THE ASSOCIATION BETWEEN EXPOSURE TO AIR POLLUTANTS AND GESTATIONAL HYPERTENSION IN WOMEN RESIDING IN URBAN HALIFAX

by

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DEDICATION PAGE

This thesis is dedicated to my parents, Lynne and Lenny, for their unwavering support, unconditional love and endless inspiration. Thank you for always saying what I needed to hear (not always what I wanted to hear) and for being there in good times, bad times and every time in between. You will both forever be my number one fans and for that I am truly grateful.

It is also dedicated to my grandmother, Betty, who I miss dearly. Her strength and wisdom inspire me every day.

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ABSTRACT

This population-based retrospective cohort study examined the relationship between exposure to air pollution during pregnancy and gestational hypertension (GH). The Atlee Perinatal Database was used to determine GH and potential covariates. Spatial estimates of air pollution were determined from land-use regression models. National Air Pollution Surveillance estimates were used for temporal adjustment. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using logistic regression. Of 11,724 singleton births analyzed, 7.7% of mothers developed GH. Significant inverse relationships were observed between GH and exposure to all pollutants (top quartile of exposure relative to lowest quartile); SO_2 (OR: 0.75; 95% CI: 0.62, 0.92), NO_2 (0.66; 0.54, 0.81), PM_1 (0.71; 0.57, 0.87), $PM_{2.5}$ (0.68, 0.56, 0.83), PM_{10} (0.71; 0.58, 0.87) toluene (0.68; 0.56, 0.83) and benzene (0.62; 0.51, 0.75). The inverse relationships could be a true protective effect or due to an unknown confounding factor coupled with a weak signal. A better understanding of the characteristics that influence the relationship between air pollution and GH may explain the observed results.

LIST OF ABBREVIATIONS AND SYMBOLS USED

µm	Micrometer
<	Less than
≤	Less than and equal to
>	Greater than
≥	Greater than and equal to
CI	Confidence interval
CO	Carbon monoxide
GH	Gestational hypertension
GIS	Geographic information systems
HRM	Halifax Regional Municipality
IQR	Interquartile range
IWK	Izaak Walton Killam Health Centre
JDAC	Joint Data Access Committee
LUR	Land-use regression
N	Quantity
NAPS	National Air Pollution Surveillance Systems
NO	Nitric oxide
NO2	Nitrogen Dioxide
NSAPD	Nova Scotia Atlee Perinatal Database
NOx	Nitrogen oxides (nitric oxide and nitrogen dioxide)
O3	Ozone
OR	Odds ratio
p	Page number
pp	Page numbers
PM	Particulate matter
PM1	Particulate matter of diameter up to 1micrometer
PM2.5	Particulate matter of diameter up to 2.5micrometers
PM10	Particulate matter of diameter up to 10 micrometer
RCP	Reproductive Care Program of Nova Scotia

RCS	Restricted cubic spline function
SO2	Sulfur dioxide
VOCs	Volatile organic compounds

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Chapter 1 INTRODUCTION

1.1 Thesis Overview

The purpose of the proposed research project is to examine the association between air pollution levels and gestational hypertension (GH). GH is defined as the development of new hypertension in pregnant women after twenty weeks gestation. When accompanied by protein in urine, the condition is called pre-eclampsia and is known to be associated with various adverse birth outcomes. The prevalence of GH disorders in Canada is approximately 6% [1,2], which equates to an estimated 300 women who developed GH per annum in urban Halifax.

Depending on the degree of hypertension and whether or not the patient is pre-eclamptic, various adverse outcomes for both the mother and baby could occur. If the baby is developed enough for delivery, the doctor will often suggest immediate delivery to stop the mother's blood pressure from increasing further. Early delivery (e.g., prematurity) is often associated with perinatal mortality and morbidity [3]. Women with more severe GH disorders (especially pre-eclampsia) may be admitted to the hospital so their condition can be monitored, which requires the use of hospital resources not needed for uncomplicated pregnancies and deliveries. Although rare, if pre-eclampsia develops into eclampsia it can cause severe seizures in the women, putting both her and the unborn child at great risk [3]. Given the potential risks associated with GH, it becomes evident that understanding why women develop hypertension during pregnancy is very important for

the prevention of this condition and thus the health and well-being of the mother and child.

Acute and chronic exposure to air pollution has been shown to be associated with an increased risk of chronic diseases, such as cardiovascular disease[4,5]. One review concluded that both short term and long term exposure to air pollutants contribute to the development of cardiovascular disease[5]. In addition, a systematic review of 34 studies concluded that there is a positive relationship between exposure to air pollution and risk of myocardial infarction[4]. Although the exact biological mechanism linking exposure to air pollution to cardiovascular disease is largely unknown, it likely has to do with inflammation[6], abnormal regulation of the cardiac autonomic system[6] or an increase in blood viscosity[7].

Many studies have been conducted examining the association between various environmental exposures and GH disorders [8]. However, only recently has air pollution been examined as a potential risk factor for GH [9-14]. This potential association between air pollution and GH is the focus of the current study. By using rich data sources for both the environmental exposure and the outcome of GH, the current research project will provide information relevant to provincial and federal policy makers in the area of air pollution.

1.2 Literature Review

1.2.1 Hypertension in Pregnancy

In women with GH, the blood pressure of the mother usually returns to normal within twelve weeks postpartum [15]. Approximately 5-10% of all pregnancies are complicated by a hypertensive disorder [16]. According to the World Health Organization, GH is the leading cause of maternal mortality among industrialized nations and accounts for approximately 16% of deaths [17]. Incidence of GH in Canada is stable. For example, a population-based study in Calgary, Canada found the incidence of GH remained unchanged around 6.3% between 1995 and 2004[1]. In contrast, the incidence of GH in Denmark increased by 2% between 1987 and 2004 [18]. Severity of GH is associated with the risk of adverse perinatal and maternal outcomes, where more severe forms are associated with a higher risk of adverse outcomes [19].

1.2.2 Established Risk Factors of Gestational Hypertension

Several risk factors for GH have been identified. A family history of GH has been shown to be related to an increased risk of developing GH. For example, women with mothers who experienced GH are at an increased risk of developing the condition themselves [20]. In addition, women with pre-existing hypertension, Type 1 diabetes mellitus, autoimmune disease, kidney disease and a history of infertility have also been shown to be at an increased risk for developing GH [21-25]. Smoking has also extensively been researched as a risk factor for GH. However, some studies have shown that smoking

throughout pregnancy or starting to smoke in the third trimester of pregnancy is protective against GH [26]. Furthermore, one study examined women who used Swedish snuff (moist powder tobacco) compared to those who smoked cigarettes during pregnancy to identify what was causing the protective effect. Cigarette smoking during pregnancy was protective against pre-eclampsia, but Swedish snuff did not have a protective effect. Therefore, the authors concluded that it is not the nicotine producing the protective effect, but rather the combustion products arising from smoking such as CO [27]. However, this seemingly protective effect is overshadowed by the other known adverse outcomes associated with smoking during pregnancy. GH in a previous pregnancy has also been shown to be a strong predictor of GH in subsequent pregnancies [28]. Obesity, multiple pregnancies and older maternal age have also been shown to be associated with an increased risk for GH [21,29].

1.2.3 Consequences of Gestational Hypertension

The most common consequence of GH is early delivery. If the baby is developed enough for delivery, it is often suggested that the baby be delivered immediately to prevent the mother's blood pressure from increasing further. However, early delivery is often associated with perinatal mortality and morbidity [30]. Although GH alone can lead to adverse outcomes for both the mother and child, the development of pre-eclampsia can result in many more serious complications. Pre-eclampsia is a maternal condition that occurs during pregnancy and is characterized by hypertension and proteinuria (excretion of more than 300 mg of protein per twenty-four hours in urine or as diagnosed by a

dipstick test) [15]. A population-based longitudinal study out of Norway found that pre-eclampsia is associated with a 30% increased risk of stillbirth. In addition, the risk of neonatal mortality is two times greater in mothers with pre-eclampsia [31]. Infants born to mothers with pre-eclampsia have a three to four times greater risk of low birth weight compared to those born to mothers without the condition [32]. Low birth weight has been shown to be a significant determinant of child and adult morbidity. Research has determined a link between low birth weight and diabetes, hypertension and coronary heart disease in both male and female adults [33]. Other potential complications as a result of pre-eclampsia for the infant include epilepsy and metabolic disorders [34].

Pre-eclampsia also has adverse effects on the mother. Between 1999 and 2004, pregnancy-related hypertensive disorders (pre-eclampsia being the most common) accounted for approximately fifteen percent of the maternal deaths in Canada [35]. Pre-eclampsia is also the most documented reason for admittance into intensive care units during the puerperal period [36].

1.2.4 Exposure to Air Pollution and Health

Researching the associations between environmental exposures and health has been a growing area of research for over thirty years. With the development of more refined methods of measuring environmental exposures, investigators have been able to examine health effects associated with these exposures that were not previously detectable. Due to this research, we now know some of the health effects of exposure to various air pollutants and the mechanisms in which this occurs. Epidemiological studies

have shown that the cardiovascular and respiratory systems are most susceptible to harm associated with exposure to air pollution [37]. The variety of air pollutants affect these systems through several different biological mechanisms depending on the specific pollutant involved.

Air pollution is derived from various sources, with the combustion of fossil fuels being the main source. Some pollutants are emitted directly into the atmosphere while others are created through chemical reactions with other pollutants in the atmosphere. Sulfur dioxide (SO_2), nitric oxide (NO) and carbon monoxide (CO) are considered primary pollutants, as they are emitted directly into the atmosphere. SO_2 is mainly emitted from the combustion of fossil fuels containing sulfur such as coal and fuel oil. NO emissions are mainly the result of motor vehicle transport. CO occurs naturally through photochemical reactions in the troposphere. It is also a by-product of iron smelting, motor vehicle transport and fuel combustion in industry. [38] Although information on CO concentrations in Halifax was not available, it has been shown to be correlated with NO_2 [39], PM[39,40], SO_2 [40], toluene and benzene [41].

Ozone (O_3) is categorized as a secondary pollutant because it is a result of the chemical reaction between NO, volatile organic compounds (VOCs) and ultra violet light. Benzene and toluene are both examples of VOCs. Motor vehicle transportation and solvent use are the major sources of VOCs emissions [42]. Nitrogen dioxide (NO_2) and some particulate matter (PM) are both primary and secondary pollutants [43]. NO_2 is mostly formed by the oxidation of nitric oxide (NO), but it is also emitted by power plants and motor vehicle exhaust. PM is separated into three categories. Coarse PM_{10} (2.5-10 μm in diameter) arises from road dust, debris, abraded soil, as well as the by-products of power

generation. Combustion of fossil fuels (mainly power generation and motor vehicle emissions) gives rise to fine $PM_{2.5}$ (<2.5 μm in diameter) and ultrafine PM (<0.1 μm in diameter) [38]. Due to the very small size of these small diameter PM, it is able to reach deep into lung tissue causing inflammation in the lungs, blood vessels or the heart and other organs[44].

The mechanisms underlying the adverse health effects that are hypothesized to result from exposure to air pollution are not well understood. However, some consistent findings have been observed. In healthy human subjects, O_3 has been shown to cause adverse health effects only if paired with exercise by increasing airway resistance, decreasing respiratory frequency and decreasing forced vital capacity [45]. NO_2, SO_2 and CO all share similar results when it comes to causing adverse health effects. Exposure to these pollutants has been associated with increases in stroke, myocardial infarction, cardiopulmonary mortality and hospital admissions due to cardiovascular and respiratory complications [46,47]. These gaseous air pollutants have been shown to stimulate an inflammatory response in the airways [43].

1.2.5 Air Pollution and Gestational Hypertension

The leading cause of mortality in the industrialized world is cardiovascular disease [6]. Exploratory research has focused on the association between air pollution and human health, specifically respiratory and cardiovascular disease. A recent systematic review examining 34 studies found that all the main air pollutants (i.e., CO, SO_2 and NO_2), with the exception of O_3 were associated with a significant increase in myocardial

infarction risk. The authors suggest several biological mechanisms that could explain this association including inflammation, abnormal regulation of the cardiac autonomic system, increased blood viscosity and an increase in vasoconstrictors [4]. Although the magnitude of the association between air pollutant exposure and myocardial infarction risk is not as strong as other risk factors such as smoking, it is still significant and affects many people in the population.

Studying this association in pregnancy is of much interest given that GH disorders are a leading cause of perinatal and maternal mortality [48,49]. In addition, due to more stress being put on the cardiovascular system during pregnancy, pregnant women are more susceptible to hypertension [50]. GH disorders (including pre-eclampsia) account for 2-8% of all pregnancy complications and 25% of maternal deaths [51]. Babies of mothers with gestational hypertension are more likely to have low birth weight, be small for gestational age and preterm [30].

There is a large body of literature dedicated to understating the relationship between air pollution and hypertension in general, but the research literature on GH is limited, as studying this association is a somewhat novel concept in this field. In addition, the majority of the research in this area has focused on trimester of exposure, rather than smaller intervals that may be more accurate. For example, in one prospective cohort study following 1,684 pregnant women, exposures to O_3 and PM_{10} in the first trimester of pregnancy lead to increased blood pressure in late pregnancy [9]. The authors measured exposure to carbon monoxide, sulfur dioxide, nitrogen dioxide, O_3 and particulate matter with the use of air monitoring stations at each zip code. To calculate the exposure concentrations of each pollutant for each trimester of pregnancy, daily concentrations in

each area were averaged and then linked to the participants based on zip code. The significant association between particulate matter as well as ozone and hypertension was found only for the first twenty weeks of pregnancy and was stronger for nonsmokers than smokers [9].

Similar results were found in a recent retrospective case-control study out of Los Angeles, California [52]. The authors examined maternal exposure to nitrogen dioxide, ozone, carbon monoxide and particulate matter. The air quality levels for each pollutant were averaged for relevant time periods for each participant and then mapped spatially to their residences. Inverse distance squared weighting was used for up to four of the closest monitoring stations to the residence. Maternal exposure to PM and CO in the first trimester of pregnancy was associated with a significant increase in the odds of hypertensive disorders during pregnancy. For example, the odds of developing a pregnancy-induced hypertensive disorder was 3.94 (95% confidence interval; 1.81, 8.55) with every 7 $\mu g/m^3$ increase in $PM_{2.5}$ concentration in the first trimester of pregnancy. A significant positive association was also found between maternal exposure to O_3 in the second trimester and GH disorders [52].

However, in a prospective cohort study based in the Netherlands, investigators examined exposure to PM and NO_2 and their association with blood pressure and diagnosable GH in 7,006 pregnant women. Geographic Information Systems (GIS)-based modeling techniques and continuous monitoring data were used to measure exposures to air pollution. The home addresses of participants were used to examine individual exposure during pregnancy. Data on GH and pre-eclampsia were retrieved from the hospital registry. They found that elevated exposure to PM was associated with an

increased risk of GH but there was no significant association for exposure to NO_2. Although no association between maternal blood pressure and exposure to PM was observed for the first trimester of pregnancy, exposure to PM was associated with higher blood pressure in the second and third trimesters of pregnancy [10].

