5-2-2016 12:00 AM

A Link Between Paediatric Asthma and Obesity: Are They Caused by the Same Environmental Conditions?

Phylicia Gonsalves, *The University of Western Ontario*

Supervisor: Dr. Piotr Wilk, *The University of Western Ontario*

A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Epidemiology and Biostatistics

Abstract

The highly associated paediatric conditions of asthma and overweight have seen dramatic increases over the past few decades. This thesis explored air pollution exposure as a potential underlying mechanism of co-morbid asthma and overweight among adolescents aged 12 to 18 years. Data from the Canadian Community Health Survey were merged with a database containing estimates of air pollution as assessed by particulate matter ≤ 2.5 microns ($PM_{2.5}$) concentrations at the postal code centroid in southwestern Ontario. Logistic regression was used to conduct the analysis. Adolescents were more likely to be overweight as $PM_{2.5}$ concentrations increased. There was no significant association between $PM_{2.5}$ and asthma and co-morbid asthma and overweight. The positive association between $PM_{2.5}$ and overweight found in this study, and the literature supporting a causal relationship between air pollution and asthma, suggests a need to further explore the role of air pollution as a shared risk factor.

Keywords

Adolescents, asthma, overweight, obesity, co-morbid, common risk factor, air pollution, particulate matter, National Pollutant Release Inventory, Canadian Community Health Survey

Acknowledgments

I would first like to thank my supervisor, Dr. Piotr Wilk, for his unwavering guidance and support throughout my Master's Degree. His expertise and honesty have dramatically improved my writing ability, and I have come such a long way under his mentorship. Most importantly, I am forever grateful for his patience and understanding towards the unforeseen obstacles I have faced these last few years. I will never forget this.

To my committee member, Dr. Jason Gilliland, for his constructive feedback, and whose intriguing research has sparked my personal interest in the role of the environment in public health issues.

To Dr. Neil Klar, for agreeing to serve as a committee member on such short notice, and in that small amount of time, bringing such unique and valuable insight that had greatly enhanced the final quality of my thesis.

I would also like to extend my gratitude towards Dr. Kathy Speechley, Dr. Greta Bauer, and Rebecca Waldie. I thank them for their compassion, assistance, and in some instances, going above and beyond to make the last few challenging years run as smoothly as possible. Many thanks also to Bradley Corbett and Sara Tumpane at the UWO and York University Research Data Centres for their assistance on the data front and their sensitivity to my timely needs.

To my family and closest friends: while you may not have contributed to this thesis in tangible ways, I thank you for your love, moral support, and for being the best team of cheerleaders throughout this entire process. And finally to Alex, who I can never adequately thank for believing in me no matter what – you have inspired me to remain positive under all circumstances and none of this would have been possible without you.

Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

BMI	Body mass index
BPA	Bisphenol A
CAC	Criteria air contaminant
CAPI	Computer-assisted personal interviewing
CATI	Computer-assisted telephone interviewing
CCHS	Canadian Community Health Survey
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CO	Carbon monoxide
CRP	C-reactive protein
IL-6	Interleukin-6
IOTF	International Obesity Task Force
NO_2	Nitrogen dioxide
NO_x	Nitrogen oxides
O_3	Ozone
OR	Odds ratio
PAH	Polycyclic aromatic hydrocarbon
$PM_{2.5}$	Particulate matter less than or equal to 2.5 microns
PM_{10}	Particulate matter less than or equal to 10 microns
POP	Persistent organic pollutant
SD	Standard deviation
SE	Standard error
SO_2	Sulphur dioxide
SO_x	Sulphur oxides
TPM	Total particulate matter
VOC	Volatile organic compounds
WHO	World Health Organization

Chapter 1

1 Introduction and Literature Review

1.1 Introduction

Asthma and obesity are two of the most common chronic conditions affecting paediatric populations.[1] The prevalence of each condition has seen substantial increases over the past few decades in Canada[2,3] and worldwide,[4-6] and both have considerable physical and psychological consequences that plague children and adolescents well into adulthood. The morbidity associated with asthma and obesity causes a reduction in quality of life and productivity, and places a large economic burden on the Canadian healthcare system.[7,8]

In addition to the parallel increases in asthma and obesity, many studies have found high levels of association between these two conditions.[9-11] This finding is of great concern because individuals with both asthma and obesity generally have poorer health than those with only one of these conditions.[12] One area of research that is important for the formulation of targeted strategies for co-morbid conditions is that which examines their developmental origins. However, there is no single explanation for how asthma and obesity are linked. Longitudinal studies have indicated that high body mass precedes and increases the risk of asthma, although the reverse has been shown in some studies, suggesting that asthma may lead to the onset of obesity.[13,14] Since both of these conditions commonly originate in early childhood and proximally in time, a direct causal relationship between asthma and obesity may not be the only explanation for their co-morbid existence. Rather, common risk factors in early life may be contributing to the increasing prevalence of both conditions at such a young age.

Although research to date has examined the role of individual-level predictors associated with each of these health conditions, the role of environmental predictors has been largely unexplored. Addressing the common root causes embedded in the environment has been identified as an important next step in tackling this co-morbid epidemic.[15] Research has shown that air pollution is contributing to the individual growing rates of asthma and

obesity,[16,17] suggesting this environmental exposure is a common risk factor for both conditions. Assessing the effects of air pollution on asthma and obesity together would therefore be a significant contribution towards understanding the etiology of this co-morbid relationship. This improved understanding may provide vital information to be used in the design of preventive and intervention strategies directed towards children and adolescents who are at a higher risk of having both conditions.

To achieve this research goal, I will first provide an overview of the asthma epidemic (Section 1.2) and overweight/obesity epidemic (Section 1.3) among children and adolescents, by outlining the prevalence, time trends, and health risks associated with each condition. Section 1.4 will discuss the importance of examining asthma and overweight/obesity together by reviewing research that has assessed the association between them, and highlighting the importance of examining common risk factors as underlying mechanisms of this co-morbidity. Section 1.5 discusses potential individual and environmental common risk factors of asthma and obesity, and the need to explore the role of the environment; the end of this section outlines air pollution in particular as a potential environmental cause that needs to be considered (Section 1.5.5). Section 1.6 provides a comprehensive definition of air pollution and highlights children and adolescents as especially susceptible to its health effects. The remainder of this section describes the relationship between air pollution and asthma (Section 1.6.4), overweight/obesity (Section 1.6.5), and co-morbid asthma and overweight/obesity (Section 1.6.6). These sections present the mechanisms through which air pollution causes each condition, reviews of studies assessing these relationships, as well as summarize the limitations of research in these areas. Following this literature review, and an overall summary (Section 1.7), Chapter 2 provides the current plan of study, including specific objectives and hypotheses, followed by methods (Chapter 3), results (Chapter 4), and discussion of findings (Chapter 5).

1.2 The Asthma Epidemic

This section provides the definition of asthma, its prevalence, trends, and associated health consequences. This discussion illustrates paediatric asthma as an increasing public

health problem in Canada that needs to be addressed as the health costs faced by asthmatic children and adolescents are particularly pronounced.

1.2.1 Definition

Asthma is a lung disorder, where inflammation and mucous production causes bronchi swelling and narrowing of the airways. Airflow is restricted resulting in a range of mild to life-threatening breathing difficulties. Asthma symptoms include shortness of breath, coughing, wheezing, and chest tightness, and diagnosis is generally based on presence of these symptoms in addition to respiratory diagnostic testing.

There is no gold standard definition for measuring asthma prevalence.[18] Instead, various measurement instruments are used, such as physician diagnosis, self-reported symptoms via questionnaires, physiological measures like lung function (i.e., the volume and flow of air during inhalation and exhalation) and bronchial responsiveness (i.e., lung function after inhaling chemicals that induce bronchoconstriction), or a combination of these methods. For example, self-reported asthma is validated by testing the questionnaire against results of a physiological investigation, or by comparing self-reported answers with a clinical diagnosis.[19]

Epidemiological prevalence studies should use methods that are simple, inexpensive, practical, and will allow for the comparison of asthma prevalence among diverse populations. Large survey questionnaires of self-reported asthma, preferably validated in the target population, is thus suggested as the method of choice.[18]

1.2.2 Prevalence, Trends, and Health Risks

Overall prevalence in Canada: Asthma is one of the most common chronic diseases in childhood and adolescence. The prevalence of this paediatric illness has substantially increased over the past few decades and its death rates have doubled between 1980 and 1993.[20] In 1978/79, the prevalence of asthma among Canadian children and adolescents aged 0 to 14 years was 2.5% - though this percentage had risen only marginally to 3.1% in 1983/84, by 1994/95, asthma prevalence had increased to 11.2%.[2] In 1994/1995, 11% of children only, aged 0 to 11, had been diagnosed with asthma, whereas by 2000/2001,

the rate had significantly risen to more than 13%.[21] Positive trends were more substantial across periods preceding the year 2001; however, the prevalence rate of asthma still remained high after this time.[22-24]

Regional differences: Disparities in asthma prevalence have been reported across regions of Canada. While Statistics Canada has demonstrated that the 2008 national average prevalence of asthma for populations aged 12 to 19 years was 11.3%, this prevalence ranged from 6.7% in British Columbia to 16.7% in Prince Edward Island.[25]

Asthma in Ontario: Detailed asthma prevalence trends from 1996 to 2005 have been captured in Ontario through a population-based study conducted by Gershon et al.[26] During this time, the age- and sex-standardized asthma prevalence significantly increased by 55.1%. In children aged 5 to 9 years, this prevalence increased by 19.6% (from 18.8% to 22.5%) and in adolescents aged 10 to 14 years this prevalence increased by 94.7% (from 13.1% to 25.5%). In young adults aged 15 to 39 years, asthma prevalence increased by 81.5% (from 7.1% to 12.9%).

With the exception of Ontario, all estimates of asthma prevalence above were measured using self-reported data from large population-based survey questionnaires. Differences in these estimates may in part be explained by subtleties in the wording of questions across surveys, such as indicating diagnosis by a health professional.[2] It is more difficult to directly compare Ontario estimates with those of Canada, as asthma was alternatively determined using medical records of physician diagnosis. Nevertheless, these findings collectively illustrate a high magnitude of asthma prevalence and growth across time in paediatric populations nationwide.

Health risks: The primary health risk of concern for asthmatics is asthma attacks, where airway inflammation is so severe that the flow of air in and out of the lungs is reduced to a dangerous degree. In many cases, the patient is not equipped with the required medication or the medication they currently use is not effective. Every year in Canada, approximately 146,000 emergency room visits are due to asthma attacks.[27] A population-based cohort study reported the number of children and adolescents aged 2 to 17 years who had an emergency visit for the care of asthma from April 2003 to March 2005 in

Ontario.[28] A total of 32,996 children had at least one asthma-related visit to an emergency department, with 68.5% of these visits classified as with high severity.

Asthma is associated with increased risk of depression, anxiety, and panic attacks,[29] gastroesophageal reflux,[30] sleep disturbances and fatigue,[31] chronic rhinitis and sinusitis,[32] and even the development of heart disease and diabetes later in life.[33] Paediatric asthma is also significantly more likely to persist into adulthood. One prospective study determined that having asthma at age 7 was a strong predictor of having asthma at ages 29 to 32 (OR 1.59, 95% CI 1.10-2.29).[34]

1.3 The Overweight and Obesity Epidemic

In this section, overweight/obesity, its prevalence, trends, and associated health consequences are defined. This discussion illuminates paediatric overweight/obesity as an increasingly important public health problem in Canada as it presents challenges to children and adolescents' physical, emotional and social well-being and increases the risk of developing chronic diseases in adulthood.

1.3.1 Definition

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health. Body mass index (BMI) is the most basic and common method used to identify individuals who are overweight or obese and is calculated by dividing weight in kilograms by height measured in meters squared (denoted as: kg/m^2). This convenient and inexpensive measure has been recommended as a screening tool in epidemiological and population-based studies, and is a good predictor of body fatness in children and adolescents.[35-37] Paediatric body composition varies between different ages and gender. BMI generally follows a J-shaped curve across age and is different for males and females. This curve depicts young children declining in BMI after birth, followed by a gradual increase that begins at approximately 6 years of age (adiposity rebound) and levels out during late adolescence.[38] As a result, the criteria used to determine the BMI at which children and adolescents are overweight or obese are age- and sex-specific.

Several growth curves have been created using different sources of data, resulting in different reference values to define overweight/obesity status in paediatric populations. Growth charts and reference values published by the World Health Organization (WHO),[39] the United States Centers for Disease Control and Prevention (CDC),[40] and the International Obesity Task Force (IOTF)[38] are commonly used. The WHO growth reference defines overweight and obesity as having a BMI one and two standard deviations above the mean, respectively, for age and sex. In contrast, the CDC growth chart defines overweight as having a BMI between the 85th and 94th percentile for their age and sex, while those with a BMI equal to or above the 95th percentile are obese. The IOTF growth chart is based on data from six international surveys. Percentiles corresponding to the adult cut-off points for overweight and obesity (25 and 30 kg/m^2 respectively) were first determined at age 18 years, by sex. For each survey dataset, percentiles were extrapolated across childhood and adolescence with all six curves passing through adult cut-off points at 18 years. The percentiles defining overweight and obesity for each curve were then averaged to obtain age- and sex-specific reference values ranging from 2 to 18 years.

The prevalence of paediatric overweight and obesity in Canada varies considerably when using the IOTF, CDC, and WHO growth curves.[41] This variation is largely due to the different samples and statistical techniques used in the construction of each growth curve, and the criteria used to select the BMI cut-off values. In 2004, the prevalence of overweight and obesity among Canadians aged 2 to 17 was 26.2%, 28.4%, and 34.1% using growth reference defined by the IOTF, CDC, and WHO, respectively.[41] The prevalence of obesity ranged from 8.2% (IOTF) to 12.7% (WHO). Among adolescents only (12 to 17 years), the prevalence of overweight and obesity ranged from 28.0% (CDC) to 33.2% (WHO), and obesity prevalence from 9.4% (IOTF) to 12.4% (WHO). The WHO cut-off points generally yield the highest estimates of excess weight status, and the IOTF cut-off points, the lowest. It has been recommended that the IOTF reference values be used for epidemiological purposes, whereas the CDC and WHO definitions are more useful for monitoring the growth of individual children and adolescents.[5,41-43]

1.3.2 Prevalence, Trends, and Health Risks

Overall prevalence in Canada: Paediatric overweight and obesity in Canada has grown rapidly over the last three decades. In 2004, 26% of children and adolescents aged 2 to 17 years were considered overweight or obese, compared with only 15% in 1978/1979.[3] Specifically, the Canadian overweight prevalence had increased from 12% to 18%, while the prevalence of obesity tripled, from 3% to 8%. In adolescents aged 12 to 17 years, the prevalence of overweight notably doubled from 14% to 29%, while obesity prevalence had tripled from 3% to 9%.

Regional differences: There are substantial differences in the prevalence of overweight and obesity across regions of Canada. Data from the Statistics Canada 2008 Canadian Community Health Survey (CCHS) displayed that the national average prevalence of overweight/obesity was 19.3% for adolescents aged 12 to 17 years, ranging from 14.4% in Quebec to 34.8% in Newfoundland and Labrador.[44]

Overweight/obesity in Ontario: In Ontario, during the time period from 2005 to 2014, the overall prevalence of overweight/obesity for adolescents aged 12 to 17 years increased from 19.5% to 23.3%.[44] Though similar patterns were observed for males and females, overweight/obesity prevalence was higher in males across all years.

The numerous standard definitions for paediatric overweight and obesity and different methods of measuring this condition cause difficulties in the comparison of overweight and obesity prevalence across different studies.[45] All prevalence estimates of overweight and obesity above were determined using the BMI growth curve created by the IOTF; however, the overall prevalence in Canada used direct measurements of height and weight to calculate paediatric BMI, whereas provincial-level estimates were based on self-reported height and weight. Despite these inconsistencies, it is evident that the magnitude and growth in the prevalence of overweight/obesity is worrisome in paediatric populations.

Health Risks: The increased prevalence of childhood obesity has been linked to the concurrent rise of many physical health problems. Obese adolescents are more likely to

have risk factors for cardiovascular disease, such as high cholesterol or hypertension. Approximately 70% of obese individuals aged 5 to 17 years in a population-based sample were reported to have at least one risk factor.[46] Overweight/obese adolescents are at higher risk of having pre-diabetes, a condition which places them at high risk of diabetes development.[47,48] Furthermore, obese children and adolescents are at greater risk for long-term health issues such as musculoskeletal problems,[49] sleep apnea,[50] liver disease,[51] stroke,[52] many types of cancer,[53] and osteoarthritis.[52] Paediatric obesity is also significantly more likely to persist into adulthood. Children who were obese as early as 2 years of age were more likely to be obese as adults.[54]

Obese children and adolescents are more likely to be subject to socio-psychological afflictions such as stigmatization,[55] behavioural problems,[56] social isolation,[50] low self-esteem,[57,58] anxiety,[59,60] body dissatisfaction[57] and depression.[59-61] These psychological impacts are causative of the suicidal[50,62] and risk-taking behaviours that are more common among this afflicted population relative to normal weight individuals. One study indicated overweight/obese children as having a higher likelihood of ever trying cigarettes, drinking alcohol, using drugs before their last sexual encounter, currently smoking, and smoking before age 13 in comparison to their normal weight peers.[63] Eating disorders, dieting, use of diet drugs, purging (i.e., self-induced vomiting, misuse of laxatives), and conducting other unhealthy weight control behaviours are also more common in this population.[64,65]

1.4 Looking at Both Asthma and Weight Status

Given the parallel increases in paediatric asthma and obesity, it is questioned whether there is a link between these two health conditions. This section discusses the importance of examining both asthma and overweight/obesity together.

1.4.1 Asthma and Weight Status Association

As described in Sections 1.2.2 and 1.3.2, the prevalence of asthma and overweight/obesity among children and adolescents has been rapidly increasing over the past few decades in Canada. These similar trends suggest that asthma and obesity appear to be increasing alongside one another, indicating an association at the population-level.

However, asthma and obesity have also been established as significantly coinciding with each other at the individual level.

Child-level association: Recent studies have shown that asthma has been positively associated with a higher BMI, overweight, and obesity in children and adolescents.[10,11,13,66-79] Even in preschool children aged 3-5 years, the prevalence of obesity was reported as higher in asthmatic children than non-asthmatic children.[80] This illustrates a strong association between these conditions. Furthermore, when examining the relationship between measures of exacerbations in asthmatics or respiratory symptoms in non-asthmatics and overweight/obesity, a positive association in paediatric populations has been found.[11,81-84] Lung function parameters significantly decrease in relation to increased weight status and other measures of fatness, such as tricep skinfold thickness.[75,85,86] Examples of studies reporting no association between asthma and weight status[87-92] were those conducted in Asian and African American samples of children and adolescents,[93,94] where other factors associated with ethnic minorities could have accounted for these results. Overall, all the evidence stated above is indicative of a positive, co-morbid relationship between asthma and weight status at the individual level.

A Bi-directional relationship: When examining co-morbid asthma and obesity, there has been lack of agreement on which condition precedes and thus potentially causes the incidence of the other. While many causal explanations in both directions exist, there is more support in the literature for the hypothesis that obesity is preceding asthma. Prospective studies have been conducted in children and adolescents, where those who were obese or overweight at baseline had a higher incidence of asthma in childhood, adolescence, and adulthood than those who were of normal weight.[13,92,95-98] These findings are supported by a number of potential causal mechanisms of this relationship; narrowed airways in obese children due to chronic low grade systemic inflammation that modifies airway smooth muscle function, and higher levels of the proinflammatory hormone leptin may, in the end, lead to asthma.[99,100] Exercise-induced bronchospasm caused by obesity can subsequently lead to asthma development.[85,101] Obesity also causes gastroesophageal reflux and is associated with a poor diet which both contribute to asthma.[102,103]

There is also the possibility that in some children, this causal mechanism is reversed. For example, in one study examining children who were both asthmatic and obese, 66.6% were already overweight and obese at the time of asthma diagnosis, indicating that in approximately 33% of these subjects, asthma preceded obesity.[14] These findings can be explained by a number of potential causal mechanisms. Asthmatic patients may develop obesity through the side effects of common systemic corticosteroid use or reduced physical activity resulting from exercise-induced asthma.[104-106] Children with asthma also have both overall low physical endurance and increased skinfold thickness, indicating physical fitness abnormalities and increased risk of eventual overweight/obesity.[107,108] Asthma is also a possible causal risk factor for obesity because parents don't want their asthmatic children exercising, further reducing levels of physical activity.[66]

1.4.2 The Need to Study Co-morbidities in General

This section focuses on the need to study associated diseases, such as asthma and obesity, as co-morbidities rather than separately. When trying to conduct research on, treat, or prevent a condition that is highly correlated with another condition, examining each condition as a co-morbidity will provide further evidence helpful towards achieving these goals more effectively.

Importance for treatment

Co-morbidities may predict a differential clinical outcome than only having one condition. The symptoms and health risks of one condition are thought to worsen those associated with the other condition, and vice versa.[109-114] Moreover, the increased likelihood of other health problems needs to be considered when assessing a patient and selecting the most suitable treatment method. It has been proven that attention to conditions in the context of their co-morbid state improves prognosis and treatment.[112] Researching co-morbidities may reveal patterns and associations with other risk factors that can contribute to the development of more effective co-morbidity treatment methods. For example, the efficacy of asthma and overweight/obesity treatment may be improved if treatment for depression (associated with both conditions separately) is provided.[112,115]

Importance for prevention

Prevention programs for co-morbid conditions have traditionally operated separately from one another. As a result, attempts to conduct programs aimed at addressing multiple related conditions in a coalescent manner have been neglected. This disregard presents implications for prevention efforts as it is unclear whether these strategies should be broad or narrow in their target. An understanding of the etiology of co-morbidities is important for identifying targets of prevention. Therefore, to combat the burdens associated with co-morbidities, including asthma and obesity, there is a need to identify the potential disease mechanisms involved through the study of associated conditions together rather than separately. This will be discussed in the following section.

1.4.3 Identification of Potential Disease Mechanisms

The study of co-morbidities acknowledges multiple influential factors and the dynamics of more than one health condition. This approach has the potential to yield important indications about the potential disease mechanisms involved. This section will discuss in more detail the importance of understanding the underlying mechanisms involved in co-morbidity development, and specifically, asthma and overweight/obesity.

If one health condition is more likely to coexist with another, important questions are raised regarding the etiology of these conditions. There are several hypotheses on the reasons why co-morbidity may exist, and are listed as follows: (1) there is a direct causal relationship between the two, with the presence of one condition increasing the likelihood of the other to develop; (2) there is an indirect causal relationship between the two, where one condition affects a mediating variable, which subsequently increases the likelihood of the second condition; and (3) there are common risk factors that increase the likelihood of both conditions.[116]

Many incidence studies have identified a short period of time elapsed between paediatric overweight/obesity and incident asthma and vice versa (see Section 1.4.1). Since asthma and overweight/obesity frequently originate in early childhood, a direct or indirect causal relationship between the two conditions that have developed so proximally in time may

not be the only explanation for their concurrent existence.[22] Chinn and Rona[117] have reported that the increase in obesity prevalence does not solely explain the increase in asthma from 1982 to 1994. They discuss that a direct causal link between these conditions also cannot be inferred because this coexistence is of recent origin and is inconsistent across various risk factors. These findings are all suggestive of a common risk factor that has contributed to the increasing prevalence of both asthma and overweight/obesity at such a young age. If two associated conditions are primarily the result of a set of common or similar risk factors, this indicates that the pathways by which one condition develops are the same by which the other develops as well. Prioritizing and addressing these risk factors would simultaneously reduce the prevalence of both conditions, indicating this theory as quite useful for intervention. Therefore, by examining asthma and weight status at the same time, it would be easier and advantageous to investigate a potential common risk factor, such as air pollution exposure.

1.5 What is Causing Asthma and Overweight/Obesity?

This section illustrates how asthma and weight status are linked through the mechanisms of either individual (biological, behavioural, and social) or environmental (physical and social) common risk factors. After providing definitions and evidence of individual and environmental categories as potential common risk factors of asthma and overweight/obesity, the need to examine the environment (especially physical) as a potential predictor of both conditions will be outlined. Finally, air pollution, a component of the physical environment, is introduced as a potential causal factor that needs to be examined.

1.5.1 Classification of Preceding Risk Factors

Several common factors have been hypothesized to explain the increasing rates of asthma and overweight/obesity. These mechanisms are generally of biological, behavioural, social, and environmental nature, or a combination of these factors.[118,119] Biological determinants are defined as the physical characteristics of individuals, as well as factors related to the genes inherited from their parents. Examples of common biological risk

factors of asthma and overweight/obesity are sex and genetics.[12,22] Behavioural factors are the manners in which one acts or conducts oneself under normal or specified circumstances. Examples of those associated with asthma and overweight/obesity are physical activity and diet.[120-122] Social factors are defined as the rank, status, and treatment of an individual in society based on their economic, behavioural, and/or biological attributes. Two examples of social risk factors of asthma and overweight/obesity are income and education.[12,123] Finally, environmental factors are related to the physical (indoor and outdoor) and social environment in which an individual lives, works, and attends school. Indoor allergens and outdoor air pollution are examples of common physical environmental risk factors of asthma and overweight/obesity, whereas social policies and norms have been proposed as social environmental influences.[15] A more comprehensive definition and the influence of environmental factors on asthma and weight status will be provided in Section 1.5.3.

These four main groups of possible causal predictors of co-morbid asthma and overweight/obesity can be further collapsed into two categories; individual and environmental (Figure 1). Biological, behavioural, and social factors are considered individual-level predictors as they are all characteristics of a particular person that may explain their health status.[118] In contrast, physical and social environmental factors are characteristics found in the surroundings or conditions in which a person or group of people live that can collectively influence both individual and group health status.[15] Evidence for both categories of potential causal predictors of asthma and overweight/obesity will be further discussed in the following two sections.

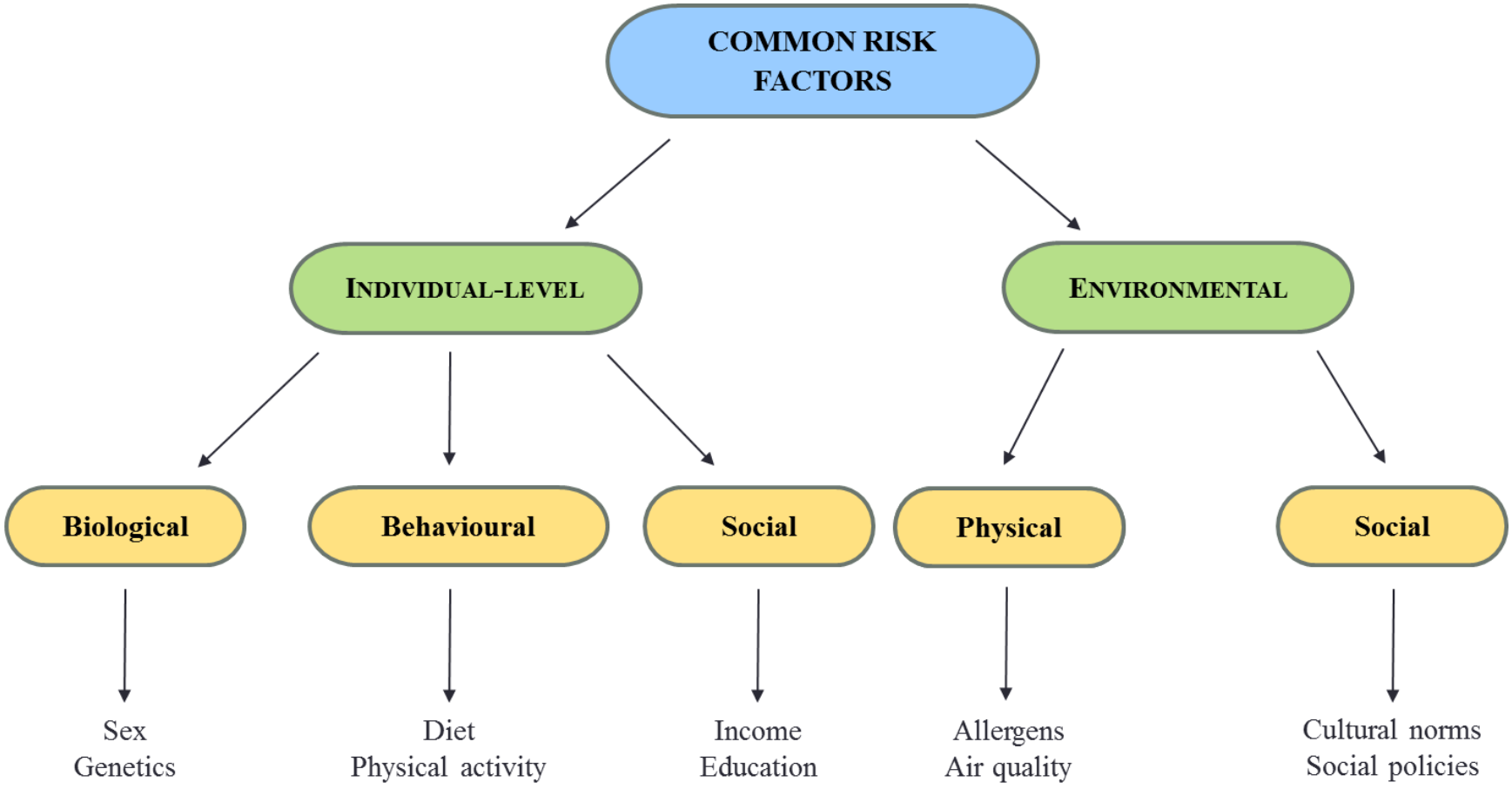

Figure 1: Categories of shared risk factors for paediatric asthma and obesity.

1.5.2 Individual-level Predictors

The hypothesized underlying mechanisms of co-morbid asthma and overweight/obesity in children and adolescents have mainly been attributed to individual-level predictors. Evidence for the individual risk factors these two conditions have in common is outlined in this section.

Sex: There is a higher risk of developing paediatric asthma and obesity in males compared to females. Stingone and colleagues[12] found that the adjusted prevalence odds ratio of asthma and overweight among males was double that of the reference group of females. Another study reported male adolescents had a significant relative risk of developing asthma associated with being overweight or obese, whereas female adolescents had a non-significant risk.[96]

Age: Age is positively associated with co-morbid asthma and obesity prevalence. Ahmad et al[10] reported that obese children were significantly more likely to have asthma compared to non-obese children in both 7-12 year olds and 13-17 year olds. However, this association was higher in those aged 13 to 17 years than in those aged 7 to 12 years. This association was non-significant in those aged 0 to 6 years, further confirming a dose-response relationship between these two conditions and age.

Income: There is a significant inverse relationship between household income and paediatric asthma and overweight. Stingone et al[12] has reported an adjusted prevalence odds ratio of co-morbid paediatric asthma and overweight of 2.47 (95% C.I.: 1.03 -5.96), comparing parental annual income of less than $20,000 to $75,000 or more. The odds ratio of paediatric asthma and obesity progressively decreased between these two income categories.

Physical activity: Physical activity appears to be a common protective factor against asthma[120] and overweight/obesity.[124] A lack of exercise may lead to reduced stretching of the respiratory airways,[103,125,126] causing a greater tendency for the muscles in the airways walls to contract abnormally when in contact with minor irritants. Likewise, each additional kilometer walked per day is associated with a significant reduction in the

likelihood of obesity.[121] It is important to note that while physical activity is exposure protective for both asthma and overweight/obesity, it can be harmful for some individuals by resulting in exercise-induced asthma.[127,128]

Second-hand smoking: Exposure to second-hand ("passive") tobacco smoke is positively associated with paediatric asthma[129] and overweight/obesity.[130]

Breastfeeding: Research has also indicated breastfeeding as a protective factor of paediatric asthma[131] and overweight/obesity[132] independently. The bioactive enzymes, hormones, growth factors, cytokines and immunological agents that are present in the milk help support healthy development.[133]

Race: A study conducted by Black et al[74] found a positive association between asthma and obesity that significantly varied by ethnicity. Although black youth were twice as likely and Hispanic youth were 25% less likely to have only asthma compared to white youth, the weight status and asthma relationship was stronger in Hispanic and weaker in black youth. These findings are supported by Stingone et al,[12] where a prevalence odds ratio of co-morbid asthma and overweight of 3.18 (95% C.I.: 1.06 -9.50) comparing Puerto Rican to white children, was reported.

Other individual factors: Other common risk factors for asthma and overweight/obesity include, but are not limited to, parental education,[123,134] prenatal diet,[135,136] paediatric diet,[137,138] genetic susceptibility,[139,140] maternal overweight,[141,142] levels of adipokines in early life,[22] high birth weight,[143,144] and rapid weight gain in the first year of life.[144,145]

1.5.3 Environmental Predictors

Environmental factors have two main components: physical and social. This section gives a more detailed definition of the physical and social environment and their corresponding influence on asthma and weight status.

Physical environment: Health Canada defines the physical (or "built") environment as encompassing all buildings, spaces, and products that are created and modified by people.[146] For example, it comprises our homes, schools, workplaces, parks/recreation

areas, business areas, industries, roads, highways, electric transmission lines, and even underground waste disposal sites and subway trains. Constructs of the physical environment impacts factors such as indoor and outdoor air pollution, climatic conditions, allergens, safety and crime, land use and development, and modes of transportation.[15]

Research indicates that physical environments in which we live, play, and attend school and work influences various health conditions including asthma and weight status.[15,147-149] For example, one primary causal mechanism for asthma is exposure to indoor and outdoor air pollution, which is increased by industries and automobile use.[16,150] A principal mechanism for overweight/obesity has been described as a decline in physical activity levels and adoption of a more sedentary lifestyle due to lack of access to safe areas and sprawling neighbourhoods that have increased reliance on automobiles for transportation.[15] Many other characteristics of the physical environment have been found as common contributors to asthma and overweight/obesity, including housing quality and construction,[151,152] spatial mobility (neighbourhood walkability/bikeability), land use and development,[153,154] indoor allergens,[155,156] safety and crime,[151,157] and air quality.[158,159] The paediatric asthma and overweight/obesity association has also been identified as strong particularly in samples residing in urban or highly polluted areas,[66,75,78,160,161] both key characteristics of the physical environment.

