An investigation of the association between maternal and early life exposure to urban greenness and the incidence of childhood asthma

By

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Abstract

Several epidemiological studies have investigated the possible role that living in areas with greater amounts of greenspace has on the development of childhood asthma. These studies have yielded inconsistent findings, and not all have explored the relevance of timing of exposure. This research was done to address gaps in this area.

The role of residential surrounding greenness on the risk of incident asthma was studied using a retrospective cohort study design that consisted of 982,131 singleton births in Ontario, Canada between 2006 and 2013. Two measures of greenness, the Normalized Different Vegetation Index (NDVI) and the Green View Index (GVI), were assigned to the residential addresses of these infants. Longitudinally based diagnoses of asthma were determined by using provincial administrative health data. The extended Cox hazards model was used to characterize associations between greenness measures and asthma (up to age 12 years) while adjusting for several risk factors.

An interquartile range increase (0.08) of the NDVI during childhood, within a residential buffer of 250m was associated with a 4% (95%CI=0.95-0.96) reduced risk of asthma, however, no association was noted after adjusting for ambient concentrations of air pollution (HR=0.99;95%CI=0.99-1.01).

These findings suggest that greenness is not associated with the development of asthma, and those investigations of this topic account for the possible confounding role of air pollution. However, greenness may reduce the risk of developing asthma for children diagnosed at older age, and for those children born during the spring and summer seasons.

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List of Abbreviations

Abbreviation	Description
aOR	Adjusted Odds Ratio
BIS	BORN Information System
BORN	Better Outcomes Registry and Network
BRQ	Brief Respiratory Questionnaire
CANUE	Canadian Urban Environmental Health Research Consortium
CI	Confidence Interval
CIHI	Canadian Institute for Health Information
DA	Dissemination Area
DAD	Discharge Abstract Database
GERD	Gastroesophageal Reflux Disease
GSV	Green Street View
GVI	Green View Index
GWR	Geographically weighted regression
ICES	Institute for Clinical Evaluative Sciences
IKN	ICES Key Number
ISAAC	International Study of Asthma and Allergies in Childhood
LiDAR	Light Detection and Ranging
LUR	Land Use Regression
MOMBABY	Linked Delivering Mother and Newborns
MODIS	Moderate Resolution Imaging Spectroradiometer
NDVI	Normalized Difference Vegetation Index
NIR	Near-Infrared wavelength Reflectance
OASIS	Ontario Asthma Surveillance Information System
OR	Odds Ratio
PEF	Peak Expiratory Flow
PHAC	Public Health Agency of Canada
RED	Red wavelength reflectance
RPDB	Registered Persons Database
SAVI	Soil Adjusted Vegetation Index
SD	Standard deviation
SDI	Socio-Demographic Index
SES	Socio-Economic Status
SHS	Second-hand Smoke
WHO	World Health Organization

1.0 Introduction

Asthma is a highly prevalent chronic disease, and in 2018, it was estimated that 339 million people worldwide were living with asthma (1). According to the most recently available statistics of the prevalence of asthma in Canada (2018), nearly 3.8 million Canadians are asthmatic (2), and of these 850,000 are less than 14 years of age (3). While a number of risk factors for asthma have been identified, its causes are not fully understood (4).

Despite an incomplete understanding of the etiology of childhood asthma, it is widely recognized that environmental exposures play an important role. Air pollution has been identified as a risk factor that influences the development (5), and the exacerbation (6) of asthma in children. Aeroallergens, including pollens, can exacerbate asthma and contribute to seasonal variations in hospital visits for asthma (7). Moreover, chronic exposure to pollen during infancy appears to increase the risk of developing asthma during childhood (8).

More recently, a number of epidemiological studies have assessed the role that urban vegetation has on the incidence of childhood asthma (9,10). These studies have predominantly assessed chronic exposure to greenness, namely, whether residential surrounding greenness increases or decreases the risk of developing asthma. As a whole, the findings of these studies have been inconsistent with some studies reporting positive associations (11–13), while others do not (14–20).

