented correspond to the 99 percentiles, since we used this percentile as the cut-off points for outliers.

Pearson and Spearman correlations between predictor variables are reported in Appendix B. Industrial $PM_{2.5}$ and industrial SO_2 are positively correlated (Pearson correlations: r=0.66, Spearman correlations: r=0.59), while walkability and vegetation, as well as vegetation and regional background $PM_{2.5}$ levels are highly negatively related (correlation ~80%;).

Table 2 summarizes the results of all models. By comparing the Restricted Maximum Likelihood (REML)—smoothness selection criteria- of models, the multivariate models

(industrial air emission of $PM_{2.5}$ & SO_2) including all predictors have the smallest value of REML=4109.7, which indicates the best smoothness of this model. By examining the univariate models, the REMLs indicate that coordinates of centroids of CLSCs & CTs are the best fit to asthma hospital admissions since REML=4218, while median household income (REML=4330.8), environmental tobacco smoke (REML=4339.9) and vegetation (REML=4351) have slightly weaker influences. The results of the global Moran's I are small (most of the values were around < -0.001) and non-statistically significant ($p>0.05$). By comparing two multivariate models (without coordinates & with coordinates), the multivariate model with coordinates has smaller value of REML=4109.7, which indicates the better fit of this model. In this model, variables (median income, traffic, industrial air pollutants, and vegetation) that had near linear relationships (i.e. df~1) with asthma cases were analyzed with linear functions. Most of these linear associations are not statistically significant, except for income. For the linear relation with income (beta of -0.0000121, Table 2), an increase of 23751$ (corresponding to the interquartile range) is associated with a decrese of 25% (95% CI, 22%-28%) in asthma hospital admission rate (e.g. exponential of -0.0000121*23751$). The shape of the relationships between predictors and rate of asthma in univariate, as well as the relationships of predictors in multivariate models are reported in Appendix C.

Figure 1 shows the absolute value of residuals of the empty model (cases of asthma hospital admissions). The light colors indicate lower absolute value of residuals in geographic areas, and darker colors indicate high absolute values of residuals in those geographic areas. The residuals of the rates of asthma hospital admissions are standardized to values between zero and one, with a division by the maximum residual rate value per area (CTs/CLSCs). Higher asthma

hospitalization rates are noted in the southwest urbanized area of the province of Québec and on the eastern gaspesian peninsula.

Figure 2 shows the absolute values of residuals of the univariate model with the two main predictors of the asthma hospitalization rate variation, median household income and coordinates of centroid as the only independent variables by geographic areas (CTs & CLSCs), respectively. By comparing a) and b) to the figure of the model that only includes a constant, we note the important influence of the coordinates (x, y) on the rate of asthma.

Figures of Moran's I (the variogram of the spatial autocorrelation) of constant-only and full models are shown in Appendix D. These figures show that there are no significant global spatial autocorrelations. For LISA, different adjacency definitions were explored (e.g. k=6 and 8) but no notable differences were found in the clusters.

3.2.5 Discussion

This study assessed associations between asthma hospital admissions per relatively small geographic areas and multiple predictors (industrial air pollutant emissions and other socioeconomic and environmental variables). There was no association detected between asthma hospital admissions and environmental variables, but the median household income was inversely related to asthma hospital admission rates. The geographic coordinates were the main variable of the multivariate models capturing spatial trends and the unexplained spatial variance.

The median household income showed a significant inverse association with asthma hospitalization in children (both univariate and multivariate models), which is similar to results from most ecological studies (e.g. Beck et al. 2013, Ouédraogo et al. 2018). Income, as an indicator of socioeconomic status (SES), can represent a number of risk factors including poor indoor/outdoor air quality. Epidemiological individual (in opposition to ecological) studies on asthma in children have found that associations with SES are often due to other factors such as exposure to ETS and indoor air pollution related to poor housing conditions (dust mites, mould, cat dander, etc) (e.g. Palaty et al. 2012, Hiscock et al. 2012). However, in our multivariate model, the association with income was independent from the one with ETS.

The null relationships between industrial air pollutant emissions and asthma hospital admissions is in line with the current literature (see Chapter 3.1) and may be due to the fact that industrial emissions are poor indicators of exposure to pollutants. Indeed emissions are self-reported by industries and values may be unreliable. Furthermore meteorology, which influences the dispersion of the pollutants, was also not considered with emisisons in our assessments. We also used the average values of industrial emissions over 10 years which concealed temporal changes in industrial emissions and may have also influenced our results. Future work should include both spatial and temporal assessments to explore the associations of these predictors with asthma outcomes in children. On the other hand, better estimates of air pollutant exposure such as the background $PM_{2.5}$ levels from satellite estimates were positively related to asthma hospital admissions in the univariate model. However the disappereance of this association in the multivariate model suggests the existence of some confounding by the other covariates.

Contrary to other ecological studies on asthma in children, like Ouédraogo et al. (2018) and Gupta et al. (2008) who found local clustering in regions of their study area, the calculation of global Moran`s I and LISA indicated that there was no significant existence of spatial autocorrelation (e.g. no local grouping/clustering in our data). The usage of smaller geographic divisions (CTs) in our study could be a potential explanation of this unexplained discrepency.

The negative association between traffic emissions (estimated with km of major roads) and rates of hospital admissions that we report (in both univariate and multivariate models) is surprising, since epidemiological studies with both ecological (e.g. Ayres-Sampaio et al. 2014) and individual-level information have largely reported that traffic-related air pollutants such as nitrogen dioxide are positively related to asthma outcomes in children (Tetreault et al. 2016, EPA 2016, EPA 2019). Nonetheless, the controversial results could indicate the existence of biases because the length of major roads is a poor indicator of exposure to road traffic emissions. Indeed, some regions with many kilometers of major roads may be remote from urban areas with low traffic flows and pollution levels.

The negative association from the multivariate model (without coordinate x,y) between vegetation and asthma admissions suggests that vegetation may be a protective factor. As with regional $PM_{2.5}$ levels, this association was removed with the inclusion of the x,y coordinates and other variables which appear to have captured this spatial pattern. Studies published to date have reported conflicting results regarding the association between vegetation and asthma which may be due to the fact that vegetation could reduce pollutant levels but also increase pollen exposure and allergic reactions (Hartley et al. 2020).

The study suffers from many limitations, in addition to information biases related to some of the variables used to estimate exposure to air pollutants mentioned above. First, we used an ecological design to assess associations between the geographic variation of environmental and socioeconomic factors and the geographic variation in the rates of asthma hospital admissions in children. Studies of eological design are subject to the ecological fallacy, which implies that associations obtained for the small areas (i.e. for the number of cases per region) may not be consistent with associations at the individual level. In addition, the estimation of the predictor variables such as air pollution is also an important limitation of these studies given their ecological nature (i.e. for the small area and not for the individuals). The usage ecological data may also lead to confounding by group, for example if the CT/CLSC group exposure would be correlated with the risk of asthma hospital admissions in the non-exposed individuals of the CT/CLSC (Rothman et al. 2008). Thus, ecological designs do not allow for the inference of causality and care is needed in their interpretation. Nonetheless, useful observations can emerge from such studies. Indeed factors that influence the geographic variations of asthma rates are important to understand to orient preventive measures for specific areas and we used the smallest possible geographic area to assess it.

Additionnally, we used the number of children aged 0-14 years in Québec to estimate the study population of children aged 0-12 years old in this study. This could lead to systematic errors if the proportions of asthma hospital admissions in different subgroups (e.g. exposure subgroups) within the age range of 0-12 years are different compared to the proportions in different subgroups within the age range of 0-14 years. There may also remain potential confounding

effects of age and sex in our analyses if proportions of children of different age groups differ by small areas. Other factors that were not controlled for in our analyses, besides age and sex, may also confound the results.

Also, in remote areas, the geography of the units used is much larger, so the environmental information attributed to the population is less accurate. Thus, the lack of consideration of urban and rural differences is an additional drawback of our work.

It is also possible that some of the unexplained variance in the geographic variation in asthma hospital admissions that we have found (and captured by the geo-coordinates) may be related to inequalities in access to health care in different regions. Access to health care should have been considered as children of urban areas have been reported to have better contacts with health professionals and preventive health services, than children in remote areas of Quebec (Martinez et al. 2004, Haggerty et al. 2007).

Furthermore, additional limitations relate to the predictors used. We used average value of median household income of three census years to estimate the SES. Income is only one variable that may represent SES and additional variables such as education deserves additional attention. Moreover, the adjustment for income may lead to cross-level bias since some studies have shown that individual income and neighborhood average income may have separate effects on health (Schreier and Chen 2013). For the estimate of ETS, the only data that we could obtain for this factor was the CCHS survey data for much larger geographic areas (health regions) than the CTs/CLSCs, and the survey data was collected in the population of children older than 12

years of age. To estimate ETS exposure of our study population, we assumed that the proportions of exposure to ETS were the same in different age groups, and used the crude data from children aged older than 12 years to distribute them into smaller geographic areas, which meant that all the geographic areas within one health region would have the same value of ETS (Statistics Canada, 2016). It was difficult with this method to assess the association with the geographic variation of the asthma hospital admission rates since the usage of large areas reduced the variation of ETS.

3.2.6 Conclusion

Our results are in agreement with ecological studies that have shown that small areas with low SES present higher rates of asthma outcomes. Our results also suggest that there is an important variation in asthma hospitalisation rates in children that remains unexplained, and deserves further consideration.

3.2.7 References

Alwahaibi A, Zeka A. 2016. Respiratory and allergic health effects in a young population in proximity of a major industrial park in Oman. Journal of epidemiology and community health; 70(2): 174-80.

Anderson R.H, Ruggles R. Pandey K.D, Kapetanakis V, Brunekreef B, Lai C.K.W, Strachan D.P, Weiland S.K, the ISAC Phase One Study Group. 2010. Ambient particulate pollution and the world-wide prevalence of asthma, rhinoconjunctivitis and eczema in children: Phase One of the International Study of Asthma and Allergies in Childhood (ISAAC).

Occupational & Environmental Medicine; 67:293—300. [Online], doi:10.1136/oem.2009.048785

Anselin, L. 1995. Local indicators of spatial association—LISA. Geographical analysis; 27, 93-115.

Asher I.M, Stewart A.W, Mallol J, Montefort S, Lai C.KW, Khaled N.A, Odhiambo J, The ISAAC Phase One Study Group. 2010. Which population level environmental factors are associated with asthma, rhinoconjunctivitis and eczema? Review of the ecological analyses of ISAAC Phase One. Respiratory Research; 11:8. [Online], http://respiratory-research.com/content/11/1/8.

Aylin P, Bottle A, Wakefield J, Jarup L, Elliott P. 2001. Proximity to coke works and hospital admissions for respiratory and cardiovascular disease in England and Wales. Thorax; 56(3): 228-33.

Ayres-Sampaio D, Teodoro A.C, Sillero N, Santos C, Fonseca J, Freitas A. 2014. An investigation of the environmental determinants of asthma hospitalizations: An applied spatial approach, Applied Geography; 47, 10-19.

Beck A. F, Moncrief T, Huang B, Simmons J.M, Sauers H, Chen C, and Kahn R.S. 2013. Inequalities in Neighborhood Child Asthma Admission Rates and Underlying Community Characteristics in One US County, Journal of Pediatrics; 163(2): 574–580.

Digital Mapping Technologies Inc. 2019. [Online], https://www.dmtispatial.com/ESRI inc., 2019. [Online], https://www.esri.com/en-us/home.

Donkelaar A, Martin V. R, Spurr R.J.D, Burnett R.T. 2015. High-Resolution Satellite-Derived $PM_{2.5}$ from Optimal Estimation and Geographically Weighted Regression over North

America. Environmental Science & Technology; 49, 10482-10491. [Online], DOI: 10.1021/acs.est.5b02076.

Gershon A.S, Guan J, Wang C, Guan J, To T. 2010. Trends in Asthma Prevalence and Incidence in Ontario, Canada, 1996–2005: A Population Study. American Journal Epidemiology; 172, 728–736. [Online], doi: 10.1093/aje/kwq189.

Government of Canada. 2017. National Pollutant Release Inventory. [Online] https://www.canada.ca/en/services/environment/pollution-waste-management/national-pollutant-release-inventory.html.

Gupta S.R, Zhang X.Y, Sharp K.L, Shannon J.J, Weiss B.K. 2008. Geographic variability in childhood asthma prevalence in Chicago. Journal of Allergy and Clinical Immunology; 121 (3): 639-645.e1.

Haggerty L.J, Roberge D, Pineault R. 2007. Features of Primary Healthcare Clinics Associated with Patients' Utilization of Emergency Rooms: Urban–Rural Differences. Healthcare Policy; 3 (2) : 73-85.

Hartley K, Ryan P, Brokamp C, Gillespie G.L. 2020. Effect of greenness on asthma in children: A systematic review. Public Health Nursing; 37:453–460. [Online], DOI: 10.1111/phn.12701.

Hiscock R, Bauld L, Amos A, Fidler J.A, Munafò M. 2012. Socioeconomic status and smoking: a review. Annals of the New York Academy of Sciences; 1248: 107-23.

Institut national de santé publique du Québec, Indice de potentiel piétonnier. 2019. [Online], https://www.inspq.qc.ca/expertises/habitudes-de-vie-et-prevention-des-maladies-chroniques/nutrition-activite-physique-et-problemes-lies-au-poids/portrait-de-l-environnement-bati-et-de-l-environnement-des-services/indicateurs-de-l-environnement-

bati/indice-de-potentiel-pietonnier

Kanchongkittiphon W. Mendell M.J, Gaffin J.M, Wang G, Phipatanakul W. 2015. Indoor Environmental Exposure and Exacerbation of Asthma: An Update to the 2000 Review by the Institute of Medicine. Environmental Health Perspectives; 123 (1): 6-20.

Lai C, Beasley R, Crane J, Foliaki S, Shah J, Weiland S. 2009. Global variation in the prevalence and severity of asthma symptoms: Phase Three of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax published online February 22.

Marra G.and Radice R. 2010. Penalised regression splines: theory and application to medical research. Statistical Methods in Medical Research; 19 (2): 107-125.

Martinez J, Pampalon R, Hamel D, Raymond G. 2004. Does Living in Rural Communities Rather Than Cities Really Make a Difference in People's Health and Wellness? Institut National de Sante Publique du Quebec.

Moran, P. 1950. A Test for the Serial Independence of Residuals. Biometrika; 37, 178-181.

Orellano P, Quaranta N, Reynoso J, Balbi B, Vasquez J. 2017. Effect of outdoor air pollution on asthma exacerbations in children and adults: Systematic review and multilevel meta-analysis. PLoS ONE; 12(3): e0174050. [Online], https://doi.org/10.1371/journal.pone.0174050.

Ouédraogo A.M, Crighton E.J, Sawada M, To T, Brand K, Lavigne E. 2018. Exploration of the spatial patterns and determinants of asthma prevalence and health services use in Ontario using a Bayesian approach. [Online], https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0208205.

Palaty C, Shum M. 2012. Health effect from mold exposure or dampness in indoor environments. National collaborating center for environmental health. [Online],

http://www.ncceh.ca/sites/default/files/Mould_and_Health_Effects_Jul_2012.pdf.

Public Health Agency of Canada. 2018. Report from the Canadian chronic disease surveillance system: asthma and chronic obstructive pulmonary disease (COPD) in Canada, 2018. [Online], https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/diseases-conditions/asthma-chronic-obstructive-pulmonary-disease-canada-2018/pub-eng.pdf.

Rothman K.J, Lash T.L, Greenland S. 2008. Modern Epidemiology.

Schreier H.M.C, Chen E. 2013. Socioeconomic Status and the Health of Youth: A Multi-level, Multi-domain Approach to Conceptualizing Pathways. Psychological Bulletin Journal; 139(3): 606–654. doi:10.1037/a0029416.

Statistics Canada. 2016. Canadian Community Health Survery (CCHS). [Online], http://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&Id=4995

Statistics Canada. 2018. Census tract: Detailed definition. [Online], https://www150.statcan.gc.ca/n1/pub/92-195-x/2011001/geo/ct-sr/def-eng.htm.

Tetreault L.F, Doucet M, Gamache P, Fournier M, Brand A, Kosatsky T, Smargiassi A. 2016. Childhood Exposure to Ambient Air Pollutants and the Onset of Asthma: An Administrative Cohort Study in Québec. Environmental Health Perspectives; 124(8): 1276-1282.

Uphoff E, Cabieses B, Pinart M, Valdés M, Antó J.M, Wright J. 2015. A systematic review of socioeconomic position in relation to asthma and allergic diseases. European Respiratory Journal; 46: 364–374. [Online], DOI: 10.1183/09031936.00114514.

U.S. EPA. 2016. Final Report: Integrated Science Assessment for Oxides of Nitrogen – Health Criteria. U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-08/071.

U.S. EPA. 2019 Final Report: Integrated Science Assessment for Particulate Matter. U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-08/139F.

Wang Z, May S.M, Charoenlap S, Pyle R, Ott N.L, Mohammed K. Joshi A.Y. 2015. Effects of Secondhand Smoke Exposure on Asthma Morbidity and Health Care Utilization in Children: a Systematic Review and Meta-analysis. Annals of Allergy, Asthma & Immunology; 115: 396e401

Wood S, 2018. Package 'mgcv'. [Online], https://cran.r-project.org/web/packages/mgcv/mgcv.pdf.

3.2.8 Tables and figures

Table 1. Descriptive characteristics of variables by CLSCs & CTs in Québec during the year 2002-2011, n=1248.