Misclassification of exposure to air pollutants has been a limitation of past studies. One study did not take into account the distances from the participant's home addresses to the PM monitors. Therefore, participants residing one kilometer from the monitor were assigned the same exposure levels as those living 20 kilometers from the monitor[11]. True levels of PM in these areas were most likely very different due to proximity to sources of PM, which could greatly affect the results. The authors also examined the social factor of neighbourhood deprivation using the Neighbourhood Deprivation Index. Birth record data was retrieved for all births in North Carolina over a three year period to collect information on GH and pre-eclampsia or eclampsia, 222,775 women were included in the sample. The maternal home address was used to link the birth record data to the PM level data measured using monitors. A positive association was found between concentrations of PM and GH as well as neighbourhood deprivation and GH. The authors also observed that younger age, higher levels of education and any smoking during pregnancy were inversely associated with risk of hypertension [11]. The results of these studies highlight the various confounders that influence the association between air pollution and GH.

A Californian study that looked at traffic-related air pollution and risk of developing pre-eclampsia employed more accurate methods for assigning the exposure to residential address of the participant. Hospital birth records for 81,186 women were

examined for information on pre-eclampsia and other complications as well as home address of the mothers at the time of delivery. Residential addresses were geocoded with exact matches to house number[14]. Exposure data was collected hourly for NO_2, O_3, PM, CO and NO and then converted into averages for each trimester of pregnancy. These data were used to calculate levels of the air pollutants for each participant's residential address. Traffic densities were also calculated, taking into account the distance from the participant's residences to the applicable roads. A positive association was observed between exposure to local traffic-related air pollution and pre-eclampsia. [14].

A recent study out of Jacksonville, Florida examined the associations between several air pollutants (NO_2, SO_2, $PM_{2.5}$, O_3 and CO) and hypertensive disorders of pregnancy (GH, pre-eclampsia and eclampsia). The study included 22, 041 women from a population-based birth cohort whose addresses were geocoded at the street level and linked to the nearest air monitor. Pollutant concentrations were based on daily estimates from the United States Environmental Protection Agency's air quality system. Positive associations were found between NO_2, SO_2, $PM_{2.5}$, CO and hypertensive disorders of pregnancy over the full pregnancy per interquartile range (IQR) increase in pollutant concentration. When limited to individual trimester, this association remained for NO_2, SO_2 and CO in the first trimester and $PM_{2.5}$ in the second trimester [53].

Living in areas with high versus low levels of CO pollution during pregnancy has been shown to be associated with GH [12]. A cross-sectional study was conducted with a sample of 10,452 pregnant women reporting to three hospitals in Iran. Air pollution data was collected using 20 fixed and mobile air monitoring stations. Each station measured over 700 samples each year, with CO concentrations measured twice a day. Women were

divided into two groups depending on CO status (high exposure and low exposure). PM was not shown to differ between the two exposure statuses. Exposure to high levels of CO was associated with a statistically significant increase in blood pressure as well as odds of GH compared to women exposed to low levels of CO [12]. The use of a binary variable for the exposure is not as accurate as the aforementioned studies that used continuous variables. In addition, yearly averages were used to classify women as residing in areas of high or low carbon monoxide levels and no sophisticated models were used to account for spatiality. Therefore, temporality and spatiality were major limitations of this study.

Contrary to the findings of the aforementioned study, research conducted on a population of 127,370 pregnant women based in the province of Ontario, Canada found a negative dose-response relationship between maternal exposure CO and pre-eclampsia [54]. Carbon monoxide exposure levels were estimated using the postal codes of the mothers. With the lowest quartile of CO used as the reference, the odds of developing pre-eclampsia decreased with every quartile increase in CO concentration exposure [54].

Two studies used Gaussian modeling to assign pollutant levels to each participant. Guassian models are dispersion models that use a mixing zone concept to characterize pollutant dispersion over a roadway, usually taking into account traffic activities, vehicle emissions, meteorology and road geometry [55,56]. The first study included birth cohort data on 81,186 women from four hospitals in southern California. The risk of pre-eclampsia increased with each quartile increase in NO_x and $PM_{2.5}$ exposure over the full pregnancy [55]. The second study included 81,110 women from a birth cohort database out of southern Sweden. In addition to the Guassian-modelled estimated, they also looked at distance

from major roadways to maternal address. Positive associations were found between exposure to NO_x and both GH and gestational diabetes in the second trimester [56].

A recent study out of Australia used a land-use regression (LUR) model to assess traffic-related NO_2 exposure in pregnant women [13]. The model was based on season, the volume of moderate traffic roads within 50 meters and the volume of high traffic roads within 50 meters. The authors found this method accounted for 86% of the total variation in NO_2 measurements. Each IQR increase in level of exposure to traffic-related NO_2 during pregnancy as a whole and the third trimester alone was associated with a 12% and 30% increase in risk of developing pre-eclampsia, respectively. A greater effect was observed for women below the age of 20 years and over the age of 40 years as well as women with pre-existing or gestational diabetes [13].

Several different methods have been employed in research to estimate exposure to air pollution including surrogate measures based on the distance to the nearest source, inverse-distance weighted averages of all monitors within the sample location, Eulerian grid-cell models (air dispersion modeling) and LUR models. All of these methods have been used in health risk assessment studies. In a study comparing these different methods, it was found that the LUR method was more precise than the other methods in terms of spatial resolution. However, the study also concluded that a temporal component should be included in the analysis when using LUR methods to assess health risks associated with pollution exposure, as temporality is not a strength of the LUR method [57]. As this method is relatively new, few studies specific to maternal health are available that have used LUR models to estimate exposure.

1.2.6 Summary

Based on the literature outlined above, it is evident that understanding the risk factors associated with GH is important. Although several risk factors have been examined extensively, the literature on the association between maternal exposure to air pollutants and GH is limited. Several limitations are noted in the existing research on the effects of air pollutants in pregnancy. The first has been a limitation with respect to the determination of a period (or periods) of vulnerability. Secondly, much of the current research has been limited by misclassification of exposure because of the lack of specificity of pollutant data with respect to those exposed. For instance, it is often assumed that those within a certain perimeter of a monitoring station are equally exposed. Using LUR data, currently available in Halifax, exposure to specific air pollutants are able to be much more accurately assigned according to maternal residence.

Chapter 2 OBJECTIVES

The current study aimed to examine the relationship between exposure to air pollutants during pregnancy and GH in women residing in urban Halifax delivering between January 1, 2008 and December 31, 2012. Specifically, the objectives were to:

I. Examine the association between maternal exposure to NO_2, SO_2, PM_1, $PM_{2.5}$, PM_{10}, benzene and toluene and GH.
   a. Quantify the spatial associations between the exposure to air pollutants and GH, adjusting for temporality.

II. Examine the association between maternal exposure to NO_2, SO_2, PM_1, $PM_{2.5}$, PM_{10}, benzene and toluene and pre-eclampsia.

Chapter 3 METHODOLOGY

3.1 Overview of Study Design, Ethics and Funding Sources

For the current retrospective cohort study, a population-based database for the outcome and validated environmental surveillance data for the exposure variables were used. The Nova Scotia Atlee Perinatal Database (NSAPD) is a rich data source that includes several variables applicable to the current study, including GH. Information on the exposure variable was retrieved from two sources. First, LUR-modelled estimates based on data collected through the Air Health Science Division in Health Canada by air quality monitoring sites throughout urban Halifax Regional Municipality (HRM). Secondly, National Air Pollution Surveillance (NAPS) network daily estimates of air pollutants collected by a single air monitor in central Halifax governed by Environment Canada (Government of Canada). Linking the NSAPD database with the air quality data provided an opportunity to determine the association between exposure to air pollutants and GH.

This project received ethics approval from the Joint Access Data Committee (JDAC) of the Reproductive Care Program (RCP). Research Ethics Board approval at the IWK Health Centre was also received. Funding for this project was provided by the Nova Scotia Health Research Foundation and the IWK Graduate Student Research Scholarship.

3.2 Inclusion and Exclusion Criteria

The inclusion criteria for the current study are women having a singleton birth in urban Halifax from January 1, 2008 to December 31, 2012. Those who did not have a postal code concurrent with those covered by the air pollution monitors in urban HRM were excluded. In addition, women who were coded as having pre-existing hypertension and/or pre-existing hypertension complicating pregnancy in the NSAPD database were also excluded from the current study. Pre-existing hypertension was defined as any mother coded as having pre-existing hypertension complicating pregnancy, childbirth and the puerperium; pre-existing hypertensive disorder with superimposed proteinuria or pre-existing hypertension.

3.3 Data Sources

3.3.1 Nova Scotia Atlee Perinatal Database

The NSAPD is maintained by the RCP of Nova Scotia and located at the IWK Health Centre in Halifax, Nova Scotia. The database contains a wide range of information related to the prenatal period, labour and delivery and the post-partum period for pregnancies that resulted in the birth of an infant with a birth weight of 500 grams or more. Standardized data collection forms are used throughout the province. Data are abstracted from the medical records and entered into an Oracle database by trained health records personnel following discharge from the hospital. The quality assurance of data is periodically assessed through abstraction studies. These studies have shown that the

database is reliable. Furthermore, the NSAPD was used to validate stillbirth and infant death data for Statistics Canada. All hospital births occurring since 1988 are included in the database as well as information on home births since 2009. Overall, the percentage of missing values in the NSAPD is negligible for labour, delivery and infant variables. Approximately 7% of the records are missing smoking data and 18% are missing data on pre-pregnancy weight.

3.3.1.1 Gestational Hypertension Variables

The main outcome of interest, as defined by NSAPD is GH with, and without, proteinuria as documented by a clinician. Based on the Canadian Guidelines on the diagnosis of gestational hypertension, this is defined as diastolic blood pressure of $\geq$90 mmHg, based on the average of at least two measurements, taken using the same arm [2]. The second outcome of interest was pre-eclampsia, which is defined at the presence of GH with significant proteinuria. Proteinuria is defined as 0.3g/d protein in a 24-hour urine collection or 30 mg/mmol urinary creatinine in a random urine sample [2]. Participants were coded as having GH if they were coded in the NSAPD with at least one of the following; GH hypertension without significant proteinuria, hypertension-unspecified type in pregnancy or GH with significant proteinuria. Pre-eclampsia is coded in the NSAPD as GH with significant proteinuria, including HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome.

3.3.1.2 Potential Covariates

Data for several potential covariates available in the NSAPD were also considered. Treatment of potential covariates and outcome variables is described in Table 3-1 (p. 29). We chose these covariates as they have been shown to be associated with GH in past research [25,26,28,29].

The RCP was responsible for linking the NSPAD to Canadian census data by six-digit postal code to categorize each participant into a quintile of neighbourhood income. Due to a great deal of missing data for height, pre-pregnancy weight was used as a covariate instead of body mass index. Maternal smoking was dichotomized into smoker during pregnancy and non-smoker. Non-smokers were classified as mothers who did not smoke any cigarettes pre-pregnancy, at first pre-natal visit, or at time of admission for delivery. Mothers who smoked ≥ 1 cigarette pre-pregnancy but none at the first pre-natal visit, or at time of admission for delivery were also categorized as non-smokers during pregnancy. Smokers during pregnancy were classified as mothers who smoked at least one cigarette at first pre-natal visit and/or at the time of admission for delivery.

3.3.2 Air Pollution Data

Exposure to air pollution was assigned using estimates from LUR modelling and monitoring data from the NAPS network. LUR models provided fine scale estimates of air pollution concentrations at each residential location, and thus a measure of maternal exposure to air pollutants. NAPS data provided temporally resolved estimates of air

pollution at the community level. LUR estimates were scaled using the NAPS estimates to account for temporal differences in air pollutant concentrations.

3.3.2.1 LUR-Modelled Estimates

One source of air pollution data came from LUR-modelled estimates based on data collected through the Air Health Science Division in Health Canada. Air monitoring devices were used to measure levels of SO_2, NO_2, benzene, toluene and several fractions of PM ($PM_{1.0}$, $PM_{2.5}$, and PM_{10}) at 50 monitoring sites across urban HRM (Figure 3-1, p. 30). A location-allocation model was used to select optimal locations for the sites of air pollution measurement. The location-allocation model was based on population density (census population divided by the land area in km^2) and road networks within urban HRM. Weighting of road networks was based on road type, with greater weights assigned to larger, wider roads (e.g. highways). Sampling periods for this data occurred from October 20, 2010 to November 3, 2010 and January 5, 2011 to January 19, 2011. Sampling was continuous over each two week time period.

In general, LUR models are created in order to estimate exposure for a single time period, usually a seasonal or annual average. The data from various air monitoring sites throughout the sample area are used to develop models based on several predictor variables most often obtained through GIS. This model can then be applied to areas within the study area where exposure data was not available. The LUR modeling that was used to explain the variation in air pollutant concentrations and estimates of pollutants can be applied to time periods outside of the specific sampling periods. The LUR

modelling was able to predict between 42-90% of the variation in the measured air pollutants [58]. The model predicted 90% of the variability in NO_2, 65% for SO_2, 53% for $PM_{1.0}$, 51% for $PM_{2.5}$ and 42% for PM_{10}.

A review of 25 LUR studies revealed that this method in urban areas yields better or at least as accurate estimates of pollutant levels than other geo-statistical methods such as dispersion models [59]. From this, LUR-modelled air pollutant estimates have also been calculated for each six-digit postal code in the study area. Some LUR pollutant estimates were negative values, resulting from the regression modelling approach and how it handled very low values in the modelling. Any negative pollutant estimates were scaled to 0.

3.3.2.2 National Air Pollution Surveillance systems

A second source of air pollution data comes from the NAPS systems, established in 1969. The purpose of the NAPS program is to provide standardized, accurate, long-term air quality data for all of Canada. NAPS uses air monitoring devices to measure levels of SO_2, NO_2, O_3, CO and PM ($PM_{2.5}$ and PM_{10}) in 220 communities across the ten Canadian provinces and three territories, totaling over 350 monitoring sites. We only used data collected from the two monitoring sites in urban Halifax. One located on Barrington Street and the other on Granville Street approximately 140 meters apart in the downtown core. NO_2 was measured by the Barrington Street station and $PM_{2.5}$ was measured by the Granville Street station.

The NAPS network follows strict quality assurance and quality control guidelines [60]. Guidelines ensure that the data generated by the NAPS system is within ±15% of the true value. In addition, the quality of the data must be documented and traceable to a primary standard set by Canada's Institute for National Measurement Standards. The NAPS data was linked to women in the NSAPD according to time of exposure and not specific residential information since all women in the cohort resided in urban Halifax.. Therefore, the NAPS data was used to account for temporal variation in exposure. In order to examine bi-weekly estimates of exposure up to 20 weeks gestation, the NAPS data was averaged by two-week intervals and the full 20 week gestation period.

3.4 Database Linkage

Two sources of air pollution data (LUR and NAPS) were linked to individuals in the NSAPD. Estimates for all pollutants are not available through both the LUR data and NAPS data. Both estimates were available for SO_2, NO_2 and $PM_{2.5}$. Only LUR estimates were available for benzene, toluene, $PM_{1.0}$ and $PM_{10,}$ whereas only NAPS estimates were available for O_3 and CO. Due to there being a great deal of missing data for NAPS estimated SO_2 and many of the LUR SO_2 estimates being negative, SO_2 was not scaled for temporality. Therefore, NAPS scaled LUR estimates were used for, NO_2 and $PM_{2.5}$ and LUR estimates alone were used for $SO_{2,}$ benzene, toluene, PM_1 and PM_{10}.

LUR estimates were averaged over the two sampling periods and two seasons (fall and winter) in order to create one estimate for each pollutant at each sic-digit postal code in urban HRM. Air pollution data from the NAPS monitoring sites were averaged

bi-weekly up to 20 weeks gestation starting on the estimated date of conception based on the date of the mother's last menstrual period. This provides a community-level estimate of each pollutant for each two-week interval of a woman's pregnancy.

