EXPOSURE TO RESIDENTIAL AIR POLLUTION AND PHYSICIAN DIAGNOSIS OF OTITIS MEDIA DURING THE FIRST TWO YEARS OF LIFE IN BRITISH COLUMBIA, CANADA

by

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ABSTRACT

Otitis media is the leading reason children visit their doctor or consume antibiotics. It has been postulated that ambient air pollution is a risk factor for otitis, based on the known association with environmental tobacco smoke and a number of recent studies.

This research utilized administrative data to identify and follow a population-based birth cohort of 59,917 children, born during 1999-2000 in southwestern British Columbia. The incidence and recurrence of otitis media was characterized during the first three years of life and available information on risk factors were assessed. Air pollution exposures (CO, NO, NO_2, O_3, $PM_{2.5}$, PM_{10}, SO_2, black carbon, woodsmoke, point source and road proximity) were estimated for the first 24 months of life using ambient monitoring data, temporally adjusted land use regression models and proximity measures; and assigned to children based on residential postal code. The relationship between physician visits for otitis media and 2-month average pollutant exposures was assessed longitudinally. Finally, the economic burden of otitis media attributable to air pollution was calculated using data from the universal healthcare system and estimates from the literature.

Otitis media incidence was relatively low (42% at 2years; 49% at 3years) compared with previous studies and peaked in the winter and at 8-10 months of age. Male gender, First Nations status and low socio-economic status were identified as strong risk factors for otitis media in this population. In analyses that included air pollution, CO, NO, NO_2 and woodsmoke were independent risk factors before seasonal adjustment; and NO, $PM_{2.5}$ and woodsmoke were independent risk factors after seasonal adjustment. For this population, the cost of otitis media attributable to woodsmoke was valued at (2003) $420,464.

Associations were found between otitis media and some air pollutants in a large birth cohort with relatively low ambient air pollution exposure. Null or protective associations (SO_2, O_3, black carbon) may be partially explained by temporal and spatial correlations between pollutants and otitis media. If the associations observed in this study are causal, the substantial economic burden attributable to air pollution suggests that it be considered a modifiable risk factor for this important childhood disease.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

BAQS	Border Air Quality Study
BC	British Columbia
CO	carbon monoxide
DA	(Census) dissemination area
HR	hazard ratio
ICD-9	International Classification of Diseases, 9th Edition
IDW	inverse distance weighted
IQR	inter-quartile range
LUR	land use regression
NO	nitric oxide
NO2	nitrogen dioxide
O3	ozone
OR	odds ratio
PM10	particulate matter of less than 10 micrometers in aerodynamic diameter
PM2.5	particulate matter of less than 2.5 micrometers in aerodynamic diameter
RR	risk ratio
SD	standard deviation
SO2	sulphur dioxide
UBC	University of British Columbia
$\mu g/m^3$	micrograms per cubic meter of air
95% CI	95 percent confidence interval

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CO-AUTHORSHIP STATEMENT

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Michael Brauer supervised this work and contributed critical and thoughtful comments throughout. Dr Brauer also provided essential expertise in air pollution exposure assessment.

Paul Demers served on the supervisory committee and provided extensive expertise in statistical theory and methodology.

Catherine Karr served on the supervisory committee and provided insight into the pathology, diagnosis and treatment of otitis media.

Mieke Koehoorn assisted in developing the analysis plan and provided expertise in the use of administrative data for epidemiologic research.

Cornel Lencar created the air pollution variables derived from regulatory monitoring stations.

Lillian Tamburic assisted with data access and management. She also assisted in identifying data sources for the calculation of physician visit and hospitalization costs (chapter 4).

1 INTRODUCTION AND LITERATURE REVIEW

1.1 Rationale

Otitis media, or middle ear infection, is the leading reason children visit a physician or receive antibiotics (1-5). Otitis media can lead to structural damage of the middle ear and perforation of the tympanic membrane (6, 7), and it is estimated that 70-90% of Canadian children under 2 years will at some point experience hearing fluctuations due to this disease (8). When otitis is chronic or recurrent this temporary hearing loss may impact a child's ability to perceive words and acquire language during their first years of life (9), potentially impacting speech and cognition (7, 10-13).

Although this disease primarily affects young children, its overall economic burden is comparable with that of chronic respiratory diseases (14). Costs associated with otitis media have been estimated as $611 million or $21.07 per person (1994) in Canada and $5.8 billion or $109.28 per child (1998) in the United States (14, 15). Due to the high prevalence, treatment costs, associated complications and potential for long-term learning disability; identification and management of preventable risk factors is considered a high priority.

Environmental tobacco smoke is recognized as a strong risk factor for otitis media (16), likely due to alteration of immune defenses (17, 18) and increased susceptibility following inflammation of the respiratory epithelium (19). Few studies have examined ambient air pollution in relation to otitis media, but household biomass burning has been identified as a risk factor (20, 21) and an association was observed between otitis media incidence and traffic-related air pollution in Europe (22).

As part of the Border Air Quality Study (23), the work described in this thesis characterized otitis media, evaluated the relationship between otitis media and ambient air pollution and calculated the economic burden of otitis media attributable to air pollution in southwestern British Columbia, a region with lower air pollution concentrations than those found in other urban areas across Canada and the United States (24).

1.2 Research Hypothesis

Approximately 90% of all acute otitis media is caused by bacterial or viral pathogens that migrate from the nasopharynx into the eustachian tube and middle ear (25). This thesis is

based on the hypothesis that air pollution is an effect modifier in the causal pathway resulting in otitis media via suppression of the immune system (figure 1-1).

An episode of otitis media usually follows a viral upper respiratory tract infection. This is due to the disruption of mucociliary clearance, adenoid enlargement and eustachian tube congestion that occur during viral infection (17). Tubal obstruction leads to the accumulation of mucosal secretions and pathogens that enter the middle ear can then replicate, resulting in acute signs and symptoms of infection (7).

Similar to viral upper respiratory tract infections, the strong and consistent association between environmental tobacco smoke and otitis media is believed to be due to the following processes (19, 26): (i) inflammation and swelling of mucosal surfaces throughout the nasopharynx, eustachian tube and middle ear - making pathogen attachment easier, (ii) impaired mucociliary clearance leading to eustachian tube obstruction and dysfunction, (iii) decreased eustachian tube patency, and (iv) goblet cell hyperplasia leading to mucoid middle ear effusion.

Ambient air pollutants likely initiate processes similar to those mentioned above, as they have been shown to cause inflammation of the respiratory airways, mucosal swelling, decreased cilia clearance and decreased eustachian tube patency (27-30). Thus, the biological mechanism for air pollutants may be similar to that of prior viral infection, where the disruption of homeostasis results in impaired host response, pathogen proliferation and a higher probability of infection within the middle ear cavity.

In examining the above research hypothesis, this thesis will consider the following issues:

1. Examination of different outcome definitions
    a. Otitis media incidence (acute otitis media)
    b. Otitis media recurrence (recurrent otitis media)
2. Examination of different exposure windows
    a. Chronic exposure to air pollution – an impaired developing immune system means children are always more susceptible than their non-exposed counterparts.

b. Acute exposure to air pollution – an impaired response of the functioning immune system means children are more susceptible only during periods of high air pollution exposure and co-exposure to pathogens.

1.3 Literature Review

1.3.1 Urban Air Pollution

Urban air pollution is ubiquitous and exists as a complex mixture of gases, liquid droplets and particles. Primary air pollutants are emitted directly into the atmosphere while secondary pollutants are a result of chemical reactions between primary pollutants, with other secondary pollutants and atmospheric constituents (31). Primary pollutants arise from both anthropogenic (industry, residential woodburning, transportation) and natural (forests, sea spray) sources (32).

The exposure pathway from air pollution source to receptor is complex and may be modified by; time, additional sources, topography, meteorology, secondary transformation and individual/host factors (32). Meteorology acts on the transport of pollutants through diffusion and dispersion. Diffusion is the dilution of pollutants in the atmosphere while dispersion is the movement of pollutants, either horizontally (due to wind) or vertically (due to atmospheric instability) (33).

One example of an extreme impact of meteorology on pollutant concentrations is a temperature inversion. Inversions are formed when warm air lies above colder air, making conditions very stable and eliminating or minimizing vertical dispersion (33). The London fog of 1952 was caused by a temperature inversion lasting only 4 days, smoke and sulfur dioxide levels were 5-19times above regulatory guidelines, leading to approximately 12,000 excess deaths (34).

During the London fog, air pollution was largely attributable to the domestic use of dirty fuel and industry. Today, due to strict government regulations and technological improvements, the sources of primary concern in urban areas of the developed world are transportation-related (motor vehicles, marine vessels).

1.3.1.1 Common Air Contaminants

The common air contaminants listed by Environment Canada include; nitric oxide (NO), nitrogen dioxide (NO_2), ozone (O_3), sulfur dioxide (SO_2), carbon monoxide (CO), particulate matter less than 10 micrometers in aerodynamic diameter (PM_{10}) and particulate matter less than 2.5 micrometers in aerodynamic diameter ($PM_{2.5}$) (32). Combustion of fossil fuels in automobiles and marine vessels, and for generation of electricity produces CO, NO_2, SO_2, $PM_{2.5}$ and PM_{10}. As such, population growth and urban sprawl tend to lead to increases in these pollutants.

CO and NO are emitted from the combustion of fossil fuels, most importantly for transportation and electricity generation. During combustion, a small fraction of carbon will be incompletely oxidized to CO. NO will quickly react with oxygen (O_2) and O_3 to form NO_2 (35). Additionally, molecular nitrogen (N_2), which is emitted from decaying plants and animals and always present in the atmosphere, will react with the above pollutants to form NO_2. O_3 is a secondary pollutant that always occurs with other pollutants (36) and is produced by photochemical reactions between NO/NO_2 and volatile organic compounds. Because O_3 can only be formed in the presence of sunlight, levels will be highest during mid-day in the summer months (35). Also, because O_3 can react with NO to form NO_2 it is often inversely (spatially) correlated with these pollutants. NO and NO_2 levels will be higher in the winter due to the lack of photons available to form O_3 (35). For primary pollutants, reducing emissions at the source leads to reductions in atmospheric concentrations. However, for secondary pollutants, reducing concentrations is far more complex – for example, reducing local emissions of NO/NO_2 can lead to an increase in O_3. (31).

SO_2 is emitted during the combustion of sulfur containing fossil fuels, most notably coal. Current SO_2 level are fairly low due to significant reductions of sulfur content in fuel and engineering controls on coal-fired power plants (32). However, marine transportation and the oil & gas industry continue to be significant sources. SO_2 easily dissolves in water to form acid aerosols and oxidation in the presence of NO_2 can create acid rain.

Particulate matter (PM) is made up of particles of various sizes and chemical compositions. These particles are produced by incomplete combustion of fossil fuels ($PM_{2.5}$), atmospheric reactions ($PM_{2.5}$) of gases to form secondary particles and mechanical processes (PM_{10}) such

as: wind blown dust, road dust and tire wear (31). Source apportionment of PM in the western US found the main sources to be fugitive dust, transportation and woodsmoke (31). Diesel particles consist primarily of elemental carbon and carbon-based compounds. Black carbon, or elemental carbon, is produced by the incomplete combustion of carbon containing fuels (37).

1.3.1.2 Exposure Assessment

Exposure occurs when an environmental pollutant reaches a receptor, or individual, and is dependent upon the pollutant concentration and length of contact. Exposure may be modified by personal behaviors, such as playing outside mid-day when ozone levels are highest, and susceptibility, such as stage of respiratory development (38). Total personal exposure is the sum of all exposures encountered in various microenvironments (38). To calculate true personal exposure to air pollution it is necessary to collect data on where people spend their time, what the ambient concentration is in each of these locations and what fraction of time is spent at each location. Accurate estimation also requires information on the temporal and spatial variability of the pollutant(s) being studied, as ambient concentrations will not be uniform in each location (38). In epidemiology, investigators must decide on the appropriate balance between the benefit of improved accuracy and the increased resource requirements for detailed and/or individual-based exposure assessment; the most commonly employed methods include (in general order of increasing cost and accuracy) (38):

i) Classification of exposure based on a surrogate (e.g. proximity of residence to major roadways, presence of wood burning fireplace)
ii) Measured concentrations or models predicting outdoor concentrations
iii) Measurement of outdoor and indoor concentrations
iv) Measurements in all locations and collection of time-activity diaries
v) Direct measure of personal exposures

Air pollution concentrations can be directly measured at the regional, neighborhood or individual level. Models combine measurement data (emission inventories, ambient monitors, directed sampling campaigns) with additional information (meteorology, topography, source-based characteristics). Models (dispersion, land use regression) are advantageous, especially for application to large study populations, in that exposures can be

estimated for the entire study area while personal exposure measurements for a subset of the study population can be used to evaluate the model's applicability (38).

Misclassification of exposure can result in biased estimates of health effects (39), and accurate exposure assessment continues to be a challenge, particularly for large studies. Because individuals typically spend most of their time at their residence, or in the vicinity of their residence (40), residential location is a major determinant of exposure to outdoor air pollution (41, 42). However, ignoring other locations (such as daycare) will introduce bias into studies that assign exposure based solely on measured/modeled concentrations at the home address and failure to accurately capture residential mobility can also result in biased estimates.

Additionally, people spend most of their time indoors, and indoor pollutant concentrations are a result of both indoor and outdoor sources. Infiltration rates, the rate at which outdoor pollutants enter indoor environments, can be highly variable and depend on pollutant characteristics, meteorological factors and building characteristics (43). Without information on indoor sources and infiltration rates, assigning concentrations that are measured/modeled outside the home to individuals who spend most of their time indoors can also result in biased risk estimates (38).

In time-series studies, data from regional monitors are often used because of the high time-resolute data; while in cohort studies, regional monitors may not provide the necessary spatial resolution and may be used in conjunction with models. Finally, one of the most important considerations when assigning exposures is deciding upon the appropriate exposure window. The exposure window should correspond to the type of health effect being considered; acute health effects generally reflect short-term exposure windows (daily) while chronic health effects reflect the impact of long-term exposure windows (yearly) (44).

Children are a population of special concern with respect to air pollution because they: are more often outside, more physically active and thus increased ventilation and deeper breathing, more likely to be mouth breathers, inhale more air per unit of body weight, have larger lung surface area per unit of body weight, and their respiratory and immune systems are still developing (45). In addition to the above factors, children also incur higher morbidity due to acute respiratory infections, compared to older populations (46). Taken together, these

characteristics suggest a critical period during early life where children are vulnerable to the harmful effects of air pollution.

1.3.2 Otitis Media

1.3.2.1 Economic Burden

Otitis media causes significant utilization of medical services, parental lost time from work and overall reduced quality of life for young children and their parents (47). The costs for diagnosis and treatment of otitis media in children under 14 years range from $428 million (1994) or $77.01 per child in Canada to $5.8 billion (1998) or $109.28 per child in the United States (14, 15). Direct costs of otitis media include physician visits, prescriptions, surgical procedures, audiometry, speech pathology and hospitalizations related to otitis media or its complications (7). Indirect costs include caregiver lost time from work, childcare expenses and travel to and from the physician (13, 47).

The total cost of diagnosing and treating one episode of otitis media in the United States was $115.80 in 1994 (13), and recurrent episodes were more costly ($124.64) than initial episodes ($107.81). The total cost of diagnosing and treating one outpatient episode of otitis media in Canada was $295 in 2001 (48). Moreover, children incur the highest total annual expenditures per child for otitis media physician visits, prescriptions and surgical procedures during the first two years of life (15).

1.3.2.2 Pathogenesis

The anatomy of the upper respiratory system and middle ear cavity are important in understanding the pathogenesis of otitis media and thus the biological mechanisms discussed in this chapter. The outer ear and middle ear are separated by the tympanic membrane. This membrane is not air permeable but is capable of movement. For the auditory system to function, it is necessary that the middle ear cavity be filled with air of equal pressure to that of the ambient environment. When the middle ear is filled with liquid or with air of negative/positive pressure, the eustachian tube is no longer functioning properly and hearing becomes impaired.

The eustachian tubes open into the middle ear cavities at their distal ends and into the pharynx at their proximal ends. The proximal end remains closed during rest, but will open

during swallowing, yawning, sneezing or crying. This opening is essential for pressure equalization between the middle ear and ambient air. The chief functions of the eustachian tube are; (i) pressure equalization, (ii) fluid clearance via muscle contraction and cilia movement and (iii) protection (7). Unfortunately, the eustachian tube also provides a pathway for pathogens colonizing in the upper respiratory tract to enter the middle ear.

During viral infection of the upper respiratory tract, congestion of the mucosa lining the eustachian tube and middle ear promotes additional viral and bacterial infection by impairing eustachian tube function (6). Acute otitis media can be caused by many different viruses (respiratory syncytial virus, rhinovirus, influenza, adenovirus, parainfluenza, enteroviruses)(49), bacteria (*Streptococcus pneumonia*, *Haemophilus influenza*, *Moraxella catarrhalis*)(7, 50, 51) and in rare cases by an immune response to a non-pathogenic allergen (7, 51). A recent review found that up to 87% of all acute otitis media was caused by one of the three bacterial pathogens listed above (52). These bacteria are part of the commensal flora in the nasopharynx, but upon entering the middle ear they will begin to proliferate, triggering an immune response.

The middle ear cavity is sterile in a healthy child, with very few immune cells. When mucociliary clearance is impeded, pathogen proliferation in the middle ear will trigger an immune response leading to increased blood flow, increased goblet cells, eustachian tube obstruction and continued pathogen proliferation. Inflammatory cells will induce and sustain injury by generating proteolytic enzymes and reactive oxygen species (53). Pathogens will induce both systemic and local antibody responses in the middle ear (54), and the low concentrations of immunoglobulin IgG and IgA that occur after birth are thought to curtail an infants ability to fight the infection (55, 56).

Throughout the first two years of life there is continuous growth and development of the immune (57) and respiratory systems (58), while at the same time anatomical, physiological and environmental changes are also occurring (55). Young children are more susceptible to otitis media because their immature immune response and underdeveloped eustachian tubes increase the likelihood of pathogens entering the middle ear cavity (26, 59). Although the middle ear cavity is fully developed at the time of birth, the eustachian tube does not fully develop until adolescence/early adulthood (7). The most notable differences between the

infant versus adult eustachian tube include: shorter overall tube length (~18mm versus ~37mm), lower angle of the tube to the horizontal plane (0-10^{o} versus 45^{o}), immature opening mechanism due to poor muscle contact, and greater flexibility (60-62). These anatomical differences result in impaired clearance, ventilation and protection, and are responsible for the high rate of otitis media observed in infants versus adults (63). Additionally, the adenoids, which are located at the proximal ends of the eustachian tubes, are larger in children and can more easily block the tube opening when swollen due to infection (7, 17). Physiological characteristics also play a role because the infant immune system is immature and less able to destroy pathogens due to declining levels of passive antibodies following birth and breastfeeding cessation (64).

1.3.2.3 Disease Definitions

Otitis media, or middle ear infection, is described as inflammation of the middle ear without reference to etiology or pathogenesis (7). The vast majority of otitis media diagnosed in outpatient physician settings is acute otitis media, often coinciding with or following an upper respiratory tract infection.

The are three states of otitis media:

Acute otitis media is defined as the rapid onset (within 24 hours) of signs and symptoms of acute infection within the middle ear (9). In the earliest stage there will be inflammation of the mucous and tympanic membranes, leading to eustachian tube obstruction (7). This is followed by accumulation of purulent middle ear fluid, causing the tympanic membrane to bulge outward upon examination (65). Diagnosis of acute otitis media requires the presence of fluid in the middle ear and one or more local or systemic sign: otalgia (ear pain - often characterized by pulling on or rubbing the ear in the young child), otorrhea (purulent discharge from the ear), fever, or recent onset of irritability. Additional symptoms such as anorexia, vomiting or diarrhea may or may not be present (9).

Recurrent otitis media occurs when there is a defined effusion free interval between acute otitis media episodes. For the purposes of a case definition, researchers have defined this as four or more diagnoses within a twelve-month period or as three or more diagnoses within a six-month period (7, 9, 66, 67). Studies have found that otitis media recurrences occurring more than one month after initial infection are most often due to a new infection, while those

occurring less than two weeks after initial infection are mainly relapses and due to the original pathogen (68).

Chronic otitis media occurs when non-purulent middle ear effusion continues for three months or longer (65). The tympanic membrane is usually neutral or retracted (69) and hearing loss is present, but all other signs and symptoms of an acute infection (fever, pain, vomiting, etc) are missing (7). Although chronic otitis media occurs after an episode of acute otitis media, it can also create conditions in the middle ear that promote pathogen replication, leading to subsequent acute otitis media (63).

1.3.2.4 Diagnosis

Otitis media is most often diagnosed by general practitioners in outpatient settings. Pneumatic otoscopy is the recommended tool for diagnosing otitis media and provides 94% sensitivity and 80% specificity (70-72). While some US research suggests acute otitis media is over diagnosed in young populations (69, 72), this issue has not been examined in Canada. It is recommended that physicians consider the position, mobility, color and translucency of the tympanic membrane for accurate diagnosis (69). During acute otitis media the tympanic membrane has a bulging position, with limited or no mobility upon examination, blood vessels become visible and opaqueness impairs visibility of the ossicle bones (7, 70). Although specific diagnostic criteria differ slightly between specialties (73-76), it is fairly easy to diagnose uncomplicated acute otitis media in the office setting - with the notable exception of newborns, for whom diagnostic accuracy can be challenging because the small caliber of the external ear canal makes visual inspection of the tympanic membrane difficult.

1.3.2.4.1 Coding in Administrative Data

Due to the immediate and painful nature of acute otitis media, it is likely that young children are seen by a physician for diagnosis and treatment. This thesis will assess population incidence and recurrence of otitis media through disease diagnoses in administrative data. The World Health Organization has established a standard system for coding disease diagnoses, the International Classification of Diseases. Codes (9^{th} revision, ICD-9) used for otitis media include:

381 Nonsuppurative otitis media and Eustachian tube disorders

381 .**0** Acute nonsuppurative otitis media

381.**1** Chronic serous otitis media

381.**2** Chronic mucoid otitis media

381.**3** Other and unspecified chronic nonsuppurative otitis media

381.**4** Nonsuppurative otitis media, not specified as acute or chronic

381.**5** Eustachian salpingitis

381.**6** Obstruction of Eustachian tube

381.**7** Patulous Eustachian tube

381.**8** Other disorders of Eustachian tube

381.**9** Unspecified Eustachian tube disorder

382 Suppurative and unspecified otitis media

382.**0** Acute suppurative otitis media

382.**1** Chronic tubotympanic suppurative otitis media

382.**2** Chronic atticoantral suppurative otitis media

382.**3** Unspecified chronic suppurative otitis media

382.**4** Unspecified suppurative otitis media

382.**9** Unspecified otitis media

This system of coding is routinely used in administrative databases of health care utilization. In Canada, due to the universal health care system, these data are available for the entire population and provide a rich data source of information for population-based health research. However, the use of administrative data for research raises issues of data quality and validity because the data are not collected for research purposes (77). Moreover, there may be logistical, ethical and economic constraints in obtaining access to such data.

The accuracy of ICD-9 coding in administrative data has been examined for community-acquired pneumonia (78), upper gastrointestinal disease (79) and appendicitis (80). The first two studies found moderate sensitivities (56.1-78.7%) and high specificities (96.7-99.6%). The appendicitis study examined ICD-9 coding in hospital discharge abstracts and found 84.7% of the records to be accurate. There has been no assessment of the accuracy of ICD-9 coding for otitis media in Canada, but a study in Colorado found otitis media coding to be highly variable, with chronic otitis media sometimes (9-12%) being coded as acute or unspecified (81). The study in Colorado concluded that ICD-9 coding in administrative data could not be used to distinguish between recurrent and chronic otitis media but did not

examine acute otitis media. Where ICD-9 codes are specified only to the first three digits, there has been some success using linked antibiotic prescription data to identify acute infections (15, 82). Together, these studies suggest that defining otitis media based on administrative data may result in some misclassification and disease underestimation, but including antibiotic prescription data should minimize this.

1.3.2.5 Treatment

Acute otitis media spontaneously resolves in up to 70% of cases (83) but antibiotics decrease eustachian tube and middle ear inflammation, significantly improving the long-term prognosis for young children (63). Young children are more likely to receive antibiotics because they have a greater risk of recurrent infections, developing complications and having antibiotic resistant pathogens (9, 84-86). Additionally, even upon successful antibiotic treatment, 30-70% of children will have persistent middle ear effusion that can last weeks to months after initial infection (7).

In British Columbia, during the 1999-2002 period described in this thesis, practice guidelines (84) recommended physicians to administer antibiotics at the time of acute otitis media diagnosis if the child was under two years. First-line antibiotics included amoxicillin or erythromycin-sulfisoxazole, and second-line antibiotics included amoxicillin-clavulanate, azithromycin or clarithromycin. Follow-up included reexamination at 48-72 hours if not improving, evaluation at 3 months if hearing problems were suspected, and referral to an otolaryngologist if the definition for recurrent otitis media was met. Otolaryngologists may choose to treat recurrent or chronic otitis media with surgical therapies, such as tympanicentesis or myringotomy with ventilation tube insertion (7). Additionally, the pneumococcal conjugate vaccine was implemented toward the end of the study period (3) and acute otitis media was expected to decrease by approximately 6-7% upon complete coverage (87, 88).

Outpatient antibiotic prescriptions were recently analyzed for British Columbia children aged 0-15 years (3). During 1996-2003, prescriptions were highest for children aged 0-4 years and acute otitis media (185 scripts/1000 children in 2003) was the leading reason for this age group to receive prescriptions. The authors also noted a downward trend in antibiotic prescription rates over the study period, suggesting that the practice of watchful waiting may

have become more common, and that there was a switch toward more second-line antibiotics, suggesting an increase in antibiotic resistance.