Social environment: Many formal definitions of the social environment have been proposed, as it can be difficult to capture such a broad construct. Barnett and Casper[162] define the social environment as encompassing the social relationships and cultural milieus within which defined groups of people function and interact. They listed its components as social and economic processes, wealth, social, human, and health services, power relations, governments, race relations, social inequality, cultural practices, and beliefs about a place and community. The Public Health Agency of Canada[163] describes the social environment as the social support from families, friends, and the broader community. This environment is associated with civic vitality, defined as the strength of social networks within a community, region, province, or country, and is subsequently reflected in the organizations, institutions, and informal giving practices that people

create to share resources or build attachments with others. It is then stated that the health and well-being of individuals is influenced by societal norms/values, social stability, recognition of diversity, good working relationships, and cohesive communities, all factors of the social environment. A social environmental factor differs from a social individual-level predictor, where the former is a product of the surroundings in which one operates and affects a group of people (e.g., neighbourhood income), whereas the latter is a product of each individual (e.g., personal income).

Among many health conditions, research has indicated that the social environment in which we operate influences asthma and weight status.[15,164-167] For example, Chen et al[168] discovered that adverse social conditions at the family level impact asthma morbidity by directly affecting the physiological system, whereas adverse social conditions at the community level affects the health behaviours of children and adolescents with asthma. Similarly, Oliver and Hayes[169] reported that Canadian children and adolescents residing in lower socioeconomic status neighbourhoods have a higher risk of being overweight or obese compared to those living in higher socioeconomic status neighbourhoods. Additionally, Brisbon et al[15] proposed the following characteristics as potential common contributors to the asthma and obesity epidemic: cultural norms, social policies, networks (social cohesion/integration), and the social contexts found in one's school, work, family, religion, health care system, and geographic location.

1.5.4 The Need to Focus on the Physical Environment

The need to focus on the environment as a potential predictor of co-morbid asthma and overweight/obesity over individual-level common risk factors is first outlined. Reasons are then given for choosing to examine the physical rather than social environment in this context.

Environmental vs. Individual factors: The evidence in Section 1.5.3 illustrates how a number of environmental determinants may predispose individuals to expressing both asthma and overweight/obesity. As such, the coexistence of these two conditions cannot purely be attributed to common individual-level predictors. The fact that research to date has primarily focused on the role of individual-level predictors on co-morbid asthma and

overweight/obesity, elicits the need to explore environmental factors as potential underlying mechanisms of these two conditions. This requirement is supported by Brisbon et al,[15] recommending that since asthma and obesity are intricately linked in many complex ways, significant reductions in the incidence and prevalence of these conditions will require an effort to address the common root causes embedded in the environment we have built. Another study reported asthma prevalence as positively associated with BMI in four rural Northern Plains Indian reservation communities, where this association differed across all four locations.[170] The authors emphasized that these intertribal differences elicits the need for further understanding of the environmental factors associated with paediatric asthma and obesity that differ between these tribes. They further stated that acquiring knowledge on these possible risk factors could benefit disease prevention or management strategies for these co-morbid conditions.

Physical vs. Social Environment: When exploring common environmental risk factors, those of the physical environment should be prioritized. After a thorough review on physical and social environmental influences on asthma and obesity, Brisbon et al[15] concluded that this co-morbid epidemic would be positively affected through the study and modification of chiefly the physical environment. There is also more concrete evidence on the physical versus social environment as a common risk factor for asthma and overweight/obesity. Though evidence of the social environment influencing both conditions exists, social environmental factors are more difficult to capture, presenting difficulties with obtaining valid and reliable measures of these factors. Finally, Brisbon et al[15] has defined the physical environment as having a direct impact on social environmental and even individual-level predictors. The authors additionally illustrated that the physical environment exerts its influence on asthma and overweight/obesity in combination with the causal effects of both individual-level and other environmental (physical and social) factors. Since examining physical environmental risk factors of asthma and overweight/obesity may simultaneously address the role of other common risk factor categories, this further indicates the need to particularly target this macro-level predictor.

1.5.5 Linking Air Pollution to Asthma and Overweight/Obesity

The previous subsection emphasized the need to examine the physical environment as a prospective risk factor for co-morbid asthma and obesity. However, the physical environment has numerous constituents, several of which affect both conditions. Litonjua and Gold[22] have recommended that since asthma and obesity both have their beginnings in early life, future research studies need to investigate exposures early in life. Air pollution is an early life, and even prenatal period, physical environment factor. It is more difficult for individuals to control their air pollution exposures than those through other environmental routes because it is impossible to carry clean air or stop breathing when exposed to polluted air.[171] There is also some evidence that environmental air pollution may be contributing independently to the growing rates of asthma and overweight/obesity among children and adolescents.[16,17] This collectively reveals air pollution as a potential causal risk factor of these co-morbid conditions that needs to be taken into account.

1.6 Role of Air Pollution

In this section, air pollution, its types, and sources are defined. Following this is the discussion of air pollution trends in Canada, and children/adolescents as a particularly susceptible population to its health effects. Lastly, the causal mechanisms and the results of statistical analyses of the relationships between air pollution and asthma, overweight/obesity, and co-morbid asthma and overweight/obesity will be reviewed.

1.6.1 Definition and Sources of Air Pollution

Definition: Environment Canada defines air pollution as a broad term applied to any chemical, physical, or biological agent that modifies the natural characteristics of the atmosphere.[172] It is also the collection of gases, dust, fumes, or odour in amounts harmful to human health. The substances that cause air pollution are known as air pollutants, which Environment Canada has categorized into four main groups: criteria air contaminants (CACs), heavy metals, persistent organic pollutants (POPs), and toxics. Examples of CACs include total particulate matter with a diameter less than 100 microns (TPM), particulate matter with a diameter less than or equal to 10 microns (PM_{10}), particulate matter with a diameter less than or equal to 2.5 microns ($PM_{2.5}$), sulphur

oxides (SO_x), nitrogen oxides (NO_x), ozone (O_3), volatile organic compounds (VOCs), carbon monoxide (CO), and ammonia. Heavy metals include a group of metals with a relatively high atomic mass, such as lead, cadmium, and mercury. POPs are organic compounds that are resistant to environmental degradation and are capable of travelling very large distances, such as dioxins and furans, polycyclic aromatic hydrocarbons (PAHs), and hexachlorobenzene. Finally, toxics comprise a broad class of pollutants toxic or poisonous to human health and the environment (e.g., benzene), essentially overlapping with CACs, heavy metals, and POPs that possess these characteristics. These categories of air pollutants cause broader issues such as smog, acid rain, climate change, indoor air pollution, land use issues, transboundary movement of air pollutants, and poor air quality. They are also detrimental to the environment, economy, and human health due to their bioaccumulation and toxic effects. Out of the four general groups of air pollutants, CACs are definitely the largest contributor to these issues.

The dominant origin of the key air pollutants, especially CACs, is through the combustion of fossil fuels, such as crude oil, coal, natural gas, petroleum, gasoline, diesel, and fuel oils.[171] The sources responsible for the burning of these fuels are categorized as follows:

Motor vehicles: Primarily in urban areas, and progressively more in suburban areas, traffic-related (cars, buses, trucks) emissions are a major source of pollutants.[171] Minor motor vehicle sources include aircraft, locomotives, marine vessels, recreational vehicles (e.g., snowmobiles, ATVs), forklifts, and ice resurfacers. Air pollution can arise specifically through the pumping of gasoline, vehicle exhaust, and the use of engines that are not tuned or working properly. Despite recent efforts to produce cleaner and efficient combustion engines, the increasing use of motor vehicles is leading to a corresponding increase in pollutant levels.

Industry: Another dominant source includes large industrial facilities (e.g., coal-fired power plants), and smaller industries (e.g., dry cleaners). Approximately half of Canadian air pollution is produced by large industry, primarily involving combustion systems.[173] Specifically electricity and industrial energy generation in coal, oil, and gas-fired power

plants is responsible for a large proportion of air pollution emissions.[172,174] Moreover, industrial emissions from the United States contribute to smog and acid rain in some parts of Canada, where a large proportion of the air pollution in the province of Ontario is transported from the United States.[172,175]

Other minor sources: Additional sources of fuel combustion include lawn and gardening equipment, kitchen stoves, residential heating using fuel oil furnaces, water heaters, and barbecues.

Other important factors contributing to high air pollution levels are consumer products, agriculture, and transboundary air movements. Some air pollutants are road dust emissions from unpaved surfaces or naturally occurring, produced by forest fires, conifer forests, soil erosion, volcanoes, dust storms, lightning, and sea spray. Although the relative importance of each source listed in this section varies for different pollutants, the principal contributors to the most critical category of air pollutants, CACs, are industries and motor vehicles that burn fossil fuels.[174]

1.6.2 Trends in Air Pollution

As mentioned above, CACs have the largest impact on the physical environment, and subsequently, human health. Since they are also chief products of the two largest sources of air pollution, the prevalence and trends of Canadian CAC emissions will be discussed accordingly.

Over the period of 1990 to 2010, the national average of ground-level ozone has significantly increased by 10%.[176] From 1990 to 2011, emissions of ammonia increased by 22%, and TPM (including $PM_{2.5}$ and PM_{10}) by 35%.[177] This trend was based on information reported to the National Pollutant Release Inventory by industrial facilities and emission estimates from other sources such as motor vehicles, agricultural activities, and forest fires.

Conversely, other CACs relatively less critical to human health[178,179] show a different outlook. From 1990 to 2011, Canadian emissions of a number of CACs have been significantly decreasing. Environment Canada has reported the magnitude of this

decrease as 60% for SO_x, 45% for CO, 28% for VOCs, and 21% for NO_x.[177] From 1996 to 2010, sulphur dioxide (SO_2) levels declined by 62%, and nitrogen dioxide (NO_2) by 38%.[176] The reduction in these CAC levels have been mainly attributed to climatic conditions, and more rigorous vehicular emission standards from the government during this time period.

The downward trend of numerous CACs over the last two decades in Canada is viewed as a national feat. However, considering two of the CACs that pose the most widespread health threats are particulate matter and ozone,[178,179] these corresponding increasing trends are particularly worrisome. Thus, the findings discussed in this section indicate that the declining trends of less harmful CACs cannot reassure that human health is not being compromised by overall air pollution exposure. Certain populations are more susceptible to the health effects associated with these high levels of air pollution. One vulnerable population comprises of children and adolescents, due to reasons outlined in the next section.

1.6.3 Children and Adolescents as Susceptible Populations

Children and adolescents in particular may be more acutely affected by their environments due to their extrinsic mobility restriction which may hinder their ability to choose healthy behaviours.[180,181] Children and adolescents are susceptible to the effects of specifically air pollution as a result of higher levels of outdoor physical activity. One study comparing activity patterns between children and adults found that children spent more than five times the minutes per day spent by adults engaging in active sports, walking/hiking, or outdoor recreation.[171] To make matters worse, since children/adolescents are less likely to cease activity even when they are symptomatic, they present more severe health risks associated with air pollution exposure relative to older age groups.[171] Children/adolescents also have increased exposure to air pollution due to a greater amount of inhaled pollution per pound of body weight and a higher ventilation rate. Specifically, air intake of a resting infant is twice that of an adult.[181] In one study conducted in the Netherlands, though children were exposed to similar outdoor concentrations as those experienced by adults (38.5 versus 41.5 $\mu g/m^3$, respectively), children's personal exposure averaged 66.8 $\mu g/m^3$ above ambient levels versus only 20.4

$\mu g/m^3$ above ambient levels for adults.[182,183] These findings confirm the importance of examining air pollution as a common risk factor for co-morbid asthma and overweight/obesity in specifically children and/or adolescents.

Section 1.6.1-3 has elucidated the significance of assessing the role of particular types and sources of air pollution in paediatric populations. In reality, research has focused on the health effects of general air pollution exposure from multiple sources and in many age groups. Thus, in order to gain an overall understanding of the relationship between air pollution exposure and asthma and overweight/obesity, evidence for the role of any air pollutant on the development and prevalence of these two conditions will be reviewed.

1.6.4 Air Pollution and Asthma

This section discusses the mechanisms through which air pollution causes asthma, succeeded by a review for the statistical analysis of this relationship.

Causal Mechanism: Lung function is a fundamental mediator in the air pollution and asthma pathway. This is likely a result of the course of lung organogenesis. Although this process begins early in fetal life, only eighty percent of the lung alveoli are formed postnatal. Growth and changes are especially rapid in childhood and persist into adolescence.[184] The lung epithelium's incomplete development causes greater lung permeability, resulting in more significant damage from air pollution exposure and further alteration in the normal process of paediatric lung development.[171,185-189]

Airway inflammation is another significant intermediary step between air pollution exposure and the development of asthma. Research has shown that high air pollution levels have been associated with inflammation of the respiratory system.[190] This has been confirmed by evidence of a positive association between air pollutants, such as TPM, $PM_{2.5}$, PM_{10}, O_3, and SO_2, and inflammatory markers such as interleukin-6 (IL-6), tumor necrosis factor-alpha, fibrinogen, and C-reactive protein (CRP).[191-194] In asthma, the lung inflammatory response is also characterized by the recruitment and increased number of these inflammatory substances.[191,195-199] Since the peripheral airways of children are more susceptible to inflammatory narrowing than those of adults,[171] this suggests that air

pollution is especially likely to cause airway obstruction in asthmatics as a result of these inflammatory effects in paediatric populations.

Other proposed mechanisms by which air pollution could contribute to the development of asthma include oxidative stress/damage, airway wall remodelling, enhancing respiratory sensitization to allergens, affecting immunological responses, and interacting with antigenic proteins.[200]

Empirical evidence: The connection between air pollution exposure and asthma is reviewed as follows: studies examining estimated air pollution exposure and (1) asthma incidence; (2) asthma prevalence; (3) asthma exacerbations; (4) respiratory symptoms in non-asthmatics; and (5) studies examining indirect air pollution exposure and asthma. Considering a broad scope of studies allows for a better understanding of the comprehensive role air pollution has played in asthma status to date.

Incidence studies

The majority of studies that have examined the effects air pollution on the incidence of paediatric asthma have revealed a positive association.[16,147,200-208] The prospective design of these studies satisfy the requirement for temporality, allowing the inference of causation between these two variables. A few of the remaining studies illustrating an ambiguous causal relationship between air pollution and incident asthma are those that measure community-level exposure.[204,205] Measuring pollution exposure at this community level may have attenuated the true association as the grouping of individuals reduces the variation of exposure that exists between individuals within each cluster. In two individual-level studies, there was also no association between air pollution and incident asthma among infants and children respectively.[209,210]

Prevalence studies

Many prevalence studies have shown a strong and positive association between a variety of air pollutants and paediatric asthma.[16,211-218] These prevalence studies have captured larger sample sizes and a wider variety of air pollutants than incidence studies, both strengths contributing to the validity of these positive findings. However, more

associations that were not significant have been found in prevalence compared to incidence studies.[200,208,212,218-222] These findings may be a result of measuring community-level air pollution, or due to measuring prevalence, where it is unknown whether or not study subjects had developed asthma prior to air pollution exposure. Despite the lack of known temporality in prevalence studies, a bi-directional relationship is not of any concern, as it is impossible for asthma to cause air pollution. Moreover, these few null findings are clarified by studies using longitudinal data that primarily confirm a positive association.

Exacerbation studies

Since there is evidence of a linkage between air pollution and asthma, a positive association between air pollution levels and symptom exacerbations in asthmatics is anticipated. This assumption has been strongly supported by several studies,[158,223-231] where exacerbations are commonly quantified by the number of hospital admissions and emergency department visits, worsening of asthma symptoms, or increased bronchodilator usage corresponding to different air pollutant levels in asthmatics. Some exacerbation studies have alternatively discovered null and negative associations.[224,227,232,233] However, some of these results may be biased due to reasons such as asthmatics experiencing frequent exacerbations they have become accustomed to, therefore deciding against the very time consuming hospital admission process. While exacerbation studies do contribute to an overall understanding of the air pollution and asthma relationship, asthma diagnosis rather than severity is a more valid measure in this context, reducing the likelihood of inconsistent findings.

Respiratory symptoms

Research has shown that increased levels of air pollution are associated with higher levels of respiratory symptom (i.e., wheezing, coughing, shortness of breath, chest tightness) incidence and prevalence in non-asthmatics.[217,222,234-242] Seeing that respiratory symptoms are positively associated with asthma,[243] this evidence supports air pollution as a potential risk factor of this outcome. Zhao et al[244] however, identified that although there were many significant results between air pollution and respiratory symptoms in non-

asthmatics, none of the air pollution and cumulative asthma diagnosis associations were significant. This suggests symptoms in non-asthmatics are not the best proxy measures for being diagnosed with asthma as a consequence of air pollution. A few other respiratory symptom studies have also shown null and even negative associations.[214,222,234,245]

Indirect measures of air pollution

Even air pollution proxy measures are positively associated with paediatric asthma. For example, truck and general traffic density and counts have been noted to increase the likelihood of asthma incidence, prevalence, symptoms, exacerbations, and reduced lung function.[217,246-253] Children living closer to major roads are more likely to be asthmatic.[16,240,248,253-260] Though there are null associations between traffic-related measures and asthma,[220,221,249,255,259,261-266] the difficulty in accounting for different types of roads (e.g., freeway or main roads) in exposure measurement and failure to validate traffic indicators with pollutants may be explanations for inconsistencies in the literature.[267]

Summary

The literature has repeatedly demonstrated a positive association between measures of air pollution and asthma. Though there have been some findings of no association, many of these studies measured air pollution at the community level, whereas individual-level studies, which were able to capture better microscale differences in pollution, have reported a positive association. It is likely that community-level studies fail to capture the microscale variations in air pollution exposure between individuals within each community, resulting in bias towards unity. When assessing the relationship between air pollution and asthma, quantifying air pollution exposure at a smaller level than the community level might then be more useful. In addition, the effects of more directly estimated air pollution on asthma incidence or prevalence rather than exacerbations and symptoms should be of primary focus. Otherwise, there is generally good evidence that air pollution is a potential causative agent of asthma.

1.6.5 Air Pollution and Weight Status

In this section, the mechanisms through which air pollution causes overweight/obesity are elaborated, followed by a review of their association.

Causal Mechanism: The primary mechanisms through which air pollution causes overweight/obesity are potentially systemic inflammation, suppressed adiponectin release, decreased physical activity, and low birth weight followed by early adiposity rebound. These intermediary factors are explained below.

High air pollution levels are causative of systemic inflammation. This has been confirmed by evidence of a positive association between multiple air pollutants and influential inflammatory markers (see Section 1.6.4). Studies have also shown that increased production of adipose tissue inflammatory markers are involved in obesity-associated metabolic syndrome and inflammation.[196,268-270] These findings are specifically sustained by a positive association between CRP levels and overweight/obesity, and a positive correlation between IL-6 and percent body fat.[195,271-273] Lastly, it has been determined that higher levels of these inflammatory response substances are expressed in the adipose tissue as a result of high air pollution exposure,[274] therefore representing potential cellular mediators in the pathway between air pollution and the development of overweight/obesity.

Air pollution has been found to suppress adiponectin release.[275-277] Since this protein hormone is negatively associated with triglyceride and intramyocellular lipid content, its suppression results in increased adiposity.[276] This outcome is confirmed by studies that have reported lower levels of adiponectin in obese compared to non-obese adolescents,[278] indicating adiponectin as a conceivable mediating mechanism through which air pollution causes overweight/obesity.

Another mechanism through which air pollution manifests its effects on overweight/obesity is through lack of physical activity. Increased urbanization has resulted in high-density traffic, low air quality, and high pollution levels, wherefore residing at distances greater than 200 metres from highly travelled main roads are

recommended to support healthy paediatric air consumption.[279] Many children and adolescents live within this advised distance, and are accordingly exposed to high levels of air pollution that irritate the skin, eyes and other body systems. Air pollution specifically causes a decrease in oxygen striation and lower VO_2 max, both impairing exercise performance, and causing adverse symptoms such as pain upon inspiration, shortness of breath, and change in respiratory frequency when exercising.[280-283] Consequentially, many children stay indoors either by choice or through the concern of their guardians, reducing physical activity. This notion is supported by numerous studies which have consistently reported significant inverse associations between traffic density, parental concerns about traffic, or annual mean $PM_{2.5}$ concentration and physical activity, fitness, or active commuting to school.[284-290] The role of physical activity as a mediator between the air pollution and overweight/obesity relationship is illustrated by studies reporting an increased probability of overweight/obesity, BMI, and skinfold thickness as a consequence of decreased physical activity.[124,291-294] In fact each additional kilometer walked per day is associated with a 4.8% reduction in the likelihood of obesity.[121] These findings thus signify a lack of exercise as a more proximal risk factor to the distal effects of air pollution on overweight/obesity development.

A fourth mechanism through which air pollution exerts its effects on overweight/obesity is low birth weight followed by early adiposity rebound in childhood. Prenatal exposure to many air pollutants such as $PM_{2.5}$, PM_{10}, O_3, NO_2, NO_x, CO, SO_2, and PAHs, are inversely associated with fetal size, birth weight, head circumference, and birth length.[295-302] Higher levels of pollutants also increase the risk of delivering small for gestation age and preterm babies.[295,299,300,303-305] These measures of low birth weight/size are commonly associated with an earlier than normal adiposity rebound (younger than 6 years of age; see Section 1.3.1), subsequently increasing the risk of paediatric and/or adult obesity.[144,306-310]

Empirical Evidence: Considering research on the association between air pollution and overweight/obesity generally differs in the type of exposure quantified, this relationship is reviewed accordingly: studies examining the effects of (1) estimated air pollution

exposure; (2) early life (prenatal, perinatal) air pollution exposure; and (3) indirect exposure to air pollution, on weight status.

Estimated exposure

The effect of estimated air pollutants on obesity has primarily been investigated using animal models. These studies all discovered a positive association between exposure to CACs and measures of obesity (e.g., adiposity, weight gain).[274,277,311,312] Alternatively, a connection between estimated air pollution exposure and obesity in adults was displayed in a study conducted by Carwile and Michels,[313] examining the effects of the environmental contaminant Bisphenol A (BPA). The authors demonstrated that relative to participants in the lowest BPA exposure quartiles, the upper three had cumulatively higher odds of general and central obesity and greater waist circumference. While food, water, and soil are other sources of BPA, the presence of this contaminant in urban ambient outdoor air (especially PM) has been confirmed by many studies,[314-316] signifying air pollution as a potential risk factor of overweight/obesity. However, much more exposure estimate studies conducted on humans rather than animals is required to strengthen this inference.

Pre/perinatal exposure

Most of the studies indicating causal effects of air pollution on the development of obesity in humans have explored prenatal or perinatal exposure. This type of exposure has been partially ascribed to air pollutants classified as environmental estrogens (e.g., PAHs, BPA, dioxins), due to a recent hypothesis that exposure to these endocrine disrupting chemicals in utero alters metabolic programming early in life[159] and generates abnormalities in homeostatic control systems necessary for the maintenance of normal body weight throughout one's life.[317] These hypotheses were initially guided by in vitro and animal studies showing that brief pre/perinatal exposure to environmental estrogens increased body weight with age and accelerated adipocyte formation.[318-323] Rundle et al[159] later confirmed this association in humans when reporting that prenatal exposure to ambient estrogenic PAHs predicted higher BMI z-score and obesity at 5 and 7 years of age, and increased fat mass at 7 years. As previously mentioned, the effects of prenatal

exposure have also been attributed to many CACs (e.g., $PM_{2.5,}$ PM_{10}, O_3, NO_2) that increase the risk of low birth weight and subsequent early adiposity rebound, both factors that negatively influence overweight/obesity development.

Indirect exposure

Transport sector activity produces about a quarter of greenhouse gas emissions,[324] all associated with many adverse health effects.[325,326] The few studies that accordingly examined the role of this air pollution proxy measure on overweight/obesity reported a positive association.[287,324,327-329] Most of this effect has been explained by greater distance travelled by motor vehicles in comparison to larger car/engine size and lower active travel[324]; one possibility for this discovery is larger motorized travel distance increases carbon dioxide production, subsequently leading to obesity.[330] Jerrett et al[17] recognized that the majority of studies examining the effects of traffic on the current obesity epidemic are cross-sectional, and conducted a longitudinal study following children aged 9-10 years annually until age 18 accordingly. Air pollution exposure was based on traffic density, where increased exposure within 150 metres of the home was associated with a significant increase in BMI at age 18. This study was the first of its kind to measure the effects of a dominant source of critical pollutants on obesity incidence in human adolescents. However, a more direct quantification of air pollution is required to draw more sound conclusions.

Summary

Overall, estimated exposure to key CACs in children/adolescents have not been used to explore the relationship between air pollution and paediatric overweight/obesity. Evidence supporting estimated air pollution exposure as a risk factor for overweight/obesity mainly used animal models, whereas research examining humans have used pre/perinatal or indirect exposure measures. In fact, the study conducted by Jerrett et al[17] is considered the best illustration of this relationship in children/adolescents to date, where only air pollution proxy measures were used. This is unlike the literature illustrating the air pollution and paediatric asthma relationship, where human exposure to common critical pollutants are more directly quantified (see Section 1.6.4). Otherwise,

the numerous positive associations and their elucidated causal mechanisms provided in this section imply that air pollution increases the risk of developing overweight/obesity.

1.6.6 Air Pollution and Asthma and Weight Status

Overall, the literature has shown that environmental pollution may stimulate the onset and/or exacerbation of asthma and also may separately affect the accumulation of body fat. However, evidence of air pollution as a preceding risk factor of concurrent paediatric asthma and obesity is required to understand its role in their coexistence. In this section, the role the environment and specifically air pollution plays on the simultaneous incidence/prevalence of both asthma and overweight/obesity in children and adolescents will be reviewed.

Causal Mechanism: While the mechanisms through which air pollution causes co-morbid asthma and overweight/obesity have not been identified to date, the causal pathways involved in the separate relationships between air pollution and asthma or weight status are likely to play a role. Some of these mechanisms are common to both independent pathways, such as systemic inflammation. Huang et al[331] corroborates the presence of this shared intermediary factor by reporting that inflammatory markers known to increase with high air pollution exposure were significantly elevated in obese asthmatic compared to normal subjects. Additionally, many studies have displayed high levels of inflammatory markers as associated with all three variables. A second potential mechanism common to both independent pathways is decreased physical activity. Airway narrowing caused by air pollution could transiently and permanently decrease exercise capacity and subsequent physical activity.[283] Reduced physical activity increases the risk of poor respiratory function and obesity, signifying the prospect of this causal pathway. Another shared mechanism is suppressed adiponectin release. Similar to the air pollution and overweight/obesity pathway described in Section 1.6.5, air pollution decreases adiponectin levels, [275,277] consequently influencing asthma. This is supported by studies demonstrating a lower serum concentration of this hormone in asthmatics relative to controls, after adjusting for BMI.[332]

A combination of the unshared causal mechanisms (e.g., lung function, low birth weight followed by early adiposity rebound) could also be responsible for the relationship between air pollution and co-morbid asthma and overweight/obesity. It is then likely that the mechanism(s) through which air pollution simultaneously causes both conditions is/are unique to each individual. More research on these specific and novel pathways would be useful towards understanding the etiology of this co-morbidity.

Empirical Evidence: Research on the relationship between air pollution, asthma, and weight status can be mainly classified as follows: studies examining (1) if weight status modifies the air pollution and asthma association; (2) the effects of estimated air pollution exposure on asthma and overweight/obesity; and (3) the effects of indirect exposure to air pollution on asthma and overweight/obesity.

Weight status as an effect modifier

Research on the air pollution, asthma, and overweight/obesity relationship has largely investigated whether weight status modifies the association between air pollution and respiratory symptoms/asthma. Deposition of fine particles in the respiratory tract is positively correlated with BMI, suggesting that greater weight may increase the risk of asthma from inhalation of pollution particles.[333] This rationale for weight status as an effect modifier of the air pollution and asthma relationship is supported by a study conducted by Bennett et al.[334] The authors revealed that greater BMI and adiposity resulted in greater acute ozone-induced decrements in pulmonary function, in non-asthmatic young adults. Guided by analogous studies conducted on genetically modified obese mice,[335-338] Bennett et al[334] discovered this association for the first time in humans. Dong et al[339] later investigated this relationship in children from Northeast China, where the positive association between PM_{10}, SO_2, NO_2, and O_3 and asthma/respiratory symptoms was consistently stronger in those that were overweight or obese than among those of normal weight. The numerous studies illustrating the effect of air pollution on asthma as dependent on weight status is indicative of a significant relationship between these three variables.

Estimated exposure

A study conducted by Xu et al[340] evaluated the relationship between estimated short-term exposure to $PM_{2.5}$ and inflammatory responses in mice during and two months after the 2008 Beijing Olympic Games. Air pollution levels significantly decreased during the Games due to air quality control measures that were implemented by the government. During and after the Games, macrophages and inflammatory markers had significantly increased in the lung and visceral fat with increasing $PM_{2.5}$. However, these numbers were even higher after compared to those during the Games. The authors noted that the lung inflammatory response in asthmatics is characterized by an increased number of these substances, while adipose tissue macrophages and inflammatory substances accumulate in obesity development, advocating air pollution as a potential causal factor of asthma and obesity. Short-term air quality improvements may even prevent/improve these co-morbid outcomes by reducing systemic inflammation, a key underlying mechanism in this pathway. Although evidence from animal studies are considered weaker, the most widely used animal model of human disease was studied (genetically modified C57BL/6 mice), justifying the review of these results. Still, studies examining the effects of estimated air pollution exposure in humans instead of animals would produce more valid findings. This limitation and the use of lung and adipose tissue inflammatory markers as outcomes rather than asthma and overweight/obesity diagnosis, collectively presents significant gaps to be addressed.

Indirect exposure

Many studies have demonstrated that overweight and obesity are positively associated with asthma/respiratory symptoms in children living in highly polluted areas.[66,75,78,160,161] However, a direct comparison to less polluted areas is required to determine whether this co-morbidity varies by different exposure levels. This necessity has been addressed by a few studies investigating the effects of indirect measures of air pollution exposure on paediatric asthma and obesity.[341-343] For instance, air pollution levels in urban areas are generally higher than in rural areas; Lawson and colleagues[341] sought to confirm the existence of an urban-rural gradient in asthma prevalence among Canadian youths and to evaluate whether this gradient was mediated by obesity status. Asthma prevalence became progressively lower as the degree of rurality increased, with a significant

difference between urban and rural regions. Obesity status did not mediate this significant association, indicating asthma occurring as a result of urban/rural status, regardless of obesity. However, obesity was reported as independently and positively associated with asthma, indicating this coexisting relationship is potentially due to a third variable associated with this urban-rural gradient. This hypothesis is supported by Suh et al,[342] where the association between BMI and asthma symptoms in boys was significantly positive among metropolitan, provincial, and industrial areas, whereas null in rural areas. Seeing both studies proposed the environment as a likely mechanism through which this relationship exists, along with a known association between air pollution levels and urban/rural status, a conceivable mechanism is the physical environmental factor, air pollution.

Another example of an indirect exposure study is the comparison of asthma and overweight/obesity across larger geographical regions. Perez-Padilla et al[343] reported higher obesity prevalence and poorer lung function among Mexican-Americans than Mexicans. Seeing that the United States is generally more polluted than Mexico, air pollution could be one of the factors influencing the geographic difference in these outcomes.

While there is evidence of positive association between air pollution proxy measures and co-morbid asthma and overweight/obesity, comparing the prevalence of these two conditions across large geographic areas (e.g., urban versus rural, countries) is not as effective as the comparison between individuals, as cluster effects need to be taken into account. In addition, examining this co-morbidity across a better urban-rural gradient may capture the influence of air pollution exposure more accurately. Finally, employing a more direct measurement of air pollution would allow for more valid conclusions.

Summary

Although the evidence provided in the above sections indicates air pollution as a potential risk factor of asthma and overweight/obesity separately, it is more difficult to conclude this exposure is a preceding risk factor of these conditions as a co-morbidity. First, there is relatively narrower evidence in the literature regarding the association between air

pollution and co-morbid asthma and overweight/obesity. Existing evidence mostly focuses whether weight status is an effect modifier of the air pollution and asthma relationship, and indirect/proxy measures of air pollution, asthma, and overweight/obesity are frequently used. Short-term air pollution exposure has mainly been quantified, whereas the examination of long-term exposure is required to observe any realistic influence on asthma and obesity development. A number of studies exploring these three variables have also focused on animal models. Most importantly, there is no evidence to date of a study examining the effect of estimated air pollution on the simultaneous development/prevalence of asthma and overweight/obesity in humans. To acquire a better understanding of the etiology of this co-morbidity and explore air pollution as a possible root cause in paediatric populations, there is a distinct requirement to address this significant gap.

1.7 Summary

With the high rates of paediatric asthma and overweight/obesity, it is important that effective efforts are made towards tackling this co-morbid epidemic. Left neglected, these children and adolescents face serious long-term health ramifications more so than children that have only one of these conditions. While many studies support an association between asthma and weight status, the exact nature of this coexistence remains unclear; as a result, identifying a root cause for treatment/prevention strategies is a challenging task. There is currently some evidence that air pollution is potentially contributing to the growing rates of separate asthma and overweight/obesity, suggesting this environmental exposure is a common risk factor of these two conditions as a co-morbidity. Since better understanding of these two separate pathways will contribute to an overall understanding of the potential air pollution and co-morbid asthma and overweight/obesity association, it would be useful to examine the relationships between the following: (1) estimated microscale air pollution exposure and asthma incidence or prevalence; and (2) estimated air pollution exposure (excluding pre/perinatal) and overweight/obesity in paediatric populations. Though the literature indicates that air pollution may stimulate the separate onset of asthma and overweight/obesity, it is more difficult to conclude that this exposure is a preceding risk factor of these conditions as a

co-morbidity. The causal mechanisms involved in this latter pathway are less understood, and there is no evidence to date of a study investigating the effect of estimated air pollution on the simultaneous incidence/prevalence of asthma and overweight/obesity in humans. Future approaches to this co-morbid epidemic need to address this gap to provide insight on the specific disease mechanisms involved and appropriately tailor prevention/intervention strategies.

This thesis begins to explore a potential underlying mechanism of paediatric co-morbid asthma and overweight/obesity in a local Canadian context. It examines the effect of more directly estimated microscale air pollution exposure on the separate and simultaneous prevalence of asthma and overweight/obesity. The objectives of this thesis are further detailed in Chapter 2.

