EFFECT OF AMBIENT AIR POLLUTION ON DEVELOPMENT OF CHILDHOOD ASTHMA

by

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ABSTRACT

Asthma prevalence is increasing worldwide and the causes of this increase are largely unknown. There is increasing recognition of the importance of early environmental exposures in childhood asthma development. Outdoor air pollution has been shown to trigger asthma symptoms but its role in incident disease remains controversial. To address these questions, I investigated the effect of in utero and first year of life exposure to ambient air pollution on risk of asthma diagnosis in a nested case-control study.

All children born in Southwestern British Columbia in 1999 and 2000 (N=37,401) were assessed for incidence of asthma diagnosis at age 3 - 4 years using hospitalization and primary physician records. Exposure to ambient air pollution was estimated for the gestational period and first year of life using high-resolution pollution surfaces derived from government monitoring station data as well as land use regression models adjusted for temporal variation. Conditional logistic regression analyses were used to estimate effects of CO, NO, NO_2, PM_{10}, $PM_{2.5}$, O_3, SO_2, black carbon, wood smoke and proximity to roads and point sources on asthma diagnosis.

Elevated risks of asthma diagnosis were observed with increased early life exposure to CO, NO, NO_2, PM_{10}, SO_2, black carbon and proximity to point sources. Effects were generally larger for first year exposures than in utero exposures, and larger for girls than boys.

The results indicate that early life exposure to air pollution is associated with increased risk of asthma diagnosis in early childhood. Although the effect sizes are small, air pollution exposure in urban areas is ubiquitous so may have significant effects at the population level. These results should be confirmed when children are older and asthma diagnosis is more robust.

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ABBREVIATIONS

$\mu g/m^3$	micrograms per cubic meter of air
95% CI	95 percent confidence interval
BC	British Columbia
CO	carbon monoxide
DA	(census) dissemination area
ETS	environmental tobacco smoke
GIS	geographic information system
ICD-9	International Classification of Diseases, 9^{th} Edition
IDW	inverse distance weighted
LUR	land use regression
NO	nitric oxide
NO_2	nitrogen dioxide
O_3	Ozone
OR	Odds ratio
PM_{10}	particulate matter smaller than 10 micrometers in aerodynamic diameter
$PM_{2.5}$	particulate matter smaller than 2.5 micrometers in aerodynamic diameter
SO_2	sulphur dioxide

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CO-AUTHORSHIP STATEMENT

The work presented in this thesis was conducted and disseminated by the Master's candidate. The study presents a unique contribution to the larger Border Air Quality Study. The candidate developed the specific study design, statistical analysis, and health outcome examined with the assistance of the thesis committee. Previous research by the Border Air Quality Study team established the birth cohort and the exposure assessment data used in the study.

The candidate prepared the manuscript draft and co-authors (Paul Demers, Michael Brauer, Catherine Karr, Mieke Koehoorn, Cornal Lencar and Lillian Tamburic) provided critical evaluations. The manuscript was submitted for publication and underwent further peer-review. The manuscript as it appears in the thesis (Chapter 2) is the result of comments from the co-authors as well as anonymous peer-review.

1. BACKGROUND

1.1 Epidemiology of Asthma

1.1.1 Prevalence and Trends

Asthma is a chronic disease that is estimated to affect over 150 million children and adults worldwide (WHO 2003). Paediatric asthma rates generally range from 5-15% (WHO 2003), however, rates vary substantially around the world, in some cases with more than 20-fold differences between countries. The International Study of Asthma and Allergies in Childhood (ISAAC) study measured asthma symptoms in 56 countries and found that prevalence varied from a low of 2% in Indonesia to a high of approximately 35% in the UK (Beasley et al. 1998). Australia, UK, and New Zealand consistently show the highest asthma prevalence while Eastern European and developing countries have low prevalence (Asher et al. 2006; Beasley et al. 1998). The prevalence of ever-diagnosed asthma among Canadian children aged 4-11 is 15.6%; it is the most common chronic disease in Canadian children (Public Health Agency of Canada 2007). In general, worldwide studies of asthma prevalence have determined that prevalence is higher in Western countries than in developing countries and as countries become more Westernized or areas become more urban, asthma rates increase (Beasley et al. 2000).

Asthma prevalence rates in children have been rising in recent decades worldwide (Burr et al. 1989; CDC 1998; Hartert and Peebles 2000; Manfreda et al. 1993; Yunginger et al. 1992). The increase is estimated to be 5-6% annually (Hartert and Peebles 2000). In

Canada, asthma prevalence rates showed dramatic increases during the 1980's and have since tapered (Manfreda et al. 1993; Public Health Agency of Canada 2007). Changing diagnostic patterns or medical care may contribute to the increase in the estimated prevalence but are unlikely to account for the whole of the increase (Burr et al. 1989; Manfreda et al. 1993). Due to the rapid nature of the increase, genetic factors are also unlikely to be a main contributor. Therefore environmental factors have been implicated in playing an important role (von Mutius 2000). Despite research efforts, however, the specific environmental causes of the "asthma epidemic" are still largely unknown (Martinez 2001).

1.1.2 Clinical Features and Diagnosis of Asthma

Characteristic symptoms of asthma include shortness of breath, chest tightness, wheezing, coughing, and sputum production, the severity of which can vary greatly by individual and within an individual over time. Exercise, exposure to allergens, indoor and outdoor air pollution including environmental tobacco smoke, and viral infections are common triggers for asthma symptoms. These promote airway inflammation, hyperresponsiveness and bronchospasm, which serve to acutely narrow the airways and incite mild to severe attacks (Boulet et al. 1999; NHLBI 2007). Chronic inflammation and its effects on airway structure are believed to be the underlying mechanism behind development of persistent asthma. Controlling this inflammation is a major goal of asthma treatment (Boulet et al. 1999; NHLBI 2007; Warner 2001). Asthma is a chronic disease and no medical cure or intervention strategy to prevent its initial development has been identified. However, symptoms can be controlled to reduce impairment. Optimal management involves identification and control of triggering agents as well as

appropriate medication management through ongoing assessment and monitoring of disease status (Becker et al. 2005; Boulet et al. 1999; NHLBI 2007).

The primary diagnostic test for asthma is spirometry, which can demonstrate the characteristic airflow obstruction of asthmatic airways. Methacholine testing can be helpful when asthma is suspected but spirometry is normal or nearly normal, since this provides diagnosis of airway hyperresponsiveness, a key feature of asthma. Peak expiratory flow is less useful in diagnosis than patient monitoring of disease status over time, given variability in monitors, reference values, and patient technique (Boulet et al. 1999; NHLBI 2007).

Asthma symptoms commonly begin in early childhood, prior to age 3 years (NHLBI 2007). Unfortunately, children less than 5 years of age are generally unable to perform spirometry, increasing the challenge of diagnosing asthma is this age group. In practice, diagnosis of asthma in young children relies on medical history including symptom history, child and family history of atopy, as well as physical examination (Becker et al. 2005; Boulet et al. 1999; NHLBI 2007). However, respiratory symptoms common in asthma (e.g. wheeze, cough) are common in infancy and may reflect other respiratory conditions such as acute respiratory infections rather than chronic asthma (Dodge et al. 1996; Martinez 1999; Seear and Wensley 1997). Family history of asthma is the most consistent predictor of persistent asthma in an infant (WHO 2003). Persistent asthma is also more likely if infants experience severe or recurrent wheezing (especially after the age of one), chronic cough, and wheezing not associated with a viral infection (Becker et al. 2005; Boulet et al. 1999; NHLBI 2007). Nonetheless, even in the presence of family history and/or characteristic symptoms the diagnosis of asthma is uncertain in

early childhood (Kurukulaaratchy et al. 2003; Lau et al. 2003; Martinez et al. 1995; Seear and Wensley 1997).

1.1.3 Childhood Wheezing Phenotypes

Wheezing, a common pediatric asthma symptom, is extremely common in infancy. However, for most infants, this does not represent chronic disease, as the majority of infants will cease to have symptoms by three years of age. Three distinct phenotypes of wheezing illness in young children have been described based on longitudinal cohort studies: transient infant wheezing, nonatopic wheezing of the toddler and early school years, and atopic wheezing/asthma (Stein et al. 1997; Stein and Martinez 2004; Taussig et al. 2003).

The landmark longitudinal study, the Tucson Children's Respiratory Study, reported that 80% of children wheezing in the first year of life are transient wheezers, 60% in the second year, and 30-40% in the third year (Taussig et al. 2003). Transient wheezers did not have an increased family history of asthma nor did they exhibit markers of allergy. Although these children were not at increased risk of wheeze in adolescence, their airways remained smaller than children who never wheezed in childhood, suggesting they may be at increased risk of developing chronic obstructive pulmonary disease in adulthood.

The non-atopic wheezers were represented by a group of children who continue to wheeze past the age of three and often had a history of lower respiratory tract infection in early life. These children most often developed acute airway obstruction in response to infection, leading to an increased risk of wheeze that gradually decreased with age. This

group was no more likely than other children to be atopic. Lung function in this group, measured at age six and eleven, was lower than in those who did not have a lower respiratory infection in early life (Taussig et al. 2003).

The minority of the children who wheeze in early childhood go on to develop persistent, atopic asthma. Cohort studies have shown that approximately 40% of children with persistent wheezing at three to four years of age still wheeze at school-age (Kurukulaaratchy et al. 2003; Taussig et al. 2003). These children exhibit atopy, bronchial responsiveness, and decreased lung function. Most children with atopic asthma will develop symptoms and sensitization to aeroallergens by age six (Taussig et al. 2003). The age of onset and severity of asthma in childhood are predictors of severity in later life (Kjellman and Hesselmar 1994; NHLBI 2007; Taussig et al. 2003).

As these wheezing phenotypes have different risk factors and different prognoses, distinguishing them is an important goal for both clinical treatment and epidemiologic studies of childhood asthma. Various approaches have been developed to identify chronic asthma from among infants with wheeze, including a clinical index that is based on frequency of wheezing during the first three years of life, parental history of asthma or eczema and other clinical features such as eosinophilia, wheezing without colds, and allergic rhinitis (Castro-Rodriguez et al. 2000). Three-quarters of children with a positive clinical index at three years had asthma in the school years, while over 95% of children with a negative index never presented with asthma in the school years. Therefore, relatively easily assessed clinical parameters can improve the diagnosis of asthma in early childhood, but uncertainty remains and no widely accepted diagnostic criteria have been adapted to date (Becker et al. 2005; Boulet et al. 1999; NHLBI 2007). The inability to

differentiate among early childhood wheezing phenotypes to identify asthma in early life remains an important limitation in all early childhood studies of asthma.

1.1.4 Asthma Development

Genetic predisposition plays a significant role in asthma development. Having a parent or sibling with asthma doubles an individual's risk of developing the disease (Arshad et al. 2005; Dik et al. 2004; Haby et al. 2001; Ronmark et al. 2002; WHO 2003). Many candidate genes for asthma have been identified and are reviewed by Ober and Hoffjan (2006).

Genetic risk alone does not account for the observed patterns of asthma incidence. As described previously, there are large geographic differences in asthma prevalence, with rates in many industrialized countries far higher than in developing countries. Dramatic differences in prevalence persist even between genetically similar groups (Beasley et al. 1998). Asthma incidence has also been rising steadily in recent decades, especially in developed nations (Beasley et al. 2000). Therefore, environmental factors are believed to contribute considerably to asthma development (Beasley et al. 2000; Hartert and Peebles 2000; von Mutius 2001).

Current understanding of asthma development is that disease onset occurs through an interaction between genetic susceptibility and appropriate environmental exposures (Becker and Chan-Yeung 2002; Martinez 2001; Miller and Ho 2008). Gene-environment interactions in disease development could occur through a variety of patterns. For example, it may be necessary for both genetic susceptibility and environmental exposure to be present for disease to occur, or specific genetic polymorphisms may increase

susceptibility to an environmental exposure (Martinez 2001). Many gene-environment interactions have been identified in asthma development (Hoffjan et al. 2005; Kabesch et al. 2004; London 2007).

One pathway through which the environment is thought to interact with genetic disease risk is through epigenetic modification (Miller and Ho 2008; Ober and Thompson 2005). Epigenetic modification refers to changes in DNA that do not involve the sequence of base pairs, but can modify the expression of genes. Examples of epigenetic processes include histone modifications and methylation of DNA. Epigenetic modifications may be inherited or occur after conception though various environmental exposures. Since the majority of epigenetic modifications occur in early life (in utero and shortly after birth), exposures occurring in this period have the potential to significantly influence later disease risk (Miller and Ho 2008). Epigenetic modifications have been observed to influence asthma onset, severity, and remission patterns (reviewed by Miller and Ho 2008).

Environmental Risk Factors

No single environmental factor has been identified that would account for the distribution of asthma prevalence in all populations. It is likely that multiple environmental factors are involved, both protective and detrimental, with a different combination of factors affecting different populations (Asher et al. 2006). Various lifestyle factors of populations and individual families appear to influence asthma risk, including socioeconomic status (Erzen et al. 1997), living in an urban setting (Dik et al. 2004), exposure to allergens (Jaakkola et al. 2005; Sears et al. 2003), number of siblings (Infante-Rivard et al. 2001; Lewis et al. 1995; Lewis and Britton 1998; Wickens et al.