Variables	Minimum	Maximum	Median	Mean	SD	1st Qu.	3rd Qu.	IQR
Rates of asthma hospital admissions per 1000 in children aged ≤14 years *	1.35	88.36	21.96	25.46	15.04	14.49	32.93	18.44
Median household income ($)	23523	122536	58670	60361	17167	46823	70574	23751
Regional background air pollutant ($PM_{2.5}$) (ug/m³)	0.00	10.83	8.94	8.27	2.11	6.55	10.11	3.56
Km of major roads (km)	0.00	3.51	0.01	0.15	0.47	0.00	0.07	0.07
Industrial emissions of $PM_{2.5}$ (tons/year)	0.00	150.00	0.00	1.91	11.70	0.00	0.00	0.00
Industrial emissions of SO_2 (tons/year)	0.00	2637.30	0.00	15.20	138.11	0.00	0.00	0.00
Environmental Tobacco Smoke (ETS) (%) **	15.47	25.83	18.20	18.13	2.91	15.47	20.37	4.90
Vegetation index	0.00	142.52	80.585	84.07	19.62	69.70	95.90	26.20
Walkability index	1.50	98.75	59.47	59.69	21.44	44.40	76.92	32.52

SD: standard deviation, 1st Qu: first quartile, 3rd Qu: third quartile. IQR: interquartile range

*: The numerator of the rate of asthma hospital admissions is the total number of cases of asthma hospital admissions in children over the period of 2002-2011, and the denominator is the annual average population of children aged 0-14 years in Québec.

** 1248 CTs/CLSCs divisions were attributed the value of their health region (n=15).

Table 2. Summary of the asthma models for census geographic areas including CLSCs & CTs in Québec during the years 2002-2011, n=1248.

Predictors	REML	Global Moran's I	Beta (β)	Degree of freedom	p
Constant-only Models					
Constant	4393.2	-0.0013			
Constant			-0.2053		<0.001
Median household income ($)	4330.8	-0.0014		2.028	<0.001
Regional background $PM_{2.5}$ (ug/m³)	4364.6	-0.0013		5.144	<0.001
Traffic (km)	4386.1	-0.0013		1.009	<0.001
Traffic (km)	4385.4	-0.0013	-0.1307		<0.001
Industrial air pollutants ($PM_{2.5}$) (ton)	4393.1	-0.0013		2.330	0.154
Industrial air pollutants (SO_2) (ton)	4393.7	-0.0013		1.996	0.244
Envrionmental Tobacco Smoke (%)	4339.9	-0.0096		8.231	<0.001
Vegetation index	4351.2	-0.0014		3.636	<0.001

Walkability index	4368.4	-0.0015		2.266	<0.001
Coordinate (x,y)	4218	-0.0012		24.360	<0.001
Multivariate Models withough coordinates					
Without coordinate (x,y)	4252.5	-0.0012			
Median household income ($)				1.001	< 0.001
Median household income ($)			-1.108e-05		<0.001
Regional background $PM_{2.5}$ (ug/m³)				4.971	<0.001
Traffic (km)				1.001	<0.001
			-0.1699		<0.001
Industrial air pollutants ($PM_{2.5}$) (ton)				1.001	0.481
Industrial air pollutants ($PM_{2.5}$) (ton)			0.0011		0.480
Industrial air pollutants (SO_2) (ton)				3.269	0.203
Envrionmental Tobacco Smoke (%)				7.639	< 0.001
Vegetation index				3.476	0.024
Walkability index				1.001	0.108
Walkability index			-0.0023		0.107
Multivariate Models with coordinates					
Coordinate (x,y)	4109.7	-0.0001		25.602	< 0.001
Median household income ($)				1.001	< 0.001
Median household income ($)			-1.21e-05		< 0.001
Regional background $PM_{2.5}$ (ug/m³)				3.389	0.148
Traffic (km)				1.001	0.044
Traffic (km)			-0.0731		0.044
Industrial air pollutants ($PM_{2.5}$) (ton)				1.001	0.514
Industrial air pollutants ($PM_{2.5}$) (ton)			0.0009		0.513
Industrial air pollutants (SO_2) (ton)				1.004	0.456
Industrial air pollutants (SO_2) (ton)			-8.275e-05		0.454
Envrionmental Tobacco Smoke (%)				4.578	<0.001
Vegetation index				1.001	0.269
Vegetation index			-0.0019		0.269
Walkability index				1.859	0.555

REML: Restricted Maximum Likelihood.
Beta (β): coefficient per one unit increase.

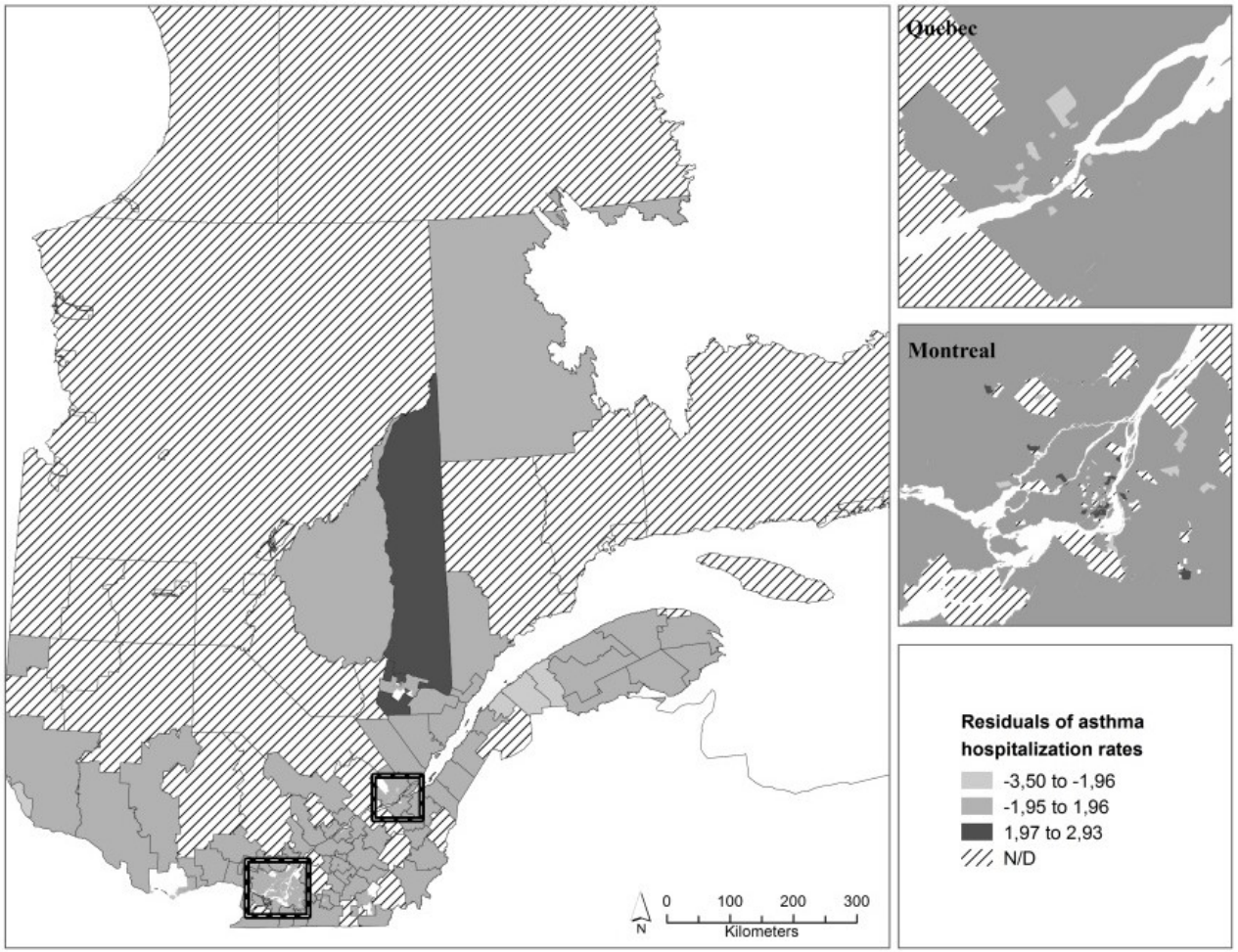


Figure 1. Map of residuals of asthma hospitalization rates in children 0-12 years from the model with a constant only, by CLSCs & CTs in Québec during the years 2002-2011. The absolute values of residuals of asthma hospital admissions rates are transformed to values between zero and one, with a division by the maximum residual rate value per area (CTs/CLSCs).

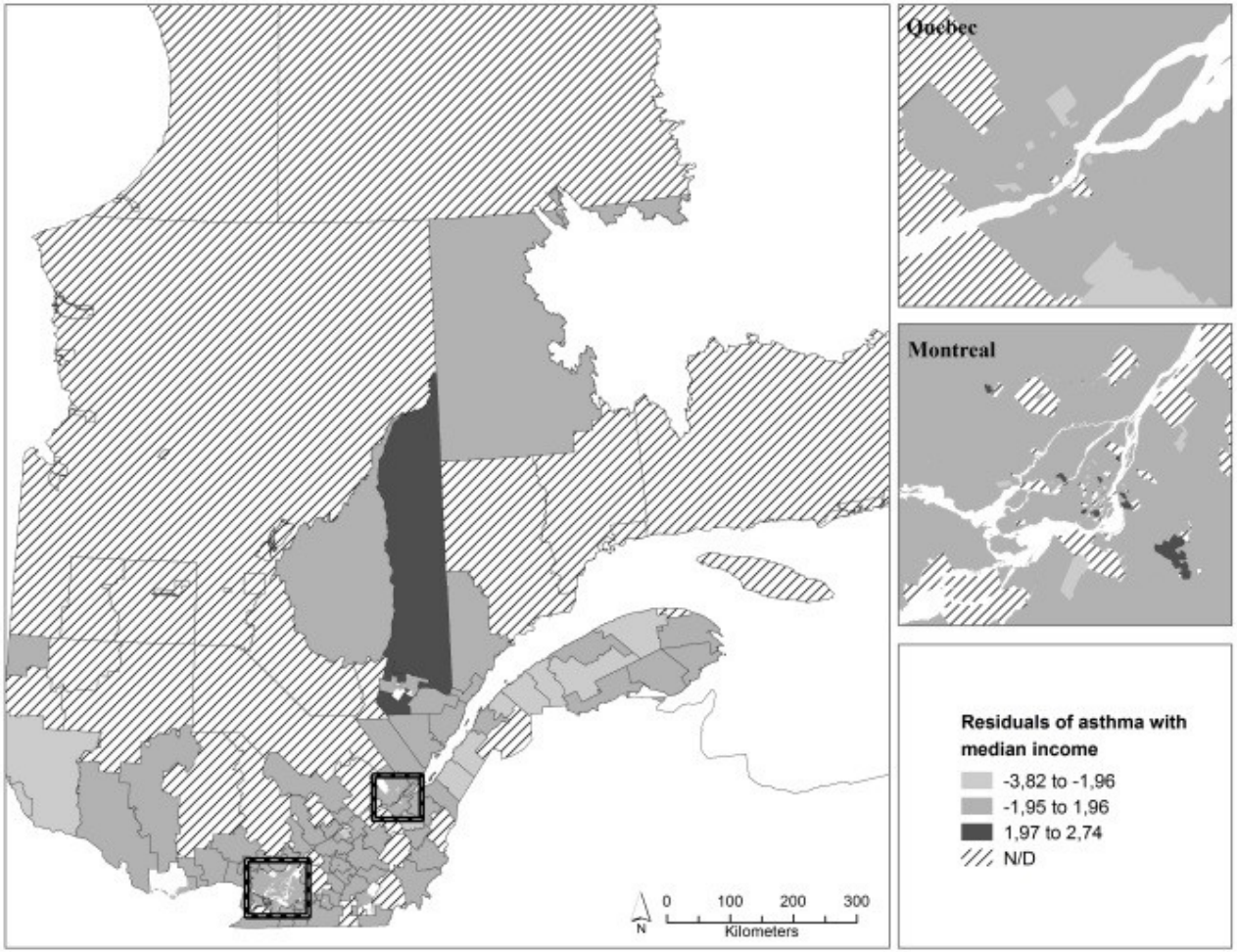


Figure 2. Maps of absolute residuals of asthma hospitalization rates in children 0-12 years by CLSCs & CTs in Québec during the years 2002-2011 of univariate model with A) median household income as independent variable.

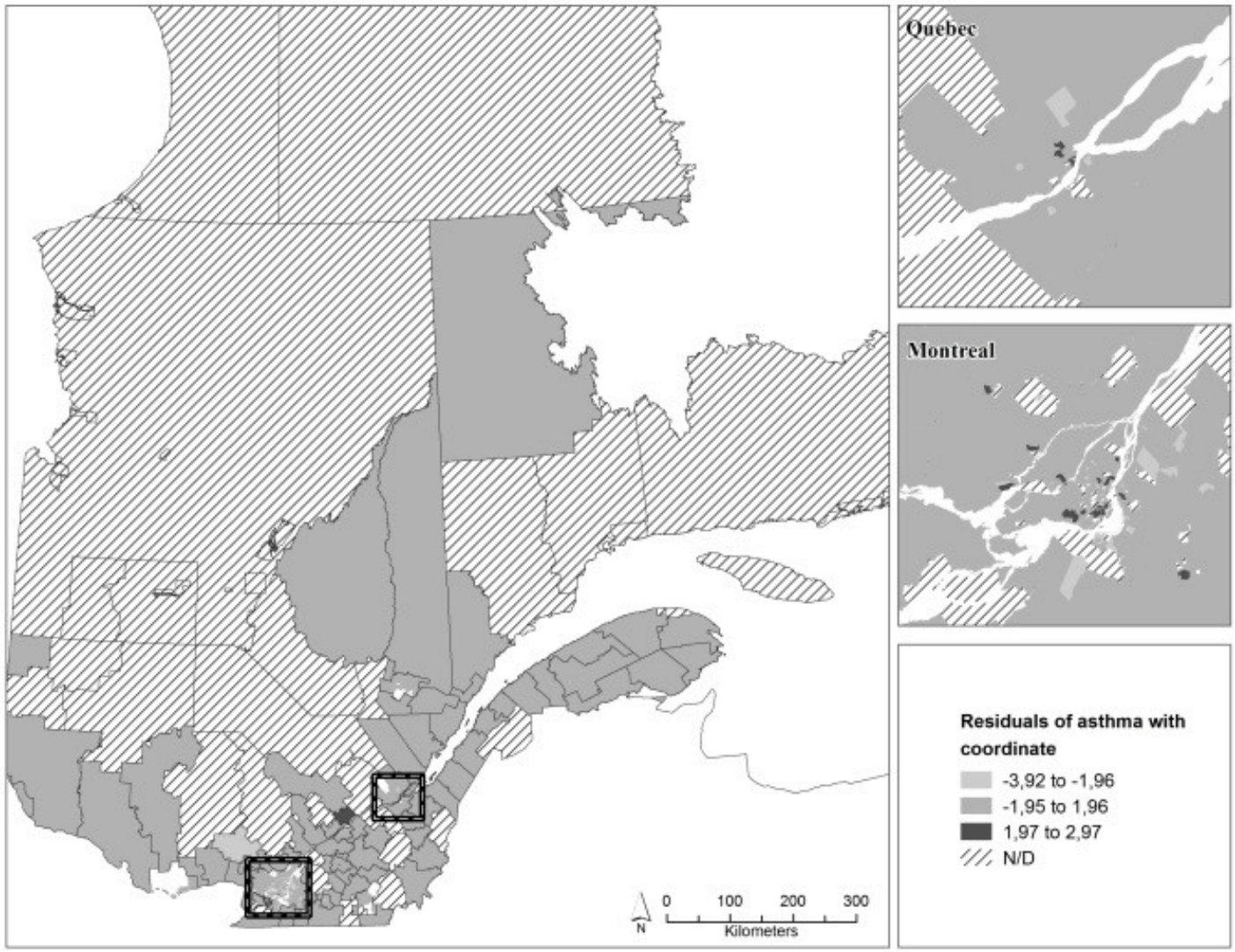


Figure 2 (continue). Maps of absolute residuals of asthma hospitalization rates in children 0-12 years by CLSCs & CTs in Québec during the years 2002-2011 of univariate model with B) coordinate as independent variable.

3.2.9 Appendix

Appendix A

The conversion of geography, population and income among census year 2001, 2006 and 2011

During the study period of 2001-2011, three censuses were completed respectively in 2001, 2006, and 2011. The geographic divisions used for emission calculation and to report asthma hospitalisation rates are census tracts (CTs) for metropolitan areas and local health service centers (CLSCs) outside metropolitan areas. In the case where CT and CLSC sectors are overlapped on a territory, the portion of the CT in the CLSC is deleted. In this way, for each parcel of territory, only one geographic unit is used.

In order to obtain the 2001, 2006 and 2011 population counts and income for each sector, we used the census information for CTs for metropolitan areas. For sectors outside metropolitan areas, we used the information of the smallest census geographic unit with income data covering all of Canada called the dissemination areas (DAs) (the CTs only covers metropolitan areas). The population numbers of DAs within a CLSC territory were then summed and the income averaged.

The geography of CTs was relatively stable between 2001 and 2011, however the geography of the DAs was completely reorganized between 2001 and 2006, and it also slightly changed between 2006 and 2011. Therefore, DAs in 2001 and 2011 were converted to the DA geography of the 2006; the 2006 CLSC divisions were also used; each DA was assigned to a CLSC by a spatial query (ArcGis 9.3).

While converting to the 2006 DA geography, the following sector discordances were found between 2001, 2006, and 2011 censuses (CTs or DA) and population and income were therefore computed as follows:

Several sectors in 2001 or 2011 correspond to a single sector in 2006

Population: the sum of each sector of 2001 or 2011 included in the single CT or DA of 2006.

Income: for all the sectors (2001 or 2011) included in one single sector of 2006, the mean weighed for the population of all the sectors of 2001 or 2011 corresponding to the sector of 2006 was calculated.

A single sector in 2001 or 2011 corresponds to several sectors in 2006

Population: the population of sectors (2001 or 2011) is divided equally by the number of CTs or DAs in 2006 included in those of 2001 or 2011.

Income: the amount of income in each sector of 2001 or 2011 corresponding to 2006 is the same.

Several sectors of 2006 correspond to several sectors of 2001 or 2011

Population: When several sectors of 2006 corresponded to many sectors in 2001 (or 2011), the 2001 (or 2011) total population of all census blocks in a 2006 DA was used. The block is the smallest census division for which only total population count is released (population by age group and income are not available for blocks). We assumed that in blocks, the distribution of the 2001 (or 2011) population by age group was similar to the distribution in each 2001 DA of origin. Thus, if there was 10% children and 90 % adults in a 2001 DA, the distribution of the population in each block of this 2001 DA was 10% children and 90% adults. We summed the children 2001 (or 2011) population of blocks included in each 2006 DA.