The relevance of some environmental exposures with respect to asthma likely differs by age. Past research has demonstrated that children are likely more vulnerable

than adults to the respiratory health effects from air pollution (21). This may be due to a number of factors including children have developing respiratory and immune systems, as well as activity patterns that vary as children age, as well as substantial differences with adults (22). Previous studies have also demonstrated that the timing of the exposure matters in the etiology of childhood asthma, with authors positing that prenatal exposures play a critical role (23). Indeed, some suggest that these differences in risk may vary across trimesters of pregnancy. For example, a Canadian study found stronger associations between air pollution and asthma in the second trimester (24), but elsewhere, a U.S. based found that associations were most pronounced in the third trimester (25). Therefore, for environmental exposures, it is important to consider to what extent associations vary according to the timing of exposure (e.g., pregnancy, infancy, and later childhood). The association between childhood asthma and greenness has also been shown to vary by the biological sex of the infant (at birth) (17), maternal history of asthma (14), maternal age (14), season of birth (19), and socio-demographic status (17).

With this background, the overall aim of this thesis is to investigate associations between long-term exposure to residential surrounding urban greenness, and the incidence of childhood asthma. This includes an assessment of variations in the exposure-response relationships across different exposure periods spanning from pregnancy, through early childhood. In addition, a secondary objective of this thesis is to explore whether associations between greenness and asthma vary by: biological sex, maternal history of asthma, maternal age at birth, socio-demographic status, and season of birth.

It is also important to note that the collection and analyses of the data presented in this thesis was adversely impacted by the COVID-19 pandemic, including limitations in

accessing more detailed data from the ICES datasets. Specifically, as analysis was done remotely, for issues related to privacy and confidentiality some data elements were converted from continuous to classification variables. This is not fundamentally expected to change the findings presented in this thesis. Analyses are underway using the more complete dataset for the purposes of producing a peer-reviewed publications.

1.1 Asthma

1.1.1 Definition and Clinical Classification of Asthma

Asthma is a chronic disease of the bronchial tree, and this disease is related to airflow restriction in the lungs (26). Symptoms of asthma may include shortness of breath, coughing, chest tightness, and wheezing (26). Asthma usually first appears in childhood, and is often associated with other characteristics of atopic diseases, such as eczema and hayfever (4). Symptoms of asthma often improve as children age, and with some children, asthma resolves at a later age (27). A portion of asthmatic children require treatments to manage asthma, and these may include inhaled corticosteroids (28).

Asthma is typically diagnosed based on a physical examination. This examination includes listening to signs of wheezing and coughing while breathing, and lung function tests such as spirometry and Peak Expiratory Flow (PEF). PEF measures the maximum speed of expiration, and unlike spirometry tests, are administered to children less than 6 years old (29). A spirometry test measures the amount and the speed of air entering and exiting the lungs, but it is generally not used in children who are less than 6 years of age (29). In some cases, physicians use X-rays or allergy tests to identify other underlying conditions that contribute to asthmatic symptoms (29). These symptoms can be a precursor of asthma. For example, some suggest that approximately 40% of children who

wheeze when they catch a cold or respiratory infection are eventually diagnosed with asthma (4,30).

Asthma is a commonly diagnoses disease that varies substantially in severity from mild incidental wheezing to severe life-threatening airways closure (31). Individuals with mild intermittent asthma may have symptoms from two times a month to two times a week, yet these symptoms are mild enough so as not to hinder most activities. However, for these individuals, exercise can lead to wheezing, a tight chest, and coughing (32). In mildly persistent asthma, symptoms tend to occur more than twice a week, however, the person does not usually experience symptoms several times a day (33). In contrast, those with moderate persistent asthma have symptoms most days (34). Severe asthma is defined as having persistent asthma symptoms (35), and those with severe asthma tend to experience symptoms throughout the day (27). Children with persistent asthma typically do not respond well to medication, even if taken regularly, and those with severe asthma experience significant limitations in activities of daily living (31,36).

Triggers of childhood asthma include airway infections, allergens, irritants, exercise, and stress (37). It is important to recognize and avoid the triggers for asthma treatment in children, and for some, the best way to prevent an asthma attack is the use a quick-relief inhaler when asthma-related symptoms flares-up (37). At present, there is no cure for asthma, although having a healthy lifestyle and avoiding allergens and other environmental stimuli are helpful to managing asthma (38,39).

1.1.2 The Epidemiology of Childhood Asthma

In this section, the epidemiological features of childhood asthma are reviewed. This section includes descriptive statistics by country, calendar period, as well as behavioural, and social risk factors.