Chapter 2

2 Objectives and Hypotheses

2.1 Overall Objective

This thesis aims to explore a potential underlying mechanism of paediatric co-morbid asthma and overweight/obesity by examining the effect of air pollution on separate and co-morbid paediatric asthma and overweight/obesity. No study has specifically analyzed air pollution as a potential risk factor for both conditions together. Exploring the effect of air pollution on either asthma or overweight/obesity will provide further insight on whether this environmental exposure is a common risk factor for both conditions. For the purposes of this thesis, the word "effect" refers to the association between air pollution and these paediatric outcomes.

Focus on adolescence: The effects of air pollution on paediatric co-morbid asthma and overweight/obesity will be examined among adolescents. Adolescence is an important developmental bridge between childhood and adulthood. The physical and psychosocial changes that occur during this time provide insight on early childhood risk factors, and foresee threats to adult health and quality of life. In addition, asthma and obesity are more associated with one another in adolescents compared to children.[10]

Both overweight and obesity will be assessed as measures of excess weight status. As such, overweight and obese adolescents are both referred to as overweight for the remainder of this thesis.

Sub-analysis: Lastly, the effect of air pollution on co-morbid asthma and overweight will be analyzed by taking into account factors that are associated with this exposure and paediatric co-morbidity. These potential effect modifiers have been identified as geographic location, income, age, and sex.

Geographic Location

It is important to consider geographic area of residence when examining the relationship between air pollution and co-morbid asthma and overweight. Previous evidence demonstrates that the environmental factors related to air pollution are most prevalent/pronounced in urban areas, resulting in higher ambient air pollution in these areas versus non-urban areas.[344-348] Furthermore, the highest levels of air pollutants critical to human health are found in urban areas.[349] This is explained by the steady increase of commuting in urban settings, while pollutants of industrial and heating origin have also remained a significant source in these areas. The literature also highlights the asthma and overweight association as strongest in urban areas (see Section 1.6.6). While this evidence collectively advocates a stronger air pollution and concurrent asthma and overweight relationship among those residing in urban areas, this co-morbidity has yet to be examined across an urban-rural gradient.

Urban core status is a measure of geographic location that captures a suitable urban-rural gradient. In this study, the strength of association between the air pollution and co-morbid asthma and overweight will be compared between adolescents living in an urban core and those living outside of an urban core.

Income

Income is another pertinent factor to be taken into account when examining the air pollution and co-morbid asthma and overweight relationship. Air pollution is a factor incorporated into housing prices, where property values are often higher in areas of better air quality.[350] Realtors are aware that, regardless of one's income, buyers would prefer to live in clean areas that are not detrimental to health. Many families feel more comfortable that these areas offer a cleaner environment for their children to be exposed.[351] However, families with higher levels of income are more likely to actually purchase residences in less polluted areas. This rationale is supported by studies demonstrating low income as associated with poor air quality and higher levels of air pollution that adversely affect individual health.[352-354] Total household income is found as negatively associated with ozone and particulate matter exposure levels.[355] Likewise, evidence for a significant negative association between household income and co-morbid asthma and overweight

(see Section 1.5.2) indicates that low income is also a risk factor of this paediatric outcome. It is currently unknown whether the air pollution and co-morbid asthma and overweight relationship is affected by household income. This thesis will compare this association between adolescents residing in households of high and low income.

Age

It is important to examine the different stages of adolescence when assessing the air pollution and co-morbid asthma and overweight relationship. Paediatric age is associated with air pollution exposure levels.[356] Section 1.5.2 also discusses a significantly positive association between paediatric age and co-morbid asthma and overweight. As such, this study will examine whether the strength of the association between air pollution and co-morbid asthma and overweight varies across age groups in adolescence. Identifying the specific stage of adolescence where the effects of pollution on this co-morbidity is strongest is crucial for the targeting of disease reduction strategies to a particular narrower age group.

Sex

Finally, it is important to consider sex when assessing the relationship between air pollution and co-morbid asthma and overweight. Villarreal-Calderon et al[357] reported that males spend significantly more time outdoors on weekdays and weekends than their female peers, regardless of age. This finding among others[185,358,359] reveals air pollution exposure as greater in males relative to females. Section 1.5.2 also discusses the risk of co-morbid asthma and overweight as more likely in males compared to females. Though the evidence as a whole is suggestive of a stronger air pollution and co-morbid asthma and overweight association among males, this relationship has yet to be compared by sex.

2.2 Specific Objectives

Objective 1

The first goal of this thesis is to assess:

a) The relationship between air pollution concentrations and asthma in adolescents.

b) The relationship between air pollution concentrations and overweight in adolescents.

Objective 2

The second objective of this thesis is to assess the relationship between air pollution concentrations and co-morbid asthma and overweight in adolescents.

Objective 3

The third objective of this thesis is to assess if the effect of air pollution concentrations on co-morbid asthma and overweight is different for:

(a) Adolescents residing in an urban core and those not residing in an urban core.
(b) Adolescents residing in a high versus low income household.
(c) Younger versus older adolescents.
(d) Males and females.

2.3 Hypotheses

Objective 1

Based on previous literature, it is expected that as air pollution concentrations increase, asthma in adolescents is more likely to increase. Similarly, a significant positive association between air pollution concentrations and overweight in adolescents is expected.

Objective 2

No previous studies have examined the effect of air pollution on co-morbid asthma and overweight in adolescents. It is hypothesized that as air pollution concentrations increase, co-morbid asthma and overweight is more likely to increase.

Objective 3

(a) Urban core: It is expected that the association between air pollution concentrations and concurrent asthma and overweight will be different for

adolescents residing in an urban core and non-urban core. Specifically, it is hypothesized that as air pollution concentrations increase, co-morbid asthma and overweight in urban core adolescents is more likely to increase. No such association is anticipated among adolescents living in a non-urban core area.

(b) Income: It is hypothesized that the relationship between air pollution and co-morbid asthma and overweight will be positive for both high and low household income adolescents; however, adolescents from low income households are expected to have a higher probability of co-morbid asthma and overweight than high income adolescents across all air pollution concentrations.

(c) Age: It is expected that the effect of air pollution concentrations on co-morbid asthma and overweight will be positive in younger and older adolescents; however, it is anticipated that the probability of having both conditions will be higher in older adolescents than among those who are younger, at all pollution concentrations.

(d) Sex: It is hypothesized that the association between air pollution and concurrent asthma and overweight will be different for males and females. Specifically, it is expected that as air pollution concentrations increase, co-morbid asthma and overweight is more likely to increase in both males and females; however, this association is expected to be stronger in males than females.

Chapter 3

3 Methods

This thesis assessed the effects of air pollution concentrations on asthma, overweight, and co-morbid asthma and overweight, and whether the air pollution and co-morbid asthma and overweight relationship is modified by urban core status, income, age, and sex. This chapter begins with an overview of the data and study population used in this thesis (Section 3.1). Following is an overview of the measurement instruments used in the analysis (Section 3.2), and a detailed description of all preliminary and regression analyses performed (Section 3.3). This chapter concludes with a discussion in Section 3.4 of other statistical considerations such as the software and estimation method used, measures of model fit, missing data, and survey weights.

3.1 Data Sources and Study Population

Three data sources were used to assess the effect of air pollution on co-morbid asthma and overweight among adolescents: (1) the Canadian Community Health Survey (CCHS)[360] was used to measure the outcome variables of interest and their associated covariates, as well as (2) the Environment Canada 2009 National Pollutant Release Inventory (NPRI)[361] and (3) 1996 to 2000 meteorological data[362] which were used to measure exposure to air pollutionat the postal code level.

CCHS: The CCHS is a cross-sectional survey that collects health status, health determinant, and health care utilization information for the population of Canada. The CCHS was conducted biennially from 2001 through 2005, and starting in 2007 data collection was executed annually. For the present thesis, five annual data files from 2007 through 2011 were combined to increase the sample size. The CCHS target population were persons aged 12 years and older living in private dwellings in the 10 provinces and three territories. This target population excluded persons living on Indian Reserves or Crown lands, those residing in institutions, full time members of the Canadian Forces, and those residing in certain remote regions, resulting in 98% coverage of the Canadian population. The survey was predetermined to consist of approximately 130,000

respondents over a two year period. Computer-assisted interviewing was used to collect survey data. CCHS employed two different modes of computer-assisted interviewing: computer-assisted personal interviewing (CAPI) was used to conduct interviews in person, whereas computer-assisted telephone interviewing (CATI) conducted interviews via telephone. More detailed information about the CCHS can be found in publicly available user guides, provided by Statistics Canada.[360]

NPRI: $PM_{2.5}$ emissions data were obtained from the Environment Canada 2009 NPRI, a federal inventory of industrial pollutant releases to air, water, and land disposals and transfers for recycling in 2009. This inventory is publicly accessible and includes information collected from facilities that meet compulsory reporting requirements for over 300 substances, including key air pollutant emission estimates.

NPRI data have increasingly achieved and maintained a high level of quality by ensuring data relevance, accuracy, reliability, completeness, understandability, accessibility, and timeliness.[363] Industries that meet NPRI reporting requirements are necessitated by law to submit information that fit these dimensions of data quality; penalties are given to those that do not report on time and submit false or misleading emissions information.

Meteorological data: Meteorological data were obtained from Aermod-ready surface and upper air datasets, created by Environment Canada.[362] The surface data site was located at the London International Airport in London, Ontario, and the upper air data station was located at White Lake, Michigan. The surface meteorological sites used ceiling height, wind speed, wind direction, air temperature, total cloud opacity, and total cloud amount, while taking into account three different wind independent surface conditions, from 1996 to 2000. These three surface parameters were all set to urban values, a 50/50 mixture of coniferous and deciduous forests, and a 45/45/5/5 mixture of grassland, cultivated land, coniferous forests, and deciduous forests, respectively.

The surface meteorological data were pre-processed to yield a minimum wind speed of about 1 m/s, and to reduce missing data. These pre-processing steps involved setting hours with calm (equal to zero) or very low wind speeds (i.e., less than 4 km/h) to 4 km/h, setting calm wind directions to a "missing" value, and applying linear interpolation

to meteorological elements that had up to six consecutive missing hours. If there were more than 5% missing data after the above processing, imputation was performed using data from the nearest station with similar geographic conditions.

Study Population: All analyses were conducted on adolescents between the ages of 12 and 18 years residing in southwestern Ontario, which is defined as a sub region of southern Ontario in the province of Ontario, Canada. The city of London is the geographic center of this region. It extends north to south from the Bruce Peninsula to Lake Erie shorelines and east to south-west from Guelph to Windsor. Its population in 2011 was estimated at approximately 3,514,700, accounting for 32.1% of Ontario's entire population. The CCHS provides a categorical measure for the health region associated with the postal code residence of each respondent. The 14 CCHS health regions corresponding to southwestern Ontario are the Brant County, Elgin-St. Thomas, Grey Bruce, Haldimand-Norfolk, Halton Regional, Huron County, Chatham-Kent, Lambton, Middlesex-London, Oxford County, Perth District, Waterloo, Wellington-Dufferin-Guelph, and Windsor Essex County health units.

Since paediatric BMI does not hold its usual interpretation during pregnancy due to significant physiological changes, adolescents who were pregnant at the time of the survey were excluded from the analysis. Based on all the above inclusion/exclusion criteria, the sample size and response rates for each survey year are provided in Appendix A. The final sample consisted of selected adolescents residing in southwestern Ontario, who responded to any of the five CCHS survey cycles, 2007 through 2011 (n=2,974).

3.2 Measurement Instruments

This section describes how the outcome and exposure variables, and their associated covariates, used in the analysis were measured.

Asthma: Across all CCHS cycles, self-reported asthma status was measured using a binary variable representing the question "Do you have asthma?" that can be answered "Yes" or "No". This variable was re-coded as Yes = 1 and No = 0 (reference category).

Those that responded "Don't know", "Refusal", or chose not to answer the question (all missing data) were excluded from the analysis.

Overweight: Overweight was assessed using BMI, which was calculated as weight in kilograms divided by height in metres squared (kg/m^2). The CCHS provided self-reported values for weight and height (without shoes on). The IOTF growth curve, providing age- and sex-specific BMI cut-off points,[38] was then used to determine overweight status. This variable was coded as Yes = 1 and No = 0, indicating not being overweight as the reference category.

Respondents with missing data for height and weight were excluded from the analysis, since their BMI could not be determined. Adolescents with biologically implausible values for height, weight, and BMI as defined by the CDC[364] were also excluded from the analysis.

Asthma and Overweight: The binary indicator for co-morbid asthma and overweight was created by grouping respondents into two categories. These categories corresponded to being both asthmatic and overweight (coded as Yes = 1) and not being both asthmatic and overweight (coded as No = 0; the reference group). Adolescents with missing data for either of the separate variables, asthma and overweight, were considered "missing" for this co-morbid indicator and excluded from the analysis.

Air pollution: For the purposes of this study, air pollution exposure was measured using estimates of $PM_{2.5}$. $PM_{2.5}$ exposure estimates were computed by researchers at the Human Environments Analysis Laboratory (HEAL) at Western University Canada.[365] Industrial $PM_{2.5}$ emissions data released from the 2009 NPRI were combined with local meteorological data (1996 to 2000 surface and upper air datasets for southwestern Ontario), and modelled in Aermod.[366] Then coupled with ArcGIS,[367] the output of this entire modelling process produced a continuous variable estimating 2009 $PM_{2.5}$ concentration values ($\mu g/m^3$) at the postal code centroid in southwestern Ontario. These values were modelled at a 24-hour averaging period as the Ontario Ministry of the Environment measures the Ambient Air Quality Criteria (AAQC) for particulate matter on a 24-hour averaging time. The AAQC for $PM_{2.5}$ is 30 $\mu g/m^3$ for a 24 hour averaging

period.[368] Although this thesis examined outcome data collected from 2007 to 2011, and exposure data measured in 2009, $PM_{2.5}$ is relatively stable over a five year span.

The $PM_{2.5}$ exposure data are representative of only industrial sources. $PM_{2.5}$ values calculated for each postal code should thus be interpreted as concentrations relative (not absolute) to all other postal code areas in southwestern Ontario.

$PM_{2.5}$ had a considerable positively skewed distribution. Outliers were identified as values beyond four standard deviations (SD) around the weighted mean of $PM_{2.5}$[369]; these comprised of 1.01% (n=27) of the data points. Outliers were then recoded to these cut-off values (mean + 4 SDs = 1.83755 $\mu g/m^3$). A quadratic variable for $PM_{2.5}$ was computed by squaring the above continuous variable, to explore a potential nonlinear effect of $PM_{2.5}$ concentrations in each study objective.

Urban Core: Urban core status was operationalized as a binary variable, based on the CCHS variable measuring urban and rural areas of residence. Each respondent was classified as residing in a rural area, primary urban core, urban fringe, urban area outside a census metropolitan area/census agglomeration, secondary urban core, or mix of urban and rural areas. For this study, the urban core variable was created by collapsing this CCHS variable into two categories: residing in a primary or secondary urban core (coded as Yes = 1), or not residing in these two urban core areas (representative of the remaining four geographic areas of residence; coded as No = 0; the reference category).

Income: Income was approximated using the CCHS variable that groups respondents' total household income into 12 categories in the 2007 and 2008 surveys, 14 categories in the 2009 and 2010 surveys, and 15 categories in 2011. Thus, the original groups were re-coded to match the coding of 2007 and 2008, into the following categories: 1 = No income; 2 = Less than $5,000; 3 = $5,000 to $9,999; 4 = $10,000 to $14,999; 5 = $15,000 to $19,999; 6 = $20,000 to $29,999; 7 = $30,000 to $39,999; 8 = $40,000 to $49,999; 9 = $50,000 to $59,999; 10 = $60,000 to $79,999; 11 = $80,000 to $99,999; 12 = $100,000 or more. Respondents with missing values (19.9%; n=592) were assigned to one of 12 income categories based on Statistics Canada 2006 Census data reporting median total household income before taxes and deductions for each forward sortation area in

southwestern Ontario.[370] This variable was treated as continuous in the present thesis, and was centred around its weighted mean to improve the interpretability of the intercept in the regression analysis.

To assess whether income modifies the association between $PM_{2.5}$ and co-morbid asthma and overweight, the continuous indicator for income was also categorized into two groups: less than $60,000 (coded lower = 0; the reference category) and greater than or equal to $60,000 (coded higher = 1). The value of $60,000 was used based on Ontario's 2005 median total household income before taxes and deductions of $60,455.[370] Even though this median value was used to measure "higher" versus "lower" income, it is recognized that this value is higher than Canada's 2005 before-tax low income cut-offs (often used to estimate poverty), ranging from $14,313 to $55,022 according to community and family size.[371]

Age: The CCHS provided a continuous measure of age in years by computing the difference between the date of interview and respondent's date of birth. To improve the interpretability of the intercept in the regression analysis, age was centered by subtracting the constant 12 from every value of the variable (redefining the 0 point as the youngest adolescent age).

To assess whether age modifies the association between $PM_{2.5}$ and co-morbid asthma and overweight, the continuous indicator for age was categorized into two groups: 12 to 15 years (coded younger = 0; the reference category) and 16 to 18 years (coded older = 1).

Sex: Across all CCHS cycles, this binary variable composed of two categories, Male and Female. Sex was re-coded as Male = 1 and Female = 0 (the reference category).

3.3 Statistical Analysis

Data Linkage: Before any statistical analyses were carried out, the $PM_{2.5}$ exposure and CCHS outcome data were linked using a postal code variable present in both datasets. In the CCHS, this variable represented each respondent's postal code of residence, and in the $PM_{2.5}$ exposure dataset, this variable represented all 58,632 postal codes in

southwestern Ontario at which concentration values of $PM_{2.5}$ were measured. The linkage step was also performed to select adolescents only residing in southwestern Ontario.

Preliminary Analysis: The prevalence of asthma, overweight, and co-morbid asthma and overweight was estimated for all adolescents aged 12 to 18 years residing in southwestern Ontario, Ontario, and Canada and compared across urban core residence status, household income levels, adolescent age groups, and sex. Descriptive statistics were computed for the pollution exposure, confounding, and effect modifier variables. This included the calculation of frequencies for categorical variables (urban core status, income, age and sex), and means and standard deviations for continuous variables ($PM_{2.5}$, income and age).

Regression Analysis: Logistic regression was used to assess the three study objectives outlined in Section 2.2. This statistical technique models the effect of one or a set of independent variables on the likelihood of a single binary outcome. Independent variables can be continuous or categorical.

The equation for the multiple logistic regression model is as follows:

$$logit(\pi_i) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_n X_n$$

where π_i is the probability of the outcome

X_i (i = 1, ... , n) are the independent variables

β_0 is the intercept

β_i (i = 1, ... , n) are the slope coefficients (also called regression parameters)

$logit$ is the ln(odds of the outcome); that is, $\ln\left(\frac{\pi_i}{1-\pi_i}\right)$

The intercept (β_0) denotes the log odds of the outcome when $X_i = 0$ (after centering variables where required). Given the logistic regression equation above, exponentiating the intercept gives us the odds of the outcome when $X_i = 0$.

When interpreting the effect of a continuous independent variable, exponentiating a regression coefficient (β_i) estimates the odds ratio of the outcome for every one-unit increase in X_i, adjusting for all other independent variables in the model.

For categorical independent variables, $e^{(\beta_i)}$ is the odds ratio of the outcome comparing the higher category of X_i to its reference category (e.g., males vs. females), adjusted for all other independent variables in the model.

Objective 1

The first objective examined the relationships between $PM_{2.5}$ concentrations and two outcomes in adolescents: (1) asthma; and (2) overweight. The first set of regression models measured the effect of $PM_{2.5}$ on asthma. The second set of regression models measured the effect of $PM_{2.5}$ on overweight. Past research suggests that air pollution exposure is associated with geographic location, income, age, and sex (see Section 2.1). These four factors are also risk factors of paediatric asthma[10,26,341,372-374] and paediatric overweight.[357,375-377] As such, the effects of $PM_{2.5}$ on both outcomes, adjusted for the effects of the covariates urban core status, continuous income, continuous age, and sex, were also estimated. For each crude and adjusted model, the linear effect of $PM_{2.5}$ was evaluated by default. All results (significant or non-significant) from these models will be discussed accordingly. The crude and adjusted quadratic effects of $PM_{2.5}$ were also assessed; however, only statistically significant results from these models will be discussed.

The predicted probabilities of separate asthma and overweight were computed across a range of $PM_{2.5}$ exposure levels. Predicted probabilities were calculated using the intercept and regression coefficients obtained from the unadjusted default linear models for the associations between $PM_{2.5}$ and these two outcomes. Unadjusted, instead of adjusted, probabilities were reported to allow for comparison of probabilities across all study objectives, and because the main effects are the primary focus of this study. For each association, if results from the quadratic model were statistically significant, the predicted probabilities for the unadjusted curvilinear effect were computed in place of those for the linear effect. For each percentile value of $PM_{2.5}$, the sum of the natural logarithm of the

odds was first calculated using the first equation below. Given the second formula below, the result of the previous step was converted to odds by exponentiation, and the odds were then transformed to probabilities.

$$logit(\pi_i) = \beta_0 + \beta_1 PM_{2.5i}$$

$$\Pr(asthma\ and\ overweight|PM_{2.5} = X_i) = \frac{\exp(\beta_0 + \beta_1 X_i)}{1 + \exp(\beta_0 + \beta_1 X_i)}$$

The latter formula denotes the probability that an adolescent has asthma and is overweight, separately, at a given $PM_{2.5}$ exposure level. These predicted probabilities were plotted separately for each model.

Objective 2

The second objective was to estimate an overall relationship between $PM_{2.5}$ concentrations and co-morbid asthma and overweight in adolescents. This was achieved using logistic regression that measured the effect of $PM_{2.5}$ on the asthma and overweight variable. The effect of $PM_{2.5}$ adjusted for urban core status, continuous income, continuous age, and sex was also evaluated. For all crude and adjusted associations, both the linear and quadratic effects of $PM_{2.5}$ were assessed. The linear models were examined by default, whereas quadratic models were conducted as an additional test.

Using the formulas provided above, the crude predicted probabilities of co-morbid asthma and overweight were calculated and plotted across a range of $PM_{2.5}$ exposure levels.

Objective 3

The third objective explored whether the association between $PM_{2.5}$ concentrations and co-morbid asthma and overweight in adolescents was different across four factors: (1) urban core residence status; (2) income; (3) age; and (4) sex. This was accomplished using four sets of unadjusted and adjusted logistic regression models that assessed the presence of interaction between $PM_{2.5}$ and one of the modifiers listed above at a time. The remaining three factors were also kept in the adjusted models as confounders. Models

testing for the interaction between $PM_{2.5}$ and either income or age used categorical, instead of continuous, measures of these two individual-level characteristics (see Section 3.2). For each set of interaction models, if the results were not statistically significant, then the main $PM_{2.5}$ and co-morbid asthma and overweight association controlling for the covariate of interest (parallel effect) was tested. Both the linear and quadratic effects of $PM_{2.5}$ were estimated for all models. The linear models were examined by default, whereas quadratic models were conducted as an additional test.

The predicted probabilities of co-morbid asthma and overweight were computed across a range of $PM_{2.5}$ exposure levels. Using the log odds obtained from the unadjusted interaction models, probabilities were calculated for the following groups of adolescents: (1) those residing in an urban core and those not residing in an urban core; (2) those residing in a higher income household and those residing in a lower income household; (3) younger and older; and (4) males and females. If the results from an interaction model were not statistically significant (see above), then predicted probabilities for the main association controlling for the covariate of interest (urban core status, categorical income, categorical age, or sex) were computed instead. The formulas used to calculate predicted probabilities are provided in the Objective 1 section above; however, the addition of the regression term for the covariate of interest (e.g., $\beta_2 sex_i$) is required, and if significant, the interaction term between $PM_{2.5}$ and the modifier of interest (e.g., $\beta_3 PM_{2.5i} \times sex_i$). Finally, predicted probabilities were plotted separately for each model, and within each model, separately for the stratified groups of adolescents (e.g., males and females).

3.4 Other Statistical Considerations

Software and Data Access: All preliminary analyses and main analyses were executed using SAS 9.4 software. These analyses were conducted at the Research Data Centres at Western University and York University.

Assessing Model Fit: For the first and second objective, the fit of all sets of analogous crude and adjusted models were compared. For the third objective, all curvilinear interaction models were compared to their nested linear interaction models. Likelihood ratio tests were used to compare the fit of these models.

The likelihood ratio test is a type of chi-square difference test that uses the log likelihood values and degrees of freedom for each of the models being compared. After defining the nested models specified by the null and alternative hypotheses, the likelihood ratio test is calculated via the following formula:

$$\chi^2_{df} = -2L_O - (-2L_A)$$

where L_O is the log likelihood for the model specified under the null hypothesis

L_A is the log likelihood for the model specified under the alternative hypothesis

df is the difference between the degrees of freedom in the models specified under the null and alternative hypotheses.

The larger the value of the test statistic (greater difference between L_O and L_A), the better the fit of the alternative model with respect to the null.

Missing Data: A small percentage of respondents, 0.1% (n=3), 9.6% (n=286), and 9.7% (n=289) had missing data for the asthma, overweight, and co-morbid asthma and overweight variables, respectively. Considering these variables are all outcomes of interest, these individuals (n=289) were excluded from all preliminary and main analyses, reducing the final sample size of 2,974 to 2,685 (see Section 3.1). Due to the imputation method implemented using Statistics Canada Census data (see Section 3.2), the indicator for income had no missing data in all analyses. The remaining analysis variables, $PM_{2.5}$, urban core, age, and sex, had no missing data.

Since almost 10% of the final sample were excluded, respondents with and without missing outcome data (n=289 and n=2,685, respectively) were compared on all covariates. T-tests for continuous variables and Pearson's chi-square tests for categorical variables were calculated to assess potential differences that could impact the results. Results from this analysis are provided in Appendix B.

Survey Weights: When sampling individuals to participate in the CCHS, there were unequal probabilities of selection and different proportions of individuals that chose not

to respond across each survey cycle. Statistics Canada provided sampling weights for each cycle to ensure analysis estimates are representative of the Canadian population.

All sampling weights were rescaled after applying the study population inclusion/exclusion criteria, after removing cases with missing data, and prior to merging the CCHS survey files for analysis. For each cycle, weights were adjusted by dividing each individual's sampling weight by the mean sampling weight of the total eligible respondents. All analyses, including preliminary, and logistic regression analyses assessing the three study objectives, were conducted using these adjusted weights.

Chapter 4

4 Results

Descriptive characteristics of the sample are first presented in this chapter, including the prevalence of asthma, overweight, and both conditions (Section 4.1). Following is a discussion of the association between $PM_{2.5}$ concentrations and asthma and overweight separately and simultaneously (Sections 4.2 and 4.3). This chapter concludes with a discussion of whether the relationship between $PM_{2.5}$ and co-morbid asthma and overweight is modified by urban core status, income, age, and sex (Section 4.4).

4.1 Sample Characteristics

Regional Differences in Outcome Variables: Among the adolescent population aged 12 to 18 years residing in Canada, 11.6% had asthma, 21.7% were overweight, and 3.0% had both conditions, whereas in Ontario, 11.3% had asthma, 22.3% were overweight, and 2.8% had both conditions (Table 1). Among adolescents residing in southwestern Ontario, 11.6% were asthmatic; 25.0% were overweight; 3.2% had both conditions (Table 1). While the prevalence of asthma and both conditions were relatively similar across these three regions, overweight prevalence in southwestern Ontario was higher than that of Ontario and Canada.

Table 1: Separate and co-morbid asthma and overweight prevalence in adolescent respondents to the CCHS in southwestern Ontario, Ontario, and Canada.

Region N (%)			
	Southwestern Ontario	Ontario	Canada
Asthma			
Yes	310 (11.6%)	1,135 (11.3%)	3,320 (11.6%)
No	2,375 (88.4%)	8,892 (88.7%)	25,388 (88.4%)
Total	2,685	10,027	28,708
Overweight			
Yes	671 (25.0%)	2,236 (22.3%)	6,227 (21.7%)
No	2,014 (75.0%)	7,791 (77.7%)	22,481 (78.3%)
Total	2,685	10,027	28,708
Asthma and Overweight			
Yes	86 (3.2%)	285 (2.8%)	846 (3.0%)
No	2,599 (96.8%)	9,742 (97.2%)	27,862 (97.0%)

Covariates: A total of 2,685 respondents between the ages 12 and 18 years residing in southwestern Ontario were analyzed in this study. The descriptive characteristics of these adolescents are provided in Table 2. Fifty-three percent of the sample were male. About two thirds (64.9%) of the respondents resided in an urban core area, and 61.5% of respondents had a household income greater than or equal to $60,000. The average age was 15.1 ± 1.9 years, with 54.7% of adolescents between 12 and 15 years, and 45.3% between 16 and 18 years. The average $PM_{2.5}$ exposure concentration was 0.29 ± 0.29 $\mu g/m^3$.

Table 2: Characteristics of adolescent respondents to the CCHS who reside in southwestern Ontario.

	Frequency (%)
Urban core residence	
Yes	1,742 (64.9%)
No	943 (35.1%)
Income	
Higher (Greater than or equal to $60,000)	1,650 (61.5%)
Lower (Less than $60,000)	1,035 (38.5%)
Age	
12-15 years	1,469 (54.7%)
16-18 years	1,216 (45.3%)
Sex	
Male	1,426 (53.1%)
Female	1,259 (46.9%)
	Mean (SD)
$PM_{2.5}$ exposure	0.29 (0.29)
Income	9.7 (2.2)
Age	15.1 (1.9)

Abbreviations: SD (standard deviation); $PM_{2.5}$ (particulate matter with an aerodynamic diameter of 2.5 μm or less, $\mu g/m^3$)

Outcome Variables by Urban Core Indicator: Asthma prevalence was relatively higher in those residing in an urban core area (12.1% versus 10.5% in non-urban core area), whereas overweight prevalence was higher in those residing in a non-urban core area (26.3% versus 24.3%); see Table 3. The prevalence of co-morbid asthma and overweight were similar across urban core and non-urban core areas (3.4% versus 2.9%, respectively). The chi-square tests for differences across urban core status were not statistically significant for asthma (χ^2=1.7210, p=0.1896), overweight (χ^2=1.2558, p=0.2624), and both conditions (χ^2=0.4470, p=0.5038).

Table 3: Separate and co-morbid asthma and overweight across urban core residence status among adolescent respondents to the CCHS residing in southwestern Ontario.

Urban Core Status N (%)		
	Urban core	Non-urban core
Asthma (χ^2=1.7210, p=0.1896)		
Yes	211 (12.1%)	99 (10.5%)
No	1,531 (87.9%)	844 (89.5%)
Total	1,742	943
Overweight (χ^2=1.2558, p=0.2624)		
Yes	423 (24.3%)	248 (26.3%)
No	1,319 (75.7%)	695 (73.7%)
Total	1,742	943
Asthma and Overweight (χ^2=0.4470, p=0.5038)		
Yes	59 (3.4%)	27 (2.9%)
No	1,683 (96.6%)	916 (97.1%)
Total	1,742	943

Outcome Variables by Income Groups: Asthma prevalence for adolescents living in a higher income household was 11.5%, and for those living in a lower income household, 11.7%; see Table 4. The chi-square test for differences across income levels was not statistically significant (χ^2 = 0.0467, p = 0.8290). Overweight prevalence in adolescents residing in lower income households was higher than that among adolescents residing in higher income households (27.5% versus 23.4%). The chi-square test for differences across income was statistically significant (χ^2=5.5948, p=0.0180). The prevalence of co-morbid asthma and overweight was 3.2% and 3.3% in higher versus lower income adolescents, respectively, with a non-significant chi-square test for differences, χ^2=0.0530, p=0.8179.

Table 4: Separate and co-morbid asthma and overweight across household income levels among adolescent respondents to the CCHS residing in southwestern Ontario.

Household Income Level N (%)		
	Higher	Lower
Asthma (χ^2=0.0467, p=0.8290)		
Yes	189 (11.5%)	121 (11.7%)
No	1,461 (88.5%)	914 (88.3%)
Total	1,650	1,035
Overweight (χ^2=5.5948, p=0.0180)		
Yes	386 (23.4%)	285 (27.5%)
No	1,264 (76.6%)	750 (72.5%)
Total	1,650	1,035
Asthma and Overweight (χ^2=0.0530, p=0.8179)		
Yes	52 (3.2%)	34 (3.3%)
No	1,598 (96.8%)	1,001 (96.7%)
Total	1,650	1,035

Outcome Variables by Age Groups: The prevalence of asthma for those aged 16 to 18 years, 13.0%, was higher than that among adolescents aged 12 to 15 years, 10.3% (Table 5). The chi-square test for differences across these adolescent age groups was statistically significant (χ^2=4.8345, p=0.0279). Adolescents aged 12 to 15 years and 16 to 18 years had an overweight prevalence of 26.1% and 23.7%, respectively. The chi-square test for differences in overweight across age groups was not statistically significant (χ^2=1.9985, p=0.1574). The prevalence of co-morbid asthma and overweight was higher in older versus younger adolescents (4.0% and 2.5%, respectively), with a significant chi-square test for differences, χ^2=4.6757, p=0.0306.

Table 5: Separate and co-morbid asthma and overweight across adolescent age groups among CCHS respondents residing in southwestern Ontario.

Age Group N (%)		
	12-15 years	16-18 years
Asthma (χ^2=4.8345, p=0.0279)		
Yes	152 (10.3%)	158 (13.0%)
No	1,317 (89.7%)	1,058 (87.0%)
Total	1,469	1,216
Overweight (χ^2=1.9985, p=0.1574)		
Yes	383 (26.1%)	288 (23.7%)
No	1,086 (73.9%)	928 (76.3%)
Total	1,469	1,216
Asthma and Overweight (χ^2=4.6757, p=0.0306)		
Yes	37 (2.5%)	49 (4.0%)
No	1,432 (97.5%)	1,167 (96.0%)
Total	1,469	1,216

Outcome Variables by Sex: Asthma prevalence was relatively higher in females (12.7% versus 10.5%), whereas overweight prevalence was notably higher in males (28.5% versus 21.0%); see Table 6. The prevalence of co-morbid asthma and overweight was similar for males and females (3.3% versus 3.1%, respectively). The chi-square test for differences across sex was not significant for asthma (χ^2=3.1967, p=0.0738), statistically significant for overweight (χ^2=20.3906, p<0.0001), and not significant for co-morbid asthma and overweight (χ^2=0.0465, p=0.8293).