Income: The average income for 2001 or 2011, for the DA geography of 2006, was the average of the income from each DA of the block of origin (i.e. in 2001 or 2011), weighed by the proportion of the population of the block in a 2006 DA.

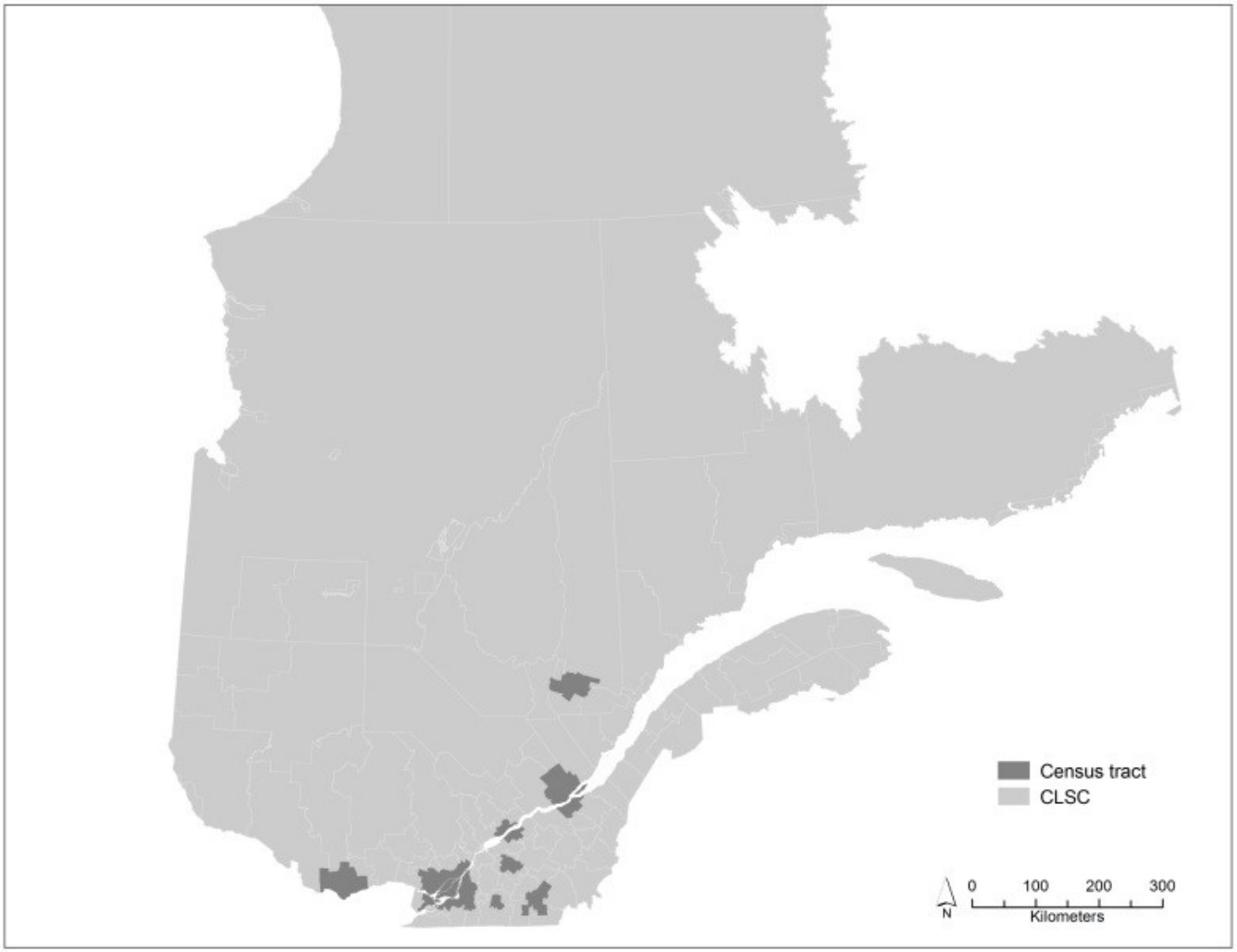


Figure A. Map of geographic sectors (CT and CLSC)

Appendix B
Pearson correlations and Spearman correlations

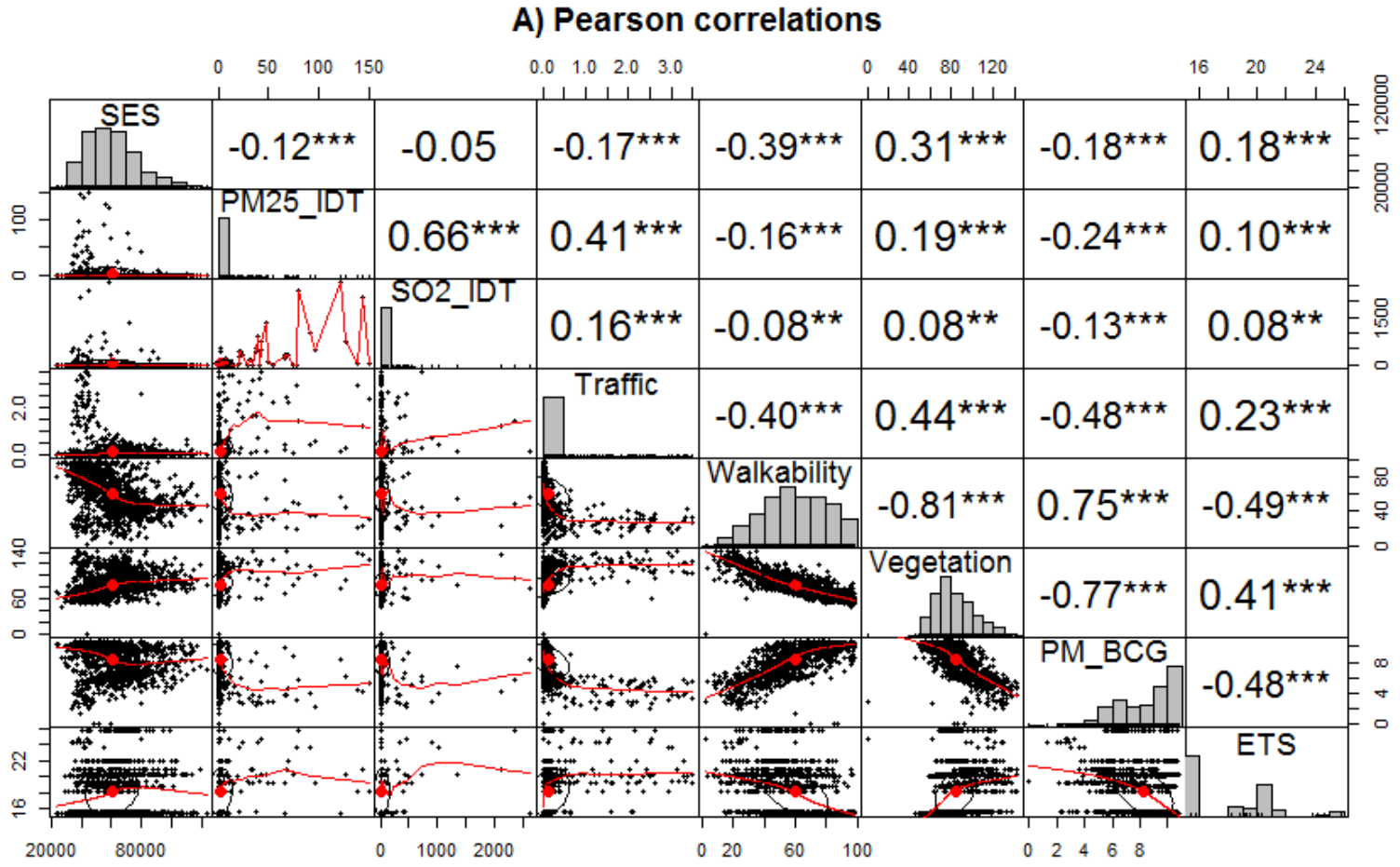


Figure B. A) Pearson correlations between predictors.

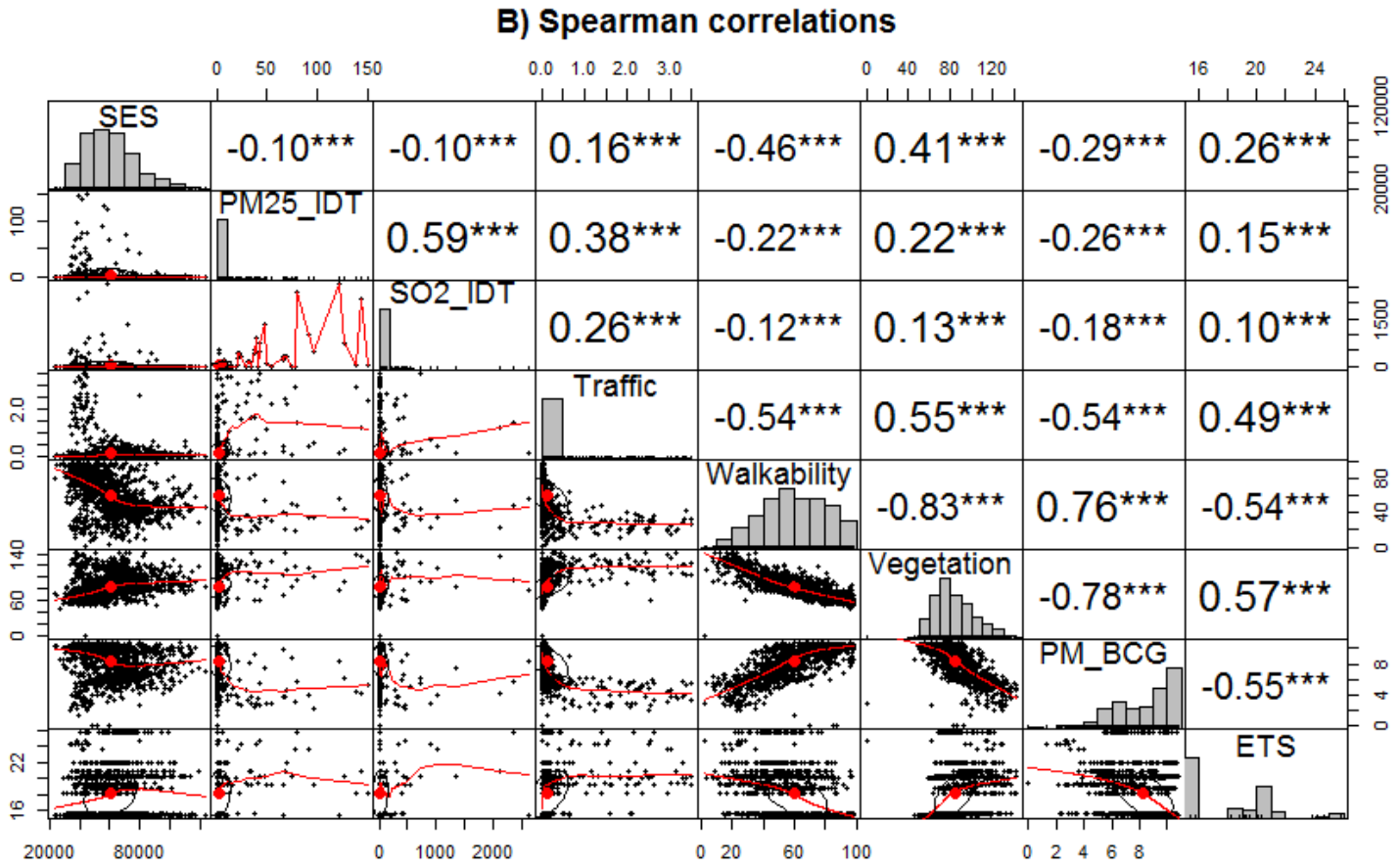
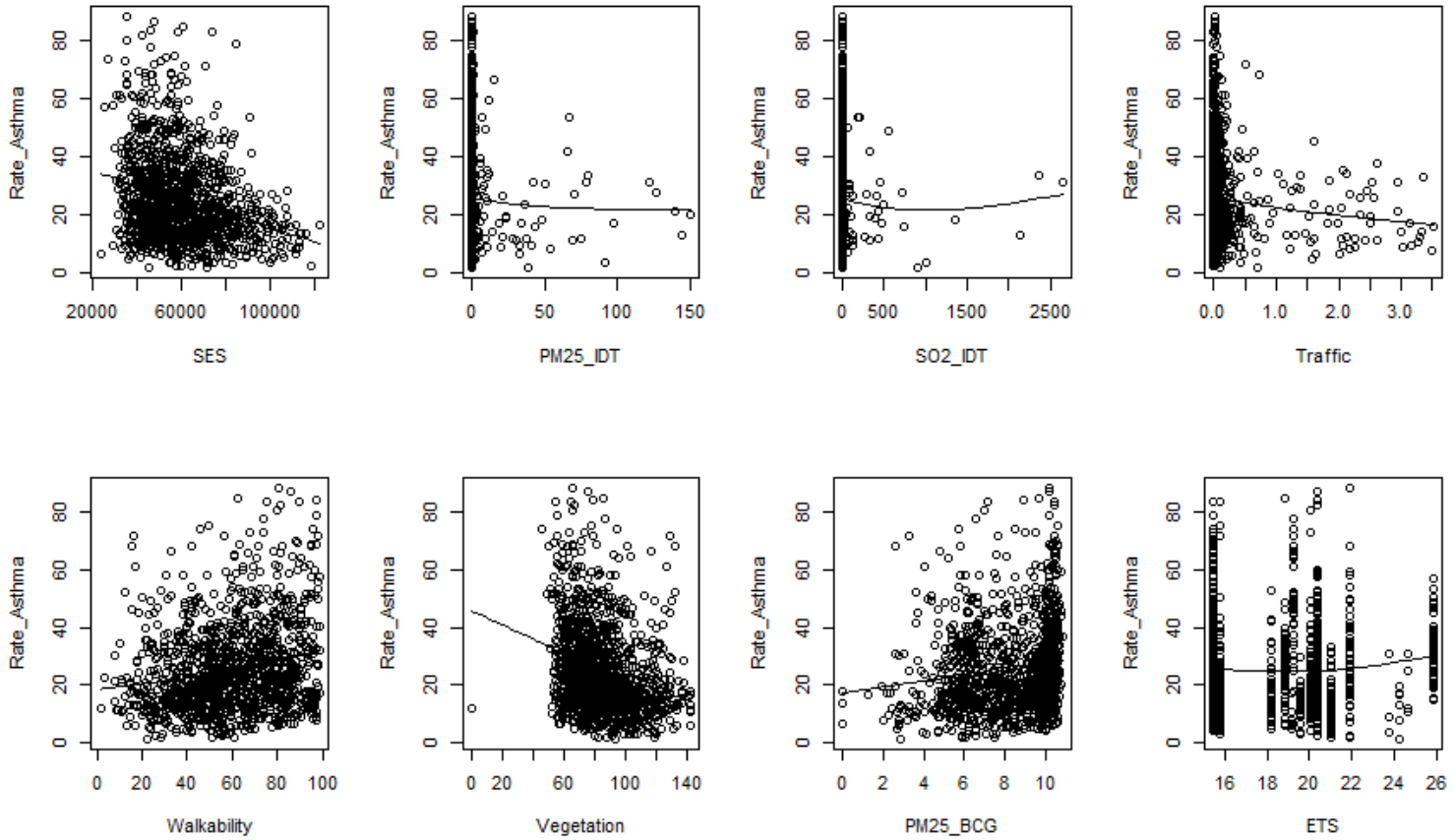
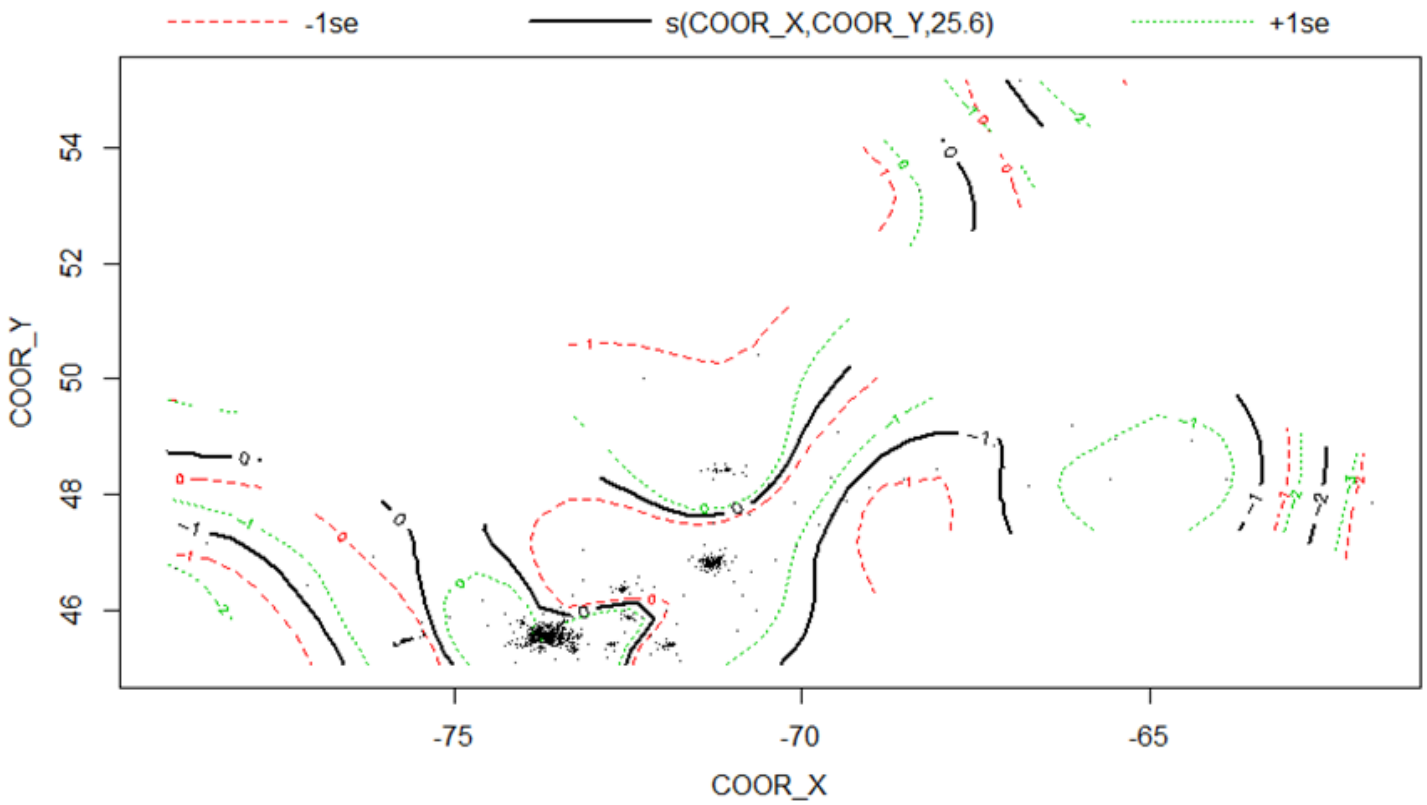