1999), day care attendance (Haby et al. 2001; Infante-Rivard et al. 2001; Wickens et al. 1999), early childhood infections (Arshad et al. 2005; Dik et al. 2004; Haby et al. 2001; Ronmark et al. 2002), breastfeeding (Dell and To 2001; Gdalevich et al. 2001; Haby et al. 2001; Lewis et al. 1995; Oddy et al. 2000), and living on a farm (Braun-Fahrlander 2001; Riedler et al. 2001; Von Ehrenstein et al. 2000). Examination of these lifestyle risk factors, especially the protective effects of day care attendance and some childhood infections, has led to the formulation of the hygiene hypothesis. It postulates that the rise in allergic diseases and asthma is due to increasingly hygienic environments that do not provide sufficient microbial stimuli to allow for the normal maturation of the immune system and development of appropriate immunologic responses (von Mutius 2001). This hypothesis remains controversial; however, it is consistent with many worldwide trends for asthma prevalence.

Low birth weight and premature birth have also been consistently associated with increased asthma risk (Dik et al. 2004; Lewis et al. 1995; Seidman et al. 1991; Svanes et al. 1998). Of the various air pollutants studied, including outdoor air pollution, only environmental tobacco smoke has been consistently associated with increased asthma risk (Gilliland et al. 2001; Haberg et al. 2007; Jaakkola and Gissler 2004; Lodrup Carlsen et al. 1997; Stick et al. 1996).

1.1.5 Sensitive Periods of Exposure

Environmental exposures that occur in early-life are the most influential for later asthma risk (Peden 2000). Children are more vulnerable to environmental exposures for many reasons. First, they are simply exposed to higher doses: children breathe more air and ingest more food and water than adults do relative to their body weight. They are

also more likely to spend time outside exercising and breathe through the mouth, which increase intake of air pollutants. Second, pollutants have a greater effect on the rapidly developing organ systems of foetuses and children. Dietert and colleagues (2000) discussed the unique vulnerabilities of the foetus and infant in the Immune and Respiratory Systems Group Summary of the Workshop to Identify Critical Windows of Exposure for Children's Health. They highlight that children cannot be thought of as small adults with respect to pollutant exposures because they are more susceptible to health effects. Both the respiratory and immune systems undergo rapid development during the intrauterine period and infancy. Interference with normal development at these crucial stages may therefore have long lasting consequences. Immaturity of metabolic pathways also means that foetuses and young children are unable to clear toxicants as effectively (Dietert et al. 2000). Finally, most epigenetic modifications occur in utero and shortly after birth, potentially affecting gene expression and disease susceptibility (Miller and Ho 2008).

Children's unique vulnerability to pollutants has been observed in epidemiological studies of asthma. For example, a case-control study nested within the population-based California Children's Health Study examined exposures to wood and oil smoke, soot, cockroach, herbicides, pesticides, farm animals and dust, and infections. They found that exposures occurring in the first year of life had a significant effect on asthma risk but exposures occurring after the first year of life did not (Salam et al. 2004). Similarly, environmental tobacco smoke exposure during early-life affects asthma risk (Arshad et al. 2005; Haberg et al. 2007; Wang and Pinkerton 2008), while exposure in

later life is associated with asthma exacerbation but not development of new asthma (Gilliland et al. 2001).

1.2 Administrative Data and Asthma

The British Columbia Linked Health Database (BCLHD) is one of the most comprehensive health databases in the world. It links various population-based databases in British Columbia, including Medical Services Plan records, hospital separations records, and births and deaths records (Chamberlayne et al. 1998; CHSPR 2008). The Medical Services Plan records include information on nearly every outpatient physician visit and medical procedure billed to the provincial medical plan. Enrolment in the provincial plan is mandatory for residents of the province (BC Ministry of Health 2007) and therefore it captures data at a population level. Physician billing claims to the medical plan require an ICD (International Classification of Diseases) code indicating the primary reason for the encounter as well as administrative details, including physician, date, location, and patient's address. Personal Health Numbers that are unique to individuals can be used to link this data to other provincial databases, including the Perinatal Database. The Perinatal Database collects detailed information on every birth in the province, including maternal and birth characteristics.

Administrative databases such as these offer great promise in epidemiological research because they provide a comprehensive, longitudinal and population-based record of health information. This eliminates issues of recall and selection bias inherent in survey-based research. A comparison of longitudinal studies showed that administrative data provide consistently high rates of follow-up that are not always achievable with primary data collection, which is subject to issues of non-response (Roos et al. 1987).

Therefore, administrative data offers an efficient and economical means to examine disease incidence and trends over long periods.

The major caveat with using administrative data is that it is not collected for clinical health outcome assessment. While physician-billing records contain a diagnostic code to indicate the primary diagnosis, they do not contain any clinical details, such as measures of lung function or blood pressure. Unusual symptoms or a lack of clear diagnostic criteria may lead to recording of unreliable diagnoses, or the physician may simply record an incorrect code. These issues call into question the validity of using administrative data for identifying disease cases.

Several studies in Canada have evaluated the use of administrative records to identify asthma cases for health research. To et al. examined asthma diagnoses in the Ontario billing databases for children aged 0-18 years. They found that the diagnosis entered by the primary care physician in a patient's chart was very reliably recorded in the administrative database, with 99% overall agreement (To et al. 2006). The recorded diagnoses were also validated against chart review by an expert panel that was blind to the physicians' recorded diagnoses. These independent assessments of charts agreed well with the administrative data; overall sensitivity was found to be 91% and specificity 83%. For young children (aged 0-2), the sensitivity was lower at 75% but rose to 96% for the 3-5 year old group. Specificity remained consistently at or above 83%. Based on this data, the authors suggest that diagnostic uncertainty in childhood asthma accounts for a significantly greater portion of false positive cases than incorrect coding.

The relative accuracy of asthma coding was also demonstrated by Blais and collegues (2006), who examined the validity of Quebec's administrative databases. They

verified administrative asthma diagnoses against chart recorded asthma diagnoses in individuals aged 16-80. They found that the databases were a valid measure of asthma. These studies indicate that physicians do record asthma diagnoses reliably in billing records.

A study in Manitoba found that the algorithm used to identify asthma cases from administrative data has an effect on the validity of findings as compared with self report (Lix et al. 2006). They considered various algorithms combining hospital separations data, outpatient physician visits, and prescription data and validated them against survey data on asthma. For children aged 12-18, specificity remained high for all algorithms (92-97%) but sensitivity varied significantly (from 16-87%) depending mainly on the number of years of data examined. As the number of years of data increased the sensitivity of the measure increased. Three years of data on outpatient and hospital visits yielded sensitivity of approximately 50% and specificity above 95%. The study did not examine younger children but it is reasonable to expect that young children may require fewer years of data to capture asthma diagnoses due to more frequent physician visits. These studies indicate that administrative databases, especially if available over several years, are a sensitive and specific measure of physician-diagnosed asthma. However, the inability to differentiate transient wheezing from persistent asthma in early age remains a significant source of uncertainty.

To at al. (2007) shed some light the ability of administrative data to predict asthma recurrence in children. They used the Ontario administrative database to identify children who were diagnosed with asthma prior to the age of six and tracked their asthma diagnoses until the age of 11. Asthma diagnosis was defined as a minimum of one

hospital diagnosis or two physician diagnoses prior to the age of six. Children who continued to have asthma diagnoses past the age of six were considered to be persistent asthma cases. They found that by age 12, half the children were in remission. Children with a hospital admission or more than four physician diagnoses prior to the age of six had a 2 to 3-fold risk of having recurrent asthma at age 12. Therefore, hospital admission and frequent physician visits in young age are signs of persistent asthma (To et al. 2007).

Kozyrskyj et al. also examined asthma recurrence using administrative data. Using Manitoba's administrative databases, they followed children with asthma or bronchitis diagnoses, as well as children with prescriptions for asthma medication. They found that children who had asthma diagnoses or prescriptions not limited to winter were three to six times more likely to have persistent asthma in the following years (Kozyrskyj et al. 2004). Children with diagnoses limited to winter were more likely to have chronic bronchitis (Kozyrskyj et al. 2003). Although asthma diagnosis will always be uncertain in young age, it appears that administrative data can help identify persistent asthma.

1.3 Outdoor Air Pollution

1.3.1 Major Outdoor Air Pollutants

The composition of outdoor air pollution depends on many factors including emission sources, climatic conditions, and land patterns. The major monitored pollutants are ozone, carbon monoxide, sulphur dioxide, nitrogen oxides, and particulate matter (Metro Vancouver 2006; WHO 2006). In the past, lead was also of concern due to its effects on children's neurobehavioral development but airborne levels in most developed countries have dropped dramatically over the last 25 years with the removal of leaded gasoline. With coal no longer a major energy source within urban centres and restrictions

on sulphur content in fuel, sulphur dioxide is also of diminishing concern in many developed, urban areas. Instead, traffic-related emissions are now the main threat to air quality in Western cities (WHO 2006), including the Lower Fraser Valley (Metro Vancouver 2006).

Carbon Monoxide

Carbon monoxide (CO) is the most common air pollutant, with measured levels often an order of magnitude larger than other common air pollutants. It is an odourless gas released by the incomplete combustion of carbon-containing fuels (Metro Vancouver 2006). The main emission source is vehicles. In the Lower Fraser Valley, an estimated 90% of CO is from the transportation sector (Metro Vancouver 2006), which is typical for urban areas (US EPA 2008). CO is widely distributed in urban areas but concentrations are higher near major roads during peak traffic. Concentrations can also become elevated with stagnant winds and temperature inversion, when pollutants are trapped under a layer of warm air and do not disperse. These conditions are more common during the colder months. Long-term averages of CO in the Lower Fraser Valley have shown a decreasing trend since the 1980's (Metro Vancouver 2006).

Ozone

Ozone (O_3) is a secondary pollutant that forms in the atmosphere through a reaction of nitrogen oxides and volatile organic compounds in the presence of sunlight. The level of O_3 depends on the presence of these precursors. Volatile organic compounds are released from vegetation, as well as from cars, trucks, and the evaporation of industrial solvents, while nitrogen oxides are released mainly from transportation sources (Metro Vancouver 2006). Due to the requirement for sunlight, O_3 levels have clear

temporal patterns: levels peak in the late afternoon and are highest in the warmer summer months. O_3 is widely distributed and levels are often higher in suburban areas than in high traffic areas (WHO 2006). In the Lower Fraser Valley, long-term average O_3 levels have shown a slight upward trend since the 1990's (Metro Vancouver 2006).

Particulate Matter

Particulate matter has no specific chemical composition but rather refers to a complex mixture of small particles. Health concerns and monitoring efforts are targeted at particles with an aerodynamic diameter less than 10 micrometers (referred to as PM_{10}) because they can be inhaled and deposited into the lungs. A subgroup of PM_{10} is fine particulate matter, or particles with an aerodynamic diameter less than 2.5 micrometers (referred to as $PM_{2.5}$), which are able to penetrate deep into the lungs (WHO 2006). Approximately half the PM_{10} emitted in the Lower Fraser Valley is composed of $PM_{2.5}$, which is typical for an urban area in North America (Metro Vancouver 2006). Primary sources of particulate matter include combustion by a variety of industrial and mobile sources and suspension of dust and soil particles into air by wind and traffic. Fine particulate matter can also be formed in the atmosphere as a secondary pollutant by reactions of sulphur dioxide, nitrogen oxides and ammonia. Particulate matter levels are higher near emission sources, such as roadways (WHO 2006). Long-term average levels of PM_{10} and $PM_{2.5}$ in the Lower Fraser Valley have remained largely unchanged since the 1990's (Metro Vancouver 2006).

Nitrogen Oxides

Nitrogen oxides are a group of reactive gases, of which nitrogen dioxide (NO_2) and nitric oxide (NO) are of greatest concern and commonly monitored. NO and NO_2 are

both released from the combustion of fossil fuels. NO is the primary pollutant released during combustion and it reacts with ozone in the atmosphere to form NO_2. The main source of nitrogen oxides in urban areas is motor vehicles; in the Lower Fraser Valley, they contribute approximately 87% of total nitrogen oxide emissions (Metro Vancouver 2006). As expected, both gases are highest near traffic sources. Long-term average NO_2 levels in cities worldwide vary from 15-60 $\mu g/m^3$ (WHO 2006). Levels in the Lower Fraser Valley range from approximately 15 to 40 $\mu g/m^3$, with the highest levels in downtown Vancouver. Long-term average levels of NO_2 in the Lower Fraser Valley have shown a decreasing trend since the late 1980's (Metro Vancouver 2006).

Sulphur Dioxide

Sulphur dioxide (SO_2) is a long-established public health concern. It accumulated to extremely high levels in smog episodes during the 1950s and 1960s when coal was heavily used in cities. Today, SO_2 levels in most developed countries are dramatically lower than in the past (WHO 2006). The major source of SO_2 remains the combustion of sulphur-containing fossil fuels, mainly heavy fuel oil and coal. Other fossil fuels, including petrol, diesel, and natural gas have relatively low sulphur content. Significant emitters include oil refineries, marine vessels and motor vehicles. Average levels ranging from 5 to upwards of 80 $\mu g/m^3$ have been measured in cities worldwide, but levels in Western cities typically range from 10 to 30 $\mu g/m^3$ (WHO 2006). Current levels of SO_2 in the Lower Fraser Valley are below 10 $\mu g/m^3$. Long-term averages have decreased since the late 1980's but have remained stable in recent years (Metro Vancouver 2006).