Table 6: Separate and co-morbid asthma and overweight across sex among adolescent respondents to the CCHS residing in southwestern Ontario.

Sex N (%)		
	Males	Females
Asthma (χ^2=3.1967, p=0.0738)		
Yes	150 (10.5%)	160 (12.7%)
No	1,276 (89.5%)	1,099 (87.3%)
Total	1,426	1,259
Overweight (χ^2=20.3906, p<0.0001)		
Yes	407 (28.5%)	264 (21.0%)
No	1,019 (71.5%)	995 (79.0%)
Total	1,426	1,259
Asthma and Overweight (χ^2=0.0465, p=0.8293)		
Yes	47 (3.3%)	39 (3.1%)
No	1,379 (96.7%)	1,220 (96.9%)
Total	1,426	1,259

4.2 Effect of $PM_{2.5}$ on Separate Asthma and Overweight

The first objective of this thesis is to examine the relationship between $PM_{2.5}$ and asthma and $PM_{2.5}$ and overweight among adolescents. For each association, the linear and curvilinear effects of $PM_{2.5}$ were assessed using logistic regression, and their corresponding estimates are provided in Tables 7 and 8. As the linear models were examined by default, their results will be further described throughout this section and illustrated in Figure 2, regardless of statistical significance. Figure 2 was created via the conversion of log odds from the unadjusted linear models to predicted probabilities of asthma and overweight across a range of $PM_{2.5}$ exposure percentiles (see Section 3.3). For ease of interpretation, the figures displayed Sections 4.3 and 4.4 were also created using this method. Since all quadratic models were considered to be an additional test to the default linear models, their corresponding results are shown in Tables 7 and 8, but are not discussed, as none of them was statistically significant.

The effect of $PM_{2.5}$ on adolescent asthma in the unadjusted model was negative (OR 0.93, 95% CI 0.61-1.41; Table 7); see Figure 2. However, this effect was not statistically significant (p=0.7271). After controlling for urban core status, income, age, and sex, the effect of $PM_{2.5}$ on asthma remained non-significant (OR 0.89, 95% CI 0.58-1.37, p=0.5980; Table 7). A likelihood ratio test comparing the crude and adjusted model was also performed, and the results were not statistically significant ($0.05 \leq p < 0.10$).

The unadjusted odds ratio for overweight associated with a one $\mu g/m^3$ increase in $PM_{2.5}$ was 1.47 (95% CI 1.11-1.95; see Table 8), and statistically significant (p=0.0071). Figure 2 presents this positive effect in terms of expected probabilities of overweight, where it is observed that as $PM_{2.5}$ exposure levels increase, the probability that an adolescent is overweight increases. The $PM_{2.5}$ and overweight association remained significant after controlling for the effects of urban core status, income, age, and sex (OR 1.50, 95% CI 1.12-1.99, p=0.0059; Table 8). The likelihood ratio test comparing the crude and adjusted model was also statistically significant ($p<0.005$).

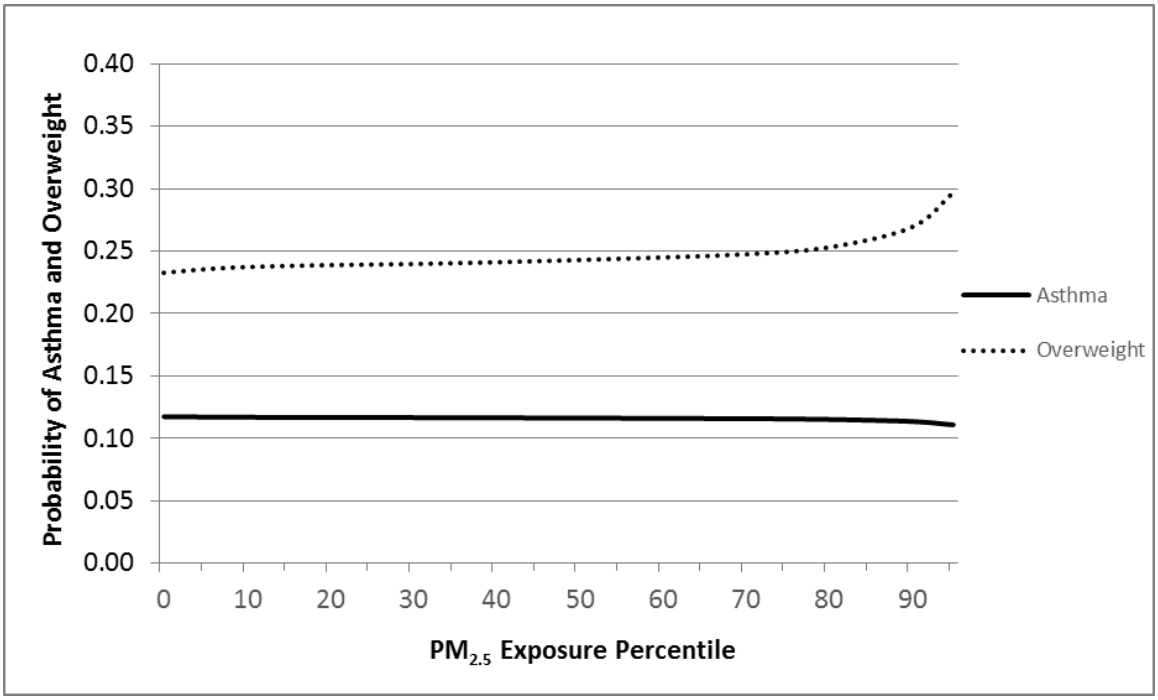

Figure 2: Crude predicted probabilities of separate asthma and overweight across $PM_{2.5}$ exposure percentiles among adolescents residing in southwestern Ontario.

Table 7: Logistic regression models exploring the effect of $PM_{2.5}$ on asthma among adolescents residing in southwestern Ontario.

		Log odds	SE	p
Linear Effect				
	Crude OR (95% CI)			
$PM_{2.5}$	0.93 (0.61, 1.41)	-0.0745	0.2136	0.7271
	Adjusted[a] OR (95% CI)			
$PM_{2.5}$	0.89 (0.58, 1.37)	-0.1168	0.2214	0.5980
Curvilinear Effect				
	Crude OR (95% CI)			
$PM_{2.5}$	1.29 (0.36, 4.70)	0.2556	0.6587	0.6980
$PM_{2.5}^2$	0.80 (0.34, 1.87)	-0.2282	0.4348	0.5997
	Adjusted[a] OR (95% CI)			
$PM_{2.5}$	0.96 (0.25, 3.69)	-0.0423	0.6876	0.9510
$PM_{2.5}^2$	0.95 (0.40, 2.27)	-0.0507	0.4434	0.9090

Note: Results significant at the 5% level ($p < 0.05$) are highlighted in bold.
Abbreviations: OR (odds ratio); CI (confidence interval); SE (standard error); p (probability); $PM_{2.5}$ (particulate matter with an aerodynamic diameter of 2.5 µm or less, $\mu g/m^3$)
[a]Adjusted for the effects of urban core status, income, age, and sex.

Table 8: Logistic regression models exploring the effect of $PM_{2.5}$ on overweight among adolescents residing in southwestern Ontario.

		Log odds	SE	p
Linear Effect				
	Crude OR (95% CI)			
$PM_{2.5}$	**1.47 (1.11, 1.95)**	**0.3857**	**0.1434**	**0.0071**
	Adjusted[a] OR (95% CI)			
$PM_{2.5}$	**1.50 (1.12, 1.99)**	**0.4030**	**0.1462**	**0.0059**
Curvilinear Effect				
	Crude OR (95% CI)			
$PM_{2.5}$	0.59 (0.24, 1.46)	-0.5361	0.4651	0.2490
$PM_{2.5}^2$	**1.83 (1.04, 3.22)**	**0.6042**	**0.2886**	**0.0363**
	Adjusted[a] OR (95% CI)			
$PM_{2.5}$	0.65 (0.25, 1.69)	-0.4297	0.4880	0.3786
$PM_{2.5}^2$	1.71 (0.95, 3.08)	0.5386	0.2998	0.0725

Note: Results significant at the 5% level ($p < 0.05$) are highlighted in bold.
Abbreviations: OR (odds ratio); CI (confidence interval); SE (standard error); p (probability); $PM_{2.5}$ (particulate matter with an aerodynamic diameter of 2.5 µm or less, $\mu g/m^3$)
[a]Adjusted for the effects of urban core status, income, age, and sex.

4.3 Overall Effect of $PM_{2.5}$ on Co-morbid Asthma and Overweight

The second objective of this thesis is to assess the relationship between $PM_{2.5}$ concentrations and co-morbid asthma and overweight in adolescents. Logistic regression was used to examine the linear and curvilinear effect of $PM_{2.5}$ on co-morbid asthma and overweight, and the corresponding estimates from both models are provided in Table 9. In this section, only results from the default linear models will be further discussed and illustrated in Figure 3 as unadjusted predicted probabilities of co-morbid asthma and overweight, regardless of statistical significance. Results from the curvilinear models are also presented in Table 9; however, none of them was significant.

The crude odds ratio for co-morbid asthma and overweight was 1.18 (95% CI 0.59-2.36; Table 9), but this effect was not statistically significant (p=0.6330); see Figure 3. After controlling for the effects of urban core status, income, age, and sex, the overall effect of $PM_{2.5}$ remained non-significant (OR 1.14, 95% CI 0.56-2.31, p=0.7187; Table 9). A likelihood ratio test was executed to compare the crude and adjusted model. This test also yielded a non-significant result (p>0.10).

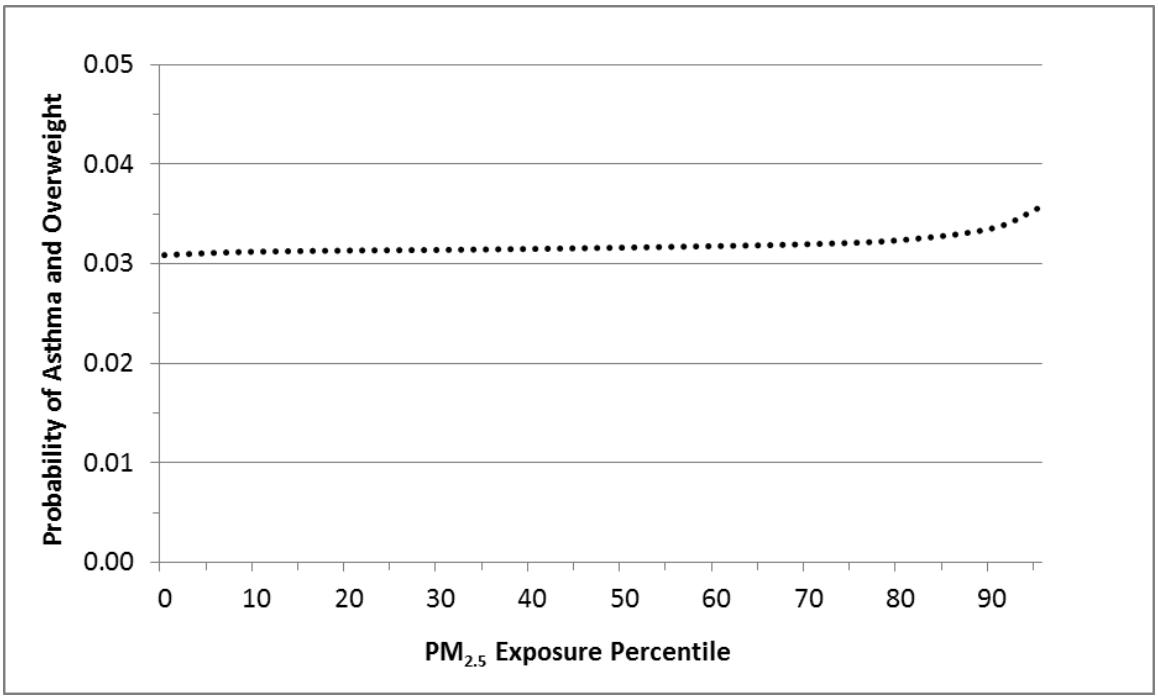

Figure 3: Crude predicted probabilities of co-morbid asthma and overweight across $PM_{2.5}$ exposure percentiles among adolescents residing in southwestern Ontario.

Table 9: Logistic regression models exploring the effect of $PM_{2.5}$ on co-morbid asthma and overweight among adolescents residing in southwestern Ontario.

		Log odds	SE	p
Linear Effect				
	Crude OR (95% CI)			
$PM_{2.5}$	1.18 (0.59, 2.36)	0.1679	0.3515	0.6330
	Adjusted[a] OR (95% CI)			
$PM_{2.5}$	1.14 (0.56, 2.31)	0.1303	0.3617	0.7187
Curvilinear Effect				
	Crude OR (95% CI)			
$PM_{2.5}$	0.57 (0.06, 5.27)	-0.5545	1.1311	0.6240
$PM_{2.5}^2$	1.59 (0.42, 6.03)	0.4648	0.6798	0.4942
	Adjusted[a] OR (95% CI)			
$PM_{2.5}$	0.43 (0.04, 4.43)	-0.8396	1.1874	0.4795
$PM_{2.5}^2$	1.85 (0.47, 7.33)	0.6156	0.7025	0.3808

Note: Results significant at the 5% level ($p < 0.05$) are highlighted in bold.
Abbreviations: OR (odds ratio); CI (confidence interval); SE (standard error); p (probability); $PM_{2.5}$ (particulate matter with an aerodynamic diameter of 2.5 µm or less, $\mu g/m^3$)
[a]Adjusted for the effects of urban core status, income, age, and sex.

4.4 Stratified Effect of $PM_{2.5}$ on Co-morbid Asthma and Overweight

The third objective of this thesis is to examine whether the effect of $PM_{2.5}$ concentrations on co-morbid asthma and overweight is different for the following groups of adolescents: (1) those residing in an urban core and those not residing in an urban core; (2) those residing in households with higher versus lower income; (3) younger and older; and (4) males and females. This was accomplished using four sets of linear and curvilinear logistic regression models that assess the presence of interaction between $PM_{2.5}$ and one of the following characteristics at a time: urban core status, income, age, and sex. If the interaction effect for each set of models was not statistically significant, then the overall linear and curvilinear $PM_{2.5}$ and co-morbid asthma and overweight relationship controlling for the covariate of interest, was examined. The estimates corresponding to all unadjusted models stated above are provided in Tables 10 to 13. Estimates from the adjusted models are presented in Appendix C. Regardless of statistical significance, results from the default linear models are further described throughout this section and illustrated in Figures 4 to 7 as crude predicted probabilities of co-morbid asthma and overweight. All of the quadratic models yielded non-significant results, and are therefore not discussed. Likelihood ratio tests were also performed to compare all curvilinear interaction models to their nested linear interaction models, and the results were not statistically significant ($p>0.10$).

Urban Core Status: The interaction effect between $PM_{2.5}$ and urban core status was statistically significant in the unadjusted linear model ($p=0.0138$; Table 10); that is, the $PM_{2.5}$ and co-morbid asthma and overweight association is significantly different for adolescents residing in urban core and non-urban core areas. This difference in the main association across urban core status is illustrated in Figure 4. Among adolescents residing in an urban core area, there is a slight increase in the probability of co-morbid asthma and overweight as $PM_{2.5}$ exposure concentrations increase. Conversely, the effect of $PM_{2.5}$ is quite pronounced among adolescents residing in a non-urban core area, where a substantial decrease in co-morbid asthma and overweight across increasing $PM_{2.5}$ levels is observed. The rate of decline in co-morbid asthma and overweight across $PM_{2.5}$ values is

much steeper for non-urban core adolescents than the rate of incline for their urban core peers, further indicating a non-parallel effect. After controlling for the effects of income, age, and sex, this linear interaction remained significant (p=0.0147; Appendix C).

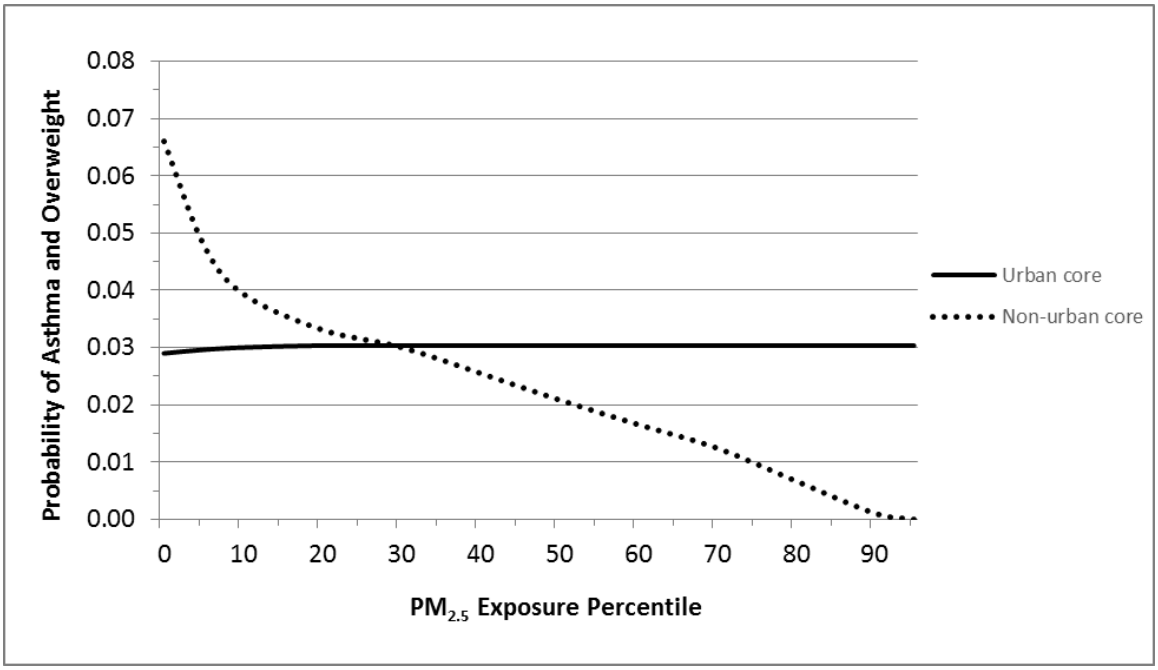

Figure 4: Crude predicted probabilities of co-morbid asthma and overweight across $PM_{2.5}$ exposure percentiles among adolescents residing in urban core and non-urban core areas in southwestern Ontario.

Table 10: Crude logistic regression models exploring whether the effect of $PM_{2.5}$ on co-morbid asthma and overweight is modified by urban core residence status among adolescents residing in southwestern Ontario.

	OR (95% CI)	Log odds	SE	p
Linear Effect				
$PM_{2.5}$	**0.00 (0.00, 0.28)**	**-8.0409**	**3.4600**	**0.0201**
Urban core (No=0)	**0.28 (0.10, 0.80)**	**-1.2780**	**0.5356**	**0.0170**
$PM_{2.5}$*urban core[a]	**5246.94 (5.74, 4796514.18)**	**8.5654**	**3.4786**	**0.0138**
Curvilinear Effect				
$PM_{2.5}$	0.00 (0.00, 1.87)	-9.2520	5.0394	0.0664
$PM_{2.5}^2$	22.11 (0.00, 115629306.70)	3.0961	7.8929	0.6949
Urban core (No=0)	**0.25 (0.07, 0.92)**	**-1.3933**	**0.6656**	**0.0363**
$PM_{2.5}$*urban core[a]	19335.54 (0.73, 514754167.50)	9.8697	5.1988	0.0576
$PM_{2.5}^2$*urban core[b]	0.04 (0.00, 240097.41)	-3.1545	7.9304	0.6908

Note: Results significant at the 5% level ($p < 0.05$) are highlighted in bold.
Abbreviations: OR (odds ratio); CI (confidence interval); SE (standard error); p (probability); $PM_{2.5}$ (particulate matter with an aerodynamic diameter of 2.5 μm or less, $\mu g/m^3$)
[a]Interaction between linear effect of $PM_{2.5}$ and urban core status.
[b]Interaction between curvilinear effect of $PM_{2.5}$ and urban core status.

Income: The interaction effect between $PM_{2.5}$ and income was not significant in the crude linear model (p=0.1821; Table 11); that is, the $PM_{2.5}$ and co-morbid asthma and overweight relationship is similar for adolescents residing in higher versus lower income households. Instead there was a non-significant, positive relationship between $PM_{2.5}$ exposure and co-morbid asthma and overweight for both higher and lower income adolescents (OR 1.18, 95% CI 0.59-2.35, p=0.6368; Table 11). However, the odds ratio for co-morbid asthma and overweight comparing higher to lower income adolescents was 0.95 (95% CI 0.61-1.48; Table 11) and not significant (p=0.8262). Figure 5 shows this parallel effect, where adolescents residing in higher income households are slightly less likely to have both conditions compared to lower income adolescents across all $PM_{2.5}$ concentrations. The interaction effect for the linear model remained non-significant after controlling for urban core status, age, and sex (p=0.1771; Appendix C).

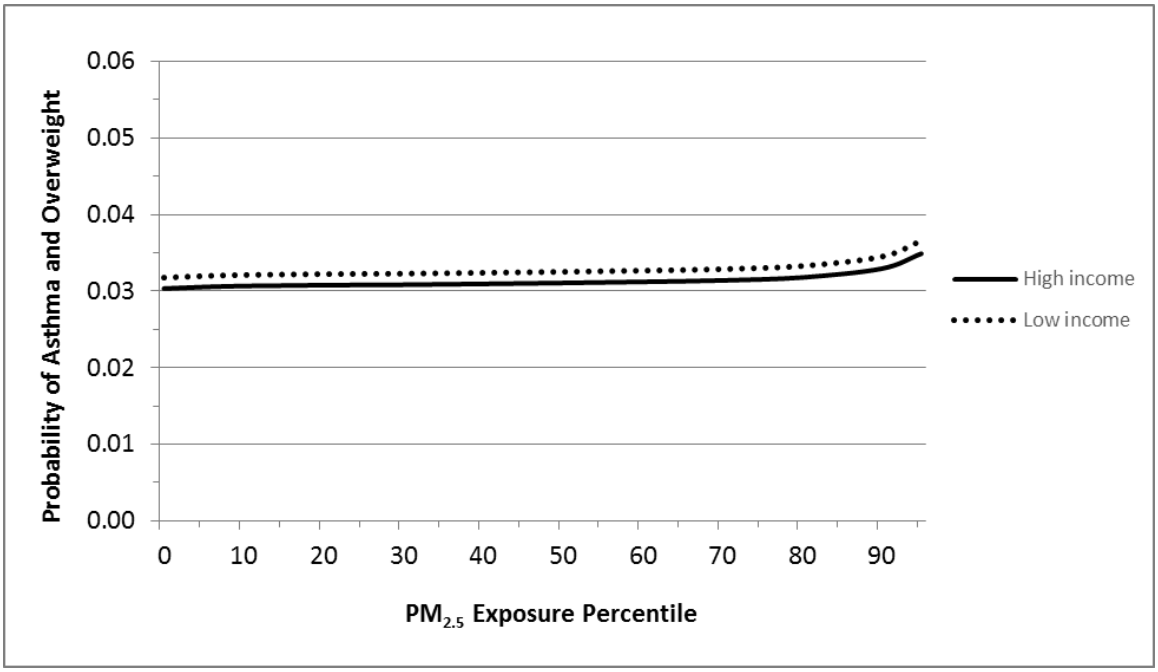

Figure 5: Crude predicted probabilities of co-morbid asthma and overweight across $PM_{2.5}$ exposure percentiles among adolescents residing in a higher and lower income household in southwestern Ontario.

Table 11: Crude logistic regression models exploring whether the effect of $PM_{2.5}$ on co-morbid asthma and overweight is modified by household income among adolescents residing in southwestern Ontario.

	OR (95% CI)	Log odds	SE	p
Model 1				
$PM_{2.5}$	0.52 (0.12, 2.38)	-0.6452	0.7708	0.4026
Income (Lower=0)	0.68 (0.36, 1.29)	-0.3868	0.3269	0.2367
$PM_{2.5}$*income	3.17 (0.58, 17.32)	1.1551	0.8657	0.1821
Model 2				
$PM_{2.5}$	0.11 (0.00, 6.46)	-2.1630	2.0554	0.2926
$PM_{2.5}^2$	2.91 (0.24, 35.85)	1.0686	1.2811	0.4042
Income (Lower=0)	0.54 (0.20, 1.48)	-0.6137	0.5118	0.2304
$PM_{2.5}$*income	12.21 (0.10, 1511.11)	2.5024	2.4583	0.3087
$PM_{2.5}^2$*income	0.38 (0.02, 7.39)	-0.9622	1.5114	0.5244
Model 3				
$PM_{2.5}$	1.18 (0.59, 2.35)	0.1661	0.3518	0.6368
Income (Lower=0)	0.95 (0.61, 1.48)	-0.0491	0.2236	0.8262
Model 4				
$PM_{2.5}$	0.57 (0.06, 5.23)	-0.5662	1.1328	0.6172
$PM_{2.5}^2$	1.60 (0.42, 6.08)	0.4711	0.6806	0.4889
Income (Lower=0)	0.95 (0.61, 1.47)	-0.0546	0.2238	0.8071

Note: Results significant at the 5% level ($p<0.05$) are highlighted in bold.
Abbreviations: OR (odds ratio); CI (confidence interval); SE (standard error); p (probability); $PM_{2.5}$ (particulate matter with an aerodynamic diameter of 2.5 µm or less, $\mu g/m^3$)
Models: (1) interaction between linear effect of $PM_{2.5}$ and income; (2) interaction between curvilinear effect of $PM_{2.5}$ and income; (3) linear effect of $PM_{2.5}$ controlling for the effect of income; (4) curvilinear effect of $PM_{2.5}$ controlling for the effect of income

Age: The interaction effect between $PM_{2.5}$ and age was not significant in the unadjusted linear model (p=0.0540; Table 12). This indicates a similar effect between adolescents aged 12 to 15 years and 16 to 18 years' probability of co-morbid asthma and overweight across increasing $PM_{2.5}$ concentrations. As $PM_{2.5}$ exposure levels increase, the probability of co-morbid asthma and overweight increases in both adolescent age groups (OR 1.17, 95% CI 0.58-2.33; Table 12). This overall effect was not significant (p=0.6653). However, the odds ratio for co-morbid asthma and overweight comparing older adolescents to younger adolescents was 1.60 (95% CI 1.04-2.47; Table 12) and statistically significant (p=0.0327). These results are illustrated in Figure 6, where older adolescents have a significantly higher probability of both conditions compared to their younger peers across all $PM_{2.5}$ concentrations. After adjusting for urban core status, income, and sex, the interaction for the linear model remained non-significant (p=0.0505; Appendix C).

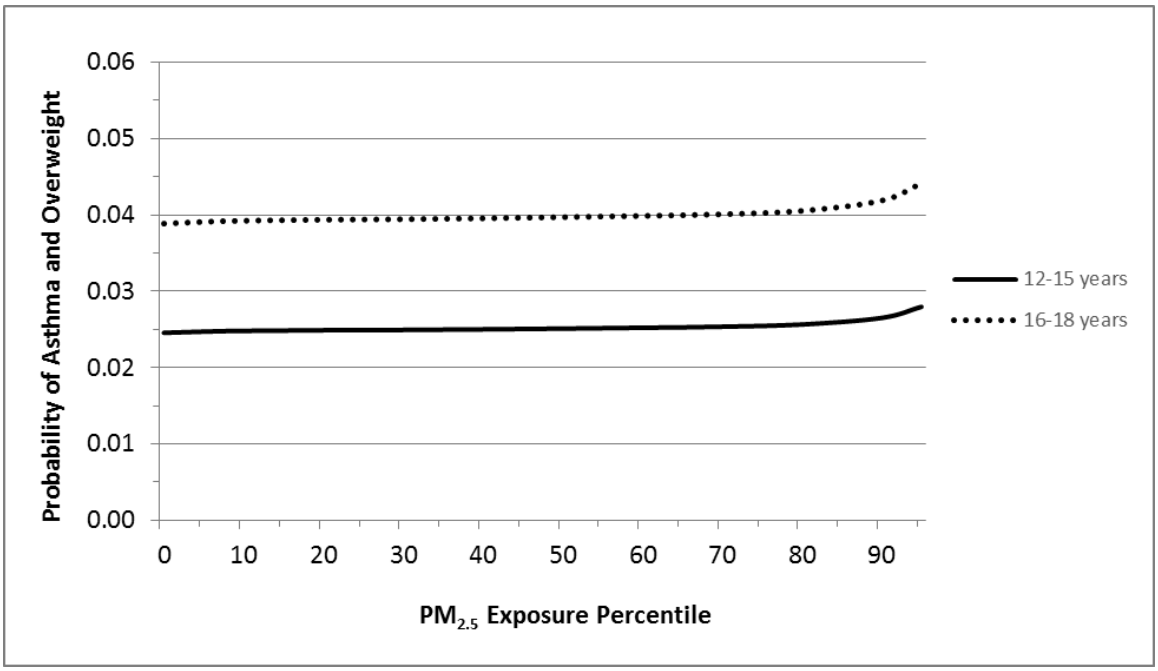

Figure 6: Crude predicted probabilities of co-morbid asthma and overweight across $PM_{2.5}$ exposure percentiles among adolescents aged 12 to 15 and 16 to 18 years residing in southwestern Ontario.

Table 12: Crude logistic regression models exploring whether the effect of $PM_{2.5}$ on co-morbid asthma and overweight is modified by age among adolescents residing in southwestern Ontario.

	OR (95% CI)	Log odds	SE	p
Model 1				
$PM_{2.5}$	2.20 (0.97, 4.97)	0.7876	0.4160	0.0584
Age (Younger=0)	**2.51 (1.35, 4.66)**	**0.9196**	**0.3157**	**0.0036**
$PM_{2.5}$*age	0.22 (0.05, 1.03)	-1.4918	0.7743	0.0540
Model 2				
$PM_{2.5}$	1.36 (0.06, 30.73)	0.3069	1.5910	0.8470
$PM_{2.5}^2$	1.34 (0.22, 8.11)	0.2902	0.9200	0.7524
Age (Younger=0)	2.43 (0.92, 6.41)	0.8863	0.4957	0.0738
$PM_{2.5}$*age	0.26 (0.00, 23.78)	-1.3588	2.3101	0.5564
$PM_{2.5}^2$*age	0.97 (0.05, 17.64)	-0.0254	1.4773	0.9863
Model 3				
$PM_{2.5}$	1.17 (0.58, 2.33)	0.1528	0.3531	0.6653
Age (Younger=0)	**1.60 (1.04, 2.47)**	**0.4714**	**0.2207**	**0.0327**
Model 4				
$PM_{2.5}$	0.55 (0.06, 4.94)	-0.6037	1.1235	0.5910
$PM_{2.5}^2$	1.63 (0.43, 6.11)	0.4874	0.6747	0.4701
Age (Younger=0)	**1.61 (1.04, 2.48)**	**0.4742**	**0.2208**	**0.0318**

Note: Results significant at the 5% level ($p<0.05$) are highlighted in bold.
Abbreviations: OR (odds ratio); CI (confidence interval); SE (standard error); p (probability); $PM_{2.5}$ (particulate matter with an aerodynamic diameter of 2.5 μm or less, $\mu g/m^3$)
Models: (1) interaction between linear effect of $PM_{2.5}$ and age; (2) interaction between curvilinear effect of $PM_{2.5}$ and age; (3) linear effect of $PM_{2.5}$ controlling for the effect of age; (4) curvilinear effect of $PM_{2.5}$ controlling for the effect of age

Sex: The interaction effect between $PM_{2.5}$ and sex was statistically significant in the unadjusted linear model (p=0.0121; Table 13); that is, the $PM_{2.5}$ and co-morbid asthma and overweight association is significantly different for male and female adolescents. This non-parallel effect is displayed in Figure 7. Among males, there is a slight increase in co-morbid asthma and overweight as $PM_{2.5}$ concentrations increase, whereas among females, there appears to be a considerable decrease in the probability of having both conditions across increasing $PM_{2.5}$ exposure concentrations. Females' rate of decline in co-morbid asthma and overweight is much steeper than the rate of incline observed in males. After adjusting for the effects of urban core status, income, and age, this linear interaction remained significant (p=0.0114; Appendix C).

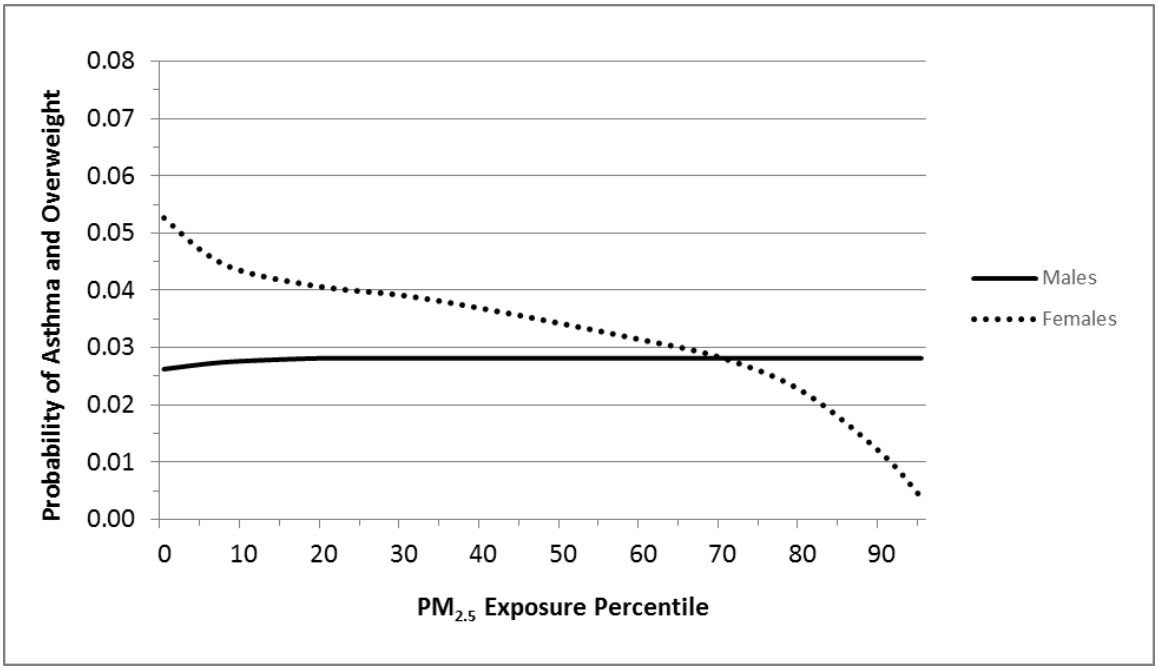

Figure 7: Crude predicted probabilities of co-morbid asthma and overweight across $PM_{2.5}$ exposure percentiles among male and female adolescents residing in southwestern Ontario.