Figure B (continue). B) Spearman correlations between predictors.
SES ($): median income as socio-economic status. PM25_IDT (ton): industrial air emission of fine particulate matter. SO2_IDT (ton): industrial air emission of sulfure dioxide. Traffic (km): traffic-related air pollution. Walkability: index of walkability. Vegetation: index of vegetation. PM_BCG (ug/m³): regional background air pollution (fine particulate matter). ETS (%): environmental tobacco smoke. ***: p<0.01

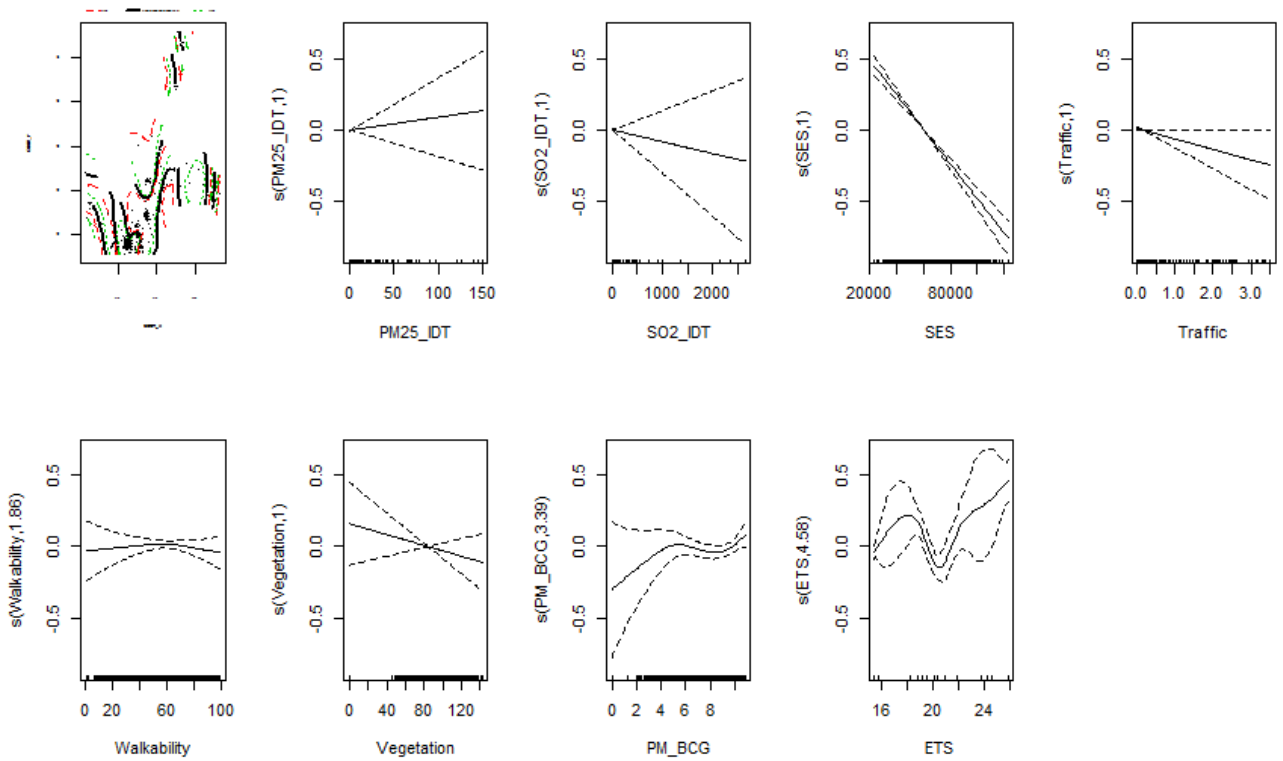
Appendix C
Relationships between rate of asthma hospital admissions and predictors





A) Univariate models

Figure C. Relationships between rate of asthma hospital admission and predictors: A) Univariate models.

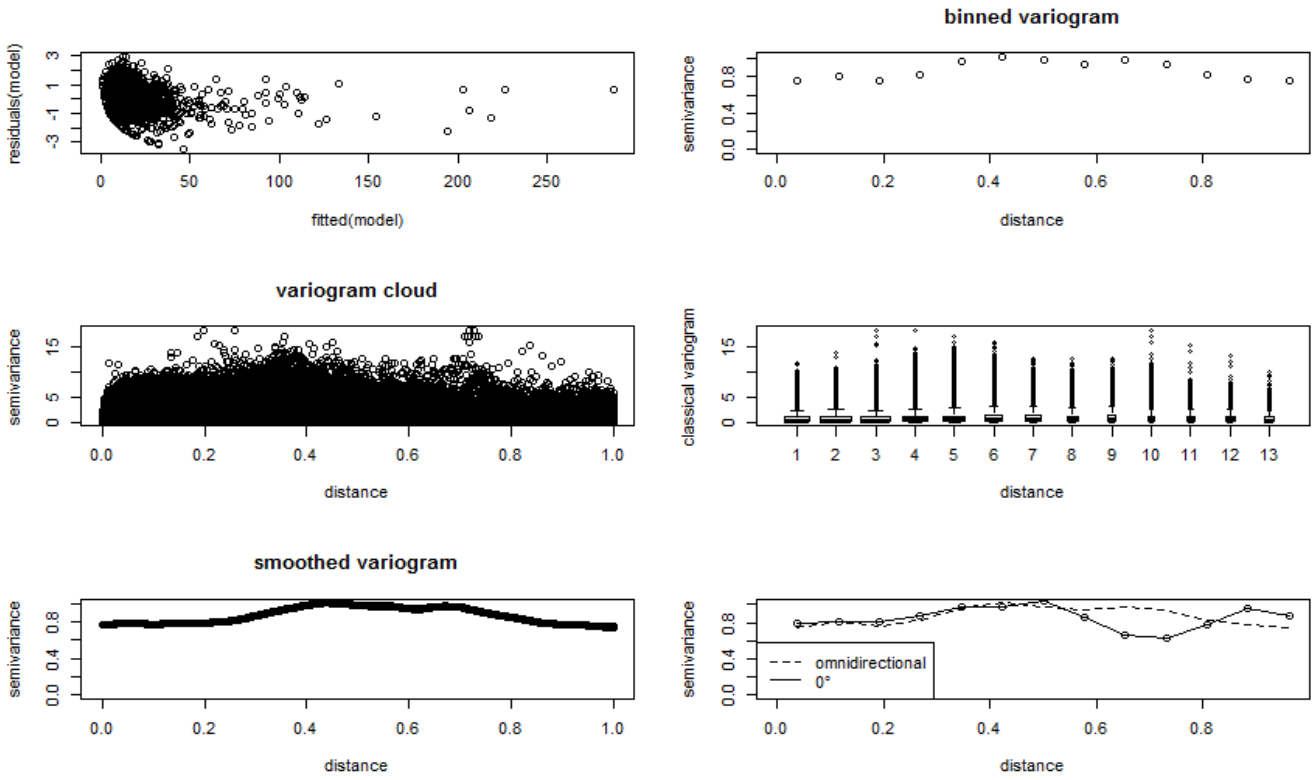


B) Multivariate models with coordinate (x, y)

Figure C (continue). B) Multivariate models with coordinate (x, y).
Rate_Asthma: rate of asthma hospital admission. PM25_IDT (ton): industrial air emission of fine particulate matter. SO2_IDT (ton): industrial air emission of sulfure dioxide. SES ($): median income as socio-economic status. Traffic (km): traffic-related air pollution. Walkability: index of walkability. Vegetation: index of vegetation. PM_BCG (ug/m³): regional background air pollution (fine particulate matter). ETS (%): environmental tobacco smoke. SE: standard error. COOR_X: coordinate x axis. COOR_Y: coordinate y axis. S(): s spline function in R. Walkability: index of walkability.

Appendix D
Variogram of spatial autocorrelations

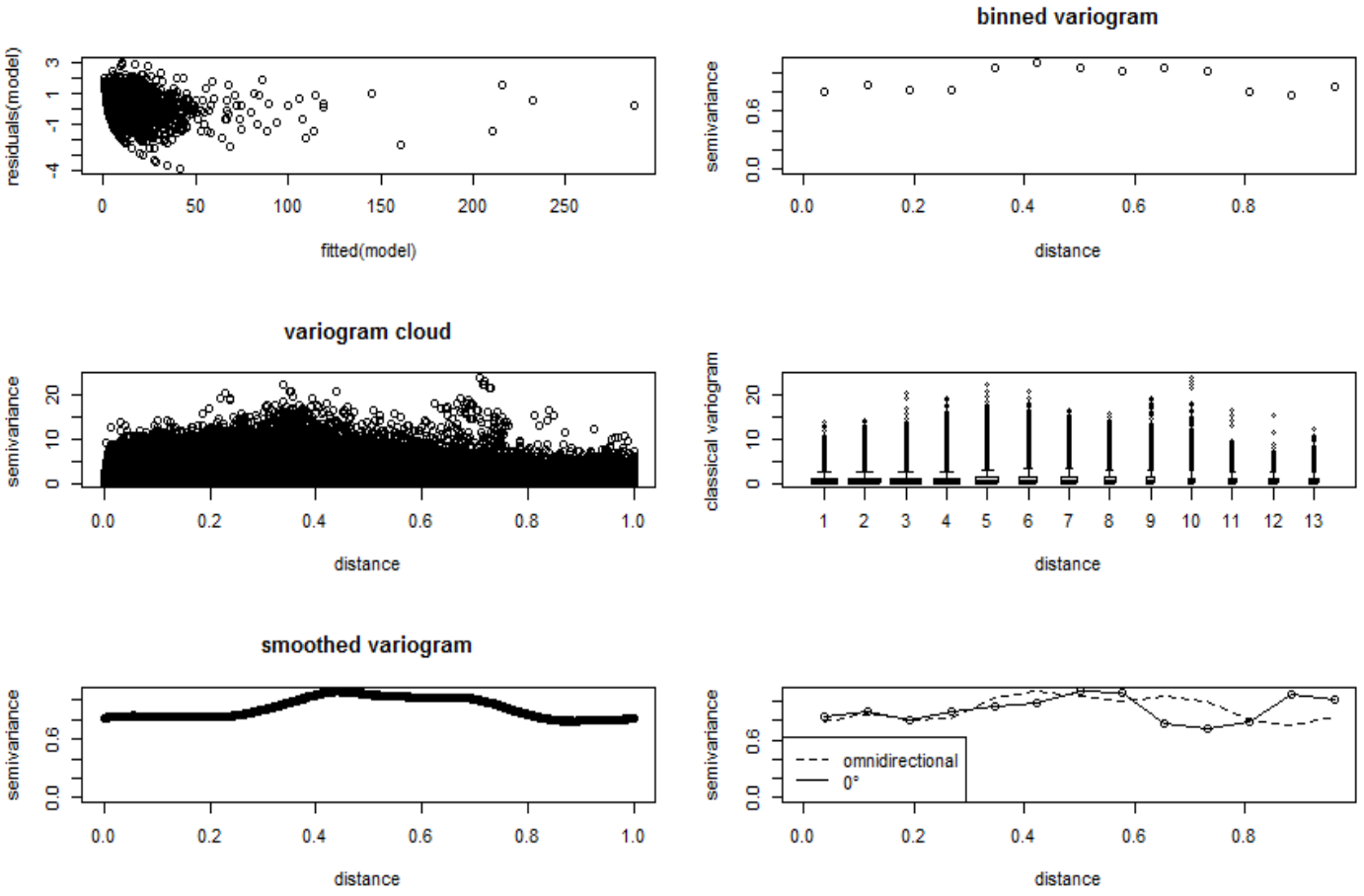
Empty Model



A) Empty model

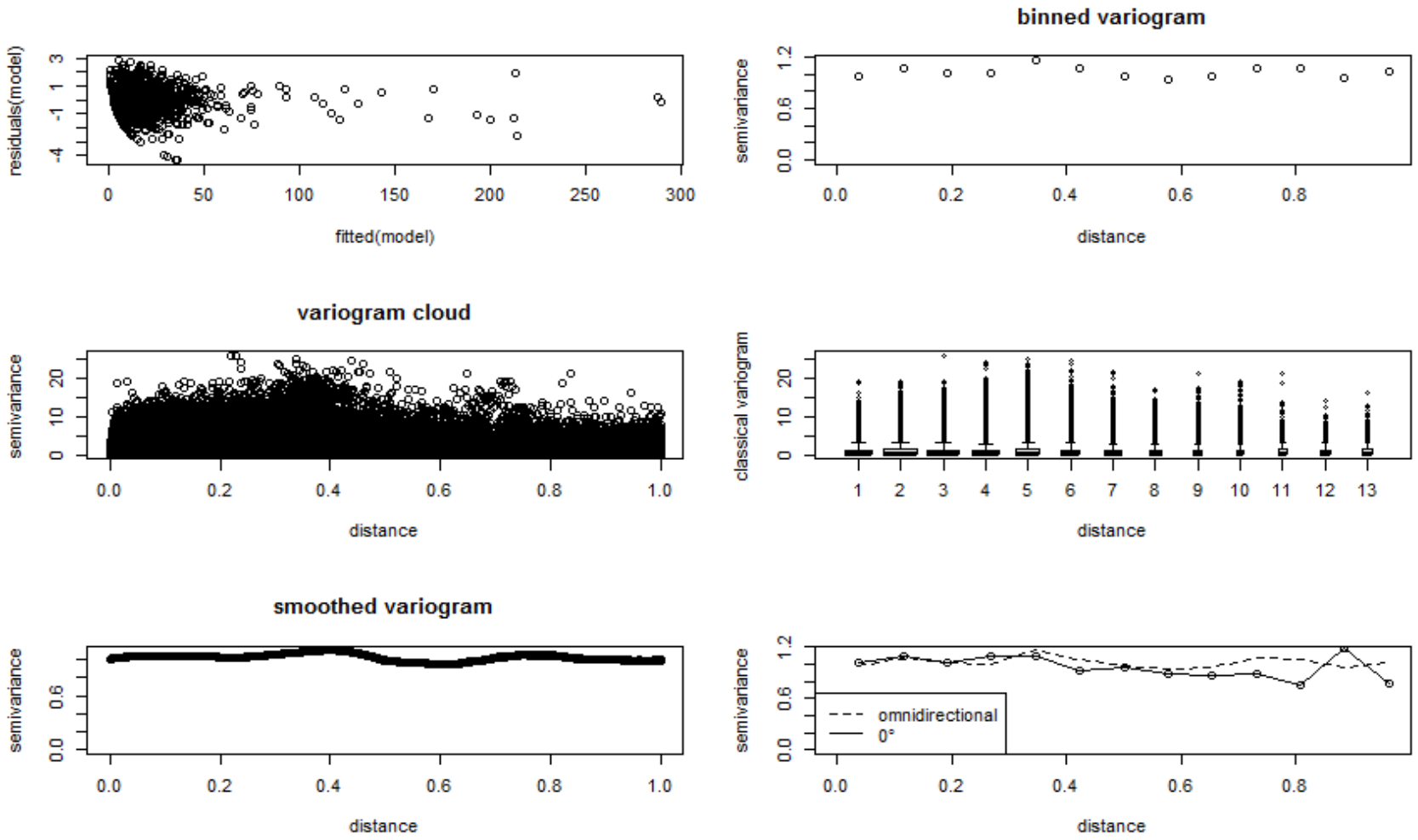
Figure D. The calculation of variogram of spatial autocorrelation of different models. A) Empty model.

Multivariate Models



B) Without coordinate & with industrial emissions ($PM_{2.5}$&SO_2)

Figure D (continue). B) Without coordinate & with industrial emissions ($PM_{2.5}$&SO_2)



C) With coordinate & with industrial emissions ($PM_{2.5}$&SO_2)

Figure D (continue). C) With coordinate & with industrial emissions ($PM_{2.5}$&SO_2).

3.3 Article 3: A fixed effect analysis of the variation of air pollution and annual rates of asthma onset in children for the years 2002 to 2011 within regions of Québec (Canada)

Xiaohui Geng[1], Sophie Goudreau[2], Michel Fournier[2], Audrey Smargiassi[3]

Status of paper and contributions of co-authors

This article is not published.

The contributions of co-authors on this paper are as follows:

1. Xiaohui Geng is the doctoral Candidate. Xiaohui Geng conceptualized the paper with her director, developed the statistical programs and performed the analyses and prepared the draft paper.
2. Sophie Goudreau is the coauthor of this spatial analysis article. She provided the datasets of variables for the spatial analysis, and wrote the context of appendix A. Moreover, she provided review and feedbacks for the writing of this paper.
3. Michel Fournier is the coauthor of this spatial analysis article. He provided statistical consultation for Xiaohui Geng. Moreover, he provided review and feedbacks for the writing of this paper.
4. Audrey Smargiassi is the thesis Supervisor. She conceptualized the study with the student, coordinated the availability of datasets and statistical consultation and oversaw the work. She provided valuable input and feedback on for the writing of this paper.