1.3.2 Assessing Exposure

Assessing long-term exposure to air pollution has always been a significant challenge. Early studies of the health effects of long-term air pollution exposure estimated pollution at the community level, thereby assigning each person in the community the same level of exposure based on monitoring data. For example, the Harvard Six Cities Study used community-level data on air pollution with individual-level data on risk factors to show an association between fine particulate matter and excess mortality (Dockery et al. 1993). However, within-community differences in air pollution are often as large as or larger than between-community differences (for example Zhu et al. 2002). Therefore, people living in the same community may have considerably different exposures and assigning them the same exposure leads to significant misclassification and bias to the null. Community differences other than air pollution levels may also confound associations. Therefore, research interest has shifted to assessing within-community differences in exposure.

One of the simplest approaches to examining within-community air pollution variation is proximity to emission sources, such as industrial facilities and roads. Commonly, subjects are classified as exposed or unexposed based on their location being within a specified distance of an emission source. Proximity information may be supplemented with information about the source, such as the type of road or the volume of traffic on the road (Jerrett et al. 2005). Levels of many pollutants, such as NO_2, are highly elevated near major roadways and remain above background levels approximately 300 m from highways (Zhu et al. 2002). Therefore, source proximity does approximate human exposure. However, proximity measures are still crude estimates of exposure as

they do not account for wind patterns or land topography and do not incorporate measured values of pollutants.

Another approach to estimating within-community differences in air pollution exposure is constructing continuous pollution maps from monitoring data recorded at a limited number of sites. The simplest method for creating a pollution map is assigning each point in the region the value recorded at the nearest monitor, thereby capturing some of the regional variation. However, this approach creates artificial boundaries between monitors. More sophisticated interpolation methods have been developed to create smooth, continuous surfaces from limited monitoring sites. Common interpolation methods include kriging and inverse distance weighting (Jerrett et al. 2005). Interpolation methods are effective at capturing temporal variation in air pollution levels by utilizing continuous monitoring data. However, they do not incorporate factors such as terrain or local emission factors that may be missed by sparse monitoring networks. Therefore, they do not capture spatial variability in pollutants very effectively (Marshall et al. 2008).

Land use regression (LUR) modelling improves the spatial resolution of pollution maps by taking into account land use and traffic characteristics. In LUR, a least-squares regression model is developed to predict measured pollutant values at a fixed number of locations using surrounding land use characteristics as predictors (Henderson et al. 2007; Jerrett et al. 2005). This regression equation is then used to predict pollutant levels at unmeasured locations and create a continuous map (for example Henderson et al. 2007). By developing pollution maps based on nearby emission characteristics, LUR is more focused on assessing exposure to specific emission sources, namely traffic, as compared with inverse distance weighting which measures general ambient pollution levels. In

many settings, this method has been shown to provide good predictions of pollutant levels. R-squared values have ranged from 0.56-0.87 for NO_2 (Briggs 2007; Henderson et al. 2007), 0.57-0.62 for NO (Henderson et al. 2007), 0.39-0.81 for filter absorbance (Brauer et al. 2003; Henderson et al. 2007) and 0.52-0.73 for PM2.5 (Brauer et al. 2003; Henderson et al. 2007). The method is superior to interpolation methods for capturing small-scale variation in pollutant levels; however, unlike interpolation methods, LUR modelling does not incorporate continuous monitored values of pollutants but estimates temporal variation from trends. This is an imperfect adjustment and results in exposure estimates that are less sensitive to temporal variation than methods that use continuous monitoring data (Marshall et al. 2008).

1.4 Asthma and Air Pollution

1.4.1 Asthma Exacerbation by Pollutants

There is strong evidence that exposure to elevated levels of outdoor air pollution exacerbates existing cases of asthma. Studies have found that medical visits for asthma increase following days with elevated air pollution levels. This has been observed in many settings, including Toronto, Ontario (Thurston et al. 1994), Saint John, New Brunswick (Stieb et al. 1996), Seattle, Washington (Norris et al. 1999; Schwartz et al. 1993), Santa Clara County, California (Lipsett et al. 1997) and European cities (Helsinki, Barcelona, Paris and London) (Sunyer et al. 1997). The benefits of air pollution reductions on asthma exacerbation were demonstrated during the Atlanta Summer Olympic games in 1996 when transportation restrictions reduced air pollution levels in the city and medical visits for asthma decreased significantly (Friedman et al. 2001).

Chronic exposure to high levels of air pollution is also associated with increased asthma symptoms. Asthmatic children who live in high pollution areas, such as near major roadways, have increased asthma severity, frequency of symptoms, use of medication and need for medical attention than asthmatic children living in less polluted areas (Dockery et al. 1989; Edwards et al. 1994; English et al. 1999; Gent et al. 2003; Holguin et al. 2007; Lipsett et al. 1997; McConnell et al. 1999). Residence in a high-pollution area has also been associated with decreased lung function (Holguin et al. 2007; McCreanor et al. 2007) and increased levels of inflammatory markers (Allen et al. 2008; McCreanor et al. 2007) among asthma patients.

1.4.2 Outdoor Air Pollution and Development of Asthma

The evidence of a causal relationship between air pollution exposure and asthma is far less conclusive than evidence for asthma exacerbation (Donaldson et al. 2000; Koenig 1999; von Mutius 2000; WHO 2003). Disease patterns suggest that traffic-related pollutants are more important than traditional air pollutants, such as SO_2, in asthma development. The 1990 reunification of East and West Germany offered an opportunity to compare genetically similar populations with different air pollution exposures. Asthma rates were found to be higher in West Germany where overall pollution was lower but traffic-related pollutants such as NO_2 were higher (von Mutius et al. 1994). Several studies have also found that asthma rates are higher in urban areas than in rural areas, suggesting the urban environment may contribute to asthma development (Andrew Aligne et al. 2000; Dik et al. 2004; Shima et al. 2003). Therefore, investigations of air pollution and asthma development have focused on urban air pollution.

Many cross-sectional studies have examined the association between air pollution levels and asthma prevalence with mixed results. Although many found that air pollution levels were associated with increased asthma prevalence (Carbajal-Arroyo et al. 2007; Guo et al. 1999; Nicolai et al. 2003; van Vliet et al. 1997; Wanga et al. 1999), others have found that pollution levels were only associated with asthma symptoms, not prevalence of the disease (Braun-Fahrlander et al. 1997; Ciccone et al. 1998; Hirsch et al. 1999; Wjst et al. 1993). These studies have focused on school-age children (ranging from 6-14 years) because asthma diagnosis is relatively robust at this age. However, a major limitation of the cross-sectional study design is approximating exposure at a single point in time and not taking into account historic exposures. Etiologically relevant exposures are likely to occur during early life (Dietert et al. 2000).

Studies that do attempt to measure historic levels have demonstrated the importance of early life exposures. Zmirou at al. (2004) retrospectively assessed exposure from birth and found that lifetime estimates of exposure to air pollution were not associated with asthma in children aged 4-14, but exposures during the first three years of life were a significant risk factor. Similarly, Studnicka et al. (1997) studied asthma prevalence among a group of seven-year olds who had resided in the same community for a minimum of two years and assessed historic nitrogen dioxide levels. They found that prevalence of asthma was associated with long-term NO_2 levels. Therefore, lack of exposure information for early-life may account for null findings in many cross-sectional studies.

Longitudinal studies have also been conducted to examine air pollution exposure and asthma development. Several studies of schoolchildren in Japanese communities

have followed respiratory symptoms and air pollution over several years. A three-year study of children (aged 9-10 at study entry) found that outdoor concentrations of NO_2 were associated with asthma incidence during follow-up, but not asthma prevalence at the start of the study (Shima and Adachi 2000). Similarly, a larger study of Japanese schoolchildren studied from age six until age 12 found that nitrogen dioxide levels were not associated with asthma prevalence but were associated with asthma incidence during follow-up (Shima et al. 2002). In the same cohort, residence near a major roadway was associated with both the prevalence and the incidence of asthma (Shima et al. 2003).

McConnell et al. (2002) investigated ozone and the incidence of asthma in school-aged children. Participating children had no history of asthma at the start of the study and ranged in age from nine to 16. They were followed for five years. Exposure to air pollution was estimated by community measures of ozone and the number of outdoor sports played by the children. The authors reasoned that a greater number of outdoor sports indicated a greater amount of time spent outside exercising and therefore greater exposure. The study found that children who played three or more sports in high-ozone communities had 3.3 times (95% CI: 1.9-5.8) increased risk for developing asthma compared with children playing no sports in the same community. Number of sports played had no effect on asthma risk in communities with low ozone.

These longitudinal studies provide important evidence implicating air pollution in asthma development. However, most asthma patients have symptoms by the age of six (NHLBI 2007; Yunginger et al. 1992). Studies of incident asthma among school-aged children therefore eliminate a significant proportion of asthma cases. These studies also

do not assess early life exposure, which may account for the finding that air pollution levels were not associated with asthma prevalence in many longitudinal studies.

Birth cohort studies are the most promising epidemiological study design for assessing the role of air pollution on asthma development. They allow for assessment of exposure during the most sensitive period of development and before asthma symptoms are present.

To date, few birth cohort studies have examined air pollution and asthma development. Gehring et al. (2002) studied a birth cohort of 1,756 infants from Munich, Germany for the first two years of life. GIS-based modelling was used to estimate exposure to NO_2, $PM_{2.5}$, and $PM_{2.5}$ absorbance (soot) based on home addresses at birth. Dry cough at night and cough without an infection were associated with air pollution exposures in the first and second years of life. For example, NO_2 was associated with an odds ratio of 1.36 (1.07-1.74) for dry cough at night in the first year of life. Effect sizes for other pollutants were similar in first year and attenuated in the second year. Other symptoms associated with asthma (including wheeze) were not associated with air pollution levels.

An extended analysis that included the Munich birth-cohort plus an additional 1821 infants from the larger Munich metropolitan area found similar results, though attenuated (Morgenstern et al. 2007). They estimated the effects of NO_2, $PM_{2.5}$, soot, and proximity to major roads on respiratory symptoms in the first and second years of life. Elevated odds ratios were observed for cough without infection, dry cough at night, asthmatic bronchitis, and sneezing/runny nose in first and second years although not all reached statistical significance.

Continued follow-up of the Munich birth-cohorts has confirmed a positive association between traffic-related air pollution and asthma (Morgenstern et al. 2008). The children have been followed up to the age of six years and assessed for asthma and asthmatic bronchitis by parental questionnaire. Exposures to NO_2, $PM_{2.5}$ and soot were estimated using land use regression modelling and overall traffic emission exposure was estimated by distance to major roads. All the exposures examined were associated with elevated risks of asthma diagnosis: $PM_{2.5}$ was associated with a 1.12 times increased risk (95% CI: 0.94-1.29) per 1 $\mu g/m^3$ increase, soot was associated with a 1.56 times increased risk (95% CI: 1.03 – 2.37) per $0.2x10^{-5}$/m increase, NO_2 was associated with a 1.04 times increased risk (95%: 0.67-1.39) per 6.4 $\mu g/m^3$ increase, and residence within 50 m of a major road was associated with a 1.66 times increased risk (95%: 1.01-2.59) of asthma diagnosis. Air pollution exposure was also associated with elevated risks of sensitization to outdoor allergens. These results provide some of the strongest evidence to date for a causal association between air pollution and allergic disease, including asthma.

Two other European birth-cohort studies followed children up to the age of four to examine asthma symptoms. Brauer et al. examined traffic-related air pollution and respiratory symptoms in a birth-cohort in the Netherlands (Brauer et al. 2007). A land use regression model was used to assign exposure to the birth addresses of approximately 4000 children. Exposure to higher levels of traffic-related air pollution was associated with increased risks of doctor diagnosed asthma: 1.3 times increased risk per 0.6×10^{-5}/m increase in level of soot, 1.20 times increased risk per 10 $\mu g/m^3$ increase in NO_2, and 1.20 increased risk per 3.3 $\mu g/m^3$ increase in $PM_{2.5}$.

Nordling et al. (2008) prospectively followed a Swedish cohort of children (n=4,089) from birth. Exposure to traffic related pollutants (nitrogen oxides and PM_{10}) was assessed through the first year of life using emission databases and dispersion modelling. Questionnaires tracked the respiratory symptoms of children over the four years and three-quarters of children underwent clinical examination at four years of age. A difference of 44 $\mu g/m^3$ in nitrogen oxide exposure in the first year of life was associated with a 1.6 times (95% CI: 1.09-2.36) increased risk of persistent wheezing (defined as beginning prior to the age of two and persisting past the age of three). Exposures in first year were also associated with increased sensitization to inhalant allergens and lower lung function at four.

These prospective birth-cohort studies indicate that early exposure to traffic-related air pollution is associated with small increases in risk of asthma symptoms and diagnosis, although inconsistency remains with respect to specific symptoms. Further follow-up is required to make associations with persistent asthma.

In utero Exposure

Both foetal and infant environmental exposures are believed to be important for later disease risks but to date no birth cohort studies have examined foetal exposures to air pollution and later asthma incidence. In contrast, environmental tobacco smoke exposure in utero has been consistently identified as a risk factor for asthma, independent of exposures occurring after birth (DiFranza et al. 2004; Gilliland et al. 2001; Haberg et al. 2007; Jaakkola and Gissler 2004; Lodrup Carlsen et al. 1997; Stick et al. 1996). In fact, intrauterine exposures have been found to increase asthma risk at least as much as post-birth exposures (Haberg et al. 2007), and in some cases more (Gilliland et al. 2001).

Like environmental tobacco smoke, outdoor air pollution is a complex mixture of potentially toxic gases and inhalable particles. Environmental tobacco smoke and air pollution have both been linked to intrauterine growth retardation and premature birth (Bobak 2000; Brauer et al. 2008; Horta et al. 1997; Kramer 1987; Slama et al. 2007). Therefore, it is clear that intrauterine exposure to air pollution warrants research attention.