Table 13: Crude logistic regression models exploring whether the effect of $PM_{2.5}$ on co-morbid asthma and overweight is modified by sex among adolescents residing in southwestern Ontario.

	OR (95% CI)	Log odds	SE	p
Linear Effect				
$PM_{2.5}$	**0.05 (0.00, 0.88)**	**-3.0415**	**1.4867**	**0.0408**
Sex (Female=0)	**0.40 (0.19, 0.86)**	**-0.9096**	**0.3899**	**0.0197**
$PM_{2.5}$*sex[a]	**46.42 (2.32, 928.62)**	**3.8377**	**1.5286**	**0.0121**
Curvilinear Effect				
$PM_{2.5}$	224.33 (0.00, 351457727.90)	5.4131	7.2779	0.4570
$PM_{2.5}^2$	0.00 (1.09×10^{-19}, 297836.51)	-15.5393	14.3592	0.2792
Sex (Female=0)	0.97 (0.17, 5.65)	-0.0304	0.8988	0.9730
$PM_{2.5}$*sex[a]	0.01 (0.00, 25801.81)	-4.3383	7.3963	0.5575
$PM_{2.5}^2$*sex[b]	4727466.53 (0.00, 8.23×10^{18})	15.3689	14.3804	0.2852

Note: Results significant at the 5% level ($p<0.05$) are highlighted in bold.
Abbreviations: OR (odds ratio); CI (confidence interval); SE (standard error); p (probability); $PM_{2.5}$ (particulate matter with an aerodynamic diameter of 2.5 μm or less, $\mu g/m^3$)
[a]Interaction between linear effect of $PM_{2.5}$ and sex.
[b]Interaction between curvilinear effect of $PM_{2.5}$ and sex.

Chapter 5

5 Discussion

The prevalence of paediatric asthma and overweight has increased over the past few decades. Children and adolescents who are overweight are more likely to develop asthma, and vice versa, indicating these conditions as co-morbid in paediatric populations. To effectively tackle this increasing co-morbidity, it is pertinent to understand and identify any potential root causes. Research to date has assessed the role of individual-level risk factors (e.g., income, sex). The main goal of this thesis was to alternatively consider the environment, specifically air pollution, as a potential underlying mechanism. This main goal consists of three specific objectives: 1) to examine the associations between air pollution and asthma and between air pollution and overweight in adolescents; 2) to examine the association between air pollution and co-morbid asthma and overweight in adolescents; and 3) to examine whether the association between air pollution and co-morbid asthma and overweight varies by urban core status, household income, age, and sex.

This chapter begins with a discussion of our findings pertaining to the study objectives mentioned above (Section 5.1). Possible mechanisms and explanations for our main findings are also offered in this section. Section 5.2 discusses the strengths of this study and Section 5.3 discusses study limitations. Finally, this chapter concludes with an overall summary of the present thesis and the implications of our work for practice and future research (Section 5.4).

5.1 Overview of Findings

5.1.1 Objective 1

Asthma

We hypothesized that exposure to air pollution would be positively associated with adolescent asthma. Our hypothesis was not confirmed. In our study, there was no association between $PM_{2.5}$ and asthma among adolescents. This finding is inconsistent

with previous literature, which has generally established air pollution as a risk factor for paediatric asthma.[16,201,207,267,378]

Studies reporting no association between air pollution and asthma have primarily measured community-average levels of pollution,[200,204,205,208] a limitation said to reduce exposure variation and consequentially drive estimates towards the null. These community-level findings are inconsistent with individual-level studies showing that air pollution, particularly traffic-related, is associated with both the incidence and prevalence of asthma.[200,208] The present study sought to validate findings from these individual-level studies. However, we did not measure traffic-related air pollution, illustrating a potential reason why our findings were not consistent with those from individual-level studies. Gasana et al[16] discussed that any conflicting epidemiological data on the air pollution and asthma association may be a result of using different instruments and indicators to measure air pollution (e.g., motor vehicles vs. industry, $PM_{2.5}$ vs. NO_2). Moreover, literature has suggested that air pollutants may play a part in causing paediatric asthma, mainly amongst those living or attending school in close proximity to areas of high motor-vehicle traffic.[16,200] Perhaps adolescents residing in closer proximity to industrial sites are also more likely to have asthma[379-381]; however, we did not explore this possibility.

Despite our findings, the previously mentioned causal mechanisms (e.g., airway inflammation, reduced lung function; Section 1.6.4), and large body of statistically significant results (see Section 1.6.4) generally favour a positive association between air pollution and asthma. More research is needed to determine whether industrial air pollution has a different influence on asthma than traffic-related pollution.

Overweight

We expected that exposure to air pollution would be positively associated with overweight in adolescents. Our hypothesis was confirmed with statistically significant results; that is, as $PM_{2.5}$ exposure levels increased, the probability that an adolescent is overweight increased. This study is the first to examine the effect of estimated air pollution on overweight in adolescents. There are, however, animal model studies that

have determined estimated air pollution exposure as a risk factor for overweight,[274,277,311,312] consistent with our findings. Our results are also supported by findings from studies that examined the effects of pre/perinatal air pollution exposure or indirect exposure to air pollution (e.g., traffic density) on overweight in humans.[17,159,287,317,319,322-324,328,329] Though further research needs to be done in order to validate our findings, based on the current literature (i.e., indirect air pollution, animal models), it is not surprising that we found this relationship to be positive and statistically significant.

Many studies have shown that exposure to $PM_{2.5}$ is associated with a systemic pro-inflammatory response.[191-193,382] This response largely takes place in adipose tissue, increasing the risk of obesity development.[274,340] Even short-term $PM_{2.5}$ exposure, in the presence of a normal diet, causes an increase in visceral and subcutaneous fat, and an increase in adipocyte size in both types of fat.[312] The above scientific data suggest that air pollution exposure alone may potentiate adiposity, and poses a potential mechanism for the findings in our study. Also, industrial pollution is popularly viewed as prominent and detrimental to air quality and general health.[383] This perception would likely alter the behaviours of parents and adolescents residing in close proximity to industrial sites, such as decreasing levels of outdoor physical activity to avoid exposure. The risk of overweight would consequently increase. This other possible mechanism is of utmost importance given the confluence of increasing levels of air pollution and shifts in diet/exercise in urban populations.[312]

Overall, our results and the supporting literature suggest there is a positive association between air pollution and overweight. However, more evidence on the effect of estimated air pollution on adolescent overweight is needed. If air pollution truly causes overweight, this would present a challenge for Canadian public health professionals by introducing yet another target to consider when developing strategies for overweight prevention and management.

5.1.2 Objective 2

We hypothesized that there would be a positive association between air pollution exposure and co-morbid asthma and overweight in adolescents. However, our findings did not support this hypothesis. We observed an increase in co-morbid asthma and overweight as $PM_{2.5}$ levels increased, however, this relationship was not statistically significant. No other study has examined the effect of air pollution on the incidence or prevalence of co-morbid asthma and overweight. Accordingly there is no body of evidence to support our findings.

Despite our non-significant results, there is still reason to believe that a positive association may exist. One of the hypotheses on why co-morbidities develop has been attributed to common risk factors that increase the likelihood of both conditions (Section 1.4.3). Previous literature has shown that environmental pollution may stimulate the onset and exacerbation of asthma, and may separately contribute to the growing rates of overweight (see Sections 1.6.4 and 1.6.5). These findings suggest air pollution is a risk factor that is common to both conditions. It would thus be expected that air pollution is associated with an increase in the prevalence of co-morbid asthma and overweight in paediatric populations. It is important to note, however, that the present study discovered a significant association between $PM_{2.5}$ and overweight, but no association between $PM_{2.5}$ and asthma. Since the presence of significant association between $PM_{2.5}$ and co-morbid asthma and overweight depends on $PM_{2.5}$ being a significant risk factor for each condition separately, it may not be surprising that $PM_{2.5}$ was not associated with co-morbid asthma and overweight in our study.

Thus, more studies are needed to assess the relationship between air pollution and co-morbid asthma and overweight. Our findings can be used as a benchmark for comparison in future studies exploring air pollution as a potential underlying mechanism of this paediatric co-morbidity.

5.1.3 Objective 3

The third objective of this thesis investigated if the association between air pollution and co-morbid asthma and overweight is different across the following four characteristics:

urban core residence status (yes versus no), household income (higher versus lower), adolescent age (12 to 15 years versus 16 to 18 years), and sex (males versus females). There were no studies in the literature that examined these specific research questions. Therefore, inferences made from the results presented in this section must be conjectural, and future research on these questions is needed to validate our respective findings.

Urban Core Status

We hypothesized that the effect of air pollution on co-morbid asthma and overweight would be different for adolescents residing in an urban core and for those not residing an urban core. The effect of air pollution was expected to be positive among urban core adolescents, and no association was anticipated for non-urban core adolescents. The first part of our hypothesis was confirmed; that is, the $PM_{2.5}$ and co-morbid asthma and overweight association was significantly different across urban core status.

For urban core adolescents there was a slight increase in co-morbid asthma and overweight as $PM_{2.5}$ concentrations increased, fairly consistent with what we expected, although, a much larger effect was anticipated. Published evidence has displayed a strong relationship between asthma and overweight particularly in urban settings.[66,75,78,160,161] Suh et al[342] reported a significant association between asthma symptoms and BMI in male children residing in urban areas, whereas no association was found among their rural peers. Environmental factors that differ between geographic areas are plausible causes of this co-morbid association; air pollution levels are known to be higher in urban areas than non-urban areas. Urban core topography is also dominated by tall buildings, which weaken and calm winds responsible for the dispersal and dilution of pollutants. Therefore in an urban core, air pollution is more concentrated in an adolescent's breathing zone.[384] It then makes sense that in our study, $PM_{2.5}$ had a positive effect on co-morbid asthma and overweight among adolescents residing in an urban core.

For non-urban core adolescents however, the story is quite different. The present study found a marked decline in co-morbid asthma and overweight across increasing $PM_{2.5}$ levels. That is, the probability of this co-morbidity was highest among adolescents exposed to lower air pollution concentrations. This finding was not expected. It is

important to note that in non-urban areas, increases in adolescent overweight is associated with an increased level of "rurality."[385] Increasing rurality is also associated with lower ambient air pollution.[345,347] Since overweight is a risk factor for asthma, the present study might have accordingly captured a higher probability of co-morbid asthma and overweight in areas with the highest level of rurality. It is also possible that our measurement instrument did not capture $PM_{2.5}$ concentrations as properly in non-urban core areas compared to urban core areas. Geographic and spatial gaps exist in Canada's air quality monitoring network, largely because the technical capacity to monitor air pollution is limited in rural areas.[386]

Overall, our findings suggest the effect of air pollution on co-morbid asthma and overweight is quite different across categories of urban core status. Though high pollution exposure may be of greater concern for urban core adolescents, this needs to be verified.

Income

We first hypothesized that the association between air pollution and co-morbid asthma and overweight would be positive, regardless of household income. However, adolescents from low income households were expected to have an overall higher probability of co-morbid asthma and overweight than adolescents from high income households, across all air pollution concentrations.

Our findings of a non-significant interaction between $PM_{2.5}$ and household income supported our hypothesis that the effect of air pollution on co-morbid asthma and overweight is similar for adolescents from high and low income households. These results may be due to both income groups being equivalently susceptible to the health effects of air pollution, though for different reasons: Children with family incomes less than $50,000 spend more time outdoors on weekdays compared to their higher income peers,[356] increasing their degree of pollution exposure. Air pollution is also generally more prevalent in low income areas.[354] Though it appears that high income buffers children's exposure to the effects of air pollution, this group may be just as vulnerable as low income children. Many high income families reside in heavily polluted cities; in fact,

large urbanized areas mainly have higher earnings than smaller urban areas and rural areas.[387] Research has also found that the association between particulate pollution and poor health was higher in wealthier areas compared to more deprived ones.[388,389] However, it was proposed that wealthier people may appear more vulnerable to air pollution because they are relatively protected from competing risk factors of poor health (e.g., substance abuse) plaguing disadvantaged groups. It is also important to note that these income group differences were not always large enough to provide a statistically significant effect modification by socioeconomic status. Cakmak et al[390] likewise reported that the association between air pollution and cardiac disease (another systemic inflammatory disease) is not significantly influenced by income, further supporting our hypothesis for a similar effect.

The second part of our hypothesis was not confirmed. Although there was a positive association between $PM_{2.5}$ exposure and co-morbid asthma and overweight in higher and lower income adolescents, this effect was not statistically significant. The non-significant association between $PM_{2.5}$ and co-morbid asthma and overweight among all adolescents was also not anticipated (see Section 5.1.2), and may explain similar findings across income levels. The final part of our hypothesis was also not confirmed; across all $PM_{2.5}$ concentrations, there was no significant difference in the probability of co-morbid asthma and overweight between higher and lower income adolescents, inconsistent with previous evidence of significant inverse relationship between household income and this co-morbidity.[12] These results may not be surprising since our preliminary analysis revealed that asthma alone was virtually the same across income levels (see Table 4), a finding that also conflicts with previous literature.[12,372]

Overall, our findings suggest the effect of air pollution is similar across higher and lower income adolescents, and are consistent with previous evidence of a non-significant interaction between air pollution and income.

Age

We hypothesized that the effect of air pollution on co-morbid asthma and overweight would not be modified by adolescent age. Instead, a similar positive association was

expected for both younger and older adolescents. Lastly, older adolescents were expected to have a higher probability of co-morbid asthma and overweight across all pollution concentrations.

Our findings of a non-significant interaction between $PM_{2.5}$ and age supported the first part of our hypothesis; that is, the effect of air pollution on co-morbid asthma and overweight is similar for adolescents aged 12 to 15 years and 16 to 18 years. These results are consistent with previous research demonstrating the effect of air pollution on asthma alone as similar across paediatric age,[391] and may be a result of younger and older adolescents having a similar level of vulnerability to the health effects of air pollution, albeit for different reasons. Total time spent outdoors and participation in outdoor sports are higher among adolescents aged 13 to 15 years compared to those aged 16 to 19 years.[356] Individuals participating in sports breathe more deeply and rapidly allowing more air pollution to enter the lungs. Younger adolescents also have a higher breathing rate (i.e., inhale more air per unit of body weight) than their older peers.[181] Though these factors make younger paediatric populations quite susceptible to air pollution, older adolescents may be just as sensitive. Avoidance behaviour (e.g., limiting outdoor physical activity, remaining indoors) is less actively undertaken by the parents of older adolescents, potentially increasing their exposure to poor air quality.[392] Older age is also associated with an increase in low-grade systemic inflammation,[393] which may exacerbate the inflammatory health effects of air pollution. Evidently there is no consensus on which adolescent age group is more susceptible to the effects of air pollution, which may explain our findings of a non-differential $PM_{2.5}$ effect across age.

The second part of our hypothesis was not supported as we found that the association between $PM_{2.5}$ exposure levels and co-morbid asthma and overweight in younger and older adolescents was not statistically significant. These results relate to the non-significant association between $PM_{2.5}$ and co-morbid asthma and overweight among all adolescents (see Section 5.1.2). The final part of our hypothesis however, was confirmed; older adolescents were significantly more likely to have asthma and overweight than younger adolescents. Our results are consistent with a study conducted by Ahmad and colleagues,[10] who reported the strength of the association between asthma and obesity

increases with paediatric age. Possible explanations for these mutual findings include the increased likelihood of systemic inflammation and developing co-morbid illnesses among older age groups.[393,394]

Overall, the effect of air pollution appears to be similar for younger and older adolescents. Though it may be argued that the age ranges 12 to 15 years and 16 to 18 years are too narrow to detect any significant main effects differences (which is why many studies tend to group all adolescents into just one category), we expect that a number of biological and behavioural factors vary across adolescents of different ages.[392] It is thus worth further exploring the effect of adolescent age on the relationship between air pollution and co-morbid asthma and overweight.

Sex

We hypothesized that the effect of air pollution on co-morbid asthma and overweight would be modified by sex. The effect of air pollution was expected to be positive for both groups but stronger among males than females. The first part of our hypothesis was confirmed. There was a statistically significant interaction between $PM_{2.5}$ and sex, indicating the effect of $PM_{2.5}$ on co-morbid asthma and overweight was different for males and females.

Although a much larger effect was anticipated, our study confirmed the second part of our hypothesis and the findings of past studies,[17,213,342] by suggesting a potential positive association between the air pollutant, $PM_{2.5}$, and asthma and overweight in boys. These findings may be explained by gender-specific behaviours. Boys tend to spend more time outdoors than girls on weekdays and weekends.[356,357] More boys than girls go outside to hang out/play with friends, participate in sports, and ride-off road vehicles, while girls are more likely to be outside reading or studying.[356] This high level of outdoor activity may increase the degree of air pollution exposure in adolescent males (via rapid breathing), subsequently elevating their risk of systemic inflammatory conditions.

Among females, however, we found that there was a considerable decrease in the probability of co-morbid asthma and overweight as $PM_{2.5}$ exposure concentrations

increased. This finding was not expected. Previous evidence of a positive association between air pollution and asthma, and air pollution and overweight in adolescent females[17,213,391] contradicts our findings of an inverse relationship between $PM_{2.5}$ and these two conditions as a co-morbidity. Current literature suggests that the effect of air pollution on paediatric asthma and overweight may be weaker in females compared to males. Girls are less active than boys when spending time outdoors (see above), decreasing their degree of systemic air pollution exposure. There may be competing risk factors for asthma and overweight in females, making them less susceptible to air pollution. For example, female puberty is marked by hormonal changes such as increased estrogen, shown to increase asthma incidence, physiological and ectopic fat, and serum leptin concentrations.[82,395] It is also possible that our measurement tool did not capture personal $PM_{2.5}$ exposure as properly in females as in males. $PM_{2.5}$ exposure values were calculated for each respondent's neighbourhood area of residence only. However, girls are more likely than boys to visit public places such as the downtown area, movies, and malls, and to use these spaces as alternatives to hanging out in their neighbourhood.[396] As a result of these behaviours, personal $PM_{2.5}$ exposure among females may largely deviate from the ambient levels measured in the present study, and the accuracy of our female findings would be affected accordingly.

Overall, our results suggest the effect of air pollution on co-morbid asthma and overweight is quite different across sex. Though it appears the effect of high pollution concentrations is more worrisome among males, further verification is required.

5.2 Strengths

First of its Kind: Research has primarily attributed the underlying mechanisms of co-morbid asthma and overweight in children and adolescents to individual-level risk factors. However, Brisbon et al[15] illustrated there are also common root causes embedded in the built environment; these environmental factors need to be addressed in order to significantly reduce levels of this co-morbidity. To our knowledge, the present study is the first to further explore this recommendation by presenting a prevalence estimate of co-morbid asthma and overweight as a result of environmental influences accordingly.

Important insight is provided on the role played by air pollution, providing a potential target for intervention in public health planning.

Representativeness of the CCHS and NPRI: A fundamental strength of this project was the use of a: (1) national population-based survey (CCHS) to measure outcome variables of interest and their associated covariates; and (2) a nationally representative inventory of industrial pollutant emissions (NPRI) to measure the exposure variable of interest.

The central objective of the CCHS was to gather health-related data from a large sample of respondents at the health region level. It can thus be ensured that the CCHS provided a representative sample of the adolescent population residing in the 14 health regions of southwestern Ontario.

The 2008 NPRI contained data on 100% of Canadian operating coal-fired power plants, primary metal smelters, steel mills, oil sands facilities, off-shore oil and gas platforms, crude oil refineries, major automobile assembly plants, Portland cement manufacturing facilities, and pulp and paper mills.[397] These estimates are likely similar for the 2009 NPRI. In addition, Environment Canada's rigorous efforts towards compliance promotion, expanding reporting requirements, and the maintenance of high quality data, ensures that exposure estimates used in the present study are accurate, reliable, and quite representative of industrial $PM_{2.5}$ emissions in southwestern Ontario.

Air Pollution Exposure Variation: $PM_{2.5}$ exposure was measured in such a way that allowed us to assess differences between individuals at a micro level. This decision takes into account the microscale variations in air pollution exposure that exists between each geographic location in southwestern Ontario. Alternatively measuring pollution exposure at the community level, where individuals would be clustered based on proximal postal code areas, would have eliminated the variation in $PM_{2.5}$ exposure between subjects within each cluster.

The present thesis also selected a study location with sufficient exposure variation. When Zhao et al[244] examined the association between air pollution and paediatric asthmatic symptoms, air pollution concentrations were quantified only in heavily polluted urban

areas of Taiyuan, China. The authors later discussed that the high general air pollution level in their study location may have limited the possibility of acquiring adequate variation in the overall air pollution exposure. The present research project alternatively examined the effect of $PM_{2.5}$ concentrations among adolescents residing across the different geographical areas of southwestern Ontario.

Finally, air pollution concentrations vary with the meteorological conditions in a given area.[398] For example, the degree to which $PM_{2.5}$ is discharged from an industrial source and concentrated into a particular area, depends on wind speed/direction and air temperature. Our study used such parameters in the calculation of $PM_{2.5}$ exposure values for each postal code area in southwestern Ontario, a methodological step that captures the significant impact of meteorology on air pollution exposure variation.

5.3 Limitations

Temporality: Due to the cross-sectional design of this study, and temporal mismatch between data sources (see Section 3.1), temporality cannot be assured. This study is unable to determine if $PM_{2.5}$ is a causal factor that leads to the development of asthma, overweight, and co-morbid asthma and overweight. Instead, only an association between $PM_{2.5}$ and these three outcomes can be identified. Though it is unknown whether study subjects had developed asthma and/or overweight prior to when $PM_{2.5}$ exposure was measured, a bi-directional relationship is not of any concern as it is impossible for asthma and overweight to cause or influence air pollution levels. A cross-sectional design allows us to address the primary objective of this study, which is to acquire a better understanding of the etiology of paediatric asthma and overweight.

Interview Mode: Interview mode has produced a notable difference in reported key health indicators of the CCHS. A study conducted using the CCHS cycle 2.1 (2003) indicated possible mode effects between using CAPI (in person interviewing) and CATI (telephone interviewing).[399] Significant differences in point estimates were found between both modes for many health indicators including self-reported height and weight. From these measures, obesity (BMI score of 30 or higher) was derived in the mode study for respondents aged 18 years or older, and was determined as significantly higher for CAPI

(17.9%) than CATI (13.2%). CATI underestimation has been attributed to social desirability,[399] whereas in person it is harder to report incorrect values. Although these mode differences in self-reported height and weight were established among adults, the results are likely applicable to adolescents. This bias in reporting presents the possibility of study estimates being representative of CCHS respondents who were interviewed using one mode over the other. Some recommendations were made to improve this discrepancy for future cycles of CCHS, therefore, benefiting the present study. For example, the same area/telephone frames and CAPI/CATI ratios used in cycle 2.1 were implemented in cycle 3.1, and interviewer procedures were reinforced among both collection methods.

Measurement Instruments: Assessing asthma via questionnaire might have resulted in the misclassification of this outcome. This self-reported question did not require a physician diagnosis, and was not tested for reliability or validity in the CCHS. Published studies however, have indicated that there is high accordance between self-reported asthma and medical records; when compared with a clinical diagnosis of asthma, the average sensitivity of self-reported asthma was 68%, and the average specificity was 94%.[19] Overall, obtaining a self-report of physician diagnosis is recognized as a reliable and commonly used method for identifying asthma in epidemiologic studies.[19,204]

There is also the possibility that asthma was underestimated in the CCHS due to a high prevalence of asthma under-diagnosis in paediatric populations. Siersted et al[400] found that undiagnosed asthma comprised approximately one third of all asthma cases identified among Danish adolescents aged 12 to 15 years. These findings are largely due to two-thirds of those undiagnosed not reporting their symptoms to a doctor. Physicians may also fail to appreciate the importance of respiratory symptoms that are presented to them. For example, these symptoms have been inaccurately ascribed to a lack of physical fitness among those with a high body mass or low physical activity.[96,400] Undiagnosed asthma is more prevalent in females compared to males,[400] indicating the prospect of differential bias in asthma prevalence by sex in the present study.

This study used BMI to determine adolescent weight status. One limitation of using BMI is its failure to differentiate between fat mass and lean body mass (i.e., muscle and bone).[37,401,402] Concern then arises over this screening tool misclassifying weight status. For example, overestimation is likely prevalent among those with high lean body mass for their height, or muscular builds. Individuals with a large body frame (high bone mass) for their height, but very little body fat, may also be erroneously labelled as overweight on the BMI scale. This limitation is quite pertinent in adolescence, where during this developmental period, there can be substantial increases in both muscle and bone mass.[401] BMI's inability to account for body frame size can alternatively result in overweight underestimation. Namely, adolescents carrying a high level of fat mass for a very small body frame, might have a BMI value that categorizes them as normal weight, when in contrast, they should be considered overweight for their frame. There are several methods, such as dual-energy x-ray absorptiometry, that can assess overall body fat and fat distribution. However, factors such as accessibility, simplicity, cost, and ease of use are restricted with respect to these instruments, making them unsuitable measures of adiposity for the current study.[5] Despite concerns associated with using BMI to identify overweight adolescents, this measure has been recommended for epidemiologic and population-based research due to its feasibility, and positive correlation with direct measures of body fatness, metabolic risk in youth, and disease in adulthood.[36,403-405]

Another limitation involves the use of self-reported height and weight to calculate BMI. Most studies have found that individuals generally underestimate their weight and overestimate their height.[406] As a result, the prevalence of obesity based on self-reported data tends to be underestimated. Females underestimate their weight more than males.[406,407] Inaccurate self-reporting is usually more prevalent among younger youth compared to their older peers.[407,408] Overweight youth underestimate their weight more than normal weight youth.[406,407] This reporting bias among higher BMI individuals would affect study estimates of overweight by making them more conservative.

Despite concerns over self-report bias, a high correlation exists between self-reported and measured height and weight.[409,410] Overall, self-reported height and weight are not likely

to influence conclusions about study estimates in population-based epidemiological studies, and are considered valid measures for these types of studies.[411,412]

The $PM_{2.5}$ variable has some limitations worth noting. First, the exposure data are representative of emissions from industrial sources alone. These data do not account for other sources of $PM_{2.5}$ that are present in southwestern Ontario's air-shed such as transboundary pollutants and emissions from transportation and agriculture. In fact, open sources, such as construction operations and dust from paved and unpaved road, emit the majority of $PM_{2.5}$ in Canada but were not accounted for in the present study.[174] The concentration values calculated by HEAL are thus only representative of a small fraction of the total amount of $PM_{2.5}$ that could be expected over any 24-hour averaging period within each postal code area. This causes misclassification of the overall $PM_{2.5}$ exposure in the present study. Nevertheless, since the isolated effects of industrial air pollution on asthma and overweight have never been explored, using this measure is a valuable addition to the literature.

Second, the $PM_{2.5}$ data is incomplete as not all industrial facilities report to the NPRI. In 2008, there were lower rates of reporting coverage for facilities such as foundries, pits and quarries, rubber and plastics manufacturing plants, forest product manufacturing facilities, and wastewater facilities. These lower rates are mainly ascribed to falling below compulsory reporting thresholds or a result of certain facilities not reporting to the NPRI as required.[397]

Third, $PM_{2.5}$ values were created by combining emissions data released from the NPRI in 2009 with local meteorological data in southwestern Ontario from 1996 to 2000 (see Section 3.2). Since atmospheric conditions greatly impact the level of air pollution an area is exposed to,[398] obtaining meteorological data closer to 2009 would have been more appropriate. Calculating annual $PM_{2.5}$, averaged over a three year period, would have provided more stable estimates of exposure than a single year average.[413] These options were not available at the time of analysis.

Finally, $PM_{2.5}$ values were calculated for each respondent's postal code area of residence in 2009. However, adolescents spend a large portion of their day in other locations (e.g.,

school, alternative residence) likely exposed to different $PM_{2.5}$ concentrations. This concern is confirmed by Delfino et al[233] who demonstrated that personal $PM_{2.5}$ (measured by a portable monitor worn during waking hours) was only moderately correlated with ambient $PM_{2.5}$ (r=0.64) among children and adolescents residing in Southern California, and the association between $PM_{2.5}$ and airway inflammation was more robust for personal exposure than ambient exposure. It is also unknown whether respondents to the CCHS before or after 2009 were actually exposed to their assigned concentrations, as some respondents may have resided in a different postal code area than in 2009. Our measurement instrument did not account for pollution exposure in these other postal code areas that may have contributed to their health outcomes. These flaws may collectively misclassify the final sample's true level of exposure, presenting information bias and regression attenuation into the study.

Missing Data: A sensitivity analysis compared adolescents with and without missing data (Appendix B). Both groups were significantly different on all covariates, indicating that excluding adolescents with missing data from the analysis may potentially impact study results. These significant differences may be due to comparing very unequal sample sizes (n=289 and n=2,685). Burton and Altman[414] discuss that the maximum amount of missingness in any variable is tolerable if there is only a small number of cases with overall missing data (i.e., less than 10%); in the present study, 9.7% of the final sample had missing data.

5.4 Implications and Future Research

Our cross-sectional study sought to examine the etiology of co-morbid asthma and overweight in adolescents. Co-morbidity development may be a result of common risk factors that increase the likelihood of both conditions separately. In accordance with Brisbon et al,[15] who proposed these common root causes are largely components of our environment, the role played by air pollution exposure was explored.

It was revealed that adolescents are more likely to be overweight as $PM_{2.5}$ concentrations increase in areas of residence. However, no significant association was found between $PM_{2.5}$ and adolescent asthma. There was also no association between $PM_{2.5}$ and co-

morbid asthma and overweight in adolescents. It is important to note however, that there is a large body of epidemiological research supporting a causal relationship between air pollution and paediatric asthma (see Section 1.6.4). Due to this evidence, and because we found a significant association between $PM_{2.5}$ and paediatric overweight, there is still reason to believe air pollution may be a shared risk factor for asthma and overweight. Finally, our study showed that the effect of $PM_{2.5}$ on co-morbid asthma and overweight was different across urban core residence status and sex. Adolescents residing in an urban core were more vulnerable to $PM_{2.5}$ than their non-urban core peers, and males were more susceptible than females. Upon targeting specific groups for intervention, perhaps concern should be raised with regard to high air pollution exposure in urban core areas and among adolescent males.

No other epidemiologic studies have measured the effect of air pollution on co-morbid asthma and overweight. Due to the paucity of research on this topic, we are unable to contextualize our findings of no association between $PM_{2.5}$ and co-morbid asthma and overweight, and our recommendation to target specific adolescent groups over others (e.g., urban core areas over non-urban core areas) cannot be conclusive. Clearly, more evidence on the subject is needed. If air pollution is actually a causal factor of this paediatric co-morbidity, the implications could be great.

One such implication is that it is quite difficult for adolescents to control their exposure to air pollution. For one, it is not possible to carry clean air or stop breathing in polluted air. Adolescents also have a higher ventilation rate, inhale a greater amount of pollution per pound body weight, and spend more time outdoors than older age groups.[171,181] There are certain behaviours that may protect one's exposure to air pollution. Children and adolescents however, are less health conscious and face extrinsic mobility restriction which may hinder their ability to choose these healthy behaviours. These protective measures may also have minimal benefits and can even lead to other health implications. For example, going indoors is generally advised when air pollution levels are high.[415] Yet outdoor air pollutants can still penetrate into the indoor environment.[416] Another recommendation is limiting outdoor physical activity when exposed to poor air quality.[415] This is because physical activity causes rapid, deeper breathing, allowing more pollutants

to enter the lungs. However, outdoor exercise has a greater effect on physical and mental well-being than exercising indoors.[417] Television viewing, computer games and other sedentary behaviours would likely increase. This behavioural change may also lead to a reduction in the numerous health benefits of regular exercise such as chronic disease prevention and enhanced strength, self-esteem, and immunity.[418]

Another implication involves air pollution potentially causing a greater disease burden among adolescents with co-morbid asthma and overweight. Adolescents with this co-morbidity already face greater health consequences than adolescents who have only one of these conditions. Compared to those who have asthma alone or are only overweight, obese asthmatics have more emergency department visits, hospitalizations, and sleep disturbances, lower lung function, and use more medication.[12,419] Obese asthmatics have more co-morbidities such as gastroesophageal reflux disease, diabetes mellitus, and hypertension.[419] Obesity alters asthma toward a more difficult-to-control/treat phenotype, and vice versa.[99,420] Finally, systemic inflammatory markers are more elevated in patients with both conditions. Air pollution, which is known to cause systemic inflammation, may therefore precipitate other chronic diseases associated with systemic inflammation such as cardiac disease, chronic heart failure, diabetes, and arteriosclerosis.[421] Society is impacted by these endpoints due to increased healthcare and medication costs, school absenteeism, out of pocket expenses, restricted activity days, and eventually, a loss of workplace productivity and lost wages due to sick time. There are also intangible costs such as pain, suffering, and reduced quality of life.

Since it is evident that co-morbid asthma and overweight is difficult to manage at the individual level, more research on the effects of air pollution on this co-morbidity would be beneficial, as these conditions may be easier to control at the environmental level. Research thus far has concentrated on risk factors of asthma and overweight that are not modifiable such as ethnicity, sex, and income.[12] Alternatively, the level of air pollution has the potential to be modified. For example, a recent study found that the economic value of reducing the health effects of air pollution, by introducing cleaner vehicles and fuels in Canada, was $24 billion over a 24-year period (compared to a cost of $6 billion for implementing this program).[422] These findings not only indicate that air pollution

levels can be improved, but also that the reduction of this exposure dramatically benefits the well-being of society. Finally, Brisbon et al[15] stressed that the prevention and management of asthma and overweight in particular will likely be achieved through the study and modification of the built environment.