3.3.1 Abstract

Air pollutant emissions and concentrations have decreased substantially over the past decades in industrialized countries, yet few studies have investigated the health benefits of such reductions. We assessed the relationships between the changes in fine particulate levels ($PM_{2.5}$) and emissions of industrial air pollutants in small areas and the change in asthma onset in children with an ecological longitudinal design for the years 2002-2011. Within 1386 small geographic units of the province of Québec (Canada), yearly new cases of asthma in children 0-12 years of age were computed from linked medico-administrative databases. Annual regional levels of $PM_{2.5}$ were estimated from ground and satellite information; tons of industrial emission of $PM_{2.5}$ & sulfur dioxide (SO_2) were from the National Pollutant Release Inventory (NPRI). Fixed effects negative binomial models were performed to assess associations between pollutant variables and counts of asthma onset with the population of children per geographical area as offset. Models were adjusted for the median annual household income from the Census, and for environmental tobacco smoke (ETS), from survey information for 15 health regions. In the multivariate regression model, there was a 3.29% decrease in the rate of cases (95%CI, 2.44-4.14) per 1 ug/m^3 decrease in the regional $PM_{2.5;}$ no association was noted with industrial emissions (RR for SO_2 per increase of 1000 tons: 0.99, 95%CI: 0.99-1.00; RR for $PM_{2.5}$ per increase of 100 tons: 0.99, 95%CI: 0.98-1.00). The decrease of ETS and the increase in income were both related to a decrease in the rate of asthma onset. The results suggest that together with changes in socio-demographic characteristics, the decrease in regional $PM_{2.5}$ levels over the years, was associated with improvements in asthma outcomes in children. Better estimates of exposure to industrial air pollutant emissions may be necessary to capture their influence on asthma rates.

[1] Doctoral Candidate, Département de santé environnementale et santé au travail, École de santé publique, Université de Montréal, Canada; Centre de recherche en santé publique de Université de Montréal.

[2] Co-authors, Direction régionale de santé publique de Montréal;

[3] Thesis Supervisor, Département de santé environnementale et santé au travail, École de santé publique, Université de Montréal, Canada; Centre de recherche en santé publique de Université de Montréal, Institut National de Santé Publique du Québec.

3.3.2 Introduction

Asthma has been defined by many official documents (WHO 2019) as a chronic respiratory disease which impacts worldwide a large scale of the population, especially children. Asthma onset indicates the start point of asthma, which is clinically identified by diagnosis.

Air pollutants from different sources (i.e. regional and road traffic sources) are among the main risk factors for asthma development in children (Subbarao et al. 2009); socio-economic conditions are also identified as risk factors of asthma onset in children (Subbarao et al. 2009). The socioeconomic status (SES) is associated with asthma onset since lower SES often indicates higher environmental exposures such as environmental tobacco smoke (ETS), indoor mold, outdoor air pollution (Ungar et al. 2011, Subbarao et al. 2009*)*.

During a relatively long-time span, both asthma onset in children and its risk factors have been changing. Air pollution contributed by road traffic (such as nitrogen dioxide) and industrial emissions of fine particles ($PM_{2.5}$) and sulphur dioxide (SO2), have decreased as well, with major regulatory actions (Foucreault 2019). In the province of Québec (Canada), as in many other parts of the world, tobacco smoking and ETS have dramatically declined in the past decades (Statistics Canada 2019). Common indicators of SES such as educational level or/and income, have increased yearly over the past 10 years in Québec (Statistics Canada 2018a). While indoor/outdoor air pollutants and relevant covariates associated with asthma outcomes have varied over time, very few studies have looked at how changes in these factors relate to changes in health outcomes.

Here we present associations between the annual changes in regional $PM_{2.5}$ (i.e. from remote sources) and local industrial emissions of $PM_{2.5}$ and SO_2, adjusted for socioeconomic conditions (household income and ETS), and the annual change in asthma onset in children <13 years, for the years 2002-2011, within small geographic areas of Québec, Canada (i.e. census tracts or local health regions called CLSC), using an ecological longitudinal design, and fixed-effect regression models (specific statistical methods for panel data).

3.3.3 Methods

Study design, population, and unit of analyses

We adopted an ecological longitudinal study design, with the population of children aged 0-12 years old residing in the province of Québec (Canada). We used the population of children aged 0-14 years old in Québec to estimate the study population (children aged 0-12 years old) because population numbers for children 0-12 years were not available. In the province of Quebec, about 70.6% of the total population live in metropolitan areas, while the total area composes only around 1.5% of the province of Québec. In this study, we used two types of geographic units for statistical analyses according to characteristics of areas. For metropolitan areas with high population density, we used the geographic delineations of census tracts (CTs). In rural areas of the province, there are no CT delineation. Therefore, we used Centre Local de Services Communautaires (CLSC) as geographic units outside metropolitan areas. Over the years, although there were changes in terms of boundaries of geographic units, Statistics Canada has documented that changes of CT delineation were not significant. Meanwhile, the populations of these units should be homogeneous due to the formation rules of these CTs (Statistics Canada

2018b). We used the delineation of the geographic units of the 2006 census and CLSC in this study.

For the years 2001, 2006, 2011, the population of children aged 0 to 14 years per geographic units was the population in these census years. To obtain the population of children aged 0 to 14 years in non-census years (2002-2005, and 2007-2010), we used the data of census years to interpolate linearly the data in these non-census years. Due to CT geographic boundary changes overtime, we converted the population of children aged 0 to 14 years of geographic areas of census years 2001 and 2011 into corresponding numbers in geographic areas of 2006. The detailed converting process is explained in Appendix A of paper 2 (Chapter 3.2; the first paper that will be published will contain the appendix).

Variables per CT/CLSC and per year

Health outcome—annual cases of asthma onset from 2002 to 2011

We used the Québec Integrated Chronic Disease Surveillance system of the Québec Institute of Public Health (INSPQ) data to calculate the annual new cases of asthma onset in children aged 12 years old or younger per CTs/CLSCs (of 2006) for the years 2002-2011. The health insurance registry (Fichier d'inscription des personnes assurées [FIPA]), the hospitalization database (MED-ÉCHO - Maintenance et exploitation des données pour l'étude de la clientèle hospitalière), the vital statistics death database, the physician claims database, and the pharmaceutical services database (for persons aged 65 and older) are the data sources for this surveillance system in Québec. This system provides annually updated data for chronic diseases and includes age, sex, and six-digit postal code of residence overtime in Québec (Blais et al. 2014).

The following validated algorithm was used to identify asthma onset cases (coded by ICD-9 493 or ICD-10-CA J45-46): either one hospital discharge showing a diagnosis of asthma (in any diagnostic field) or two physician claims for asthma (visits to the emergency room or physician's office) occurring within a two-year period. This algorithm is used for health surveillance by the Public Health Agency of Canada and by the Québec Institute of Public Health (Government of Canada 2019). Gershon et al. (2010) reported that the sensitivity of this definition in Canadian children was 89% and its specificity 72%.

Based on the postal code conversion file of 2013 (PCCF), a spatial join was performed to assign all the postal codes (PCs) of asthmatic children to the corresponding census tract (2006) or CLSC. Thus, annual counts of new asthma cases per small geographic areas (i.e. CTs/CLSCs) were obtained.

Risk factors of air pollution and covariates

The annual values of risk factors and covariates were calculated for the geographic delineation of CTs/CLSCs of the 2006 census.

Regional $PM_{2.5}$ background levels—We used bi-yearly levels of $PM_{2.5}$ (in µg/m3) estimated with satellite images and ground data (Donkelaar et al. 2015); these levels were downloaded from the website (http://fizz.phys.dal.ca/~atmos/martin/). We averaged values of all cells of 1 km x 1 km within CTs/CLSCs, to estimate the bi-yearly $PM_{2.5}$ levels from 2001 to 2012. We

estimated the yearly levels of $PM_{2.5}$ with the middle year values of $PM_{2.5}$ (e.g. 2001-2003 was used for 2002) for the years 2002-2011.

Industrial air pollutant emissions—We used emission data reported to the National Pollutant Release Inventory (NPRI) (Government of Canada 2017) to calculate yearly industrial emissions of $PM_{2.5}$ and SO_2 (in tons) within CTs/CLSCs for the years 2002 to 2011. Annual tons of $PM_{2.5}$ per small area were divided by 100 while tons of SO_2 were divided per 1000.

Income—We used the median annual household income per CTs/CLSCs obtained averaging DA median annual income within CTs/CLSCs from the 2001, 2006 and 2011 Canadian censuses (Statistic Canada 2018a). We used the 2001 median income to estimate the median annual income in non-census years of 2002 and 2003, the 2006 median income to estimate the median annual income in non-census years of 2004, 2005, 2007 and 2008, and used the 2011 median annual income to estimate the median annual income in non-census year of 2009 and 2010. The average median income per small area was divided by 10,000.

Environmental Tobacco Smoke (ETS) — the available data related to ETS exposure was on non-smokers older than 12 years old exposed to ETS in Health Regions provided by cycles 2003, 2007/2008, 2013/2014 of the Canadian Community Health Survey (CCHS). We assumed that the exposure of children aged 0-12 years old was similar to the exposure of non-smokers older than 12 years old. Proportions of non-smokers' ETS exposure were only available for 15 of the 18 health regions in Québec (no data was available for Nord-du-Québec, Nunavik, and Terres-Cries-de-la-Baie-James). Data for 2003 were used for years 2002, 2003; 2007/8 were used for

years 2007, 2008, and data for 2013/14 were used for 2012. The yearly proportions of ETS for the 15 Health Regions were used to estimate the exposure per CTs/CLSCs of children aged 0-12 years old, attributing the ETS Health Region large scale values to the CTs/CLSCs embedded in their geography.

Statistical methods

For the annual values of asthma onset per CT/CLSC, we replaced values equal or fewer than 5 cases with the value of 2.5. Counts smaller than 5 cases cannot be released for confidentiality reasons. Then, we excluded the observations without population, median income, $PM_{2.5}$ regional background and ETS information.

Fixed effects modeling— We used univariate and multivariate fixed effects negative binomial models (Allison 2005); fixed effects modeling is an approach used for panel data. We used the population of children aged 0-14 years per geographical area as an offset to assess associations between the time trend of predictor variables and the time trend of count of asthma onset in children nested within geographic areas. We used STATA (version 13.1) to run these models. Negative Binomial models were used instead of Poisson models due to over-dispersion.

3.3.4 Results

The dataset had a total of 13,980 observations, which is the multiplication of 1,398 CT/CLSC divisions and the total years of the study period (2002-2011) before remove missing data from variables; the number of observations of the complete dataset used for statistical analysis was

13,401 after removing missing data from independent variables—the percentage of removed combined missing data is around 4% of total observations.

Figure 1 shows the time trend of annual values of the variables averaged for all geographic units for the period 2002 to 2011. To avoid the difference of units introduced by absolute values in this figure, we present values for each year, as a percentage of the value of the 2002 baseline year. The percentage of the annual rate of asthma onset decreased along the years from 2002 to 2011 by almost half. The percentage of the levels of most environmental variables also decreased with time (background regional $PM_{2.5}$ levels, industrial SO_2 emissions, and ETS), except for $PM_{2.5}$ industrial emissions that first increased before decreasing since 2008. Income consistently increased since 2002.

Table 1 presents descriptive characteristics of the dependent and independent variables per CLSC/CT and year in Québec for the period 2002-2011. The annual rate of asthma cases per 1,000 (count of asthma onset/population aged 0-14 years old*1,000) in children aged 12 years old or younger had a large variation from a minimum 1.14 to a maximum 500 with a median value of 10.44 per 1000 children per year. The difference between minimum values and maximum values of industrial air pollutant emissions ($PM_{2.5}$/SO_2) were also large, 0-16.35*100 tons/year in $PM_{2.5}$ and 0-63.08*1000 tons/year in SO_2, respectively. The median values of these two predictors were zero, which indicates that the majority of geographic units and years had no industrial air pollutant emissions.

Pearson and Spearman correlations between predictor variables are reported in Appendix B. Industrial air emissions of $PM_{2.5}$ were highly (>0.45) and positively related to industrial air emissions of SO_2, while the correlation between other variables were smaller than 0.2.

Table 2 summarizes the results of the fixed effects models. For univariate models, there was a decrease of 16.36% in the rate of cases per increase of 10,000$ of income (95%CI, 15.61-17.10), and an increase of 13.17% in the rate of cases for an increase of 1 $\mu g/m^3$ in the regional $PM_{2.5}$ levels (95% CI, 12.55-13.78). The results with industrial emissions showed a counterintuitive decrease of 2.84% in the rate of cases per increase of 100 tons in industrial $PM_{2.5}$ emissions (95% CI, 1.55-4.11); there was a decrease of 10.06% per 1000 tons increase in industrial SO_2 emissions (95% CI, 4.04-15.7). An increase of 1 percent of ETS was associated with an increase of 3.67% in rate of cases (95% CI, 3.53-3.80).

For the multivariate model, the associations between the annual rate of asthma onset per 1000 children and most independent variables had similar directions as the univariate models, but the values changed. As for industrial emissions in the multivariate model, they were not related to asthma onset in children. The rate of asthma onset cases decreased by 1.63% along with the increase of 10,000$ of median income (95%CI, 0.36-2.88). There was an increase of 3.29% in the rate of cases with an increase of 1 $\mu g/m^3$ in regional $PM_{2.5}$ levels (95% CI, 2.44-4.14). The associations between industrial air emissions ($PM_{2.5}$ & SO_2) were null; the incidence rate ratios (IRR) were respectively 0.99 (95%CI, 0.99-1.00) and 0.99 (95%CI, 0.98-1.00) per 1000 and 100 tons increase in industrial SO_2 and $PM_{2.5}$ emissions. The IRR values for ETS indicated an

increase of 2.83% in the rate of cases (95%CI: 2.57-3.09) for an increase of 1% in ETS exposure in the full model.

3.3.5 Discussion

This study examined the association between the time trend of cases of asthma onset in children per small geographic areas and the time trend of industrial air pollutant emissions and other environmental and sociodemographic variables from 2002 to 2011 in the province of Québec. We did not find significant associations between the changes in industrial air pollutant emissions and the changes in the rate of asthma onset. However, our findings suggest that neighborhood changes in regional $PM_{2.5}$ levels and in ETS, which have both decreased over the years, are associated with improvements in asthma onset in Québec. Meanwhile, along with the increase of median income, the annual rate of asthma onset has also decreased.

The decrease in the annual rate of asthma onset with the decrease in the regional background of $PM_{2.5}$ levels and ETS and the increase in income are in agreement with the current evidence. Indeed, ETS and socioeconomic status (shown here with income) are confirmed main risk factors for asthma onset in children (Burke et al. 2012, Uphoff et al. 2015). Exposure to $PM_{2.5}$ has also been suggested to induce asthma onset in children (EPA 2019).

We report no association between industrial emission (SO_2 & $PM_{2.5}$) reduction and the change in asthma onset rate in the past 10 years in Québec. This result is also in line with our systemic review of studies performed in individuals (see chapter 3, section 3.1) which indicated that there was no clear association between industrial air emissions and respiratory health outcomes in

children. As explained in this review, which also pertains to the current study, this lack of association may be due to the rough nature of industrial emission data used. Indeed, emissions are self-reported by industries; they do not consider that meteorology influences the dispersion of the pollutants in the atmosphere. Thus, the indicators used in most studies contain errors that are likely to bias results towards the null.

Although a few studies used fixed-effect approaches to assess the relationship between the temporal trend in air pollutant levels and the temporal trend in health outcomes, this approach has not been used to assess associations with asthma onset in children. For example, Chay et al. (2003) used a fixed effects approach and reported a reduction in mortality with the reduction in total suspended particulate pollution induced by the Clean Air Act of 1970 across US counties. Using the same approach, Correia et al. (2013) assessed the effect of air pollution control on life expectancy in 545 US counties for the period 2000 to 2007. Their results showed that for every 10 μg/m3 decline in $PM_{2.5}$ levels, there was a significant increase in life expectancy of 0.35 years. Henneman et al. (2019) also reported improvements in six cardiac and respiratory health outcomes—all cardiovascular disease, chronic obstructive pulmonary disorder, cardiovascular stroke, heart failure, ischemic heart disease, and respiratory tract infections—with coal emission reduction between 2005 and 2012 across USA using similar statistical methods. Comparing to these studies, our study used smaller geographic units (CTs/CLSCs) in Québec, which reduces the ecological error; we are also first to report on variables associated with changes in asthma onset rates.

While fixed effects modeling is an interesting approach to study changes in health outcomes overtime, it is based on an epidemiological ecological design. Results from studies using ecological designs should not be used to infer causality because they are subject to the ecological fallacy. Indeed, associations obtained for small areas may not be consistent with associations at the individual level. However, longitudinal ecological designs are less biased than non-temporal ecological assessments in that in assessing within-region long-term temporal changes in both predictors and health outcomes, the potential bias due to unmeasured constant confounding factors is reduced (Liker et al. 1985). Nonetheless, confounding factors may still bias the results. Confounding was indeed evident with the change from negative associations with industrial emissions in the univariate models, to null associations in the full model. Furthermore, the decrease in the annual rate of asthma onset that was observed with income could reflect the temporal trend in asthma onset that relates to inflation rate, which has increased during the period of the study in Canada; thus the inversed relationship between median income and asthma onset in children could be confounded by inflation, or by other variables not considered in this study. Meanwhile, the usage of median household income may be a source of cross-level biases through effect modification by group since individual income and neighborhood average income may influence health in a separate manner as some studies have shown (Schreier and Chen 2013).

Additionally, it is possible that some of the unexplained temporal variations in the rate of asthma onset relates to some unaccounted temporal variations of potential risk factors. The changes in health care use, in vegetation, in traffic air pollution and walkability could all impact the change in asthma onset overtime, and they have not been considered here.

Another limitation of our study is that we did not analyze the combined effects of geographical variation and time trends in socioeconomic and environmental factors. Here we did not study the effects between geographic areas. More complex assessments, also considering the geographical autocorrelation would be necessary for that. The study provides insights regarding the influence on asthma onset, of changes in environmental and socioeconomic variables and also insights regarding measures that may have been efficient to reduce morbidity, which is nonetheless innovative.