Based on the maternal postal code from the NSAPD, we established an individual-level maternal exposure estimate for each of the air pollutants measured using the LUR models. For pollutants provided by LUR only, we examined whether long term exposure is associated with increased likelihood of developing GH.

For pollutants available through both LUR and NAPS, the two methods were combined to provide short term (e.g., bi-weekly) estimates for each woman's residential location. Specifically, the LUR values assigned to each woman by postal code were scaled using the NAPS data to account for temporal variation and used to investigate effects of exposure to air pollutants on the risk of GH. The LUR and NSAPD linkage was carried out by the RCP.

3.5 Analysis of Pollution Data

In order to accurately assign exposure levels to each pregnant mother included in the study, two sources were used. The LUR-modeled air quality data allowed for a better spatial estimation of the individual-level exposure to air pollutants experienced by the mothers during pregnancy. In addition, temporality plays an important role when analyzing this relationship and was accounted for using the NAPS data. This allowed us to account for both spatial and temporal variation in the air pollution data for those

pollutants that were measured using both methods. Each mother included in the study was assigned an exposure level for each individual pollutant.

For those pollutants not measured using both the LUR method and NAPS, only the LUR estimate was used to give an estimate of exposure based on postal code. For pollutants measured by both techniques, the average exposures for each pollutant for the first 20 weeks of gestation as well as more specific time periods (i.e. two-week intervals) were calculated from the NAPS data. In order to determine estimates for these time periods, daily averages for each pollutant were calculated based on hourly measurements. This enabled us to calculate averages of estimated pollutant exposure for each woman by two-week intervals and the full 20 week gestation period. The bi-weekly air pollution estimates (up to 20 weeks) create 10 categories for assessing the association between air pollution and gestational hypertension at different time periods of gestation. If a daily estimate was missing, the estimate from the day prior and the day after were averaged to create a value for the missing data point.

To assign better spatial estimates of maternal exposure to pollutants during pregnancy, the annual averaged LUR-modeled pollutant concentration estimates were used based on residential postal code of the mother at the time of delivery. Accounting for seasonal effects of the exposure data was data driven. No significant variability in exposure was seen between seasons, thus weighting pollutant estimates based on time spent pregnant in each season was not necessary.

Scaling the spatial LUR estimates by temporal NAPS estimates was completed using a validated method by Ross and colleagues [61]. Temporally scaled LUR-modelled

estimates have been used in various birth cohort studies[61,62] For each pollutant available, a ratio was computed of the two-week NAPS estimate average for each mother to the annual NAPS estimate average for the year corresponding to the year used for the LUR modelling (2010). The spatial LUR-modelled estimate was then multiplied by this ratio to produce the temporally adjusted spatial estimate (equations 1 and 2). These two-week windows of exposure were also averaged over 20 weeks to examine the exposure over the full 20 weeks of gestation.

1. $\left(\frac{\text{NAPS average over 2 weeks}}{\text{NAPS annual average for 2010}}\right) = \text{Temporal ratio}$

2. Temporal ratio * LUR estimate (for each postal code) =
   Temporally adjusted spatial estimate of pollutant concentration

3.6 Calculation of Smallest Detectable Relative Risk

Sample size calculations were carried out for the binary outcome variable 'GH'. The population for the current study was predetermined by the number of live births of women residing in urban Halifax during the study period (2008-2012). During this study period, there were 15,284 live births of women who resided in urban Halifax. Due to exclusion criteria (number of fetuses >1, pre-existing hypertension), 14,594 were included in the study when using only the LUR-modelled estimates. Smallest detectable relative risk calculations were performed using assuming an alpha error of 0.05 and 80% power. A rate of 6% was approximated for gestational hypertension among women with low exposure to air pollutants based on previous estimates [1,2]. OpenEpi software was used to conduct all power analyses.

Assuming an alpha error of 0.05 and 80% power, a sample size of 7,297 was required to detect a risk ratio of 1.5 based solely on the LUR estimates. Prevalence of those exposed was based on the lowest quartile of air pollution being the referent and the top quartile representing exposed. Therefore, the available sample size enabled us to detect a small increase in the relative risk of developing GH for the exposure to LUR-modelled air pollution risk factor.

Unfortunately, much data were missing for the NAPS estimates available between 2008 and 2012. Therefore, the available sample sizes for the NAPS scaled LUR estimates were smaller than for the LUR estimates alone. Using NO_2 scaled LUR-modelled estimates as an example and assuming an alpha error of 0.05 and 80% power, a sample size of 2,604 was required to detect a risk ratio of 1.7.

3.7 Data Analysis

SAS version 9.3 was employed for all of the statistical analyses. Collinearity across LUR-modeled pollutants was assessed using Pearson's correlation coefficients. To compare continuous variables between the two outcome groups, Wilcoxon Mann-Whitney U Tests were used and Chi-square tests were be used for categorical variables. Kruskal-Wallis tests were used to compare continuous variables between exposure quartiles. Logistic regression was conducted for each individual pollutant to analyze the relationship between maternal exposure to each air pollutant and GH while adjusting for confounding factors. Variables that are known in the literature to be highly associated with GH were included in the initial model and remained in the model regardless of their

significance throughout the modelling process. These variables included maternal age and smoking status during pregnancy. All potential confounders were included in the initial model. Variables were tested for removed from the model individually in order of increasing significance. Variables that caused a change in the odds ratio (OR) for the air pollutant of 5% or more in any level of the pollutant were included in the final model.

Spatial pollutant estimates (LUR) were adjusted for temporality by NAPS when available as described in section 4.5. The final models included the exposure of interest (i.e. pollutants), maternal age, smoking status during pregnancy and any other variables meeting the criteria outlined above. Exposure levels for each pollutant were modeled as categorical variables using quartiles. The lowest quartile was used as the referent category. ORs and 95% confidence intervals (CI) were estimated from the model.

A restricted cubic spline (RCS) function was used to test for a dose-response relationship for the NO_2 exposure. The RCS was also used as a way to justify categorizing the pollutant variables by generating p-values for overall association and non-linear association. Knots for the RCS function were located at the 5^{th}, 25^{th}, 50^{th}, 75^{th} and 95^{th} percentiles of NO_2 exposure concentration. NO_2 was chosen to be used for these analyses given that LUR models accounted for 90% of the variability in NO_2, which was the highest of all the pollutants measured.

Logistic regressions were also run on data stratified by neighbourhood income (lowest three quintiles of income versus highest two quintiles), pre-pregnancy weight (> 90kg pre-pregnancy versus normal weight), smoking (smoking during pregnancy versus no smoking during pregnancy) and age (> 35 years versus ≤ 35 years). These stratified

analyses were completed to allow us to better understand the relationship between exposure to air pollution and GH, by ruling out the possibility that it is these factors, not air pollution driving the observed association ORs and 95% CIs were compared between strata.

Separate logistic regressions were conducted for each pollutant to examine the association between maternal exposure to each pollutant and pre-eclampsia. The same covariates determined to be included in the models examining the outcome of GH were also used for these analyses. Again, maternal age and smoking status during pregnancy were forced into the models. ORs and 95% confidence intervals (CI) were estimated from the model.

Table 3-1 Treatment of variables in the Atlee Perinatal Database

Variable	Description	Treatment of Variable
Birth year	Year of delivery	Remained in 5 categories: 2008, 2009, 2010, 2011, 2012
Maternal Age	Mother's age at time of delivery	Remained continuous and grouped into 6 categories: < 20 years, 20-24, 25-29, 30-34, 35-29, ≥ 40
Maternal neighbourhood income quintile	Neighbourhood income (from Canadian census data) based on mother's postal code	Categorized into quintiles
Pre-pregnancy weight	Mother's self-reported weight at first prenatal visit (kg)	Remained continuous and grouped into > 90 kg and ≤ 90 kg
Parity	Total number of live and still births (gestational age > 24 weeks) not including present pregnancy	Dichotomized: parity =0 or parity > 0
Smoking status during pregnancy	Smoking status of mother pre-pregnancy, at first pre-natal visit and at the time of admission for delivery	Dichotomized: smoker or non-smoker
Sex of child	Sex of infant delivered	Remained dichotomized: male or female
Pre-existing diabetes	Yes or no	Remained dichotomized: yes or no
Gestational diabetes	Yes or no	Remained dichotomized: yes or no

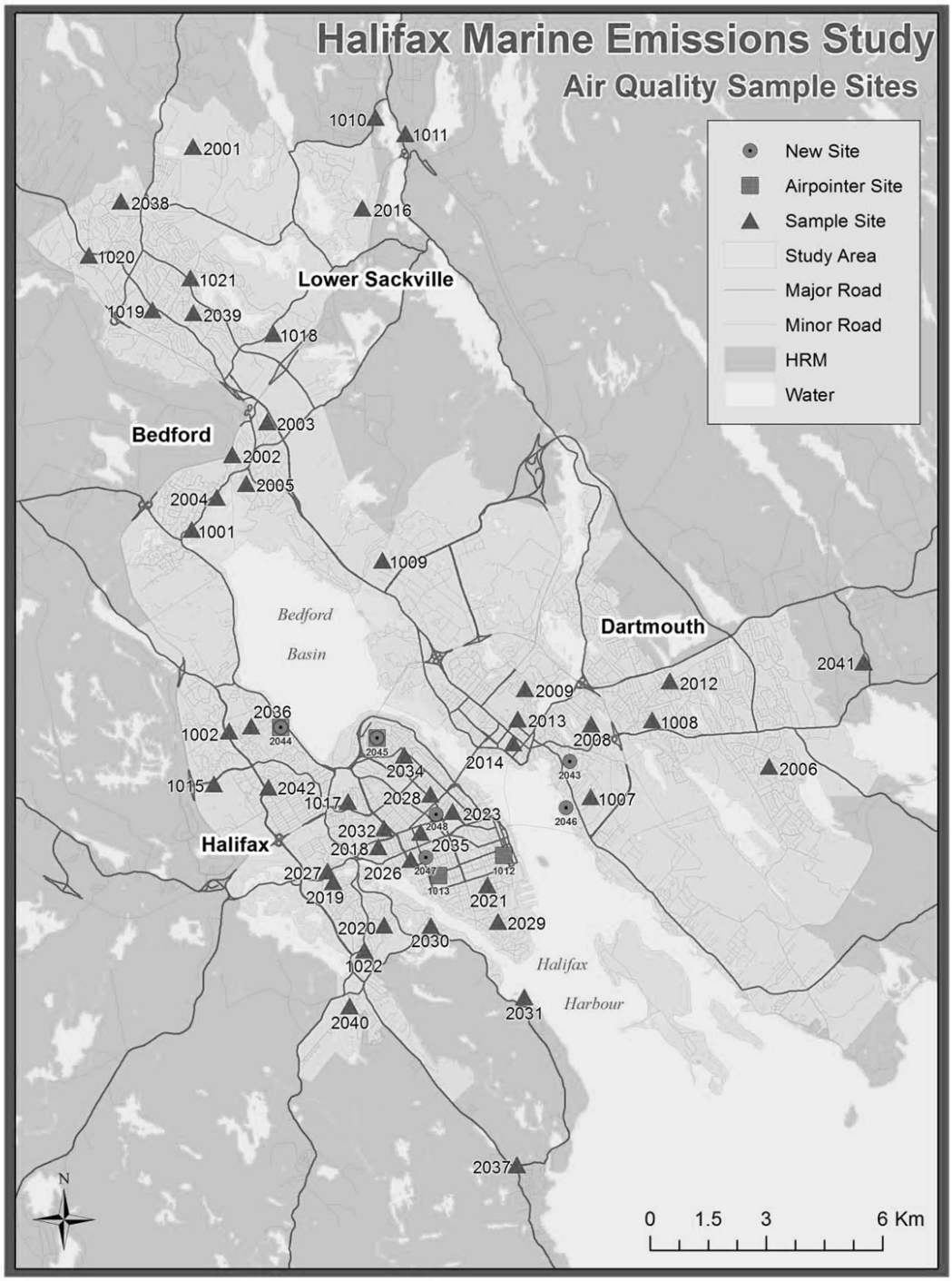

Figure 3-1 Study area and location of air pollution monitors

Note. *Source:* Rainham and Dummer (2011) [58]

Chapter 4 RESULTS

4.1 Description of Cohort

Of 15,284 mothers who gave birth between 2008 and 2012 with postal codes in urban Halifax at the time of delivery, 14,594 met inclusion criteria. A total of 690 mothers were excluded from the study due to delivering >1 fetus and/or having pre-existing hypertension, as coded in the NSAPD. Of the 14,594 mothers included in the study, 7.6% were diagnosed with GH and 1.5% were diagnosed with pre-eclampsia (Figure 4-1, p. 64).

All remaining women were linked to LUR estimates of NO_2, PM_1, $PM_{2.5}$, PM_{10}, benzene and toluene. Due to missing values in the LUR database for concentrations of SO_2 for some postal codes, 13,987 mothers were linked to LUR estimates of SO_2. The sample sizes for the temporally-adjusted spatial estimates were much smaller due to incomplete NAPS data. These data were missing due to the stations not being continuously operational during the study period or not meeting the quality assurance guidelines for Environment Canada and Health Canada. There were 6,518 mothers linked to scaled estimates of NO_2 and 5,390 linked to scaled estimates of PM2.5 (Figure 4-2, p65).

A detailed description of the characteristics of the study cohort is provided in Table 4-1 (p. 39). There were only missing values for three of the variables of interest. Maternal smoking status was missing for 1.3% of the participants and maternal neighbourhood income was missing for 1.5%. Pre-pregnancy weight data was missing for

19.4% of participants. SO_2 estimates for 4.3% of the study sample were not geocoded by postal code to participants and therefore these participants were not included in any analyses involving SO_2. The mean (SD, range) for mother's age was 29.8 years (5.6, 15-48) and the mean for pre-pregnancy weight was 69.1 kg (17.2, 65-194).

4.1.1 Characteristics of Cohort by Gestational Hypertension Status

Table 4-2 (p39) shows the associations between GH and variables of interest from the NSAPD. Several variables were shown to be significantly different at ($p < 0.05$) between those with and those without GH including smoking status during pregnancy, birth year, pre-pregnancy weight, parity, gestational diabetes and pre-existing diabetes. Having a pre-pregnancy weight > 90 kg, gestational diabetes, pre-existing diabetes and no previous deliveries were shown to be associated with a greater risk of GH. Those who smoked during pregnancy were not as likely to be diagnosed with GH. Neighbourhood income and GH were also significantly associated, with mothers diagnosed with GH tending to live in areas with lower neighbourhood income compared to women without GH.

4.2 Description of Pollutant Levels and Correlations in Halifax

Estimates for all pollutants are shown in Table 4-3 (p42). For the pollutant estimates derived from LUR models as well as being measured by NAPS, the raw NAPS estimates were greater for all. The range of pollution concentration was especially large

for NO_2 and $PM_{2.5}$ as measured by NAPS. Concentrations of SO_2 were low across urban Halifax with very little variation. LUR modeled pollution estimates were moderately positively correlated with Pearson's correlation coefficients ranging from r = 0.20 to r = 0.78 (Table 4-4, p.43). Benzene and toluene were the most highly correlated (r = 0.78), while the smallest correlation coefficient was observed for $PM_{2.5}$ and both PM_{10} and benzene (r = 0.20).