The results of the current study may be used as a benchmark for future research examining the effects of air pollution or the role of the environment on co-morbid asthma and overweight. Given the public health implications discussed above, we should continue exploring this relationship until we achieve a satisfactory buildup of knowledge to conclude whether air pollution causes this co-morbidity or not. Ideally, future work would use a longitudinal study design with actual measurements of weight and height and validation of reported asthma. To enhance the accuracy of exposure measurement, quantifying air pollution from all sources (e.g., industry, transportation, agriculture, transboundary) needs to be considered. This can be achieved by using ambient air monitoring data, or if feasible, personal exposure monitors for each subject. In addition, research should further investigate whether the effects of air pollution vary by other risk factors such as geographic residency, age, sex, and measures of socioeconomic status, to provide effective targets for intervention. Overall, conducting further studies as such will bring us closer to understanding the etiology of paediatric asthma and overweight, which is important for guiding public health strategies taken towards this co-morbid epidemic.

References

1. Torpy JM, Campbell A, Glass RM. JAMA patient page. Chronic diseases of children. *JAMA*. Feb 17 2010;303(7):682.

2. Millar WJ, Hill GB. Childhood asthma. *Health Rep*. Winter 1998;10(3):9-21 (ENG); 29-22 (FRE).

3. Shields M. Overweight and obesity among children and youth. *Health Rep*. Aug 2006;17(3):27-42.

4. Braman SS. The global burden of asthma. *Chest*. Jul 2006;130(1 Suppl):4S-12S.

5. Lobstein T, Baur L, Uauy R. Obesity in children and young people: a crisis in public health. *Obes Rev*. May 2004;5 Suppl 1:4-104.

6. Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet*. Aug 26 2006;368(9537):733-743.

7. Krahn MD, Berka C, Langlois P, Detsky AS. Direct and indirect costs of asthma in Canada, 1990. *Cmaj*. Mar 15 1996;154(6):821-831.

8. Anis AH, Zhang W, Bansback N, Guh DP, Amarsi Z, Birmingham CL. Obesity and overweight in Canada: an updated cost-of-illness study. *Obes Rev*. Jan 2010;11(1):31-40.

9. Ford ES. The epidemiology of obesity and asthma. *J Allergy Clin Immunol*. May 2005;115(5):897-909; quiz 910.

10. Ahmad N, Biswas S, Bae S, Meador KE, Huang R, Singh KP. Association between obesity and asthma in US children and adolescents. *J Asthma*. Sep 2009;46(7):642-646.

11. Visness CM, London SJ, Daniels JL, et al. Association of childhood obesity with atopic and nonatopic asthma: results from the National Health and Nutrition Examination Survey 1999-2006. *J Asthma*. Sep 2010;47(7):822-829.

12. Stingone JA, Ramirez OF, Svensson K, Claudio L. Prevalence, demographics, and health outcomes of comorbid asthma and overweight in urban children. *J Asthma*. Nov 2011;48(9):876-885.

13. Papoutsakis C, Priftis KN, Drakouli M, et al. Childhood overweight/obesity and asthma: is there a link? A systematic review of recent epidemiologic evidence. *J Acad Nutr Diet*. Jan 2013;113(1):77-105.

14. Silva MJ, Ribeiro MC, Carvalho F, Goncalves Oliveira JM. Atopic disease and body mass index. *Allergol Immunopathol (Madr).* Jul-Aug 2007;35(4):130-135.

15. Brisbon N, Plumb J, Brawer R, Paxman D. The asthma and obesity epidemics: the role played by the built environment--a public health perspective. *J Allergy Clin Immunol.* May 2005;115(5):1024-1028.

16. Gasana J, Dillikar D, Mendy A, Forno E, Ramos Vieira E. Motor vehicle air pollution and asthma in children: A meta-analysis. *Environ Res.* Aug 2012;117:36-45.

17. Jerrett M, McConnell R, Chang CC, et al. Automobile traffic around the home and attained body mass index: a longitudinal cohort study of children aged 10-18 years. *Prev Med.* Jan 2010;50 Suppl 1:S50-58.

18. Kemp T, Pearce N, Crane J, Beasley R. Problems of measuring asthma prevalence. *Respirology.* Sep 1996;1(3):183-188.

19. Toren K, Brisman J, Jarvholm B. Asthma and asthma-like symptoms in adults assessed by questionnaires. A literature review. *Chest.* Aug 1993;104(2):600-608.

20. Centers for Disease Control and Prevention. Asthma mortality and hospitalization among children and young adults--United States, 1980-1993. *MMWR Morb Mortal Wkly Rep.* May 3 1996;45(17):350-353.

21. Garner R, Kohen D. Changes in the prevalence of asthma among Canadian children. *Health Rep.* Jun 2008;19(2):45-50.

22. Litonjua AA, Gold DR. Asthma and obesity: common early-life influences in the inception of disease. *J Allergy Clin Immunol.* May 2008;121(5):1075-1084; quiz 1085-1076.

23. von Hertzen L, Haahtela T. Signs of reversing trends in prevalence of asthma. *Allergy.* Mar 2005;60(3):283-292.

24. Statistics Canada. *Asthma, by age group and sex (Percent).* Ottawa, Canada: Statistics Canada; 2012. http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/health49b-eng.htm. Accessed February 1, 2013.

25. Statistics Canada. *Asthma, by sex, provinces and territories (Percent).* Ottawa, Canada: Statistics Canada; 2013. http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/health50b-eng.htm. Accessed April 20, 2014.

26. Gershon AS, Guan J, Wang C, To T. Trends in asthma prevalence and incidence in Ontario, Canada, 1996-2005: a population study. *Am J Epidemiol.* Sep 15 2010;172(6):728-736.

27. Canadian Lung Association. *Lung facts: 1994 update*. Ottawa, Canada: Canadian Lung Association; 1994.

28. Guttmann A, Zagorski B, Austin PC, et al. Effectiveness of emergency department asthma management strategies on return visits in children: a population-based study. *Pediatrics*. Dec 2007;120(6):e1402-1410.

29. Goodwin RD, Fergusson DM, Horwood LJ. Asthma and depressive and anxiety disorders among young persons in the community. *Psychol Med*. Nov 2004;34(8):1465-1474.

30. Field SK, Underwood M, Brant R, Cowie RL. Prevalence of gastroesophageal reflux symptoms in asthma. *Chest*. Feb 1996;109(2):316-322.

31. Vir R, Bhagat R, Shah A. Sleep disturbances in clinically stable young asthmatic adults. *Ann Allergy Asthma Immunol*. Sep 1997;79(3):251-255.

32. Annesi-Maesano I. Epidemiological evidence of the occurrence of rhinitis and sinusitis in asthmatics. *Allergy*. 1999;54 Suppl 57:7-13.

33. Yun HD, Knoebel E, Fenta Y, et al. Asthma and proinflammatory conditions: a population-based retrospective matched cohort study. *Mayo Clin Proc*. Oct 2012;87(10):953-960.

34. Jenkins MA, Hopper JL, Bowes G, Carlin JB, Flander LB, Giles GG. Factors in childhood as predictors of asthma in adult life. *Bmj*. Jul 9 1994;309(6947):90-93.

35. Pietrobelli A, Faith MS, Allison DB, Gallagher D, Chiumello G, Heymsfield SB. Body mass index as a measure of adiposity among children and adolescents: a validation study. *J Pediatr*. Feb 1998;132(2):204-210.

36. Dietz WH, Robinson TN. Use of the body mass index (BMI) as a measure of overweight in children and adolescents. *J Pediatr*. Feb 1998;132(2):191-193.

37. Sweeting HN. Measurement and definitions of obesity in childhood and adolescence: a field guide for the uninitiated. *Nutr J*. 2007;6:32.

38. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *Bmj*. May 6 2000;320(7244):1240-1243.

39. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ*. Sep 2007;85(9):660-667.

40. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat 11*. May 2002(246):1-190.

41. Shields M, Tremblay MS. Canadian childhood obesity estimates based on WHO, IOTF and CDC cut-points. *Int J Pediatr Obes.* May 3 2010;5(3):265-273.

42. Lau DC, Douketis JD, Morrison KM, Hramiak IM, Sharma AM, Ur E. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children [summary]. *CMAJ.* Apr 10 2007;176(8):S1-13.

43. Secker D. Promoting optimal monitoring of child growth in Canada: using the new WHO growth charts. *Can J Diet Pract Res.* Spring 2010;71(1):e1-3.

44. Statistics Canada. *Body mass index, overweight or obese, self-reported, youth, by sex, provinces and territories (Percent).* Ottawa, Canada: Statistics Canada; 2013. http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/health84b-eng.htm. Accessed May 11, 2013.

45. Ball GD, McCargar LJ. Childhood obesity in Canada: a review of prevalence estimates and risk factors for cardiovascular diseases and type 2 diabetes. *Can J Appl Physiol.* Feb 2003;28(1):117-140.

46. Freedman DS, Mei Z, Srinivasan SR, Berenson GS, Dietz WH. Cardiovascular risk factors and excess adiposity among overweight children and adolescents: the Bogalusa Heart Study. *J Pediatr.* Jan 2007;150(1):12-17.e12.

47. Li C, Ford ES, Zhao G, Mokdad AH. Prevalence of pre-diabetes and its association with clustering of cardiometabolic risk factors and hyperinsulinemia among U.S. adolescents: National Health and Nutrition Examination Survey 2005-2006. *Diabetes Care.* Feb 2009;32(2):342-347.

48. Tirosh A, Shai I, Afek A, et al. Adolescent BMI trajectory and risk of diabetes versus coronary disease. *N Engl J Med.* Apr 7 2011;364(14):1315-1325.

49. Stovitz SD, Pardee PE, Vazquez G, Duval S, Schwimmer JB. Musculoskeletal pain in obese children and adolescents. *Acta Paediatr.* Apr 2008;97(4):489-493.

50. Daniels SR, Arnett DK, Eckel RH, et al. Overweight in children and adolescents: pathophysiology, consequences, prevention, and treatment. *Circulation.* Apr 19 2005;111(15):1999-2012.

51. Imhof A, Kratzer W, Boehm B, et al. Prevalence of non-alcoholic fatty liver and characteristics in overweight adolescents in the general population. *Eur J Epidemiol.* 2007;22(12):889-897.

52. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health.* 2009;9:88.

53. Kushi LH, Byers T, Doyle C, et al. American Cancer Society Guidelines on Nutrition and Physical Activity for cancer prevention: reducing the risk of cancer

with healthy food choices and physical activity. *CA Cancer J Clin*. Sep-Oct 2006;56(5):254-281; quiz 313-254.

54. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. The relation of childhood BMI to adult adiposity: the Bogalusa Heart Study. *Pediatrics*. Jan 2005;115(1):22-27.

55. Latner JD, Stunkard AJ. Getting worse: the stigmatization of obese children. *Obes Res*. Mar 2003;11(3):452-456.

56. Braet C, Mervielde I, Vandereycken W. Psychological aspects of childhood obesity: a controlled study in a clinical and nonclinical sample. *J Pediatr Psychol*. Feb 1997;22(1):59-71.

57. Loth KA, Mond J, Wall M, Neumark-Sztainer D. Weight status and emotional well-being: longitudinal findings from Project EAT. *J Pediatr Psychol*. Mar 2011;36(2):216-225.

58. Swallen KC, Reither EN, Haas SA, Meier AM. Overweight, obesity, and health-related quality of life among adolescents: the National Longitudinal Study of Adolescent Health. *Pediatrics*. Feb 2005;115(2):340-347.

59. Anderson SE, Cohen P, Naumova EN, Jacques PF, Must A. Adolescent obesity and risk for subsequent major depressive disorder and anxiety disorder: prospective evidence. *Psychosom Med*. Nov 2007;69(8):740-747.

60. Kubzansky LD, Gilthorpe MS, Goodman E. A prospective study of psychological distress and weight status in adolescents/young adults. *Ann Behav Med*. Apr 2012;43(2):219-228.

61. Erickson SJ, Robinson TN, Haydel KF, Killen JD. Are overweight children unhappy?: Body mass index, depressive symptoms, and overweight concerns in elementary school children. *Arch Pediatr Adolesc Med*. Sep 2000;154(9):931-935.

62. Eaton DK, Lowry R, Brener ND, Galuska DA, Crosby AE. Associations of body mass index and perceived weight with suicide ideation and suicide attempts among US high school students. *Arch Pediatr Adolesc Med*. Jun 2005;159(6):513-519.

63. Ratcliff MB, Jenkins TM, Reiter-Purtill J, Noll JG, Zeller MH. Risk-taking behaviors of adolescents with extreme obesity: normative or not? *Pediatrics*. May 2011;127(5):827-834.

64. Cornette R. The emotional impact of obesity on children. *Worldviews Evid Based Nurs*. 2008;5(3):136-141.

65. Boutelle K, Neumark-Sztainer D, Story M, Resnick M. Weight control behaviors among obese, overweight, and nonoverweight adolescents. *J Pediatr Psychol*. Sep 2002;27(6):531-540.

66. Figueroa-Munoz JI, Chinn S, Rona RJ. Association between obesity and asthma in 4-11 year old children in the UK. *Thorax*. Feb 2001;56(2):133-137.

67. von Mutius E, Schwartz J, Neas LM, Dockery D, Weiss ST. Relation of body mass index to asthma and atopy in children: the National Health and Nutrition Examination Study III. *Thorax*. Nov 2001;56(11):835-838.

68. Gold DR, Damokosh AI, Dockery DW, Berkey CS. Body-mass index as a predictor of incident asthma in a prospective cohort of children. *Pediatr Pulmonol*. Dec 2003;36(6):514-521.

69. Corbo GM, Forastiere F, De Sario M, et al. Wheeze and asthma in children: associations with body mass index, sports, television viewing, and diet. *Epidemiology*. Sep 2008;19(5):747-755.

70. Rizwan S, Reid J, Kelly Y, Bundred PE, Pearson M, Brabin BJ. Trends in childhood and parental asthma prevalence in Merseyside, 1991-1998. *J Public Health (Oxf)*. Dec 2004;26(4):337-342.

71. Tsai HJ, Tsai AC, Nriagu J, Ghosh D, Gong M, Sandretto A. Associations of BMI, TV-watching time, and physical activity on respiratory symptoms and asthma in 5th grade schoolchildren in Taipei, Taiwan. *J Asthma*. Jun 2007;44(5):397-401.

72. Sybilski AJ, Raciborski F, Lipiec A, et al. Obesity - a risk factor for asthma, but not for atopic dermatitis, allergic rhinitis and sensitization. *Public Health Nutr*. Apr 17 2014:1-7.

73. Kwon HL, Ortiz B, Swaner R, et al. Childhood asthma and extreme values of body mass index: the Harlem Children's Zone Asthma Initiative. *J Urban Health*. May 2006;83(3):421-433.

74. Black MH, Smith N, Porter AH, Jacobsen SJ, Koebnick C. Higher prevalence of obesity among children with asthma. *Obesity (Silver Spring)*. May 2012;20(5):1041-1047.

75. Luder E, Melnik TA, DiMaio M. Association of being overweight with greater asthma symptoms in inner city black and Hispanic children. *J Pediatr*. Apr 1998;132(4):699-703.

76. Cassol VE, Rizzato TM, Teche SP, et al. Obesity and its relationship with asthma prevalence and severity in adolescents from southern Brazil. *J Asthma*. Jan-Feb 2006;43(1):57-60.

77. Bender BG, Fuhlbrigge A, Walders N, Zhang L. Overweight, race, and psychological distress in children in the Childhood Asthma Management Program. *Pediatrics.* Oct 2007;120(4):805-813.

78. Gennuso J, Epstein LH, Paluch RA, Cerny F. The relationship between asthma and obesity in urban minority children and adolescents. *Arch Pediatr Adolesc Med.* Dec 1998;152(12):1197-1200.

79. Jones SE, Merkle SL, Fulton JE, Wheeler LS, Mannino DM. Relationship between asthma, overweight, and physical activity among U.S. high school students. *J Community Health.* Dec 2006;31(6):469-478.

80. Vargas PA, Perry TT, Robles E, et al. Relationship of body mass index with asthma indicators in head start children. *Ann Allergy Asthma Immunol.* Jul 2007;99(1):22-28.

81. Carroll CL, Stoltz P, Raykov N, Smith SR, Zucker AR. Childhood overweight increases hospital admission rates for asthma. *Pediatrics.* Oct 2007;120(4):734-740.

82. Castro-Rodriguez JA, Holberg CJ, Morgan WJ, Wright AL, Martinez FD. Increased incidence of asthmalike symptoms in girls who become overweight or obese during the school years. *Am J Respir Crit Care Med.* May 2001;163(6):1344-1349.

83. Scholtens S, Wijga AH, Seidell JC, et al. Overweight and changes in weight status during childhood in relation to asthma symptoms at 8 years of age. *J Allergy Clin Immunol.* Jun 2009;123(6):1312-1318.e1312.

84. Belamarich PF, Luder E, Kattan M, et al. Do obese inner-city children with asthma have more symptoms than nonobese children with asthma? *Pediatrics.* Dec 2000;106(6):1436-1441.

85. Kaplan TA, Montana E. Exercise-induced bronchospasm in nonasthmatic obese children. *Clin Pediatr (Phila).* Apr 1993;32(4):220-225.

86. Fung KP, Lau SP, Chow OK, Lee J, Wong TW. Effects of overweight on lung function. *Arch Dis Child.* May 1990;65(5):512-515.

87. Schachter LM, Peat JK, Salome CM. Asthma and atopy in overweight children. *Thorax*. Dec 2003;58(12):1031-1035.

88. Vazquez-Nava F, Morales Romero J, Crodova Fernandez JA, et al. Association between obesity and asthma in preschool Mexican children. *ScientificWorldJournal.* 2010;10:1339-1346.

89. Antonio MA, Ribeiro JD, Toro AA, Piedrabuena AE, Morcillo AM. [Evaluation of the nutritional status of children and adolescents with asthma]. *Rev Assoc Med Bras.* Oct-Dec 2003;49(4):367-371.

90. Vignolo M, Silvestri M, Parodi A, et al. Relationship between body mass index and asthma characteristics in a group of Italian children and adolescents. *J Asthma.* Apr 2005;42(3):185-189.

91. Peters JI, McKinney JM, Smith B, Wood P, Forkner E, Galbreath AD. Impact of obesity in asthma: evidence from a large prospective disease management study. *Ann Allergy Asthma Immunol.* Jan 2011;106(1):30-35.

92. Zhang Z, Lai HJ, Roberg KA, et al. Early childhood weight status in relation to asthma development in high-risk children. *J Allergy Clin Immunol.* Dec 2010;126(6):1157-1162.

93. Brenner JS, Kelly CS, Wenger AD, Brich SM, Morrow AL. Asthma and obesity in adolescents: is there an association? *J Asthma.* Sep 2001;38(6):509-515.

94. Henkin S, Brugge D, Bermudez OI, Gao X. A case-control study of body mass index and asthma in Asian children. *Ann Allergy Asthma Immunol.* May 2008;100(5):447-451.

95. Xu B, Pekkanen J, Laitinen J, Jarvelin MR. Body build from birth to adulthood and risk of asthma. *Eur J Public Health.* Sep 2002;12(3):166-170.

96. Gilliland FD, Berhane K, Islam T, et al. Obesity and the risk of newly diagnosed asthma in school-age children. *Am J Epidemiol.* Sep 1 2003;158(5):406-415.

97. Hancox RJ, Milne BJ, Poulton R, et al. Sex differences in the relation between body mass index and asthma and atopy in a birth cohort. *Am J Respir Crit Care Med.* Mar 1 2005;171(5):440-445.

98. Flaherman V, Rutherford GW. A meta-analysis of the effect of high weight on asthma. *Arch Dis Child.* Apr 2006;91(4):334-339.

99. Beuther DA, Weiss ST, Sutherland ER. Obesity and asthma. *Am J Respir Crit Care Med.* Jul 15 2006;174(2):112-119.

100. Shore SA, Fredberg JJ. Obesity, smooth muscle, and airway hyperresponsiveness. *J Allergy Clin Immunol.* May 2005;115(5):925-927.

101. del Rio-Navarro B, Cisneros-Rivero M, Berber-Eslava A, Espinola-Reyna G, Sienra-Monge J. Exercise induced bronchospasm in asthmatic and non-asthmatic obese children. *Allergol Immunopathol (Madr).* Jan-Feb 2000;28(1):5-11.

102. Bowrey DJ, Peters JH, DeMeester TR. Gastroesophageal reflux disease in asthma: effects of medical and surgical antireflux therapy on asthma control. *Ann Surg*. Feb 2000;231(2):161-172.

103. Tantisira KG, Weiss ST. Complex interactions in complex traits: obesity and asthma. *Thorax*. Sep 2001;56 Suppl 2:ii64-73.

104. Delgado J, Barranco P, Quirce S. Obesity and asthma. *J Investig Allergol Clin Immunol*. 2008;18(6):420-425.

105. Glazebrook C, McPherson AC, Macdonald IA, et al. Asthma as a barrier to children's physical activity: implications for body mass index and mental health. *Pediatrics*. Dec 2006;118(6):2443-2449.

106. Hollman GA, Allen DB. Overt glucocorticoid excess due to inhaled corticosteroid therapy. *Pediatrics*. Mar 1988;81(3):452-455.

107. Strunk RC, Rubin D, Kelly L, Sherman B, Fukuhara J. Determination of fitness in children with asthma. Use of standardized tests for functional endurance, body fat composition, flexibility, and abdominal strength. *Am J Dis Child*. Sep 1988;142(9):940-944.

108. Firrincieli V, Keller A, Ehrensberger R, et al. Decreased physical activity among Head Start children with a history of wheezing: use of an accelerometer to measure activity. *Pediatr Pulmonol*. Jul 2005;40(1):57-63.

109. Shore SA. Obesity and asthma: possible mechanisms. *J Allergy Clin Immunol*. May 2008;121(5):1087-1093; quiz 1094-1085.

110. Malykhina AP, Wyndaele JJ, Andersson KE, De Wachter S, Dmochowski RR. Do the urinary bladder and large bowel interact, in sickness or in health? ICI-RS 2011. *Neurourol Urodyn*. Mar 2012;31(3):352-358.

111. Klein DN. Different reasons for comorbidity require different solutions. *World Psychiatry*. Feb 2004;3(1):28.

112. Rubin NJ. Severe asthma and depression. *Arch Fam Med*. Apr 1993;2(4):433-440.

113. Ledford DK, Lockey RF. Asthma and comorbidities. *Curr Opin Allergy Clin Immunol*. Feb 2013;13(1):78-86.

114. Boulet LP. Influence of comorbid conditions on asthma. *Eur Respir J*. Apr 2009;33(4):897-906.

115. Markowitz S, Friedman MA, Arent SM. Understanding the Relation Between Obesity and Depression: Causal Mechanisms and Implications for Treatment. *Clinical Psychology: Science and Practice*. 2008;15(1):1-20.

116. Andrews G, Atkinson E, Baker A, et al. *Comorbid mental disorders and substance use disorders: epidemiology, prevention and treatment*. Sydney: Commonwealth of Australia; 2003. http://www.health.gov.au/internet/publications/publishing.nsf/Content/drugtreat-pubs-comorbid-toc. Accessed April 26, 2013.

117. Chinn S, Rona RJ. Can the increase in body mass index explain the rising trend in asthma in children? *Thorax*. Nov 2001;56(11):845-850.

118. Centers for Disease Control and Prevention. *Social Determinants of Health. Definitions*. Atlanta, GA: Centers for Disease Control and Prevention; 2014. http://www.cdc.gov/socialdeterminants/Definitions.html. Accessed February 12, 2014.

119. Public Health Agency of Canada. *What Determines Health?* Ottawa, Canada: Public Health Agency of Canada; 2011. http://www.phac-aspc.gc.ca/ph-sp/determinants/index-eng.php. Accessed February 12, 2014.

120. Rasmussen F, Lambrechtsen J, Siersted HC, Hansen HS, Hansen NC. Low physical fitness in childhood is associated with the development of asthma in young adulthood: the Odense schoolchild study. *Eur Respir J*. Nov 2000;16(5):866-870.

121. Frank LD, Andresen MA, Schmid TL. Obesity relationships with community design, physical activity, and time spent in cars. *Am J Prev Med*. Aug 2004;27(2):87-96.

122. Hjellvik V, Tverdal A, Furu K. Body mass index as predictor for asthma: a cohort study of 118,723 males and females. *Eur Respir J*. Jun 2010;35(6):1235-1242.

123. Lamerz A, Kuepper-Nybelen J, Wehle C, et al. Social class, parental education, and obesity prevalence in a study of six-year-old children in Germany. *Int J Obes (Lond)*. Apr 2005;29(4):373-380.

124. Hernandez B, Gortmaker SL, Colditz GA, Peterson KE, Laird NM, Parra-Cabrera S. Association of obesity with physical activity, television programs and other forms of video viewing among children in Mexico city. *Int J Obes Relat Metab Disord*. Aug 1999;23(8):845-854.

125. Thomson RJ, Bramley AM, Schellenberg RR. Airway muscle stereology: implications for increased shortening in asthma. *Am J Respir Crit Care Med*. Sep 1996;154(3 Pt 1):749-757.

126. Skloot G, Permutt S, Togias A. Airway hyperresponsiveness in asthma: a problem of limited smooth muscle relaxation with inspiration. *J Clin Invest*. Nov 1995;96(5):2393-2403.

127. Cypcar D, Lemanske RF, Jr. Asthma and exercise. *Clin Chest Med*. Jun 1994;15(2):351-368.

128. Kawabori I, Pierson WE, Conquest LL, Bierman CW. Incidence of exercise-induced asthma in children. *J Allergy Clin Immunol*. Oct 1976;58(4):447-455.

129. Strachan DP, Cook DG. Health effects of passive smoking. 6. Parental smoking and childhood asthma: longitudinal and case-control studies. *Thorax*. Mar 1998;53(3):204-212.

130. Apfelbacher CJ, Loerbroks A, Cairns J, Behrendt H, Ring J, Kramer U. Predictors of overweight and obesity in five to seven-year-old children in Germany: results from cross-sectional studies. *BMC Public Health*. 2008;8:171.

131. Oddy WH, Holt PG, Sly PD, et al. Association between breast feeding and asthma in 6 year old children: findings of a prospective birth cohort study. *Bmj*. Sep 25 1999;319(7213):815-819.

132. Bergmann KE, Bergmann RL, Von Kries R, et al. Early determinants of childhood overweight and adiposity in a birth cohort study: role of breast-feeding. *Int J Obes Relat Metab Disord*. Feb 2003;27(2):162-172.

133. Newburg DS, Walker WA. Protection of the neonate by the innate immune system of developing gut and of human milk. *Pediatr Res*. Jan 2007;61(1):2-8.

134. Mielck A, Reitmeir P, Wjst M. Severity of childhood asthma by socioeconomic status. *Int J Epidemiol*. Apr 1996;25(2):388-393.

135. Hollingsworth JW, Maruoka S, Boon K, et al. In utero supplementation with methyl donors enhances allergic airway disease in mice. *J Clin Invest*. Oct 2008;118(10):3462-3469.

136. Godfrey KM, Sheppard A, Gluckman PD, et al. Epigenetic gene promoter methylation at birth is associated with child's later adiposity. *Diabetes*. May 2011;60(5):1528-1534.

137. Chatzi L, Apostolaki G, Bibakis I, et al. Protective effect of fruits, vegetables and the Mediterranean diet on asthma and allergies among children in Crete. *Thorax*. Aug 2007;62(8):677-683.

138. Berkey CS, Rockett HR, Field AE, et al. Activity, dietary intake, and weight changes in a longitudinal study of preadolescent and adolescent boys and girls. *Pediatrics*. Apr 2000;105(4):E56.

139. Laitinen T, Rasanen M, Kaprio J, Koskenvuo M, Laitinen LA. Importance of genetic factors in adolescent asthma: a population-based twin-family study. *Am J Respir Crit Care Med*. Apr 1998;157(4 Pt 1):1073-1078.

140. Anderson PM, Butcher KE. Childhood obesity: trends and potential causes. *Future Child*. Spring 2006;16(1):19-45.

141. Reichman NE, Nepomnyaschy L. Maternal pre-pregnancy obesity and diagnosis of asthma in offspring at age 3 years. *Matern Child Health J*. Nov 2008;12(6):725-733.

142. Gibson LY, Byrne SM, Davis EA, Blair E, Jacoby P, Zubrick SR. The role of family and maternal factors in childhood obesity. *Med J Aust*. Jun 4 2007;186(11):591-595.

143. Remes ST, Patel SP, Hartikainen AL, Jarvelin MR, Pekkanen J. High birth weight, asthma and atopy at the age of 16 yr. *Pediatr Allergy Immunol*. Sep 2008;19(6):541-543.

144. Reilly JJ, Armstrong J, Dorosty AR, et al. Early life risk factors for obesity in childhood: cohort study. *BMJ*. Jun 11 2005;330(7504):1357.

145. Rona RJ, Smeeton NC, Bustos P, Amigo H, Diaz PV. The early origins hypothesis with an emphasis on growth rate in the first year of life and asthma: a prospective study in Chile. *Thorax*. Jul 2005;60(7):549-554.

146. Health Canada, Division of Childhood and Adolescence. *Natural and built environments*. Ottawa, Canada: Health Canada; 2002.

147. Corburn J, Osleeb J, Porter M. Urban asthma and the neighbourhood environment in New York City. *Health Place*. Jun 2006;12(2):167-179.

148. Dietz WH, Jr., Gortmaker SL. Factors within the physical environment associated with childhood obesity. *Am J Clin Nutr*. Apr 1984;39(4):619-624.

149. Hallstrand TS, Fischer ME, Wurfel MM, Afari N, Buchwald D, Goldberg J. Genetic pleiotropy between asthma and obesity in a community-based sample of twins. *J Allergy Clin Immunol*. Dec 2005;116(6):1235-1241.

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

151. Troy LM, Miller EA, Olson S. *Hunger and Obesity: Understanding a Food Insecurity Paradigm: Workshop Summary*. Washington, DC: The National Academies Press; 2011.

152. Northridge J, Ramirez OF, Stingone JA, Claudio L. The role of housing type and housing quality in urban children with asthma. *J Urban Health*. Mar 2010;87(2):211-224.

153. Wright RJ, Fisher EB. Putting Asthma into Context: Community Influences on Risk, Behavior, and Intervention. In: Kawachi I, Berkman LF, eds. *Neighborhoods and Health*. Oxford: Oxford University Press; 2003.

154. Saelens BE, Sallis JF, Black JB, Chen D. Neighborhood-based differences in physical activity: an environment scale evaluation. *Am J Public Health*. Sep 2003;93(9):1552-1558.

155. Salo PM, Xia J, Johnson CA, et al. Indoor allergens, asthma, and asthma-related symptoms among adolescents in Wuhan, China. *Ann Epidemiol*. Sep 2004;14(8):543-550.

156. Huang SL, Shiao G, Chou P. Association between body mass index and allergy in teenage girls in Taiwan. *Clin Exp Allergy*. Mar 1999;29(3):323-329.

157. Gupta RS, Zhang X, Springston EE, et al. The association between community crime and childhood asthma prevalence in Chicago. *Ann Allergy Asthma Immunol*. Apr 2010;104(4):299-306.

158. Friedman MS, Powell KE, Hutwagner L, Graham LM, Teague WG. Impact of changes in transportation and commuting behaviors during the 1996 Summer Olympic Games in Atlanta on air quality and childhood asthma. *JAMA*. Feb 21 2001;285(7):897-905.

159. Rundle A, Hoepner L, Hassoun A, et al. Association of childhood obesity with maternal exposure to ambient air polycyclic aromatic hydrocarbons during pregnancy. *Am J Epidemiol*. Jun 1 2012;175(11):1163-1172.

160. He QQ, Wong TW, Du L, et al. Respiratory health in overweight and obese Chinese children. *Pediatr Pulmonol*. Oct 2009;44(10):997-1002.

161. Kattan M, Kumar R, Bloomberg GR, et al. Asthma control, adiposity, and adipokines among inner-city adolescents. *J Allergy Clin Immunol*. Mar 2010;125(3):584-592.

162. Barnett E, Casper M. A definition of "social environment". *Am J Public Health*. Mar 2001;91(3):465.

163. Public Health Agency of Canada. *What Makes Canadians Healthy or Unhealthy?* Ottawa, Canada: Public Health Agency of Canada; 2013. http://www.phac-aspc.gc.ca/ph-sp/determinants/determinants-eng.php#socenviron. Accessed February 13, 2014.

164. Hill JO, Wyatt HR, Reed GW, Peters JC. Obesity and the environment: where do we go from here? *Science*. Feb 7 2003;299(5608):853-855.

165. Chen E, Schreier HM. Does the social environment contribute to asthma? *Immunol Allergy Clin North Am*. Aug 2008;28(3):649-664, x.

166. Williams DR, Sternthal M, Wright RJ. Social determinants: taking the social context of asthma seriously. *Pediatrics*. Mar 2009;123 Suppl 3:S174-184.

167. Franzini L, Elliott MN, Cuccaro P, et al. Influences of physical and social neighborhood environments on children's physical activity and obesity. *Am J Public Health*. Feb 2009;99(2):271-278.

168. Chen E, Chim LS, Strunk RC, Miller GE. The role of the social environment in children and adolescents with asthma. *Am J Respir Crit Care Med*. Oct 1 2007;176(7):644-649.

169. Oliver LN, Hayes MV. Effects of neighbourhood income on reported body mass index: an eight year longitudinal study of Canadian children. *BMC Public Health*. 2008;8:16.

170. Noonan CW, Brown BD, Bentley B, et al. Variability in childhood asthma and body mass index across Northern Plains American Indian communities. *J Asthma*. Jun 2010;47(5):496-500.

171. Trasande L, Thurston GD. The role of air pollution in asthma and other pediatric morbidities. *J Allergy Clin Immunol*. Apr 2005;115(4):689-699.

172. Environment Canada. *Air*. Gatineau, QC: Environment Canada; 2013. http://www.ec.gc.ca/air/. Accessed February 21, 2014.