1.5 Study Rationale

Asthma prevalence among children is rising worldwide and there is great interest in uncovering the causes of this increase. The role of outdoor air pollution in asthma development remains controversial. Several birth cohort studies in Europe suggest that air pollution is associated with inception of asthma symptoms, but results have not been consistent and often have not reached statistical significance, perhaps due to limited sample sizes. Therefore, further research of air pollution and asthma incidence is necessary. Furthermore, despite evidence that fetuses are uniquely vulnerable to environmental exposures, no study to date has examined the effect of intrauterine air pollution exposure and asthma development. This study seeks to address this important gap in knowledge by assessing air pollution exposure throughout intrauterine development as well as the first year after birth. Specifically, this study addresses the question: what is the effect of in utero and first year exposures to air pollution on the risk of asthma development in early childhood? This study is made possible by the rich data sources available in British Columbia. The BC Linked Health Database provides individual-level information on medical diagnoses and potential confounders for the population. This reduces issues of selection bias, loss to follow-up and small sample sizes

that are common problems in cohort studies. Exposure assessment data for the region are also powerful. The multidisciplinary Border Air Quality Study team in southwestern BC and northwestern Washington has utilized the air pollution monitoring data with additional monitoring campaigns and land use data to create detailed, fine-resolution pollution maps for the region. This significantly improves upon epidemiological studies that rely on a small number of central monitors to assign exposures.

Furthering our understanding of the role of air pollution on asthma development has important policy implications in British Columbia and elsewhere. The populations of cities are growing, thereby exposing increasing numbers of people to urban air pollutants. Evidence of the impact of air pollution on asthma can guide future development, including transportation and land use planning.

This study is a component of the Border Air Quality Study which investigates the health effects of air pollution in southwestern British Columbia and northwestern Washington.

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2. EFFECT OF EARLY LIFE EXPOSURE TO AIR POLLUTION ON DEVELOPMENT OF CHILDHOOD ASTHMA[1]

2.1 Introduction

Asthma is the most common chronic disease in childhood (WHO 2006). Its prevalence is high and has generally increased worldwide over the latter part of the 20th century (Asher et al. 2006; WHO 2006). While explanations for relatively rapid changes in prevalence are unknown, environmental factors, independently and jointly with genetic factors, are thought to be responsible. Exposure to outdoor air pollution is one suggested environmental risk factor for development of asthma (Institute of Medicine 2000; von Mutius 2000). While air pollution has been consistently shown to exacerbate existing asthma (English et al. 1999; Lipsett et al. 1997; McConnell et al. 1999; McConnell et al. 2006; Nicolai et al. 2003; Norris et al. 1999), there are limited investigations of asthma onset and air pollution.

Earlier studies that did not find air pollution to be associated with increased asthma incidence have generally relied on simple measures of traffic proximity and density to estimate exposure (Ciccone et al. 1998; English et al. 1999; Wjst et al. 1993). More recent studies have used modeling approaches that provide high-resolution estimates of neighborhood scale variations in air pollution. Several studies using this

[1] A version of this chapter will be submitted for publication. Clark NA, Demers PA, Karr C, Koehoorn M, Lencar C, Tamburic L, Brauer M. Effect of early life exposure to air pollution on asthma development.

approach have observed increases in asthma incidence or asthma symptoms for children exposed to higher levels of traffic-related air pollution (Brauer et al. 2002; Brauer et al. 2007; Gauderman et al. 2005; Gehring et al. 2002; McConnell et al. 2006; Zmirou et al. 2004). However, perhaps due to limited sample sizes, not all results have reached statistical significance (Zmirou et al. 2004).

Evidence for environmental tobacco smoke (ETS) has shown that pre- and post-birth exposures are independently associated with increased asthma incidence (Haberg et al. 2007). Although air pollution exposures prior to the age of 2 to 3 years appear to be most important for asthma development (McConnell et al. 2006; Zmirou et al. 2004) the effect of pre-birth, or in utero, exposure has not to our knowledge been examined.

Accordingly, our goal was to examine the effect of in utero and first year exposures to ambient air pollutants, estimated at the individual level, on the risk of asthma diagnosis at 3 to 4 years of age. Pollutant exposures investigated were: carbon monoxide (CO), nitrogen oxides (NO and NO_2), particulate matter (PM_{10} and $PM_{2.5}$), ozone (O_3), sulfur dioxide (SO_2), black carbon, wood smoke, and proximity to roads and point sources. This study was the first population-based birth-cohort study to explore the relationship between ambient air pollution exposure and asthma risk. It is also unique in assessing the effect of in utero air pollution exposure on development of childhood asthma.

2.2 Methods

2.2.1 Cohort Identification

The cohort comprised all 1999-2000 births in South-western British Columbia (BC) identified by linking administrative datasets from the BC Ministry of Health Services, the BC Vital Statistics Agency, and the BC Perinatal Database Registry. The study region includes the metropolitan centers of Victoria (population=325,000) and Vancouver (population=2,250,000) as well as the surrounding areas within the same airshed. To be eligible, children and their mothers registered for the provincial medical plan (registration is mandatory for residents so essentially everyone living in the province is registered) and resided in the study area for the duration of pregnancy and the first year of life. Children were excluded for low birth weight (<2500 g), preterm birth (<37 weeks gestation) or multiple births. These exclusions were necessary because they may confound the association between air pollution and asthma; low birth weight and gestational period have been found to be associated with both asthma and air pollution exposure in this cohort (Brauer et al. 2008), as well as in other studies (Bobak 2000; Dik et al. 2004; Salam et al. 2005; Wang and Pinkerton 2007). The effect of air pollution on infant bronchiolitis and middle ear infection have also been studied in this cohort (descriptive data in Koehoorn et al. 2008 and MacIntyre E. et al. 2008 (submitted)).

Residential histories were compiled using BC Ministry of Health data, which includes records for hospital discharges, primary care physician billing records, and medical plan registration. An individual's residential postal code was recorded at each contact with the health care system. After excluding invalid and non-residential postal codes (approximately 10%), individual residential histories were constructed for mothers

throughout pregnancy and children throughout the first year of life. Where a new postal code overlapped in dates with use of an old postal code, the move date was set as the first occurrence of the new postal code. Where no overlap occurred, the move date was set at the midpoint of the clinical encounters with two postal codes.

2.2.2 Outcome Measure

Asthma diagnoses were identified from children's primary care physician billing records and hospital discharge records from birth to the end of 2003 based on ICD-9 (International Classification of Diseases, 9th edition) code 493. Each contact with the health care system is recorded with a diagnostic code to indicate the primary reason for the contact. Asthma cases were defined as children with a minimum of two primary care physician diagnoses in a rolling 12-month period or a minimum of one hospital admission for asthma.

We also performed a sensitivity analysis to test the robustness of results to different administrative definitions of asthma. The analyses were repeated with 1) a more inclusive definition of asthma that included children with only one asthma diagnosis (in hospital or primary care setting) and 2) a more restrictive definition of asthma that included only children with at least three primary care asthma diagnoses or one hospital diagnosis.

2.2.3 Covariates

The Vital Statistics database provided the birth date and sex of each child. In addition, we collected individual-level information on birth weight and gestational length from the BC Vital Statistics Clinical Birth Data, as well as maternal smoking during

pregnancy, maternal age, number of siblings and intention to breastfeed from the BC Perinatal Database. The BC Perinatal Database collects this information on nearly all pregnancies in the province. Individual-level data was not available on socioeconomic factors; income quintiles and maternal education level quartiles were assigned at the level of Census Dissemination Areas (DAs). This is the smallest geographic area for which census data is distributed, with each DA containing approximately 400-700 people.

2.2.4 Exposure Measures

Air pollution exposure was estimated using regulatory monitoring data, land use regression (LUR) modeling, and proximity to stationary pollution sources, as described elsewhere (Brauer et al. 2008; Henderson et al. 2007; Larson et al. 2007). Briefly, exposures were assigned at the level of 6-digit postal codes. This corresponds to one edge of a block in urban areas, but is larger where population-density is lower. The regulatory monitoring network consists of daily measurements at 24 monitors for O_3, 22 for NO and NO_2, 14 for SO_2, 19 for CO and PM_{10} and 7 for $PM_{2.5}$. Exposures were assigned according to two approaches: 1) nearest monitor method, in which the closest working monitor within 10 km was used to assign exposure for each day at the postal code, and 2) inverse distance weighting (IDW), in which the daily values at the three closest monitors within 50 km were weighted by their inverse distance (1/d) to the postal code of interest.

Annual average air pollution LUR models were also developed for the region using measurement data (from targeted intensive sampling campaigns) along with geographic information system (GIS) data on road density, population density, elevation, and type of land use. LUR modeling was used to develop high-resolution (10 meters) maps of NO, NO_2, $PM_{2.5}$ and black carbon. These models have improved spatial resolution as

compared with the monitoring network approaches, but lower temporal resolution due to sampling data from a single year. For each LUR model, the corresponding monitoring network data for each pollutant were fit with monthly dummy variables and a covariate for linear trend (Times Series Forecasting System, version 9; SAS Institute Inc., Cary, NC, USA). For black carbon, the PM2.5 trend was used as there were no corresponding regulatory monitoring network data. From these models, we applied month–year adjustment factors to each LUR map to estimate monthly average concentrations (Brauer et al. 2008; Henderson et al. 2007).

A targeted sampling campaign was also used to develop a regional model of residential wood smoke exposure (Larson et al. 2007). Using this model, postal codes in the top tertile of exposure to wood smoke (based on measurements of levoglucosan, a wood burning marker) were classified as being in a wood burning area. Since woodsmoke is emitted seasonally, days were classified as woodburning days based on a relationship between temperature (heating degree days) and measured concentrations of levoglucosan. Wood smoke exposure was then estimated as the total number of burning days spent in a wood burning area.

Proximity to roadways and industrial point sources were also used as estimates of ambient air pollution exposure. Residential postal codes were defined as being within 50 m or 150 m from highways and major roads (DMTI ArcView street file dataset for BC, Canmap Streetfiles, v2006.3, 2006). Exposure was then estimated as the total number of days spent in proximity to each road type.

To estimate exposure to pollutants from industrial point sources, each point source was assigned an index value based on its pollutant contribution (PM2.5, sulfur oxides,

nitrogen oxides, and volatile organic compounds) relative to other point sources in the region. Examples of industrial point sources considered are power plants, waste treatment facilities, paper production plants and shipyards. Exposure at each postal code was then determined by an inverse distance weighted summation of emissions from point sources within 10 km.

For all exposure metrics, an average exposure was calculated for gestational life and the first year of life. These exposure estimates were weighted by the time spent at each residence to incorporate individual residential histories derived from BC Ministry of Health data.

The study methodology was reviewed and approved by the University of BC Behavioral Research Ethics Board (H07-01549).

2.2.5 Statistical Analysis

Descriptive statistics of the cohort's demographic factors, covariates of interest, and exposure estimates were performed for children meeting the case definition of asthma and those that did not. We used a nested case-control design to examine the association of air pollutants and incident asthma. Each asthma case was randomly matched to five controls by sex and month and year of birth. To assess the relationship of air pollution exposures on asthma diagnosis, unadjusted and covariate-adjusted conditional logistic regression analyses were performed. Covariates previously hypothesized to have an effect on asthma status were included in multivariate regressions based on statistical significance in bivariate regressions. Pollutants were entered into models in two ways: as continuous variables and as categorical variables based on the quartile of exposure. Odds ratios for continuous pollutants were calculated over a standard interval (1, 10 or 100) of

the same order of magnitude as the interquartile range to allow for easy comparability to other studies. The models were repeated for each sex separately. Wood smoke exposure was entered as a continuous variable (number of days spent in wood smoke area) while proximity to roadways was entered into models as an indicator variable (0/1) for ever having been in roadway proximity.

2.3 Results

2.3.1 Study Cohort Description

BC Vital Statistics data identified 59,917 births in the region in 1999 and 2000. Of these, 41,565 (69.4%) children met the study criteria of living in the study area during gestational life and the first year of life and having complete medical plan registration through to 2003. 2,967 were excluded due to low birth weight or preterm birth, 216 for multiple births, and 981 due to missing covariate information. Of the eligible children, 37,401 children (90%) were included in the final cohort from which cases and controls were drawn. Additional children were excluded for specific analyses where exposure information was not available.

A total of 3,482 children (9.3%) met the case definition for asthma (2 primary care asthma diagnoses in rolling 12-month period or one hospital diagnosis). The majority (64%) of these cases were male. Of the cases, 496 (14.2%) had been hospitalized for asthma and all but 29 (0.01%) of the hospitalized children also had a primary care diagnosis of asthma. The mean age of initial asthma diagnosis was 19.7 ±12.6 months, while the median was 17.0 months.

Table 2.1 provides covariate information for the cohort, stratified by asthma status. Children meeting the case definition of asthma differed from the rest of the cohort

for certain covariates, namely, maternal age and education, breastfeeding, socioeconomic status, number of siblings, birth weight, and gestational period. There were no differences with respect to native status or reported smoking during pregnancy.