3.3.6 Conclusion

Our results suggest that variations in ambient regional air pollutants ($PM_{2.5}$), SES and ETS are predictors of the variation in asthma onset rates in children in regions of Québec (Canada). Together with results from studies with different epidemiological designs, the results from our current study support the notion that public health efforts aimed at decreasing ambient air pollution and at increasing socioeconomic conditions (also related to decrease in ETS) could induce decrements in asthma rates. Future work using additional variables is warranted to confirm our results suggesting that the time trend of environmental and sociodemographic factors have influenced the time trend of asthma onset in children.

3.3.7 References

Allison P. 2005. Fixed Effects Regression Methods for Longitudinal Data Using SAS. SAS Institute.

Blais C, Jean S, Sirois C, Rochette L, Plante C, Larocque I, Doucet M, Ruel G, Simard M,

Gamache P, Hamel D, St-Laurent D, E´ mond V. 2014. Quebec Integrated Chronic Disease Surveillance System (QICDSS), an innovative approach. Chronic Diseases and Injuries in Canada; 34(4), 226-35.

Burke H, Leonardi-Bee Jo, Hashim A, Pine-Abata H, Chen Y, Cook D. G, Britton J. R, McKeever T. M. 2012. Prenatal and Passive Smoke Exposure and Incidence of Asthma and Wheeze: Systematic Review and Meta-analysis. PEDIATRICS; 129 (4), 735-743.

Chay K, Greenstone M. 2003. The clean air act of 1970 and adult mortality. Journal of Risk and Uncertainty; 27(3), 279-300.

Correia W.A, Pope III C.A, Dockery W.D, Wang Y, Ezzati M, Dominici F. 2013. The Effect of Air Pollution Control on Life Expectancy in theUnited States: An Analysis of 545 US counties for the period 2000 to 2007. Epidemiology; 24(1), 23–31.

Donkelaar A, Martin V. R, Spurr R.J.D, Burnett R.T. 2015. High-Resolution Satellite-Derived $PM_{2.5}$ from Optimal Estimation and Geographically Weighted Regression over North America. Environmental Science & Technology; 49, 10482-10491. [Online], DOI: 10.1021/acs.est.5b02076.

FOUCREAULT, M-A. 2019. Bilan de la qualité de l'air au Québec 2016. Québec, ministère de l'Environnement et de la Lutte contre les changements climatiques, Direction générale du suivi de l'état de l'environnement, 25 p. +8 annexes. [Online], www.environnement.gouv.qc.ca/air/bilan/qualite-airquebec-2016.htm.

Gershon A.S, Guan J, Wang C, Guan J, To T. 2010. Trends in Asthma Prevalence and Incidence in Ontario, Canada, 1996–2005: A Population Study. American Journal Epidemiology; 172, 728–736. doi: 10.1093/aje/kwq189

Government of Canada. 2017. National Pollutant Release Inventory. [Online],

https://www.canada.ca/en/services/environment/pollution-waste-management/national-pollutant-release-inventory.html.

Government of Canada. 2019. Canadian Chronic Disease Surveillance System 2000/2001-2016/2017. [Online], https://open.canada.ca/data/en/dataset/9525c8c0-554a-461b-a763-f1657acb9c9d

Henneman L.R.F., Choirat C., Zigler C.M. 2019. Accountability Assessment of Health Improvements in the United States Associated with Reduced Coal Emissions Between 2005 and 2012. Epidemiology; 30 (4): 477-485. [Online], https://open.canada.ca/data/en/dataset/9525c8c0-554a-461b-a763-f1657acb9c9d

Liker K, Augustyniak S, Duncan G.J. 1985. Panel Data and Models of Change: A Comparison of First Difference and Conventional Two-Wave Models. Social Science Research; 14:80-101.

Rothman K.J, Lash T.L, Greenland S. 2008. Modern Epidemiology

Schreier H.M.C, Chen E. 2013. Socioeconomic Status and the Health of Youth: A Multi-level, Multi-domain Approach to Conceptualizing Pathways. Psychological Bulletin Journal; 139(3): 606–654. doi:10.1037/a0029416.

Statistics Canada. 2018. Income, Pensions, Spending and Wealth. [Online], https://www150.statcan.gc.ca/n1/en/subjects/income_pensions_spending_and_wealth?HPA=1

Statistics Canada. 2018. Census tract: Detailed definition. [Online], https://www150.statcan.gc.ca/n1/pub/92-195-x/2011001/geo/ct-sr/def-eng.htm

Statistics Canada. 2019. Smoking, changes between 1994/1995 and 2004/2005, 2006/2007,

2008/2009 and 2010/2011. [Online], https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310043801&pickMembers%5B0%5D=1.6&pickMembers%5B1%5D=2.1&pickMembers%5B2%5D=3.1

Subbarao P, Becher A, Brook R.J, Daley D, Mandhane J.P, Miller E.G, Turvey E.S, Sears R.M. 2009. Epidemiology of asthma: risk factors for development. Expert review of clinical immunology; 5(1), 77-95.

Ungar J.W, Paterson J.M, Gomes T, Bikangaga P, Gold M, To T, Kozyrskyj L.A. 2011. Relationship of Asthma management, socioeconomic status, and medication insurance characteristics to exacerbation frequency in children with asthma. Annals of allergy, asthma & immunology; 106, 17–23.

Uphoff E, Cabieses B, Pinart M, Valdés M, Anto J. M, Wright J. 2015. A Systematic Review of Socioeconomic Position in Relation to Asthma and Allergic Diseases. European Respiratory Journal; 46: 364-374

U. S. Environmental Protection Agency. 2019. Integrated Science Assessment (ISA) for Particulate Matter (Final Report). EPA/600/R-19/188.

World Health Organization. 2019. Asthma. [Online], https://www.who.int/news-room/q-a-detail/asthma

3.3.8 Tables & figures

Table 1. Asthma rates and characteristics of predictor variables for all areas (CLSC/CT) of Québec, for the years 2002-2011 (n=13,401).

Variables	Minimum	Maximum	P25	Median	P75	Mean	SD
Rate of asthma cases in ≤12 years of age per 1,000 children-year [a]	1.14	500.00	6.79	10.44	14.53	12.29	12.57
Median annual household income ($)/10,000	1.01	26.41	4.67	5.90	7.22	6.19	2.19
Regional annual background of $PM_{2.5}$ levels (μg/m³)	0.62	16.50	6.39	8.67	9.80	8.23	2.46
Annual industrial emissions of $PM_{2.5}$ (tons/100)	0.00	16.35	0.00	0.00	0.00	0.07	0.59
Annual industrial emissions of SO_2 (tons/1,000)	0.00	63.08	0.00	0.00	0.00	0.11	1.26
Annual Environmental Tobacco Smoke (ETS) (%) [b]	11.38	37.75	16.64	20.58	23.52	20.34	5.07

CT: census tract.
CLSC: Centre Local de Services Communautaires.
P25: 25%; P75: 75%.
SD: standard deviation.
[a] Note that the population of children 0-14 was used to calculate the rates.
[b] There were 15 health regions and the 1,340 CTs/CLSCs divisions were attributed the value of their health region; ETS is for those older than 12 years of age and it is used as a proxy variable for children.

Table 2. Univariate and multivariate associations between annual predictors and the rate of asthma onset in children for the geographic areas of CLSC & CT in Québec during the years 2002-2011, n=13,401.

Variables	Coefficient	95% CI	IRR	95% CI
Crude Models				
Median household income (*10,000$)	-0.1786	(-0.1874, -0.1698)	0.8364	(0.8290, 0.8439)
Regional background of $PM_{2.5}$ levels (ug/m³)	0.1237	(0.1183, 0.1291)	1.1317	(1.1255, 1.1378)
Industrial $PM_{2.5}$emissions (*100 ton)	-0.0288	(-0.0419, -0.0156)	0.9716	(0.9589, 0.9845)
Industrial SO_2 emissions (*1000)	-0.1060	(-0.1708, -0.0412)	0.8994	(0.8430, 0.9596)

Envrionmental Tobacco Smoke (%)	0.0360	(0.0347, 0.0373)	1.0367	(1.0353, 1.0380)
Multivariate Model with all variables				
Median household income (*10,000$)	-0.0164	(-0.0292, 0.0036)	0.9837	(0.9712, 0.9964)
Regional background $PM_{2.5}$ ($\mu g/m^3$)	0.03233	(0.0241, 0.0405)	1.0329	(1.0244, 1.0414)
Industrial air pollutants ($PM_{2.5}$) (*100 ton)	-0.0091	(-0.0203, 0.0022)	0.9910	(0.9799, 1,0022)
Industrial air pollutants (SO_2) (*1000 ton)	-0.0092	(-0.0130, 0.0055)	0.9908	(0.9871, 0.9945)
Envrionmental Tobacco Smoke (%)	0.0279	(0.0254, 0.0304)	1.0283	(1.0257, 1.0309)

CT: census tract.

CLSC: Centre Local de Services Communautaires.

IRR: Incidence rate ratio.

[a] Note: ETS is for those older than 12 years of age and it is used as a proxy variable for children.

Figure 1. Time trend of the annual percentage of all variables from 2002 to 2011, averaged for all areas. Annual values are in percent of 2002 values. Asthma: % of annual rate of asthma onset in children aged 0-12, ses: % of annual median income, pm25_BG: % of annual background regional $PM_{2.5}$ levels, pm25: % of annual industrial air emissions of fine particulate matter ($PM_{2.5}$), so2: % of annual industrial air emissions of sulfur dioxide (SO_2), ets: % of annual proportion of Environmental Tobacco Smoke (ETS) exposure in individuals older than 12 years of age.

3.3.9 Appendix

Appendix A

The conversion of geography, population and income among census year 2001, 2006 and 2011

See Appendix A of chapter 3.2. First paper to be published will include the appendix to which the other paper will refer to.

Appendix B

Pearson Correlations & Spearman Correlations

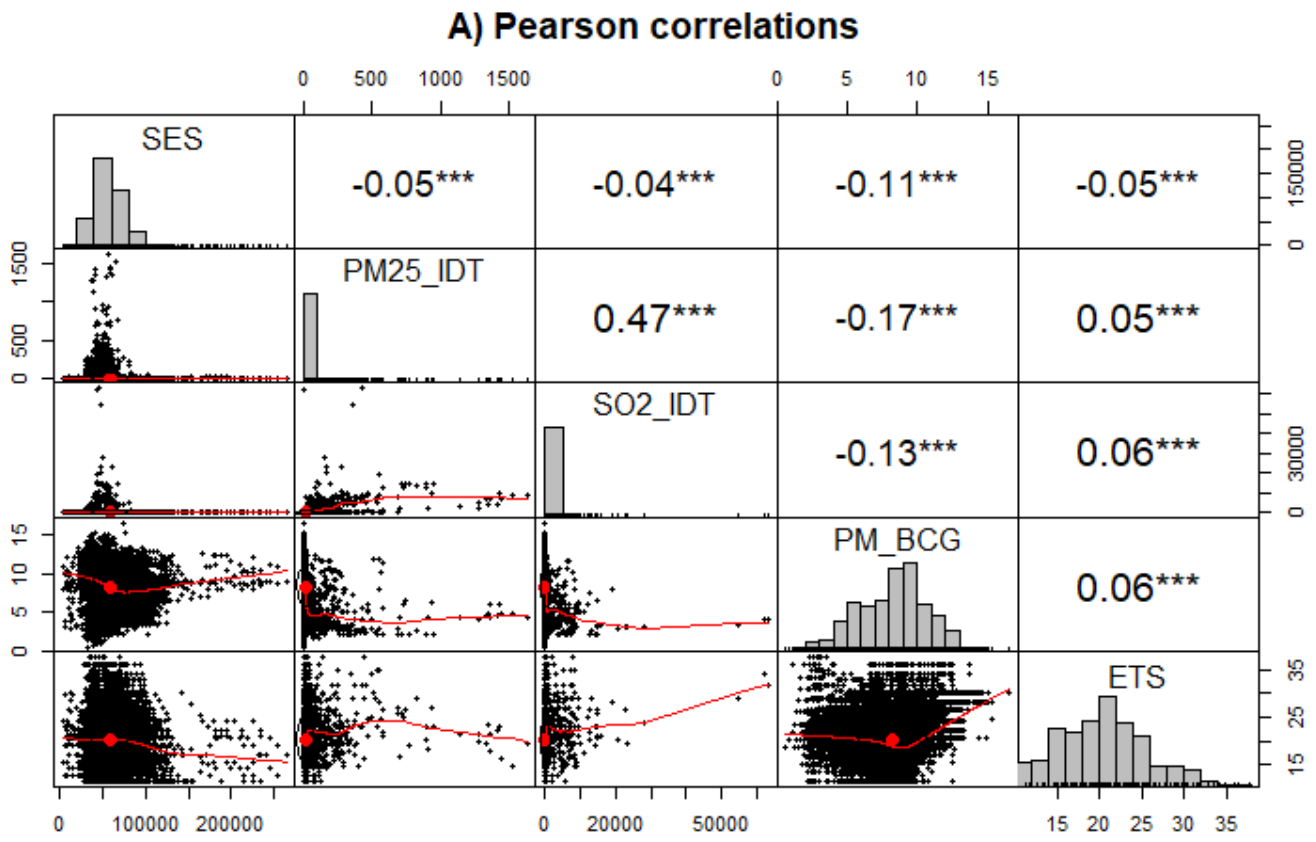


Figure B. A) Pearson correlations of annual predictor variables for small areas (CT/CLSC).

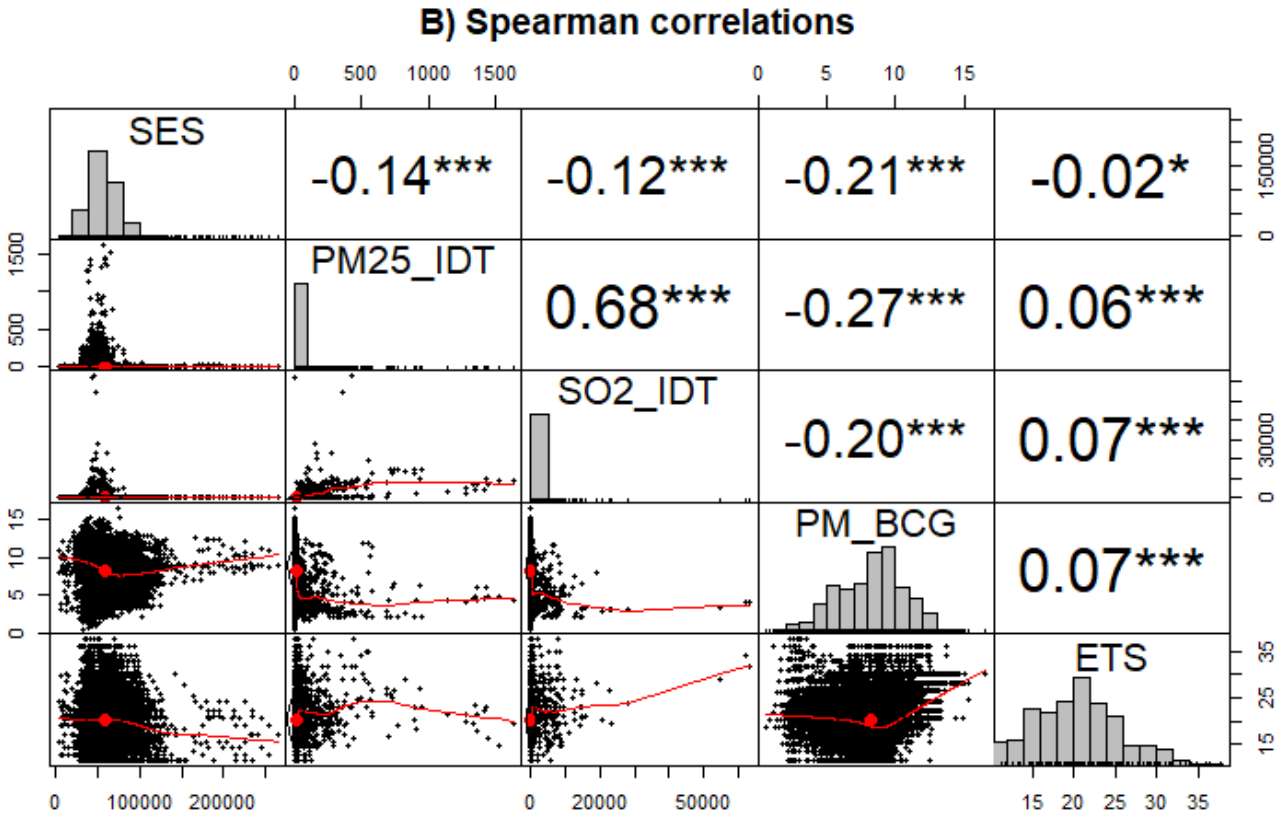


Figure B (continue). B) Spearman correlations of annual predictor variables for small areas (CT/CLSC).
SES ($): income as proxy for socioeconomic status. PM25_IDT (ton): annual industrial air emission of fine particulate matter. SO2_IDT (ton): annual industrial air emission of sulfur dioxide (SO_2). PM_BCG ($\mu g/m^3$): background regional fine particulate levels ($PM_{2.5}$). ETS: Environmental Tobacco Smoke in individuals older than 12 years of age. ***: $p<0.001$

CHAPTER 4. DISCUSSION & CONCLUSION

In the following text, we discuss the main results of the thesis and the contribution to the field of environmental epidemiology, limitations, and the conclusion of this dissertation.

The general objective of this dissertation was to assess the association between industrial air pollutant emissions and asthma outcomes in children. To address this objective, a systematic review of the current evidence was first performed (Chapter 3.1). Then, ecological analyses were conducted to study the spatial (Chapter 3.2) and the temporal (Chapter 3.3) trends in asthma morbidity in children that relate to industrial air pollutant emissions and to other socioeconomic and environmental factors.