The increasing resistance of bacterial pathogens to certain broad-spectrum antibiotics has impacted the way physicians respond to respiratory infections (7, 89). Antibiotic use is linked to antibiotic resistance because antibiotics eliminate the normal flora of the nasopharynx, making children more susceptible to new pathogens, leading to increased nasopharyngeal carriage of resistant pathogens (83). Furthermore, antibiotics are administered to children in doses that neutralize free floating bacterial cells but not bacterial biofilms (90). Bacterial biofilms are multi-cellular communities of bacterial cells that rely on intercellular signaling to adapt to changes in their environment and express antibiotic resistance (91), and they have been identified in children as young as 6 months with recurrent acute otitis media (92).

The vast majority of children who fail initial acute otitis media treatment will be between 2-24 months of age (50) and approximately 30% will have antibiotic resistant infections (9). A study of children undergoing myringotomy or typanometry in Toronto identified resistance to penicillin in 24% of the cultured *Streptococcus pneumonia*, 40% of the *Haemophilus influenza* and 100% of the *Moraxella catarrhalis* samples (93). Due to increasing antibiotic resistance observed in the most common bacterial acute otitis media pathogens, focus has shifted from treatment to prevention strategies (83, 85).

1.3.2.6 Epidemiology

The epidemiology of otitis media has received considerable attention. Young age has previously been discussed as an important factor in disease pathogenesis (59, 94) and the highest age-specific incidence occurs at 6-18 months (64, 95). Young age is also very important for children who develop recurrent otitis media (96), these children are unable to clear middle ear effusion, making them susceptible for re-infection (95) – 50% of those with otitis media prior to 6 months will go on to develop recurrent disease (7, 63, 97, 98). Furthermore, children with no history of disease by their third birthday are unlikely to ever have chronic or recurrent infections (7). Otitis media also exhibits the same seasonal trend observed with upper respiratory tract infections, peaking in the winter months (64, 99) and dipping during the summer (9, 100, 101).

A documented increase in otitis media rates during the 1980s and 90s lead to considerable investigation of otitis media risk factors (95, 102), particularly; male gender, atopy, premature birth, aboriginal status, ethnicity, breastfeeding, older siblings, daycare, socio-economic status and environmental tobacco smoke. There is consistent evidence for male gender (66, 103, 104), aboriginal status (105-110), craniofacial anomalies, the presence of older siblings, early attendance at daycare and group size of daycare (9, 64, 66, 111), socio-economic status (112) and environmental tobacco smoke (16, 21, 99). There is also some evidence for breastfeeding (7, 66, 113) and atopy (106, 114, 115). To date, the evidence for premature birth (116-118), birth season and ethnicities other than aboriginal (119) has been mixed. Both breastfeeding and atopy can be linked to the immune system, while older siblings and daycare attendance result in increased pathogen exposure. There are also clear relationships between these risk factors. For example, children who attend daycare at a younger age are probably breastfed for a shorter duration, and children exposed to environmental tobacco smoke are probably in families of lower socio-economic status (96).

Environmental tobacco smoke is most strongly associated with otitis media during the first year of life (95) and exposure likely acts through alteration of immune defenses (120) and eustachian tube dysfunction (17, 18). Two meta-analyses have examined the evidence for environmental tobacco smoke (121, 122); the first calculated a pooled odds ratio (OR) of 1.19(95%CI:1.05-1.35) using 4 cohort studies and a pooled OR of 1.58(1.11-2.24) using 7 case-control studies for otitis media, the second calculated a pooled OR of 1.48(1.08-2.04) for recurrent otitis media (122). Postnatally, maternal smoking is a stronger risk factor than paternal smoking (66, 123) and gestational exposure is a risk factor independent of postnatal maternal smoking (16, 66, 124). Although important, postnatal tobacco smoke may not be enough to alter the course of otitis media as one study found an increased risk only in the presence of additional otitis media risk factors (125).

Despite the considerable attention that otitis media has received, unexplained variability in disease susceptibility and incidence persists. Due to concerns regarding rising incidence and antibiotic resistance, further explanations need to be explored.

1.3.2.7 Otitis Media and Air Pollution

The use of biomass for cooking has been identified as a risk factor for otitis media in two studies from the developing world; a case-control study in Mozambique found children under 2 years to have an OR of 3.09(2.00-4.78) for otitis media if living in homes that burned charcoal or wood as sources of energy versus cleaner fuels (21), and a study in Nigeria found the use of wood as cooking fuel to be significantly associated with acute otitis media in children aged 1-4 years (126). Both of these studies examined extremely high concentrations of air pollution in relation to what is measured in the developed world. In a case-control study in rural New York the use of wood burning stoves was significantly associated with otitis media (OR:1.73(1.03-2.89)) (127) but a second study during the first year of life for over 900 infants found no association for wood burning in the home (106).

Few studies have examined the impact of outdoor air pollution. Living in high air pollution areas was associated with acute otitis media during the first year of life (OR:2.01(1.05-3.84)) in Spain (128) and living in regions with high air pollution was associated with otitis media in Brazil (129). Recently, improved air quality was associated with decreased rates of otitis media in US children (130). Unfortunately, these studies provided no information on the specific air pollutant component or mixture responsible, and potential confounding is a limitation for all of these studies. In another regional comparison, the prevalence rates of otitis media decreased (31% to 26%) with improvements in total suspended particulate and SO_2 in a group of children examined in a series of repeated cross-sectional surveys after German reunification (131, 132).

A study from the Netherlands (133) followed almost 3,000 children from birth to age two and found increased risks of physician diagnosed ear, nose and throat infections with exposure to $PM_{2.5}$ (OR: 1.20(1.01-1.42)), soot (1.15(1.00-1.33)), and NO_2 (1.16(1.00-1.34)) after adjustment for passive smoking, maternal education, gender, siblings, breastfeeding, parental atopy, gas stove, pets, ethnicity and region (133).

In a follow-up to this study and in the first specific examination of urban air pollution and physician diagnosed otitis media, Brauer et al (22) followed more than 4,000 children from birth to age two (The Netherlands (n=3,714); Munich, Germany (n=665)) and found an increased risk of otitis media for exposure to $PM_{2.5}$ (Netherlands: OR:1.13(1.00-1.27);

Munich: 1.24(0.84-1.83)), particle absorbance (1.10(1.00-1.22); 1.10(0.86-1.41)), and NO_2 (1.14(1.03-1.27); 1.14(0.87-1.49)). Annual air pollution concentrations were assigned based on residence at birth, and calculated from traffic-related air pollution land use regression models. The models were based on 40 measurement sites in each country and the models for The Netherlands explained more variability in the measurement data than did those for Munich . This study adjusted for: sex, parental atopy, maternal education, older siblings, maternal smoking during pregnancy, environmental tobacco smoke, gas cooking, indoor moulds, dampness, breastfeeding and pets.

In summary, there is strong evidence for environmental tobacco smoke and growing evidence for indoor biomass and ambient air pollution as risk factors for otitis media. To understand the biological mechanisms involved it is important to consider the experimental evidence. Due to the paucity of experimental data on air pollution and otitis media, a review of the extensive data on air pollution and respiratory infection/immune suppression follows.

1.3.3 Air Pollution and Respiratory Infection

When air pollutants are inhaled, their first contact is with the respiratory epithelium; and gases will disperse more readily than particles. The penetration and toxicity of gases depends on the partial pressure in the mixture, diffusibility and solubility. Gaseous pollutants are deposited along the epithelium by chemical reactions and the point of contact depends on the characteristics of the pollutant – SO_2 has high solubility so it will react mainly in the upper airways, while O_3 and NO_2 have relatively lower solubility so they mostly react in the lower airways, particularly in the transitional zone (46). Particles will deposit on the respiratory tract by a number of mechanisms (settling, inertial impaction, diffusion) depending on their aerodynamic properties with PM_{10} primarily depositing in the upper airways and $PM_{2.5}$ mainly depositing in the pulmonary regions (134).

The mucosa of the eustachian tube and middle ear is similar in structure and function to that of the respiratory epithelium ; therefore it is likely that air pollutants can similarly impact the mucosa of all three regions (135). Defence mechanisms of the respiratory epithelium include; pulmonary surfactant, mucus secreting goblet cells, mucociliary clearance, phagocytosis by alveolar macrophages, local and systemic innate and acquired immunity (46). Most urban air pollutants will cause damage to the respiratory epithelium through direct

or indirect oxidizing pathways, leading to increased cytokine production and inflammation (136). Antioxidants such as uric acid and glutathione are present in pulmonary surfactant and protect the lining from oxidants, but sufficient exposure will overwhelm the antioxidant system and result in ciliostasis of the upper and lower airways (135), which in turn prevents nasal and bronchial mucosa from filtering pathogens (46). Some air pollutants will indirectly recruit immune cells to the respiratory system via release of pro-inflammatory cytokines and cells such as neutrophils will begin synthesizing reactive oxygen species locally, causing additional damage (134, 137).

There are no controlled studies on children's exposure to air pollution, but short-term acute exposure of healthy adults suggest that oxidant pollutants may play a role in increasing susceptibility to viral infections:

NO_2 causes reduced mucociliary clearance, lipid peroxidation of cell membranes (138), epithelial hyperplasia, impaired mucociliary function of nasal epithelium (139), impaired alveolar macrophage function, suppressed antibacterial defences (140) and signals the immune system to send inflammatory cells to the respiratory system (141-143). Repeated exposure to NO_2 results in decreased alveolar macrophages and lymphocytes in peripheral blood (144).

O_3 is a stronger oxidant than NO_2 and can disrupt the epithelial barrier, leading to increased permeability. This disruption may allow entry of potentially toxic particulate across the epithelia (53, 145, 146) and partially explains the synergistic effects observed with O_3 and other pollutants (147). O_3 also impairs mucociliary clearance, causes inflammation of the nasal mucosa, stimulates the release of inflammatory mediators, impairs phagocytosis by macrophages, and may impair the ability of neutrophils to respond to bacterial pathogens (53, 141, 148). O_3 increases susceptibility to inhaled pathogens by inactivating phagocytic cells, particularly macrophages (149).

The principle response mechanism of the lung to inhalation of particulate matter is clearance. Insoluble particles captured by bronchial secretions are eliminated by coughing or mucociliary clearance (150). However, particulate matter may impair mucocilliary clearance and has been shown to induce oxidative stress in human bronchial epithelial cells, increasing the production of proinflammatory cytokines (151, 152), resulting in decreased microbial

elimination (153-157). The effects of particulate matter are not solely determined by particle size, the amount of cytokine produced in response to PM_{10} is more than ten times the amount produced for the same mass of $PM_{2.5}$ (158, 159).

Numerous studies have shown that air pollution adversely affects respiratory defense mechanisms and makes the infant/child respiratory system more susceptible to infection (27-30, 111, 160, 161). Specifically, NO, NO_2 and O_3 have been shown to exacerbate viral inflammation and increase the susceptibility of epithelial cells to viral injury (162-164). The oxidative stress produced by particulate matter and oxidizing pollutants can increase susceptibility to infection (158), exacerbate the inflammatory effects of viral infections (29), and may reduce viral uptake by alveolar macrophages (165). Additionally, $PM_{2.5}$ exposure in children was shown to significantly modify serum antibody levels suggesting that $PM_{2.5}$ may lead to systemic immune changes independent of pathogen exposure (28).

Epithelial damage is a critical initiation step in increasing susceptibility to infection (143) and can be caused by numerous air pollutants and viral pathogens (46). Exposure of viral infected cells to NO_2, O_3, PM_{10}, carbon black or diesel particles exacerbates viral infection by producing additional pro-inflammatory cytokines, resulting in more infected cells (147, 166-169). However, not all results have been consistent, alveolar macrophages incubated with virus and then exposed to O_3 showed no altered susceptibility (170) while exposure to PM_{10} resulted in a 50% decrease in viral uptake (165), and a dose-dependent increase in survival of Streptococcus pneumonia (171).

There are a large number of observational studies that have examined the impact of air pollution on children's respiratory health. A full review of these studies is not necessary to understand the research hypothesis of this dissertation; however, the more notable studies are briefly considered here. In two German birth cohorts followed until the age of two, traffic related pollution was associated with cough during the first year of life without infection OR:1.34(1.11-1.61) for $PM_{2.5}$, 1.32(1.10-1.59) for PM absorbance, 1.40(1.12-1.75) for NO_2; and dry cough at night 1.31(1.07-1.60) for $PM_{2.5}$, 1.27(1.04-1.55) for PM absorbance, 1.36(1.07-1.74) for NO_2 (172) and effects were attenuated during the second year of life. Increasing levels of PM_{10} were associated with acute respiratory illness in Kenyan children (20) where respiratory disease was found to be a function of PM_{10} exposure concentration

with odds ratios ranging from 3.01(1.59-5.70) at 2-500µg/m^3 to 5.40(2.85-10.22) at 4-7,000µg/m^3. In Toronto, PM_{10} was associated with childhood hospitalizations for respiratory tract infections (OR:1.15(1.02-1.30) for boys and 1.18(1.01-1.36) for girls, for a 6.5ug/m^3 increase in PM_{10}) but there were no significant findings for $PM_{2.5}$, CO, SO_2 or O_3 (173). Biomass fuel use was associated with acute respiratory illness (OR:2.2(1.16-4.19)) in a cross-sectional study of children (n=3,559) under 5 years in Zimbabwe (174) and increased rhinitis, sinusitis and upper respiratory tract infections were found in Brazilian children living in high versus low air pollution regions (175).

1.3.3.1 Summary of Evidence

Based on experimental and epidemiologic studies, there is consistent evidence suggesting an association between a number of pollutants (NO_2, O_3, $PM_{2.5}$, PM_{10} and diesel exhaust) and increased susceptibility to respiratory infection. There is also a large amount of evidence to suggest that air pollution causes more severe illness during respiratory infection, which may suggest an association with recurrent and chronic infectious disease (46). Despite biological plausibility, and well-known associations between air pollution and similar childhood respiratory outcomes, there is little evidence for a causal association between urban air pollution and otitis media and there is a need for examination in a longitudinal study (22).

1.4 The Border Air Quality Study

The research described in this thesis was conducted as part of the Border Air Quality Study (BAQS). This study includes a number of research projects aimed at evaluating the health impacts of air pollution in the Georgia Basin / Puget Sound Airshed (http://www.cher.ubc.ca/UBCBAQS/welcome.htm).

The study region, the Georgia Basin Airshed, is located in Southwestern British Columbia (BC), Canada and includes the municipalities of Vancouver and Victoria. The population within this area was approximately 3 million in 2002 and is expected to exceed 4 million by 2020 (32). Although air pollution concentrations in this region tend to be lower than those found in other urban areas across Canada and the United States (24); this population growth is likely to result in urban sprawl, increased transportation and energy consumption.

In this region, residential woodburning contributes to air pollution in the winter while agricultural sources become important in the spring and summer. Industrial and transportation emissions (motor vehicles and marine transport) are important sources of air pollution throughout the year, with the latter peaking during morning and evening hours (32). Thus, there exists considerable temporal and spatial variability in air pollutant concentrations (176).

1.4.1 Data Sources

The BC Linked Health Database, funded by the Ministry of Health and situated in the Centre for Health Services and Policy Research at UBC (177), provided information from: vital statistics births, vital statistics deaths, registry file updates, outpatient physician billings, hospital separations, and Canadian census data for the province of British Columbia. This was the data source used to identify and follow the study population, create a residential history file, assess otitis media physician visits and hospitalizations throughout the first three years of life, and assess otitis media risk factors. All data were linked based on personal health number, except for census data, which was linked based on census dissemination area.

The BC College of Pharmacists provided information on all prescriptions filled by the study population throughout the first three years of life, based on the PharmaNet database. Archived guidelines for the diagnosis and treatment of acute otitis media were obtained from the BC Ministry of Health Services for the study period of interest (1999-2003). Only those prescription antibiotics that were routinely administered for treatment of acute otitis media were linked to the study population. This data source was linked, based on personal health number, to outpatient physician visits for otitis media and used for sensitivity analyses.

The BC Reproductive Care Program Perinatal Database Registry provided additional information on otitis media risk factors for all enrolled mothers (approximately 90% of all births in the study area)(178). Because these data had not previously been used for epidemiologic research, a validation study using hospital chart data was conducted to ensure that the variables of interest had been recorded into the database with sufficient accuracy (178). This data was linked, based on personal health number, to each child.

BAQS provided information on urban air pollutants modeled at the home address for each month of follow-up (179). This data were linked, based on geographic postal code, to each

child. This data was updated using the registry file to adjust for residential mobility during the study period.

The study procedures were reviewed and approved by the UBC Behavioral Research Ethics Board (Appendix A).

1.4.2 Population

The study population included every child born in the Georgia Basin Airshed from January 1, 1999 to December 31, 2000 (n=59,917). Children were identified based on the maternal residential postal code, listed on their birth certificate. Each child was followed until the age of three years. Thus, follow-up began January 1, 1999 and ended December 31, 2003.

1.4.3 Otitis Media Assessment

Otitis media was defined from outpatient physician billing data based on ICD-9 coding:

381 = non-suppurative otitis media and eustachian tube disorders

381.0 = acute non-suppurative otitis media

382 = suppurative and unspecified otitis media

382.0 = acute suppurative otitis media

382.9 = unspecified otitis media.

All follow-up visits were removed, based on a 14 day exclusion, prior to creating case definitions for recurrent otitis media.

Sensitivity analyses for acute otitis media were completed by linking otitis media physician visits with antibiotic prescriptions.

1.4.4 Risk Factor Assessment

Information was collected on the following otitis media risk factors: age, season, gender, older siblings, First Nations, maternal smoking during pregnancy, breastfeeding initiation, maternal age at birth, gestational age, birth weight, neighborhood level family income, female educational level and rural residence. There was no known data source to control for daycare attendance at the population level, but previous research has found socio-economic status to be highly predictive of daycare status (180, 181).

1.4.5 Air Pollution Exposure Assessment

Exposures were estimated at the centre of each postal code and linked to children based on their residential history file for the study period, measured as monthly averages for the first two years of life. Previous two-month and cumulative first year exposure windows were assigned for each child-month. Air pollution exposures were estimated using three approaches: (i) regulatory monitoring networks, (ii) dedicated sampling campaigns used to develop land use regression models of spatial variation in source specific pollution, and (iii) proximity measures for road type and point sources.

Regulatory monitors were used to assign exposures for ambient: NO/ NO_2 (n=22 locations), CO (n=19), $PM_{2.5}$ (n=7), PM_{10} (n=19), SO_2 (n=14) and O_3 (n=24). Two approaches were considered, the nearest monitor within 10km of each postal code and an inverse distance weighted (1/distance) average of up to three monitors within a 50km circular buffer. For both approaches, monthly monitoring data was considered missing if there was a gap of more than 5 consecutive days or if there were more than 10 days missing in total. Monthly averages were computed for each child for the full duration of follow-up. Exposures were updated using the residential history file and weighted by time spent at multiple residences (postal codes).

The traffic land use regression (LUR) was developed after measuring NO/ NO_2 (n=116), $PM_{2.5}$ (n=25) and black carbon (n=39) at predetermined sites throughout the study area (182, 183). For NO, the model had an R^2 of 0.62 and included the number of major roads within 100m and 1,000m radius buffers of the measurement sites, the number of secondary roads within a 100m buffer, the population density within a 2,500m buffer, and elevation. For NO_2, the model ($R^2 = 0.56$) included the same variables as above plus the amount of commercial land use within 750m. For $PM_{2.5}$, the model ($R^2 = 0.52$) included the amount of commercial and industrial land use within 300m, the amount of residential land use within 750m, and elevation. For black carbon, the model ($R^2 = 0.56$) included the number of secondary roads within a 100m buffer, distance to the nearest highway, and the amount of industrial land use within 750m. Evaluations, based on comparison to additional measurements and cross-validation analysis, indicated that the $PM_{2.5}$ and black carbon models did not perform as well as the NO or NO_2 models. Using the LUR models, smooth spatial surfaces of predicted

(annual average) concentrations were generated for the entire study area at a resolution of 10m. The surfaces were then smoothed (Focal Statistics, ArcGis Spatial Analyst; ArcGIS) to remove abrupt changes and edge effects to more accurately reflect the measured effect of proximity to roadways (Gilbert et al. 2003). For each LUR model, the corresponding monitoring network data for each pollutant were fit with a 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 $PM_{2.5}$ trend was used because there was no corresponding regulatory monitoring network data. From these models, month–year adjustment factors were applied to each surface to estimate monthly average concentrations. Monthly averages were computed for each child for the full duration of follow-up. Exposures were updated using the residential history file and weighted by time spent at multiple residences (postal codes).

The woodsmoke surface (182, 184) was developed through mobile monitoring of particle light absorption, throughout the study area on cold, clear winter nights (n=19). Fixed monitors were located at control sites and potential hotspots to collect 2week samples of levoglucosan, a biomass combustion tracer compound, and $PM_{2.5}$. Postal codes in the top tertile of woodsmoke $PM_{2.5}$, as estimated from the model, were classified as wood burning areas and daily temperature data were used to identify time periods during which elevated concentrations of woodsmoke were present in these areas (179). The number of woodsmoke days for each month of follow-up were calculated and assigned to each child. Exposures were updated using the residential history file and weighted by time spent at multiple residences (postal codes).

Proximity of residential postal codes to expressways, primary highways, secondary highways, and major arterial roads was measured using 50m and 150m buffers (DMTI Arc View street file dataset for BC, Canmap Streetfiles, v2006.3, 2006). Proximity to point sources was measured using an index, assigned to each point source in the study area that reported yearly emissions to the federal government of Canada. This index was assigned to each point source based on its pollutant contribution relative to other point sources in the study area. A proximity-weighted summation of emissions was assigned to each residential postal code using buffers of 10kilometers (179). Again, data were calculated and assigned to children for each month of follow-up, adjusting for residential mobility.

1.5 Study Objective

The objective of this thesis is to examine air pollution as a preventable risk factor for otitis media in a population-based birth cohort (figure 1-1). Prior to investigating this research hypothesis, it is necessary to investigate the utility of using administrative data to characterize otitis media incidence and recurrence at the population level. Subsequent to examining the research hypothesis, the economic burden of otitis media attributable to urban air pollution will be assessed.

Specific objectives include:

(1) Identify birth cohort of children born January 1, 1999 to December 31, 2000 whose maternal residential postal code matches a predefined set of postal codes for the Georgia Basin Airshed.

(2) Linkage of otitis media and risk factor data to cohort.

(3) Examine the utility of using administrative data to characterize the incidence and recurrence of otitis media during the first three years of life; and assess the quality of risk factor data available at the population level (chapter 2).

(4) Follow children through the first two years of life through contacts with the healthcare system to establish a residential history file.

(5) Linkage of exposure data to children based on residential postal code in the residential history file.

(6) Investigate the association between residential air pollution exposure and otitis media (chapter 3).

(7) Calculate the total cost of otitis media treatment and diagnosis for the study population (chapter 4).

(8) Assess the economic burden of otitis media attributable to urban air pollution (chapter 4).

1.5.1 List of Chapters

The layout of this thesis conforms to the manuscript-based thesis guidelines of UBC. Chapter 1 includes the study rational and hypothesis, a review of the pertinent scientific literature relating to urban air pollution and otitis media, the study objective and a summary of the data used for this thesis. Chapter 2 includes the data sources listed in figure 1-2 and characterizes the incidence, recurrence and risk factors for otitis media in the study population throughout the first three years of life. Chapter 2 also evaluates the feasibility of using administrative data presented in chapters 3 & 4. Chapter 3 includes the data sources listed in figure 1-2 and examines the association between urban air pollution and otitis media during the first two years of life - the main research hypothesis of this thesis (figure 1-1). Chapter 4 assesses the total economic impact of otitis media for the study population and evaluates the attributable burden of the findings described in chapter 3. Chapter 5 summarizes the results of chapters 2-4 and discusses their implications with respect to strengths and limitations. This chapter concludes by commenting on the state of the research hypothesis and future recommendations for research.

Air pollution is likely to modify a young child's susceptibility to acute otitis media primarily via an inflammatory response. The response begins when air pollutants enter the upper respiratory system causing local inflammation, mucosal swelling, decreased cilia clearance and decreased eustachian tube patency. This, in turn, leads to impaired host response, pathogen proliferation and greater probability of infection within the middle ear cavity.

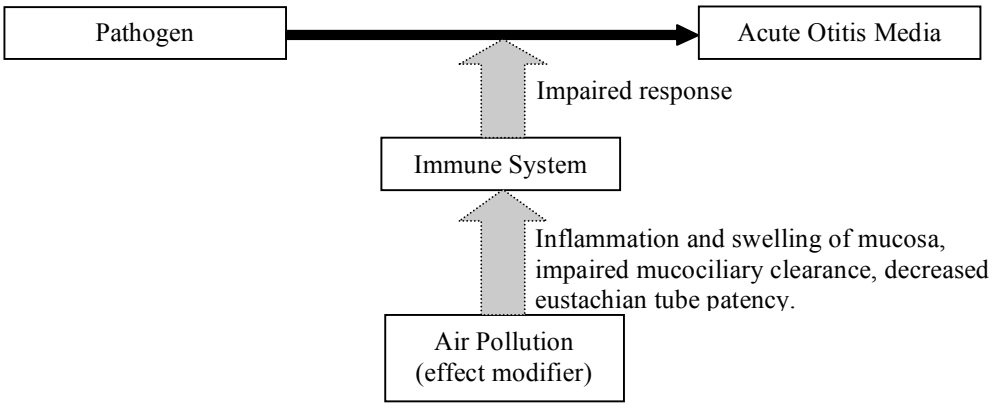

Figure 1- 1. Hypothesized mechanism linking ambient air pollution exposure to increased susceptibility to acute otitis media.