Regional variations in asthma

Worldwide, the prevalence of asthma has risen in recent decades (40), and it varies substantially by region (41). According to the International Study of Asthma and Allergies in Childhood (ISAAC), in 2008, the estimated prevalence of severe asthma in children 6-7 years of age ranges from approximate nil in Pune, India to a high of 20.3% in Costa Rica (42). Severe asthma symptoms in the ISAAC study were defined, using self-reported questionnaire data from parents, as more than four attacks of wheezing, and more than one night a week of sleep disturbances caused by wheezing. This study reported that asthma symptoms in developing countries were more common and severe relative to high-income countries. Furthermore, an estimated 16.5% of subjects around the world with severe asthma never received an asthma diagnosis (42). The prevalence of undiagnosed asthma was highest in Africa at 40.2%, while it was the lowest in English-speaking countries (5.8%) (42). In the component of the ISAAC study for Canada, the estimated prevalence of severe asthma in Hamilton and Saskatoon was 17.2% and 11.2%, respectively, among young children aged 6 to 7. These estimates were similar to those found in Western countries (43)

Variations by Age

Asthma disproportionally affects children more than adults (44,45). In Canada, the percentage of children and youth with physician-diagnosed asthma in 2011-2012 was

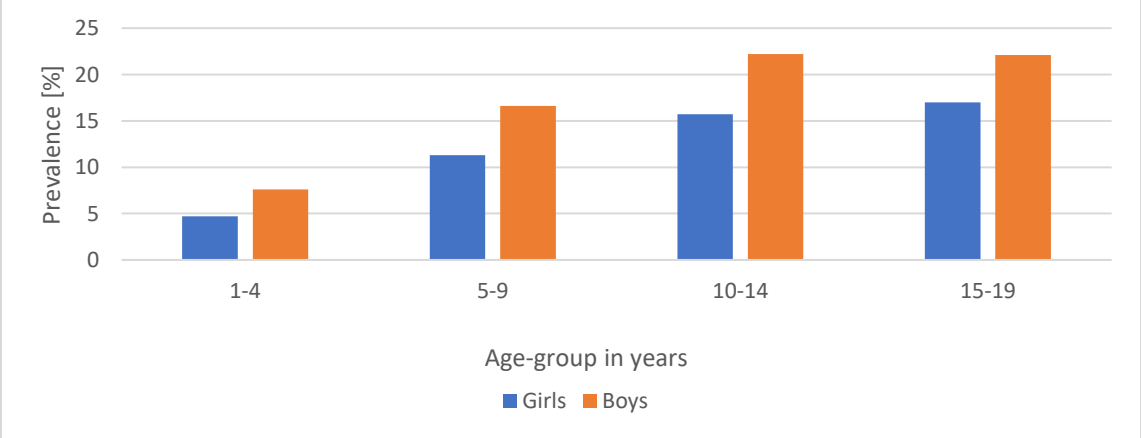
62% higher than in adults (46). An estimated 6.2% of Canadian children aged 1 – 4, 14% of children aged 5–9 and 19% of children and youth aged 10-14 were living with physician-diagnosed asthma in 2011-2012 (46). Also, asthma hospitalization rates were higher among children who were less than 5 years of age when compared to older children between 2013 and 2016 (3).

Incidence rates for asthma by age-group exhibit similar patterns to prevalence-based measures, but with a peak incidence occurring at an earlier age. The peak incidence rate was observed among those in the 1–4 age group with 2796.4 cases per 100,000 population for boys and 1821.6 cases per 100,000 population for girls.

Variations by sex

The prevalence of asthma is more common among boys than girls (47). For example, in Canada in 2011-12, among those aged 10-14, the prevalence of asthma among boys and girls was 22.2%, and 15.7%, respectively (Figure 1). Similarly, among those aged 5-9, the prevalence of diagnosed asthma is higher in boys (16.6%) than girls (11.3%) (2).

Figure 1: Self-reported prevalence of physician-diagnosed asthma among Canadians aged ≤19 years, by age-group and sex, Canada, 2011–2012.