2.3.2 Exposure Assessment

As expected for this study region (Southwestern BC), the mean pollutant levels were low (Table 2.2) relative to international guidelines. The LUR model estimated higher exposures than the monitor based assessments, in general, with the greatest discrepancy observed for NO exposure assessment. Results from the two monitor based approaches (nearest monitor and IDW) were highly correlated (r=0.7–0.9) (Pearson correlation coefficients) and yielded very similar results so only the results from the IDW approach are reported. Because ozone (O_3) was inversely correlated with the primary traffic-related pollutants (r= -0.7– -0.9) the observed associations were largely protective. Also, the high ozone peaks that occur both daily and seasonally are lost through long-term averaging of exposure, further limiting our ability to examine the pollutant's effects. The correlations between different pollutants were generally high and multi-pollutant models were not feasible.

Pregnancy and first year exposures were moderately correlated. Correlations were highest (r=0.7–0.9) for IDW measures of NO_2, NO, SO_2, O_3 and CO. LUR estimates of NO_2, NO and $PM_{2.5}$ were moderately correlated (r=0.5–0.8). IDW estimates of black carbon and particulate matter had the lowest correlations (r=0.4–0.5). The overall trend was that average exposures were slightly lower in first year than in pregnancy with the exception of particulate matter, NO, and SO_2. Asthmatic children had higher mean

exposures for NO, NO_2, CO, PM_{10}, black carbon, SO_2 and point sources (two-sided t-test $p<0.05$) than non-asthmatic children.

Table 2.2 also shows the number of children living in wood smoke areas or in proximity to major roads (within 150m from a highway or 50m from a major road). Only a small number of children lived near major roads and these were not significantly different by asthma status (chi-square test $p >0.05$). Residence in a wood smoke area also did not differ by asthma status (chi-square test $p >0.05$).

2.3.3 Logistic Regression

Table 2.3 provides the results of risk estimates for asthma diagnosis with our exposure measures. The effect size estimates for first year of life exposures are generally larger than for in utero exposures. Adjustment for covariates had relatively small effects on the resulting odds ratios, most often increasing the effect sizes slightly. IDW exposure estimates for NO, NO_2, CO, PM_{10}, and SO_2 all showed elevated risks of asthma diagnosis for both in utero and first year average exposures. LUR modelling showed less consistent results. NO exposure was significantly elevated for in utero exposure and reached borderline statistical significance for first year exposure. NO_2 exposure was elevated only for first year exposures. $PM_{2.5}$ exposure was not associated with increased asthma risk for IDW or LUR exposure estimates. Black carbon exposure was associated with a 14% (95% CI: 1-29%) increase in asthma risk. An interquartile increase (30 points) on the industrial point source index was consistently associated with a 10-11% (95% CI: 4-18%) increase in asthma risk. Wood smoke and proximity to roads were not associated with increased asthma risk.

When the pollutant exposures were entered into models as categorical variables indicating the quartile of exposure, similar results emerged (Table 2.4). Upper quartiles of exposure for NO, NO_2, CO, PM_{10}, SO_2, black carbon and point sources showed elevated odds ratios with respect to the lowest quartile of exposure. However, for many pollutants, including NO, NO_2, CO, and SO_2, the trend across quartiles was not consistently linear.

Table 2.5 shows the results of multivariate conditional logistic regressions stratified by sex. For all pollutants, with the exception of PM_{10} and road proximity, the effect sizes are larger for girls than boys. Associations with PM_{10} did not vary by sex, while for road proximity effect sizes were larger for boys. However, only a small number of asthmatic children resided in proximity to major roads (during intrauterine development, 181 children of whom 73 were girls and during first year, 135 children of whom 53 were girls) so the confidence intervals for this analysis are wide. As in the non-stratified analysis, $PM_{2.5}$ and wood smoke exposures were not associated with increased asthma risk for either sex.

2.3.4 Sensitivity Analysis

Sensitivity analyses were performed to test the robustness of the results to differing administrative data definitions of asthma. When the case definition was broadened to include children who only had one physician diagnosis of asthma, the number of asthma cases increased to 6,708 (17.9% of cohort). The resulting odds ratios for air pollution exposure were attenuated. The decreases were most significant for black carbon (6-8% decrease in point estimate) and least significant for particulate matter and point sources (1% decrease). The other pollutant odds ratios decreased by approximately

4%. When the definition of asthma was made more specific by requiring a minimum of three physician diagnoses the number of asthma cases decreased to 2,580 (6.9% of cohort). This asthma case definition resulted in 2-3% higher point estimates of odds ratios for NO and NO_2, approximately 1% increases for CO, SO_2, particulate matter, point sources and black carbon in utero and a 7% increase for black carbon in first year. Overall, there was a consistent trend that as the specificity of the asthma case definition increased, the association with air pollution exposure strengthened.

2.4 Discussion

We found that higher exposure to ambient air pollution in early life was associated with elevated risks of asthma diagnosis in pre-school aged children based on clinical records. Traffic-related pollutants (NO, NO_2, CO, and black carbon) were associated with the highest risk estimates. PM_{10}, SO_2, and residence near industrial point sources were also associated with elevated asthma risk, while $PM_{2.5}$, wood smoke, and road proximity did not show elevated risks. The results from this population-based study strengthen the emerging evidence that air pollution exposure plays a role in childhood asthma development, although these findings should be confirmed in additional cohorts of children, particularly as they reach school age and asthma diagnosis is more robust.

This study improves upon previous work done in the area in various respects. First, due to the availability of administrative data this study was population based and could track asthma incidence from birth. Exposures were estimated on an individual-level using various methods and for a number of key pollutants. Exposure misclassification was reduced further by developing residential histories for pregnancy and the first year of life.

To our knowledge, this was also the first study to examine the effects of in utero air pollution exposure on pediatric asthma risk. Other effects of air pollution on the developing fetus have been reported, for example lower birth weight (Bobak 2000; Slama et al. 2007), small for gestational age (Brauer et al. 2008), pre-term births (Bobak 2000; Brauer et al. 2008; Ritz et al. 2000), and intrauterine mortality (Pereira et al. 1998). In addition, ETS exposure during in utero development has been consistently associated with increased asthma risk (DiFranza et al. 2004; Gilliland et al. 2001; Haberg et al. 2007).

The risk estimates we found are similar to the results of other birth cohort studies. Brauer et al. (2007) used LUR models to estimate the effect of traffic derived pollutants on asthma incidence among four-year-old children. They found odds ratios of 1.20 per 10 $\mu g/m^3$ increase in NO_2 and 1.30 per $0.6x10^{-5}/m$ increase in black carbon. They also found an elevated risk of 1.20 per 3.3 $\mu g/m^3$ increase in $PM_{2.5}$, which was not identified in this study. Morgenstern et al. (2008) also estimated air pollution exposure using LUR modelling and examined effects on risk of asthma diagnosis in six-year-old children. They found odds ratios of 1.12 per 1 $\mu g/m^3$ increase in $PM_{2.5}$, 1.56 per $0.2x10^{-5}/m$ increase in black carbon and 1.04 per 6.4 $\mu g/m^3$ increase in NO_2.

Exposure estimates based on IDW showed as large or larger effects than observed with LUR modelling.

A major challenge in studying the effects of in utero air pollution exposure is differentiating the effects of pre- and post-birth exposures since they are often highly correlated. The correlations are reduced, however, if residential moves are taken into account. A unique advantage of this study was our access to complete residential history

throughout pregnancy and the first year of life and ability to incorporate changes in exposure. Moves during this period of life are relatively common; we found that 38% of mothers moved during pregnancy and a further 6% of children moved in the first year post-birth. Incorporation of residential history improved exposure estimates and provided some heterogeneity between pre- and post-birth exposures, although they were still moderately correlated.

The separate analyses for in utero and first year exposures indicated that first year exposures appeared to be more important for asthma risk. However, we cannot eliminate the possibility that this result was due to a misclassification bias due to lack of temporal precision in the residential histories; in utero exposures were more likely to have been misclassified than first year exposures. Addresses at birth were accurately recorded and postal code updates can be verified against the mother's data. Such verification is not available for pregnancy data. Moving rates did not differ by asthma status so this misclassification appears to be non-differential. Furthermore, exposure estimates are based on home residence and do not account for mobility to different settings. This is also likely to lead to greater misclassification of exposure among pregnant women than newborns. Short–term monitoring data of pregnant women in Vancouver found that exposure estimates using LUR modelling correlated moderately well with monitor measurements ($r=0.54$ for NO) and were improved when limited to samples in which women spent >65% of time at home ($r=0.72$) (Nethery et al. 2007). Since it is expected that a greater proportion of time is spent at home post-birth than pre-birth, exposure estimates are likely to be more accurate post-birth. These exposure assessment errors

would be expected to lead to a bias to the null for the intrauterine period. Therefore, we cannot determine which period of exposure is more important.

Asthma risks due to air pollution were generally larger for girls for both in utero and first year exposures. As expected, girls had a lower incidence of asthma (making up 36% of cases) but despite the smaller numbers, associations with pollutants were significantly elevated (with the exceptions of wood smoke, $PM_{2.5}$ and road proximity). Several previous studies have also found that girls are more susceptible to air pollution, with higher risks of asthma (McConnell et al. 2006; van Vliet et al. 1997) and greater effects on lung function (Peters et al. 1999). However, this is not a consistent finding as other studies have found boys to be more susceptible (Gehring et al. 2002). Indeed, the current results also showed some inconsistency as proximity to major roads was associated with elevated risks for boys but not girls. However, the quality of this analysis is compromised by small numbers of children (especially girls due to lower asthma incidence) and the limitations of road proximity for approximating exposure.

Proximity to roads is commonly used to approximate exposure because of its relative ease as compared with monitoring methods. While many studies have found asthma symptoms to be associated with proximity to major roads (Gauderman et al. 2005; McConnell et al. 2006; Morgenstern et al. 2007), this is not a consistent finding (English et al. 1999). Simple proximity measures do not capture exposure accurately as they lack information on traffic density, vehicle mix, wind patterns, topography, land use characteristics and other influences on pollution levels (Brauer et al. 2003; Henderson et al. 2007; Jerrett et al. 2005). Therefore, proximity is inferior to measured levels of pollutants for assessing exposure. This may explain why proximity to roads was not

found to be associated with increased asthma risk in this study. Our study was further challenged by the small number of children residing in proximity to major roads. Nonetheless, we did observe consistently elevated risks with measured and modelled values of traffic-derived pollutants, indicating that traffic-related exposure is important.

The industrial point source index is subject to many of the same limitations as the road proximity measure. Individual exposure to point sources is estimated by a single figure that takes into account the relative emissions (of PM2.5, sulfur oxides, nitrogen oxides, and volatile organic compounds) and proximities of all point sources within a 10 km radius. It lacks data on topography, wind direction and other exposure influencing characteristics. Despite these limitations, we observed elevated asthma risks associated with the point source index. This may partially indicate a socioeconomic effect; the point source index was among the only exposure indices that were reduced after adjustment for covariates. The reduction was primarily as a result of adjustment for income and education status.

Residential wood smoke contributes a considerable fraction of particulate matter to portions of the study area in the winter months (Ries F. and Brauer M. unpublished data). The current model captured the distribution of wood smoke in the area well as judged by validation of the model (Larson et al. 2007). Despite this, wood smoke exposure was not found to be associated with increased asthma risk. Previous studies have associated wood smoke with adverse respiratory effects in children, including exacerbation of asthma (Allen et al. 2008; Zelikoff et al. 2002); however, its role in asthma development requires more research.

While the use of linked administrative datasets allowed us to conduct a population-based study including important covariates and residential history, these datasets also have limitations, such as the lack of clinical details and information on asthma severity. However, our estimates of asthma incidence are consistent with previous findings in similar age ranges (Dik et al. 2004; Jaakkola et al. 2005). Furthermore, the validity of our findings are supported by a recent validation study of administrative data in a similar health care setting. It found that asthma codes were a highly sensitive and specific measurement of asthma as compared with experts' review of medical charts (To et al. 2006). These results were also verified for young children aged 0-5, for whom sensitivity and specificity remained high, especially for the 3-5 year old group (above 80%). Due to universal and free access to physician visits, we also believe that any misclassification of asthma status was non-differential and therefore would be expected to bias the results to the null.

The inclusion of residential history in our study is a major strength but the administrative data used to develop residential histories does not provide precise move dates. A move was inferred when individuals reported a new postal code at health care system contacts. Examination of the data indicated that postal codes were likely not updated at every health care system contact, especially in an outpatient setting (McGrail and Wong Fung 1999). Therefore, move dates are only estimates and limited our ability to identify accurately children who experienced different exposures pre- and post-birth.

Covariates' associations with asthma largely agreed with findings of previous studies. This includes associations with sex (Dik et al. 2004; Ronmark et al. 2002; Schaubel et al. 1996), breastfeeding (Dell and To 2001; Gdalevich et al. 2001),

socioeconomic status (Wickens et al. 1999), and birth weight and gestational period (Dik et al. 2004; Ronmark et al. 2002; Schaubel et al. 1996). Previous results for associations with maternal age and parity have not been consistent (Dik et al. 2004; Haby et al. 2001; Infante-Rivard et al. 2001; Wickens et al. 1999; Svanes et al. 1998). Limitations of the Perinatal Database likely underlie the reason that we did not see an expected effect of maternal smoking on asthma risk. The smoking variable in the Perinatal Database relies on maternal self-report and does not capture maternal exposure to second-hand cigarette smoke. This variable therefore was not a sensitive indicator of children who were exposed to ETS.