4.2.2 Characteristics of Cohort by Nitrogen Dioxide Quartile

Given that LUR models accounted for 90% of the variability in NO_2, associations between quartile of NO_2 exposure and covariates available in the NSAPD are also presented (Table 4-5, p. 43). All covariates with the exception of birth year, sex of child and pre-existing diabetes were significant at ($p < 0.05$). Women in the lowest quartile of NO_2 exposure were the oldest, on average. In terms of smoking during pregnancy, the highest proportion of smokers was in the third quartile. Women in the highest quartile of NO_2 exposure tended to live in areas of low neighbourhood income, while those in the lowest quartile of NO_2 exposure tended to live in areas of high neighbourhood income. The proportion of women with pre-pregnancy weight $\geq$ 90 kg was similar across the first, second and third quartiles of NO_2 exposure, but was lower in the fourth quartile. Women in the second quartile of NO_2 exposure had the highest proportion of gestational diabetes, while those in the highest quartile had the lowest proportion of gestational diabetes.

4.3 Associations between Exposure to Air Pollutants and Gestational Hypertension

NO_2 was used for model building in order to find confounding variables. These variables were then included in the models for all pollutants for consistency as the pollutants of interest have been shown to be correlated in various studies [40,41,61,63]. Pre-pregnancy weight dichotomized and parity were the only covariates that remained in the model after backwards deletion. Maternal age and smoking status during pregnancy were forced into the model as previously described. A separate multivariate logistic regression was completed for each individual pollutant. After exclusion for missing data on variables included in the model, 11,724 mothers were included in the analyses for LUR-modelled pollutants (with the exception of SO_2).

Unadjusted odds ratios (UORs) and adjusted odds ratios (AORs) are presented by pollutant and source in Tables 4-6 to 4-12 (pp. 46-49). An inverse relationship between exposure to NO_2 and GH was found when comparing the fourth quartile of exposure to the first. This inverse association was observed for both LUR-modelled (AOR=0.66, 95% CI=0.54-0.81) and LUR scaled by NAPS (0.53, 0.38-0.73) estimates. Adjustment for covariates caused little change in the ORs (Table 4-6, p. 46). A RCS function was also completed for the association between LUR-modelled NO_2 exposure and GH (Figure 4-3, p66). Knots for the RCS function were placed at 5, 25, 50, 75 and 95 percentiles of LUR-modelled NO_2 exposure. The function was adjusted for pre-pregnancy weight, parity, smoking status during pregnancy and age to coincide with the logistic regression models. Contrast results of the RCS function showed a significant overall association ($p < 0.0001$)

and a significant non-linear association (p=0.0008), which justified not using NO_2 as a continuous variable.

Due to missing values, 11,220 mothers were included in analyses involving LUR-modelled SO_2. An inverse relationship between exposure to LUR-modelled SO_2 in the fourth quartile and GH was observed (0.75, 0.62-0.92; Table 4-7, p. 46). An inverse relationship was also found between exposure to the fourth quartile of LUR-modelled PM_1 and GH (0.71, 0.57-0.87; Table 4-8, p. 47). When comparing the fourth to the first quartile of $PM_{2.5}$ exposure, an inverse relationship was found between both LUR-modelled estimates (0.68, 0.56-0.83) and NAPS scaled LUR estimates (0.70, 0.49-0.99) and GH (Table 4-9, p. 47). Inverse relationships were observed between exposure to LUR-modelled PM_{10} in the third (0.76, 0.63-0.92) and fourth (0.71, 0.58-0.87) quartiles and GH compared to the first quartile (Table 4-10, p. 48).

Significant inverse associations were observed between exposure to the second (0.78, 0.65-0.94), third (0.77, 0.64-0.94) and fourth (0.62, 0.51-0.75) quartiles of LUR-modelled benzene exposure and GH (Table 4-11, p. 48). Finally, an inverse relationship was also found between exposure to the fourth quartile of LUR-modelled toluene exposure and GH (0.68, 0.56-0.83; Table 4-12, p. 49). Minimal differences in ORs were evident after adjustment for covariates in the models of SO_2, PM_1, $PM_{2.5}$, PM_{10}, benzene and toluene.

4.4 Stratified Associations between Exposure to Air Pollutants and Gestational Hypertension

Stratified analyses by neighbourhood income and maternal smoking status during pregnancy were completed for all pollutants in order to better understand the observed results. Neighbourhood income was stratified by lowest three quintiles and highest two quintiles. In general, the inverse association between NO_2 exposure and GH was more significant for the high neighbourhood income stratum than the low income stratum (Table 4-13, p. 50). Significant inverse associations were observed between LUR-modelled NO_2 exposures in the fourth quartile and GH for both income groups. However, when using NAPS scaled LUR NO_2 as the exposure, a significant inverse relationship was found only between the fourth quartile of exposure and GH for the low income stratum.

For LUR-modelled $PM_{2.5}$, a significant inverse relationship between the fourth quartile of exposure and GH was observed only in the low income stratum. This was also the case for NAPS scaled LUR estimates of $PM_{2.5}$ (Table 4-14,p. 51).

Similar results were found for SO_2, PM_1, PM_{10} and toluene. For all of these LUR-modelled pollutants, a significant inverse relationship was found between the fourth quartile of exposure and GH for those in the low income stratum, but not those in the high income stratum (Tables 4-15 to 4-18, pp. 51-53). A significant inverse relationship was observed between exposure to benzene in the third and fourth quartiles and GH in the low income stratum. In addition, a significant inverse relationship was observed

between exposure to benzene in the fourth quartiles and GH in the high income stratum (Table 4-19, p. 53).

No statistically significant associations were found between exposure to air pollutants and GH in the stratum of women who smoked during pregnancy. Significant inverse associations were observed for exposure to all pollutants (including those scaled by NAPS) in the fourth quartile and GH in the non-smoking stratum (Tables 4-20 to 4-26, pp. 54-57). In addition, this inverse association was also observed for the second and third quartiles of benzene exposure and the second quartile of PM_{10} exposure in the non-smoking stratum. A log likelihood ratio test showed no significant interaction between pollutants and smoking status during pregnancy.

Stratified analyses were also completed for the association between maternal exposure to NO_2 and GH by maternal age (>35 years or ≤35 years) and pre-pregnancy weight (>90 kg or normal weight). Significant inverse associations between exposure in the fourth quartile and GH was found only in the normal weight stratum for both LUR-modelled and NAPS scaled LUR-modelled estimates of NO_2 (Table 4-27, p. 58). A log likelihood ratio test showed no significant interaction between NO_2 and pre-pregnancy weight.

Significant inverse relationships were observed in both maternal age stratum for exposure to both LUR-modelled and NAPS scaled LUR-modelled NO_2 in the fourth quartile and GH (Table 4-28, p. 59).

4.5 Associations between Exposure to Air Pollutants and Pre-Eclampsia

As described above (Section 5-3), the variables included in the models for the GH outcome were also used in the models examining the outcome of pre-eclampsia. Therefore, pre-pregnancy weight, parity, maternal age and smoking status during pregnancy were included in the final model. For all pollutants, either inverse or non-significant associations were found between exposure to increasing levels of air pollutants and GH, with the first quartile used as the reference. UORs and AORs are presented by pollutant and source in Tables 4-29 to 4-35 (pp. 60-63).

A significant inverse association was found between exposure to the highest quartile of LUR scaled by NAPS NO_2 exposure and pre-eclampsia (0.51, 0.35-0.73; Table 4-29, p. 6046). A significant inverse association was also found between the highest quartile of LUR-modelled benzene exposure and pre-eclampsia (0.49, 0.31-0.77; Table 4-34, p. 62). No significant associations were found between exposures to LUR modelled NO_2 (Table 4-29, p. 60), SO_2 (Table 4-30, p. 60), PM_1 (Table 4-31, p61), PM_{10} (Table 4-33, p. 62) or toluene (Table 4-35, p. 63) and pre-eclampsia. In addition, no significant associations were found between exposure to LUR-modelled or LUR scaled by NAPS $PM_{2.5}$ (Table 4-32, p. 61) and pre-eclampsia.

Table 4-1 Characteristics of Cohort

Variable		Frequency [a] (%)
Maternal Age		
	<20	682 (4.7)
	20-24	2480 (17.0)
	25-29	4090 (28.0)
	30-34	4721 (32.3)
	35-39	2189 (15.0)
	≥40	432 (3.0)
Smoking during pregnancy		
	Y	2540 (17.4)
	N	11945 (81.8)
Birth Year		
	2008	2992 (20.5)
	2009	2931 (20.1)
	2010	2952 (20.2)
	2011	2885 (19.8)
	2012	2834 (19.4)
Neighbourhood Income		
	Lower	3579 (24.5)
	Lower-middle	3092 (21.2)
	Middle	3062 (21.0)
	Upper-middle	2602 (17.8)
	Highest	2036 (14.0)
> 90kg pre-pregnancy		
	Y	1346 (9.2)
	N	10418 (71.4)
Parity		
	0	7341 (50.3)
	>0	7251 (49.7)
Sex of child		
	M	7549 (51.7)
	F	7045 (48.3)
Gestational diabetes		
	Y	547 (3.8)
	N	14047 (96.2)
Pre-existing diabetes		
	Y	99 (0.7)
	N	14495 (99.3)

[a] Frequencies may not total sample size due to missing values

Table 4-2 Frequencies and associations between gestational hypertension and covariates available in the Atlee Perinatal Database

Variable	GH (N= 1117) N[a] (%)	No GH (N= 13477) N[a] (%)	Significance (p-value)
Maternal Age (categorical)			
<20	48 (4.3)	634 (4.7)	0.88 [b]
20-24	183 (16.4)	2297 (17.0)	
25-29	313 (28.0)	3777 (28.9)	
30-34	364 (32.6)	4357 (32.3)	
35-39	179 (16.0)	2010 (14.9)	
≥40	30 (2.7)	402 (3.0)	
Maternal Age (continuous)			
Mean (SD)	29.8 (5.6)	29.7 (5.6)	0.42 [c]
Smoking during pregnancy			
Yes	155 (13.9)	2385 (17.8)	0.001 [b]
No	958 (86.1)	10987 (82.2)	
Birth Year			
2008	158 (17.0)	1650 (15.3)	0.12 [b]
2009	202 (21.8)	2144 (19.9)	
2010	176 (19.0)	2128 (19.8)	
2011	151 (16.3)	2121 (19. 7)	
2012	53 (5.7)	578 (5.7)	
Neighbourhood Income			
Lower	278 (25.1)	3301 (24.9)	0.08 [c]
Lower-middle	246 (22.2)	2846 (21.5)	
Middle	256 (23.1)	2806 (21.2)	
Upper-middle	201 (18.1)	2401 (18.1)	
Highest	127 (11.5)	1909 (14.4)	
Pre-pregnancy weight > 90 kg			
Yes	276 (29.7)	1070 (9.9)	<0.0001 [b]
No	654 (70.3)	9764 (90.1)	
Pre-pregnancy weight			
Mean (SD)	80.5 (22.3)	68.1 (16.2)	<0.0001 [c]

Variable	GH (N= 1117) N (%)	No GH (N= 13477) N (%)	Significance (p-value)
Parity			
0	754 (67.5)	6587 (48.9)	<0.0001 [b]
>0	363 (32.5)	6888 (51.1)	
Sex of Child			
M	579 (51.8)	6970 (51.7)	1.0 [b]
F	539 (48.2)	6506 (48.3)	
Gestational Diabetes			
Yes	116 (10.4)	431 (3.2)	<0.0001 [b]
No	1001 (89.6)	13046 (96.8)	
Pre-existing Diabetes			
Yes	21 (1.9)	78 (0.6)	<0.0001 [b]
No	1096 (98.1)	10723 (99.3)	

[a] Frequencies may not total sample size due to missing values
[b] P-value based on chi-square test
[c] P-value based on Wilcoxon Mann-Whitney U Test

Table 4-3 Air pollution concentrations by source

Variable	Source	Range	Median	Mean	SD
SO_2 (ppb)	LUR	0 – 7.8	0	0	0.6
	NAPS	0 – 26.7	1.8	2.4	2.4
NO_2 (ppb)	LUR	0 – 12.1	4.9	5.0	2.3
	NAPS	2.1 – 36.7	11.1	11.6	4.6
PM_1 ($\mu g/m^3$)	LUR	1.9 – 3.3	2.7	2.7	0.19
$PM_{2.5}$ ($\mu g/m^3$)	LUR	0.4 - 1.6	1.1	1.1	0.1
	NAPS	0.5 – 28.1	6.9	7.2	3.7
PM_{10} ($\mu g/m^3$)	LUR	0 – 4.8	3.4	3.3	0.5
Toluene ($\mu g/m^3$)	LUR	0.3 – 2.6	0.4	0.5	0.2
Benzene ($\mu g/m^3$)	LUR	0.2 – 1.1	0.4	0.4	0.1

Abbreviations: $\mu g/m^3$ – micrograms per meter cubed; LUR – Land-use regression; NAPS – National Air Pollution Surveillance; NO_2 – nitrogen dioxide; PM – particulate matter; ppb – parts per billion; SD – standard deviation; SO_2 – sulfur dioxide

Table 4-4 Pearson's correlation coefficients for LUR-modeled pollutants

Pollutant	N	Pearson Correlation Coefficient						
		NO_2	SO_2	PM_1	$PM_{2.5}$	PM_{10}	Benzene	Toluene
NO_2	14594	1.00	0.51	0.70	0.45	0.54	0.46	0.38
SO_2	13987		1.00	0.30	0.30	0.32	0.33	0.23
PM_1	14594			1.00	0.53	0.37	0.28	0.31
$PM_{2.5}$	14594				1.00	0.20	0.20	0.24
PM_{10}	14594					1.00	0.40	0.28
Benzene	14594						1.00	0.79
Toluene	14594							1.00

Abbreviations: LUR – Land-use regression; NO_2 – nitrogen dioxide; PM – particulate matter; SO_2 – sulfur dioxide

Table 4-5 Associations between LUR-modelled NO2 quartile of exposure and covariates available in the Atlee Perinatal Database

Variable	N[a] (%)				Significance (p-value)
	Quartile 1 N=3651	Quartile 2 N=3644	Quartile 3 N=3642	Quartile 4 N=3657	
Maternal Age (categorical)					
<20	154 (4.2)	148 (4.1)	197 (5.4)	183 (5.0)	<0.0001 [b]
20-24	461 (12.6)	629 (17.3)	726 (19.9)	664 (18.2)	
25-29	993 (27.2)	1066 (29.2)	1013 (27.8)	1018 (27.8)	
30-34	1334 (36.5)	1206 (33.1)	1104 (30.3)	1077 (29.4)	
35-39	602 (16.5)	489 (13.4)	506 (13.9)	592 (16.2)	
≥40	107 (2.9)	106 (2.9)	96 (2.6)	123 (3.4)	
Maternal Age (continuous)					
Mean (SD)	30.4 (5.4)	29.6 (5.5)	29.3 (5.8)	29.7 (5.8)	<0.0001 [c]
Smoking during pregnancy					
Yes	519 (14.3)	656 (18.1)	753 (20.9)	612 (16.9)	<0.0001 [b]
No	3110 (85.7)	2965 (81.9)	2854 (79.1)	3016 (83.1)	
Birth Year					
2008	754 (20.6)	747 (20.5)	765 (21.0)	726 (19.8)	0.2 [b]
2009	748 (20.5)	740 (20.3)	717 (19.7)	726 (19.4)	
2010	792 (21.7)	726 (19.9)	725 (19.9)	709 (19.4)	
2011	673 (18.4)	717 (19.7)	749 (20.6)	746 (20.4)	
2012	684 (18.7)	714 (19.6)	746 (20.4)	750 (20.5)	
Neighbourhood Income Quintile					
Lower	364 (10.0)	650 (18.0)	1066 (29.7)	1499 (42.4)	<0.0001 [c]
Lower-middle	508 (14.0)	906 (25.1)	844 (23.5)	834 (23.6)	
Middle	842 (23.2)	1001 (27.8)	709 (15.9)	510 (14.4)	
Upper-middle	1104 (30.4)	585 (16.2)	535 (14.9)	378 (10.7)	
Highest	816 (22.4)	464 (12.9)	440 (12.2)	316 (8.9)	
Pre-pregnancy weight > 90 kg					
Yes	356 (12.1)	385 (13.0)	358 (12.2)	247 (8.5)	<0.0001 [b]
No	2588 (87.9)	2577 (87.0)	2582 (87.8)	2671 (91.5)	
Pre-pregnancy weight (continuous)					
Mean (SD)	70.4 (17.1)	69.9 (17.6)	69.3 (17.5)	66.8 (16.1)	<0.0001 [c]
Parity					
0	1716 (47.0)	1761 (48.3)	1817 (49.9)	2047 (56.0)	<0.0001 [b]
>0	1935 (53.0)	1882 (51.7)	1825 (50.1)	1609 (44.0)	
Sex of Child					
M	1910 (52.3)	1885 (51.7)	1896 (52.1)	1858 (50.8)	0.6 [b]
F	1741 (47.7)	1759 (48.3)	1745 (47.9)	1799 (49.2)	