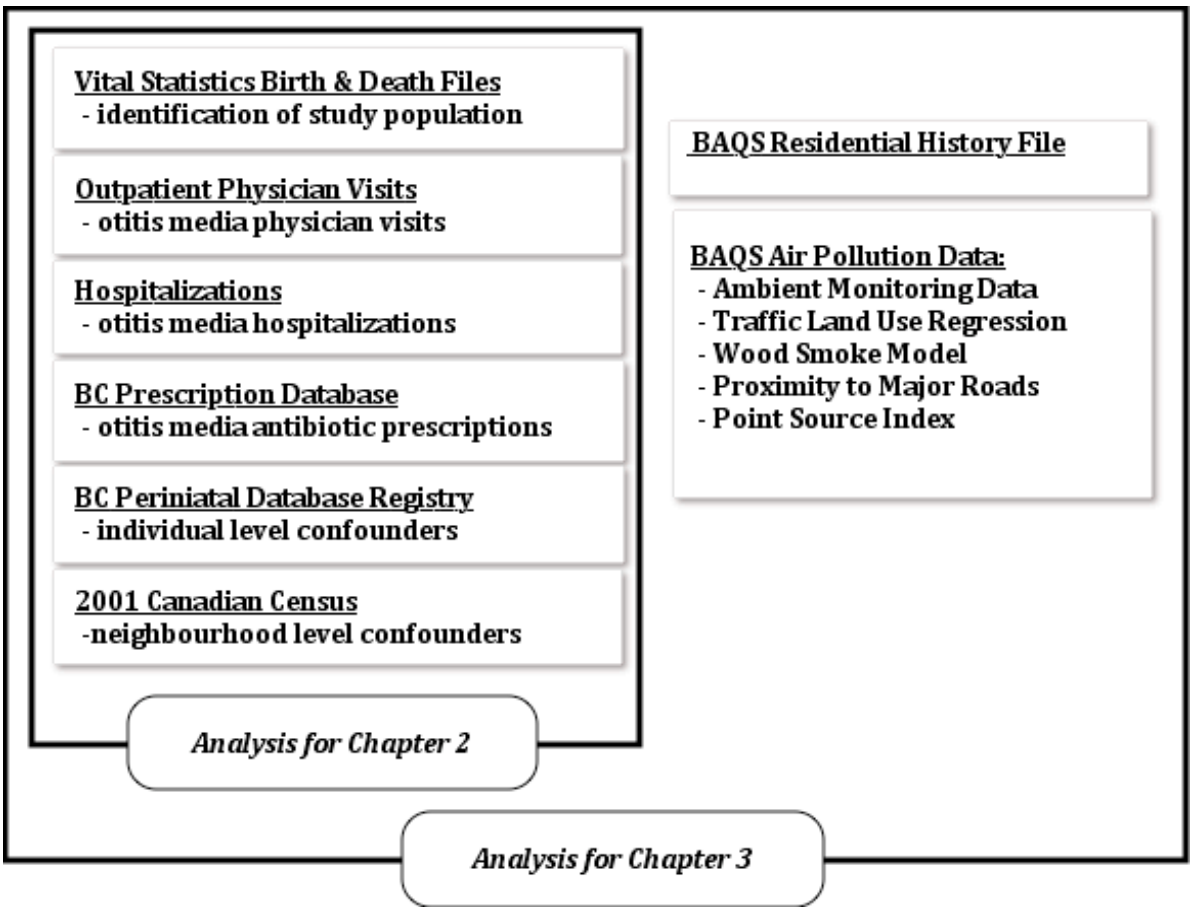

Figure 1- 2. List of data sources used in chapters 2-4.

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2 OTITIS MEDIA INCIDENCE AND RISK FACTORS IN A POPULATION-BASED BIRTH COHORT[1]

2.1 Introduction

Otitis media is the most common reason young children are prescribed antibiotics and a leading reason for physician visits (1, 2). Due to the high incidence, treatment costs, potential for long-term learning disability and increasing antibiotic resistance, accurate characterization of incidence trends and associated risk factors is essential (3). Unfortunately, there have been few studies that follow children through the first years of life (4, 5). Instead, most studies have been cross-sectional (6, 7) or have examined a population from a particular hospital, clinic or physician office.

Otitis media incidence peaks at between 6 to 18 months of age and exhibits the same seasonal trend as upper respiratory tract infections, which often precede and concur with otitis (8). Male gender, First Nations status, lack of breastfeeding, older siblings, daycare, passive smoke exposure and low socioeconomic status have been consistently identified as risk factors during early childhood (9-13). Birth weight, gestational age and season of birth have also been studied but with less consistent findings (14, 15).

As part of an ongoing study (16) we had the opportunity to longitudinally examine otitis media during the first three years of life in a large population-based birth cohort from British Columbia (BC). This research aims (i) to characterize the population incidence, recurrence and risk factors for otitis media and (ii) to evaluate the utility of linking administrative data for population-based epidemiological studies.

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2.2 Methods

2.2.1 Population

This was a case-control analysis nested within a population-based birth cohort. Vital statistics birth certificate information was collected from the BC Linked Health Database, maintained by the Centre for Health Services and Policy Research. The BC Ministries of Health were the original source for the BC Linked Health Database extract. Every singleton birth in southwestern BC from January 1, 1999 to December 31, 2000 was identified based on maternal postal code and date of birth. Children who died during follow-up or those with incomplete risk factor information were excluded.

2.2.2 Outcome Measure

The BC Linked Health Database also provided information on all outpatient physician visits during the first three years of life based on children's unique personal health number (PHN) and date of encounter. Otitis media physician visits were identified using ICD-9 coding: 381-nonsuppurative otitis media and eustachian tube disorders, 381.0-acute nonsuppurative otitis media, 382-suppurative and unspecified otitis media, 382.0-acute suppurative otitis media and 382.9-unspecified otitis media. Any visit occurring within two weeks of a previous visit was assumed to be a follow-up or treatment failure and was therefore excluded. Recurrent otitis media (ROM) was defined as four or more visits during a twelve-month window or as three or more during a six-month window (8).

Prescription records for antibiotics used to treat acute otitis media (17) were obtained from the BC College of Pharmacists and data were linked to otitis media physician visits, based on PHN and allowing a 0-4 day lag between physician and pharmacy visit. Linked data were used for sensitivity analyses.

2.2.3 Risk Factors

Gender and month of birth were obtained from birth certificates. First Nations status, as defined by federal billing data, was ascertained from birth hospitalization files. Information on older siblings, maternal smoking during pregnancy, breastfeeding initiation, birth weight, gestational age and maternal age were obtained from the BC Reproductive Care Program Perinatal Database Registry. This registry includes all women who receive prenatal care in

the province of BC (approximately 90% of all births)(18). These data were linked to physician and prescription data by PHN. Neighborhood income, female education and rural residence at time of birth were obtained from the 2001 Canadian census. These data were linked to the cohort based on census dissemination area (approximately four city blocks in an urban area).

The University of British Columbia (UBC) Behavioral Research Ethics Board approved this study (Appendix A). The Centre for Health Services and Policy Research at UBC completed all data linkages by either personal health number or dissemination area. All personal identifiable information (full date of birth, postal code and personal health number) were removed from the linked dataset prior to release.

2.2.4 Statistical Analysis

Maternal age, birth weight, gestational age and female education were converted into categorical variables for analyses. Age and month of first visit were calculated from birth certificate and physician visit data. Independent t-tests and chi-square statistics were used to examine univariate differences between children who had at least one physician visit or recurrent otitis media and those who did not. Conditional logistic regression was used to model the association between risk factors and the likelihood of one physician visit and recurrent otitis media separately. Due to the strong influence of season and age on otitis media incidence, cases and controls were matched (1:1) on month and year of birth using frequency sampling. Risk factors with a p-value of less than 0.05 in univariate models were included in multivariate models to obtain adjusted odds ratios. If two variables were highly correlated (>0.50) only one was chosen for the adjusted model based on the log-likelihood ratio test and the Wald statistic. All statistical analyses were completed using SAS 9.1 (SAS Institute, Cary NC, 2002).

2.3 Results

2.3.1 Population

There were 58,705 singleton births during the study period and physician visit data was available for every child. Children were excluded due to missing or erroneous risk factor information (n=8,156) and death (n=73). The final cohort included 50,474 children (86% of

all births). There were no significant differences in outcome or available risk factor distribution between the original and final cohort (data not shown).

2.3.2 Outcome Measure

The 14-day exclusion removed 23% of the otitis media physician visits, leaving 57,695 visits during the first three years of life. The total number of visits per child ranged from zero to twenty. The greatest rate of visits occurred during the first (21 per 100 children) and second (20 per 100 children) years of life. Overall, there were 38 physician visits per 100 child-years and the mean number of visits per child was 1.14 (standard deviation (SD) =1.82). The total number of visits for each child is in figure 2-1.

There were 24,551 (48.6%) children with at least one visit for otitis media: 12,045 during the first year, 8,573 during the second year and 3,933 during the third year of life. There were 3,952 (7.8%) recurrent otitis media cases identified from the 7,571 (15%) children who had at least three visits during follow-up. Among those defined as recurrent otitis media cases, 72% had their first visit before 12 months. The age at first visit is shown in figure 2-2 for children with at least one visit and for those children who became recurrent otitis media cases. The mean age of first visit was 16 months for recurrent otitis media controls and 10 months for recurrent otitis media cases. Males consistently had more visits during the first 20 months of life. Figure 2-3 illustrates the month of first physician visit by birth season.

2.3.3 Risk Factors

Maternal age ranged from 14 to 51 years (mean=31; SD=5.4), birth weight ranged from 450 to 6072 grams (mean= 3451; SD=353) and gestational age ranged from 22 to 43 weeks (mean=38.9; SD=1.8). Additional information on the risk factor distribution is provided in table 2-1.

2.3.4 Regression Analyses

In univariate analyses (table 2-1), the greatest odds for one or more visit were for First Nations status, maternal age under 20 years, living in neighborhoods with the lowest female education, male gender, maternal smoking during pregnancy and birth weight of greater than 4000grams. The results for recurrent otitis media were similar to those for one or more visit.

In multivariate analyses (table 2-1), male First Nations children living with older siblings in rural areas whose mothers smoked during pregnancy had the greatest odds of otitis media. Non-initiation of breastfeeding was surprisingly associated with lower odds in both adjusted models, although this effect was non-significant for recurrent otitis media. Birth weight of more than 4000grams was associated with greater. Gestational age was not included in the adjusted models. Odds ratios (OR) lowered with increasing maternal age. Relative to children born in the highest income and female education neighborhoods, odds lowered for children born in low income but were higher for those born in low female education neighborhoods. ORs for male gender, older siblings, birth weight and maternal age under 20 years were stronger in the adjusted recurrent otitis media model versus the model of one or more visit.

There were 15,712 children who filled an antibiotic prescription within four days of their otitis media physician visit (64% of those with a physician visit for otitis media). These children were considered acute otitis media cases because they would have received the prescription at the initial physician visit or at a subsequent follow-up visit, if watchful waiting was used for the first 48-72 hours. Multivariate modeling using these data confirmed the results presented in table 2-1 (results not shown) with the exception of the odds ratios for breastfeeding initiation and rural residence which both became non-significant. Because antibiotic data could only be linked to 64% of the otitis media visits it is probable that some disease misclassification occurred. The outcome definition may have captured eustachian tube disorders and chronic otitis media with effusion by including the broad 3-digit ICD9 codes. A sub-analysis using visits coded specifically for acute otitis media (ICD9: 381.0 & 382.0) was completed but the results (not shown) were generally not statistically significant (only 7% of all visits used 4-digit ICD9 coding). Exceptions were the estimates for breastfeeding initiation and rural residence, which both changed to the expected direction and became statistically significant.

Separate, unmatched, analyses examined birth season (table 2-2). Children born during the spring and winter had higher odds for at least one otitis media visit during the first year of life but this association became negligible beyond the first year of life.

2.4 Discussion

To accurately assess the population-level incidence and risk factors for otitis media in British Columbia we employed Canada's universal healthcare databases and linked multiple administrative data. We identified every child born in our study region during a two-year period and the availability of comprehensive data allowed us to follow each child through the first three years of life and evaluate many otitis media risk factors.

2.4.1 Otitis Media Incidence and Recurrence

This study found otitis media incidence during the first year of life to be at the lower bound of other studies (22% versus 21-64%) but the median age of first visit (8-10 months) concurs with those studies (19-22). The data here are more recent than previous studies and may reflect changes in physician practices and regional differences. Regardless, otitis media continues to be the main reason young children receive antibiotics in BC (2).

73% of the children with at least three visits during follow-up (n=7,571) had their initial visit during the first year of life. Additionally, children with a visit for otitis media prior to their first birthday were 7 times more likely to become recurrent otitis media cases by their third birthday, when compared to children who had their visit in later years. This observation suggests that those children who initially present earlier, do so as a result of an underlying vulnerability.

2.4.2 Otitis Media Risk Factors

This study found spring and winter birth to be positively associated with otitis media during the first year of life. This is contrary to previous findings that found spring birth to be protective (23) and fall birth to be a risk factor (11) for otitis media. These children are probably at greater risk because those born in the spring reach 8-10 months of age during the seasonal peak following their birth. More importantly, although children may be at increased risk partly due to the timing of their birth, this effect is only observed during the first year of life.

The estimates for gender and older siblings were slightly lower than those found in the US but concur with studies from northern Europe (10, 24-28). Interestingly, this study found the gender difference to level off at approximately 20 months. It is possible that gender

differences in respiratory maturity or immune system development exist at birth but become less important as children develop (14).

In this study it was not possible to identify mothers who quit smoking during their pregnancy or to identify the presence of other smokers in the home. This probably resulted in some misclassification where children in our 'no' category were actually exposed. This type of bias would attenuate the estimated odds ratios toward the null and may explain the difference between the adjusted recurrent otitis media estimate here (OR=1.16) and those of two meta-analyses that examined parental smoking (OR=1.38 and 1.76)(24, 29).

This same type of bias may be present for the First Nations status variable because it required children to be registered with the federal government. Thus, although the largest odds ratios were for First Nations children, these may be biased toward the null. While unmeasured socioeconomic factors could be responsible, genetics could also play a role in making these infants more susceptible (12, 30, 31). Although First Nations children were more often born overweight versus their non-First Nations counterparts; the numbers were too small to have influenced the findings for high birth weight.

This study joined several others in not finding a protective role for breastfeeding in respect of infection (24, 32). However, the variable used, 'breastfeeding initiated at time of discharge from hospital', did not measure duration or exclusivity of breastfeeding as used in previous studies (33) which are better indicators of the protective capacity of breastfeeding. Provincial data found that 69% of new mothers breastfed for at least 3 months in 1999, suggesting that approximately 20% of our cohort were breastfed, but for a duration of less than 3 months (34).

Maternal age and female education had an inverse relationship with otitis media, while the opposite relationship was found with neighborhood income. Canada's universal healthcare system ensures every child has a physician so it is unlikely that children of low-income neighborhoods have less access to physicians. It is more probable that children living in high-income neighborhoods are more likely to attend daycare. Rural residence was associated with otitis media but this may be partially explained by rural families having more children as this study adjusted for parity but not the number of older siblings. While the neighborhood income, female education and rural residence data were linked to this cohort based on

dissemination area, it is important to note that they were robust enough in the multivariate models to adjust for individual level risk factors.

2.4.3 Study Limitations

Information on daycare attendance, duration of breastfeeding and racial groups other than First Nations was not available at the population level and therefore could not be considered in this study. This study could not include emergency room visits but it is standard practice for emergency room physicians to recommend children follow-up with their family physician. A physician visit could result in more than one diagnosis and otitis media diagnoses may not be recorded during visits where a more serious disease was also diagnosed. It is also possible that caregivers will not seek medical attention for every episode of otitis media, especially if physicians are unlikely to prescribe antibiotics.

During the study period there was a growing tendency for physicians to use the 'wait and see' approach for the management of otitis media (35). However, during the study period it was standard for physicians to treat children under two years with antibiotics if acute otitis media was suspected and more than 85% of the physician visits were for these children (17).

This is the largest Canadian population-based study of otitis media and its associated risk factors. This study demonstrates the utility of linking multiple administrative databases to examine childhood illness. For example, by following the methodology described here, future research could examine the impact of interventions or other changes in clinical practice and disease management. Otitis media incidence is comparatively low in this region but it remains the most common reason young children receive antibiotics. The greatest estimates were for male First Nations children with young mothers who live in neighborhoods with low female education.

2.5 Acknowledgements

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and Charles Best Canada Graduate Scholarship. M. Koehoorn was supported in part by a MSFHR Scholar Award.

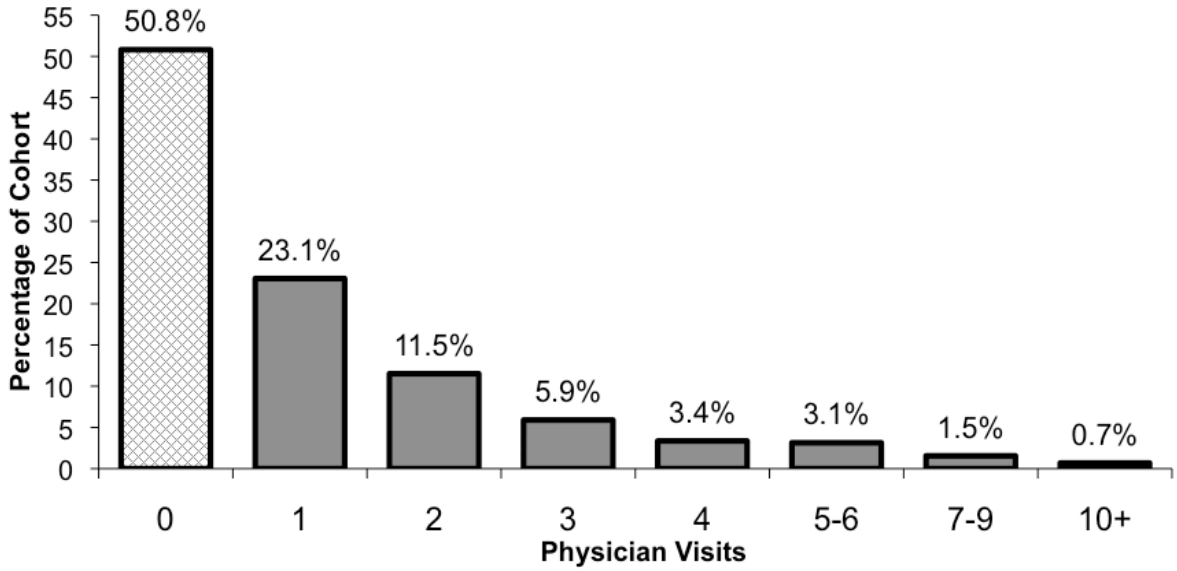

Figure 2- 1. Breakdown of birth cohort by the total number of otitis media physician visits during the first three years of life.

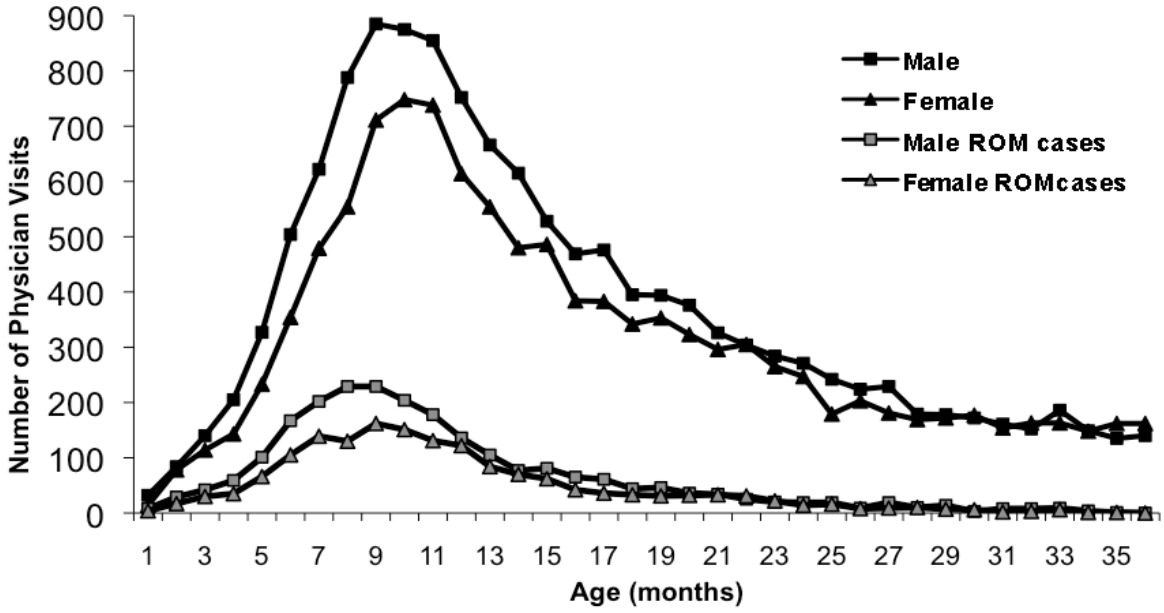

Figure 2- 2. Age at first physician visit for otitis media during the first three years of life, by gender and recurrent otitis media status.

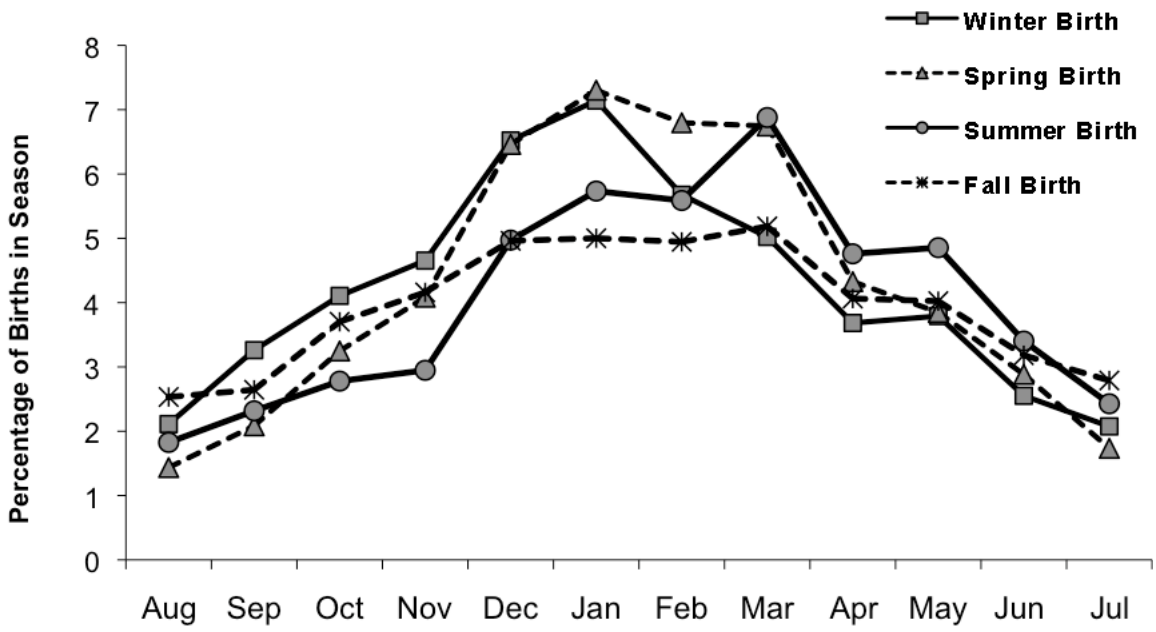

Figure 2- 3. Month of first physician visit for otitis media, by season of birth during the first three years of life.

Table 2- 1. Conditional logistic regression results for initial and recurrent otitis media.

	Cohort Percentage	Initial Otitis Media Odds Ratio (95%CI)		Recurrent Otitis Media Odds Ratio (95%CI)	
		Univariate	Multivariate*	Univariate	Multivariate*
Total	100				
Gender					
Male	51.5	1.24 (1.20-1.28)	1.23 (1.19-1.27)	1.34 (1.26-1.43)	1.32 (1.24-1.41)
Female	48.5	reference	reference	reference	reference
Older Siblings					
Yes	53.9	1.14 (1.10-1.18)	1.18 (1.14-1.22)	1.28 (1.20-1.36)	1.32 (1.23-1.41)
No	46.1	reference	reference	reference	reference
Maternal Smoking during Pregnancy					
Yes	10.4	1.24 (1.17-1.31)	1.16 (1.09-1.23)	1.17 (1.07-1.29)	1.09 (0.98-1.20)
No	89.6	reference	reference	reference	reference
Initiation of Breastfeeding					
No	8.7	0.87 (0.81-0.92)	0.83 (0.78-0.89)	1.04 (0.93-1.16)	0.97 (0.87-1.09)
Yes	91.3	reference	reference	reference	reference
First Nations Status					
Yes	2.4	1.71 (1.52-1.92)	1.47 (1.30-1.65)	1.70 (1.43-2.02)	1.45 (1.21-1.73)
No	97.6	reference	reference	reference	reference
Birth Weight (grams)					
> 4000	13.5	1.23 (1.17-1.30)	1.18 (1.12-1.24)	1.24 (1.14-1.36)	1.16 (1.07-1.27)
2500-4000	81.7	reference	reference	reference	reference
< 2500	4.8	0.89 (0.82-0.97)	0.95 (0.88-1.03)	1.05 (0.91-1.22)	1.10 (0.95-1.28)
Gestational Age (weeks)					
> 41	1.6	0.98 (0.85-1.12)	-	0.82 (0.63-1.08)	-
37-41	90.5	reference	-	reference	-
30-36	6.3	0.99 (0.93-1.06)	-	1.15 (1.02-1.29)	-
< 29	0.4	1.07 (0.87-1.31)	-	1.57 (1.14-2.15)	-
Maternal age (years)					
< 20	3.1	1.36 (1.22-1.51)	1.34 (1.20-1.49)	1.49 (1.26-1.76)	1.53 (1.28-1.82)
20-24	13.0	1.10 (1.04-1.17)	1.09 (1.03-1.15)	1.09 (0.99-1.22)	1.09 (0.98-1.22)
25-29	28.7	reference	reference	reference	reference
30-34	33.8	0.93 (0.89-0.98)	0.93 (0.89-0.97)	1.07 (0.98-1.16)	1.05 (0.97-1.14)
35-39	18.1	0.87 (0.83-0.92)	0.86 (0.82-0.91)	0.93 (0.85-1.03)	0.90 (0.82-0.99)
> 40	3.3	0.75 (0.68-0.83)	0.74 (0.66-0.81)	0.80 (0.65-0.98)	0.76 (0.62-0.93)
Neighborhood Income Level					
1 (lowest)	20.2	0.96 (0.90-1.02)	0.83 (0.78-0.88)	0.98 (0.88-1.09)	0.85 (0.76-0.95)
2	21.3	0.92 (0.87-0.97)	0.82 (0.77-0.87)	0.96 (0.87-1.07)	0.86 (0.77-0.96)
3	21.0	1.00 (0.95-1.06)	0.92 (0.87-0.97)	1.02 (0.92-1.13)	0.94 (0.85-1.05)
4	20.4	0.98 (0.92-1.03)	0.93 (0.88-0.98)	0.96 (0.87-1.07)	0.92 (0.83-1.02)
5 (highest)	17.1	reference	reference	reference	reference
Neighborhood Female Post-secondary Education					
1 (lowest)	25.3	1.27 (1.21-1.34)	1.30 (1.23-1.37)	1.29 (1.18-1.41)	1.27 (1.15-1.41)
2	25.1	1.20 (1.14-1.25)	1.20 (1.15-1.27)	1.18 (1.08-1.29)	1.17 (1.06-1.28)
3	24.7	1.10 (1.05-1.16)	1.10 (1.05-1.16)	1.10 (1.00-1.20)	1.09 (0.99-1.19)
4 (highest)	24.9	reference	reference	reference	reference
Residence Indicator					
Rural	10.9	1.18 (1.12-1.25)	1.16 (1.10-1.23)	1.12 (1.02-1.24)	1.10 (1.00-1.21)
Urban	89.1	reference	reference	reference	reference

*Multivariate models are adjusted for gender, siblings, maternal smoking, breastfeeding, First Nations status, birth weight, maternal age, neighborhood income, neighborhood female

education and residence.