173. Health Canada. *Sources of Air Pollution*. Ottawa, Canada: Health Canada; 2013. http://www.hc-sc.gc.ca/ewh-semt/air/out-ext/sources/index-eng.php. Accessed April 28, 2013.

174. Environment Canada. *National Air Pollutant Emissions*. Gatineau, QC: Environment Canada; 2014. http://www.ec.gc.ca/indicateurs-indicators/default.asp?lang=en&n=E79F4C12-1. Accessed May 26, 2014.

175. Yap D, Reid N, De Brou G, Bloxam R. *Transboundary Air Pollution in Ontario*. Toronto, ON: Ontario Ministry of the Environment; 2005. http://www.airqualityontario.com/downloads/TransboundaryAirPollutionInOntario2005.pdf. Accessed April 28, 2013.

176. Environment Canada. *Minimizing Threats to Air Quality*. Gatineau, QC: Environment Canada; 2013. http://www.ec.gc.ca/dd-sd/default.asp?lang=En&n=04A29031-1. Accessed April 28, 2013.

177. Environment Canada. *2011 Air Pollutant Emission Summaries and Historical Emission Trends*. Gatineau, QC: Environment Canada; 2013.

178. Province of British Columbia. *Common Pollutants*. Victoria, BC: Government of British Columbia; 2013. http://www.bcairquality.ca/101/common-pollutants.html. Accessed April 28, 2013.

179. Geduld J. *No Breathing Room: National Illness Costs of Air Pollution.* Ottawa, Canada: Canadian Medical Association; 2008. http://www.healthyenvironmentforkids.ca/sites/healthyenvironmentforkids.ca/files/No_Breathing_Room.pdf. Accessed May 27, 2014.

180. Kytta M. Children's independent mobility in urban, small town, and rural environments. In: Camstra R, ed. *Growing up in a changing urban landscape*. Assen: Royal Van Gorcum; 1997.

181. Miller MD, Marty MA, Arcus A, Brown J, Morry D, Sandy M. Differences between children and adults: implications for risk assessment at California EPA. *Int J Toxicol.* Sep-Oct 2002;21(5):403-418.

182. Janssen NA, Hoek G, Harssema H, Brunekreef B. Childhood exposure to PM10: relation between personal, classroom, and outdoor concentrations. *Occup Environ Med.* Dec 1997;54(12):888-894.

183. Janssen NA, Hoek G, Brunekreef B, Harssema H, Mensink I, Zuidhof A. Personal sampling of particles in adults: relation among personal, indoor, and outdoor air concentrations. *Am J Epidemiol.* Mar 15 1998;147(6):537-547.

184. Dietert RR, Etzel RA, Chen D, et al. Workshop to identify critical windows of exposure for children's health: immune and respiratory systems work group summary. *Environ Health Perspect*. Jun 2000;108 Suppl 3:483-490.

185. Peters JM, Avol E, Gauderman WJ, et al. A study of twelve Southern California communities with differing levels and types of air pollution. II. Effects on pulmonary function. *Am J Respir Crit Care Med.* Mar 1999;159(3):768-775.

186. Gauderman WJ, Avol E, Gilliland F, et al. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med.* Sep 9 2004;351(11):1057-1067.

187. Rojas-Martinez R, Perez-Padilla R, Olaiz-Fernandez G, et al. Lung function growth in children with long-term exposure to air pollutants in Mexico City. *Am J Respir Crit Care Med.* Aug 15 2007;176(4):377-384.

188. Delfino RJ, Quintana PJ, Floro J, et al. Association of FEV1 in asthmatic children with personal and microenvironmental exposure to airborne particulate matter. *Environ Health Perspect*. Jun 2004;112(8):932-941.

189. Avol EL, Gauderman WJ, Tan SM, London SJ, Peters JM. Respiratory effects of relocating to areas of differing air pollution levels. *Am J Respir Crit Care Med.* Dec 1 2001;164(11):2067-2072.

190. Koren HS, Devlin RB, Graham DE, et al. Ozone-induced inflammation in the lower airways of human subjects. *Am Rev Respir Dis.* Feb 1989;139(2):407-415.

191. Shima M. Air pollution and serum C-reactive protein concentration in children. *J Epidemiol.* Sep 2007;17(5):169-176.

192. Thompson AM, Zanobetti A, Silverman F, et al. Baseline repeated measures from controlled human exposure studies: associations between ambient air pollution exposure and the systemic inflammatory biomarkers IL-6 and fibrinogen. *Environ Health Perspect*. Jan 2010;118(1):120-124.

193. Chuang KJ, Chan CC, Su TC, Lee CT, Tang CS. The effect of urban air pollution on inflammation, oxidative stress, coagulation, and autonomic dysfunction in young adults. *Am J Respir Crit Care Med.* Aug 15 2007;176(4):370-376.

194. van Eeden SF, Tan WC, Suwa T, et al. Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants (PM(10)). *Am J Respir Crit Care Med.* Sep 1 2001;164(5):826-830.

195. Michelson PH, Williams LW, Benjamin DK, Barnato AE. Obesity, inflammation, and asthma severity in childhood: data from the National Health and Nutrition Examination Survey 2001-2004. *Ann Allergy Asthma Immunol.* Nov 2009;103(5):381-385.

196. Olafsdottir IS, Gislason T, Thjodleifsson B, et al. C reactive protein levels are increased in non-allergic but not allergic asthma: a multicentre epidemiological study. *Thorax*. Jun 2005;60(6):451-454.

197. Yokoyama A, Kohno N, Sakai K, Kondo K, Hirasawa Y, Hiwada K. Circulating levels of soluble interleukin-6 receptor in patients with bronchial asthma. *Am J Respir Crit Care Med.* Nov 1997;156(5):1688-1691.

198. Scannell C, Chen L, Aris RM, et al. Greater ozone-induced inflammatory responses in subjects with asthma. *Am J Respir Crit Care Med.* Jul 1996;154(1):24-29.

199. Takemura M, Matsumoto H, Niimi A, et al. High sensitivity C-reactive protein in asthma. *Eur Respir J.* May 2006;27(5):908-912.

200. Gowers AM, Cullinan P, Ayres JG, et al. Does outdoor air pollution induce new cases of asthma? Biological plausibility and evidence; a review. *Respirology.* Aug 2012;17(6):887-898.

201. Gehring U, Wijga AH, Brauer M, et al. Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. *Am J Respir Crit Care Med.* Mar 15 2010;181(6):596-603.

202. Carlsten C, Dybuncio A, Becker A, Chan-Yeung M, Brauer M. Traffic-related air pollution and incident asthma in a high-risk birth cohort. *Occup Environ Med.* Apr 2011;68(4):291-295.

203. Shima M, Nitta Y, Ando M, Adachi M. Effects of air pollution on the prevalence and incidence of asthma in children. *Arch Environ Health*. Nov-Dec 2002;57(6):529-535.

204. McConnell R, Berhane K, Gilliland F, et al. Asthma in exercising children exposed to ozone: a cohort study. *Lancet*. Feb 2 2002;359(9304):386-391.

205. McConnell R, Islam T, Shankardass K, et al. Childhood incident asthma and traffic-related air pollution at home and school. *Environ Health Perspect*. Jul 2010;118(7):1021-1026.

206. Brauer M, Hoek G, Smit HA, et al. Air pollution and development of asthma, allergy and infections in a birth cohort. *Eur Respir J*. May 2007;29(5):879-888.

207. Jerrett M, Shankardass K, Berhane K, et al. Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement. *Environ Health Perspect*. Oct 2008;116(10):1433-1438.

208. Anderson HR, Butland BK, van Donkelaar A, et al. Satellite-based Estimates of Ambient Air Pollution and Global Variations in Childhood Asthma Prevalence. *Environ Health Perspect*. Sep 2012;120(9):1333-1339.

209. Brauer M, Hoek G, Van Vliet P, et al. Air pollution from traffic and the development of respiratory infections and asthmatic and allergic symptoms in children. *Am J Respir Crit Care Med*. Oct 15 2002;166(8):1092-1098.

210. Oftedal B, Nystad W, Brunekreef B, Nafstad P. Long-term traffic-related exposures and asthma onset in schoolchildren in oslo, norway. *Environ Health Perspect*. May 2009;117(5):839-844.

211. Penard-Morand C, Raherison C, Charpin D, et al. Long-term exposure to close-proximity air pollution and asthma and allergies in urban children. *Eur Respir J*. Jul 2010;36(1):33-40.

212. Wang TN, Ko YC, Chao YY, Huang CC, Lin RS. Association between indoor and outdoor air pollution and adolescent asthma from 1995 to 1996 in Taiwan. *Environ Res*. Oct 1999;81(3):239-247.

213. Guo YL, Lin YC, Sung FC, et al. Climate, traffic-related air pollutants, and asthma prevalence in middle-school children in taiwan. *Environ Health Perspect*. Dec 1999;107(12):1001-1006.

214. Mi YH, Norback D, Tao J, Mi YL, Ferm M. Current asthma and respiratory symptoms among pupils in Shanghai, China: influence of building ventilation, nitrogen dioxide, ozone, and formaldehyde in classrooms. *Indoor Air*. Dec 2006;16(6):454-464.

215. Dell SD, Jerrett M, Beckerman B, et al. Presence of other allergic disease modifies the effect of early childhood traffic-related air pollution exposure on asthma prevalence. *Environ Int*. Apr 2014;65:83-92.

216. Goren AI, Hellmann S. Prevalence of respiratory symptoms and diseases in schoolchildren living in a polluted and in a low polluted area in Israel. *Environ Res*. Feb 1988;45(1):28-37.

217. Nicolai T, Carr D, Weiland SK, et al. Urban traffic and pollutant exposure related to respiratory outcomes and atopy in a large sample of children. *Eur Respir J*. Jun 2003;21(6):956-963.

218. Kim JJ, Smorodinsky S, Lipsett M, Singer BC, Hodgson AT, Ostro B. Traffic-related air pollution near busy roads: the East Bay Children's Respiratory Health Study. *Am J Respir Crit Care Med*. Sep 1 2004;170(5):520-526.

219. Peters JM, Avol E, Navidi W, et al. A study of twelve Southern California communities with differing levels and types of air pollution. I. Prevalence of respiratory morbidity. *Am J Respir Crit Care Med*. Mar 1999;159(3):760-767.

220. Jedrychowski W, Flak E. Effects of air quality on chronic respiratory symptoms adjusted for allergy among preadolescent children. *Eur Respir J*. Jun 1998;11(6):1312-1318.

221. Janssen NA, Brunekreef B, van Vliet P, et al. The relationship between air pollution from heavy traffic and allergic sensitization, bronchial hyperresponsiveness, and respiratory symptoms in Dutch schoolchildren. *Environ Health Perspect*. Sep 2003;111(12):1512-1518.

222. Ramadour M, Burel C, Lanteaume A, et al. Prevalence of asthma and rhinitis in relation to long-term exposure to gaseous air pollutants. *Allergy*. Dec 2000;55(12):1163-1169.

223. Spira-Cohen A, Chen LC, Kendall M, Lall R, Thurston GD. Personal exposures to traffic-related air pollution and acute respiratory health among Bronx schoolchildren with asthma. *Environ Health Perspect*. Apr 2011;119(4):559-565.

224. Garty BZ, Kosman E, Ganor E, et al. Emergency room visits of asthmatic children, relation to air pollution, weather, and airborne allergens. *Ann Allergy Asthma Immunol*. Dec 1998;81(6):563-570.

225. Migliaretti G, Cavallo F. Urban air pollution and asthma in children. *Pediatr Pulmonol*. Sep 2004;38(3):198-203.

226. Rabinovitch N, Strand M, Gelfand EW. Particulate levels are associated with early asthma worsening in children with persistent disease. *Am J Respir Crit Care Med*. May 15 2006;173(10):1098-1105.

227. Gent JF, Triche EW, Holford TR, et al. Association of low-level ozone and fine particles with respiratory symptoms in children with asthma. *JAMA*. Oct 8 2003;290(14):1859-1867.

228. Lee SL, Wong WH, Lau YL. Association between air pollution and asthma admission among children in Hong Kong. *Clin Exp Allergy*. Sep 2006;36(9):1138-1146.

229. Glad JA, Brink LL, Talbott EO, et al. The relationship of ambient ozone and PM(2.5) levels and asthma emergency department visits: possible influence of gender and ethnicity. *Arch Environ Occup Health*. Apr 2012;67(2):103-108.

230. McConnell R, Berhane K, Gilliland F, et al. Air pollution and bronchitic symptoms in Southern California children with asthma. *Environ Health Perspect*. Sep 1999;107(9):757-760.

231. Delfino RJ, Gong H, Jr., Linn WS, Pellizzari ED, Hu Y. Asthma symptoms in Hispanic children and daily ambient exposures to toxic and criteria air pollutants. *Environ Health Perspect*. Apr 2003;111(4):647-656.

232. Goldstein IF, Weinstein AL. Air pollution and asthma: effects of exposures to short-term sulfur dioxide peaks. *Environ Res*. Aug 1986;40(2):332-345.

233. Delfino RJ, Staimer N, Gillen D, et al. Personal and ambient air pollution is associated with increased exhaled nitric oxide in children with asthma. *Environ Health Perspect*. Nov 2006;114(11):1736-1743.

234. Patel MM, Hoepner L, Garfinkel R, et al. Ambient metals, elemental carbon, and wheeze and cough in New York City children through 24 months of age. *Am J Respir Crit Care Med*. Dec 1 2009;180(11):1107-1113.

235. Hunt A, Crawford JA, Rosenbaum PF, Abraham JL. Levels of household particulate matter and environmental tobacco smoke exposure in the first year of life for a cohort at risk for asthma in urban Syracuse, NY. *Environ Int*. Oct 2011;37(7):1196-1205.

236. Pershagen G, Rylander E, Norberg S, Eriksson M, Nordvall SL. Air pollution involving nitrogen dioxide exposure and wheezing bronchitis in children. *Int J Epidemiol*. Dec 1995;24(6):1147-1153.

237. Dockery DW, Speizer FE, Stram DO, Ware JH, Spengler JD, Ferris BG, Jr. Effects of inhalable particles on respiratory health of children. *Am Rev Respir Dis*. Mar 1989;139(3):587-594.

238. Delfino RJ, Murphy-Moulton AM, Becklake MR. Emergency room visits for respiratory illnesses among the elderly in Montreal: association with low level ozone exposure. *Environ Res*. Feb 1998;76(2):67-77.

239. Cheng Y, Jin Y, Wang H, Zhao C. [Effects of air pollution from coal-burning on respiratory diseases and symptoms in children]. *Wei Sheng Yan Jiu*. Aug 2002;31(4):266-269.

240. Liu MM, Wang D, Zhao Y, et al. Effects of outdoor and indoor air pollution on respiratory health of Chinese children from 50 kindergartens. *J Epidemiol*. 2013;23(4):280-287.

241. Morgenstern V, Zutavern A, Cyrys J, et al. Respiratory health and individual estimated exposure to traffic-related air pollutants in a cohort of young children. *Occup Environ Med*. Jan 2007;64(1):8-16.

242. Jung KH, Hsu SI, Yan B, et al. Childhood exposure to fine particulate matter and black carbon and the development of new wheeze between ages 5 and 7 in an urban prospective cohort. *Environ Int*. Sep 15 2012;45:44-50.

243. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med*. Oct 2000;162(4 Pt 1):1403-1406.

244. Zhao Z, Zhang Z, Wang Z, Ferm M, Liang Y, Norback D. Asthmatic symptoms among pupils in relation to winter indoor and outdoor air pollution in schools in Taiyuan, China. *Environ Health Perspect*. Jan 2008;116(1):90-97.

245. Garcia-Marcos L, Guillen JJ, Dinwiddie R, Guillen A, Barbero P. The relative importance of socio-economic status, parental smoking and air pollution (SO2) on asthma symptoms, spirometry and bronchodilator response in 11-year-old children. *Pediatr Allergy Immunol*. May 1999;10(2):96-100.

246. Edwards J, Walters S, Griffiths RK. Hospital admissions for asthma in preschool children: relationship to major roads in Birmingham, United Kingdom. *Arch Environ Health*. Jul-Aug 1994;49(4):223-227.

247. Duhme H, Weiland SK, Keil U, et al. The association between self-reported symptoms of asthma and allergic rhinitis and self-reported traffic density on street of residence in adolescents. *Epidemiology*. Nov 1996;7(6):578-582.

248. van Vliet P, Knape M, de Hartog J, Janssen N, Harssema H, Brunekreef B. Motor vehicle exhaust and chronic respiratory symptoms in children living near freeways. *Environ Res*. 1997;74(2):122-132.

249. Wjst M, Reitmeir P, Dold S, et al. Road traffic and adverse effects on respiratory health in children. *BMJ*. Sep 4 1993;307(6904):596-600.

250. Weiland SK, Mundt KA, Ruckmann A, Keil U. Self-reported wheezing and allergic rhinitis in children and traffic density on street of residence. *Ann Epidemiol*. May 1994;4(3):243-247.

251. Arnedo-Pena A, Puig-Barbera J, Bellido-Blasco JB, et al. Risk factors and prevalence of asthma in schoolchildren in Castellon (Spain): a cross-sectional study. *Allergol Immunopathol (Madr).* May-Jun 2009;37(3):135-142.

252. Brunekreef B, Janssen NA, de Hartog J, Harssema H, Knape M, van Vliet P. Air pollution from truck traffic and lung function in children living near motorways. *Epidemiology.* May 1997;8(3):298-303.

253. Lin S, Gomez MI, Hwang SA, Munsie JP, Fitzgerald EF. Self-reported home environmental risk factors for childhood asthma: a cross-sectional study of children in Buffalo, New York. *J Asthma.* May 2008;45(4):325-332.

254. McConnell R, Berhane K, Yao L, et al. Traffic, susceptibility, and childhood asthma. *Environ Health Perspect.* May 2006;114(5):766-772.

255. English P, Neutra R, Scalf R, Sullivan M, Waller L, Zhu L. Examining associations between childhood asthma and traffic flow using a geographic information system. *Environ Health Perspect.* Sep 1999;107(9):761-767.

256. Murakami M, Ono M, Tamura K. Health problems of residents along heavy-traffic roads. *J Hum Ergol (Tokyo).* Dec 1990;19(2):101-106.

257. Morgenstern V, Zutavern A, Cyrys J, et al. Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. *Am J Respir Crit Care Med.* Jun 15 2008;177(12):1331-1337.

258. Lin S, Munsie JP, Hwang SA, Fitzgerald E, Cayo MR. Childhood asthma hospitalization and residential exposure to state route traffic. *Environ Res.* Feb 2002;88(2):73-81.

259. Shima M, Nitta Y, Adachi M. Traffic-related air pollution and respiratory symptoms in children living along trunk roads in Chiba Prefecture, Japan. *J Epidemiol.* Mar 2003;13(2):108-119.

260. Oosterlee A, Drijver M, Lebret E, Brunekreef B. Chronic respiratory symptoms in children and adults living along streets with high traffic density. *Occup Environ Med.* Apr 1996;53(4):241-247.

261. Venn A, Lewis S, Cooper M, et al. Local road traffic activity and the prevalence, severity, and persistence of wheeze in school children: combined cross sectional and longitudinal study. *Occup Environ Med.* Mar 2000;57(3):152-158.

262. Lewis SA, Antoniak M, Venn AJ, et al. Secondhand smoke, dietary fruit intake, road traffic exposures, and the prevalence of asthma: a cross-sectional study in young children. *Am J Epidemiol.* Mar 1 2005;161(5):406-411.

263. Livingstone AE, Shaddick G, Grundy C, Elliott P. Do people living near inner city main roads have more asthma needing treatment? Case control study. *BMJ*. Mar 16 1996;312(7032):676-677.

264. Wilkinson P, Elliott P, Grundy C, et al. Case-control study of hospital admission with asthma in children aged 5-14 years: relation with road traffic in north west London. *Thorax*. Dec 1999;54(12):1070-1074.

265. Miyake Y, Yura A, Iki M. Relationship between distance from major roads and adolescent health in Japan. *J Epidemiol*. Nov 2002;12(6):418-423.

266. Spengler JD, Jaakkola JJ, Parise H, Katsnelson BA, Privalova LI, Kosheleva AA. Housing characteristics and children's respiratory health in the Russian Federation. *Am J Public Health*. Apr 2004;94(4):657-662.

267. Gauderman WJ, Avol E, Lurmann F, et al. Childhood asthma and exposure to traffic and nitrogen dioxide. *Epidemiology*. Nov 2005;16(6):737-743.

268. Bullo M, Garcia-Lorda P, Salas-Salvado J. Plasma soluble tumor necrosis factor alpha receptors and leptin levels in normal-weight and obese women: effect of adiposity and diabetes. *Eur J Endocrinol*. Mar 2002;146(3):325-331.

269. Bruun JM, Verdich C, Toubro S, Astrup A, Richelsen B. Association between measures of insulin sensitivity and circulating levels of interleukin-8, interleukin-6 and tumor necrosis factor-alpha. Effect of weight loss in obese men. *Eur J Endocrinol*. May 2003;148(5):535-542.

270. Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. *J Am Soc Nephrol*. Nov 2004;15(11):2792-2800.

271. Hiura M, Kikuchi T, Nagasaki K, Uchiyama M. Elevation of serum C-reactive protein levels is associated with obesity in boys. *Hypertens Res*. Jul 2003;26(7):541-546.

272. Vozarova B, Weyer C, Hanson K, Tataranni PA, Bogardus C, Pratley RE. Circulating interleukin-6 in relation to adiposity, insulin action, and insulin secretion. *Obes Res*. Jul 2001;9(7):414-417.

273. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Low-grade systemic inflammation in overweight children. *Pediatrics*. Jan 2001;107(1):E13.

274. Sun Q, Yue P, Deiuliis JA, et al. Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. *Circulation*. Feb 3 2009;119(4):538-546.

275. Hugo ER, Brandebourg TD, Woo JG, Loftus J, Alexander JW, Ben-Jonathan N. Bisphenol A at environmentally relevant doses inhibits adiponectin release from

human adipose tissue explants and adipocytes. *Environ Health Perspect*. Dec 2008;116(12):1642-1647.

276. Ben-Jonathan N, Hugo ER, Brandebourg TD. Effects of bisphenol A on adipokine release from human adipose tissue: Implications for the metabolic syndrome. *Mol Cell Endocrinol.* May 25 2009;304(1-2):49-54.

277. Xu X, Liu C, Xu Z, et al. Long-term exposure to ambient fine particulate pollution induces insulin resistance and mitochondrial alteration in adipose tissue. *Toxicol Sci.* Nov 2011;124(1):88-98.

278. Weiss R, Dufour S, Groszmann A, et al. Low adiponectin levels in adolescent obesity: a marker of increased intramyocellular lipid accumulation. *J Clin Endocrinol Metab.* May 2003;88(5):2014-2018.

279. Brugge D, Durant JL, Rioux C. Near-highway pollutants in motor vehicle exhaust: a review of epidemiologic evidence of cardiac and pulmonary health risks. *Environ Health.* 2007;6:23.

280. DeMeo DL, Zanobetti A, Litonjua AA, Coull BA, Schwartz J, Gold DR. Ambient air pollution and oxygen saturation. *Am J Respir Crit Care Med.* Aug 15 2004;170(4):383-387.

281. McDonnell WF, Horstman DH, Hazucha MJ, et al. Pulmonary effects of ozone exposure during exercise: dose-response characteristics. *J Appl Physiol Respir Environ Exerc Physiol.* May 1983;54(5):1345-1352.

282. Yu IT, Wong TW, Liu HJ. Impact of air pollution on cardiopulmonary fitness in schoolchildren. *J Occup Environ Med.* Sep 2004;46(9):946-952.

283. Cakmak S, Dales R, Leech J, Liu L. The influence of air pollution on cardiovascular and pulmonary function and exercise capacity: Canadian Health Measures Survey (CHMS). *Environ Res.* Nov 2011;111(8):1309-1312.

284. Black JL, Macinko J. Neighborhoods and obesity. *Nutr Rev*. Jan 2008;66(1):2-20.

285. Davison KK, Lawson CT. Do attributes in the physical environment influence children's physical activity? A review of the literature. *Int J Behav Nutr Phys Act*. 2006;3:19.

286. de Vries SI, Bakker I, van Mechelen W, Hopman-Rock M. Determinants of activity-friendly neighborhoods for children: results from the SPACE study. *Am J Health Promot*. Mar-Apr 2007;21(4 Suppl):312-316.

287. Timperio A, Salmon J, Telford A, Crawford D. Perceptions of local neighbourhood environments and their relationship to childhood overweight and obesity. *Int J Obes (Lond).* Feb 2005;29(2):170-175.

288. Timperio A, Ball K, Salmon J, et al. Personal, family, social, and environmental correlates of active commuting to school. *Am J Prev Med*. Jan 2006;30(1):45-51.

289. Kerr J, Rosenberg D, Sallis JF, Saelens BE, Frank LD, Conway TL. Active commuting to school: Associations with environment and parental concerns. *Med Sci Sports Exerc*. Apr 2006;38(4):787-794.

290. Wen XJ, Balluz LS, Shire JD, Mokdad AH, Kohl HW. Association of self-reported leisure-time physical inactivity with particulate matter 2.5 air pollution. *J Environ Health*. Jul-Aug 2009;72(1):40-44; quiz 45.

291. Gordon-Larsen P, Nelson MC, Page P, Popkin BM. Inequality in the built environment underlies key health disparities in physical activity and obesity. *Pediatrics*. Feb 2006;117(2):417-424.

292. Padez C, Mourao I, Moreira P, Rosado V. Prevalence and risk factors for overweight and obesity in Portuguese children. *Acta Paediatr*. Nov 2005;94(11):1550-1557.

293. Danielzik S, Czerwinski-Mast M, Langnase K, Dilba B, Muller MJ. Parental overweight, socioeconomic status and high birth weight are the major determinants of overweight and obesity in 5-7 y-old children: baseline data of the Kiel Obesity Prevention Study (KOPS). *Int J Obes Relat Metab Disord*. Nov 2004;28(11):1494-1502.

294. Landsberg B, Plachta-Danielzik S, Much D, Johannsen M, Lange D, Muller MJ. Associations between active commuting to school, fat mass and lifestyle factors in adolescents: the Kiel Obesity Prevention Study (KOPS). *Eur J Clin Nutr*. Jun 2008;62(6):739-747.

295. van den Hooven EH, Pierik FH, de Kluizenaar Y, et al. Air pollution exposure during pregnancy, ultrasound measures of fetal growth, and adverse birth outcomes: a prospective cohort study. *Environ Health Perspect*. Jan 2012;120(1):150-156.

296. Jedrychowski W, Bendkowska I, Flak E, et al. Estimated risk for altered fetal growth resulting from exposure to fine particles during pregnancy: an epidemiologic prospective cohort study in Poland. *Environ Health Perspect*. Oct 2004;112(14):1398-1402.

297. Salam MT, Millstein J, Li YF, Lurmann FW, Margolis HG, Gilliland FD. Birth outcomes and prenatal exposure to ozone, carbon monoxide, and particulate matter: results from the Children's Health Study. *Environ Health Perspect*. Nov 2005;113(11):1638-1644.

298. Hansen CA, Barnett AG, Pritchard G. The effect of ambient air pollution during early pregnancy on fetal ultrasonic measurements during mid-pregnancy. *Environ Health Perspect*. Mar 2008;116(3):362-369.

299. Ballester F, Estarlich M, Iniguez C, et al. Air pollution exposure during pregnancy and reduced birth size: a prospective birth cohort study in Valencia, Spain. *Environ Health*. 2010;9:6.

300. Bobak M. Outdoor air pollution, low birth weight, and prematurity. *Environ Health Perspect*. Feb 2000;108(2):173-176.

301. Wilhelm M, Ghosh JK, Su J, Cockburn M, Jerrett M, Ritz B. Traffic-related air toxics and term low birth weight in Los Angeles County, California. *Environ Health Perspect*. Jan 2012;120(1):132-138.

302. Perera FP, Whyatt RM, Jedrychowski W, et al. Recent developments in molecular epidemiology: A study of the effects of environmental polycyclic aromatic hydrocarbons on birth outcomes in Poland. *Am J Epidemiol*. Feb 1 1998;147(3):309-314.

303. Choi H, Rauh V, Garfinkel R, Tu Y, Perera FP. Prenatal exposure to airborne polycyclic aromatic hydrocarbons and risk of intrauterine growth restriction. *Environ Health Perspect*. May 2008;116(5):658-665.

304. Ritz B, Yu F, Chapa G, Fruin S. Effect of air pollution on preterm birth among children born in Southern California between 1989 and 1993. *Epidemiology*. Sep 2000;11(5):502-511.

305. Ritz B, Wilhelm M, Hoggatt KJ, Ghosh JK. Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles. *Am J Epidemiol*. Nov 1 2007;166(9):1045-1052.

306. Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJ. Early adiposity rebound in childhood and risk of Type 2 diabetes in adult life. *Diabetologia*. Feb 2003;46(2):190-194.

307. Eriksson JG, Kajantie E, Lampl M, Osmond C, Barker DJ. Small head circumference at birth and early age at adiposity rebound. *Acta Physiol (Oxf)*. Jan 2014;210(1):154-160.

308. Whitaker RC, Pepe MS, Wright JA, Seidel KD, Dietz WH. Early adiposity rebound and the risk of adult obesity. *Pediatrics*. Mar 1998;101(3):E5.

309. Druet C, Stettler N, Sharp S, et al. Prediction of childhood obesity by infancy weight gain: an individual-level meta-analysis. *Paediatr Perinat Epidemiol*. Jan 2012;26(1):19-26.

310. Rolland-Cachera MF, Deheeger M, Maillot M, Bellisle F. Early adiposity rebound: causes and consequences for obesity in children and adults. *Int J Obes (Lond)*. Dec 2006;30 Suppl 4:S11-17.

311. Xu Z, Xu X, Zhong M, et al. Ambient particulate air pollution induces oxidative stress and alterations of mitochondria and gene expression in brown and white adipose tissues. *Part Fibre Toxicol.* 2011;8:20.

312. Xu X, Yavar Z, Verdin M, et al. Effect of early particulate air pollution exposure on obesity in mice: role of p47phox. *Arterioscler Thromb Vasc Biol.* Dec 2010;30(12):2518-2527.

313. Carwile JL, Michels KB. Urinary bisphenol A and obesity: NHANES 2003-2006. *Environ Res.* Aug 2011;111(6):825-830.

314. Kang JH, Kondo F, Katayama Y. Human exposure to bisphenol A. *Toxicology.* Sep 21 2006;226(2-3):79-89.

315. Yamamoto T, Yasuhara A, Shiraishi H, Nakasugi O. Bisphenol A in hazardous waste landfill leachates. *Chemosphere.* Feb 2001;42(4):415-418.

316. Matsumoto H, Adachi S, Suzuki Y. Bisphenol A in ambient air particulates responsible for the proliferation of MCF-7 human breast cancer cells and Its concentration changes over 6 months. *Arch Environ Contam Toxicol.* May 2005;48(4):459-466.

317. Heindel JJ, vom Saal FS. Role of nutrition and environmental endocrine disrupting chemicals during the perinatal period on the aetiology of obesity. *Mol Cell Endocrinol.* May 25 2009;304(1-2):90-96.

318. Nikaido Y, Yoshizawa K, Danbara N, et al. Effects of maternal xenoestrogen exposure on development of the reproductive tract and mammary gland in female CD-1 mouse offspring. *Reprod Toxicol.* Aug-Sep 2004;18(6):803-811.

319. Somm E, Schwitzgebel VM, Toulotte A, et al. Perinatal exposure to bisphenol a alters early adipogenesis in the rat. *Environ Health Perspect.* Oct 2009;117(10):1549-1555.

320. Masuno H, Kidani T, Sekiya K, et al. Bisphenol A in combination with insulin can accelerate the conversion of 3T3-L1 fibroblasts to adipocytes. *J Lipid Res.* May 2002;43(5):676-684.

321. Masuno H, Iwanami J, Kidani T, Sakayama K, Honda K. Bisphenol a accelerates terminal differentiation of 3T3-L1 cells into adipocytes through the phosphatidylinositol 3-kinase pathway. *Toxicol Sci.* Apr 2005;84(2):319-327.

322. Newbold RR, Padilla-Banks E, Snyder RJ, Jefferson WN. Developmental exposure to estrogenic compounds and obesity. *Birth Defects Res A Clin Mol Teratol.* Jul 2005;73(7):478-480.

323. Newbold RR, Padilla-Banks E, Snyder RJ, Jefferson WN. Perinatal exposure to environmental estrogens and the development of obesity. *Mol Nutr Food Res*. Jul 2007;51(7):912-917.

324. Goodman A, Brand C, Ogilvie D. Associations of health, physical activity and weight status with motorised travel and transport carbon dioxide emissions: a cross-sectional, observational study. *Environ Health*. Aug 3 2012;11(1):52.

325. Woodcock J, Banister D, Edwards P, Prentice AM, Roberts I. Energy and transport. *Lancet*. Sep 22 2007;370(9592):1078-1088.

326. Woodcock J, Edwards P, Tonne C, et al. Public health benefits of strategies to reduce greenhouse-gas emissions: urban land transport. *Lancet*. Dec 5 2009;374(9705):1930-1943.

327. Boehmer TK, Lovegreen SL, Haire-Joshu D, Brownson RC. What constitutes an obesogenic environment in rural communities? *Am J Health Promot*. Jul-Aug 2006;20(6):411-421.

328. Giles-Corti B, Macintyre S, Clarkson JP, Pikora T, Donovan RJ. Environmental and lifestyle factors associated with overweight and obesity in Perth, Australia. *Am J Health Promot*. Sep-Oct 2003;18(1):93-102.

329. Lopez-Zetina J, Lee H, Friis R. The link between obesity and the built environment. Evidence from an ecological analysis of obesity and vehicle miles of travel in California. *Health Place*. Dec 2006;12(4):656-664.

330. Frank LD, Sallis JF, Conway TL, Chapman JE, Saelens BE, Bachman W. Many pathways from land use to health: associations between neighborhood walkability and active transportation, body mass index, and air quality. *Journal of the American Planning Association*. 2006;72(1):75-87.

331. Huang F, del-Rio-Navarro BE, Monge JJ, et al. Endothelial activation and systemic inflammation in obese asthmatic children. *Allergy Asthma Proc*. Sep-Oct 2008;29(5):453-460.