Variable	N[a] (%)				Significance (p-value)
	Quartile 1 N=3651	Quartile 2 N=3644	Quartile 3 N=3642	Quartile 4 N=3657	
Gestational Diabetes					
Yes	119 (3.3)	182 (5.0)	146 (4.0)	100 (2.7)	<0.0001 [b]
No	3532 (96.7)	3462 (95.0)	3496 (96.0)	3557 (97.3)	
Pre-existing Diabetes					
Yes	16 (0.4)	26 (0.7)	34 (0.9)	23 (0.6)	0.08 [b]
No	3635 (99.6)	3618 (99.3)	3608 (99.1)	3634 (99.4)	

[a] Frequencies may not total sample size due to missing values
[b] *p*-value based on chi-square test
[c] *p*-value based on Kruskal-Wallis test

Table 4-6 Unadjusted and adjusted odds ratios and 95% confidence intervals for the associations between nitrogen dioxide exposure during pregnancy and gestational hypertension

Pollutant	Source	Pollutant Quartile (ppb)	N	UOR	95% CI	AOR[a]	95% CI
NO_2	LUR	**1:** 0 – 3.0	11724	1.00	Reference	1.00	Reference
		2: 3.1- 4.8		0.94	0.78, 1.13	0.93	0.77, 1.12
		3: 4.9 – 6.4		0.91	0.76, 1.10	0.91	0.75, 1.09
		4: 6.5 – 12.1		0.66	0.54, 0.81	0.66	0.54, 0.81
	LUR scaled by NAPS[b]	**1:** 0 – 3.0	5207	1.00	Reference	1.00	Reference
		2: 3.1 – 4.5		0.81	0.61, 1.07	0.81	0.61, 1.08
		3: 4.6 – 6.1		0.85	0.64, 1.12	0.82	0.62, 1.10
		4: 6.2 – 11.8		0.53	0.39, 0.73	0.53	0.38, 0.73

[a] Adjusted for maternal age, smoking during pregnancy, pre-pregnancy weight and parity
[b] NAPS estimates are based on 20 week average.

Abbreviations: AOR – adjusted odds ratio; CI – confidence interval; LUR – Land-use regression; NAPS – National Air Pollution Surveillance; NO_2 – nitrogen dioxide; ppb – parts per billion; UOR – unadjusted odds ratio

Table 4-7 Unadjusted and adjusted odds ratios and 95% confidence intervals for the associations between sulfur dioxide exposure during pregnancy and gestational hypertension

Pollutant	Source	Pollutant Quartile (ppb)	N	UOR	95% CI	AOR[a]	95% CI
SO_2	LUR	**1:** 0 – 0	11220	1.00	Reference	1.00	Reference
		2: 0 – 0		0.87	0.72, 1.05	0.86	0.70, 1.04
		3: 0 – 0		1.00	0.83, 1.20	0.99	0.82, 1.20
		4: 0 – 7.8		0.76	0.62, 0.92	0.75	0.62, 0.92

[a]Adjusted for maternal age, smoking during pregnancy, pre-pregnancy weight and parity

Abbreviations: AOR – adjusted odds ratio; CI – confidence interval; LUR – Land-use regression; ppb – parts per billion; SO_2 – sulfur dioxide; UOR – unadjusted odds ratio

Table 4-8 Unadjusted and adjusted odds ratios and 95% confidence intervals for the associations between particulate matter of diameter < 1μm exposure during pregnancy and gestational hypertension

Pollutant	Source	Pollutant Quartile (μg/m^3)	N	UOR	95% CI	AOR[a]	95% CI
PM_1	LUR	**1:** 1.9 – 2.6	11724	1.00	Reference	1.00	Reference
		2: 2.6 – 2.7		1.06	0.88, 1.28	1.05	0.87, 1.27
		3: 2.7 – 2.8		1.11	0.92, 1.33	1.14	0.94, 1.37
		4: 2.9 – 3.3		0.70	0.57, 0.86	0.71	0.57, 0.87

[a]Adjusted for maternal age, smoking during pregnancy, pre-pregnancy weight and parity

Abbreviations: AOR – adjusted odds ratio; CI – confidence interval; LUR – Land-use regression; PM_1 – particulate matter of diameter < 1μm; UOR – unadjusted odds ratio

Table 4-9 Unadjusted and adjusted odds ratios and 95% confidence intervals for the associations between particulate matter of diameter < 2.5μm exposure during pregnancy and gestational hypertension

Pollutant	Source	Pollutant Quartile (ppb)	N	UOR	95% CI	AOR[a]	95% CI
$PM_{2.5}$	LUR	**1:** 0.5 – 1.0	11724	1.00	Reference	1.00	Reference
		2: 1.1 – 1.1		0.96	0.80, 1.15	0.96	0.79, 1.15
		3: 1.1 – 1.2		0.96	0.80, 1.15	0.96	0.79, 1.15
		4: 1.3 – 1.6		0.70	0.58, 0.85	0.68	0.56, 0.83
	LUR scaled by NAPS[b]	**1:** 0.4 – 0.9	4278	1.00	Reference	1.00	Reference
		2: 1.0 – 1.3		0.93	0.68, 1.29	0.96	0.70, 1.34
		3: 1.3 – 1.4		0.89	0.64, 1.23	0.90	0.64, 1.24
		4: 1.5 – 2.2		0.69	0.49, 0.97	0.70	0.49, 0.99

[a]Adjusted for maternal age, smoking during pregnancy, pre-pregnancy weight and parity
[b]NAPS estimates are based on 20 week average

Abbreviations: AOR – adjusted odds ratio; CI – confidence interval; LUR – Land-use regression; NAPS – National Air Pollution Surveillance; $PM_{2.5}$ – particulate matter of diameter < 2.5μm; UOR – unadjusted odds ratio

Table 4-10 Unadjusted and adjusted odds ratios and 95% confidence intervals for the associations between particulate matter of diameter < 10µm exposure during pregnancy and gestational hypertension

Pollutant	Source	Pollutant Quartile (µg/m^3)	N	UOR	95% CI	AOR[a]	95% CI
PM_{10}	LUR	**1:** 0 – 3.1	11724	1.00	Reference	1.00	Reference
		2: 3.1 – 3.3		0.99	0.83, 1.18	0.96	0.79, 1.15
		3: 3.4 – 3.5		0.79	0.65, 0.95	0.76	0.63, 0.92
		4: 3.6 – 4.8		0.75	0.62, 0.91	0.71	0.58, 0.87

[a]Adjusted for maternal age, smoking during pregnancy, pre-pregnancy weight and parity

Abbreviations: AOR – adjusted odds ratio; CI – confidence interval; LUR – Land-use regression; PM_{10} – particulate matter of diameter < 10µm; UOR – unadjusted odds ratio

Table 4-11 Unadjusted and adjusted odds ratios and 95% confidence intervals for the associations between benzene exposure during pregnancy and gestational hypertension

Pollutant	Source	Pollutant Quartile (µg/m^3)	N	UOR	95% CI	AOR[a]	95% CI
Benzene	LUR	**1:** 0.2 – 0.3	11724	1.00	Reference	1.00	Reference
		2: 0.3 – 0.4		0.80	0.67, 0.96	0.78	0.65, 0.94
		3: 0.4 – 1.1		0.76	0.64, 0.92	0.77	0.64, 0.93
		4: 0.42 – 1.07		0.63	0.52, 0.76	0.62	0.51, 0.75

[a]Adjusted for maternal age, smoking during pregnancy, pre-pregnancy weight and parity

Abbreviations: AOR – adjusted odds ratio; CI – confidence interval; LUR – Land-use regression; UOR – unadjusted odds ratio

Table 4-12 Unadjusted and adjusted odds ratios and 95% confidence intervals for the associations between toluene exposure during pregnancy and gestational hypertension

Pollutant	Source	Pollutant Quartile (µg/m^3)	N	UOR	95% CI	AOR[a]	95% CI
Toluene	LUR	1: 0.3- 0.3	11724	1.00	Reference	1.00	Reference
		2: 0.4 – 0.4		0.89	0.74, 1.07	0.85	0.71, 1.03
		3: 0 .4 – 0.5		0.90	0.75, 1.08	0.87	0.72, 1.05
		4: 0.5 – 2.6		0.71	0.59, 0.87	0.68	0.56, 0.83

[a]Adjusted for maternal age, smoking during pregnancy, pre-pregnancy weight and parity

Abbreviations: AOR – adjusted odds ratio; CI – confidence interval; LUR – Land-use regression; UOR – unadjusted odds ratio

Table 4-13 Odds ratios and 95% confidence intervals for the associations between nitrogen dioxide exposure during pregnancy and gestational hypertension stratified by high and low neighbourhood income

Pollutant	Source	Q	Lowest 3 quintiles of neighbourhood income			Highest 2 quintiles of neighbourhood income		
			N	OR	95% CI	N	OR	95% CI
NO_2	LUR	1	7756	1.00	Reference	3795	1.00	Reference
		2		1.02	0.80, 1.29		0.79	0.58, 1.98
		3		0.98	0.77, 1.24		0.75	0.54, 1.04
		4		0.68	0.53, 0.88		0.64	0.43, 0.95
	NAPS scaled LUR[a]	1	3494	1.00	Reference	1591	1.00	Reference
		2		1.00	0.69, 1.43		0.56	0.33, 0.94
		3		1.02	0.71, 1.46		0.62	0.37, 1.03
		4		0.57	0.38, 0.85		0.63	0.35, 1.13

[a] NAPS estimates are based on 20 week average

Abbreviations: CI – confidence interval; LUR – Land-use regression; NAPS – National Air Pollution Surveillance; NO_2 – nitrogen dioxide; OR – odds ratio; Q – quartile of pollutant exposure

Table 4-14 Odds ratios and 95% confidence intervals for the associations between particulate matter of diameter < 2.5µm exposure during pregnancy and gestational hypertension stratified by high and low neighbourhood income

Pollutant	Source	Q	Lowest 3 quintiles of neighbourhood income			Highest 2 quintiles of neighbourhood income		
			N	OR	95% CI	N	OR	95% CI
$PM_{2.5}$	LUR	1	7756	1.00	Reference	3795	1.00	Reference
		2		1.03	0.82, 1.30		0.89	0.66, 1.20
		3		0.94	0.75, 1.17		1.04	0.75, 1.43
		4		0.69	0.55, 0.87		0.73	0.48, 1.10
	NAPS scaled LUR[a]	1	2982	1.00	Reference	1403	1.00	Reference
		2		0.83	0.56, 1.23		1.01	0.59, 1.72
		3		0.89	0.60, 1.31		0.88	0.51, 1.52
		4		0.60	0.40, 0.91		0.63	0.32, 1.21

[a] NAPS estimates are based on 20 week average

Abbreviations: CI – confidence interval; LUR – Land-use regression; NAPS – National Air Pollution Surveillance; OR – odds ratio; $PM_{2.5}$ – particulate matter of diameter < 2.5µm; Q – quartile of pollutant exposure

Table 4-15 Odds ratios and 95% confidence intervals for the associations between sulfur dioxide exposure during pregnancy and gestational hypertension stratified by high and low neighbourhood income

Pollutant	Source	Q	Lowest 3 quintiles of neighbourhood income			Highest 2 quintiles of neighbourhood income		
			N	OR	95% CI	N	OR	95% CI
SO_2	LUR	1	7526	1.00	Reference	3524	1.00	Reference
		2		0.82	0.65, 1.05		0.98	0.72, 1.33
		3		0.94	0.74, 1.78		1.10	0.80, 1.52
		4		0.73	0.58, 0.92		0.79	0.51, 1.22

Abbreviations: CI – confidence interval; LUR – Land-use regression; OR – odds ratio; SO_2 – sulfur dioxide; Q – quartile of pollutant exposure

Table 4-16 Odds ratios and 95% confidence intervals for the associations between particulate matter of diameter < 1μm exposure during pregnancy and gestational hypertension stratified by high and low neighbourhood income

Pollutant	Source	Q	Lowest 3 quintiles of neighbourhood income			Highest 2 quintiles of neighbourhood income		
			N	OR	95% CI	N	OR	95% CI
PM_1	LUR	1	7756	1.00	Reference	3795	1.00	Reference
		2		1.13	0.90, 1.42		1.00	0.73, 1.37
		3		1.14	0.91, 1.42		1.04	0.75, 1.46
		4		0.64	0.50, 0.81		0.94	0.65, 1.37

Abbreviations: CI – confidence interval; LUR – Land-use regression; OR – odds ratio; PM_1 – particulate matter of diameter < 1μm; Q – quartile of pollutant exposure

Table 4-17 Odds ratios and 95% confidence intervals for the associations between particulate matter of diameter < 10μm exposure during pregnancy and gestational hypertension stratified by high and low neighbourhood income

Pollutant	Source	Q	Lowest 3 quintiles of neighbourhood income			Highest 2 quintiles of neighbourhood income		
			N	OR	95% CI	N	OR	95% CI
PM_{10}	LUR	1	7756	1.00	Reference	3795	1.00	Reference
		2		0.97	0.78, 1.22		0.98	0.72, 1.33
		3		0.83	0.66, 1.05		0.62	0.44, 0.88
		4		0.69	0.54, 0.88		0.88	0.63, 1.24

Abbreviations: CI – confidence interval; LUR – Land-use regression; OR – odds ratio; PM_{10} – particulate matter of diameter < 10μm; Q – quartile of pollutant exposure

Table 4-18 Odds ratios and 95% confidence intervals for the associations between Toluene exposure during pregnancy and gestational hypertension stratified by high and low neighbourhood income

Pollutant	Source	Q	Lowest 3 quintiles of neighbourhood income			Highest 2 quintiles of neighbourhood income		
			N	OR	95% CI	N	OR	95% CI
Toluene	LUR	1	7756	1.00	Reference	3795	1.00	Reference
		2		0.89	0.70, 1.12		0.78	0.56, 1.09
		3		0.86	0.68, 1.09		0.87	0.64, 1.19
		4		0.64	0.51, 0.82		0.83	0.57, 1.21

Abbreviations: CI – confidence interval; LUR – land-use regression; OR – odds ratio; Q – quartile of pollutant exposure

Table 4-19 Odds ratios and 95% confidence intervals for the associations between Benzene exposure during pregnancy and gestational hypertension stratified by high and low neighbourhood income