Table 2- 2. Adjusted logistic regression results for initial otitis media, examining birth season by year of life.

	Cohort Percentage	Entire Follow-up Odds Ratio* (95%CI)	1st Year of Life Odds Ratio* (95%CI)	2nd Year of Life Odds Ratio* (95%CI)
Season of Birth				
Winter	21.7	1.15 (1.09-1.21)	1.35 (1.26-1.44)	0.94 (0.86-1.02)
Spring	27.3	1.15 (1.10-1.21)	1.42 (1.33-1.51)	0.89 (0.83-0.97)
Summer	26.6	1.05 (1.00-1.10)	1.12 (1.05-1.19)	0.99 (0.92-1.07)
Fall	24.3	reference	reference	reference

*Models are adjusted for gender, siblings, maternal smoking, breastfeeding, First Nations status, birth weight, maternal age, neighborhood income, neighborhood female education and residence.

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3 EXPOSURE TO RESIDENTIAL AIR POLLUTION AND OTITIS MEDIA DURING THE FIRST TWO YEARS OF LIFE[2]

3.1 Introduction

Otitis media is the main reason children under five years receive antibiotics and a leading reason for physician visits (1, 2). Those diagnosed with otitis before six months of age are at increased risk for recurrent and chronic otitis media throughout childhood and the resultant economic burden is comparable with that of chronic respiratory diseases (3).

Ambient air pollutants have been shown to adversely affect respiratory defense mechanisms, making the respiratory system more susceptible to infection (4-8). Specifically, NO, NO_2 and O_3 have been shown to exacerbate viral inflammation, impair mucosal cilia clearance and increase the susceptibility of epithelial cells to viral injury by increasing their permeability. Particulate matter has been shown to induce oxidative stress in human bronchial epithelial cells, leading to increased susceptibility to infection (9) and may reduce viral uptake by alveolar macrophages (10). Environmental tobacco smoke is a strong risk factor for otitis media (11), likely due to alteration of immune defenses (12, 13) and increased susceptibility following inflammation of the respiratory epithelium (14). Few studies have examined ambient air pollution in relation to otitis, but indoor biomass burning has been identified as a risk factor (15, 16) and an association was observed with traffic-related air pollution in Europe (17).

As part of the Border Air Quality Study, we evaluated the relationship between otitis media and ambient air pollution in southwestern Canada, a region with lower air pollution concentrations than those found in other urban areas across Canada and the United States but with a rapidly growing population (18). Despite this, ambient air pollution has been associated with small for gestational age and premature birth, infant bronchiolitis and childhood asthma in this region (19-21).

[2] A version of this chapter will be submitted for publication. MacIntyre, E.A., Karr, C.J., Koehoorn, M., Demers, P.A., Tamburic, L., Lencar, C., Brauer, M. (2010) Exposure to Residential Air Pollution and Otitis Media During the First Two Years of Life.

3.2 Methods

3.2.1 Study Area and Population

This retrospective population-based birth cohort study included all births in the Georgia Basin Airshed (a region including the municipalities of Vancouver and Victoria) during a two-year period. Every singleton birth from January 1, 1999 to December 31, 2000 was identified based on maternal residential postal code and date of birth listed on birth certificates (n=59,917). Utilizing the universal healthcare system, the cohort was established and followed through the first 24months of life by extracting data from a series of administrative datasets obtained from the British Columbia (BC) Ministries of Health, the BC Vital Statistics Agency, and the BC Perinatal Database Registry. The Centre for Health Services and Policy Research at the University of British Columbia (UBC) completed all data linkages via personal health number (PHN) or geographical region, where individual linkage was not possible. Personal identifiable information (full date of birth, postal code and PHN) were removed prior to release of the linked dataset. The UBC Behavioral Research Ethics Board approved this study (Appendix A).

A residential history file was created from residential postal codes recorded at each physician visit or hospitalization during the first 24 months of life. Where there was a change in postal code, the move date was set as the midpoint between contacts if non-overlapping, or at the first date of the new address if overlapping. The first month of life was excluded from this analysis due to the difficulty in diagnosing otitis media in newborns and to allow a postnatal time window of exposure (22). Children who died during follow-up, moved away from the study region or were missing covariate information were excluded.

3.2.2 Outcome

The BC Ministry of Health provided information on outpatient physician visits coded as otitis media (ICD-9 codes: 381-nonsuppurative otitis media and eustachian tube disorders, 381.0-acute nonsuppurative otitis media, 382-suppurative and unspecified otitis media, 382.0-acute suppurative otitis media, 382.9-unspecified otitis media). Data were extracted and linked based on each child's unique PHN. Details on the use of these data for otitis media diagnoses have been described in detail elsewhere (23)(chapter 2). To ensure follow-

up visits were not counted as separate infections, any visit within 14 days of a previous visit was excluded.

We obtained information on antibiotic prescriptions from the BC College of Pharmacists. Data were linked to physician visits at the individual-level based on PHN and service date, allowing for up to 4 days between physician and pharmacy visit. Otitis media visits with a linked antibiotic prescription were considered acute otitis media and used for sensitivity analyses.

3.2.3 Covariates

Sex, season of birth, First Nations status, older siblings, maternal smoking during pregnancy, birthweight, gestational age, breastfeeding initiation and maternal age were linked to cohort members at the individual level using PHN. Neighborhood income, neighborhood female education and rural residence were linked based on census dissemination area. Dissemination areas range in size depending on population density, but the typical size in urban regions is approximately four square city blocks. Maternal age and female education were converted into categorical variables for analyses.

3.2.4 Air Pollution Exposure

Exposures were estimated at the centre of each postal code and linked to children based on their residential history, measured in months. The postal code typically corresponds to one block face in urban areas, but may be considerably larger in rural areas with low population density. For each child-month, two-month exposure windows were assigned by averaging the current and previous months estimated exposure where continuous measures were used. Air pollution exposures were estimated using three approaches: (i) regulatory monitoring networks operated by the BC Ministry of Environment and Metro Vancouver, (ii) dedicated sampling campaigns used to develop land use regression models of spatial variation in source specific pollution, and (iii) measures of proximity to highways/major roads and point sources. Exposures were updated using the residential history file and weighted by time spent living at multiple residences.

Regulatory monitors collected information on NO/ NO_2 (n=22 locations), CO (n=19), $PM_{2.5}$ (n=7), PM_{10} (n=19), SO_2 (n=14) and O_3 (n=24). Monthly average exposures for these 7

pollutants were estimated using 2 methods; assigning the nearest monitor within a 10km circular buffer, and calculating an inverse distance weighted (IDW) average of up to three monitors closest to the residential postal code and within a 50km circular buffer. Monthly monitoring data was considered missing if there was a gap of more than 5 consecutive days or if there were more than 10 days missing in total.

The traffic-related pollution land use regression (LUR) models were developed after measuring NO/ NO_2 (n=116), $PM_{2.5}$ (n=25) and black carbon (n=39) at predetermined sites throughout the study area (24, 25). The final LUR models (R^2: NO=0.62, NO_2=0.56, $PM_{2.5}$=0.52, black carbon=0.56) included combinations of; population density, elevation, type and amount of land zoning, number of various road types and distance to highways using buffers of 100-2500meters. Comparisons with additional measurements and cross-validation analysis indicated that the NO and NO_2 models performed better than the $PM_{2.5}$ and black carbon models. Spatial surfaces of predicted (annual average) concentrations generated for the entire study area at a resolution of 10m were smoothed (Focal Statistics, ArcGis Spatial Analyst; ArcGIS) to remove abrupt changes and edge effects, providing a more accurate reflection of the measured effect of proximity to roadways (26). For each LUR model, the corresponding monitor data were fit with a monthly dummy variable and a covariate for linear trend (Times Series Forecasting System, version 9; SAS Institute Inc., Cary, NC, USA), the $PM_{2.5}$ trend was used for black carbon. From these models, a month–year adjustment factor was applied to estimate monthly average concentrations.

The woodsmoke surface (24) was developed through mobile monitoring of particle light absorption, throughout the study area on cold, clear winter nights (n=19). These measurements were combined with fixed-location monitoring of levoglucosan, a biomass combustion tracer compound, and $PM_{2.5}$ to develop a spatial woodsmoke model for the study area. Postal codes in the top tertile of woodsmoke $PM_{2.5}$, as estimated from the model, were classified as wood burning areas and heating-degree days (based on daily temperature data) were used to identify time periods during which elevated concentrations of woodsmoke were present in these areas (27). The number of woodsmoke days was calculated for each month of follow-up.

Proximity to point sources was estimated using an index assigned to each point source in the study area reporting yearly emissions to the federal government. The pollutant contribution for each point source was assessed in relation to other point sources in the study area and a proximity-weighted summation of emissions was assigned to each residential postal code using a circular buffer of 10kilometers (27). Proximity of residential postal codes to expressways, primary highways, secondary highways, and major arterial roads was measured using 50m and 150m wide buffers (DMTI Arc View street file dataset for BC, Canmap Streetfiles, v2006.3, 2006). Road type proximity was coded as a categorical variable.

3.2.5 Statistical Analysis

The association between residential air pollution exposure and physician diagnosis of otitis media was assessed longitudinally using generalized estimating equations with a logit link function and a first order auto-regressive working correlation matrix to account for correlation between months for the same child. Directed acyclic graphs were used to identify potential confounders. For each analysis, children were excluded if they had missing exposure data for any month during follow-up. An otitis media event month was defined by having a physician diagnoses for otitis media on any day in that month. Analyses were stratified by sex, First Nations, maternal smoking, older siblings gestational age, otitis media season and age. Otitis media season was a 4 level categorical variable based on the otitis media rate for each of the 47 months of the study, with cut-offs at the 25^{th}, 50^{th} and 75^{th} percentiles. Continuous measures of exposure were converted into quartiles to investigate possible non-linear associations between air pollution and otitis media. Finally, sensitivity analyses restricted to children living in urban areas, restricted to event months where a physician diagnoses was linked to an antibiotic prescription, and restricted to event months for children diagnosed with multiple episodes of otitis media, were completed. All statistical analyses were completed using SAS 9.1 (SAS Institute, Cary NC, 2002).

3.3 Results

There was complete information for 45,513 children (76% of all births). Children were excluded due to: missing covariate information, death, or incomplete residential history. There were no significant differences in outcome, available covariate or exposure distributions between the original and final cohort used for the analyses (data not shown).

The cohort was 51.5% male, 53.9% had older siblings, 2.1% were First Nations, 92.0% were breastfed and 10.3% had mothers who reported smoking during pregnancy. Maternal age ranged from 14 to 51 years (mean=31; SD=5.4). The proportion of females in each dissemination area with a post-secondary education ranged from 6.9% to 100% (mean=37.3; SD=11.7).

During the first 2 years of life 42.0% (19,115) of the cohort had at least one physician visit for otitis media, 27.2% (12,369) had at least one visit with a linked antibiotic prescription and 17.0% (7,740) moved at least once. Otitis media incidence was strongly influenced by age and season, peaking at 8-10 months and during the winter (23). Figure 3-1 illustrates the trend, over time, for otitis media physician visits and selected exposures.

Mean air pollution concentrations are listed in table 3-1 and were relatively low compared to regulatory guidelines. The land use regression models predicted pollutant concentrations of zero in the absence of all predictors of traffic-related air pollution. Ambient monitoring data were very similar across both the nearest monitor and inverse distance weighted approaches; thus, only results for the inverse distance weighted approach will be included here. Correlations for the ambient monitoring data were: 0.73-0.84 between NO, NO_2 & CO; 0.32-0.67 between $PM_{2.5}$, PM_{10} & SO_2; and -0.72--0.24 between O_3 and all other pollutants. Correlations for the land use regression (LUR) estimates were: 0.73 between NO and NO_2; and 0.56 between $PM_{2.5}$ and black carbon. Across these two approaches (IDW – LUR for the same pollutant), pollutant correlations were; 0.64 for NO, 0.62 for NO_2 and 0.18 for $PM_{2.5}$.

Table 3-2 shows the crude and adjusted risk estimates and 95% confidence intervals from the longitudinal analysis. Although risk estimates were generally robust to adjustment for otitis media risk factors (sex, First Nations, older siblings, maternal smoking during pregnancy, maternal age, neighborhood income and female education), some were highly sensitive to adjustment for otitis media season; specifically those with strong seasonal trends throughout the year (figure 3-1). Upon adjusting for otitis media season; estimates for NO (IDW and LUR), woodsmoke and CO decreased and the estimate for CO became non-significant; estimates for NO_2 (IDW and LUR) changed direction; the estimate for IDW $PM_{2.5}$ increased and was statistically significant, while the estimates for LUR $PM_{2.5}$, black carbon and PM_{10} increased but were non-significant. There was little difference in the estimates for O_3 and

point source index after adjusting for season. Protective associations were found for O_3, which was expected given the strong negative correlations between O_3 and traffic-related pollutants (CO, NO & NO_2). Protective associations were initially observed with all particulate air pollution and point source proximity measures; but the estimates for $PM_{2.5}$ (IDW and LUR) and PM_{10} increased after adjustment for season. Residential woodsmoke was strongly associated with otitis media in all models. Adjusted estimates for road proximity were inconsistent, with some measures (expressways and secondary highways) indicating positive associations, but overall results did not follow the expected patterns relating exposure intensity to road type: expressway > primary highway > secondary highway > major road. There were low numbers of children residing in close proximity to all road types except major roads.

Stratifications by First Nations, maternal smoking during pregnancy, older siblings and gestational age are presented in table 3-3. There was no difference across gender (full results in tables B-1 and B-2). Effect estimates for First Nations children (n=1,309) were elevated for all measures of air pollution from the land use regression models and for O_3 and PM_{10}; but were generally not statistically significant. Estimates for children whose mothers smoked during pregnancy were elevated for black carbon, and those for children born before 30 weeks gestation were elevated for ozone. Stratification by otitis media season (table 3-4) identified strong associations with PM_{10} and $PM_{2.5}$ (LUR) in the low season (summer). Finally, during the first 6 months of life (table 3-5) O_3 and woodsmoke were the only pollutants with elevated effect estimates; while estimates for NO and $PM_{2.5}$ were elevated in subsequent months of life. Quartile analyses were completed for the continuous measures to further investigate the associations; results (adjusted for otitis media season) confirmed those in table 3-2, with increasing estimates by increasing quartile of NO (IDW and LUR) and IDW $PM_{2.5}$ and decreasing estimates by increasing quartile of black carbon, NO_2 (IDW and LUR), SO_2, O_3 and point source (tables B-6 and B-7). Sensitivity analyses using acute otitis media (physician visit linked with antibiotic prescription) yielded results similar to those in table 3-2 but with slightly larger confidence intervals (table B-10).

3.4 Discussion

To date, this is the largest and most comprehensive study to examine the association between air pollution and otitis media. We identified every child born in our study region during a two-year period and each child was followed through the first two years of life based on contacts with the universal healthcare system. The availability of linked health and administrative data allowed us to include a number of known otitis media risk factors as potential confounders. The population-based design eliminated selection bias. Children who where excluded from the final cohort did not differ significantly from those with complete data, when comparing otitis media incidence, gender, month/year of birth, or available covariate information.

We observed positive associations with exposure to vehicle exhaust markers (NO, CO, $PM_{2.5}$) and woodsmoke. Associations for other particulate matter metrics, SO_2 and O_3 were largely protective. Overall, despite our emphasis on exposure estimates that were focused primarily on spatial contrasts in exposure, the findings of increased otitis media risk were for pollutants that had strong seasonal patterns similar to that of otitis media (figure 3-1). NO_2 results were strongly affected by adjustment for otitis media season. This suggests that the univariate association between NO_2 and otitis media was driven purely by the temporal association between the two (figure 3-1). Moreover, these findings suggest that the timing of exposure is critical since elevated risks are seen mainly when the spatial and temporal variability of air pollution are considered together. Although the road proximity measures do not include a temporal aspect, these results were difficult to interpret as very low numbers of children lived in close proximity to expressways and highways, and findings were not consistent across different metrics. For $PM_{2.5}$ and SO_2, monitor coverage was much lower compared to other monitored pollutants and we therefore may not have captured adequate spatial variability in our estimates for these pollutants.

Theoretically, the exposures estimated from ambient monitoring data should provide the most temporal variation, while the exposures from the LUR models also incorporate spatial variation. Further, the regulatory monitors are strategically located to capture regional and 'urban background' pollution and have limited ability to capture neighborhood pollution; LUR, on the other hand, is ideally suited to capture source specific pollution (28). Of the

pollutants with estimates from both ambient monitors and LUR models (NO, NO_2 & $PM_{2.5}$), otitis media risk estimates were consistent across the different exposure metrics for NO and NO_2, but not $PM_{2.5}$. As reported previously (25), the $PM_{2.5}$ and black carbon LUR models performed worse in model evaluations than did those for NO and NO_2.

The results for ozone are not surprising as ozone had a strong negative (spatial) correlation with NO, NO_2 and CO. These findings may have also been driven by the strong inverse seasonality trend between ozone and otitis media (figure 3-1). However, when analyses were stratified by event season (table B-8) the adjusted estimate for ozone became 1.24(1.16-1.31) for events during the summer (July - September) and 1.20(1.14-1.25) for events during the winter (January - March).

Previous literature examining the relationship between air pollution and otitis media is sparse; and often limited by small sample size, relatively crude exposure assessment, adjustment of potential confounders and study design. In a cross-sectional analysis of children in Spain, those residing in regions of high air pollution had greater odds of acute otitis media during the first year of life (OR 2.01;CI:1.05-3.84) after adjustment for sex, older siblings, smoking, socioeconomic status and breastfeeding (29). Unfortunately, it is unclear what pollutant(s) or pollutant sources were most responsible for this finding. A recent study in the United States examined data from the National Health Interview Survey through 1997-2006 and found statistically significant reductions in the frequency of otitis media; this reduction was partially attributed to reductions in ambient air pollutants (CO, NO_2, SO_2 and PM), although potential confounding was noted as an important limitation (30). In another regional comparison, the prevalence rates of otitis media decreased from 31% to 26% with decreases in total suspended particulate and sulfur dioxide in a group of children examined in a series of repeated cross-section surveys after German reunification (31). In the Netherlands, a two year birth cohort of almost 3,000 children found an increased risk of otitis media for exposure to $PM_{2.5}$ (OR 1.13; 95% CI:1.00-1.27), black carbon (OR 1.10; CI:1.00-1.22), and NO_2 (OR 1.14; CI:1.03-1.27) (17) based on annual averaged exposures estimated from LUR models. Although the present study did not find an association with black carbon; the findings for NO and IDW $PM_{2.5}$ do suggest an association with fossil fuel combustion.

We found robust associations between exposure to residential woodsmoke and otitis media. A similar association, although with considerably higher air pollution exposures, was found in a case-control study of children under two years in Mozambique which reported elevated odds for otitis media (OR 3.09; CI:2.00-4.78) if families used charcoal or wood as sources of energy (15). Additionally, a case-control study in rural New York found an odds ratio of 1.73(CI:1.03-2.89) for otitis media in children whose families used wood burning stoves (32) but a second study examining otitis media in the first year of life for over 900 infants found no association after adjustment (33). An important distinction is that the abovementioned studies identified wood burning in the home while this study modeled ambient residential woodsmoke at the neighborhood level.

While some of our findings, and those of the studies described above, suggest an association between air pollution exposure and otitis media, a causal relationship requires a plausible biological mechanism. Acute otitis media is caused by bacterial or viral pathogens that migrate from the nasopharynx into the eustachian tube and middle ear. Tubal obstruction leads to the accumulation of mucosal secretions and pathogens then replicate resulting in acute signs and symptoms of infection (1). Often, an episode of otitis media follows a viral upper respiratory tract infection, this is likely due to the disruption of mucociliary clearance and tubal occlusion from enlarged adenoids that occur during viral infection (13). The exact mechanism by which the exposures in this study lead to otitis media is not well understood. Because air pollutants cause inflammation of the respiratory airways, mucosal swelling, decreased cilia clearance and decreased eustachian tube patency (7, 34-37), the mechanism might be similar to that of prior viral infection, where the disruption of homeostasis results in impaired host response (38-41), pathogen proliferation and greater chance of infection within the middle ear cavity.

This study was population-based and incorporated detailed individual spatiotemporal exposure estimates accounting for residential mobility; but there remains several limitations to our methodology. Importantly, the study region exhibits air pollution concentrations that are lower than most urban areas and the exposure range may have been too narrow to detect a signal. Additional limitations arise from our use of administrative data to create the birth cohort, compile residential histories, and obtain outcome/covariate information. Although we included a large number of children, privacy legislation prohibited examination of exposure

windows less than 2 months (only the month and year of birth was released for each child). Further, due to the analytical challenges and difficulty interpreting results, we decided not to assess multi-pollutant models or interactions between air pollution and season.

To date, there has been no research examining the diagnostic accuracy of otitis media in BC. If children were over-diagnosed because physicians/caregivers were more knowledgeable or vigilant it would bias the estimates toward the null. Physician visit, while not a perfect measure, is more objective and less biased than parental reporting of symptoms, which has been used in previous studies. There was potential for misclassification of disease in this study because both acute otitis media (ICD9: 381.0 & 382.0) and broader or unspecified otitis media (IDC9: 381, 382 & 382.9) codes were used. It was necessary to include the broad 3-digit codes in our case definition because 93% of our outpatient physician visits were coded to only 3-digits. Since 35% of the children with an otitis media physician visit did not have a linked antibiotic prescription, it is likely that some of these were visits for eustachian tube disorders and chronic otitis media (a result of using the broad ICD9 381 & 382 codes) while the remainder was probably acute otitis that resolved without antibiotics. This limitation is inherent in using administrative databases for population-based research. Due to the nature of the administrative data available for this study we could not account for emergency room visits. However, it is standard practice for emergency room physicians to recommend that children see their family doctor for a follow-up after an emergency room diagnosis and this visit would then be captured by our methodology.

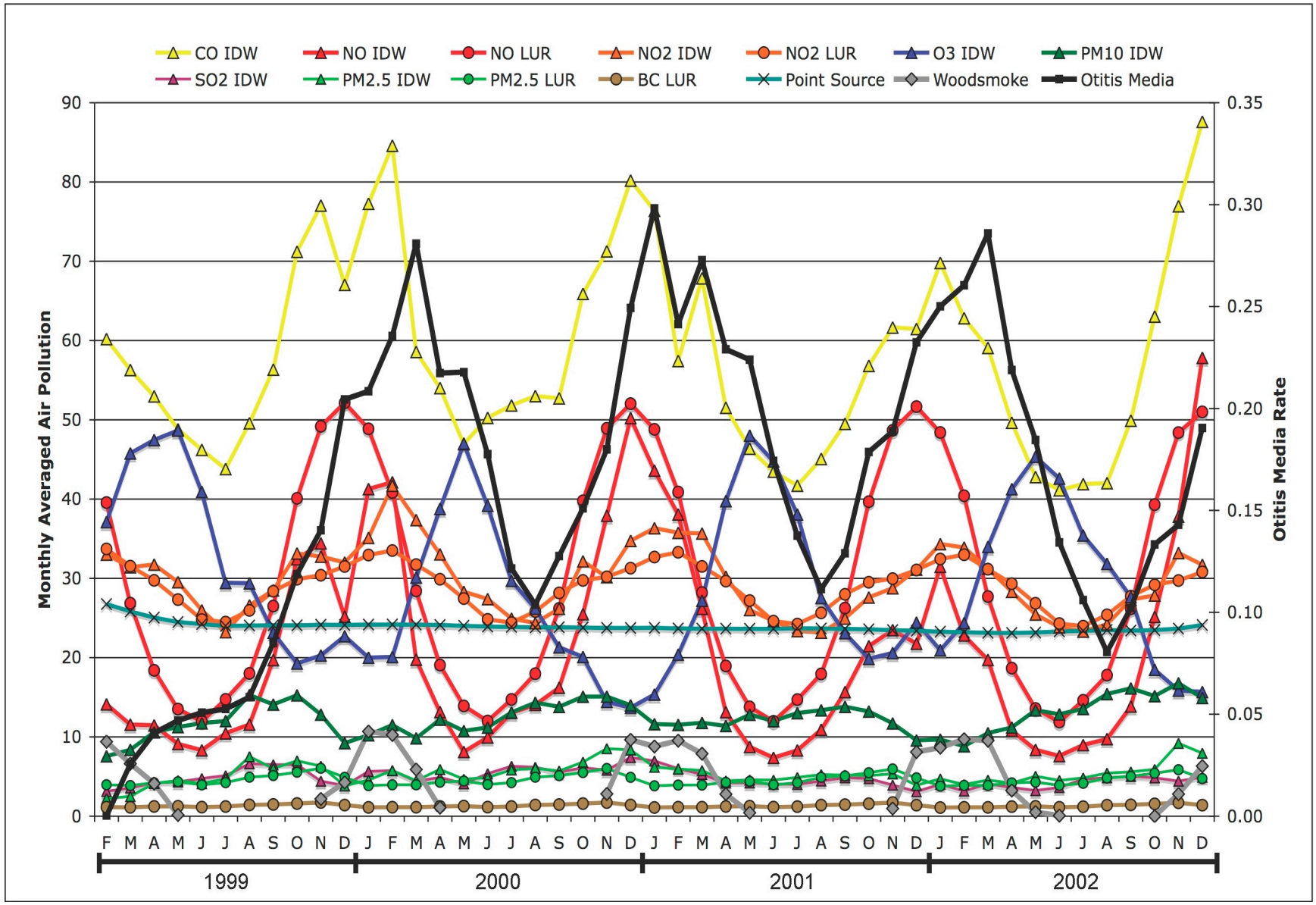
Although changes in residence were accounted for in this study, there was no data available on time spent in other locations, such as daycare. Further, during the first two years of life children likely spend considerable time indoors so correlations between indoor and outdoor pollutant concentrations should also be considered. The observed association between PM_{10} and otitis media during the low otitis season is probably a result of increased time spent outdoors during the summer. This study was also not able to assess daycare attendance, duration of breastfeeding or ethnicity (with the exception of First Nations), as information on these potential risk factors was not available at the individual level. This study also could not identify mothers who quit smoking during their pregnancy or identify the presence of other smokers in the home.