Adapted from Public Health Agency of Canada (2)

Temporal trends in Canada:

In Canada, the prevalence of physician-diagnosed asthma decreased slightly from 13% to 10% for children aged 1 to 9 years old between the years 2000–2001 and 2011–2012 (2). However, in contrast, the prevalence of asthma among children aged 10 to 19 increased from 9% to 20% during this same period (2). In 2014, it was estimated that, among Canadians less than 15 years of age, approximately 15% were living with asthma (48).

1.1.2.1 Risk Factors for Childhood Asthma

There are a number of risk factors for childhood asthma. These factors include lifestyle behaviours, genetics, maternal and paternal factors, and environmental exposures (4). A brief summary of the findings from the literature on these risk factors is provided in this section.

Low birthweight:

Low birthweight has been found to increase the risk of childhood asthma (49). Low birthweight is commonly defined as a weight, at full-term birth, that is less than 2500g or 5 lbs (8 ounces) (50). A meta-analysis of epidemiological studies on this topic, which included 13 cohort studies, reported that infants, weighing less than 2.5 kg at term had a 16% (95% CI: 12.8% to 19.7%) increased risk of developing asthma relative to those with a birthweight between 2.5 and 4.0 kg (51). In addition, preterm birth has been shown to be associated with an increased risk of developing childhood asthma (52,53).

Maternal age:

Maternal age at delivery has been extensively investigated as a possible risk factor for childhood asthma. However, according to a recent systematic review, there are some inconsistencies in the associations of maternal age at delivery and childhood asthma (54). In this systematic review, some studies found that advanced maternal age is associated with an increased risk of asthma, while, other studies found this association in children born to younger mothers, or reported no association (54).

Maternal history of asthma:

A family history of asthma and allergy has been associated with an increased risk of developing childhood asthma (55). Findings from a meta-analysis found that maternal history of asthma was more strongly associated with the development of childhood asthma relative to a parental history of asthma (56). In this study, the risk of asthma in infants whose mothers had was threefold higher (Odds Ratio (OR): 3.04; 95% CI: 2.59–3.56) when compared to mothers with no history of asthma (56). The corresponding odds ratio for paternal history was 2.44 (95% CI: 2.14–2.79). Further, a recent study in Canada found increased risks of childhood asthma in children born to older mothers with a history of asthma (57).

Exposure to second-hand cigarette smoke:

Exposure to second-hand cigarette smoke (SHS), or environmental tobacco smoke, has been shown to increase the risk of developing several childhood respiratory diseases, including asthma (58). Children exposed to SHS, have been shown to have an increased risk of developing asthma (59,60). Findings from a recent systematic review and meta-analysis found that children exposed to parental SHS had a 24% increased risk

of developing asthma when compared to those with no exposure (OR = 1.24; 95% (CI) = 1.20-1.28) (56). Previous findings suggest that exposures received during pregnancy may contribute to increased risks of developing childhood asthma (61,62).

Socioeconomic status:

Lower socioeconomic status has been shown to be associated with an increased risk of developing asthma (63). Further, many social determinants of health such as housing, neighbourhood safety, and access have been shown to impact the health of children with asthma with those of lower socioeconomic status faring worse (64). A systematic review of asthma, across all ages, reported that across 183 studies, the pooled odds ratio of prevalent asthma in the most affluent sociodemographic category (based on income and education) was 1.38 (95% CI: 1.37–1.39) compared to those in the lowest (65). A pooled analysis of 10 European cohorts found that women with lower levels of educations were more likely to have children who later developed asthma (66). Similar patterns have also been reported in Ontario where children born in more deprived neighbourhoods were at greater risk of incident asthma (HR 1.11; 95% CI, 1.09-1.13) when compared to those who were not (67).

Parity and birth order:

Parity refers to the number of times a woman has given birth to a fetus with a gestational age of at least 24 weeks (68). Parity has been linked to the risk of developing childhood asthma. For example, a record linkage study in the UK found that the risk of asthma was lower among first-born children (69). As parity and birth order are closely connected to maternal age, epidemiological studies need to collect data for all three of

these characteristics to understand the individual contribution of each on the trajectories of childhood asthma.