The systematic review (Chapter 3.1) suggests no evidence of an association between short-term exposure to industrial air pollutants and asthma outcomes in children. However, cross-sectional studies using questionnaire information indicate that residential proximity to industry, and thus, long-term exposure to industrial air pollutants is related to asthma prevalence in children. Nonetheless, important heterogeneity between results was noted. Furthermore, only weak epidemiological study design (e.g. mostly cross-sectional studies) and methods (e.g. exposure assessment based on residential proximity) were noted for published studies. The spatiotemporal analyses conducted in Chapters 3.2 and 3.3 also suggest no evidence of association between the long term exposure to industrial emissions of $PM_{2.5}$ and SO_2 and asthma morbidity in children (e.g. asthma onset hospital admissions).

The negative results of our spatial assessments (Chapter 3.2) contribute to the conflicting and very limited evidence that exists from the few ecological studies on the influence of the

geographic variation in industrial air pollution and asthma outcomes. Indeed, while Alwahaibi et Zekal (2016) found a positive association between asthma medical consultations in children living within 10 km of an industrial park in Oman (RR=3.7; 95%CI=3.1 to 4.5), Aylin et al. (2001) reported no association between exposure to coke works and asthma hospital admissions in children under 5 years (RR=1.07; 95% CI=0.98 to 1.18) in England and Wales.

Although our spatiotemporal analyses did not address most limitations highlighted in the literature review, methods that we used to study the influence of industrial air pollutant emissions on the spatial and the temporal trends of asthma outcomes were an improvement compared to those of the few previous ecological studies (Alwahaibi et Zekal 2016, Aylin et al. 2001). While we used an ecological design, GAM models were used in Chapter 3.2 to consider the nonlinearity of the associations between the spatial variation in industrial air pollutant emissions and in asthma hospital admissions in children; previous studies used simpler statistical methods like correlations and did not consider the non linearity of such associations (Alwahaibi et Zekal 2016, Aylin et al. 2001). Furthermore, by using a large number of small areas compared to previous studies, we reduced the ecological error (Alwahaibi et Zekal 2016, Aylin et al. 2001). For the temporal assessments (Chapter 3.3), associations between industrial air pollutant emissions and asthma outcomes in children were explored with an ecological longitudinal design and fixed effects models which provide more robust evidence than simple cross-sectional ecological assessments (Ben-Shlomo 2005).

The longitudinal ecological design used in the temporal analyses is better than cross-sectional ecological assessments because it controls for potential confounders that differ between areas

but not overtime. This approach that we used to relate temporal changes in industrial emissions to asthma incidence by CT/CLSC longitudinally has the distinct advantage of controlling, by design, for relatively constant variables, even unmeasured ones that may also affect asthma incidence (such as genetics, medical practice and access to health care, lifestyle, and sociodemographic characteristics), thereby eliminating potentially large sources of bias. Only time-varying confounders need to be adjusted for in such analyses. Few studies have used a longitudinal ecological design with fixed effects models to assess associations between temporal changes in pollutants levels and health outcomes. This design was used by Henneman et al. (2019), to assess the accountability of cardio-respiratory health improvements in the United States related to the reduction of coal emissions. Correia et al. (2013) also used this design to assess the increase in life expectancy related to improvements in $PM_{2.5}$ levels. No previous study had assessed associations between temporal changes in environmental exposures and temporal changes in asthma onset rates in children, as we have done in Chapter 3.3.

Furthermore, while our temporal analyses suggested no association between the long term exposure to industrial air pollutant emissions and asthma onset in children, the association with the temporal changes in $PM_{2.5}$ from regional sources is interesting. This association is in line with results of studies using data at an individual level that have reported associations between regional $PM_{2.5}$ levels and asthma onset in children (e.g. Tetreault et al. 2016, EPA 2019). Our association between the temporal changes in $PM_{2.5}$ from regional sources and the temporal changes in asthma onset rates highlights health benefits that may have resulted from improvements in air quality in the province of Québec over the past years. The improvement in air quality is partly due to reductions in industrial emissions (Government of Canada 2019),

although we did not find an association with the decrease in industrial emissions. Our temporal analyses also suggest the potential gains that may have related to past efforts aimed at reducing smoking.

Although we did not find associations between industrial air pollutant emissions of $PM_{2.5}$ and SO_2 and asthma outcomes in children in Chapters 3.2 and 3.3, we noted expected associations between the spatiotemporal variations in asthma outcomes and income. Unfortunately, our estimates of associations between small area average income and asthma outcome rates cannot easily be compared to those of other studies because of differences in risk factors and asthma outcome variables and methods used. Beck et al. (2013), for example, reported associations between neighborhood asthma admission rates and SES markers (household income, individuals below the poverty line, adults with college education or greater, unemployment rate, and households without access to a car), and neighborhood surrounding environment markers (home value, renter occupied homes, vacant homes, and population density), with correlations. The Pearson r was >0.65 for neighborhood's percentage of individuals below the poverty line, percentage of households without access to a car, and percentage of vacant homes. Nonetheless like us, most ecological studies reported negative associations between income or other markers of SES and rates of asthma outcomes (e.g. Ouédraogo et al. 2018, Ray et al. 1998, Claudio et al. 2009).

Thus, the current dissertation makes contributions to the understanding of the effects of industrial and other air pollutants, on asthma outcomes in children. As mentioned above, the association between temporal changes in $PM_{2.5}$ from regional sources and changes in asthma

onset from our temporal analyses (Chapter 3.3) is new and contributes to the understanding of the health benefits of air pollution reduction. Also, the systematic review provides directions for future studies. It highlights the need for well-conducted studies to assess associations between exposure to particulate and gaseous pollutants from industries and asthma outcomes in children, namely individual-level studies using longitudinal design and refined and harmonised exposure assessment methods to improve risk estimation (Geng et al. 2019, Chapter 3.1). Furthermore, both the spatial and temporal analyses displayed the relation that exists in small areas of Québec between income and asthma morbidity in children. Although this association is not new *per se*, it is expressed at an ecological geographic scale smaller and thus with fewer errors than in previous studies (Ray et al. 1998, Claudio et al. 2009, Ouédraogo et al. 2018). It reinforces the necessity for community relevant public health strategies aimed at reducing material deprivation in various geographic areas. These may include strategies to improve housing and education which could have collateral benefits for asthma by reducing indoor/outdoor air pollutant exposure, as those who are in lower SES groups, often experience worse indoor/outdoor air quality (Brown et al. 2015).

Despite these contributions, there are a number of limitations that should be acknowledged as they affect the validity of the results of the thesis. First, we did not assess the quality of the studies considered in the review paper (Chapter 3.1); nonetheless, we consider that most studies were not of high quality. Second, we did not assess possible drivers of the large heterogeneity that was noted, such as the type of point source; such assessment was impossible and would require a greater standardization of future study designs and methods, including definitions of outcomes, exposure, and harmonization of confounders included in the analyses. We did not

restrict the age of the children in the studies that were included in the review, which might have contributed to the large heterogeneity of the associations of the studies assessed.

As for the spatial and temporal analyses (Chapters 3.2 and 3.3), the limitations are mainly related to the ecological design and to the quality of the exposure information used. The ecological study design implies that associations obtained for the small areas may not be consistent with associations at the individual level. There is the potential of an ecological fallacy/aggregation bias since the individual variations of variables were concealed (Szklo and Nieto 2000). Thus, the ecological design does not allow for the inference of causality at the individual level, and care is needed in the interpretation of results for Chapters 3.2 and 3.3. Nonetheless, as mentioned above, useful observations for geographic areas can still emerge from ecological studies.

The aggregated ETS information used in Chapters 3.2 and 3.3 is particularly concerning. Indeed, ETS information was only available for 15 health regions; the ETS exposure was thus assumed constant for all individuals, of all CTs/CLSCs of a region. Furthermore, the survey data used to estimate ETS in children was based on data for the population of non-smokers exposed to second-hand smoke aged 12 years and older. This is imperfect as some studies have shown that children younger than 12 years old can have a higher exposure than older populations since they spend more time with smoking parents or caregivers (Max et al. 2009). The misrepresentation of this variable influences the direction of the association between ETS and asthma morbidity in both spatial and temporal analyses; it also influences the adjustment by this variable, of other associations such as with industrial emissions. The ecological data used in this study not only naturally lead to the usual failure of ecological analyses to reflect the effect at the individual

level. The usage of a constant value in a large health region may also conceal the heterogeneity within regions, which may lead to missing information. The combination of missing information and the misrepresentation mentioned above may make our results different from the corresponding associations at the individual level within groups of the same population (Rothman et al. 2008).

In Chapter 3.2 on spatial analyses, the ecological aggregation was not only per small areas; temporal aggregation was also made, which also contributed to biases. The total counts of asthma hospital admissions over 10-years and the average of yearly values of environmental and socioeconomic risk factors (SES, ETS, regional background $PM_{2.5}$ levels and industrial air emissions of $PM_{2.5}$&$SO_{2,}$ walkability and vegetation) concealed between year variations. This could contribute to the fact that we did not detect associations between industrial air pollutant emissions and asthma hospital admissions in spatial analyses. However, in the temporal analyses in Chapter 3.3, no association was found between industrial emissions and asthma onset rates even though yearly values were used. Nonetheless, differences between areas were ignored in these analyses, thus future studies should combine both geographic and temporal variations to explore the interaction of these two patterns.

Selection bias is not an issue in Chapter 3.2 and 3.3 because information from the entire population was studied with the administrative health data used; this is the case because of the universal health care coverage in Québec.

There is novertheless issues regarding the use of hospital admission data in chapter 3.2. Indeed, for the spatial analyses (Chapter 3.2), asthma hospital admissions were used as an outcome and what they represent is unclear. Since hospitalizations could be due to severe respiratory symptoms that lead to the diagnosis of asthma, or to severe asthma exacerbations in a child with prior diagnosis, it is not possible to differentiate these two conditions based on this type of data. It is also influenced by access to medication, and it is thus difficult to define the health outcome based on this source of information alone.

The poor quality of the exposure information used led to information bias in Chapters 3.2 and 3.3, which undermines the internal validity of the results. Indeed, we used the NPRI database to estimate the exposure of children to industrial air pollutant emissions. This data is based on self-reported values by industries which may report lower emissions to limit public scrutiny. Emissions are also usually mathematically calculated and with different methods, and rarely based on emission measurements; they thus include many errors (Government of Canada 2017). Furthermore, only emissions are considered, not meteorology, thus the estimates that we used are a poor proxy of exposure because emissions are not dispersed into the atmosphere. In the spatial analysis, indirect information was also used to estimate exposure to traffic pollutants. Such exposure was estimated with the length of major roads, which neglects the influence of meteorology, traffic volume and also the influence of the built environment on pollutant dispersion. Such errors in estimating exposure to industrial emissions and road traffic pollution are non differential. In ecological studies, they are likely to lead to bias away from the null (Rothman et al. 2008). This misclassification of exposure may partly explain the

counterintuitive negative association found between traffic-related air pollution and asthma hospital admissions (Chapter 3.2).

There are also limitations in the spatial and temporal analyses associated with the study population and the geographic delineations for different census years (census year 2001, 2006, 2011); these also contributed to information biases. Firstly, we adopted the geographic delineation of 2006 for the spatiotemporal analyses; thus the median income and the population related to the 2001 and 2011 geographic areas were converted according to the geographic areas of 2006 which likely introduced errors. Both spatial and temporal analyses also used the population of children aged 0-14 years old as offset in statistical modeling, not the population 0-12 years corresponding to the population for the outcome assessment; this also led to biases. Namely, if the proportions of exposed subgroups within the population of children aged 0-14 years old are different from the proportions of subgroups within the population of children aged 0-12 years old, the associations between risk factors and asthma outcomes could be biased toward null associations or an opposite direction.

Confounding is also a concern for analyses of Chapter 3.2 and 3.3. Although a number of environmental and sociodemographic variables were used, associations noted, such as with income or regional $PM_{2.5}$ levels, or the null associations, such as with industrial emissions, may be influenced to other uncontrolled variables. Notably, we only used the household income to represent the SES; we could have included other variables, such as education or compiled the Pampalon indicator for the unit of analyses of the spatiotemporal analyses (Pampalon et al. 2014). Controlling for categories of joint distributions within groups such as poor exposed to

ETS, rich exposed to ETS, poor and rich not exposed to ETS would have been better for reducing ecological biases. In the temporal analyses (Chapter 3.3), we also overlooked the existence of an association between inflation and income which could confound the association between income and the rate of asthma onset. The association noted between income and the rate of asthma onset could also represent the time trend in asthma onset unrelated to income but to other unknown factors.

Cross-level biases which are specific to ecological studies, are also likely in our studies. Usually, confounding by group and effect modification by group are the sources of cross-level biases (Rothman et al. 2008). The former would occur if CT/CLSC group exposure (e.g. ETS, industrial and traffic-related air pollution, regional air pollution) would be correlated with the risk of asthma outcomes in the non-exposed individual of the CT/CLSC. The latter would occur if the association with a risk factor at the individual level, would be separate from the association with the same risk factor but at the group level. Individual income and neighborhood average income for example, have been shown to influence health independently (Schreier and Chen 2013); because of that, associations adjusted for income are likely to suffer from cross-level bias. Unfortunately, the ecological data we used cannot be used to check cross-level bias because the confounding by group and effect modification by group are defined at an individual level. The lack of individual level data from our spatiotemporal analyses undermines the ability of our assessments to generate biological inferential results. Although we used advanced non-linear GAM models and fixed effects model to fit the ecological data, which are more advanced methods than those used in previous studies, there may be substantial bias of unknown direction in our results (Rothman et al. 2008).

In consideration of all these limitations, the internal validity of our spatiotemporal studies is low. Thus caution is warranted in extrapolating results of Chapters 3.2 and 3.3 to other states/provinces or countries, even if similar data can be collected.

Conclusion

The results of the thesis show very limited evidence of associations between exposure to particulate and gaseous industrial air pollutants (e.g. $PM_{2.5}$, SO_2) and asthma outcomes in children. This is surprising in light of the current literature supporting effects of same ambient air pollutants but from other sources.(e.g. regional/remote and local traffic sources). The lack of association from our review of the literature and our spatiotemporal analyses suggests that accurate approaches to estimate exposure are crucial and needed to properly assess effects of industrial emissions. Dispersion models are among the best approaches to assess exposure to industrial emissions and cohort studies using such estimates should be performed to improve our understanding of the relations that exist between long term exposure to pollutants from industrial emissions and asthma in children.

REFERENCES

Almqvist C, Pershagen G, Wickman M. 2005. Low socioeconomic status as a risk factor for asthma, rhinitis and sensitization at 4 years in a birth cohort. Clinical & Experimental Allergy; 35(5), 612–618. doi:10.1111/j.1365-2222.2005.02243.x

Alwahaibi A, Zekal A. 2016. Respiratory and allergic health effects in a young population in proximity of a major industrial park in Oman. Journal of epidemiology and community health; 70(2): 174-80.

American meteorological society. 2018. [Online], http://glossary.ametsoc.org/wiki/Regional_air_pollution

Anderson R.H, Ruggles R, Pandey K.D, Kapetanakis V, Brunekreef B, Lai C.K.W, Strachan D.P, Weiland S.K, the ISAAC Phase One Study Group. 2010. Ambient particulate pollution and the world-wide prevalence of asthma, rhinoconjunctivitis and eczema in children: Phase One of the International Study of Asthma and Allergies in Childhood (ISAAC). Occupational and Environmental Medicine; 67:293-300. doi:10.1136/oem.2009.048785

Asher M.I, Stewart A.W, Mallol J, Montefort S, Lai C.K.W, Ait-Khaled N, Odhiambo J, The ISAAC Phase One Study Group. 2010. Respiratory Research; 11 (8): 1-10. [Online], http://respiratory-research.com/content/11/1/8

Aylin P, Bottle A, Wakefield J, Jarup L, Elliott P. 2001. Proximity to coke works and hospital admissions for respiratory and cardiovascular disease in England and Wales. Thorax; 56(3): 228-33.

Ayres-Sampaio D, Teodoro CA, Sillero N, Santos C, Fonseca J, Freitas A. 2014. An investigation of the environmental determinants of asthma hospitalizations: An applied spatial approach. Applied Geography; 47:10-19.

Bateson T.F, Schwartz J. 2008. Children's response to air pollutants. Journal of

toxicology and environmental health Part A; 71(3): 238-43.

Beck A. F, Moncrief T, Huang B, Simmons J.M, Sauers H, Chen C, and Kahn R.S. 2013. Inequalities in Neighborhood Child Asthma Admission Rates and Underlying Community Characteristics in One US County, Journal of Pediatrics; 163(2): 574–580.

Ben-Shlomo 2005. Real epidemiologists don't do ecological studies? International Journal of Epidemiology; 34, 1181-1182.

Brown T, Dassonville C, Derbez M, Ramalho O, Kirchner S, Crump D, Mandin C. 2015. Relationships between socioeconimic and lifestyle factors and indoor air quality in French Dwellings. Environmental Research; 140:385-396.

Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, ChEN Y, Cook D.G, Britton J.R, McKeever T.M. 2012. Prenatal and Passive Smoke Exposure and Incidence of Asthma and Wheeze: Systematic Review and Meta-analysis. Pediatrics; 129 (4): 735-744.

Casey J.A, Karasek D, Ogburn E.L, Goin D.E, Dang K, Braveman P.A, Morello-Frosch R. 2018. Retirements of Coal and Oil Power Plants in California: Association With Reduced Preterm Birth Among Populations Nearby. American Journal of Epidemiology;187(8):1586–1594

Correia W.A, Pope III C.A, Dockery W.D, Wang Y, Ezzati M, Dominici F. 2013. The Effect of Air Pollution Control on Life Expectancy in theUnited States: An Analysis of 545 US counties for the period 2000 to 2007. Epidemiology; 24(1), 23–31.

Claudio L, Tulton L, Doucette J, Landrigan P.J. 1999. Socioeconomic Factors and Asthma Hospitalization Rates in New York City. Journal of Asthma; 36(4), 343-350.

Dales R, Chen L, Frescura A.M, Liu L, Villeneuve P.J. 2009. Acute effects of outdoor air pollution on forced expiratory volume in 1 s: a panel study of schoolchildren with asthma.