This study found associations between increased physician visits for otitis media and a number of air pollutants, specifically woodsmoke and traffic-related pollutants. Findings for other common air pollutants had mainly protective associations, indicating the complexity of assessing relationships between air pollution and these seasonal infections. Our findings suggest that air pollution reduction strategies may be successful in reducing the overall burden of this common and costly childhood disease, particularly in regions where levels of woodsmoke or traffic-related pollutants are elevated or increasing. Future studies should consider short-term exposure windows, adjust for indoor sources of air pollution, and collect information on all microenvironments where children spend their time.

Figure 3- 1. Monthly average air pollution concentrations and otitis media event rate during the 47 months of follow-up.

All concentrations are in $\mu g/m^3$ with the exception of black carbon (BC), point source and woodsmoke: black carbon was estimated from filter absorbance and is in units of m^{-5}, point source is a unitless index and woodsmoke is in units of days of exposure for those living in woodsmoke-affected areas. The otitis media rate was calculated for each month of follow-up as the percent of child months with an otitis media event

LUR – land use regression, IDW – inverse distance weighted concentrations (3 monitors within 50 km of a residential postal code), BC – black carbon.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O3 IDW
PM10 IDW
SO2 IDW
PM2.5 IDW
PM2.5 LUR
BC LUR
Point Source
Woodsmoke
Otitis Media
Monthly Averaged Air Pollution
Otitis Media Rate
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Table 3- 1. Summary statistics of monthly averaged exposures during the first two years of life.

Pollutant	Exposure Model	Mean* [SD]	Median	Range	IQR
NO	IDW	21.9 [17.2]	17.5	0.3-168.7	20.8
NO	LUR	24.7 [16.1]	21.0	0.3-171.4	20.0
NO_2	IDW	30.1 [10.1]	29.7	2.8-62.0	14.0
NO_2	LUR	16.6 [5.0]	15.6	0.0-35.1	7.8
CO	IDW	577.6 [186.0]	559.9	13.3-1744.3	244.4
$PM_{2.5}$	IDW	5.5 [1.3]	5.3	1.3-17.4	1.6
$PM_{2.5}$	LUR	3.9 [1.9]	3.9	0.0-13.3	1.8
Black carbon	LUR	1.6 [1.2]	1.0	0.0-6.5	1.1
PM_{10}	IDW	12.4 [2.0]	12.4	4.5-23.6	2.8
SO_2	IDW	5.1 [2.9]	4.4	0.1-28.8	3.2
O_3	IDW	28.2 [11.2]	26.1	3.7-71.8	17.0
Woodsmoke	-	15.2 [8.8]	18	1-30	16
Point source	-	23.9 [19.0]	19.3	0.0-306.2	30.2

* All concentrations are in $\mu g/m^3$ with the exception of black carbon (BC), point source and woodsmoke: black carbon was estimated from filter absorbance and is in units of m^{-5}, point source is a unitless index and woodsmoke is in units of days of exposure for those living in woodsmoke-affected areas.

SD – standard deviation, IQR – interquartile range, LUR – land use regression, IDW – inverse distance weighted concentrations (3 monitors within 50 km of a residential postal code).

Table 3- 2. Crude and adjusted estimates for the association between residential air pollution and physician visits for otitis media, full cohort analysis.

Pollutant	Model	Number of Children	Crude RR (95%CI)	Adjusted 1* RR (95%CI)	Adjusted 2** RR (95%CI)	Scaled Deviance Degrees of Freedom
Exposure modeled as a continuous variable – risk estimate per an IQR increase in pollutant						
NO	IDW	41,476	1.14(1.12-1.15)	1.17(1.15-1.18)	1.03(1.01-1.05)	0.312
	LUR	37,028	1.17(1.15-1.19)	1.18(1.16-1.20)	1.08(1.05-1.10)	0.300
NO_2	IDW	41,295	1.06(1.04-1.09)	1.12(1.10-1.15)	0.89(0.87-0.92)	0.312
	LUR	37,028	1.07(1.05-1.09)	1.09(1.07-1.11)	0.95(0.93-0.97)	0.300
CO	IDW	10,402	1.12(1.10-1.14)	1.16(1.13-1.18)	1.01(0.99-1.04)	0.311
O_3	IDW	46,557	0.91(0.90-0.93)	0.90(0.88-0.92)	0.89(0.87-0.91)	0.314
$PM_{2.5}$	IDW	43,118	0.99(0.97-1.01)	1.00(0.98-1.02)	1.06(1.04-1.08)	0.313
	LUR	37,028	0.91(0.90-0.91)	0.91(0.89-0.93)	0.99(0.97-1.01)	0.300
Black carbon	LUR	37,028	0.94(0.92-0.96)	0.94(0.93-0.96)	0.99(0.97-1.01)	0.300
PM_{10}	IDW	46,917	0.77(0.75-0.78)	0.77(0.76-0.78)	1.00(0.98-1.03)	0.316
SO_2	IDW	41,506	0.84(0.82-0.86)	0.86(0.84-0.88)	0.89(0.87-0.91)	0.312
Point source index	10 km	47,974	0.76(0.74-0.78)	0.78(0.76-0.80)	0.81(0.78-0.84)	0.315
Woodsmoke	Days	39,283	1.62(1.58-1.66)	1.51(1.47-1.55)	1.32(1.27-1.36)	0.301
Exposure modeled as a categorical variable						
Expressway	<50m	104	1.05(0.86-1.29)	1.06(0.86-1.30)	1.11(0.97-1.25)	0.316
	50-150m	579	1.09(1.02-1.17)	1.08(1.00-1.16)	0.93(0.66-1.29)	
	>150m	47,633	Reference	Reference	Reference	
Primary highway	<50m	849	0.90(0.86-0.94)	0.89(0.86-0.93)	0.81(0.75-0.88)	0.316
	50-150m	2,465	0.88(0.82-0.95)	0.87(0.80-0.93)	0.76(0.67-0.86)	
	>150m	44,811	Reference	Reference	Reference	
Secondary highway	<50m	13	0.81(0.43-1.53)	0.77(0.41-1.44)	No Convergence	0.316
	50-150m	89	1.17(1.05-1.30)	1.12(1.01-1.25)	1.15(0.51-2.59)	
	>150m	48,249	Reference	Reference	Reference	
Major road	<50m	4,965	0.88(0.85-0.90)	0.91(0.89-0.93)	0.93(0.89-0.96)	0.316
	50-150m	9,286	0.92(0.89-0.95)	0.94(0.91-0.97)	0.97(0.93-1.02)	
	>150m	33,245	Reference	Reference	Reference	

* Adjusted for sex, First Nations, older siblings, maternal smoking during pregnancy, breastfeeding initiation, birth weight, maternal age, neighborhood income, neighborhood female education and rural residence.

** Adjusted for otitis media season, sex, First Nations, older siblings, maternal smoking during pregnancy, breastfeeding initiation, birth weight, maternal age, neighborhood income, neighborhood female education and rural residence.

LUR – land use regression, IDW – inverse distance weighted concentrations (3 monitors within 50 km of a residential postal code).

Table 3- 3. Adjusted estimates for the association between residential air pollution and physician visits for otitis media, subgroup analysis.

Pollutant	Model	First Nations (n=1,309)	Smoking During Pregnancy (n=6,133)	Older Siblings (n=31,696)	Gestational Age under 30 weeks (n=235)
		RR* (95%CI)	RR* (95%CI)	RR* (95%CI)	RR* (95%CI)
Exposure modeled as a continuous variable – risk estimate per an IQR increase in pollutant					
NO	IDW	0.95(0.80-1.11)	0.99(0.94-1.05)	0.98(0.96-1.00)	0.94(0.88-0.99)
	LUR	1.21(1.01-1.43)	1.09(1.04-1.14)	1.04(1.02-1.06)	1.00(0.95-1.07)
NO_2	IDW	0.73(0.65-0.83)	0.90(0.84-0.96)	0.84(0.82-0.87)	0.83(0.77-0.90)
	LUR	1.11(0.94-1.31)	0.97(0.91-1.04)	0.87(0.84-0.89)	0.84(0.78-0.91)
CO	IDW	0.87(0.73-1.02)	0.95(0.90-1.01)	0.95(0.92-0.97)	0.90(0.84-0.96)
O_3	IDW	1.09(0.96-1.24)	0.91(0.87-0.96)	0.94(0.91-0.97)	1.00(0.94-1.06)
$PM_{2.5}$	IDW	1.08(0.95-1.23)	1.06(1.01-1.11)	1.03(1.01-1.05)	0.99(0.94-1.04)
	LUR	1.02(0.93-1.19)	0.96(0.91-1.03)	0.93(0.90-0.95)	0.95(0.88-1.02)
Black carbon	LUR	1.05(0.93-1.18)	1.02(0.95-1.08)	0.93(0.90-0.96)	0.97(0.90-1.05)
PM_{10}	IDW	1.06(0.96-1.17)	0.98(0.93-1.04)	0.93(0.91-0.96)	0.93(0.86-1.00)
SO_2	IDW	0.95(0.84-1.07)	0.91(0.86-0.96)	0.87(0.85-0.89)	0.86(0.80-0.92)
Point source index	10 km buffer	0.65(0.55-0.77)	0.87(0.80-0.95)	0.74(0.71-0.77)	0.76(0.69-0.84)
Woodsmoke	Days	1.02(0.78-1.34)	1.15(1.05-1.27)	1.25(1.20-1.30)	1.24(1.11-1.39)
Exposure modeled as a categorical variable					
Expressway	<50m	2.37(1.21-4.65)	0.65(0.31-1.39)	1.07(0.82-1.40)	0.71(0.22-2.26)
	50-150m	0.61(0.40-0.93)	1.04(0.85-0.28)	1.06(0.96-1.16)	0.81(0.61-1.07)
	>150m	Reference	Reference	Reference	Reference
Primary highway	<50m	1.14(0.86-1.51)	1.01(0.85-1.20)	0.86(0.77-0.95)	0.78(0.58-1.03)
	50-150m	1.22(1.03-1.43)	1.01(0.90-1.13)	0.86(0.81-0.91)	0.86(0.74-1.01)
	>150m	Reference	Reference	Reference	Reference
Secondary highway	<50m	No Convergence	No Convergence	0.31(0.08-1.24)	No Convergence
	50-150m	0.58(0.35-0.98)	0.84(0.64-1.11)	1.08(0.93-1.26)	0.73(0.45-1.18)
	>150m	Reference	Reference	Reference	Reference
Major road	<50m	0.73(0.60-0.90)	0.97(0.88-1.07)	0.91(0.87-0.95)	0.97(0.86-1.09)
	50-150m	0.66(0.56-0.79)	1.00(0.92-1.08)	0.87(0.84-0.90)	0.95(0.87-1.04)
	>150m	Reference	Reference	Reference	Reference

* Adjusted for otitis media season, sex, First Nations, older siblings, maternal smoking during pregnancy, maternal age, neighborhood income and neighborhood female education.

LUR – land use regression, IDW – inverse distance weighted concentrations (3 monitors within 50 km of a residential postal code).

Table 3- 4. Adjusted estimates for the association between residential air pollution and physician visits for otitis media, stratified by otitis media season.

Pollutant	Model	1 (Low)	2	3	4 (High)
		RR* (95%CI)	RR* (95%CI)	RR* (95%CI)	RR* (95%CI)
Exposure modeled as a continuous variable – risk estimate per an IQR increase in pollutant					
NO	IDW	0.96(0.87-1.06)	1.00(0.97-1.04)	1.02(1.00-1.05)	0.93(0.91-0.95)
	LUR	1.03(0.94-1.13)	1.05(1.02-1.08)	1.07(1.05-1.09)	0.99(0.97-1.01)
NO_2	IDW	0.75(0.69-0.82)	0.90(0.86-0.94)	0.86(0.84-0.89)	0.83(0.81-0.85)
	LUR	0.81(0.75-0.87)	0.91(0.88-0.94)	0.92(0.89-0.94)	0.84(0.81-0.86)
CO	IDW	0.84(0.77-0.91)	0.96(0.93-0.99)	0.96(0.94-0.99)	0.90(0.88-0.93)
O_3	IDW	0.66(0.60-0.73)	0.93(0.89-0.97)	0.93(0.91-0.95)	1.00(0.98-1.03)
$PM_{2.5}$	IDW	1.19(1.12-1.27)	1.03(1.00-1.06)	1.08(1.05-1.10)	1.00(0.98-1.02)
	LUR	0.93(0.88-0.98)	0.94(0.91-0.97)	0.94(0.92-0.97)	0.89(0.87-0.92)
Black carbon	LUR	0.96(0.90-1.02)	0.95(0.92-0.98)	0.95(0.93-0.98)	0.92(0.89-0.94)
PM_{10}	IDW	1.26(1.19-1.34)	0.92(0.89-0.96)	0.98(0.95-1.02)	0.90(0.88-0.93)
SO_2	IDW	0.89(0.83-0.95)	0.84(0.81-0.87)	0.86(0.84-0.89)	0.88(0.86-0.90)
Point source index	10 km buffer	0.80(0.73-0.87)	0.81(0.78-0.85)	0.76(0.73-0.79)	0.73(0.70-0.75)
Woodsmoke	Days	0.42(0.23-0.77)	2.39(1.99-2.87)	1.29(1.23-1.36)	1.23(1.18-1.27)
Exposure modeled as a categorical variable					
Expressway	<50m	1.42(0.58-3.46)	0.86(0.53-1.40)	1.18(0.82-1.70)	1.04(0.77-1.41)
	50-150m	1.23(0.89-1.70)	1.11(0.95-1.28)	1.02(0.89-1.16)	1.06(0.95-1.17)
	>150m	Reference	Reference	Reference	Reference
Primary highway	<50m	0.74(0.52-1.04)	0.81(0.69-0.96)	0.91(0.80-1.04)	0.88(0.79-0.99)
	50-150m	0.97(0.81-1.17)	0.83(0.76-0.92)	0.91(0.84-0.99)	0.89(0.83-0.95)
	>150m	Reference	Reference	Reference	Reference
Secondary highway	<50m	1.27(0.18-9.26)	1.31(0.41-4.15)	1.42(0.57-3.49)	0.20(0.03-1.41)
	50-150m	1.39(0.84-2.29)	1.09(0.87-1.37)	1.11(0.91-1.36)	1.10(0.94-1.29)
	>150m	Reference	Reference	Reference	Reference
Major road	<50m	0.84(0.73-0.98)	0.96(0.89-1.03)	0.91(0.85-0.97)	0.94(0.89-0.98)
	50-150m	0.85(0.76-0.96)	0.92(0.87-0.97)	0.90(0.86-0.94)	0.89(0.86-0.93)
	>150m	Reference	Reference	Reference	Reference

* Adjusted for otitis media season, sex, First Nations, older siblings, maternal smoking during pregnancy, maternal age, neighborhood income and neighborhood female education.

LUR – land use regression, IDW – inverse distance weighted concentrations (3 monitors within 50 km of a residential postal code).

Table 3- 5. Adjusted estimates for the association between residential air pollution and physician visits for otitis media, stratified by age.

Pollutant	Model	2-6 months	7-12 months	13-18 months	19-24 months
		RR* (95%CI)	RR* (95%CI)	RR* (95%CI)	RR* (95%CI)
Exposure modeled as a continuous variable – risk estimate per an IQR increase in pollutant					
NO	IDW	0.90(0.86-0.94)	1.02(0.99-1.04)	1.00(0.97-1.03)	0.99(0.96-1.02)
	LUR	0.98(0.94-1.03)	1.09(1.06-1.11)	1.03(1.00-1.06)	1.03(1.01-1.06)
NO_2	IDW	0.79(0.75-0.84)	0.88(0.85-0.91)	0.88(0.85-0.91)	0.85(0.82-0.88)
	LUR	0.83(0.79-0.87)	0.91(0.89-0.94)	0.89(0.86-0.91)	0.87(0.84-0.90)
CO	IDW	0.89(0.85-0.94)	0.98(0.95-1.01)	0.96(0.93-0.99)	0.99(0.95-1.02)
O_3	IDW	1.01(0.95-1.07)	0.91(0.88-0.94)	0.95(0.92-0.98)	0.93(0.90-0.97)
$PM_{2.5}$	IDW	0.95(0.90-0.99)	1.04(1.01-1.07)	1.07(1.04-1.09)	1.10(1.07-1.14)
	LUR	0.90(0.86-0.95)	0.92(0.89-0.94)	0.93(0.90-0.96)	0.92(0.89-0.95)
Black carbon	LUR	0.92(0.87-0.96)	0.95(0.92-0.98)	0.93(0.91-0.96)	0.94(0.91-0.97)
PM_{10}	IDW	0.93(0.88-0.99)	0.90(0.87-0.94)	0.96(0.92-0.99)	0.97(0.93-1.00)
SO_2	IDW	0.79(0.75-0.82)	0.87(0.85-0.89)	0.92(0.89-0.94)	0.88(0.86-0.91)
Point source index	10 km buffer	0.72(0.67-0.77)	0.74(0.71-0.77)	0.78(0.74-0.81)	0.77(0.74-0.81)
Woodsmoke	Days	1.26(1.16-1.38)	1.30(1.24-1.36)	1.29(1.23-1.36)	1.21(1.14-1.28)
Exposure modeled as a categorical variable					
Expressway	<50m	1.31(0.70-2.45)	1.00(0.69-1.43)	1.12(0.78-1.62)	1.03(0.69-1.54)
	50-150m	0.97(0.73-1.28)	1.04(0.92-1.18)	0.96(0.84-1.09)	1.14(1.01-1.29)
	>150m	Reference	Reference	Reference	Reference
Primary highway	<50m	0.77(0.59-1.00)	0.86(0.75-0.97)	0.82(0.71-0.94)	0.98(0.85-1.13)
	50-150m	0.79(0.67-0.93)	0.83(0.77-0.90)	0.91(0.84-0.99)	0.94(0.86-1.02)
	>150m	Reference	Reference	Reference	Reference
Secondary highway	<50m	1.19(0.16-8.57)	0.21(0.03-1.52)	1.71(0.74-3.95)	0.67(0.16-2.74)
	50-150m	0.71(0.37-1.37)	0.92(0.74-1.14)	0.91(0.75-1.11)	1.34(1.14-1.57)
	>150m	Reference	Reference	Reference	Reference
Major road	<50m	0.89(0.80-1.00)	0.97(0.91-1.02)	0.92(0.87-0.98)	0.90(0.84-0.96)
	50-150m	0.91(0.83-0.99)	0.88(0.84-0.92)	0.90(0.86-0.94)	0.92(0.87-0.96)
	>150m	Reference	Reference	Reference	Reference

* Adjusted for otitis media season, sex, First Nations, older siblings, maternal smoking during pregnancy, maternal age, neighborhood income and neighborhood female education.

LUR – land use regression, IDW – inverse distance weighted concentrations (3 monitors within 50 km of a residential postal code).

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4 THE BURDEN OF EARLY CHILDHOOD OTITIS MEDIA ATTRIBUTABLE TO AIR POLLUTION IN BRITISH COLUMBIA, CANADA[3]

4.1 Introduction

Otitis media, or middle ear infection, is one of the most common childhood diseases in the developed world. It is the second most common reason for children to visit a physician and the number one reason children receive antibiotics (1-3). Prior to implementation of the heptavalent conjugate vaccine, acute otitis media was responsible for 92% of all pneumococcal disease in Canada (4). Acute otitis media causes significant utilization of medical services, parental lost time from work and overall reduced quality of life for young children and their parents (5). Existing estimates of costs for diagnosis and treatment in children under 14 years range from $428 million (1994), or $77.01 per child, in Canada to $5.8 billion (1998), or $109.28 per child, in the United States (6, 7). Direct costs of otitis media include physician visits and referrals, prescriptions, surgical procedures, audiometry, speech pathology and hospitalizations related to otitis media or its complications (8). Indirect costs include caregiver lost time from work, childcare expenses and travel to and from the physician (5, 6, 9, 10).

As part of the Border Air Quality Study (11), we evaluated the relationship between otitis media and ambient air pollution in a population based birth cohort in southwestern British Columbia (BC), Canada (chapter 3). The study found a positive association between otitis media and woodsmoke, after adjustment for season; and these findings suggest that air pollution reduction strategies may be successful in reducing the overall burden of this common and costly childhood disease, particularly in regions where levels of woodsmoke are elevated or increasing. This study aims to: (i) estimate the total cost of otitis media diagnosis and treatment during the first two years of life for the above birth cohort, and (ii) estimate the cost of otitis media attributable to woodsmoke. Additionally, we compare this estimated

[3] A version of this chapter will be submitted for publication. MacIntyre, E.A., Tamburic, L., Karr, C.J., Demers, P.A., Brauer, M. (2010) The Burden of Early Childhood Otitis Media Attributable to Air Pollution in British Columbia, Canada.

attributable cost to those associated with traffic-related air pollution and maternal smoking during pregnancy; with the latter two being well-recognized modifiable risk factors for otitis media (12, 13).

4.2 Methods

The total cost of otitis media diagnosis and treatment for the study population during the first two years of life was calculated as the sum of outpatient physician contacts, prescription antibiotics, inpatient surgical procedures, emergency room visits and caregiver lost time from work. The first three items were calculated from provincial data and the last two were estimated using previously published data.

4.2.1 Actual Costs

The BC Ministries of Health provided information on all outpatient physician contacts and hospitalizations coded as otitis media (International Classification of Disease version 9 codes 381 & 382) for children born in Southwestern BC between January 1, 1999 - December 31, 2000 (n=59,917) (12). Data were extracted for the first 2 years of life for each child. The study region included the municipalities of Vancouver and Victoria and captured 72.5% of all live births in the province of BC during this period. The outpatient visit data included principal diagnosis, itemized fee codes for physician payments, physician specialty and location. Fee codes were assigned costs (in 2003 dollars) based on the BC Medical Services Commission Payment Schedule for 2003 (14). The hospitalization data included principal diagnosis requiring hospitalization and procedure codes (Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures). The unit cost for the most common procedure, myringotomy with insertion of ventilation tubes, was previously assessed (15) in 1994 dollars for the BC Children's Hospital, and this was inflated to 2003 dollars using the Consumer Price Index published by Statistics Canada. This cost includes preoperative assessments, otolaryngologist and anesthesiologist costs, surgical supplies, recovery room and hospital overhead.

The BC College of Pharmacists provided information on all antibiotic prescriptions for these 59,917 children during the first two years of life. Antibiotics routinely used to treat otitis media were identified from practice guidelines (archived guidelines, (16)) and data were linked to otitis media physician contacts based on service dates, allowing a 4-day lag

between physician contact for otitis media and pharmacy visit to fill a prescription for otitis media. Antibiotic costs (ingredient costs plus professional fees) were originally recorded in 1999 through 2002 dollars, these were inflated to 2003 dollars using the Consumer Price Index published by Statistics Canada.

4.2.2 Estimated Costs

There was no cost data available at the population level for emergency room visits for otitis media and parent/caregiver lost time from work due to otitis media. Because both of these data have been previously identified as important components of total otitis media costs (5), we estimated their contribution using Monte Carlo estimates based on data from a previous study that estimated the total cost of otitis media in Canada using 1994 dollars (for Canadian children under 14 years) (6). Estimated costs were assigned a mean, range and lognormal distribution, based on previous literature (6, 17). The model was specified with both certain (actual) and uncertain (estimated) components. One thousand iterations were completed in each simulation. For each iteration the model was executed using different randomly sampled values to identify a range of possible outcomes, or total costs, and their likelihood of occurring. One hundred simulations were completed to optimize the estimate of total costs.