Medication use:

The use of antibiotics in children during the first year of life does not increase the risk of asthma, but some studies have found an increased of incident asthma if the child receives more courses of antibiotics (70,71). While the risk is low for the child, the use of antibiotics during pregnancy is related to increased offspring asthma severity. In a recent systematic review, 9 out of 12 studies on the outcome of asthma, statistically significant relationships were reported between asthma in offspring and prenatal antibiotics use. The range was between (OR 1.13, 95% CI: 1.02-1.24) to (OR 3.19, 95% CI:1.52–6.67) (72). The timing of exposure, however, had no effect on childhood asthma risk among pregnant women receiving a single antibiotic course (73,74).

Season of birth:

Some studies have suggested that the season of birth is related to the development of childhood asthma (75–78). However, these findings are inconsistent. For example, one nationwide cohort study reported that children born during the fall and winter seasons are at an increased risk of asthma development compared to those born in the summer season (76). This study found that there was a 24% increased risk (HR=1.24, 95%CI: 1.17-1.33) of asthma among children after two years of age compared to summer. It was speculated this could be due to a higher rate of respiratory infections during the cold seasons causing children born in fall and winter to be exposed to higher levels of respiratory infections early on. Further, children born during summer do not experience high pollen counts until the next spring (infants usually spend their first six months of life indoors), whereas

children born during fall and winter will be exposed to high pollen counts earlier when spring season arrives (76). In contrast, a large cohort study in Israel concluded that children born during the summer season are at a greater risk of developing asthma compared with a winter birth (77).

Heartburn (gastroesophageal reflux disease):

Asthma attacks and heartburn often occur at the same time (79). Heartburn can aggravate asthma attacks, and asthma can exacerbate heartburn, especially severe heartburn (80). This condition is called gastroesophageal reflux disease (GERD). A systematic review on GERD and asthma in children, found only five studies of 20 used a case-control study design with 1314 cases with asthma and 2434 controls without asthma. The average prevalence of GERD in these five case-control studies was 4.8% in controls and 22.0% in asthma cases with a pooled odds ratio of 5.6 (95% CI: 4.3–6.9) (81).

1.1.2.2 Environmental Risk Factors for Childhood Asthma

Air pollution:

Many environmental factors have been identified as risk factors for the development of asthma, and exposure to outdoor air pollution has likely drawn the most attention (5). Air pollution can impact asthma in two distinct ways. First, short-term, or acute exposure to air pollution can trigger adverse respiratory events (82). For example, daily increases in air pollution are associated with increased numbers of emergency department visits for asthma in all ages, but especially in children and the elderly (22). The second way air pollution exposures can influence asthma is through longer-term, or chronic, exposures that increase the risk of developing asthma (5). Children are more

susceptible to the health effects of air pollution relative to adults for many reasons including narrower airways, more rapid rate of breathing, and developing lungs (21).

A study of Ontario singleton birth found that perinatal exposure to ambient air pollution is associated with childhood development of asthma (24). Researchers found second-trimester exposures to $PM_{2.5}$ and NO_2 increase the risk of developing asthma by 7% and 6% respectively. Hazard Ratio (HR) per interquartile range (IQR) increase for $PM_{2.5}$ was 1.07 (95% CI: 1.06-1.09) and HR per IQR increase for NO_2 was 1.06 (95% CI 1.03-1.08) (24). An updated version of this dataset was used in this thesis.

From a Canadian perspective, urban air pollution is important given that nearly 80% of Canadians live in urban areas (83). The primary source of air pollution is anthropogenic sources that arise from transportation-related air pollution (TRAP) (83). TRAP is a mixture of particulate matter (PM), polycyclic aromatic hydrocarbons (PAH), volatile organic compounds (VOC), and gases such as nitrogen oxides (NO, NO_2) and carbon monoxide (CO). Nitrogen dioxide (NO_2) is often used as a marker of traffic pollution because it is strongly correlated with roadways (84). Fine particulate matter ($PM_{2.5}$) pollution refers to particulate matter with a median aerodynamic diameter of fewer than 2.5 micrometers. These particles can be inhaled more deeply, and relative to larger particles pose more of a human health hazard (84,85).

A recent meta-analysis of epidemiological studies found that children who live in higher areas of traffic-related pollution are more likely to develop asthma (86). This highlights the relevance of longer-term exposure to air pollution. This meta-analysis found that an interquartile range increase in annual average $PM_{2.5}$ level (3.2 $\mu g/m^3$) was

associated with an increased odds of incident asthma (OR: 1.28; 95% CI: 1.10-1.49). This same study reported a similar association for NO_2 (86).