Pollutant	Source	Q	Lowest 3 quintiles of neighbourhood income			Highest 2 quintiles of neighbourhood income		
			N	OR	95% CI	N	OR	95% CI
Benzene	LUR	1	7756	1.00	Reference	3795	1.00	Reference
		2		0.75	0.60, 0.94		0.89	0.65, 1.22
		3		0.72	0.58, 0.90		0.85	0.62, 1.17
		4		0.64	0.51, 0.80		0.58	0.40, 0.86

Abbreviations: CI – confidence interval; LUR – Land-use regression; OR – odds ratio; Q – quartile of pollutant exposure

Table 4-20 Odds ratios and 95% confidence intervals for the associations between nitrogen dioxide exposure during pregnancy and gestational hypertension stratified by maternal smoking status

Pollutant	Source	Q	Non-smoker			Smoker		
			N	OR	95% CI	N	OR	95% CI
NO_2	LUR	1	9753	1.00	Reference	2051	1.00	Reference
		2		0.90	0.74, 1.10		1.42	0.82, 2.48
		3		0.87	0.71, 1.05		1.49	0.87, 2.55
		4		0.64	0.52, 0.79		1.13	0.62, 2.04
	NAPS scaled LUR[a]	1	4370	1.00	Reference	837	1.00	Reference
		2		0.81	0.81, 1.09		0.87	0.37, 2.05
		3		0.79	0.79, 1.08		1.35	0.62, 2.93
		4		0.47	0.33, 0.66		1.12	0.50, 2.54

[a] NAPS estimates are based on 20 week average

Abbreviations: CI – confidence interval; LUR – Land-use regression; NAPS – National Air Pollution Surveillance; NO_2 – nitrogen dioxide; OR – odds ratio; Q – quartile of pollutant exposure

Table 4-21 Odds ratios and 95% confidence intervals for the associations between sulfur dioxide exposure during pregnancy and gestational hypertension stratified by maternal smoking status

Pollutant	Source	Q	Non-smoker			Smoker		
			N	OR	95% CI	N	OR	95% CI
SO_2	LUR	1	9319	1.00	Reference	1981	1.00	Reference
		2		0.93	0.76, 1.13		0.59	0.33, 1.05
		3		0.98	0.80, 1.19		1.23	0.76, 2.00
		4		0.79	0.64, 0.97		0.78	0.45, 1.33

Abbreviations: CI – confidence interval; LUR – Land-use regression; OR – odds ratio; SO_2 – sulfur dioxide; Q – quartile of pollutant exposure

Table 4-22 Odds ratios and 95% confidence intervals for the associations between particulate matter of diameter < 1μm exposure during pregnancy and gestational hypertension stratified by maternal smoking status

Pollutant	Source	Q	Non-smoker			Smoker		
			N	OR	95% CI	N	OR	95% CI
PM_1	LUR	1	9753	1.00	Reference	2051	1.00	Reference
		2		0.99	0.82, 1.21		1.67	0.99, 2.80
		3		1.10	0.90, 1.34		1.48	0.90, 2.44
		4		0.71	0.58, 0.88		0.65	0.34, 1.26

Abbreviations: CI – confidence interval; LUR – Land-use regression; OR – odds ratio; PM_1 – particulate matter of diameter < 1μm; Q – quartile of pollutant exposure

Table 4-23 Odds ratios and 95% confidence intervals for the associations between particulate matter of diameter < 2.5μm exposure during pregnancy and gestational hypertension stratified by maternal smoking status

Pollutant	Source	Q	Non-smoker			Smoker		
			N	OR	95% CI	N	OR	95% CI
$PM_{2.5}$	LUR	1	9753	1.00	Reference	2051	1.00	Reference
		2		0.93	0.76, 1.13		1.28	0.76, 2.16
		3		0.95	0.78, 1.15		1.30	0.79, 2.16
		4		0.69	0.56, 0.84		0.91	0.51, 1.64
	NAPS[a] scaled LUR	1	3585	1.00	Reference	693	1.00	Reference
		2		0.92	0.65, 1.30		1.02	0.43, 2.43
		3		0.88	0.62, 1.24		0.99	0.42, 2.30
		4		0.66	0.45, 0.95		0.90	0.36, 2.23

[a] NAPS estimates are based on 20 week average

Abbreviations: CI – confidence interval; LUR – Land-use regression; NAPS – National Air Pollution Surveillance; OR – odds ratio; $PM_{2.5}$ – particulate matter of diameter < 2.5μm; Q – quartile of pollutant exposure

Table 4-24 Odds ratios and 95% confidence intervals for the associations between particulate matter of diameter < 10μm exposure during pregnancy and gestational hypertension stratified by maternal smoking status

Pollutant	Source	Q	Non-smoker			Smoker		
			N	OR	95% CI	N	OR	95% CI
PM_{10}	LUR	1	9753	1.00	Reference	2051	1.00	Reference
		2		0.99	0.82, 1.21		1.11	0.67, 1.82
		3		0.78	0.64, 0.96		0.88	0.88, 1.50
		4		0.78	0.64, 0.96		0.74	0.74, 1.29

Abbreviations: CI – confidence interval; LUR – Land-use regression; OR – odds ratio; PM_{10} – particulate matter of diameter < 10μm; Q – quartile of pollutant exposure

Table 4-25 Odds ratios and 95% confidence intervals for the associations between benzene exposure during pregnancy and gestational hypertension stratified by maternal smoking status

Pollutant	Source	Q	Non-smoker			Smoker		
			N	OR	95% CI	N	OR	95% CI
Benzene	LUR	1	9753	1.00	Reference	2051	1.00	Reference
		2		0.75	0.62, 0.91		1.16	0.72, 1.89
		3		0.72	0.60, 0.88		1.01	0.60, 1.70
		4		0.62	0.51, 0.76		0.81	0.48, 1.38

Abbreviations: CI – confidence interval; LUR – Land-use regression; OR – odds ratio; Q – quartile of pollutant exposure

Table 4-26 Odds ratios and 95% confidence intervals for the associations between toluene exposure during pregnancy and gestational hypertension stratified by maternal smoking status

Pollutant	Source	Q	Non-smoker			Smoker		
			N	OR	95% CI	N	OR	95% CI
Toluene	LUR	1	9753	1.00	Reference	2051	1.00	Reference
		2		0.93	0.76, 1.13		0.70	0.41, 1.21
		3		0.92	0.76, 1.12		0.78	0.46, 1.32
		4		0.69	0.56, 0.85		1.02	0.63, 1.66

Abbreviations: CI – confidence interval; LUR – Land-use regression; OR – odds ratio; Q – quartile of pollutant exposure

Table 4-27 Odds ratios and 95% confidence intervals for the associations between nitrogen dioxide exposure during pregnancy and GH stratified by pre-pregnancy weight > 90 kg and pre-pregnancy weight ≤ 90 kg

Pollutant	Source	Q	Pre-pregnancy weight ≤ 90 kg			pre-pregnancy weight ≤ 90 kg		
			N	OR	95% CI	N	OR	95% CI
NO_2	LUR	1	10418	1.00	Reference	1346	1.00	Reference
		2		0.91	0.74, 1.13		0.95	0.67, 1.36
		3		0.95	0.77, 1.18		1.79	0.54, 1.14
		4		0.59	0.47, 0.75		1.23	0.84, 1.81
	NAPS scaled LUR[a]	1	4592	1.00	Reference	615	1.00	Reference
		2		0.78	0.55, 1.10		0.87	0.52, 1.47
		3		0.92	0.76, 1.28		0.66	0.38, 1.14
		4		0.50	0.34, 0.73		0.90	0.50, 1.63

[a] NAPS estimates are based on 20 week average

Abbreviations: CI – confidence interval; LUR – Land-use regression; NAPS – National Air Pollution Surveillance; NO_2 – nitrogen dioxide; OR – odds ratio; Q – quartile of pollutant exposure

Table 4-28 Odds ratios and 95% confidence intervals for the associations between nitrogen dioxide exposure during pregnancy and GH stratified by dichotomized maternal age

Pollutant	Source	Q	Maternal age ≤ 35 years			Maternal age > 35 years		
			N	OR	95% CI	N	OR	95% CI
NO_2	LUR	1	9609	1.00	Reference	2115	1.00	Reference
		2		0.97	0.79, 1.19		0.84	0.58, 1.28
		3		0.96	0.78, 1.18		0.74	0.49, 1.14
		4		0.69	0.55, 0.86		0.56	0.36, 0.86
	NAPS scaled LUR[a]	1	4248	1.00	Reference	959	1.00	Reference
		2		0.88	0.64, 1.21		0.62	0.33, 1.17
		3		0.96	0.70, 1.31		0.53	0.28, 1.00
		4		0.56	0.40, 0.81		0.44	0.23, 0.86

[a] NAPS estimates are based on 20 week average

Abbreviations: CI – confidence interval; LUR – Land-use regression; NAPS – National Air Pollution Surveillance; NO_2 – nitrogen dioxide; OR – odds ratio; Q – quartile of pollutant exposure

Table 4-29 Unadjusted and adjusted odds ratios and 95% confidence intervals for the associations between nitrogen dioxide exposure during pregnancy and pre-eclampsia

Pollutant	Source	Pollutant Quartile (ppb)	N	UOR	95% CI	AOR[a]	95% CI
NO_2	LUR	**1:** 0 3.0	11724	1.00	Reference	1.00	Reference
		2: 3.1- 4.8		0.86	0.57, 1.28	0.85	0.56, 1.28
		3: 4.9 – 6.4		0.98	0.66, 1.46	1.00	0.67, 1.48
		4: 6:5 – 12.1		0.68	0.48, 1.06	0.72	0.47, 1.11
	LUR scaled by NAPS[b]	**1:** 0 – 3.0	5207	1.00	Reference	1.00	Reference
		2: 3.1 – 4.5		0.80	0.59, 1.09	0.80	0.58, 1.11
		3: 4.6 – 6.1		0.84	0.61, 1.14	0.82	0.59, 1.12
		4: 6.2 – 11.8		0.50	0.35, 0.72	0.51	0.35, 0.73

[a]Adjusted for maternal age, smoking during pregnancy, pre-pregnancy weight and parity
[b]NAPS estimates are based on 20 week average

Abbreviations: AOR – adjusted odds ratio; CI – confidence interval; LUR – Land-use regression; NAPS – National Air Pollution Surveillance; NO_2 – nitrogen dioxide; ppb – parts per billion; UOR – unadjusted odds ratio

Table 4-30 Unadjusted and adjusted odds ratios and 95% confidence intervals for the associations between sulfur dioxide exposure during pregnancy and pre-eclampsia

Pollutant	Source	Pollutant Quartile (ppb)	N	UOR	95% CI	AOR[a]	95% CI
SO_2	LUR	**1:** 0 – 0	11220	1.00	Reference	1.00	Reference
		2: 0 – 0		0.94	0.61, 1.47	0.95	0.61, 1.48
		3: 0 – 0		1.34	0.89, 2.02	1.37	0.91, 2.07
		4: 0 – 7.8		1.02	0.66, 1.57	1.08	0.70, 1.67

[a]Adjusted for maternal age, smoking during pregnancy, pre-pregnancy weight and parity

Abbreviations: AOR – adjusted odds ratio; CI – confidence interval; LUR – Land-use regression; ppb – parts per billion; SO_2 – sulfur dioxide; UOR – unadjusted odds ratio

Table 4-31 Unadjusted and adjusted odds ratios and 95% confidence intervals for the associations between particulate matter of diameter < 1μm exposure during pregnancy and pre-eclampsia

Pollutant	Source	Pollutant Quartile (μg/m^3)	N	UOR	95% CI	AOR[a]	95% CI
PM_1	LUR	**1:** 1.9 – 2.6	11724	1.00	Reference	1.00	Reference
		2: 2.6 – 2.7		0.87	0.58, 1.31	0.85	0.57, 1.28
		3: 2.7 – 2.8		1.09	0.74, 1.60	1.11	0.75, 1.64
		4: 2.9 – 3.3		0.63	0.40, 0.98	0.66	0.42, 1.03

[a]Adjusted for maternal age, smoking during pregnancy, pre-pregnancy weight and parity

Abbreviations: AOR – adjusted odds ratio; CI – confidence interval; LUR – Land-use regression; PM_1 – particulate matter of diameter < 1μm; UOR – unadjusted odds ratio

Table 4-32 Unadjusted and adjusted odds ratios and 95% confidence intervals for the associations between particulate matter of diameter < 2.5μm exposure during pregnancy and pre-eclampsia

Pollutant	Source	Pollutant Quartile (ppb)	N	UOR	95% CI	AOR[a]	95% CI
$PM_{2.5}$	LUR	**1:** 0.5 – 1.0	11724	1.00	Reference	1.00	Reference
		2: 1.1 – 1.1		0.98	0.66, 1.46	0.98	0.66, 1.47
		3: 1.1 – 1.2		0.97	0.65, 1.45	0.98	0.66, 1.47
		4: 1.3 – 1.6		0.72	0.46, 1.10	0.72	0.47, 1.11
	LUR scaled by NAPS[b]	**1:** 0.4 – 0.9	4278	1.00	Reference	1.00	Reference
		2: 1.0 – 1.3		0.90	0.63, 1.28	0.93	0.65, 1.34
		3: 1.3 – 1.4		0.82	0.57, 1.17	0.83	0.57, 1.20
		4: 1.5 – 2.2		0.67	0.46, 0.98	0.68	0.46, 1.00

[a]Adjusted for maternal age, smoking during pregnancy, pre-pregnancy weight and parity
[b]NAPS estimates are based on 20 week average

Abbreviations: AOR – adjusted odds ratio; CI – confidence interval; LUR – Land-use regression; NAPS – National Air Pollution Surveillance; $PM_{2.5}$ – particulate matter of diameter < 2.5μm; UOR – unadjusted odds ratio

Table 4-33 Unadjusted and adjusted odds ratios and 95% confidence intervals for the associations between particulate matter of diameter < 10µm exposure during pregnancy and pre-eclampsia

Pollutant	Source	Pollutant Quartile (µg/m^3)	N	UOR	95% CI	AOR[a]	95% CI
PM_{10}	LUR	**1:** 0 – 3.1	11724	1.00	Reference	1.00	Reference
		2: 3.1 – 3.3		1.08	0.72, 1.61	1.07	0.72, 1.59
		3: 3.4 – 3.5		0.95	0.63, 1.44	1.00	0.66, 1.49
		4: 3.6 – 4.8		0.77	0.50, 1.19	0.72	0.46, 1.13

[a]Adjusted for maternal age, smoking during pregnancy, pre-pregnancy weight and parity

Abbreviations: AOR – adjusted odds ratio; CI – confidence interval; LUR – Land-use regression; PM_{10} – particulate matter of diameter < 10µm; UOR – unadjusted odds ratio

Table 4-34 Unadjusted and adjusted odds ratios and 95% confidence intervals for the associations between benzene exposure during pregnancy and pre-eclampsia

Pollutant	Source	Pollutant Quartile (µg/m^3)	N	UOR	95% CI	AOR[a]	95% CI
Benzene	LUR	**1:** 0.2 – 0.3	11724	1.00	Reference	1.00	Reference
		2: 0.3 – 0.4		0.80	0.67, 0.96	0.72	0.49, 1.08
		3: 0.4 – 1.1		0.76	0.64, 0.92	0.81	0.55, 1.19
		4: 0.42 – 1.07		0.63	0.52, 0.76	0.49	0.31, 0.77

[a]Adjusted for maternal age, smoking during pregnancy, pre-pregnancy weight and parity