4.2.3 Air Pollution

The assessment of woodsmoke and traffic-related air pollution has been described in detail elsewhere (18-21). Briefly, woodsmoke was measured throughout the Vancouver metropolitan area through mobile monitoring of particle light absorption on 19 cold, clear winter nights (22). This mobile monitoring data was combined with data from fixed-location monitoring sites to develop a spatial woodsmoke map for the entire study area. Postal codes in the top tertile of woodsmoke particulate matter, as estimated from the model, were classified as wood burning areas and daily temperature data were used to identify time periods during which elevated concentrations of woodsmoke were present in these areas. Woodsmoke was found to be strongly associated with otitis media in all analyses, even after adjusting for season. Spatial maps of traffic-related air pollutants were created through land use regression (20), based on monitoring data from predetermined sites and traffic variables. Of the traffic-related pollutants considered, nitric oxide performed best ($R^2=0.62$) and included the following predictors: number of major roads within 100m and 1,000m, number

of secondary roads within 100m, the population density within 2,500m, and elevation (20). Temporal trends were assessed from regional monitoring network data and models were fit with a monthly dummy variable and a covariate for linear trend. Woodsmoke and traffic-related air pollution were assigned to children based on their residential postal code. Additionally, information was collected on maternal smoking during pregnancy from a prenatal questionnaire and the adjusted risk estimate for otitis media has been included for comparison (12).

4.2.4 Statistical Analysis

Cost data were converted into 2003 Canadian dollars and total costs for otitis media outpatient physician contacts, antibiotic prescriptions and inpatient surgeries were calculated for each child. The total of all actual and estimated costs for otitis media in the study population were calculated. Estimates were scaled to the national level and compared with previous economic costing of otitis media. The attributable fraction of otitis media due to woodsmoke, traffic-related air pollution and maternal smoking during pregnancy were calculated based on adjusted risk estimates and the prevalence of exposure among the study population (chapter 3). For traffic-related air pollution, woodsmoke and maternal smoking during pregnancy, the population attributable risk percent was estimated as: [(total incidence – incidence among unexposed)/ total incidence]. Analyses were completed using SAS 9.1 (SAS Institute, Cary NC, 2002) and @Risk 5.5 (Palisade Corporation, Ithaca NY, 2009). The UBC Behavioral Research Ethics Board approved this study (Appendix A). Personal identifiable information (date of birth, postal code and personal health number) was not available to the researchers.

4.3 Results

4.3.1 Actual Costs

Of the 59,917 children identified in the population-based birth cohort, 24,827 (41.5%) had at least one outpatient physician contact for otitis media during the first two years of life. Outpatient physician contacts accounted for the largest portion of actual otitis media costs, followed by antibiotic prescriptions and inpatient surgeries (table 4-1). The outpatient physician contacts were primarily physician visits (83.9%) and consultations (11.5%). Cost

breakdowns for outpatient physician visits and antibiotic prescriptions are shown in tables 4-2 and 4-3, respectively. The most common physician visit was in a general practitioner office (96.1%), followed by a specialist follow-up (2.9%); and the most common antibiotic was penicillin (79.7%), followed by clarithromycin (8.9%) and azithromycin (5.0%).

The distribution of the actual costs for otitis media diagnosis and treatment was not equal across the population. Although 51.5% of the birth cohort was male and 2.5% were First Nations, male children incurred 57.8% of the total costs and First Nations children incurred 3.8%. There was also a notable trend by neighborhood female educational attainment (from Canadian Census), where children living in neighborhoods with the lowest quartile of female education incurred a higher proportion of otitis media costs (27.5%) and a lower proportion of costs was incurred by children in the highest quartile neighborhoods (22.1%), but this trend was not statistically significant. Children with at least one inpatient surgery for otitis media (n= 473; 0.8%) incurred 16.7% of the total actual costs for otitis media; and children with at least one antibiotic for otitis media (n=16,070; 26.8%) incurred 79.3% of the total actual costs for otitis media. Finally, children who received their first physician contact for otitis media before the age of 12 months (n=14,519; 24.2%) incurred 72.3% of the total actual costs.

4.3.2 Estimated Costs

The estimated costs for emergency room visits and caregiver lost time from work are presented in table 4-4. The total estimated cost for otitis media diagnosis and treatment during the first two years of life for the 59,917 children of British Columbia was $4,225,773 ($4,064,015-$4,402,587) in 2003 dollars. Visits within 14 days of a previous visit were assumed to be follow-up visits and were excluded prior to calculating the total number of otitis media episodes for the cohort, the resulting cost per outpatient episode of otitis media was $83.25. Based on the cost per child ($70.53 ($67.83-$73.48)), the total cost for the Canadian population of 0-2 year olds in 2003 (n=662,877) was $46,750,802 ($44,961,231-$48,706,939), assuming identical otitis media incidence and cost of diagnosis and treatment across all Canadian provinces and territories.

4.3.3 Air Pollution Attributable

The exposure prevalences for woodsmoke, traffic and maternal smoking during pregnancy were 31%, 100% and 10%, respectively. The prevalence for woodsmoke was calculated based on the cohort percentage living in neighborhoods with the highest tertile of woodsmoke exposure during the winter. The entire population was assumed to be exposed to traffic related air pollution. The prevalence for maternal smoking during pregnancy was based on the percentage of mothers who reported smoking during pregnancy. Corresponding risk estimates for woodsmoke, traffic and maternal smoking during pregnancy were 1.32, 1.08 and 1.06, respectively (chapter 3). The population attributable fraction for woodsmoke (when adjusting for season) in the highest tertile during the month of otitis media was 10.0%, this is equivalent to $420,464($404,369-438,057) in 2003 Canadian dollars. The attributable fraction for an inter quartile increase in traffic-related air pollution (nitric oxide) in the month of infection was 15.2% before adjusting for season but was reduced to 7.4% after adjusting the estimate for season, this is equivalent to $312,707($300,737-$325,791) in 2003 dollars. For comparison, the population attributable fraction of otitis media for maternal smoking during pregnancy was 1.6%, this is equivalent to $68,458($65,837-$71,322) in 2003 dollars – however this is an underestimate because there was likely some misclassification in the variable used to classify smoking during pregnancy (12).

4.4 Discussion

This study used data from a population-based birth cohort to define otitis media outpatient and inpatient contacts with the health system. The estimates of population attributable fraction were derived from population-based estimates of risk for this birth cohort.

4.4.1 Cost of Otitis Media

In Quebec and Manitoba, Canada, the cost per otitis media episode has been estimated as $295 in 2001 dollars (23) whereas in this study it was estimated as $83.25 in 2003 dollars. This difference could be due to a number of factors; in this study we may have overestimated the number of unique otitis media episodes by using a 14-day restriction, and the cost calculated by Petit and colleagues (23) may have been for more severe disease because only pneumoccocal otitis media was considered. However, Morrow et al (4) calculated the

national cost of acute otitis media in Canadian children during the first year of life to be $41,304,250($37,550,500-$46,939,991) in 2001 dollars using age specific incidence rates from Quebec and Manitoba, and this estimate is fairly close to the $46,750,802 (2003) that was estimated in this study for children during the first two years of life. Furthermore, in the United States, the total cost of diagnosing and treating one episode of otitis media was $115.80 in 1994 (9). The only study to estimate the national cost of otitis media in Canada was Coyte et al (6). This study estimated the national cost of otitis media for the entire Canadian population under 14 years as $428 million (1994) or $77.01 (1994) per child; and this is also somewhat close to the $70.53 (2003) per child estimated in this study. Although it is difficult to compare these results with previous otitis media costing studies, mainly due to differences in data sources and methodologies, the similarity with our estimates lends validity to the methodology used here.

In scaling the total cost estimate for southwestern British Columbia to all of Canada we ignored regional differences in otitis media incidence and diagnosis and treatment costs. This likely underestimated the true national burden because the study area of southwestern British Columbia has low rates of otitis media as compared with other regions of Canada and the United States (12, 24), and physician fees are lower than those in other Canadian provinces (15). Further, implementation of the pneumococcal conjugate vaccine began in the study area in 2001 and was expected to lead to a 6-7% reduction in otitis media (25). However, this has not been confirmed and a study in Quebec, Canada found a 13.2% reduction in otitis media physician claims following implementation of the pneumococcal conjugate vaccine (26).

A unique strength of this study is that actual costs were used for outpatient physician contacts and antibiotic prescriptions, providing more accuracy than estimates based on nation survey or expenditure data. Similar to previous research (6, 7), this study found physician visits and prescription drugs to be responsible for the majority of otitis media costs. Although costs for emergency room visits and caregiver lost time from work both had to be estimated using previous literature, these represented less than one-third of total costs, 7.9% and 23% respectively.

This study assessed the cost of otitis media diagnosed by a physician. Due to the notable increase in watchful waiting (1), there may have been some children who were not brought to

the physician for suspected otitis media because caregivers assume physicians will not prescribe antibiotics for the infection. Additional direct costs such as research and prevention programs, lost daycare fees and transportation costs to and from physicians/hospitals were not included in this study. Finally, the cost of otitis media calculated in this study was for the first two years of life only. For the 1% (n=611) of the cohort who incurred 20% of the total actual otitis media costs, there will likely be additional costs for follow-up and treatment beyond the second year of life and these were not assessed. However, previous research has shown that children incur the highest total annual expenditures per child for otitis media physician visits, prescriptions and surgical procedures during the first two years of life (7).

Due to data limitations it was not possible to assign costs to 0.05% of the outpatient physician contacts (fee item codes were retired prior to 2003), 1.17% of the antibiotic prescriptions (due to missing data) and 10.9% of the hospitalizations (those involving more than one day of hospitalization and/or those involving procedures other that myringotomy). Antibiotic data with missing ingredient costs was imputed based on standardized costs, but professional fees could not be imputed. Finally, while it was not possible to determine the number of children who presented with otitis media in an emergency room, only 5 of the 518 children hospitalized for otitis media were admitted through the emergency room and it would have been recommended that all other children see their family physician for a follow-up visit.

4.4.2 Burden of Air Pollution

Considerable societal costs can be attributed to air pollution-related illness, but few studies have considered the cost due to childhood disease (27). This is the first study to calculate the burden of otitis media attributable to air pollution. Environmental tobacco smoke has long been recognized as an important risk factor for otitis media during childhood (13); and comparison with prevalence estimates (11% for household exposure) from the 2003 Canadian Community Health Survey (28) suggest that removing tobacco smoke from the home would result in a 2.1% reduction in otitis media during childhood. This figure is considerably lower than those calculated for traffic-related air pollution and woodsmoke in this study.

In this population, more children were exposed to woodsmoke (31.4% of the population) than maternal smoking during pregnancy (10.4% of the population); and although all children were exposed to traffic-related air pollution, the cost of otitis media attributable to woodsmoke was greatest. Further, while implementation of the pneumococcal conjugate vaccine was expected to reduce otitis media incidence by 6-7%, this study found that reducing woodsmoke or traffic-related air pollution would reduce otitis media incidence by 10.0% or 7.4%, respectively. The findings for woodsmoke have important implications for developed countries, where biomass is commonly used for heating in areas with cold winter climates (29), and may also be relevant to developing countries, where biomass combustion is commonly used for cooking and heating (30).

According to the World Health Organization, the global burden of acute lower respiratory infection in children under the age of five attributed to biomass combustion accounts for 32 million disability adjusted life years (30). Unfortunately, otitis media has only recently been identified as an outcome of interest with respect to air pollution exposure. Thus, the true burden of biomass combustion is likely much greater than previous estimates because the economic benefit of reducing this disease is substantial.

This study used a population-based sample representative of southwestern British Columbia and assessed the burden of otitis media attributable to air pollution, specifically source-specific pollutants such as woodsmoke. The results suggest that in residential neighborhoods with significant woodsmoke pollution in the winter, clean technologies implemented at the home may significantly reduce the impact of this disease. These results should be useful to policy makers when conducting cost-benefit analyses of policies aimed at reducing air pollution in urban areas. Additionally, the methodology used to assess the total cost of otitis media can be replicated to measure the economic impact of interventions, such as implementation of the pneumococcal vaccine or educational programs aimed at reducing modifiable risk factors for otitis media.

Table 4- 1. Breakdown of actual otitis media diagnosis and treatment costs during the first two years of life.

Group	Number (%)	Cost (%)
Outpatient Physician Contacts		
Outpatient Physician Visits*	60,377 (64.73%)	$1,872,090.02 (64.57%)
Outpatient Consultations (Emergency Medicine, Pediatrics, Anesthesiology)	4,160 (4.46%)	$257,184.38 (8.87%)
Outpatient Surgery, Procedures & Laboratory Fees	619 (0.66%)	$66,188.93 (2.28%)
Miscellaneous (referrals, call outs, counseling)	913 (0.98%)	$27,578.24 (0.95%)
Audiometry & Impedance testing	856 (0.92%)	$7,568.85 (0.26%)
Antibiotic Prescriptions**	25,836 (27.70%)	$426,100.97 (14.70%)
Inpatient Myringotomy with Tube insertion	518 (0.56%)	$242,828.04 (8.37%)
Total	93,276 (100%)	$2,899,539.43 (100%)

* See table 4-2 for additional breakdown.
** See table 4-3 for additional breakdown.

Table 4- 2. Breakdown of outpatient physician visits for otitis media during the first two years of life.

Subgroup	Number (%)	Cost (%)	Cost per Physician Visit
General Practitioner Office Visit	58,042 (96.13%)	$1,791,327.95 (95.69%)	$30.86
Follow-up with a Specialist	1,720 (2.85%)	$53,108.65 (2.84%)	$30.88
Hospital Visit	452 (0.75%)	$16,995.94 (0.91%)	$37.60
Home visit	93 (0.15%)	$4,850.09 (0.26%)	$52.15
Emergency Visit	70 (0.12%)	$5,807.39 (0.31%)	$82.96
Total	60,377 (100%)	$1,872,090.02 (100%)	$31.01

Table 4- 3. Breakdown of antibiotic prescriptions for otitis media during the first two years of life.

Subgroup	Number (%)	Cost (%)	Cost per Prescription
Penicillins	20,599 (79.73%)	$267,905.31 (62.87%)	$13.01
Clarithromycin	2,208 (8.55%)	$75,951.27 (17.82%)	$34.40
Azithromycin	1,297 (5.02%)	$44,153.87 (10.36%)	$34.04
Erythromycin/ Sulfisoxazole	1,069 (4.14%)	$28,247.37 (6.63%)	$26.42
Erythromycin	663 (2.57%)	$9,843.15 (2.31%)	$14.85
Total	25,836 (100%)	$426,100.97 (100%)	$16.49

Table 4- 4. Model inputs used to calculate the total cost of otitis media diagnosis and treatment.

Parameter	Units	Certainty	Distribution	Estimate (90%CI)	Sensitivity Regression Coefficient	Data source
Outpatient Physician Contacts	2003 $CDN	DeterministicIndependent	-	$2,230,610.42	-	BC Ministry of Health
Antibiotic Prescriptions	2003 $CDN	Deterministic Dependent	-	$426,100.97	-	BC College of Pharmacists
Inpatient Myringotomy with Tube insertion	2003 $CDN	Deterministic Dependent	-	$242,828.04	-	BC Ministry of Health, Coyte, 1998
Emergency Room Visits	2003 $CDN	Stochastic Dependent	Log-normal	$334,591.56 ($297,000-371,000)	0.98	Coyte, 1999
Caregiver lost time from work	2003 $CDN	Stochastic Dependent	Log-normal	$991,642.13 ($832,000-1,170,000)	0.22	Coyte, 1999

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5 CONCLUDING CHAPTER

5.1 Summary of Findings

This work utilized administrative data to characterize otitis media and its risk factors, assessed urban air pollution as a preventable risk factor for otitis media and quantified the economic burden of otitis media attributable to air pollution in a population-based birth cohort of British Columbia, Canada.

In chapter 2, administrative data was used to follow children through the first three years of life. The incidence (42% at 2 years; 49% at 3 years) of otitis media was reported to be low as compared with previous studies, which reported otitis media incidence as high as 83% at age three (1). Nonetheless, trends in otitis media and associations with previously identified risk factors (gender, older siblings, First Nations, etc.) were largely consistent in magnitude and direction with current literature, and validated the use of administrative data in characterizing otitis media and its risk factors at the population level.

In chapter 3, the role of air pollution as a risk factor for otitis media during the first two years of life was investigated. Analyses were restricted to the first two years of life to include the period of highest age specific incidence. The most consistent positive findings were for NO and woodsmoke; while the most consistent negative findings were for black carbon, an index of point source emission proximity, SO_2 and PM_{10}. The findings for NO_2, $PM_{2.5}$ and O_3 were not consistent. These results highlight the difficulties in analyzing the relationship between time-varying exposures and outcomes; CO, NO, NO_2 and woodsmoke were risk factors for otitis media before seasonal adjustment, while NO, $PM_{2.5}$ and woodsmoke were risk factors for otitis media after seasonal adjustment. Results for O_3 were difficult to interpret due to the strong inverse (temporal and spatial) correlation between ozone and other pollutants (NO, NO_2 and CO); effects were consistently protective in full cohort analyses, but when analyses were stratified by season ozone was associated with increased otitis media during the summer and winter (tables B-4, B-5 and B-8). Additionally, analyses using a fixed one-year exposure window from birth (versus the moving 2-month exposure window) identified only woodsmoke and O_3 to be associated with increased disease (table D-1). Woodsmoke was found to be strongly associated with otitis media in all analyses, even after adjusting for season.

In chapter 4, the total cost for otitis media diagnosis and treatment was calculated in 2003 dollars for the entire study population during the first two years of life. The majority of this total was calculated from actual cost data available at the population level, and the final total was comparable to previous estimates (2). Using this data, the economic burden of otitis media attributable to air pollution was calculated as $420,464 for woodsmoke and $312,707 for traffic-related air pollution, based on the risk estimates obtained in chapter 3.

5.2 The Use of Administrative Data

This study was made possible by the wealth of administrative data available at the population level for individuals in British Columbia (BC), Canada. The results of this study demonstrate the utility of linking multiple administrative databases to examine disease at the population level. The findings will be of interest to policy makers and may also benefit those data stewards involved, by highlighting the research value of their respective data. The methodology used in chapters 2 and 4 can be replicated to assess otitis media (or other disease) incidence, trends, potential risk factors and costs.

The population attributable fractions calculated in chapter 4 were based on risk estimates that were calculated for the entire population, making the results generalizable to the entire BC population. Further, potential limitations common to many observational studies, such as selection bias, parental reporting bias, follow-up bias and external validity were avoided by using administrative data in this study.

Although this data was a rich source of outcome and potential confounder information, and it was obtained at no cost (for students), there were considerable time delays in obtaining the data extracts (table 5-1). Additionally, the exposure windows and exposure assignment were both limited by privacy legislation as it was not possible to link exposures and health outcome data by day. For this reason, it was not possible to investigate exposure windows of less than two months in chapter 3.

5.3 Strengths and Weaknesses

5.3.1 Study Design and Statistical Analysis

The design of this population-based birth cohort study eliminated selection bias by using administrative data based upon the universal healthcare system. Children who were lost due

to incomplete residential history likely moved from the study area so any loss to follow-up bias was negligible (3). The nature of the data used for this study dictated that a longitudinal approach be used to analyze the data in chapter 3, because contacts with the healthcare system were recorded throughout follow-up based on date and age in months. Numerous techniques were used to investigate the association between air pollution and otitis media; conditional logistic regression matching on age in months, survival analysis modeling three different case definitions and generalized estimating equations. The results across these three statistical analyses were largely consistent (appendices B, C and D). Ultimately, we focused on analyses using generalized estimating equation because they allowed all otitis media event months (initial and subsequent) to be included in the analysis, while logistic regression and survival analysis were restricted to case definitions based on first incidence only.

5.3.2 Otitis Media

The identification of otitis media was based on physician diagnosis and avoided reporting bias, which has been a limitation of previous otitis media studies that relied upon parental reporting of symptoms (3). Nevertheless, there were limitations in using this data to define otitis media. The billing file used to identify otitis media contains one field for principal diagnoses. Thus, when a physician makes two diagnoses during one visit, only the principal is recorded. Due to the seriousness and potential consequences of otitis media it is likely that incident disease is recorded in this file, but for children who frequently present with disease there is a possibility that some subsequent diagnoses were not recorded. Additionally, both accuracy of physician diagnosis and accuracy of ICD-9 coding may be limitations of this study. Chapter 3 highlighted the problems using 3-digit ICD-9 codes versus the more specific 4-digit codes. Antibiotic prescriptions were linked to otitis media physician visits in an attempt to further define acute otitis media but the linkage results were surprisingly low (chapter 2) and, in absence of an adequate explanation for this discrepancy, the linked data were used only for sensitivity analyses.

5.3.3 Risk Factors and Potential Confounders

A large number of otitis media risk factors were considered in this study, but it was not possible to include; daycare, duration of breastfeeding or racial groups other than First Nations. Literature suggests that these variables are highly correlated with socioeconomic

status and they may have been partially adjusted for by including maternal age at birth, neighborhood female education and family income, which are all indicators of socioeconomic status. In chapter 2, the effect estimates for some otitis media risk factors may have been biased due to the lack of daycare information. However, it is unlikely that the effect estimates in chapter 3 were biased because there is no evidence to suggest that air pollution levels are correlated with daycare in the study area (4).

5.3.4 Air Pollution Exposure Assessment

Monthly exposures for urban air pollution were assigned to children based on their residential postal code and age in months. In rural areas, where postal codes can spread over wide geographic areas, there may have been misclassification; however, results from sensitivity analyses restricted to children living in urban areas as defined by Statistics Canada (table B-9) were consistent with the overall findings of this study. Although moves were included in this study, the exact date was not known and was approximated from physician contacts. There was also no data available on time spent in locations outside the home. Finally, the assignment of exposures based on age in months, and not days, precluded the possibility of examining exposure windows of less than 2 months.

The exposures modeled in chapter 3 were validated through personal monitoring of 62 pregnant women living in the Vancouver area during 2005-2006 (5, 6). This study found moderate agreement between personal measurements and estimates of ambient air pollution at the home – women who smoked or who lived with smokers were not included (6). Nitric oxide models performed the best at explaining spatial variability in personal exposure and there was little relationship between land use regression estimates of $PM_{2.5}$ and black carbon, with personal measurements (6). The study concluded that the effect of ambient outdoor pollution on personal measurements did not vary by the presence of indoor sources and activities and that ambient monitors were generally good predictors of temporal variability of personal exposures; for example, monitor based $PM_{2.5}$ estimates explained no spatial variability in personal measurements, while NO estimates explained mainly temporal variability and some spatial variability (5, 6).

5.3.5 Economic Costing Data

The actual cost of physician visits and antibiotic prescriptions for otitis media - the two items responsible for the majority of total otitis costs (2, 7) - were assessed from administrative data for the entire study population. This is a unique strength over previous otitis media costing studies that have estimated all otitis media components (2). Although costs for emergency room visits and caregiver lost time from work had to be estimated using previous literature, these costs represented less than one-third of total costs. Overall, the estimated cost of otitis media calculated in this study was comparable with that of previous studies.

5.4 Analytic Challenges and Discussion

The use of 2 month exposure windows introduced numerous analytical challenges due to the strong seasonal pattern of otitis media and some of the pollutants being considered. Nonetheless, this sub-chronic window was used for the primary analyses presented in chapter 3 because high pollutant exposures in the two months leading to otitis, even when season is adjusted for, seem to be important – and some of these pollutants are no longer important when exposures are averaged over the first year of life (table D-1).

The conflicting results found for the same measure of urban air pollution across different statistical analyses and levels of adjustment were likely due to the strong seasonal trend of otitis media physician visits (figure 3-1). For NO_2 measured by LUR and IDW, the temporal profile was similar to that of otitis media and in initial analyses there was a strong positive association between the two; however, when the results were adjusted for otitis media season there was a negative association between the two. This suggests that the preliminary finding was driven purely by temporal correlation and therefore cannot be attributed solely to air pollution. Visual inspection of the spatial distribution of otitis media and NO_2 (appendices E and F) in the Greater Vancouver Regional District suggested a negative spatial correlation, and may be partly responsible for the negative association found in analyses adjusted for season. It is important to note that the associations for NO and woodsmoke, which also had temporal trends similar to that of otitis media, remained positive after adjusting for season. NO was modeled using both ambient monitoring data (higher temporal resolution) and land use regression models (higher spatial resolution), and because the results for both were similar it suggests that both performed well in modeling their respective components of NO

exposures. $PM_{2.5}$ measured from the ambient monitors was non-significant before seasonal adjustment but became significant in adjusted analyses; and this measure had minimal seasonal variation throughout the study period. Furthermore, the air pollution measures that had little or no temporal trend but whose estimates changed after adjusting for otitis media season may suggest enhanced exposure to, or susceptibility to air pollution across different otitis media seasons.

Woodsmoke was consistently associated with increased risk of otitis media in all analyses and stratifications, with the exception of the low otitis media season (table 3-4) – this was likely an artifact of the temporal correlation between woodsmoke and otitis media because there was very little woodsmoke exposure during the low otitis media season.

The consistency in protective association across pollutants and exposure assessment methods makes chance associations unlikely. Some of these findings can be explained by the correlation between pollutants considered. Due to the strong inverse spatial and temporal correlation (figure 3-1) between O_3 and all other seasonal pollutants (CO, NO, NO_2, woodsmoke, and to a lesser degree $PM_{2.5}$) the only analyses expected a priori to result in positive associations with otitis media were those in seasonal stratifications. The spatial distribution of O_3 and otitis media (appendices E and F) appears to be positively correlated and may partially explain these results. As a proxy for exposure, monitor density was greatest for O_3 but due primarily to its reactivity; O_3 measurements probably have the poorest correlation with indoor concentrations, where people spend most of their time. However, infants likely spend more time outside during the summer and a previous study did find strong correlations between personal exposure and ambient levels of $PM_{2.5}$ and O_3 for children during the summer months (8).

There is also the possibility that the concentrations were simply too low to detect significant associations, this is suggested by quartile results that, when adjusted for otitis media season, indicated elevated risks for IDW PM10 and IDW PM2.5, but only for the highest quartile (table B-7). The studies in Munich and The Netherlands that evaluated the association between traffic-related air pollution and physician diagnosed otitis media reported positive associations for all variables derived from land use regression (9). However, in these studies,

unlike this one, Brauer et al examined annually averaged exposures that were, for $PM_{2.5}$ and NO_2, higher than those in chapter 3 (figure 5-2).