The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology; 34(2): 316-23.

Darin-Mattsson A, Fors S, Kareholt I. 2017. Different indicators of socioeconomic status and their relative importance as determinants of health in old age. International Journal for Equity in Health; 16:173.

Dietert RR et al. 2000. Workshop to identify critical windows of exposure for children's health: immune and respiratory systems work group summary. Environmental Health Perspectives; 108: 483-90.

Disano J, Ma Goulet J, Muhajarine N, Neudorf C, Harvey J. 2010. Socio-economic status and rates of hospital admission for chronic disease in urban Canada. Canadian Nurse; 106(1):24-9.

Dixon J.K. 2002. Kids need clean air: air pollution and children's health. Family & community Health; 24(4): 9-26.

Dominici F, Greenstone M, Sunstein RC. 2014. Particulate Matter Matters. Science; 344(6181): 257–259.

Ehteshami-Afshar S, FitzGerald J.M, Doyle-Waters M.M, Sadatsafavi M. 2016. The global economic burden of asthma and chronic obstructive pulmonary disease. The International Journal of Tuberculosis and Lung Disease; 20(1): 11–23.

Environnement et Lutte Contre les Changements Climatiques. 2011. Inventaire des émissions des principaux contaminants atmosphériques au Québec en 2008 et évolution depuis 1990. [Online], www.mddefp.gouv.qc.ca/air/inventaire/rapport2008.pdf.

Forno E, Gogna M, Cepeda A, Yanez A, Solé D, Cooper P, Avila L, Soto-Quiros M, Castro-Rodriguez J.A, Celedon J.C. 2015. Thorax; 70:898–905. doi:10.1136/thoraxjnl-2015-207199.

Geng X, Buteau S, Labelle R, Smargiassi A. 2019. Review of the effect of air pollution exposure from industrial point sources on asthmarelated effects in childhood. Environmental Epidemiology; 3: e077.

Gerhardsson de Verdier M, Gustafson P, McCrae C, Edsbacker S, Johnston N. 2017. Seasonal and geographic variations in the incidence of asthma exacerbations in the United States, Journal of Asthma; 54:8, 818-824, DOI: 10.1080/02770903.2016.1277538. [Online], https://doi.org/10.1080/02770903.2016.1277538.

Gilliland F.D, McConnell R, Peters J, Gong H. 1999. A theoretical basis for investigating ambient air pollution and children's respiratory health. Environmental Health Perspectives; 107(Suppl 3): 403-7.

The Global Asthma Report 2018. 2018. Auckland, New Zealand: Global Asthma Network. [Online], http://www.globalasthmareport.org/Global%20Asthma%20Report%202018.pdf

Goldizen F.C, Sly P.D, Knibbs L.D. 2016. Respiratory Effects of Air Pollution on Children. Pediatric Pulmonology; 51:94–108.

Gong T, Lundholm C, Rejno G, Mood C, La'ngstrom N, et al. 2014. Parental Socioeconomic Status, Childhood Asthma and Medication Use – A Population-Based Study. PLoS ONE 9(9): e106579.

Government of Canada. 2017. Common air contaminants. [Online], https://www.canada.ca/en/environment-climate-change/services/air-pollution/pollutants/common-contaminants.html

Government of Canada. 2019. [Online],

https://www.canada.ca/en/environment-climate-change/services/environmental-indicators/air-pollutant-emissions.html

Gupta R.P, Mukherjee M, Sheikh A, Strachan D.P. 2018. Persistent variations in national asthma mortality hospital admissions and prevalence by socioeconomic status and region in England. Thorax; 73:706–712. doi:10.1136/thoraxjnl-2017-210714

Gurunathan S et al. 1998. Accumulation of chlorpyrifos on residential surfaces and toys accessible to children. Environ Health Perspect; 106:9-16.

Hartley K, Ryan P, Brokamp C, Gillespie G.L. 2020. Effect of greenness on asthma in children: A systematic review. Public Health Nursing; 37:453–460.

Health Canada. 2012. Canadian Tobacco Use Monitoring Survey. [Online], www.hc-sc.gc.ca/hc-ps/tobac-tabac/research-recherche/stat/_ctums-esutc_2012/ann-eng.php#t8.

Henneman L.R.F, Choirat C, Zigler C.M. 2019. Accountability Assessment of Health Improvements in the United States Associated with Reduced Coal Emissions Between 2005 and 2012. Epidemiolgoy; 30 (4): 477-485.

Hiscock R, Bauld L, Amos A, Fidler J.A, Munafò M. 2012. Socioeconomic status and smoking: a review. Annals of the New York Academy of Sciences; 1248: 107-23.

The International Study of Asthma and Allergies in Childhood. 2017. The ISAAC Story, ISAAC's Beginnings. [Online], http://isaac.auckland.ac.nz/story/background/background.php

Kanchongkittiphon W, Mendell M. J, Gaffin J. M, Wang G, Phipatanakul W. 2015. Indoor Environmental Exposures and Exacerbation of Asthma: An Update to the 2000 Review by the Institute of Medicine. Environmental Health Perspectives; 123 (1):6-20.

Khreis H, Kelly C, Tate J, Parslow R, Lucas K, Nieuwenhuijsen M. 2017. Exposure to traffic-related air pollution and risk of development of childhood asthma: A systematic review and

meta-analysis. Environment international; 100: 1-31

Kopel L.S, Phipatanakul W, Gaffin J.M. 2014. Social Disadvantage and Asthma Control in Children. Pediatric Respiratory Reviews; 15: 256-263.

Kozyrskyj A.L, Kendall E.G, Jacoby P, Sly D.P, Zubrick R.S. 2010. Association Between Socioeconomic Status and the Development of Asthma: Analyses of Income Trajectories, American Journal of Public Health; 100(3).

Kundu S, Stone A.E. 2014. Composition and sources of fine particulate matter across urban and rural sites in the Midwestern United States. Environmental Science: Processes & Impacts; 16: 1360–1370.

Lai K.W.C, Beasley R, Crane J, Foliaki S, Shah J. 2009. Global variation in the prevalence and severity of asthma symptoms: Phase Three of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax online.

Lambert K.A, Bowatte G, Tham R, Lodge C, Prendergast L, Heinrich J, Abramson M.J, Dharmage S.C, Erbas, B. 2017. Residential greenness and allergic respiratory diseases in children and adolescents—A systematic review and meta-analysis. Environmental Research; 159, 212–221. [Online], https ://doi.org/10.1016/j.envres.2017.08.002

Larsen K, Zhu J, Feldman L.Y, Simatovic J, Dell S, Gershon A. S, To T. 2016. The Annual September Peak in Asthma Exacerbation Rates Still a Reality? Annals of the. American Thoracic Society; 13 (2): 231-239.

Lowe A.A, Bender B, Liu A.H, Soloman T, Kobernick A, Morgan W, Gerald L.B. Environmental Concerns for Children with Asthma on the Navajo Nation. Annals of the American Thoracic Society; 15 (6): 745-753.

Mahboub B. H., Al-Hammadi S., Rafique M., Sulaiman N., Pawankar R., Al Redha A., Mehta

A.2012. Population prevalence of asthma and its determinants based on European Community Respiratory Health Survey in the United Arab Emirates. BMC Pulmonary Medicine; 12 (4): 1-8.

Mallol J, Crane J, Mutius E, Odhiambo J, Keil U, Stewart A, the ISAAC Phase Three Study Group. 2013. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three: A global synthesis. Allegol Immunopathol (Madr); 41 (2): 73-85.

Max W, Sung H.Y, Shi Y. 2009. Who Is Exposed to Secondhand Smoke? Self-Reported and Serum Cotinine Measured Exposure in the U.S., 1999-2006, International Journal of Environmental Research and Public Health; 6: 1633-1648

McConnell R, Berhane K, Gilliland F, London J.S, Islam T, Gauderman W.J, Avol E, Margolis G.H, Peters M.J. 2002. Asthma in exercising children exposed to ozone: a cohort study. The Lancet; 359: 386–91.

Mendell M.J, Mirer A.G, Cheung K, Tong M, Douwes J. 2011. Respiratory and Allergic Health Effects of Dampness, Mold, and Dampness-Related Agents: A Review of the Epidemiologic Evidence. Environmental Health Perspectives; 119 (6): 748-756.

Moya J, Bearer FC, Etzel A.R. 2004. Children's Behavior and Physiology and How It Affects Exposure to Environmental Contaminants. Pediatrics; 113 (4): 996-1006.

National Institutes of Health. 2007. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management Of Asthma-Summary Report. Journal of Allergy and Clinical Immunology; 120(S5): S94–S138. [Online], https://www.nhlbi.nih.gov/files/docs/guidelines/asthgdln.pdf

Ontario Ministry of Health and Long-Term Care. 2000. Report of the Chief Medical Officer of Health--Taking Action on asthma. [Online],

www.health.gov.on.ca/en/common/ministry/publications/reports/asthma/asthma_e.pdf.

Orellano P, Quaranta N, Reynoso J, Balbi B, Vasquez J. 2017. Effect of outdoor air pollution on asthma exacerbations in children and adults: Systematic review and multilevel meta-analysis. PloS one, 12(3): e0174050.

Ouédraogo A. M, Crighton E. J, Sawada M, To T, Brand K, Lavigne E. 2018. Exploration of the spatial patterns and determinants of asthma prevalence and health services use in Ontario using a Bayesian approach. [Online], PLOS ONE https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0208205

Pampalon R, Hamel D, Gamache P, Simpson A, Philibert D.M. 2014. Validation of a deprivation index for public health: a complex exercise illustrated by the Quebec index. Chronic Diseases and Injuries in Canada; 34 (1).

Pearce N, Aıt-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, Robertson C, and the ISAAC Phase Three Study Group. 2007. Thorax; 62: 758-766. [Online], doi: 10.1136/thx.2006.070169

Public Health Agency of Canada. 2018. Report From The Canadian Chronic Disease Surveillance System: Asthma and Chronic Obstructie Pulmonary Disease (COPD) in Canada. 2018. [Online], https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/diseases-conditions/asthma-chronic-obstructive-pulmonary-disease-canada-2018/pub-eng.pdf

Ray N.F, Thamer M, Fadillioglu B, Gergen P.J. 1998. Race, Income, Urbanicity, and Asthma Hospitalization in California-A Small Area Analysis. CHEST; 113:1277-84.

Rodriguez-Villamizar L.A, Magico A, Osornio-Vargas A, Rowe B.H. 2015. The effects of outdoor air pollution on the respiratory health of Canadian children: A systematic review of

epidemiological studies. Canadian respiratory journal; 22(5): 282-92.

Reseau de Surveillance de la Qualite de L'air. 2007. Environmental Assessment Report Air Quality in Montréal. [Online], ville.montreal.qc.ca/pls/portal/docs/page/enviro_fr/media/documents/rsqa_2007_en.pdf

Rothman K.J, Lash T.L, Greenland S. 2008. Modern Epidemiology.

Samoli E, Nastos P.T, Paliatsos A.G, Katsouyanni K, Priftis K.N. 2011. Acute effect so fair pollution on pediatric asthma exacerbation: Evidence of association and effect modification. Environmental Research; 111,418–424.

Schei M.A, Hessen J.O, Smith K.R, Bruce N, McCracken J, Lopez V. 2004. Childhood asthma and indoor woodsmoke from cooking in Guatemala. Journal of Exposure Analysis and Environmental Epidemiology; 14, S110–S117. doi:10.1038/sj.jea.7500365

Schreier H.M.C, Chen E. 2013. Socioeconomic Status and the Health of Youth: A Multi-level, Multi-domain Approach to Conceptualizing Pathways. Psychological Bulletin Journal; 139(3): 606–654. doi:10.1037/a0029416.

Schwartz J. 2004. Air Pollution and Children's Health. Pediatrics; 113 (4): 1037-1043.

Seagrave J.C, McDonald D.J, Bedrick E, Edgerton S.E, Gigliotti P.A, Jansen J.J, Ke L, Naeher P.L, Seilkop K.S, Zheng M, Mauderly L.J. 2006. Lung Toxicity of Ambient Particulate Matter from Southeastern U.S. Sites with Different contributing Sources: Relationships between Composition and Effects. Environmental Health Perspectives; 114(9): 1387-1393.

Setälä H, Viippola V, Rantalainen A.L, Pennanen A, Yli-Pelkonen V. 2013. Does urban vegetation mitigate air pollution in northern conditions? Environmental Pollution; 183:104-112.

Simons E, Dell S, Moineddin R, To T. 2017. Associations between Neighborhood Walkability and Incident and Ongoing Asthma in Children, Annals of American Thoracic Society; 15 (6): 728-734.

Simons E., Dell S. D, Moineddin R, To T. 2019. Neighborhood Material Deprivation Is Associated with Childhood Asthma Development: Analysis of Prospective Administrative Data.Canadian Respiratory Journal; [Online], http://doi.org/10.1155/2019/6808206

Silvestri M, Franchi S, Pistorio A, Petecchia L, Rusconi F. 2015. Smoke Exposure, Wheezing, and Asthma Development: A Systematic Review and Meta-Analysis in Unselected Birth Cohorts. Pediatric Pulmonology; 50: 353-362.

Statistics Canada. 2019. Smoking, changes between 1994/1995 and 2004/2005, 2006/2007, 2008/2009 and 2010/2011. [Online], https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310043801&pickMembers%5B0%5D=1.6& pickMembers%5B1%5D=2.1&pickMembers%5B2%5D=3.1

Statistics Canada. 2019. Census Dataset. [Online], https://www12.statcan.gc.ca/datasets/Index-eng.cfm?Temporal=2011

Subbarao P, Becher A, Brook R.J, Daley D, Mandhane J.P, Miller E.G, Turvey E.S, Sears R.M. 2009. Epidemiology of asthma: risk factors for development. Expert review of clinical Immunology; 5(1): 77-95.

Subbarao P, Mandhane J.P, Sears R.M. 2009. Asthma: epidemiology, etiology and risk factors. Canadian Medical Association Journal; 181(9): E181-E190.

Szklo M, Nieto J.F. 2000. Epidemiology Beyound the Basics.

Taiwo A.M, Beddows D.C, Shi Z, Harrison R.M. 2014. Mass and number size distributions of particulate matter components: comparison of an industrial site and an urban background

site. Science of the Total Environment; 475: 29-3.

Tetreault L.F, Doucet M, Gamache P, Fournier M, Brand A, Kosatsky T, Smargiassi A. 2016. Childhood Exposure to Ambient Air Pollutants and the Onset of Asthma: An Administrative Cohort Study in Québec. Environmental Health Perspectives; 124(8): 1276-1282.

Thacher J.D, Emmelin A. Madaki A.J.K, Thacher T.D. 2013. Biomass fuel use and the risk of asthma in Nigerian children. Respiratory Medicine; 107, 1845-1851.

Ungar W.J, Paterson M, Gomes T, Bikangaga P, Gold M, To T, Kozyrskyj A.L. 2011. Relationship of asthma management, socioeconomic status, and medication insurance characteristics to exacerbation frequency in children with asthma. Annals of Allergy, Asthma & Immunology; 106:17–23.

Uphoff E, Cabieses B, Pinart M, Valdés M, Anto J.M, Wright J. 2015. A systematic review of socioeconomic position in relation to asthma and allergic diseases. European Respiratory Journal, 46: 364–374 | DOI: 10.1183/09031936.00114514.

U.S. Environmental Protection Agency. 2017. Integrated Science Assessment for Sulfur Oxides –Health Criteria. Office of Research and Development National Center for Environmental Assessment, RTP Division. [Online], https://www.epa.gov/isa/integrated-science-assessment-isa-sulfur-oxides-health-criteria

U.S. Environmental Protection Agency. 2019. Integrated Science Assessment for Particulate Matter. Office of Research and Development National Center for Environmental Assessment, RTP Division. [Online], https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=347534#tab-3

U.S. Environmental Protection Agency. 2019. [Online],

https://cfpub.epa.gov/si/si_public_record_report.cfm?Lab=NERL&TIMSType=&count=10000&dirEntryId=76646&searchAll=&showCriteria=2&simpleSearch=0&startIndex=30001

U.S. Environmental Protection Agency. 2019. Particulate Matter (PM). [Online], https://www.epa.gov/pm-pollution

U.S. Environmental Protection Agency. 2019. Ground Level Ozone. [Online], https://www.epa.gov/ground-level-ozone-pollution.

U.S. Environmental Protection Agency. 2019. Nitrogen Dioxide. [Online], https://www.epa.gov/no2-pollution /

United States Environmental Protection Agency. 2019. Sulfur Dioxide. [Online], https://www.epa.gov/so2-pollution /

Wang Z, May S.M, Charoenlap S, Pyle R, Ott N.L, Mohammed K, Joshi A.Y. 2015. Effects of secondhand smoke exposure on asthma morbidity and health care utilization in children: a systematic review and meta-analysis. Annals of Allergy, Asthma & Immunology; 115: 396-401.

Weichenthal A.S, Lavigne E, Evans J.G, Godri Pollitt J.K, Burnett T.R. 2016. Fine Particulate Matter and Emergency Room Visits for Respiratory Illness. American Journal of Respiratory and Critical Care Medicine; 194 (5): 577-586.

Weinmayr G, Romeo E, De Sario M, Weiland K.S, Forastiere F. 2010.Short-Term Effects of PM10 and NO2 on Respiratory Health among Children with Asthma or Asthma-like Symptoms: A Systematic Review and Meta-Analysis. Environmental Health Perspectives; 118 (4): 449-457.

World Health Organization. 2008. Children's environmental health. [Online], http://www.who.int/ceh/capacity/Children_are_not_little_adults.pdf?ua=1.

World Health Organization. 2019. [Online], https://www.who.int/respiratory/asthma/definition/en/

World Health Organization. 2019. [Online], https://www.who.int/mediacentre/news/statements/2004/statement5/en/

Yin J, Harrison R.M. 2008. Pragmatic mass closure study for PM1.0, PM2.5 and PM10 at roadside, urban background and rural sites. Atmospheric Environment; 42: 980–8.