A more significant limitation of this study was the young age of the children. Wheezing illnesses in early childhood represent multiple phenotypes. Transient wheezing is common in infants and often resolves as the children age (Martinez et al. 1995; To et al. 2007). To et al. found that among children diagnosed with asthma before the age of 6, 48.6% were in remission by age 12. Children with a hospitalization for asthma or many physician visits for asthma were at greater risk of persistent asthma by age 12 (To et al. 2007). We have addressed this issue by restricting our asthma cases to children with a hospital admission or at least two outpatient diagnoses of asthma, as these indicate severe or ongoing symptoms, respectively. Sensitivity analyses requiring three outpatient diagnoses only made the resulting odds ratios larger, indicating that air pollution is associated with ongoing respiratory symptoms consistent with asthma. This indicates that adverse respiratory effects do occur with air pollution exposure, but to ensure associations with persistent asthma the results must be confirmed when the children are older.

We were able to correct for a number of individual level variables, but socioeconomic variables could only be adjusted at the neighbourhood level. Socioeconomic adjustment may control for factors with potential effects on asthma risk such as living conditions, exposure to allergens, access to nutritious food, and exposure to chronic stress (Chen et al. 2008; Devereux and Seaton 2005; Jaakkola et al. 2005). An area-level adjustment is imperfect and may have led to some misclassification of socioeconomic status for individuals (Hanley and Morgan 2008); however, the adjustment generally had small effects on odds ratios. We also had no information on the child or family history of atopy, an important risk factor for asthma development and a potential effect modifier.

2.4.1 Conclusion

In this study, children with higher early life air pollution exposures, particularly to traffic-derived pollutants, were observed to have an increased risk of asthma diagnosis. This adds to evidence that not only does outdoor air pollution exacerbate asthma but may be associated with development of new disease. At an individual level the risk increase is small, but presents a significant increase in burden of disease on a population level because in most urban and suburban settings, traffic derived air pollution exposure is ubiquitous.

Table 2.1 Cohort characteristics by asthma status

		Non-asthmatic children (Total = 33,919)	Asthmatic children (Total = 3,482)
Frequency (percentage) :			
Male sex*		16 885 (50%)	2 222 (64%)
Native status		528 (2%)	70 (2%)
Has siblings*		18 844 (56%)	2042 (59%)
Breastfeeding initiation*		29,286 (86%)	2920 (84%)
Maternal smoking status		2625 (8%)	268 (8%)
Area based income quintile*	1	7072 (21%)	814 (23%)
	2	7350 (22%)	822 (24%)
	3	7283 (21%)	762 (22%)
	4	6582 (19%)	591 (17%)
	(highest) 5	5632 (17%)	493 (14%)
Area based maternal education quartile*	1	8083 (24%)	985 (28%)
	2	8704 (26%)	913 (26%)
	3	8668 (26%)	830 (24%)
	(highest) 4	8464 (25%)	754 (22%)
Mean (standard deviation):			
Maternal age*		31.0 years (5.1 years)	30.8 years (5.2 years)
Birth weight*		3,530 g (460 g)	3,510 g (450 g)
Gestational length*		39.4 weeks (1.1 weeks)	39.3 weeks (1.2 weeks)

* Statistically significant difference ($p<0.05$), chi-square test for frequencies and t-test for means

Table 2.2 Mean exposure levels during pregnancy and the first year of life for pre-school aged children by asthma status

			In utero				First year			
				Percentiles				Percentiles		
		N	MEAN (SD[a])	25%	50%	75%	MEAN (SD[a])	25%	50%	75%
NO - IDW[b]	Controls	16 970	19·82 (10·27)	12·76	17·94	25·69	22·36 (10·39)	15·76	20·25	27·98
(µg/m^3)	Asthma cases	3 394	20·32 (10·74)	12·74	17·95	27·15	23·04 (10·88)	15·84	20·56	30·25
NO - LUR[c]	Controls	14 005	30·38 (13·05)	21·71	27·46	35·99	30·42 (12·13)	23·09	27·05	34·28
(µg/m^3)	Asthma cases	2 801	31·03 (13·54)	22.00	27·84	36·62	30·83 (12·67)	23·39	27·11	34·39
NO_2 - IDW[b]	Controls	16 970	30·74 (8·90)	24·96	31·50	36·54	29·86 (8·85)	23·71	29·97	36·02
(µg/m^3)	Asthma cases	3 394	31·37 (9·20)	25·17	32·15	37·57	30·68 (9·06)	24·28	31·97	36·82
NO_2 - LUR[c]	Controls	14 005	31·68 (8·64)	25·77	30·06	35·07	29·50 (5·29)	25·90	28·73	32·70
(µg/m^3)	Asthma cases	2 801	31·73 (8·42)	25·96	30·33	35·16	29·82 (5·46)	26·16	28·87	33·08
CO - IDW[b]	Controls	16 240	612·2 (133·4)	507·7	610·2	698·8	605.0 (135·2)	512·9	607·2	690·1
(µg/m^3)	Asthma cases	3 248	618·8 (135·3)	520·2	612·6	705·8	617·5 (132·5)	521·6	614·5	707·8
O_3 - IDW[b]	Controls	16 795	30·48 (6·32)	26·03	30·47	34·89	28·06 (4·86)	25·09	28·33	31·57
(µg/m^3)	Asthma cases	3 359	30·05 (6·39)	25·41	30·11	34·42	27·64 (4·94)	24·32	28·11	31·28
PM_{10} - IDW[b]	Controls	17 335	11·94 (1·35)	11·08	12·15	12·85	12·37 (1.00)	11·95	12·43	13·01
(µg/m^3)	Asthma cases	3 467	12·03 (1·30)	11·21	12·23	12·89	12·42 (1.00)	12·01	12·47	13·03
$PM_{2·5}$ - IDW[b]	Controls	16 775	4·74 (1·19)	4·07	5·15	5·58	5·62 (0·61)	5·35	5·60	6·13
(µg/m^3)	Asthma cases	3 355	4·71 (1·20)	4·00	5·12	5·57	5·62 (0·61)	5·35	5·62	6·13
$PM_{2·5}$ - LUR[c]	Controls	16 270	4·67 (2·47)	3·08	4·25	5·98	4·50 (2·45)	2·95	4·14	5·68
(µg/m^3)	Asthma cases	3 254	4·78 (2·46)	3·194	4·33	6·02	4·59 (2·40)	3·10	4·18	5·70
Black carbon[d]	Controls	16 270	1·34 (0·65)	0·94	1·20	1·65	0·66 (0·33)	0·46	0·70	0·89
- LUR[c]	Asthma cases	3 254	1·37 (0·66)	0·95	1·21	1·68	0·68 (0·33)	0·49	0·72	0·91
SO_2 - IDW[b]	Controls	16 970	5·11 (2·40)	3·70	4·48	6·20	5·22 (2·55)	3·89	4·48	6·36
(µg/m^3)	Asthma cases	3 394	5·25 (2·51)	3·69	4·49	6·74	5·37 (2·69)	3·87	4·46	7·04
Point Source	Controls	17 410	23.69 (18.49)	8.03	19.46	37.43	23.12 (18.71)	7.63	18.29	37.03
index (r=10km)	Asthma cases	3 482	25.18 (18.10)	9.31	22.26	39.04	24.62 (18.36)	8.91	20.60	38.42
		N	**Frequency**	**Mean number of exposure days (SD[a])**			**Frequency**	**Mean number of exposure days (SD[a])**		
Wood smoke	Controls	14 365	6082 (42.3%)	60 (25)			6025 (41.9%)	89 (13)		
	Asthma cases	2 873	1269 (44.2%)	59 (25)			1256 (43.7%)	89 (13)		
Proximity to major	Controls	17 410	859 (4.9%)	--			658 (3.8%)	--		
roads[e]	Asthma cases	3 482	181 (5.2%)	--			135 (3.9%)	--		

[a] Standard Deviation, [b] Inverse Distance Weighted, [c] Land Use Regression, [d] Unit =10^{-5}/m increase in filter absorbance, [e] Children with residence < 150 m from a highway or < 50 m from a major road

Table 2.3 Unadjusted and adjusted odds ratios for asthma risk due to average exposure during pregnancy and the first year of life for land use regression and IDW exposure metrics.

	In utero Exposure		First year exposure	
Pollutant (exposure interval[a])	**Unadjusted (95% CI[c])**	**Adjusted[b] (95% CI[c])**	**Unadjusted (95% CI[c])**	**Adjusted[b] (95% CI[c])**
NO - IDW[d] ($10\ \mu g/m^3$)	1·05 (1·01-1·10)	1·07 (1·03-1·12)	1·07 (1·03-1·10)	1·08 (1·04-1·12)
NO – LUR[e] ($10\ \mu g/m^3$)	1·04 (1·01-1·08)	1·05 (1·02-1·09)	1·03 (1·00-1·06)	1·03 (1·00-1·07)
NO_2 – IDW[d] ($10\ \mu g/m^3$)	1·09 (1·04-1·13)	1·10 (1·05-1·15)	1·11 (1·07-1·16)	1·12 (1·07-1·17)
NO_2 – LUR[e] ($10\ \mu g/m^3$)	1·01 (0·96-1·06)	1·02 (0·97-1·07)	1·12 (1·04-1·21)	1·13 (1·04-1·23)
CO – IDW[d] ($100\ \mu g/m^3$)	1·04 (1·01-1·07)	1·07 (1·04-1·10)	1·07 (1·04-1·10)	1·10 (1·06-1·13)
O_3 – IDW[d] ($10\ \mu g/m^3$)	0·86 (0·80-0·92)	0·83 (0·77-0·89)	0·83 (0·77-0·90)	0·81 (0·74-0·87)
PM_{10} – IDW[d] ($1\ \mu g/m^3$)	1·09 (1·05-1·13)	1·09 (1·05-1·13)	1·07 (1·03-1·12)	1·07 (1·03-1·12)
$PM_{2.5}$ – IDW[d] ($1\ \mu g/m^3$)	0·95 (0·90-1·00)	0·95 (0·91-1·00)	1·02 (0·95-1·11)	1·05 (0·97-1·14)
$PM_{2.5}$ – LUR[e] ($1\ \mu g/m^3$)	1·02 (1·00-1·03)	1·02 (1·00-1·03)	1·01 (1·00-1·03)	1·01 (0·99-1·03)
Black carbon – LUR[e] (10^{-5}/m increase in filter absorbance)	1·06 (1·00-1·13)	1·08 (1·02-1·15)	1·21 (1·08-1·36)	1·14 (1·01-1·29)
SO_2 – IDW[d] ($1\ \mu g/m^3$)	1·02 (1·01-1·04)	1·03 (1·02-1·05)	1·02 (1·01-1·04)	1·03 (1·02-1·05)
Point source index (r=10km) (30 points)	1.14 (1.07-1.21)	1.11 (1.04-1.18)	1.13 (1.07-1.20)	1.10 (1.04-1.17)
Wood smoke (10 burn days)	1.01 (0.99-1.02)	1.00 (0.98-1.01)	1.01 (1.00-1.02)	1.00 (0.99-1.01)
Road proximity	1.06 (0.90-1.25)	0.97 (0.82-1.15)	1.03 (0.85-1.24)	1.01 (0.84-1.22)

[a] Standard interval (approximating interquartile range) chosen for comparability to other studies [b] Adjusted for parity, breastfeeding, income quintile and maternal education status (neighbourhood level), birth weight and gestational length, [c] 95% Confidence Interval, [d] Inverse Distance Weighted, [e] Land Use Regression

Table 2.4 Results of conditional logistic regression by exposure quartile.

Pollutant	In utero Exposure Adjusted[a] OR (95% CI[b])			First year exposure Adjusted OR[a] (95% CI[b])		
	4 vs 1	**3 vs 1**	**2 vs 1**	**4 vs 1**	**3 vs 1**	**2 vs 1**
NO - IDW[c]	1.14 (1.02-1.28)	0.93 (0.83-1.04)	1.00 (0.90-1.11)	1.18 (1.06-1.32)	0.97 (0.87-1.08)	0.96 (0.87-1.07)
NO – LUR[d]	1.14 (1.00-1.30)	1.07 (0.95-1.21)	1.04 (0.92-1.17)	1.12 (0.99-1.26)	1.07 (0.95-1.21)	1.19 (1.06-1.34)
NO_2 – IDW[c]	1.25 (1.12-1.40)	1.08 (0.96-1.20)	1.00 (0.89-1.11)	1.34 (1.21-1.50)	1.11 (0.99-1.24)	1.05 (0.94-1.17)
NO_2 – LUR[d]	1.11 (0.98-1.25)	1.10 (0.98-1.24)	1.08 (0.96-1.21)	1.16 (1.02-1.32)	1.00 (0.89-1.13)	1.09 (0.96-1.22)
CO – IDW[c]	1.23 (1.09-1.39)	1.08 (0.96-0.21)	1.13 (1.01-1.26)	1.33 (1.19-1.49)	1.20 (1.07-1.34)	1.17 (1.05-1.30)
O_3 – IDW[c]	0.75 (0.67-0.86)	0.88 (0.79-0.99)	0.89 (0.80-1.00)	0.77 (0.69-0.86)	0.82 (0.74-0.92)	0.80 (0.72-0.89)
PM_{10} – IDW[c]	1.38 (1.21-1.59)	1.28 (1.14-1.45)	1.17 (1.04-1.31)	1.24 (1.10-1.39)	1.17 (1.05-1.31)	1.13 (1.02-1.26)
$PM_{2.5}$ – IDW[c]	0.90 (0.78-1.05)	0.91 (0.78-1.07)	0.94 (0.81-1.10)	1.15 (0.98-1.34)	1.17 (1.03-1.33)	1.00 (0.89-1.13)
$PM_{2.5}$ – LUR[d]	1.07 (0.96-1.20)	1.08 (0.97-1.21)	1.03 (0.93-1.15)	1.06 (0.94-1.19)	1.06 (0.95-1.18)	1.11 (1.00-1.24)
Black carbon - LUR[d]	1.08 (0.97-1.21)	1.03 (0.92-1.15)	0.99 (0.89-1.11)	1.08 (0.97-1.21)	1.04 (0.93-1.16)	1.00 (0.90-1.11)
SO_2 – IDW[c]	1.15 (1.03-1.29)	0.95 (0.85-1.07)	1.01 (0.90-1.12)	1.12 (1.00-1.25)	0.89 (0.79-0.99)	1.01 (0.91-1.13)
Point source index	1.23 (1.11-1.37)	1.19 (1.07-1.32)	1.09 (0.98-1.21)	1.22 (1.09-1.36)	1.19 (1.07-1.33)	1.16 (1.04-1.29)

[a] Adjusted for parity, breastfeeding, income quintile and maternal education quartile (neighbourhood level), birth weight and gestational length, [b] 95% Confidence Interval, [c] Inverse Distance Weighted, [d] Land Use Regression

Table 2.5 Adjusted odds ratios for asthma risk due to average exposures during pregnancy and the first year of life, stratified by sex.