The final models presented in chapter 3 were adjusted for otitis media season. It is possible that that the association between air pollution, specifically those pollutants with strong seasonal patterns paralleling otitis media, and otitis media was over-adjusted for in these final models. This over adjustment most likely would artificially bias risk estimates toward the null – and underestimate the attributable fraction of disease. Another option that could have been used to adjust for the temporal correlation between otitis media and air pollution was to use an interaction between air pollution and season in the final models. The use of an interaction term would have reduced the concern of over-adjustment in the final models but interpretation of the resulting effect estimate would have been challenging, especially in dissemination of results to policy makers.

In summary, despite strong evidence to suggest biological plausibility for urban air pollution as a risk factor for otitis media, this study found urban air pollutants to be associated with both increased and decreased risk of otitis media.

5.5 What This Work Adds

These findings demonstrate the utility of administrative data in population-based epidemiological studies and health economics, and suggest that traffic and wood burning may be important sources of air pollutants capable of increasing the likelihood of otitis media. After adjustment for otitis media season, NO and IDW $PM_{2.5}$ were both associated with increased otitis media. The remaining measures of urban air pollution produced effect estimates that were either protective or non-significant in full cohort analyses. In stratified analyses, O_3, which was inversely correlated with all other pollutants, was a risk factor for children born during the summer months (table B-5). This may suggest that oxidative stress and the resulting damage during the first months of life critically impair the ability of the immune system to respond to invading pathogens at any age. Thus representing a critical window of susceptibility for ozone's effect on future otitis media risk.

Woodsmoke was consistently identified as an important preventable otitis media risk factor. While biomass was already discussed as a risk factor in chapter 1, the measure used in this study was neighborhood woodsmoke outside the home and at concentrations considerable

lower than inside a home burning wood for cooking. The associations for woodsmoke were consistent and robust in all analyses, including those that adjusted for otitis media season, and the attributable fraction of otitis media due to woodsmoke was valued at (2003) $420,464, accounting for 10% of the total estimated costs associated with otitis media in the study area.

In 2003 the BC government implemented a pneumococcal conjugate vaccination program that was expected to reduce otitis media incidence by 6-7%. The results of chapter 4 suggest that reducing traffic-related air pollution (by 20$\mu g/m^3$ of NO) would have a similar impact on otitis media (7.4% reduction in the overall burden by age 2), and also reductions in other health outcomes associated with air pollution.

5.6 Status of Hypothesis

The primary hypothesis for this research was that urban air pollutants enter the respiratory system and, via mechanisms similar to that of viral infections and environmental tobacco smoke, suppress the ability of the immune system to clear otitis media pathogens.

Disease initiation versus recurrence

The first challenge in investigating this hypothesis was defining acute and recurrent otitis media. Due to the lack of specificity in ICD-9 coding and the low linkage rate between physician visit and prescription data, it is likely that some chronic otitis media and eustachian tube disorders were captured in the assessed outcome. It was possible to define recurrent otitis media (for survival analysis and logistic regression) but overall there was little difference in effect estimates across different otitis media definitions (tables C-1 and D-1). Finally, results from analyses that modeled otitis media physician visits with a linked antibiotic prescription (acute otitis media) supported those presented in chapter 3 (table B-10).

Appropriate exposure windows

This study followed children through the first two years of life to include the period of greatest age-specific otitis media incidence (10), and where the effect of environmental tobacco smoke - and potentially other air pollutants - is greatest (1). Analyses stratified by age found that woodsmoke and ozone were the only pollutants associated with elevated otitis

media during the first 6 months of life; and NO and PM_{10} became important only after the 6th month of life. This study investigated moving 2 month exposure windows and annual averaged exposure for the first year of life; but due to privacy legislation it was not possible to consider shorter, more acute exposure windows. Analyses using the 2 month exposure windows were sensitive to the temporal correlation between otitis media and the pollutants being considered. Fixed exposure windows for the first year of life highlighted the importance of O_3 and woodsmoke, but the remaining pollutant estimates were protective (table D-1).

Air pollutant characteristics

The air pollutant measures considered in this study included particulate matter and gaseous pollutants. The potential mechanisms by which each of these measures could suppress the immune system have already been discussed (chapter 1). Associations were found for fine particulate and oxidizing gaseous pollutants ($PM_{2.5}$, CO, NO, NO_2, O_3) but these were not consistent. Woodsmoke, which contains a complex mixture of particulate and gaseous pollutants, was the only measure consistently associated with otitis media.

Susceptible populations

In stratified analyses, the findings across age group, birth season and event / otitis media season can partially be explained by the temporal patterns of the air pollutants and behaviors of children (eg. ozone levels higher in the summer when children are outside more often). Although stratified analyses identified no differences across gender or parity, there were elevated estimates for First Nations children and children whose mothers smoked during pregnancy, but results were generally not statistically significant. The findings for children born prior to 30 weeks gestation may have been impacted by poorer exposure assessment for these children – specifically, less time spent outdoors.

5.7 Future Work

Due to the small amount of literature examining air pollution and otitis media, additional observational research should also be conducted. Future research should aim at accurately characterizing acute and recurrent otitis media diagnosed in physician offices and emergency rooms. As in this study, cohort study designs with longitudinal analyses are best suited to

address this research question, as children can be followed throughout their development and the full burden of disease can be captured. Exposure should be assigned based on child day to allow analysis of acute exposure windows and models with multiple pollutants may be useful in understanding the associations between pollutant measures and otitis media. Additionally, exposures that occur in areas outside the home, but where children spend a lot of time, such as daycare should be incorporated. Populations of special interest should be considered such as First Nations, pre-term infants and children exposed to tobacco smoke and woodsmoke in the home.

It would also be useful to have additional potential risk factors available at the population level. The BC Reproductive Care Program collects information on the "ethnic origin" of biological parents, "smoking before pregnancy," "number of school years completed" by mother and "work type" of both biological parents; but unfortunately this information is not currently entered into the Perinatal Database Registry.

Experimental research should focus on the effects of air pollutants on the eustachian tube to confirm that the inflammation and subsequent effects initiated by air pollutants in the respiratory mucosa are also observed in eustachian tube and middle ear mucosa. Additional research examining the impact of air pollution mixtures (specifically, fine particulate and oxidizing gaseous pollutants) would also be useful to understand the relationship between air pollution and otitis media.

Finally, educational and technological interventions aimed at reducing woodsmoke and traffic-related air pollution may have a significant impact on the burden of otitis media, particularly if interventions are targeted to neighborhoods identified by the Border Air Quality Study as having high ambient air pollution levels.

Table 5- 1. Data sources and respective timeline for receiving thesis data.

Data Source	Application Submitted	Received Approval	Received Data Extract
BC Ministries of Health	March 8, 2005	May 10, 2006	1st extract: August 3, 2006 2nd extract: July 13, 2007
BC Reproductive Care Program	December 15, 2005	March 1, 2006	July 27, 2006
BC College of Pharmacists	February 14, 2007	March 16, 2007	October 10, 2007

Table 5- 2. Comparison of mean pollutant concentrations between Vancouver, The Netherlands and Munich.

	Vancouver	The Netherlands	Munich
$PM_{2.5}$	3.9(0.0-13.3)*	16.9(13.5-25.2)	13.4(12.0-21.9)
Black carbon / particle absorbance	1.6(0.0-6.5)	1.72(0.77-3.68)	1.76(1.40-4.39)
NO_2	16.6(0.0-35.1)	25.6(12.6-58.4)	27.7(19.6-64.4)

* Mean concentrations presented with minimum and maximum values.

5.8 References

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APPENDICES

Appendix A UBC Behavioral Research Ethics Board Approval Certificate

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:
Michael Brauer	UBC/College for Interdisciplinary Studies/School of Environmental Health	H05-80123

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):

Mieke W. Koehoorn
Elaina A. Macintyre
Paul Demers

SPONSORING AGENCIES:

British Columbia Centre for Disease Control - "Exposure to Air Pollution and Middle Ear Infection in Children"

PROJECT TITLE:
Exposure to Air Pollution and Middle Ear Infection in Children

EXPIRY DATE OF THIS APPROVAL: November 5, 2010

APPROVAL DATE: November 5, 2009

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. Anita Ho, Associate Chair

Appendix B Longitudinal Analyses Results, Stratifications and Sensitivities

Table B- 1. Adjusted estimates for the association between residential air pollution and physician visits for otitis media, stratified by gender and maternal smoking.

	Gender						Maternal Smoking During Pregnancy					
	Male			Female			Yes			No		
	RR*	LCL	UCL	RR*	LCL	UCL	RR*	LCL	UCL	RR*	LCL	UCL
Traffic-related Land Use Regression – extended to Georgia Basin												
Black carbon	0.93	0.91	0.96	0.97	0.94	1.00	1.01	0.95	1.08	0.94	0.92	0.96
NO	1.02	1.00	1.04	1.05	1.03	1.08	1.09	1.04	1.14	1.03	1.01	1.04
NO_2	0.87	0.84	0.89	0.89	0.86	0.92	0.97	0.91	1.04	0.87	0.85	0.89
$PM_{2.5}$	0.92	0.89	0.94	0.93	0.90	0.96	0.96	0.91	1.03	0.92	0.90	0.94
Traffic-related Land Use Regression – Greater Vancouver												
Black carbon	0.97	0.94	0.99	0.98	0.95	1.00	1.02	0.97	1.07	0.97	0.95	0.98
NO	1.00	0.98	1.02	1.02	1.00	1.05	1.09	1.03	1.16	1.00	0.99	1.02
NO_2	0.92	0.89	0.94	0.92	0.89	0.95	0.99	0.94	1.05	0.91	0.89	0.93
$PM_{2.5}$	0.97	0.95	0.99	0.97	0.94	1.00	0.99	0.94	1.05	0.97	0.95	0.99
Ambient Monitoring Network – Inverse Distance Weighted Approach												
CO	0.93	0.91	0.95	0.93	0.91	0.96	0.95	0.90	1.01	0.93	0.91	0.95
NO	0.96	0.94	0.98	0.98	0.96	1.00	0.99	0.94	1.05	0.96	0.95	0.98
NO_2	0.84	0.81	0.86	0.86	0.83	0.88	0.90	0.84	0.96	0.84	0.82	0.86
O_3	0.97	0.94	0.99	0.94	0.92	0.97	0.91	0.87	0.96	0.96	0.94	0.98
PM_{10}	0.95	0.93	0.98	0.96	0.93	0.98	0.98	0.93	1.04	0.95	0.93	0.97
$PM_{2.5}$	1.03	1.01	1.05	1.03	1.01	1.05	1.06	1.01	1.11	1.03	1.01	1.05
SO_2	0.86	0.84	0.88	0.87	0.85	0.90	0.91	0.86	0.96	0.86	0.85	0.88
Ambient Monitoring Network – Nearest Monitor Approach												
CO	0.93	0.90	0.96	0.93	0.90	0.96	0.99	0.92	1.06	0.92	0.90	0.95
NO	0.97	0.95	0.99	0.99	0.96	1.01	1.00	0.94	1.07	0.97	0.96	0.99
NO_2	0.85	0.82	0.88	0.83	0.80	0.87	0.92	0.85	0.99	0.84	0.81	0.86
O_3	0.97	0.95	0.99	0.95	0.93	0.98	0.93	0.88	0.99	0.96	0.95	0.98
PM_{10}	0.98	0.95	1.00	0.96	0.93	0.99	0.98	0.93	1.04	0.97	0.95	0.99
$PM_{2.5}$	1.03	1.00	1.06	1.05	1.01	1.08	1.10	1.03	1.18	1.03	1.01	1.05
SO_2	0.91	0.89	0.93	0.91	0.89	0.94	0.91	0.85	0.97	0.91	0.90	0.93
Point Source Index												
10km buffer	0.76	0.73	0.79	0.76	0.73	0.79	0.87	0.80	0.95	0.75	0.72	0.77
Woodsmoke												
Days	1.23	1.18	1.28	1.24	1.19	1.30	1.15	1.05	1.27	1.24	1.20	1.28

* All risk estimates are adjusted for otitis media season, sex, First Nations, older siblings, maternal smoking during pregnancy, maternal age, neighborhood income and neighborhood female education; and presented per an inter-quartile range increase in pollutant.

RR – risk ratio, LCL – lower 95% confidence interval, UCL – upper 95% confidence interval.

Table B- 2. Adjusted estimates for the association between residential air pollution and physician visits for otitis media, stratified by First Nations and parity.

	First Nations						Older Siblings					
	Yes			No			Yes			No		
	RR*	LCL	UCL	RR*	LCL	UCL	RR*	LCL	UCL	RR*	LCL	UCL
Traffic-related Land Use Regression – extended to Georgia Basin												
Black carbon	0.90	0.80	1.00	0.95	0.93	0.97	0.95	0.92	0.97	0.96	0.93	0.98
NO	1.03	0.93	1.15	1.03	1.02	1.05	1.04	1.02	1.06	1.03	1.00	1.05
NO_2	0.85	0.73	0.98	0.88	0.86	0.90	0.87	0.84	0.89	0.89	0.86	0.92
$PM_{2.5}$	0.89	0.80	1.00	0.92	0.90	0.94	0.93	0.90	0.95	0.92	0.90	0.95
Traffic-related Land Use Regression – Greater Vancouver												
Black carbon	1.05	0.93	1.18	0.97	0.95	0.98	0.96	0.94	0.99	0.98	0.96	1.00
NO	1.21	1.01	1.43	1.01	0.99	1.03	1.01	0.99	1.04	1.01	0.98	1.04
NO_2	1.11	0.94	1.31	0.92	0.90	0.94	0.92	0.89	0.95	0.92	0.89	0.95
$PM_{2.5}$	1.02	0.87	1.19	0.97	0.95	0.99	0.98	0.95	1.00	0.96	0.94	0.99
Ambient Monitoring Network – Inverse Distance Weighted Approach												
CO	0.84	0.74	0.94	0.94	0.92	0.96	0.95	0.92	0.97	0.91	0.89	0.94
NO	0.88	0.77	1.00	0.97	0.95	0.98	0.98	0.96	1.00	0.96	0.93	0.98
NO_2	0.73	0.65	0.83	0.85	0.83	0.87	0.84	0.82	0.87	0.85	0.82	0.88
O_3	1.01	0.91	1.12	0.95	0.94	0.97	0.94	0.92	0.97	0.97	0.94	0.99
PM_{10}	1.01	0.90	1.13	0.95	0.93	0.97	0.93	0.91	0.96	0.99	0.96	1.02
$PM_{2.5}$	1.02	0.93	1.11	1.03	1.02	1.05	1.03	1.01	1.05	1.03	1.01	1.06
SO_2	0.89	0.80	1.00	0.87	0.85	0.88	0.87	0.85	0.89	0.87	0.85	0.89
Ambient Monitoring Network – Nearest Monitor Approach												
CO	0.87	0.73	1.02	0.93	0.91	0.95	0.95	0.92	0.98	0.90	0.87	0.94
NO	0.95	0.80	1.11	0.98	0.96	1.00	0.99	0.97	1.01	0.96	0.94	0.99
NO_2	0.80	0.68	0.95	0.85	0.82	0.87	0.85	0.82	0.88	0.84	0.81	0.87
O_3	1.09	0.96	1.24	0.96	0.94	0.98	0.95	0.93	0.98	0.97	0.95	1.00
PM_{10}	1.06	0.96	1.17	0.97	0.95	0.99	0.95	0.92	0.98	0.99	0.96	1.02
$PM_{2.5}$	1.08	0.95	1.23	1.04	1.01	1.06	1.02	0.99	1.05	1.05	1.02	1.09
SO_2	0.95	0.84	1.07	0.91	0.90	0.93	0.90	0.88	0.93	0.92	0.90	0.95
Point Source Index												
10km buffer	0.65	0.55	0.77	0.76	0.74	0.78	0.74	0.71	0.77	0.79	0.75	0.82
Woodsmoke												
Days	1.02	0.78	1.34	1.24	1.20	1.28	1.25	1.20	1.30	1.21	1.15	1.26

* All risk estimates are adjusted for otitis media season, sex, First Nations, older siblings, maternal smoking during pregnancy, maternal age, neighborhood income and neighborhood female education; and presented per an inter-quartile range increase in pollutant.

RR – risk ratio, LCL – lower 95% confidence interval, UCL – upper 95% confidence interval.

Table B- 3. Adjusted estimates for the association between residential air pollution and physician visits for otitis media, stratified by age.

	Age (Months)											
	2-6			7-12			13-18			19-24		
	RR*	LCL	UCL	RR*	LCL	UCL	RR*	LCL	UCL	RR*	LCL	UCL
Traffic-related Land Use Regression – extended to Georgia Basin												
Black carbon	0.92	0.88	0.97	0.95	0.92	0.97	0.94	0.92	0.97	0.95	0.93	0.98
NO	0.98	0.94	1.03	1.09	1.06	1.11	1.03	1.00	1.06	1.03	1.01	1.06
NO_2	0.83	0.79	0.87	0.91	0.89	0.94	0.89	0.86	0.91	0.87	0.84	0.90
$PM_{2.5}$	0.90	0.86	0.95	0.92	0.89	0.94	0.93	0.90	0.96	0.92	0.89	0.95
Traffic-related Land Use Regression – Greater Vancouver												
Black carbon	0.97	0.93	1.01	0.98	0.95	1.00	0.96	0.94	0.99	0.96	0.94	0.99
NO	0.97	0.92	1.02	1.08	1.05	1.10	1.00	0.97	1.03	1.00	0.97	1.04
NO_2	0.90	0.85	0.95	0.94	0.91	0.97	0.92	0.89	0.95	0.92	0.89	0.95
$PM_{2.5}$	0.98	0.93	1.02	0.98	0.95	1.00	0.96	0.93	0.98	0.96	0.93	0.98
Ambient Monitoring Network – Inverse Distance Weighted Approach												
CO	0.89	0.85	0.94	0.98	0.95	1.01	0.96	0.93	0.99	0.99	0.95	1.02
NO	0.90	0.86	0.94	1.02	0.99	1.04	1.00	0.97	1.03	0.99	0.96	1.02
NO_2	0.79	0.75	0.84	0.88	0.85	0.91	0.88	0.85	0.91	0.85	0.82	0.88
O_3	1.01	0.95	1.07	0.91	0.88	0.94	0.95	0.92	0.98	0.93	0.90	0.97
PM_{10}	0.93	0.88	0.99	0.90	0.87	0.94	0.96	0.92	0.99	0.97	0.93	1.00
$PM_{2.5}$	0.95	0.90	0.99	1.04	1.01	1.07	1.07	1.04	1.09	1.10	1.07	1.14
SO_2	0.79	0.75	0.82	0.87	0.85	0.89	0.92	0.89	0.94	0.88	0.86	0.91
Ambient Monitoring Network – Nearest Monitor Approach												
CO	0.87	0.82	0.93	0.97	0.93	1.00	0.97	0.94	1.01	1.01	0.96	1.05
NO	0.90	0.86	0.95	1.03	1.00	1.06	1.01	0.98	1.05	1.00	0.97	1.04
NO_2	0.78	0.73	0.83	0.88	0.85	0.92	0.88	0.85	0.92	0.86	0.83	0.90
O_3	1.02	0.96	1.08	0.93	0.90	0.95	0.95	0.92	0.98	0.94	0.91	0.98
PM_{10}	0.92	0.87	0.98	0.92	0.89	0.96	0.99	0.96	1.03	0.98	0.94	1.02
$PM_{2.5}$	0.93	0.86	1.01	1.04	1.00	1.08	1.08	1.04	1.12	1.08	1.04	1.12
SO_2	0.84	0.80	0.88	0.92	0.89	0.94	0.95	0.93	0.98	0.93	0.90	0.95
Point Source Index												
10km buffer	0.72	0.67	0.77	0.74	0.71	0.77	0.78	0.74	0.81	0.77	0.74	0.81
Woodsmoke												
Days	1.26	1.16	1.38	1.30	1.24	1.36	1.29	1.23	1.36	1.21	1.14	1.28

* All risk estimates are adjusted for otitis media season, sex, First Nations, older siblings, maternal smoking during pregnancy, maternal age, neighborhood income and neighborhood female education; and presented per an inter-quartile range increase in pollutant.

RR – risk ratio, LCL – lower 95% confidence interval, UCL – upper 95% confidence interval.

Table B- 4. Adjusted estimates for the association between residential air pollution and physician visits for otitis media, stratified by otitis media season.

	Otitis Media Season											
	Low			Medium-Low			Medium-High			High		
	RR*	LCL	UCL	RR*	LCL	UCL	RR*	LCL	UCL	RR*	LCL	UCL
Traffic-related Land Use Regression – extended to Georgia Basin												
Black carbon	0.97	0.92	1.02	0.96	0.94	0.99	0.97	0.94	0.99	0.92	0.89	0.94
NO	1.03	0.94	1.13	1.05	1.02	1.08	1.07	1.05	1.09	0.99	0.97	1.01
NO_2	0.81	0.75	0.87	0.91	0.88	0.94	0.92	0.89	0.94	0.84	0.81	0.86
$PM_{2.5}$	0.93	0.88	0.98	0.94	0.91	0.97	0.94	0.92	0.97	0.89	0.87	0.92
Traffic-related Land Use Regression – Greater Vancouver												
Black carbon	1.00	0.96	1.04	0.98	0.96	1.00	0.98	0.96	1.01	0.95	0.93	0.97
NO	1.03	0.92	1.14	1.03	1.00	1.07	1.06	1.03	1.08	0.96	0.93	0.98
NO_2	0.87	0.80	0.93	0.95	0.92	0.98	0.94	0.91	0.97	0.89	0.87	0.92
$PM_{2.5}$	1.01	0.96	1.07	0.99	0.96	1.01	0.98	0.96	1.01	0.94	0.91	0.96
Ambient Monitoring Network – Inverse Distance Weighted Approach												
CO	0.84	0.77	0.91	0.96	0.93	0.99	0.96	0.94	0.99	0.90	0.88	0.93
NO	0.96	0.87	1.06	1.00	0.97	1.04	1.02	1.00	1.05	0.93	0.91	0.95
NO_2	0.75	0.69	0.82	0.90	0.86	0.94	0.86	0.84	0.89	0.83	0.81	0.85
O_3	0.66	0.60	0.73	0.93	0.89	0.97	0.93	0.91	0.95	1.00	0.98	1.03
PM_{10}	1.26	1.19	1.34	0.92	0.89	0.96	0.98	0.95	1.02	0.90	0.88	0.93
$PM_{2.5}$	1.19	1.12	1.27	1.03	1.00	1.06	1.08	1.05	1.10	1.00	0.98	1.02
SO_2	0.89	0.83	0.95	0.84	0.81	0.87	0.86	0.84	0.89	0.88	0.86	0.90
Ambient Monitoring Network – Nearest Monitor Approach												
CO	0.83	0.75	0.92	0.94	0.91	0.98	0.97	0.94	1.00	0.90	0.87	0.93
NO	0.96	0.86	1.06	1.00	0.96	1.04	1.04	1.01	1.06	0.94	0.92	0.96
NO_2	0.73	0.66	0.80	0.89	0.85	0.94	0.88	0.85	0.91	0.82	0.79	0.84
O_3	0.71	0.65	0.78	0.94	0.90	0.98	0.93	0.91	0.96	1.01	0.98	1.03
PM_{10}	1.23	1.17	1.31	0.91	0.87	0.94	1.00	0.97	1.03	0.94	0.91	0.97
$PM_{2.5}$	1.08	0.97	1.20	1.04	1.00	1.09	1.07	1.04	1.10	1.01	0.98	1.04
SO_2	0.95	0.89	1.01	0.90	0.86	0.93	0.90	0.87	0.93	0.93	0.91	0.94
Point Source Index												
10km buffer	0.80	0.73	0.87	0.81	0.78	0.85	0.76	0.73	0.79	0.73	0.70	0.75
Woodsmoke												
Days	0.42	0.23	0.77	2.39	1.99	2.87	1.29	1.23	1.36	1.23	1.18	1.27

* All risk estimates are adjusted for otitis media season, sex, First Nations, older siblings, maternal smoking during pregnancy, maternal age, neighborhood income and neighborhood female education; and presented per an inter-quartile range increase in pollutant.

RR – risk ratio, LCL – lower 95% confidence interval, UCL – upper 95% confidence interval.

Table B- 5. Adjusted estimates for the association between residential air pollution and physician visits for otitis media, stratified by birth season.