Abbreviations: AOR – adjusted odds ratio; CI – confidence interval; LUR – Land-use regression; UOR – unadjusted odds ratio

Table 4-35 Unadjusted and adjusted odds ratios and 95% confidence intervals for the associations between toluene exposure during pregnancy and pre-eclampsia

Pollutant	Source	Pollutant Quartile (µg/m^3)	N	UOR	95% CI	AOR[a]	95% CI
Toluene	LUR	1: 0.3- 0.3	11724	1.00	Reference	1.00	Reference
		2: 0.4 – 0.4		1.09	0.73, 1.62	1.07	0.72, 1.59
		3: 0 .4 – 0.5		1.00	0.67, 1.51	1.00	0.66, 1.49
		4: 0.5 – 2.6		0.72	0.46, 1.13	0.72	0.46, 1.13

[a]Adjusted for maternal age, smoking during pregnancy, pre-pregnancy weight and parity

Abbreviations: AOR – adjusted odds ratio; CI – confidence interval; LUR – Land-use regression; UOR – unadjusted odds ratio

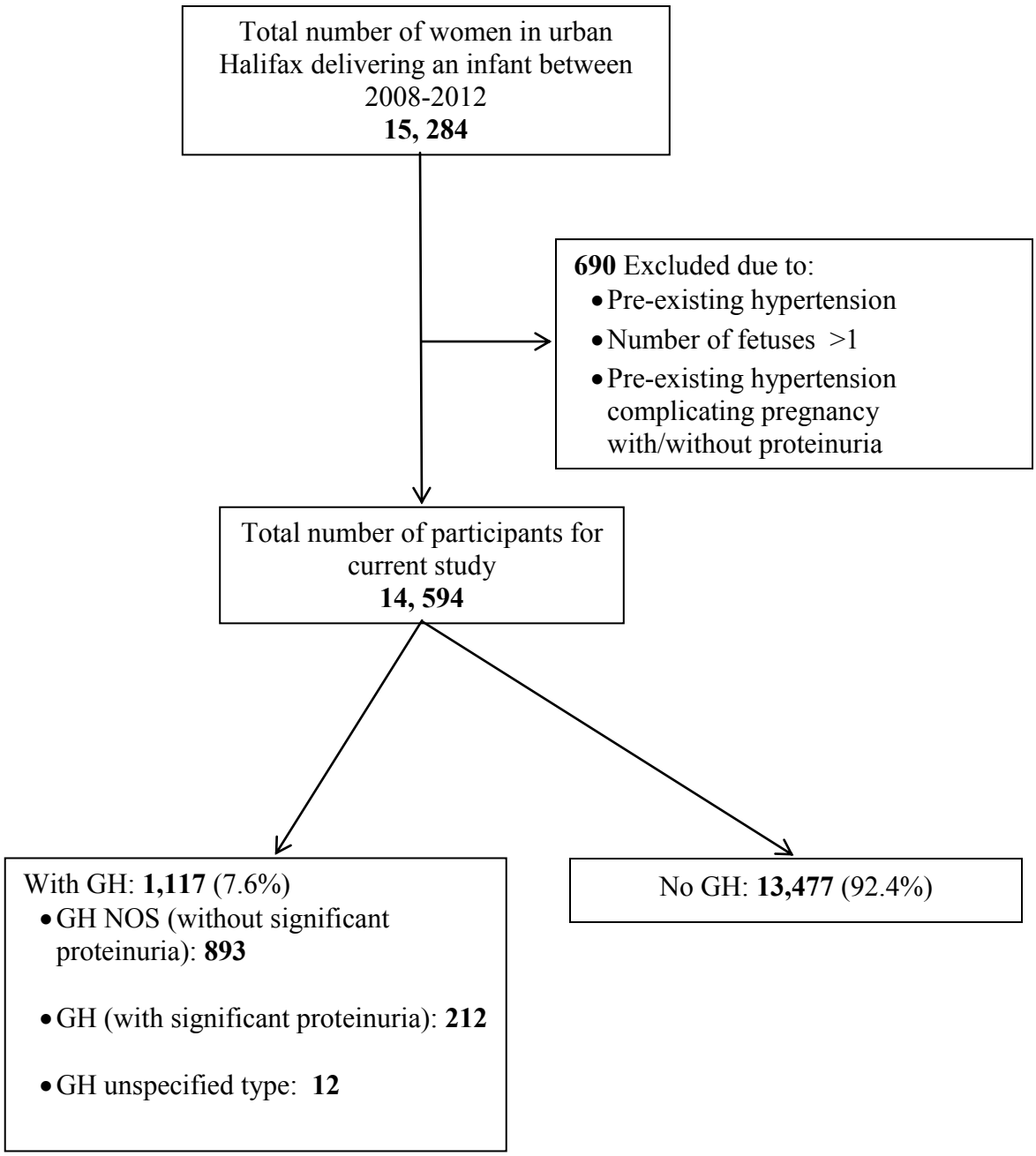

Figure 4-1 Flow diagram of participant exclusion and outcome of gestational hypertension

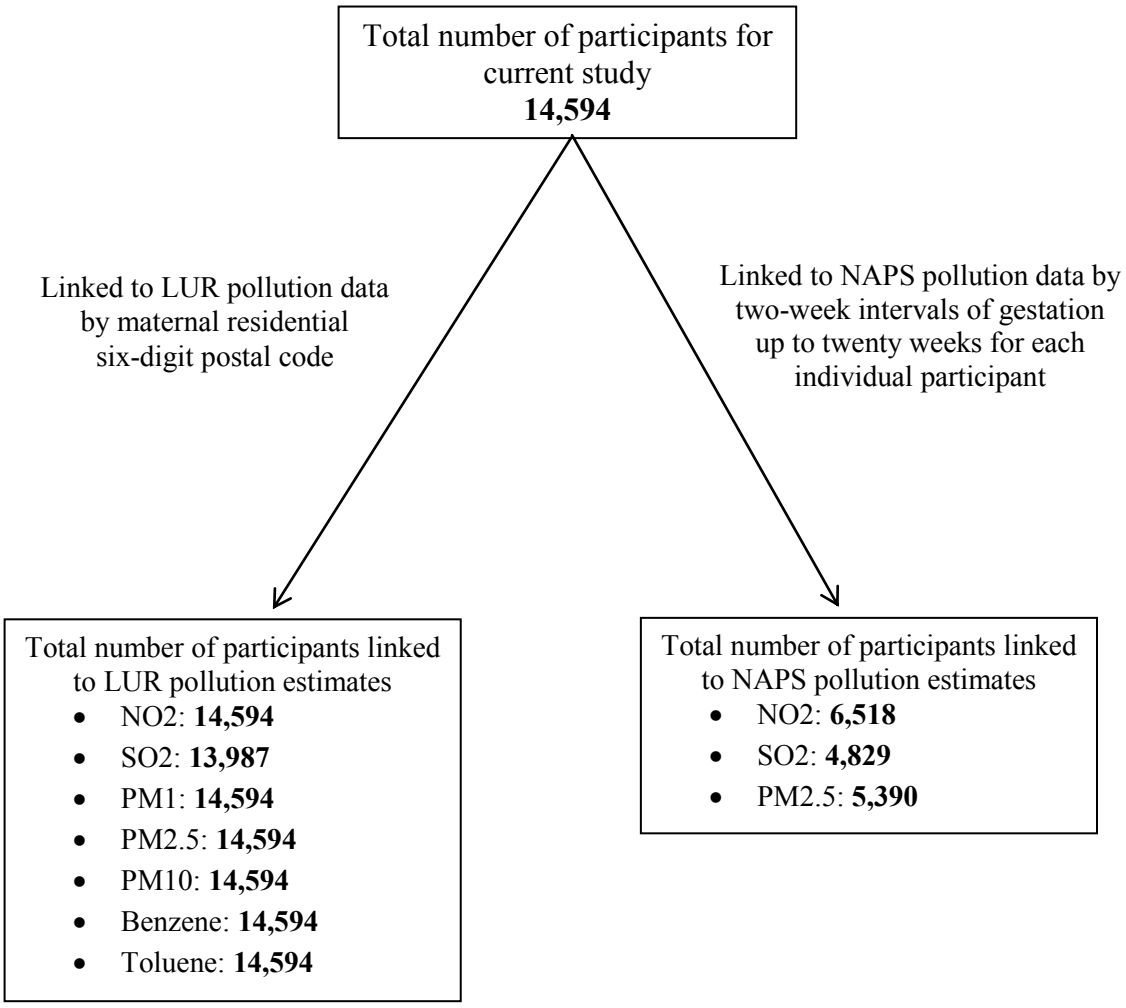

Figure 4-2 Flowchart of linkage of Atlee Perinatal Database to land-use regression derived and National Air Pollution Surveillance Systems air pollution estimates

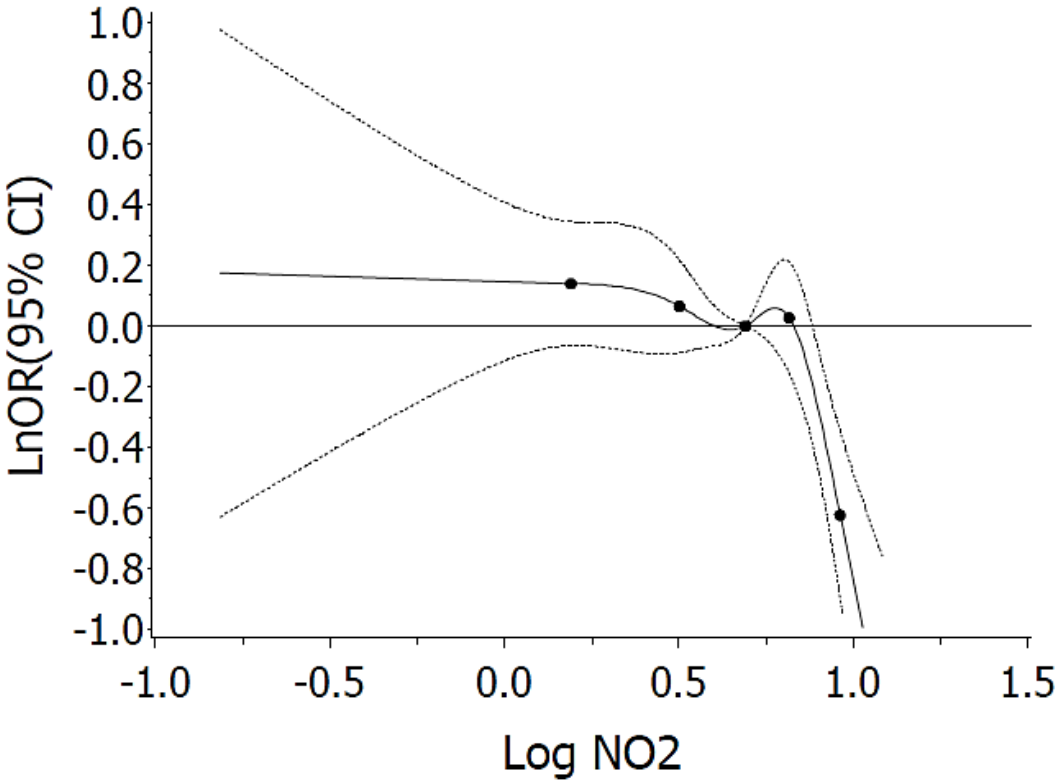

Figure 4-3 Restricted cubic spline function of the association between exposure to LUR-modelled nitrogen dioxide and gestational hypertension with knots at 5%, 25%, 50%, 75%, and 95%

Chapter 5 DISCUSSION

This thesis aimed to examine the association between maternal exposure to air pollutants during pregnancy and GH in women residing in urban Halifax. Covariates available in the NSAPD were examined by GH status. Mothers who smoked during their pregnancy were less likely to be diagnosed with GH. Living in areas of higher neighbourhood income tended to increase the risk of GH. Those with GH were also more likely to be > 90 kg pre-pregnancy, nulliparous, have gestational diabetes and pre-existing diabetes.

LUR-modelled estimates alone were used for SO_2, PM_1, PM_{10}, benzene and toluene. LUR-modelled estimates as well as LUR estimates scaled by NAPS estimates were used for NO_2 and $PM_{2.5}$ to account for temporality of the spatial estimates. Unfortunately, due to missing values in the NAPS database, the sample sizes for NAPS scaled LUR estimates were much smaller. Compared to the unadjusted models, adjustment for pre-pregnancy weight, parity, maternal age and smoking status during pregnancy in the logistic regression models caused little change in the ORs. Pre-pregnancy weight was tested as a potential confounding variable as both a continuous and a dichotomous variable. Pre-pregnancy weight was included in the model as a dichotomous variable as there was little change in the model estimates between using the variable as continuous or dichotomous. Neighbourhood income was included in the initial model but was not found to be a significant confounder and therefore remained removed from the model.

In general, maternal exposure to higher levels of air pollution was associated with a reduced risk of GH. Compared to mothers in the lowest quartile of NO_2 exposure, the risk of GH for those in the fourth quartile was reduced by a third when using the LUR-modelled estimates as the exposure. The risk of GH was reduced by almost half when using the NAPS scaled LUR estimates of NO_2. $PM_{2.5}$ was the only other pollutant scaled for temporality. Similar to what was observed with NO_2, compared to those exposed to the lowest quartile of $PM_{2.5}$ the risk of GH in mothers exposed to the highest quartile was reduced by approximately 30%. This reduction held true for both the LUR-modelled and scaled estimates of $PM_{2.5}$.. Similar results were observed for exposures to SO_2, PM_1, PM_{10}, benzene and toluene. The risk of GH was reduced by 25-38% for exposure to the highest quartile of these pollutants compared to the lowest quartile.

Stratified analyses were completed in order to better understand the inverse relationships. Stratifying data by maternal smoking status during pregnancy and neighbourhood income did not explain the observed inverse associations between exposure to air pollutants and GH, as the inverse relationship remained in both strata of neighbourhood income and for non-smokers. Had a positive relationship between air pollutant exposure and GH been found in one of the stratum, as opposed to the observed inverse relationships, we would have evidence of effect modification by that variable. For example, if a positive association was observed between exposure to NO_2 and GH for those who smoke during pregnancy only, then we could conclude that smoking during pregnancy is a modifier in the relationship between NO_2 exposure and GH. This would suggest an interaction between smoking during pregnancy and NO_2.

Additionally, data were stratified by pre-pregnancy weight and maternal age to examine the association between NO_2 exposure and GH. The inverse association between exposure to NO_2 and GH was only significant for women who were ≤ 90 kg pre-pregnancy. For LUR-modelled NO_2 exposure alone in the >90 kg pre-pregnancy stratum, the association was in the positive direction, although not significant. It could be the case that women who are > 90 kg pre-pregnancy are more susceptible to GH. Therefore, a relationship in the positive direction (although non-significant) between exposure to NO_2 and GH is observed at a lower threshold of exposure.

When examining the outcome of pre-eclampsia alone, significant inverse associations were observed only for the highest quartiles of LUR scaled by NAPS exposure to NO_2 and LUR-modelled benzene exposure. No significant associations were observed for the other pollutants of interest and pre-eclampsia.