332. Sood A, Cui X, Qualls C, et al. Association between asthma and serum adiponectin concentration in women. *Thorax*. Oct 2008;63(10):877-882.

333. Bennett WD, Zeman KL. Effect of body size on breathing pattern and fine-particle deposition in children. *J Appl Physiol (1985)*. Sep 2004;97(3):821-826.

334. Bennett WD, Hazucha MJ, Folinsbee LJ, Bromberg PA, Kissling GE, London SJ. Acute pulmonary function response to ozone in young adults as a function of body mass index. *Inhal Toxicol*. Nov 2007;19(14):1147-1154.

335. Alexeeff SE, Litonjua AA, Suh H, Sparrow D, Vokonas PS, Schwartz J. Ozone exposure and lung function: effect modified by obesity and airways

hyperresponsiveness in the VA normative aging study. *Chest*. Dec 2007;132(6):1890-1897.

336. Shore SA, Rivera-Sanchez YM, Schwartzman IN, Johnston RA. Responses to ozone are increased in obese mice. *J Appl Physiol (1985)*. Sep 2003;95(3):938-945.

337. Rivera-Sanchez YM, Johnston RA, Schwartzman IN, et al. Differential effects of ozone on airway and tissue mechanics in obese mice. *J Appl Physiol (1985)*. Jun 2004;96(6):2200-2206.

338. Johnston RA, Theman TA, Shore SA. Augmented responses to ozone in obese carboxypeptidase E-deficient mice. *Am J Physiol Regul Integr Comp Physiol*. Jan 2006;290(1):R126-133.

339. Dong GH, Qian Z, Liu MM, et al. Obesity enhanced respiratory health effects of ambient air pollution in Chinese children: the Seven Northeastern Cities study. *Int J Obes (Lond)*. Jul 31 2012.

340. Xu X, Deng F, Guo X, et al. Association of systemic inflammation with marked changes in particulate air pollution in Beijing in 2008. *Toxicol Lett*. Jul 20 2012;212(2):147-156.

341. Lawson JA, Janssen I, Bruner MW, Madani K, Pickett W. Urban-rural differences in asthma prevalence among young people in Canada: the roles of health behaviors and obesity. *Ann Allergy Asthma Immunol*. Sep 2011;107(3):220-228.

342. Suh M, Kim HH, Choi DP, et al. Association between body mass index and asthma symptoms among Korean children: a nation-wide study. *J Korean Med Sci*. Dec 2011;26(12):1541-1547.

343. Perez-Padilla R, Rojas R, Torres V, Borja-Aburto V, Olaiz G, The Empece Working G. Obesity among children residing in Mexico City and its impact on lung function: a comparison with Mexican-Americans. *Arch Med Res*. Jan 2006;37(1):165-171.

344. Van Der Zee SC, Hoek G, Harssema H, Brunekreef B. Characterization of particulate air pollution in urban and non-urban areas in the Netherlands. *Atmospheric Environment*. 1998;32(21):3717-3729.

345. Edgerton ES, Hartsell BE, Saylor RD, Jansen JJ, Hansen DA, Hidy GM. The Southeastern Aerosol Research and Characterization Study: Part II. Filter-based measurements of fine and coarse particulate matter mass and composition. *J Air Waste Manag Assoc*. Oct 2005;55(10):1527-1542.

346. Teo K, Chow CK, Vaz M, Rangarajan S, Yusuf S. The Prospective Urban Rural Epidemiology (PURE) study: examining the impact of societal influences on

chronic noncommunicable diseases in low-, middle-, and high-income countries. *Am Heart J*. Jul 2009;158(1):1-7.e1.

347. Hulin M, Caillaud D, Annesi-Maesano I. Indoor air pollution and childhood asthma: variations between urban and rural areas. *Indoor Air*. Dec 2010;20(6):502-514.

348. Verheij RA. Explaining urban-rural variations in health: a review of interactions between individual and environment. *Soc Sci Med*. Mar 1996;42(6):923-935.

349. McCubbin DR, Delucchi MA. The Health Costs of Motor-Vehicle-Related Air Pollution. *J Transp Econ Policy*. Sep 1999;33(3):253-286.

350. Chay KY, Greenstone M. Does air quality matter? Evidence from the housing market. *J Polit Econ*. 2005;113(2)376-424.

351. Black C, Collins A, Snell M. Encouraging walking: the case of journey-to-school trips in compact urban areas. *Urban Studies*. 2001;38(7):1121-1141.

352. Wheeler BW, Ben-Shlomo Y. Environmental equity, air quality, socioeconomic status, and respiratory health: a linkage analysis of routine data from the Health Survey for England. *J Epidemiol Community Health*. Nov 2005;59(11):948-954.

353. Robert SA. Socioeconomic position and health: the independent contribution of community socioeconomic context. *Annual Review of Sociology*. 1999:489-516.

354. Finkelstein MM, Jerrett M, DeLuca P, et al. Relation between income, air pollution and mortality: a cohort study. *Cmaj*. Sep 2 2003;169(5):397-402.

355. Brajer V, Hall JV. Recent evidence on the distribution of air pollution effects. *Contemporary Economic Policy*. 1992;10(2):63-71.

356. Larson L, Cordell H, Betz C, Green G. *Children's Time Outdoors: Results from a National Survey*. Proceedings of the Northeastern Recreation Research Symposium; 2011. http://scholarworks.umass.edu/cgi/viewcontent.cgi?article=1030&context=nerr. Accessed September 4, 2015.

357. Villarreal-Calderon A, Acuna H, Villarreal-Calderon J, et al. Assessment of physical education time and after-school outdoor time in elementary and middle school students in south Mexico City: the dilemma between physical fitness and the adverse health effects of outdoor pollutant exposure. *Arch Environ Health*. Sep-Oct 2002;57(5):450-460.

358. Cleland V, Crawford D, Baur LA, Hume C, Timperio A, Salmon J. A prospective examination of children's time spent outdoors, objectively measured physical activity and overweight. *Int J Obes (Lond)*. Nov 2008;32(11):1685-1693.

359. Sly PD, Flack F. Susceptibility of children to environmental pollutants. *Ann N Y Acad Sci*. Oct 2008;1140:163-183.

360. Statistics Canada. *Canadian Community Health Survey (CCHS) Annual component: User guide 2010 and 2009-2010 Microdata files*. Ottawa, Canada: Statistics Canada; 2011. http://www23.statcan.gc.ca:81/imdb-bmdi/document/3226_D7_T9_V8-eng.pdf. Accessed February 2, 2013.

361. Environment Canada. *2009 NPRI Reviewed Facility Data Release*. Gatineau, QC: Environment Canada; 2010. https://www.ec.gc.ca/inrp-npri/default.asp?lang=En&n=BA891E32-1. Accessed November 9, 2012.

362. Environment Canada. *Ontario Meteorological Data*. Gatineau, QC: Environment Canada; 2002. http://www.webmet.com/Canada/Ontario/ondata_reg_sw2.html. Accessed November 9, 2012.

363. Environment Canada. *National Pollutant Release Inventory (NPRI) - Data Quality Management Framework*. Gatineau, QC: Environment Canada; 2012. http://www.ec.gc.ca/inrp-npri/default.asp?lang=En&n=23EAF55A-1. Accessed March 7, 2013.

364. Youth Risk Behavior Surveillance System (YRBSS). *2013 YRBS Data User's Guide*. Atlanta, GA: Centers for Disease Control and Prevention; 2014. http://www.cdc.gov/healthyyouth/yrbs/pdf/YRBS_2013_National_User_Guide.pdf. Accessed September 17, 2014.

365. Gartshore A, Gilliland J. HEAL estimations of PM from 2009 NPRI using PC centroid receptors 20121109 [Excel spreadsheet]. London, ON: Human Environments Analysis Laboratory, Department of Geography, Western University; 2012.

366. Cimorelli A, Perry S, Venkatram A, et al. *Aermod: Description of Model Formulation*. Research Triangle Park, NC: United States Environmental Protection Agency; 2004. http://www.epa.gov/scram001/7thconf/aermod/aermod_mfd.pdf. Accessed March 8, 2013.

367. ESRI. *What is ArcGIS?* Redlands, CA: ESRI; 2004. http://downloads.esri.com/support/documentation/ao_/698What_is_ArcGis.pdf. Accessed March 8, 2013.

368. Standards Development Branch, Ontario Ministry of the Environment. *Ontario's Ambient Air Quality Criteria*. Toronto, ON: Ontario Ministry of the Environment; 2012. http://www.airqualityontario.com/downloads/AmbientAirQualityCriteria.pdf. Accessed November 9, 2012.

369. Parke C. *Essential First Steps to Data Analysis. Scenario-Based Examples Using SPSS*. Pittsburgh, PA: SAGE Publications; 2013. http://www.sagepub.com/upm-data/52387_MOD_5.pdf. Accessed April 9, 2015.

370. Statistics Canada. *Profile for Canada, Provinces, Territories and Forward Sortation Areas, 2006 Census*. Ottawa, Canada: Statistics Canada; 2008. http://www12.statcan.ca/census-recensement/2006/dp-pd/prof/rel/Lp-eng.cfm?LANG=E&APATH=3&DETAIL=0&DIM=0&FL=A&FREE=0&GC=0&GID=0&GK=0&GRP=1&PID=0&PRID=0&PTYPE=89103&S=0&SHOWALL=0&SUB=0&Temporal=2006&THEME=81&VID=0&VNAMEE=&VNAMEF=. Accessed December 4, 2012.

371. Statistics Canada. *Table 2. Low income cut-offs (1992 base) before tax*. Ottawa, Canada: Statistics Canada; 2015. http://www.statcan.gc.ca/pub/75f0002m/2012002/tbl/tbl02-eng.htm. Accessed May 9, 2016.

372. Claudio L, Stingone JA, Godbold J. Prevalence of childhood asthma in urban communities: the impact of ethnicity and income. *Ann Epidemiol*. May 2006;16(5):332-340.

373. Alsowaidi S, Abdulle A, Bernsen R. Prevalence and risk factors of asthma among adolescents and their parents in Al-Ain (United Arab Emirates). *Respiration*. 2010;79(2):105-111.

374. Galassi C, De Sario M, Biggeri A, et al. Changes in prevalence of asthma and allergies among children and adolescents in Italy: 1994-2002. *Pediatrics*. Jan 2006;117(1):34-42.

375. McMurray RG, Harrell JS, Bangdiwala SI, Deng S. Cardiovascular disease risk factors and obesity of rural and urban elementary school children. *J Rural Health*. Fall 1999;15(4):365-374.

376. Stamatakis E, Primatesta P, Chinn S, Rona R, Falascheti E. Overweight and obesity trends from 1974 to 2003 in English children: what is the role of socioeconomic factors? *Arch Dis Child*. Oct 2005;90(10):999-1004.

377. Nigg C, Shor B, Tanaka CY, Hayes DK. Adolescent at-risk weight (overweight and obesity) prevalence in Hawai'i. *Hawaii Med J*. Jul 2011;70(7 Suppl 1):4-10.

378. Li N, Hao M, Phalen RF, Hinds WC, Nel AE. Particulate air pollutants and asthma. A paradigm for the role of oxidative stress in PM-induced adverse health effects. *Clin Immunol*. Dec 2003;109(3):250-265.

379. Wichmann FA, Muller A, Busi LE, et al. Increased asthma and respiratory symptoms in children exposed to petrochemical pollution. *J Allergy Clin Immunol*. Mar 2009;123(3):632-638.

380. Rusconi F, Catelan D, Accetta G, et al. Asthma symptoms, lung function, and markers of oxidative stress and inflammation in children exposed to oil refinery pollution. *J Asthma*. Feb 2011;48(1):84-90.

381. Wong SL, Coates AL, To T. Exposure to industrial air pollutant emissions and lung function in children: Canadian Health Measures Survey, 2007 to 2011. *Health Rep*. Feb 17 2016;27(2):3-9.

382. Viehmann A, Hertel S, Fuks K, et al. Long-term residential exposure to urban air pollution, and repeated measures of systemic blood markers of inflammation and coagulation. *Occup Environ Med*. Sep 2015;72(9):656-663.

383. Stevens E, Cullinan P, Colvile R. Urban air pollution and children's asthma: what do parents and health professionals think? *Pediatr Pulmonol*. Jun 2004;37(6):530-536.

384. Majra J. Air Quality in Rural Areas. In: Mazzeo N, ed. *Chemistry, Emission Control, Radioactive Pollution and Indoor Air Quality*. Rijeka, Croatia: InTech; 2011.

385. Bruner MW, Lawson J, Pickett W, Boyce W, Janssen I. Rural Canadian adolescents are more likely to be obese compared with urban adolescents. *Int J Pediatr Obes*. 2008;3(4):205-211.

386. Environment Canada. *Frequently asked questions about the Air Quality Health Index (AQHI)*. Gatineau, QC: Environment Canada; 2015. https://www.ec.gc.ca/cas-aqhi/default.asp?lang=En&n=3E3FDF68-1. Accessed September 2, 2015.

387. Beckstead D, Brown W. *Provincial Income Disparities Through an Urban-rural Lens: Evidence from the 2001 Census*. Insights on the Canadian Economy Research Paper Series. Ottawa, Canada: Statistics Canada; 2005. http://www.publications.gc.ca/Collection/Statcan/11-624-M/11-624-MIE2005012.pdf. Accessed September 4, 2015.

388. Gouveia N, Fletcher T. Time series analysis of air pollution and mortality: effects by cause, age and socioeconomic status. *J Epidemiol Community Health*. Oct 2000;54(10):750-755.

389. Charafeddine R, Boden LI. Does income inequality modify the association between air pollution and health? *Environ Res*. Jan 2008;106(1):81-88.

390. Cakmak S, Dales RE, Judek S. Do gender, education, and income modify the effect of air pollution gases on cardiac disease? *J Occup Environ Med*. Jan 2006;48(1):89-94.

391. Sahsuvaroglu T, Jerrett M, Sears MR, et al. Spatial analysis of air pollution and childhood asthma in Hamilton, Canada: comparing exposure methods in sensitive subgroups. *Environ Health*. 2009;8:14.

392. Neidell MJ. Air pollution, health, and socio-economic status: the effect of outdoor air quality on childhood asthma. *J Health Econ*. Nov 2004;23(6):1209-1236.

393. Bartlett DB, Firth CM, Phillips AC, et al. The age-related increase in low-grade systemic inflammation (Inflammaging) is not driven by cytomegalovirus infection. *Aging Cell*. Oct 2012;11(5):912-915.

394. Piccirillo JF, Vlahiotis A, Barrett LB, Flood KL, Spitznagel EL, Steyerberg EW. The changing prevalence of comorbidity across the age spectrum. *Crit Rev Oncol Hematol*. Aug 2008;67(2):124-132.

395. Sood A. Sex differences: implications for the obesity-asthma association. *Exerc Sport Sci Rev*. Jan 2011;39(1):48-56.

396. Clampet-Lundquist S, Kling JR, Edin K, Duncan GJ. Moving teenagers out of high-risk neighborhoods: how girls fare better than boys. *AJS*. Jan 2011;116(4):1154-1189.

397. Environment Canada. *Overview of Findings of the National Pollutant Release Inventory (NPRI) Sector Coverage Study for the 2008 Reporting Year*. Gatineau, QC: Environment Canada; 2012. https://www.ec.gc.ca/inrp-npri/default.asp?lang=En&n=615C413A-1. Accessed March 7, 2013.

398. Elminir HK. Dependence of urban air pollutants on meteorology. *Sci Total Environ*. Nov 1 2005;350(1-3):225-237.

399. St-Pierre M, Beland Y. *Mode effects in the Canadian Community Health Survey: a Comparison of CAPI and CATI*. 2004 Proceedings of the American Statistical Association Meeting, Survey Research Methods. Toronto, ON: American Statistical Association; 2004. http://www23.statcan.gc.ca:81/imdb-bmdi/document/3226_D16_T9_V5-eng.htm. Accessed March 5, 2013.

400. Siersted HC, Boldsen J, Hansen HS, Mostgaard G, Hyldebrandt N. Population based study of risk factors for underdiagnosis of asthma in adolescence: Odense schoolchild study. *BMJ*. Feb 28 1998;316(7132):651-655; discussion 655-656.

401. Tanofsky-Kraff M, Cohen ML, Yanovski SZ, et al. A prospective study of psychological predictors of body fat gain among children at high risk for adult obesity. *Pediatrics*. Apr 2006;117(4):1203-1209.

402. Garn SM, Leonard WR, Hawthorne VM. Three limitations of the body mass index. *Am J Clin Nutr*. Dec 1986;44(6):996-997.

403. Garrow JS, Webster J. Quetelet's index (W/H2) as a measure of fatness. *Int J Obes.* 1985;9(2):147-153.

404. Li L, Pinot de Moira A, Power C. Predicting cardiovascular disease risk factors in midadulthood from childhood body mass index: utility of different cutoffs for childhood body mass index. *Am J Clin Nutr.* Jun 2011;93(6):1204-1211.

405. Janssen I, Katzmarzyk PT, Srinivasan SR, et al. Utility of childhood BMI in the prediction of adulthood disease: comparison of national and international references. *Obes Res.* Jun 2005;13(6):1106-1115.

406. Shields M, Connor Gorber S, Tremblay MS. Estimates of obesity based on self-report versus direct measures. *Health Rep.* Jun 2008;19(2):61-76.

407. Strauss RS. Comparison of measured and self-reported weight and height in a cross-sectional sample of young adolescents. *Int J Obes Relat Metab Disord.* Aug 1999;23(8):904-908.

408. Himes JH, Faricy A. Validity and reliability of self-reported stature and weight of US adolescents. *Am J Hum Biol.* Mar-Apr 2001;13(2):255-260.

409. Himes JH, Hannan P, Wall M, Neumark-Sztainer D. Factors associated with errors in self-reports of stature, weight, and body mass index in Minnesota adolescents. *Ann Epidemiol.* Apr 2005;15(4):272-278.

410. Goodman E, Hinden BR, Khandelwal S. Accuracy of teen and parental reports of obesity and body mass index. *Pediatrics.* Jul 2000;106(1 Pt 1):52-58.

411. Stunkard AJ, Albaum JM. The accuracy of self-reported weights. *Am J Clin Nutr.* Aug 1981;34(8):1593-1599.

412. Fonseca H, Silva AM, Matos MG, et al. Validity of BMI based on self-reported weight and height in adolescents. *Acta Paediatr.* Jan 2010;99(1):83-88.

413. Bachmann J, Damberg R, Caldwell J, Edwards C, Koman P. *Review of the national ambient air quality standards for particulate matter: Policy assessment of scientific and technical information. OAQPS staff paper. Final report*. Environmental Protection Agency, Research Triangle Park, NC (United States). Office of Air Quality Planning and Standards; 1996.

414. Burton A, Altman DG. Missing covariate data within cancer prognostic studies: a review of current reporting and proposed guidelines. *Br J Cancer.* Jul 5 2004;91(1):4-8.

415. Laumbach R, Meng Q, Kipen H. What can individuals do to reduce personal health risks from air pollution? *J Thorac Dis.* Jan 2015;7(1):96-107.

416. Leung DY. Outdoor-indoor air pollution in urban environment: challenges and opportunity. *Frontiers in Environmental Science.* 2015;2(69)1-7.

417. Thompson Coon J, Boddy K, Stein K, Whear R, Barton J, Depledge MH. Does participating in physical activity in outdoor natural environments have a greater effect on physical and mental wellbeing than physical activity indoors? A systematic review. *Environ Sci Technol.* Mar 1 2011;45(5):1761-1772.

418. Sothern MS, Loftin M, Suskind RM, Udall JN, Blecker U. The health benefits of physical activity in children and adolescents: implications for chronic disease prevention. *Eur J Pediatr.* Apr 1999;158(4):271-274.

419. Pakhale S, Doucette S, Vandemheen K, et al. A comparison of obese and nonobese people with asthma: exploring an asthma-obesity interaction. *Chest.* Jun 2010;137(6):1316-1323.

420. van Veen IH, Ten Brinke A, Sterk PJ, Rabe KF, Bel EH. Airway inflammation in obese and nonobese patients with difficult-to-treat asthma. *Allergy.* May 2008;63(5):570-574.

421. Magnussen H, Watz H. Systemic inflammation in chronic obstructive pulmonary disease and asthma: relation with comorbidities. *Proc Am Thorac Soc.* Dec 2009;6(8):648-651.

422. Government of Canada. *Outdoor Air Quality and Human Health.* http://publications.gc.ca/collections/Collection/H46-2-98-211E-11.pdf. Accessed February 12, 2013.

Appendices

Appendix A: Sample size and response rates by year for the Canadian Community Health Survey.

	Survey Year				
	2007	2008	2009	2010	2011
Sample Size (N)					
All respondents aged 12 years and over – Canada	65,946	66,013	61,679	63,191	63,542
Adolescents only* - Canada	6,201	6,712	6,463	6,403	6,268
Adolescents only* - Ontario	2,065	2,290	2,271	2,252	2,181
Adolescents only* - Southwestern Ontario	556	625	596	626	571
Response Rates (%)					
Overall	77.6	75.2	73.2	71.5	69.8
By health region	66.3-87.6	66.1-86.3	62.5-84.7	61.7-84.8	59.4-79.3
*Adolescents who were pregnant at the time of the survey were excluded from the analysis.					

Appendix B: Comparison of model covariates between adolescents with and without missing data.

This Appendix compares respondents that had missing data for the asthma and overweight variables (excluded from the analysis; n=289) to respondents that had no missing outcome data (included in the analysis; n=2,685) on all regression model covariates. The means of continuous variables were compared using independent samples t-tests (Table 14), and chi-square tests were used to compare both groups on all categorical covariates (Table 15). All analyses were conducted using rescaled CCHS survey weights. Compared with the included participants, participants who were excluded had a lower mean income (9.3 vs. 9.7; p=0.0028), lower mean age (14.0 vs. 15.1 years; p<0.0001), but a higher average $PM_{2.5}$ exposure concentration (0.34 vs. 0.29 $\mu g/m^3$; p=0.0138); see Table 14. Participants with missing data were also more likely to live in an urban core (77.4% vs. 64.9%; p<0.0001), more likely to live in a lower income household (47.9% vs. 38.5%; p=0.0025), more likely to be in the younger adolescent age group, (78.7% vs. 54.7%; p<0.0001), and more likely to be female (56.7% vs. 46.9%; p=0.0019); see Table 15.

After excluding adolescents with missing data from the analysis, adolescents who live in an urban core area, reside in a lower income household, who are younger, female, and are exposed to high air pollution concentrations were underrepresented in the sample. Since income and age are not expected to modify the association between air pollution and asthma and overweight, an underrepresentation of lower income and younger adolescents in the sample may not have impacted the results. However, considering that the main association is expected to be weaker among females than males, an underrepresentation of females in the sample may have caused in our results to appear stronger than they actually are. On the other hand, urban core adolescents are expected to have a stronger association between air pollution and asthma and overweight than their non-urban core peers; as a result, their underrepresentation in the sample may have made the main association appear weaker than it truly is. Since each of these covariates likely affect the main association in a different way, it is hard to determine how excluding respondents with missing data would have affected the results as a whole.

Table 14: Independent samples t-test comparing continuous covariates between adolescents with and without missing data.

	Missing Data	N	Mean	SD	t	p
$PM_{2.5}$ exposure	Yes	289	0.34	0.34	**-2.46**	**0.0138**
	No	2,685	0.29	0.29		
Income	Yes	289	9.3	2.1	**2.99**	**0.0028**
	No	2,685	9.7	2.2		
Age	Yes	289	14.0	1.8	**9.53**	**<0.0001**
	No	2,685	15.1	1.9		

Note: Results significant at the 5% level ($p<0.05$) are highlighted in bold.
Abbreviations: SD (standard deviation); t (test statistic for independent samples t-test); p (probability); $PM_{2.5}$ (particulate matter with an aerodynamic diameter of 2.5 μm or less, $\mu g/m^3$)

Table 15: Chi-square test for categorical covariates comparing adolescents with and without missing data.

	Missing Data N (%)	
	Yes	No
Urban core residence (χ^2=**17.5358**, p<**0.0001**)		
Yes	77.4%	64.9%
No	22.6%	35.1%
Income (χ^2=**9.1082**, p=**0.0025**)		
Higher	52.1%	61.5%
Lower	47.9%	38.5%
Age (χ^2=**58.6481**, p<**0.0001**)		
12-15 years	78.7%	54.7%
16-18 years	21.3%	45.3%
Sex (χ^2=**9.6832**, p=**0.0019**)		
Male	43.3%	53.1%
Female	56.7%	46.9%
Note: Results significant at the 5% level (p<0.05) are highlighted in bold. **Abbreviations:** χ^2 (chi-square test statistic); p (probability)		

Appendix C: Adjusted logistic regression models exploring whether the $PM_{2.5}$ and co-morbid asthma and overweight relationship is modified by urban core residence status, income, age, and sex.

The following provides estimates from adjusted logistic regression models that assessed the presence of interaction between $PM_{2.5}$ and one of the following modifiers at a time: urban core residence status (Table 16); income (Table 17); age (Table 18); and sex (Table 19). Each model is adjusted for the effects of the remaining three covariates. Seeing that the linear and curvilinear interaction effects between $PM_{2.5}$ and income and $PM_{2.5}$ age were not statistically significant, Table 17 and Table 18 also present adjusted estimates from models testing for a parallel effect (i.e., main association controlling for the covariate of interest - income and age, respectively).

Table 16: Adjusted logistic regression models exploring whether the effect of $PM_{2.5}$ on co-morbid asthma and overweight is modified by urban core residence status among adolescents residing in southwestern Ontario.

	OR (95% CI)	Log odds	SE	p
Linear Effect				
$PM_{2.5}$	**0.00 (0.00, 0.31)**	**-7.9425**	**3.4500**	**0.0213**
Urban core (No=0)	**0.28 (0.10, 0.80)**	**-1.2700**	**0.5349**	**0.0176**
$PM_{2.5}$*urban core[a]	**4744.78 (5.30, 4249449.49)**	**8.4648**	**3.4682**	**0.0147**
Curvilinear Effect				
$PM_{2.5}$	0.00 (0.00, 2.53)	-9.1126	5.1228	0.0753
$PM_{2.5}^2$	19.77 (0.00, 210837868.40)	2.9844	8.2564	0.7177
Urban core (No=0)	**0.25 (0.07, 0.94)**	**-1.3749**	**0.6701**	**0.0402**
$PM_{2.5}$*urban core[a]	16202.16 (0.52, 508105672.20)	9.6929	5.2824	0.0665
$PM_{2.5}^2$*urban core[b]	0.05 (0.00, 558829.67)	-3.0209	8.2933	0.7157

Notes: (1) Results significant at the 5% level ($p<0.05$) are highlighted in bold; (2) Both models are controlled for the effects of income, age, and sex.

Abbreviations: OR (odds ratio); CI (confidence interval); SE (standard error); p (probability); $PM_{2.5}$ (particulate matter with an aerodynamic diameter of 2.5 µm or less, $\mu g/m^3$)

[a]Interaction between linear effect of $PM_{2.5}$ and urban core status.

[b]Interaction between curvilinear effect of $PM_{2.5}$ and urban core status.

Table 17: Adjusted logistic regression models exploring whether the effect of $PM_{2.5}$ on co-morbid asthma and overweight is modified by household income among adolescents residing in southwestern Ontario.

	OR (95% CI)	Log odds	SE	p
Model 1				
$PM_{2.5}$	0.49 (0.10, 2.32)	-0.7064	0.7903	0.3714
Income (Lower=0)	0.68 (0.36, 1.30)	-0.3855	0.3300	0.2427
$PM_{2.5}$*income	3.29 (0.58, 18.48)	1.1894	0.8813	0.1771
Model 2				
$PM_{2.5}$	0.78 (0.00, 5.32)	-2.4455	2.1005	0.2443
$PM_{2.5}^2$	3.35 (0.27, 41.73)	1.2078	1.2875	0.3482
Income (Lower=0)	0.55 (0.20, 1.50)	-0.6046	0.5161	0.2414
$PM_{2.5}$*income	12.26 (0.10, 1560.72)	2.5064	2.4727	0.3108
$PM_{2.5}^2$*income	0.39 (0.02, 7.40)	-0.9492	1.5058	0.5285
Model 3				
$PM_{2.5}$	1.14 (0.56, 2.32)	0.1315	0.3614	0.7159
Income (Lower=0)	0.96 (0.62, 1.49)	-0.0382	0.2242	0.8648
Model 4				
$PM_{2.5}$	0.44 (0.04, 4.48)	-0.8256	1.1862	0.4864
$PM_{2.5}^2$	1.84 (0.46, 7.27)	0.6075	0.7019	0.3868
Income (Lower=0)	0.96 (0.62, 1.49)	-0.0419	0.2243	0.8518

Notes: (1) Results significant at the 5% level ($p<0.05$) are highlighted in bold; (2) All models are controlled for the effects of urban core status, age, and sex.
Abbreviations: OR (odds ratio); CI (confidence interval); SE (standard error); p (probability); $PM_{2.5}$ (particulate matter with an aerodynamic diameter of 2.5 µm or less, $\mu g/m^3$)
Models: (1) interaction between linear effect of $PM_{2.5}$ and income; (2) interaction between curvilinear effect of $PM_{2.5}$ and income; (3) linear effect of $PM_{2.5}$ controlling for the effect of income; (4) curvilinear effect of $PM_{2.5}$ controlling for the effect of income

Table 18: Adjusted logistic regression models exploring whether the effect of $PM_{2.5}$ on co-morbid asthma and overweight is modified by age among adolescents residing in southwestern Ontario.

	OR (95% CI)	Log odds	SE	p
Model 1				
$PM_{2.5}$	2.13 (0.93, 4.86)	0.7549	0.4215	0.0733
Age (Younger=0)	**2.56 (1.37, 4.79)**	**0.9394**	**0.3200**	**0.0033**
$PM_{2.5}$*age	0.21 (0.04, 1.00)	-1.5570	0.7961	0.0505
Model 2				
$PM_{2.5}$	1.07 (0.04, 26.09)	0.0723	1.6271	0.9646
$PM_{2.5}^2$	1.51 (0.24, 9.43)	0.4091	0.9363	0.6621
Age (Younger=0)	2.51 (0.94, 6.73)	0.9203	0.5031	0.0674
$PM_{2.5}$*age	0.22 (0.00, 21.39)	-1.5297	2.3431	0.5139
$PM_{2.5}^2$*age	1.08 (0.06, 19.75)	0.0791	1.4818	0.9574
Model 3				
$PM_{2.5}$	1.12 (0.55, 2.27)	0.1090	0.3637	0.7645
Age (Younger=0)	**1.60 (1.04, 2.47)**	**0.4717**	**0.2208**	**0.0327**
Model 4				
$PM_{2.5}$	0.40 (0.04, 4.12)	-0.9073	1.1858	0.4442
$PM_{2.5}^2$	1.91 (0.48, 7.53)	0.6456	0.7009	0.3570
Age (Younger=0)	**1.61 (1.04, 2.48)**	**0.4765**	**0.2210**	**0.0311**

Notes: (1) Results significant at the 5% level ($p<0.05$) are highlighted in bold; (2) All models are controlled for the effects of urban core status, income, and sex.
Abbreviations: OR (odds ratio); CI (confidence interval); SE (standard error); p (probability); $PM_{2.5}$ (particulate matter with an aerodynamic diameter of 2.5 µm or less, $\mu g/m^3$)
Models: (1) interaction between linear effect of $PM_{2.5}$ and age; (2) interaction between curvilinear effect of $PM_{2.5}$ and age; (3) linear effect of $PM_{2.5}$ controlling for the effect of age; (4) curvilinear effect of $PM_{2.5}$ controlling for the effect of age

Table 19: Adjusted logistic regression models exploring whether the effect of $PM_{2.5}$ on co-morbid asthma and overweight is modified by sex among adolescents residing in southwestern Ontario.

	OR (95% CI)	Log odds	SE	p
Linear Effect				
$PM_{2.5}$	**0.04 (0.00, 0.79)**	**-3.3520**	**1.5914**	**0.0352**
Sex (Female=0)	**0.38 (0.17, 0.84)**	**-0.9685**	**0.4071**	**0.0174**
$PM_{2.5}$*sex[a]	**60.61 (2.52, 1456.95)**	**4.1045**	**1.6223**	**0.0114**
Curvilinear Effect				
$PM_{2.5}$	93.86 (0.00, 195037030.80)	4.5418	7.4220	0.5406
$PM_{2.5}^2$	0.00 (3.24×10^{-19}, 1039239.76)	-14.3596	14.3949	0.3185
Sex (Female=0)	0.90 (0.15, 5.38)	-0.1103	0.9148	0.9041
$PM_{2.5}$*sex[a]	0.03 (0.00, 60306.79)	-3.6582	7.4825	0.6249
$PM_{2.5}^2$*sex[b]	1603180.46 (0.00, 2.86×10^{18})	14.2875	14.3937	0.3209

Notes: (1) Results significant at the 5% level ($p<0.05$) are highlighted in bold; (2) Both models are controlled for the effects of urban core status, income, and age.

Abbreviations: OR (odds ratio); CI (confidence interval); SE (standard error); p (probability); $PM_{2.5}$ (particulate matter with an aerodynamic diameter of 2.5 µm or less, $\mu g/m^3$)

[a]Interaction between linear effect of $PM_{2.5}$ and sex.

[b]Interaction between curvilinear effect of $PM_{2.5}$ and sex.

Curriculum Vitae

Name:	Phylicia Gonsalves
Post-secondary Education and Degrees:	The University of Western Ontario London, Ontario, Canada 2010 B.M.Sc. Honors (Physiology and Medical Cell Biology) The University of Western Ontario London, Ontario, Canada 2016 M.Sc. (Epidemiology and Biostatistics)
Honours and Awards:	Schulich School of Medicine and Dentistry, Western University Graduate Thesis Research Award 2013 Children's Health Research Institute Travel Fund 2013 Children's Health Research Institute Quality of Life Initiative Grant 2012-2013 Schulich School of Medicine and Dentistry, Western University Schulich Graduate Scholarship 2011-2013 Western University Dean's Honor List 2006, 2009, 2010 Western Scholarship of Excellence 2005-2006
Related Work Experience	Epidemiology Practicum Health Data Analyst Middlesex-London Health Unit 2013