	Birth Season											
	Fall (Oct-Dec)			Winter (Jan-Mar)			Spring (Apr-Jun)			Summer (Jul-Sept)		
	RR*	LCL	UCL	RR*	LCL	UCL	RR*	LCL	UCL	RR*	LCL	UCL
Traffic-related Land Use Regression – extended to Georgia Basin												
Black carbon	0.93	0.89	0.97	0.97	0.92	1.02	0.83	0.80	0.86	0.84	0.81	0.88
NO	1.10	1.06	1.13	1.40	1.36	1.44	1.25	1.22	1.28	1.02	0.99	1.06
NO_2	0.98	0.95	1.02	1.30	1.25	1.35	1.32	1.28	1.37	1.06	1.02	1.10
$PM_{2.5}$	0.91	0.87	0.95	0.90	0.86	0.95	0.83	0.80	0.87	0.85	0.82	0.89
Traffic-related Land Use Regression – Greater Vancouver												
Black carbon	0.95	0.92	0.99	0.96	0.93	1.00	0.94	0.91	0.97	0.93	0.90	0.96
NO	1.08	1.05	1.12	1.39	1.34	1.44	1.23	1.19	1.27	1.00	0.97	1.04
NO_2	0.97	0.93	1.01	1.16	1.11	1.20	1.17	1.13	1.21	1.01	0.97	1.05
$PM_{2.5}$	0.96	0.92	1.00	0.95	0.91	1.00	0.88	0.85	0.91	0.88	0.85	0.92
Ambient Monitoring Network – Inverse Distance Weighted Approach												
CO	1.07	1.02	1.11	1.33	1.28	1.39	1.19	1.15	1.24	0.99	0.95	1.03
NO	1.04	1.00	1.07	1.38	1.34	1.42	1.24	1.21	1.28	0.98	0.95	1.02
NO_2	0.94	0.90	0.98	1.23	1.17	1.30	1.29	1.24	1.36	0.98	0.93	1.02
O_3	0.93	0.89	0.97	0.66	0.63	0.69	0.91	0.87	0.95	1.09	1.05	1.14
PM_{10}	0.89	0.86	0.93	0.92	0.88	0.96	0.70	0.67	0.72	0.71	0.69	0.74
$PM_{2.5}$	1.03	0.99	1.07	1.15	1.11	1.20	0.96	0.93	0.99	0.89	0.86	0.92
SO_2	0.86	0.82	0.90	0.94	0.89	0.98	0.86	0.82	0.90	0.83	0.80	0.86
Ambient Monitoring Network – Nearest Monitor Approach												
CO	1.07	1.02	1.13	1.37	1.31	1.45	1.20	1.15	1.26	0.99	0.94	1.04
NO	1.05	1.01	1.09	1.42	1.37	1.47	1.26	1.22	1.30	0.98	0.95	1.02
NO_2	0.95	0.90	1.00	1.30	1.23	1.37	1.35	1.28	1.41	1.00	0.95	1.05
O_3	0.94	0.89	0.98	0.67	0.63	0.70	0.91	0.87	0.96	1.08	1.03	1.13
PM_{10}	0.92	0.88	0.96	0.93	0.89	0.97	0.74	0.71	0.76	0.74	0.72	0.77
$PM_{2.5}$	1.07	1.01	1.13	1.10	1.04	1.17	1.00	0.95	1.06	0.94	0.89	0.99
SO_2	0.90	0.86	0.94	0.99	0.95	1.04	0.90	0.86	0.94	0.89	0.85	0.92
Point Source Index												
10km buffer	0.77	0.72	0.82	0.82	0.76	0.88	0.76	0.72	0.81	0.74	0.70	0.78
Woodsmoke												
Days	1.51	1.43	1.59	1.84	1.74	1.94	1.67	1.59	1.75	1.37	1.30	1.44

* All risk estimates are adjusted for sex, First Nations, older siblings, maternal smoking during pregnancy, maternal age, neighborhood income and neighborhood female education; and presented per an inter-quartile range increase in pollutant.

RR – risk ratio, LCL – lower 95% confidence interval, UCL – upper 95% confidence interval

Table B- 6. Adjusted estimates for the association between residential air pollution and physician visits for otitis media, quartile analysis not adjusted for season.

		First	Second			Third			Fourth		
			RR*	LCL	UCL	RR*	LCL	UCL	RR*	LCL	UCL
Traffic-related Land Use Regression – extended to Georgia Basin											
	Black carbon	Reference	0.90	0.87	0.92	0.84	0.81	0.87	0.81	0.78	0.83
	NO	Reference	1.08	1.05	1.12	1.32	1.28	1.37	1.24	1.20	1.28
	NO_2	Reference	1.14	1.11	1.18	0.97	0.94	1.01	0.97	0.93	1.00
	$PM_{2.5}$	Reference	0.89	0.86	0.92	0.80	0.78	0.83	0.79	0.76	0.81
Ambient Monitoring Network – Inverse Distance Weighted Approach											
	CO	Reference	1.09	1.05	1.12	1.07	1.04	1.10	1.05	1.02	1.08
	NO	Reference	1.01	0.98	1.04	1.20	1.17	1.23	1.14	1.10	1.17
	NO_2	Reference	0.96	0.94	0.99	0.87	0.85	0.90	0.93	0.90	0.96
	O_3	Reference	0.95	0.93	0.98	0.86	0.84	0.88	0.91	0.88	0.94
	PM_{10}	Reference	0.87	0.84	0.89	0.70	0.68	0.72	0.64	0.62	0.65
	$PM_{2.5}$	Reference	0.82	0.80	0.85	0.83	0.81	0.85	0.90	0.88	0.93
	SO_2	Reference	0.89	0.86	0.91	0.69	0.67	0.71	0.66	0.64	0.68
Point Source Index											
	10km buffer	Reference	0.94	0.92	0.97	0.82	0.79	0.84	0.64	0.62	0.65

* All risk estimates are adjusted for sex, First Nations, older siblings, maternal smoking during pregnancy, maternal age, neighborhood income and neighborhood female education; and presented per an inter-quartile range increase in pollutant.

RR – risk ratio, LCL – lower 95% confidence interval, UCL – upper 95% confidence interval

Table B- 7. Adjusted estimates for the association between residential air pollution and physician visits for otitis media, quartile analysis adjusted for season.

		First	Second			Third			Fourth		
			RR*	LCL	UCL	RR*	LCL	UCL	RR*	LCL	UCL
Traffic-related Land Use Regression – extended to Georgia Basin											
	Black carbon	Reference	1.00	0.95	1.04	1.03	0.99	1.08	0.93	0.89	0.97
	NO	Reference	1.05	1.00	1.11	1.24	1.18	1.30	1.14	1.09	1.19
	NO_2	Reference	1.05	1.00	1.10	0.88	0.84	0.93	0.80	0.77	0.85
	$PM_{2.5}$	Reference	0.90	0.86	0.94	0.91	0.87	0.95	0.92	0.88	0.97
Ambient Monitoring Network – Inverse Distance Weighted Approach											
	CO	Reference	1.06	1.01	1.11	1.00	0.96	1.05	0.96	0.92	1.01
	NO	Reference	1.08	1.03	1.13	1.17	1.12	1.23	1.05	1.01	1.10
	NO_2	Reference	0.99	0.95	1.03	0.90	0.86	0.94	0.78	0.74	0.82
	O_3	Reference	1.02	0.98	1.06	0.87	0.84	0.91	0.87	0.84	0.91
	PM_{10}	Reference	0.87	0.84	0.90	0.85	0.82	0.89	1.03	0.98	1.08
	$PM_{2.5}$	Reference	0.86	0.83	0.90	0.92	0.88	0.96	1.06	1.01	1.10
	SO_2	Reference	0.93	0.90	0.97	0.82	0.78	0.85	0.71	0.68	0.75
Point Source Index											
	10km buffer	Reference	0.97	0.93	1.01	0.86	0.82	0.89	0.70	0.67	0.73

* All risk estimates are adjusted for otitis media season, sex, First Nations, older siblings, maternal smoking during pregnancy, maternal age, neighborhood income and neighborhood female education; and presented per an inter-quartile range increase in pollutant.

RR – risk ratio, LCL – lower 95% confidence interval, UCL – upper 95% confidence interval

Table B- 8. Adjusted estimates for the association between residential air pollution and physician visits for otitis media, stratified by event season.

Pollutant	Model	Winter (Jan-Mar)	Spring (Apr-Jun)	Summer (Jul-Sept)	Fall (Oct-Dec)
		RR* (95%CI)	RR* (95%CI)	RR* (95%CI)	RR* (95%CI)
Exposure modeled as a continuous variable – risk estimate per an IQR increase in pollutant					
NO	IDW	0.86(0.84-0.88)	0.93(0.88-0.98)	0.69(0.62-0.75)	0.97(0.94-1.00)
	LUR	0.89(0.86-0.92)	1.05(0.99-1.11)	0.74(0.67-0.82)	1.02(0.99-1.04)
NO_2	IDW	0.81(0.79-0.83)	0.84(0.81-0.87)	0.74(0.70-0.79)	0.83(0.80-0.86)
	LUR	0.81(0.79-0.83)	0.90(0.87-0.93)	0.78(0.74-0.82)	0.84(0.81-0.87)
CO	IDW	0.85(0.83-0.87)	0.91(0.87-0.95)	0.78(0.74-0.83)	0.92(0.89-0.95)
O_3	IDW	1.20(1.14-1.25)	0.98(0.94-1.03)	1.24(1.16-1.31)	1.06(0.98-1.15)
$PM_{2.5}$	IDW	1.01(0.99-1.03)	1.12(1.05-1.18)	0.88(0.83-0.93)	1.01(0.99-1.04)
	LUR	0.91()0.88-0.93	0.88(0.85-0.91)	0.90(0.86-0.93)	0.92(0.90-0.94)
Black carbon	LUR	0.93(0.91-0.96)	0.91(0.88-0.94)	0.90(0.86-0.93)	0.95(0.92-0.97)
PM_{10}	IDW	0.98(0.95-1.01)	0.93(0.88-0.97)	0.93(0.89-0.98)	0.85(0.82-0.87)
SO_2	IDW	0.89(0.87-0.91)	0.80(0.76-0.83)	0.80(0.76-0.84)	0.86(0.83-0.88)
Point source index	10 km buffer	0.74(0.71-0.77)	0.73(0.70-0.77)	0.80(0.75-0.84)	0.78(0.75-0.82)
Woodsmoke	Days	1.14(1.10-1.18)	1.51(1.41-1.63)	-	1.64(1.53-1.76)

* Adjusted for sex, First Nations, older siblings, maternal smoking during pregnancy, maternal age, neighborhood income and neighborhood female education.

Table B- 9. Adjusted estimates for the association between residential air pollution and physician visits for otitis media, analysis restricted to children living in urban areas.

		Restricted to Urban Residence		
		RR*	LCL	UCL
Traffic-related Land Use Regression – extended to Georgia Basin				
	Black carbon	0.85	0.82	0.87
	NO	1.15	1.13	1.18
	NO_2	1.19	1.16	1.22
	$PM_{2.5}$	0.83	0.80	0.85
Traffic-related Land Use Regression – Greater Vancouver				
	Black carbon	0.92	0.90	0.94
	NO	1.15	1.12	1.18
	NO_2	1.11	1.08	1.14
	$PM_{2.5}$	0.88	0.85	0.91
Ambient Monitoring Network – Inverse Distance Weighted Approach				
	CO	1.09	1.06	1.13
	NO	1.12	1.09	1.14
	NO_2	1.10	1.06	1.14
	O_3	0.98	0.95	1.01
	PM_{10}	0.75	0.73	0.77
	$PM_{2.5}$	0.94	0.92	0.96
	SO_2	0.81	0.78	0.84
Ambient Monitoring Network – Nearest Monitor Approach				
	CO	1.11	1.08	1.15
	NO	1.13	1.11	1.16
	NO_2	1.16	1.11	1.20
	O_3	0.98	0.95	1.01
	PM_{10}	0.79	0.77	0.82
	$PM_{2.5}$	0.96	0.93	1.00
	SO_2	0.87	0.84	0.90
Point Source Index				
	10km buffer	0.71	0.68	0.75
Woodsmoke				
	Days	1.53	1.47	1.60

* All risk estimates are adjusted for sex, First Nations, older siblings, maternal smoking during pregnancy, maternal age, neighborhood income and neighborhood female education; and presented per an inter-quartile range increase in pollutant.

RR – risk ratio, LCL – lower 95% confidence interval, UCL – upper 95% confidence interval

Table B- 10. Adjusted estimates for the association between residential air pollution and physician visits for otitis media with a linked antibiotic prescription.

Pollutant	Model	Number of Children	Crude RR (95%CI)	Adjusted 1* RR (95%CI)	Adjusted 2** RR (95%CI)
Exposure modeled as a continuous variable – risk estimate per an IQR increase in pollutant					
NO	IDW	41,476	1.10(1.08-1.13)	1.13(1.10-1.17)	1.01 (0.99-1.03)
	LUR	37,028	1.12(1.10-1.14)	1.14(1.10-1.17)	1.09(1.07-1.11)
NO_2	IDW	41,295	1.00(0.97-1.02)	1.05(1.01-1.09)	0.88(0.86-0.90)
	LUR	37,028	0.97(0.95-0.99)	0.99(0.96-1.01)	0.91(0.88-0.93)
CO	IDW	10,402	1.09(1.07-1.12)	1.09(1.05-1.13)	0.98(0.96-1.01)
O_3	IDW	46,557	0.87(0.85-0.89)	0.87(0.81-0.90)	0.88(0.86-0.90)
$PM_{2.5}$	IDW	43,118	1.01(1.00-1.03)	1.01(0.97-1.04)	1.07(1.05-1.09)
	LUR	37,028	0.93(0.91-0.94)	0.94(0.91-0.97)	0.94(0.92-0.96)
Black carbon	LUR	37,028	0.96(0.94-0.98)	0.96(0.94-0.99)	0.96(0.94-0.99)
PM_{10}	IDW	46,917	0.80(0.79-0.82)	0.84(0.81-0.87)	0.99(0.96-1.01)
SO_2	IDW	41,506	0.82(0.80-0.84)	0.85(0.82-0.88)	0.88(0.86-0.90)
Point source index	10 km	47,974	0.78(0.76-0.80)	0.81(0.77-0.85)	0.81(0.78-0.84)
Woodsmoke	Days	39,283	1.76(1.70-1.82)	1.64(1.55-1.74)	1.27(1.23-1.32)
Exposure modeled as a categorical variable					
Expressway	<50m	104	1.11(0.85-1.44)	0.96(0.60-1.56)	1.14(0.85-1.52)
	50-150m	579	1.24(1.13-1.36)	1.18(1.00-1.39)	1.07(0.97-1.19)
	>150m	47,633	Reference	Reference	Reference
Primary highway	<50m	849	0.93(0.84-1.03)	0.83(0.69-0.98)	0.87(0.78-0.97)
	50-150m	2,465	0.93(0.88-0.99)	0.87(0.78-0.96)	0.89(0.83-0.95)
	>150m	44,811	Reference	Reference	Reference
Secondary highway	<50m	13	0.58(0.22-1.56)	No Convergence	0.58(0.19-1.81)
	50-150m	89	1.25(1.09-1.45)	1.41(1.07-1.87)	1.14(0.98-1.33)
	>150m	48,249	Reference	Reference	Reference
Major road	<50m	4,965	0.96(0.92-1.00)	1.01(0.94-1.08)	0.97(0.92-1.01)
	50-150m	9,286	0.90(0.87-0.93)	0.94(0.89-1.00)	0.92(0.89-0.96)
	>150m	33,245	Reference	Reference	Reference

* Adjusted for sex, First Nations, older siblings, maternal smoking during pregnancy, breastfeeding initiation, birth weight, maternal age, neighborhood income, neighborhood female education and rural residence.

** Adjusted for otitis media season, sex, First Nations, older siblings, maternal smoking during pregnancy, breastfeeding initiation, birth weight, maternal age, neighborhood income, neighborhood female education and rural residence.

LUR – land use regression, IDW – inverse distance weighted concentrations (3 monitors within 50 km of a residential postal code).

Appendix C Results for Survival Analyses

Table C- 1. Adjusted estimates for the association between residential air pollution and physician visits for otitis media, using survival analysis to examine multiple case definitions.

		Otitis Media Physician Visit			Recurrent Otitis Media			Otitis Media Visit with a linked Antibiotic		
		HR*	LCL	UCL	HR *	LCL	UCL	HR *	LCL	UCL
Traffic-related Land Use Regression – extended to Georgia Basin										
	Black carbon	0.93	0.91	0.95	0.97	0.92	1.03	0.93	0.91	0.96
	NO	1.13	1.11	1.15	1.11	1.04	1.18	1.18	1.15	1.20
	NO_2	1.02	1.01	1.04	0.96	0.92	1.02	1.04	1.01	1.06
	$PM_{2.5}$	0.95	0.94	0.96	0.99	0.86	1.04	0.96	0.94	0.97
Ambient Monitoring Network – Inverse Distance Weighted Approach										
	CO	1.10	1.08	1.13	1.03	0.97	1.09	1.14	1.11	1.18
	NO	1.14	1.11	1.16	1.07	1.02	1.11	1.16	1.14	1.19
	NO_2	1.02	1.00	1.04	0.89	0.83	0.94	1.06	1.03	1.09
	O_3	0.85	0.84	0.87	0.80	0.74	0.84	0.81	0.78	0.84
	PM_{10}	0.78	0.77	0.80	0.89	0.83	0.94	0.79	0.77	0.81
	$PM_{2.5}$	1.07	1.04	1.09	1.12	1.06	1.18	1.09	1.06	1.12
	SO_2	0.89	0.87	0.91	0.82	0.78	0.86	0.90	0.87	0.92
Point Source Index										
	10km buffer	0.79	0.77	0.81	0.64	0.60	0.69	0.81	0.78	0.84
Woodsmoke										
	Days	1.13	1.12	1.15	1.14	1.11	1.18	1.15	1.14	1.16

* All risk estimates are adjusted for sex, First Nations, older siblings, maternal smoking during pregnancy, maternal age, neighborhood income and neighborhood female education; and presented per an inter-quartile range increase in pollutant.

HR – hazard ratio, LCL – lower 95% confidence interval, UCL – upper 95% confidence interval

Appendix D Results for Logistic Analyses

Table D- 1. Adjusted estimates for the association between residential air pollution and physician visits for otitis media, using conditional logistic regression to examine multiple case definitions.

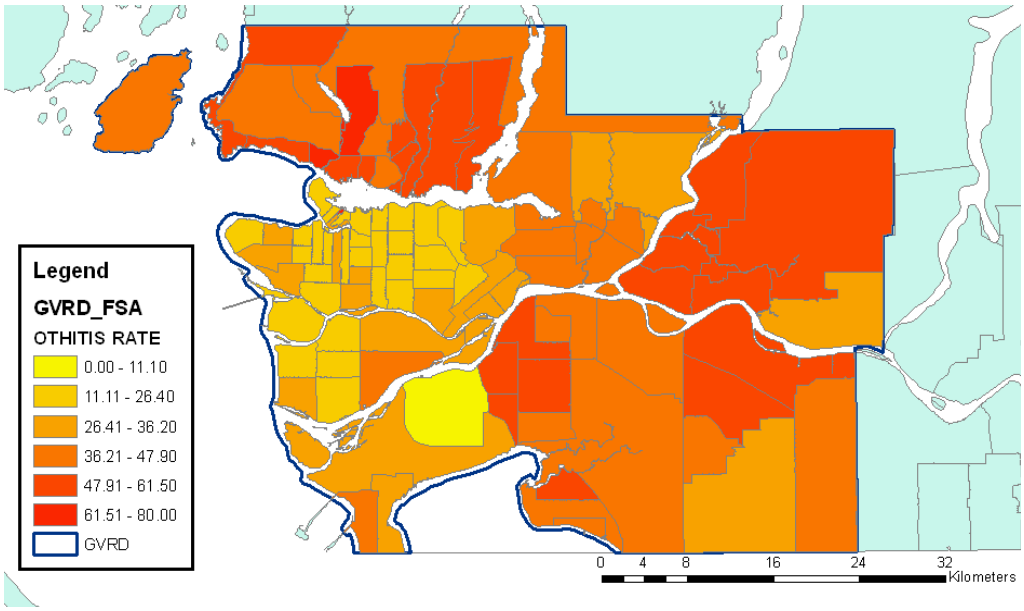
Cases and controls matched on month and year of birth. Fixed exposure window averaged over the first 12 months of life. Analyses restricted to 49,027 children who did not move.

	Otitis Media Physician Visit			Recurrent Otitis Media			Otitis Media Visit with a linked Antibiotic		
	HR*	LCL	UCL	HR *	LCL	UCL	HR *	LCL	UCL
Traffic-related Land Use Regression – extended to Georgia Basin									
Black carbon	0.95	0.93	0.97	0.93	0.89	0.97	0.95	0.93	0.97
NO	0.73	0.69	0.76	0.64	0.57	0.71	0.76	0.72	0.81
NO_2	0.85	0.83	0.88	0.82	0.77	0.87	0.87	0.84	0.90
$PM_{2.5}$	0.93	0.91	0.95	0.93	0.88	0.98	0.94	0.92	0.97
Ambient Monitoring Network – Inverse Distance Weighted Approach									
CO	0.72	0.69	0.74	0.67	0.62	0.71	0.75	0.72	0.78
NO	0.66	0.64	0.69	0.61	0.55	0.66	0.68	0.65	0.72
NO_2	0.72	0.70	0.75	0.67	0.63	0.72	0.75	0.72	0.78
O_3	2.00	1.85	2.16	2.36	2.02	2.75	1.87	1.71	2.04
PM_{10}	0.76	0.71	0.81	0.65	0.58	0.73	0.82	0.77	0.88
$PM_{2.5}$	0.70	0.65	0.76	0.62	0.55	0.70	0.70	0.65	0.75
SO_2	0.78	0.75	0.80	0.74	0.69	0.78	0.78	0.76	0.81
Point Source Index									
10km buffer	0.73	0.71	0.76	0.62	0.57	0.67	0.76	0.73	0.79
Woodsmoke									
Days	1.72	1.56	1.90	1.80	1.47	2.20	1.71	1.53	1.91

* All risk estimates are adjusted for sex, First Nations, older siblings, maternal smoking during pregnancy, maternal age, neighborhood income and neighborhood female education; and presented per an inter-quartile range increase in pollutant.

HR – hazard ratio, LCL – lower 95% confidence interval, UCL – upper 95% confidence interval

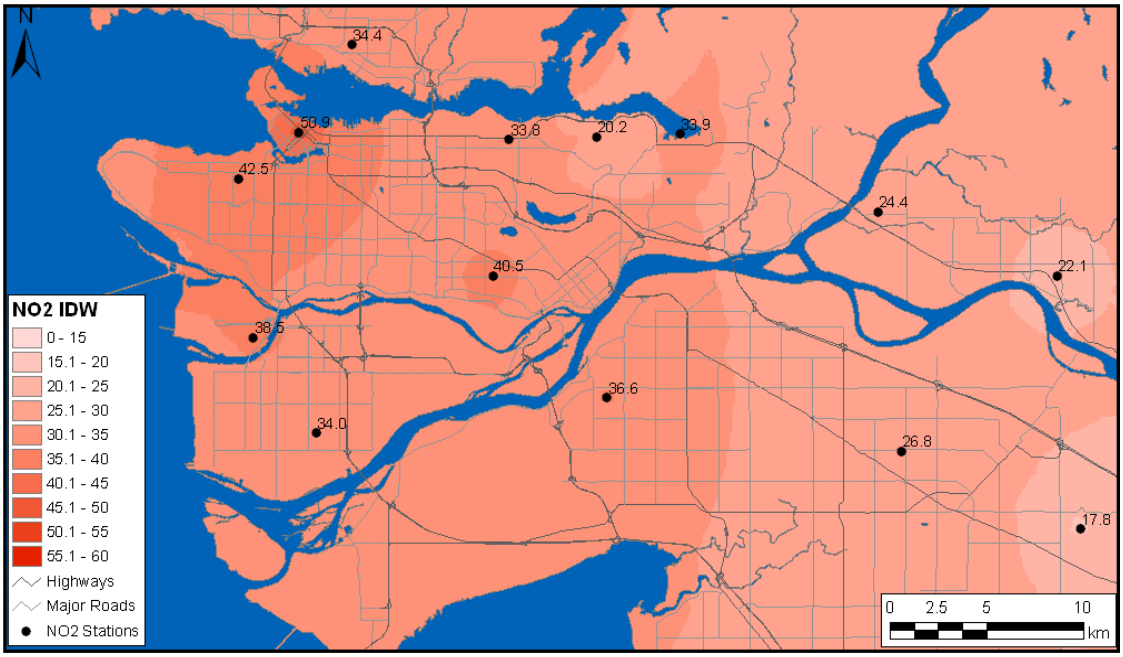
Appendix E Otitis Media Incidence in Greater Vancouver



(Border Air Quality Study, with permission)

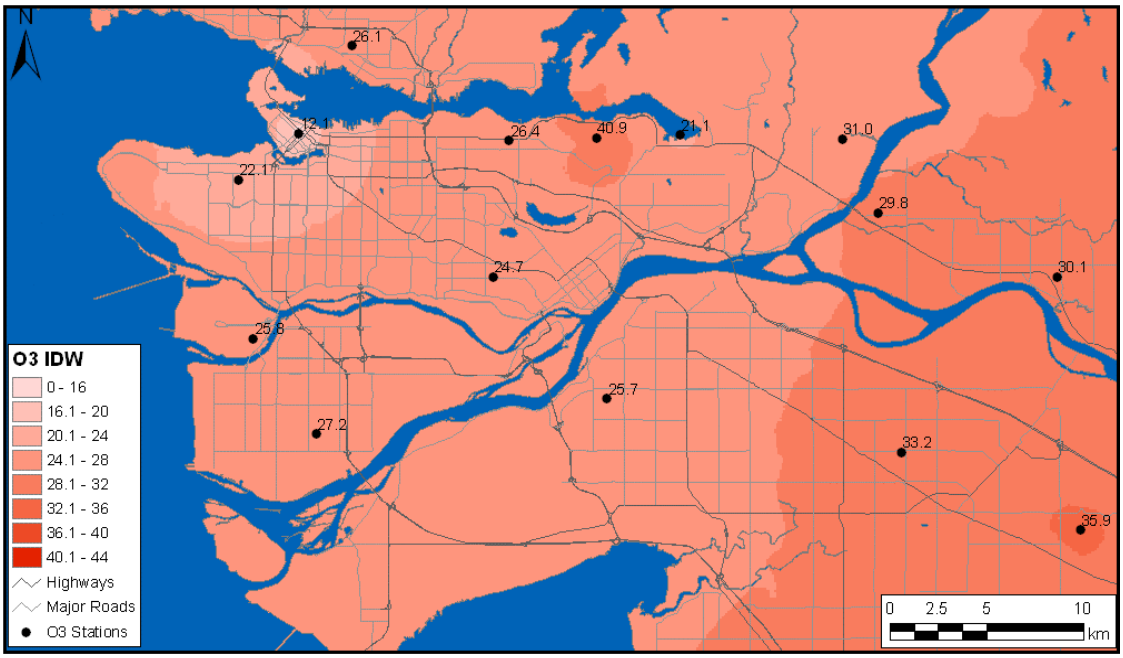
Figure E- 1. Otitis media rate (per 100 births) in the Greater Vancouver Regional District, Canada, between 1999-2002, by forward sortation area.

Appendix F Ambient Air Pollution in Greater Vancouver



(Border Air Quality Study, with permission)

Figure F- 1. Nitric oxide concentrations estimated from inverse distance weighting of ambient monitoring data.



(Border Air Quality Study, with permission)

Figure F- 2. Ozone concentrations estimated from inverse distance weighting of ambient monitoring data.