Pollutant (exposure interval[a])	In utero Exposure Adjusted[b] OR (95% CI[c])		First year exposure Adjusted OR[b] (95% CI[c])	
	Girls	Boys	Girls	Boys
NO - IDW[d] ($10\ \mu g/m^3$)	1·11 (1·04-1·19)	1·06 (1·00-1·11)	1·13 (1·06-1·20)	1·05 (1·00-1·10)
NO – LUR[e] ($10\ \mu g/m^3$)	1·06 (1·00 -1·12)	1·05 (1·01-1·09)	1·07 (1·02-1·14)	1·01 (0·97-1·05)
NO_2 – IDW[d] ($10\ \mu g/m^3$)	1·13 (1·05-1·22)	1·08 (1·02-1·15)	1·17 (1·09-1·26)	1·09 (1·03-1·16)
NO_2 – LUR[e] ($10\ \mu g/m^3$)	1·04 (0·96-1·14)	1·00 (0·94-1·06)	1·24 (1·08-1·42)	1·07 (0·96-1·19)
CO – IDW[d] ($100\ \mu g/m^3$)	1·11 (1·05-1·17)	1·04 (1·00-1·09)	1·12 (1·07-1·18)	1·08 (1·04-1·12)
O_3 – IDW[d] ($10\ \mu g/m^3$)	0·79 (0·70-0·89)	0·86 (0·78-0·94)	0·74 (0·64-0·84)	0·84 (0·76-0·94)
PM_{10} – IDW[d] ($1\ \mu g/m^3$)	1·08 (1·02-1·15)	1·10 (1·05-1·15)	1·10 (1·02-1·18)	1·05 (1·00-1·11)
$PM_{2.5}$ – IDW[d] ($1\ \mu g/m^3$)	0·98 (0·91-1·05)	0·94 (0·88-1·00)	1·10 (0·96-1·26)	1·02 (0·92-1·13)
$PM_{2.5}$ – LUR[e] ($1\ \mu g/m^3$)	1·03 (1·00-1·06)	1·01 (0·99-1·03)	1·03 (1·00-1·06)	1·00 (0·98-1·02)
Black carbon – LUR[e] (10^{-5}/m increase in filter absorbance)	1·14 (1·03-1·26)	1·05 (0·97-1·14)	1·28 (1·05-1·56)	1·07 (0·92-1·24)
SO_2 – IDW[d] ($1\ \mu g/m^3$)	1·05 (1·02-1·08)	1·03 (1·01-1·05)	1·05 (1·03-1·08)	1·02 (1·00-1·04)
Point source index (r=10km) (30 points – Interquartile range)	1.15 (1.04-1.27)	1.09 (1.01-1.17)	1.15 (1.04-1.27)	1.07 (1.00-1.16)
Wood smoke (10 burn days)	1.00 (0.97-1.02)	1.00 (0.98-1.01)	1.00 (0.98-1.01)	1.01 (0.99-1.02)
Road proximity (0/1)	0.83 (0.64-1.08)	1.07 (0.87-1.33)	0.94 (0.69-1.27)	1.06 (0.83-1.35)

[a] Standard interval (approximating interquartile range) chosen for comparability to other studies [b] Adjusted for parity, breastfeeding, income quintile and maternal education quartile (neighbourhood level),birth weight and gestational length, [c] 95% Confidence Interval, [d] Inverse Distance Weighted, [e] Land Use Regression

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3. DISCUSSION

3.1 Summary of Findings

This was the first study to examine the effect of in utero exposure to outdoor air pollutants and their effects on later asthma risk. It was also the first population-based birth cohort study to examine air pollution and the development of asthma. Elevated intrauterine and first year exposures were associated with increased risk of asthma diagnosis in early childhood. The associations were strongest for traffic-related pollutants, including NO_2, NO and CO. Elevated risks were also observed for SO_2, PM_{10}, and proximity to point sources. $PM_{2.5}$ and proximity to major roads were not associated with elevated risks of asthma. Odds ratio point estimates for intrauterine exposures tended to be smaller than for first year exposures; however, moderately high correlation between these exposures precluded a clear determination of a sensitive period for exposure. A stratified analysis by sex showed that odds ratios for girls were generally higher than for boys, indicating that girls appear to be more susceptible to the effects of air pollution.

The finding of an association between early life exposure to air pollutants and elevated risks of asthma diagnosis provides further evidence that air pollution plays a role in the development of asthma. The current results also provide further evidence that traffic-related pollutants are important in the development of asthma.

3.2 Residential Histories from Administrative Data

British Columbia maintains one of the most comprehensive health databases in the world. The BC Linked Health Database (BCLHD) contains population-level information on essentially all contacts with the medical system, as well as linkages to workers compensation claims, prescription data, and cancer incidence files (CHSPR 2008). Alone, the BCLHD is a database of health information but when this data can be linked with exposure data, it becomes an invaluable tool for epidemiological research. Residential history is one key piece of information in the database that allows us to link health information to exposure information. Where we live is an important determinant of our health, for example, it can approximate our exposure to various environmental pollutants. Therefore, the residential histories contained in the administrative data open the door to many powerful epidemiologic studies.

The Ministry of Health does not directly collect individual residential histories, rather they are compiled by researchers from a combination of address data from outpatient billing records, hospital discharge records, and health plan registry files (McGrail and Wong Fung 1999). Previous analyses of the Border Air Quality Study found that the patterns of postal codes recorded for individuals are often inconsistent. For example, two postal codes frequently overlap for a period or new postal codes may appear but not persist. I explored residential histories further by examining mothers who moved during pregnancy. I found that nearly 40% of mothers had a change in postal code during pregnancy; however, 60% of these new postal codes first appeared at the time of delivery of their child. As it is doubtful that a large number of mothers moved very close to their delivery date, I concluded that hospital admission at time of delivery was likely a

point of "catch up" on moves that occurred earlier in pregnancy. Despite observations of frequent postal code changes in the database, it appears that outpatient visits do not consistently capture all address changes. It remains unclear how addresses are recorded at outpatient visits. Clearly, the great wealth of data contained in the administrative databases comes at the cost of a thorough understanding of its origin.

Inaccuracies in the residential data can affect the interpretation of study results because it leads to errors in exposure assessment. Exposure assessment errors that do not vary depending on other variables in the study, including disease status, are defined as non-differential, and this generally leads to a bias toward the null (Rothman and Greenland 1998). A bias to the null still allows us to interpret elevated odds ratios as evidence of risk, although it does diminish potentially more significant findings. Differential error on the other hand is less predictable as it can bias results away from or toward the null (Rothman and Greenland 1998). Under specific circumstances even non-differential error can lead to bias toward or away from the null; for example, when a continuous exposure is collapsed into categories and is consistently over- or under-estimated (Brenner and Loomis 1994; Flegal et al. 1991). Therefore, inaccurate residential history data could lead to various types of bias depending on the study.

Examination of the residential history data for this study suggests that results for the in utero period are biased to the null due to non-differential misclassification of exposure. Residential follow-up consisted of the nine months of intrauterine development and the first twelve months after birth. Inclusion of birth in the follow-up provides an accurate address update: birth records and initial health plan registration can all be used to verify home address. Therefore, first year follow-up is likely to be quite accurate.

Maternal addresses cannot be verified in this manner and so may not have been as accurate. However, inaccuracies appeared to be non-differential. For example, moving rates were highly similar for cases and controls throughout follow-up so accuracy of addresses was unlikely to be influenced by disease status. This non-differential exposure error is expected to result in bias to the null. Therefore, the difference in accuracy of residential data may account for the finding that effect sizes were generally larger for first year than intrauterine exposures. However, both exposure periods consistently showed elevated odds ratios for asthma development, indicating that administrative residential histories form a reasonably accurate basis for exposure assessments.

In other studies however, differential bias resulting from inaccurate residential histories may be of concern. Generally, birth files and mother's data are not available for address verification and researchers must rely on annual updates to the registry file and medical contacts for all address updates. This may cause differential misclassification by disease status. Sick people will likely have more accurate residential information than healthy people due to more frequent hospital admissions and other health care contacts. Therefore, until the origins and complexities of residential history data are better understood, study design, analysis and interpretation will need to take into consideration the potential for errors resulting from administrative residential histories.

As we strive to understand the multifactorial and complex determinants of chronic disease, we rely on accurate long-term follow-up to determine exposures and other variables. Often environmental factors act over a long period and on an entire population, therefore making it challenging to detect their effects with small sample sizes or primary data collection techniques. Administrative databases can therefore be an essential means

of providing economical and powerful data for such studies. For many environmental exposures, residential history is the crucial link that allows this health database to be linked to exposure data. Therefore, investigation to fully understand, and possibly improve, address collection in the health database may yield great benefits for public health research in British Columbia. Address collection is already part of the system so improving it may require only minor changes. This would allow researchers to make full use of this powerful database.

3.3 Role of Air Pollution in Asthma Development

The causes of asthma have been under study for several decades without clear answers. It is evident that as with many other diseases, asthma is caused by a complex interplay of environmental influences and genetic susceptibility. Worldwide disease patterns demonstrate the importance of environmental determinants of the disease but have not lead to the identification of universal triggers (Eder et al. 2006). The role of air pollution in asthma has been a subject of significant debate. Although widely believed to exacerbate asthma, there is far less support for air pollution as a cause of new cases of the disease (von Mutius 2000). Indeed, as with many asthma risk factors studied to date, air pollution has shown relatively small effects on asthma incidence that are not consistent across all studies. Examining the current evidence in the framework of the sufficient-component cause model helps shed light on the potential role of air pollution in asthma development.

Rothman and Greenland defined a cause as "an event, condition or characteristic that preceded the disease onset and that had [it] been different in a specified way, the disease either would not have occurred or would not have occurred until some later time"

(Rothman and Greenland 2005). The constellation of causes that lead to the development of a disease for a particular person at a particular point in time is defined as a sufficient cause. This is the minimal set of conditions required to produce disease. The set of components that form a sufficient cause for disease can vary by individual; therefore, a factor that may cause disease in one person may not cause disease in another. This is illustrated in Figure 3.1, where each of the three pies forms a sufficient cause of disease in one individual. We can see that the component C would only be a cause of disease in individual 2 and furthermore, it would only be a cause of disease in the presence of components A, B, D, M and N. The sufficient-cause model demonstrates the complex nature of disease development and the challenges involved in identifying component causes.

Applying this model to asthma, let us assume that air pollution is a component cause of the disease (component C). As the illustration shows, air pollution is not necessary for disease development in all individuals: individuals 1 and 3 develop disease without exposure to air pollution. For individual II however, air pollution is a cause of asthma due to the presence of the other component causes (A, B, D, M and N), which could be other environmental exposures or genetic traits. In the absence of these other factors, air pollution will not lead to the development of disease. As observed in epidemiological studies, exposure to air pollution is neither sufficient nor necessary for asthma development. Of course, air pollution exposure is a continuous, not a dichotomous, variable. Therefore, the causal model is likely more complex, with different doses of exposure associated with different causal pies; a larger dose of air pollution exposure may require fewer component causes to lead to asthma.

This model illustrates some concepts of multifactorial disease causation, but it lacks temporality. One of the fundamental requirements for causality is establishing the temporal sequence of cause acting before effect. However, it is difficult to establish when air pollution begins to exert effects in the development and progression of asthma. Many studies have confirmed that air pollution exposure is associated with asthma severity, indicating that air pollution has effects after the development of disease. In addition, numerous studies also link air pollution with asthma incidence, implicating air pollution as a cause of asthma. However, any factor that causes disease onset to occur earlier than it would have otherwise will be associated with disease incidence and would be considered a cause of disease under the model. By definition, a sufficient cause for a disease is one that causes disease to develop *at a particular point in time*. Such a "catalyst" may or may not have a meaningful effect on disease incidence in the long-term. Therefore, air pollution must be linked with asthma incidence and prevalence in the long-term. This evidence is still lacking and more research is necessary.