Overall, the results of the current study do not support previous research examining the association between maternal exposure to air pollution and pre-eclampsia. Of the five studies that examined NO_2 as an exposure, three found a positive association between maternal exposure to NO_2 and GH [53] or pre-eclampsia [13,53,55]. Exposure measurement and assignment differed between these studies, but all studies scaled pollutant estimates to account for temporality. One study did not find a significant association between exposure to increasing concentrations of NO_2 and GH [10]. The sample size for the latter study was much smaller than the studies that found positive associations. Positive associations have also been found between maternal exposures to estimates of SO_2 that took into account both spatial and temporal characteristics and hypertensive disorders of pregnancy including GH and pre-eclampsia [53]. One study that

used temporal-spatial Kriging modelling techniques did not find a significant association between exposure to either NO_2 or SO_2 and hypertension or blood pressure during pregnancy [9].

Data on three different size fractions of PM were available for the current study. Inverse associations were found between each size of PM and GH. Contrary to these results, previous research has found positive associations between exposure to varying size fractions of PM and GH [10,11,52,53] or increasing blood pressure [9]. One study examining exposure to PM_{10} in the first trimester of pregnancy found a positive association between IQR increase in PM_{10} concentration and an increase in systolic blood pressure [9]. Another study found the odds of developing GH disorders increased by up to four times with each two SD increase in $PM_{2.5}$ concentrations. No significant association between increasing levels of PM_{10} and GH disorders were found [52]. However the latter study was a case-control design and included only a seventh of the participants as the study that found a positive association for PM_{10}.

For each $10\mu g/m^3$ increase in PM_{10} concentration, a significant increase in the risk of developing GH was found in a separate study (OR=1.72, 95% CI=1.12 – 2.63) [10]. In addition, a study that examined both $PM_{2.5}$ and PM_{10} found an increased risk of GH for each IQR increase in each size fraction of PM [11]. Finally, in one study the risk of GH disorders increased with each IQR increase in $PM_{2.5}$ in the second trimester [53]. Although no inverse relationships were observed between exposures to PM and GH in previous studies, some results are conflicting, which stresses the importance of developing better exposure metrics in this field. For example, using comparable methods for measuring air pollution concentrations as well as assigning those estimates to pregnant women would

aid in understanding why results are conflicting apart from method of exposure assessment. Unfortunately, no previous research has examined benzene and toluene with respect to GH, again highlighting the great heterogeneity that exists in this research.

Although data on CO was not available for the current study, a Canadian study did find an inverse dose-response relationship between maternal exposure to CO and pre-eclampsia [54]. LUR-modelled estimates were not available for their study, but the perinatal data was linked to the estimates of CO temporally over the entire pregnancy for each mother included. The authors stated that the protective effect of CO was similar to the protective effect exposure to CO seems to have on fetal growth restriction in pre-eclamptic women [64]. Furthermore, a study out of Sweden concluded that it is the tobacco combustion products (such as CO) that account for the protective effect we see with smoking and pre-eclampsia, rather than nicotine [27]. However, it is important to note the difference between exposures to CO through tobacco smoke and though ambient pollution, as studies examining different sources of the same pollutant may not necessarily be comparable.

The pollutants examined in the current study could be highly correlated with CO, as has been observed in past studies [40,41,63], which could account for the inverse relationships. In addition, these pollutants may have the same biological mechanism as CO when it comes to the development of GH. This mechanism is not completely understood but it likely involves CO reducing the release of fms-like tyrosine kinase from endothelial cells [65]. These kinases reduce free circulating levels of vascular endothelial growth factor as well as placental growth factor, which can lead to GH and pre-eclampsia [66]. Therefore, by reducing levels of fms-like tyrosine kinase, CO acts to increase levels of

both the placental and vascular endothelial growth factors, which in turn protect against GH and pre-eclampsia. Nictotine, on the other hand, does not influence the production of these proteins [67], further supporting the hypothesis that it is CO, not nicotine driving the protective effect of smoking on GH.

A Danish study also found an inverse relationship between NOx and blood pressure in adults aged 50-64 years. Although they did not focus on GH, the results are still notable given the findings of the current study. They measured levels of NOx five years prior to baseline up until follow-up using the Danish AirGIS modeling system. They found that long-term exposure to NOx was associated with a decrease in both diastolic and systolic blood pressure. An inverse relationship between long-term exposure to NOx and prevalence of hypertension was also found [68]. In terms of biological plausibility, a shift in sympathovagal balance could account for the inverse relationship due to an increase in vagal tone [69].

5.1 Comparison of Pollution Levels

Table 5-1 (p. 80) compares pollution levels in various cities where research on environmental exposures to air pollution and GH have been conducted. Values for studies conducted in New York City, New York and Vancouver, British Columbia and Copenhagen were also included in the table as they both used LUR-modelled estimates. Both of these studies examined the relationship between maternal exposure to air pollutants and birth outcomes [61,70]. In addition, good agreement was found between

temporally scaled LUR estimates and daily household levels of air pollution in a study out of Windsor, Ontario[62].

Levels of all relevant pollutants are the lowest in urban Halifax compared to other urban centres included in the table. The method used for generating the pollutant estimates is important when doing comparisons. Raw values taken from air monitoring stations may be very different from LUR-modelled estimates, as these estimates take into account many other components such as green space and proximity to major roadways that are not accounted for with raw values. Looking at specifically those studies that used LUR-modelled estimates of pollutants, it is still clear that the concentrations of air pollutants in Halifax are quite low.

5.2 Implications

The current study raises several questions and concerns for future research on this topic. Research examining exposure to air pollutants and GH, as well as most health outcomes is often carried out in large urban centres where industry and traffic play big roles in the concentrations of air pollutants. These areas have much higher concentrations of air pollutants than Halifax, as is demonstrated by Table 5-1 (p.80). To the author's knowledge, this was the smallest urban centre in terms of population to be used as a study area to examine the association between exposure to air pollution and GH. Given that inverse relationships were found, conducting research on environmental exposures and health outcomes in various locations would be very valuable. Being able to compare the current study to other studies conducted in different areas would aid in ensuring the

results are valid and concurrent with results from areas of similar pollutant concentrations or city characteristics.

Conducting research only in areas with high levels of air pollution does not allow for the consideration of thresholds that may exist. For example, a positive association between maternal exposure to air pollutants and GH may only exist after a certain pollutant concentration level. By only conducting research in areas of high pollution concentration, a threshold value would most likely be overlooked. It is important to recognize that the highest quartile of exposure in one location may be the lowest quartile of exposure for another location. This is especially relevant for policy makers, as they should be looking at actual pollutant concentration levels rather than groupings, such as quartiles, in order to make informed decisions for multiple locations.

As evidenced by the literature review in Chapter 2, exposure assessment can be completed in various ways. Although LUR modeling has been shown to be one of the best methods for assigning pollutant estimates spatially [59,71], arguments are made for several other methods. In addition, some studies take into account both spatiality and temporality, while others only take into account one or the other. The current study took both temporality and spatiality into account for NO_2 and $PM_{2.5}$. Again, there are various ways to scale spatial estimates for temporality and the current study used the chosen method based on its previous validity when used in population-based birth cohort studies. For exposures during pregnancy especially, including a temporal component allows one to extrapolate the pollutant measures for the time period of the pregnancy.

There are strengths and limitations to every method for assigning exposure. Air monitoring technology is constantly evolving and superior exposure metrics are being developed. Improved methods for measuring exposure to air pollutants when examining perinatal outcomes would be very advantageous in this field of research. As more research is conducted in this field, it will also be important to establish better methods for temporally adjusting spatial estimates.

The biological mechanism behind the association between maternal exposure to air pollutants and GH is not well understood. A better understanding of this mechanism could potentially allow researchers to focus on specific pollutants that may be more plausibly linked to the GH outcome. Understanding this mechanism could also help explain why an inverse relationship between exposure to air pollutants and GH is observed in areas of low pollution concentration, whereas a positive association is found in areas of higher pollution concentration.

Finally, it is possible that the observed inverse association between exposure to air pollution and GH is the result of a combination of methodological limitations. For example, the association could be due to a confounding factor that was not measured, coupled with a weak signal. The weak signal could be due to low ambient levels of air pollutants in Halifax or misclassification due to model error or an error in assigning correct values to women based on limited residential information. However, it is important to note that any misclassification is likely to be non-differential, and would bias the estimates toward the null. Therefore, misclassification of exposure does not likely explain the observed inverse relationships.

5.3 Strengths and Limitations

There are several strengths of the current study. With the use of the NSAPD and exposure databases, this was a population-based cohort study including all deliveries in urban Halifax between 2008 and 2012. The NSAPD is a rich data source, which includes important variables to consider when examining GH as an outcome. These variables include socio-demographic factors, prenatal, delivery-related and postpartum risk factors known to be associated with GH. The NSAPD has very few missing data points and is well maintained by the RCP.

In terms of the exposure, both spatiality and temporality were accounted for in the pollutant estimates. This is especially important for studies involving exposure during pregnancy to ensure that the estimates coincide with the gestational period of interest (first 20 weeks of gestation in this case). The use of LUR models provided more accurate estimations of pollution levels for each mother based on residence. The NAPS accounted for temporal differences in exposure according to each mother's first 20 weeks of gestation. Most studies examine a select few pollutants when examining health-related outcomes. The current study produced results for associations between seven different pollutants and GH.

Acknowledgement of this study's limitations is also important. The NSAPD does not include information on where the mother lived for the duration of her pregnancy. Therefore, it was assumed that she resided in the same residential postal code for the duration of her pregnancy as she did upon admittance to the IWK for delivery. A study completed on residents of Nova Scotia and Eastern Ontario, Canada showed that 12% of

women moved during their pregnancy[72]. For those who did move during their pregnancy, issues of validity surrounding exposure assignment could be present. Additionally, no occupational information is included in the NSAPD. If the mother had been working during her pregnancy in an area with air pollution levels significantly different from those in her area of residence, the exposure data could have been unrepresentative of her actual exposure. In addition, the date of GH diagnosis is not available for the mothers included in the study. If these dates were available, exposure to air pollution could be examined for only the time period during pregnancy before diagnosis. This would give a better temporal estimate of air pollution exposure.

Although the NSAPD does include a great deal of information on women delivering in Nova Scotia, information was not available for individual socioeconomic status. Census data was linked to the NSAPD to produce a neighbourhood income variable. However, this measure cannot be interpreted as an individual-level variable [73]. Using neighbourhood deprivation scores rather than neighbourhood income may be a better alternative for future studies as living in areas with higher levels of deprivation has been shown to be associated with GH [11].

Over 19% of the data on pre-pregnancy weight was missing, which lowered the sample sizes for the logistic regressions as pre-pregnancy weight was included as a confounding variable. In addition, sample sizes for NAPS scaled LUR-modelled estimates of NO_2 and $PM_{2.5}$ were much smaller than originally anticipated due to missing values in the NAPS database. As a result, adequate power to make conclusions with regard to analyses using these scaled estimates was not always achieved.

5.4 Future Directions

By linking the variables in the Atlee database pertaining to GH disorders and other birth outcomes to the data on air pollution data, other research questions that have not yet been explored can be investigated as potential hypotheses for future studies. For example, examining the association between maternal exposure to air pollution during pregnancy and low birth weight, small for gestational age and pre-term birth would be of interest given the significant associations that have been found in past research [74,75].

In order to validate the pollutant estimates assigned to each mother in the NSAPD for future studies, it would be interesting to have a subset of mothers wear personal air monitoring devices as well as global positioning system (GPS) data logging devices on their person throughout their pregnancy. The estimates measured from the personal monitor could then be compared to the estimates produced by the method outlined in this study. A study out of Vancouver supplied 62 pregnant women with personal air monitors that measured levels of NO, NO_2 and $PM_{2.5}$. The estimates measured from the personal monitors were compared to temporally adjusted LUR estimates (much like the estimates used in the current study). They found moderate agreement between the two methods and supported the use of LUR modelling in epidemiological studies [76].

Given that the biological mechanism behind the apparent association between maternal exposure to air pollution and GH is unknown, it cannot be assumed that dividing the pollutant estimates into quartiles is the most plausible method. It has been suggested that break points be used as more meaningful parameters [77]. A maximum

likelihood approach is used to find the break points, which are said to be the true parameters of the model [78].

Finally, in the current study pollutants were examined individually. However, pregnant women are exposed to a mix of various pollutants at one time and therefore it is impossible to single out any individual pollutant and conclude that the association observed is due to that pollutant alone. Grouping pollutants based on their source is becoming increasing popular in the literature due to this limitation. For example, grouping together NOx and CO as 'traffic-related air pollution' enables the researcher to examine the relationship between exposure to a variety of pollutants and the outcome of interest. Groupings of pollutants should be used for future analyses in urban Halifax.

Table 5-1 Comparison of pollutant levels in urban centres worldwide

Location	First Author (year)	Method	Mean NO_2 (ppb)	Mean $PM_{2.5}$ ($\mu g/m^3$)	Mean PM_{10} ($\mu g/m^3$)
Halifax	Poirier (2014)	LUR	5.0	1.1	3.3
New York City	Ross (2013)	LUR	27.2	11.3	
Los Angeles	Mobasher (2013)	Raw data	29.5	17.5	34.8
Perth, Australia	Pereira (2013)	LUR	23.0		
Pittsburg	Lee (2012)	Kriging	18.7	16.5	26.1
Copenhagen, Denmark	Sørensen (2012)		8.3		
Rotterdam, Netherlands	van den Hooven (2011)	GIS	21.0		30.3
North Carolina	Vinikoor-Imler (2011)	Raw data		14.5	21.9
Vancouver	Brauer (2008)	LUR	16.8	4.0	

Abbreviations: $\mu g/m^3$ – micrograms per meter cubed; GIS – geographic information systems; LUR – land-use regression; NO_2 – nitrogen dioxide; PM – particulate matter; ppb – parts per billion

Data Sources: Ross (2013) [61]; Vinikoor-Imler (2011) [11]; Mobasher (2013) [52]; Lee (2012) [9]; Brauer (2008) [70]; Pereira (2013) [13]; van den Hooven (2011) [10]

Chapter 6 CONCLUSIONS

This study used a population-based birth cohort database for the outcome of interest (GH) and potential covariates. Two sources of exposure estimates were used. Spatial LUR-modelled estimates of NO_2, SO_2, PM_1, $PM_{2.5,}$ $PM._{10}$, benzene and toluene were based on the mother's residence. These estimated were adjusted for temporality using NAPS for NO_2 and $PM_{2.5}$.

Compared to other study areas in the literature, the pollutant concentrations in urban Halifax were very low. The prevalence of GH in the study sample was 7.6%, which is slightly higher than what has been found elsewhere in Canada [1,2]. Inverse relationships between exposure to the highest pollutant quartile and GH were found for all individual pollutants. Adjustment for pre-pregnancy weight, maternal age, parity and smoking status caused negligible change in the ORs. The inverse relationships remained after stratification by several known risk factors for GH, demonstrating the robustness of these results.

The results of this study stress the importance of conducting research in areas of both high and low air pollution concentration. Much of the existing literature on this topic has shown a positive association between exposure to air pollutants and GH. However, these studies were all conducted in areas with much higher pollutant concentrations. Given the conflicting results, future research should focus on finding a threshold for pollutant concentration at which point the association may start to change direction.

In addition, establishing better temporo-spatial modelling techniques for air pollution exposure assignment when investigating health outcomes would be valuable. Comparing results between studies proves to be difficult when very different methods are used to assign pollutant estimates to each participant. Determining what the best methods are for pollution estimate assignment in perinatal epidemiology should be a priority.

Continued research on the association between maternal exposure to air pollution and GH is crucial to understanding this relationship. With a better understanding of the biological mechanism behind the apparent association, investigators will be able to focus on certain pollutants or groups of pollutants and windows of vulnerability. Rapidly evolving technology for air pollution measurement may help reduce exposure assignment misclassification for research on air pollution and health outcomes.

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