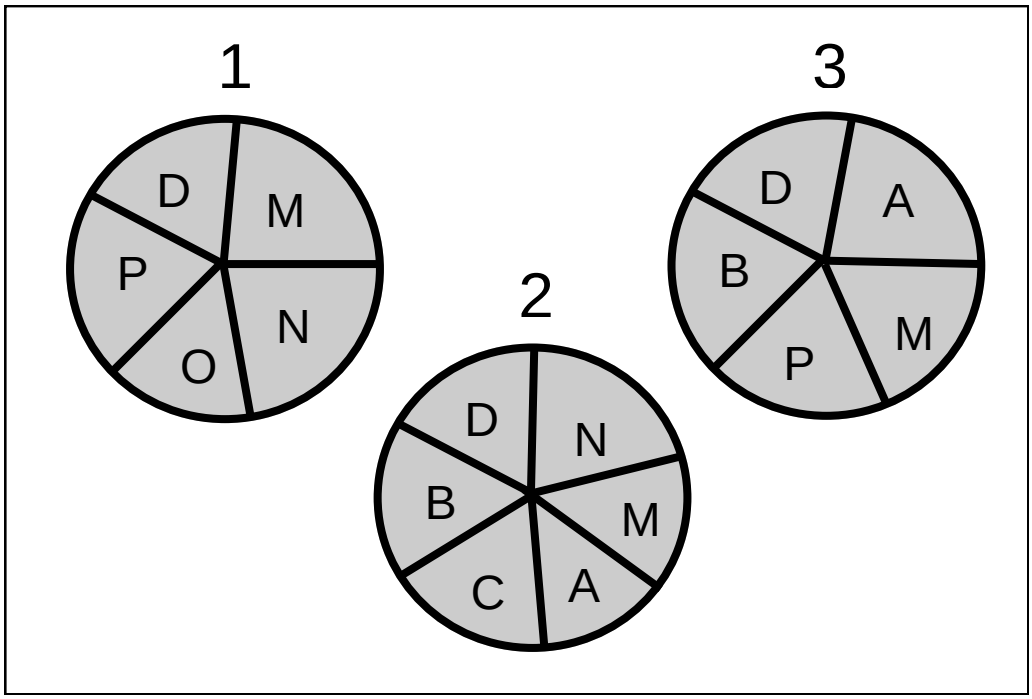

Figure 3.1 **Illustration of a causal mechanism of disease. Each pie represents a one sufficient cause for disease, made up of component causes represented by letters.**

3.4 Policy Implications

Asthma affects 16% of children aged 4 to 11 in Canada and costs more than $600 million annually to treat (Public Health Agency of Canada 2007); clearly, policies to reduce asthma incidence are a public health priority. The current finding that a modifiable exposure is associated with an increased risk of asthma indicates a potential opportunity for prevention. To date, air pollution has been associated with small increases in asthma risk and children have not been followed to assess associations with persistent asthma, perhaps leading sceptics to conclude that there is insufficient evidence to warrant policy changes. However, air pollution exposure is extremely common and even small effect sizes can have important health effects at the population level. Furthermore, air pollution is clearly associated with other detrimental health effects. Although we have yet to confirm an association with persistent asthma, air pollution is consistently associated with adverse respiratory effects in children, including respiratory symptoms and long-term reductions on lung growth (Andersen et al. 2008; Avol et al. 2001; Gauderman et al. 2000; Gauderman et al. 2004). Air pollution is also convincingly associated with asthma exacerbation (McCreanor et al. 2007; Schwartz et al. 1993; Sunyer et al. 1997) and reductions in exposure have been associated with lung health improvements and reduced attacks for asthmatic patients (Friedman et al. 2001; McCreanor et al. 2007). Air pollution is also associated with many non-respiratory effects, including arrhythmia (Peters et al. 2000), atherosclerosis (Hoffmann et al. 2007; Künzli et al. 2005), and myocardial infarction (Peters et al. 2001; Pope et al. 2006). Consequently, reductions in air pollution exposure are expected to not only reduce the incidence and severity of asthma, but other health conditions as well.

Although it is becoming evident that reductions in air pollution exposure would have many health benefits, it is far less clear what policies can achieve these reductions. The major emission source in the Georgia Air Basin and the source most consistently linked with asthma development is motor vehicle traffic. Significant reductions in regional ambient levels would be costly, likely requiring extensive changes to the transportation network. Therefore, rather than focusing on large scale emission reductions a more feasible policy approach is to focus on reducing human exposure. There are several approaches to achieve this: increase the distance between people and emission sources, reduce air pollution sources at the neighbourhood-level, and encourage personal protective measures for individuals. Efforts to reduce asthma incidence should specifically focus on the exposures of pregnant women and young children, however, all segments of the population are likely to benefit.

Evidence indicates that children who live near major roads have higher asthma incidence and experience more asthma symptoms than children who live away from major roads (Brunekreef et al. 1997; Salam et al. 2008). Therefore, reducing the number of residential homes, daycares, and schools located near major roads is an important long-term policy objective. However, development policies must also consider the transportation needs of the community. Simply expanding development away from major urban centres is not an effective long-term solution. Suburban sprawl increases the distances people need to travel and encourages the use of personal vehicles, thereby increasing emissions. Dense, mixed land-use urban communities on the other hand can reduce the need for personal vehicles by reducing the distances that people travel (Saelens et al. 2003). In order to prevent bringing emission sources and people in close

proximity however, urban development must be accompanied by appropriate plans for low-emission transportation alternatives.

The major emission source in close proximity to people is motor vehicles. Policies that reduce vehicle use, especially within residential communities, can help reduce personal exposure. Mixed-land use is one approach to this. By including both residential and commercial land-use within neighbourhoods, distances to amenities are shortened and become more accessible by foot or bicycle (Frank and Pivo 1994). Currently an estimated 12-13% of residents in Vancouver and Victoria bike for utilitarian (non-recreational) trips (Winters et al. 2007). However, there is evidence to indicate that higher urban densities, mixed land-use and bicycling infrastructure, such as designated bike lanes, encourage higher ridership (Frank and Pivo 1994; Pucher and Buehler 2006). Therefore, investment in bicycling-friendly communities may help reduce the need for personal motor vehicles. Finally, improvements to public transportation networks are also important because they provide an alternative to the personal vehicle for longer commutes and winter climates, where bicycling and walking are not always feasible options. There are opportunities to reduce emission sources even in urban communities, thereby reducing personal exposure to air pollution.

Study results like these commonly raise the question, "so what can I do to protect myself and my children?" In Canada, citizens are becoming familiar with the Air Quality Health Index, which relays daily regional air quality information to the public and allows vulnerable citizens to take precautions (Environment Canada 2008). However, this is of limited utility in asthma prevention because it does not reduce long-term exposure. Primary prevention of air pollution related health effects requires long-term changes to

pollutant levels in our surroundings. Future community planning policies will play a key role in reducing air pollutants in our surroundings, but there are personal choices we can make that will reduce our air pollution exposure today and in the future. We spend an estimated 64-70% of time inside our homes (Klepeis et al. 2001; Leech et al. 1996) and this is likely to be even higher for young infants. Therefore, the home environment is an important determinant of our exposure. Many outdoor pollutants, such as fine particulates, penetrate into the indoor environment (Dockery and Spengler 1981). HEPA filters have been shown to reduce pollutant levels inside the home (Barn et al. 2007). Limiting indoor sources of pollutants is also important for reducing exposure, for example, by venting gas stoves and not smoking indoors. However, many personal protective measures are of limited utility in reducing exposure to outdoor air pollution and are not feasible at the population level. Therefore, perhaps the most important step we can take as individuals is to demonstrate our commitment to clean air through our personal choices. Choosing low-emission transportation, living close to where we work, and voicing our concerns to policy makers are all important steps to influencing the air quality of the region.

3.5 Direction of Future Research

The essential next step in research is to follow existing birth-cohorts into school age. The handful of birth-cohort studies that have examined air pollution and asthma incidence have only followed children up to a maximum age of six (Morgenstern et al. 2008). In order to determine whether air pollution is associated with persistent asthma, birth-cohorts should be followed up until school age or later when asthma diagnosis is more certain.

In British Columbia, continuing follow-up of the current birth-cohort is relatively simple. The administrative health database will continue to track the children's health care contacts for as long as they reside in British Columbia. Similarly, ongoing air pollution data is available for the Georgia Air Basin to allow for life-time exposure estimates in addition to in utero and first year exposure estimates. Re-confirmation of the positive association between elevated air pollution exposure and asthma incidence in school age children followed since birth would help provide strong evidence of a meaningful causal relationship.

Findings in British Columbia should be supported by studies in other settings, using different data sources. The birth-cohorts established in Munich have so far been analysed up to the age of six and ongoing follow-up continues (Morgenstern et al. 2007; Morgenstern et al. 2008). Primary data collection methods allow for far more detailed covariate information than is possible using administrative data. If followed up to school age and beyond, analysis of these cohorts will also provide important evidence regarding the role of air pollution in asthma development.

In other areas, gene-environment studies of asthma show promise for helping us improve our understanding of the effects of air pollution on asthma development. Advancements in gene technology have allowed for rapid and economical means of detecting genetic polymorphisms, thus opening the door to studies of gene-environment interactions. Research has already begun to examine how our response to air pollutants varies according to our genotype, with promising results. Studies have found that individuals with certain polymorphisms incur increased risks from air pollution exposure (London 2007; Peden 2005). Continuing this line of research is important for it will help

us better understand the development of asthma, and the potential role of air pollution on this process.

Finally, a neglected but vitally important area of research is furthering our understanding of the benefits of air pollution reductions. Despite countless studies linking elevated air pollution levels to asthma exacerbation, few studies have examined the benefits of air pollution reductions, especially in the long term. One of the exceptions is the California Children's Health Study, which tracked lung function growth in adolescent children who moved to different communities. The results were encouraging: adolescents who moved to areas with lower PM showed increased growth in lung function, while children who moved to higher PM communities showed decreased growth in lung function (Avol et al. 2001). This demonstrates the potential for health improvements with air pollution reductions. Further work in this area, in different locations and ideally in young children, would help provide a strong evidence base for policy makers about the benefits of air pollution reductions. The unique vulnerability of young children means reductions in air pollution at this age may yield the most dramatic improvements in health and deserves further study.

3.6 Conclusion

Evidence implicating air pollution as a cause of asthma continues to accumulate. This study adds to the evidence base of previous birth-cohort and asthma incidence studies that even low-level air pollution exposure can increase asthma risk. It is the first study to examine in utero exposure to air pollution and suggest that it may increase asthma risk in children. Although the effect sizes found were small (as in other studies of air pollution and asthma incidence), they are significant in light of the fact that air

pollution exposure is ubiquitous. When exposure is essentially population-wide, small effects still have public health significance. Urbanization continues at a rapid pace and exposure to traffic related air pollution is increasing despite overall decreases in many traditional pollutants (Peden 2005). Although dramatic air pollution reductions appear unfeasible in the short-term, practical opportunities do exist to reduce human exposure. This is likely just one of many steps that will be required to significantly reduce asthma incidence. However, unlike many other implicated asthma causes, air pollution exposure is modifiable and reductions have many co-benefits.

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APPENDIX A – ETHICS APPROVAL

The University of British Columbia
Office of Research Services
Behavioural Research Ethics Board
Suite 102, 6190 Agronomy Road,
Vancouver, B.C. V6T 1Z3

CERTIFICATE OF APPROVAL - FULL BOARD

PRINCIPAL INVESTIGATOR:	INSTITUTION / DEPARTMENT:	UBC BREB NUMBER:
Paul A. Demers	UBC/College for Interdisciplinary Studies/Occupational & Environmental Hygiene	H07-01549

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
UBC	Point Grey Site

Other locations where the research will be conducted:
N/A

CO-INVESTIGATOR(S):
Nina Clark
Michael Brauer

SPONSORING AGENCIES:
Michael Smith Foundation for Health Research

PROJECT TITLE:
The effect of air-pollution exposure in pregnancy and early childhood on respiratory health

REB MEETING DATE:	CERTIFICATE EXPIRY DATE:
July 12, 2007	**July 12, 2008**

DOCUMENTS INCLUDED IN THIS APPROVAL: **DATE APPROVED: July 18, 2007**

Document Name	Version	Date

The application for ethical review and the document(s) listed above have been reviewed and the procedures were found to be acceptable on ethical grounds for research involving human subjects.

Approval is issued on behalf of the Behavioural Research Ethics Board

Dr. Peter Suedfeld, Chair
Dr. Jim Rupert, Associate Chair
Dr. M. Judith Lynam, Associate Chair
Dr. Laurie Ford, Associate Chair

The University of British Columbia
Office of Research Services
Behavioural Research Ethics Board
Suite 102, 6190 Agronomy Road,
Vancouver, B.C. V6T 1Z3

CERTIFICATE OF APPROVAL- MINIMAL RISK RENEWAL

PRINCIPAL INVESTIGATOR:	DEPARTMENT:	UBC BREB NUMBER:
Paul Demers	UBC/College for Interdisciplinary Studies/School of Environmental Health	H07-01549

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
UBC	Vancouver (excludes UBC Hospital)

Other locations where the research will be conducted:
N/A

CO-INVESTIGATOR(S):
Nina Clark
Michael Brauer

SPONSORING AGENCIES:
Michael Smith Foundation for Health Research

PROJECT TITLE:
The effect of air-pollution exposure in pregnancy and early childhood on respiratory health

EXPIRY DATE OF THIS APPROVAL: June 25, 2009

APPROVAL DATE: June 25, 2008

The Annual Renewal for Study have been reviewed and the procedures were found to be acceptable on ethical grounds for research involving human subjects.

Approval is issued on behalf of the Behavioural Research Ethics Board

Dr. M. Judith Lynam, Chair
Dr. Ken Craig, Chair
Dr. Jim Rupert, Associate Chair
Dr. Laurie Ford, Associate Chair
Dr. Daniel Salhani, Associate Chair
Dr. Anita Ho, Associate Chair