Indoor air pollution:

Indoor air pollution can be a risk factor for childhood asthma due to the fact that children spend a lot of their time at home (39,87). Indoor air pollution may be influenced by home heating, fumes from cooking, house dust mites, cockroaches, SHS, and pets (mainly cats and dogs) (88). Young children who are sensitive to indoor air pollution, and are at the long-term exposure may continue to have asthma symptoms in adolescence and adulthood, and their lung function is worse than non-sensitive children (87,89).

1.2 Greenness

1.2.1 Background

Natural environments can exert an important role on human health and wellbeing (90,91). High-intensity developments in urban areas have often disregarded the importance of the presence of parks and other green spaces on human health (92). Exposure to the natural environment is associated with numerous environmental benefits such as improving air quality, mitigating the effects of the extreme temperature of urban heat islands, reducing noise pollution, and providing shelter from ultraviolet radiation (93,94).

In addition to the impacts that urban vegetation has on harmful environmental exposures, a series of epidemiological studies suggest that urban vegetation improves health via several different pathways. Greenness provides important opportunities for more social interactions (95) and spaces for recreational activities (96). It has been linked

to healthier birthweights (97), reduced mortality rates (98), increased physical activity (97), and improved general health (98).

1.2.2 Methods to characterize exposure to greenness

There are two fundamentally different approaches to assigning exposure to greenness in epidemiological studies, namely, self-reported and objective methods. The use of objective methods to assign exposure to greenness has the important advantage that measurement error is less likely to be differential by health status than self-reported measures (99). However, self-reported measures of greenness can provide participants the opportunity to provide a more detailed description of greenness, including features that they find most relevant (100). In this section, these approaches are described in greater detail.

1.2.2.1 Self-reported measures of greenness

Self-reported measures of greenness rely on study participants to provide data on features of green spaces, and how they interact with them. This could include questionnaires that ask participants to provide information on a variety of features of greenness including the amount, quality, accessibility, diversity and frequency of interaction (101). A strength of these subjective measures of greenness is that the questionnaires allow for the collection of very detailed data on several aspects of vegetation. An important weakness, however, is that the accuracy of participants' responses to these questions may vary by health status. Specifically, individuals who lead a more active lifestyle, or are healthy enough to move around their neighbourhoods, may have a greater awareness of nearby greenness features. As a result, there may be

differential exposure measurement error in greenness by health status, and this could introduce bias into epidemiological studies of greenness and health (102).

1.2.2.2 Objective measures of greenness

In contrast to self-reported measures, objective measures of greenness can be derived for participants for whom residential, or other relevant geolocations, can be determined. This method produces an estimate of greenness exposure that is unlikely to have differential error by the health status of the participants. However, this does not imply that other sources of bias, such as participation bias may be present in a study. A limitation of this objective approach is that measures of greenness may be somewhat limited, and not capture specific aspects of greenness relevant to biological pathways that impact health. For example, there are multiple species of trees, and types of vegetation and these may have differential impacts on providing shelter from UV, buffering against noise, or reducing air pollution concentrations. Furthermore, features of greenness change over the course of a year, and from year to year and these may not be readily captured retrospectively, or prospectively with objectively defined measures. The use of objective measures of greenness provides a way to standardize these measures of greenness between studies, including in different regions and countries. Below, is a description of some of the more prominent objective measures of greenness that have been used in epidemiological research.

The Normalized Difference Vegetation Index:

The Normalized Difference Vegetation Index (NDVI) is the most commonly used measure of greenness in epidemiological research (103). The NDVI is based on remote-sensing data, and thus provides a skyview measure (104). It is derived using information

collected from the Moderate Resolution Imaging Spectroradiometer (MODIS) satellite sensors (105). The data used to derive the NDVI are based on the spectral reflectance measurements that are acquired in the visible regions, or red band, and then acquired in the near-infrared regions. Mathematically, the NDVI is computed based on the following algorithm:

$$NDVI = \frac{NIR - RED}{NIR + RED} \qquad \text{Equation (1)}$$

where the NIR and RED represent the amount of near-infrared wavelength reflectance, and the amount of red wavelength reflectance, respectively (104). The NDVI provides a measure of overall vegetation and ranges from -1 to 1 with higher values denoting areas with more vegetation. Typically, one can interpret NDVI values between 0.6 and 0.8 to represent areas with dense vegetation, medium values (0.2 to 0.3) represent grasslands and shrubs, and extremely low values (0.1 and below) to represent barren areas such as sand, rock, water, or snow (100,103). The NDVI is usually estimated for months that correspond to the growing season, and when there is no snow cover. Measures of the NDVI are typically computed for areas within specified buffer distances from specific geolocation (i.e., latitude and longitude). Epidemiological studies commonly assign greenness to an individual's place of residence and many will consider different buffer distances of 100, 250, 500, and 1000 m (106).

The NDVI has the limitation that it is unable to differentiate between types of vegetation such as grasses, tree canopies, and shrubs. As a result, the NDVI may not represent the best greenness measure to capture some pathways relevant for health studies. Nonetheless, it is widely used because it is available historically, and can be mapped in any region of the world.

Figure 2: Illustration of the Normalized Difference Vegetation Index (NDVI) for Ottawa, Canada

Source (107)

Soil Adjusted Vegetation Index:

In areas that the soil surface is exposed (i.e., area less than 40% vegetative cover), the reflectance of light in red and near-infrared (NIR) wavelengths can influence vegetation index values (108). The soil-adjusted vegetation index (SAVI) was developed as an extension of the NDVI to minimize soil influences. It is derived by multiplying the NDVI by (1+L) where L is the soil brightness correction factor into the denominator of the NDVI equation (109).

$$NDVI = \frac{NIR - RED}{NIR + RED + L} \times (1 + L) \qquad \text{Equation (2)}$$

L is constrained by 0 and 1 when the amount or cover of green vegetation is very high (L=0), then SAVI = NDVI; and L=1, when the area has no green vegetation (108).

The Green View Index:

The Green View Index (GVI) is derived from Google Street View (GSV) panoramas (110). The GVI provides a measure of vegetation at street level and can estimate presence of tree canopies (111). The GVI score represents the percentage of vegetation along the streets, and therefore, values for this metric range between 0 and 100. The GVI has been previously described, and applied in an Ottawa-based analysis of greenness and physical health (112).

The advantage of the GVI method compared to the other measures, such as the NDVI, is that it captures the urban greening profile from the street view rather than from above (113). In other words, it better characterizes what individuals see as they walk in and around their neighbourhoods. The GVI, unlike the NDVI, is able to differentiate between low-level grasses and tree canopies. While the GVI offers this advantage, it is limited because it is computationally intensive to create a measure for each geographical coordinate as each estimate relies on 6 high-resolution images that are typically taken at one moment in time.

Light Detection and Ranging:

Light Detection and Ranging (LiDAR) is a remote sensing method that uses light (pulsed laser) to determine variable distances by targeting an object (115). LiDAR systems allow scientists to examine the surface of the Earth, including natural environments (115,116). The strengths of LiDAR is that this measure is capable of collecting elevation data in a dense forest, and it can be used to map inaccessible areas. In contrast, LiDAR is unable to penetrate thick vegetation and does not work well in areas where there are large reflections or high sun angles (117).

1.3 Greenness and childhood asthma

This section reviews the epidemiological studies that investigated associations between chronic exposure to greenness and childhood asthma. It begins with a review of the possible biological pathways whereby greenness may impact the risk of developing asthma.

1.3.1 Greenness pathways that increases the risk of asthma

There are a number of possible pathways whereby chronic (i.e., longer-term) exposure to greenness may impact the risk of developing asthma. Some have suggested that residential greenness increases a child's exposure to microbial antigens, which in turn alters the immune system leading to an increased risk of developing asthma (118). Alternatively, it has been suggested proximity to greenness increases the risk of developing asthma because children living in these areas are more likely to be exposed to pollen (119). For example, a population-based birth cohort study in New York City found that tree canopy cover near the prenatal address was associated with a higher incidence of allergic sensitization to tree pollen (11).

1.3.2 Greenness pathways that reduce the risk of asthma

It has been suggested that increased biodiversity of vegetation reduces the risk of several inflammatory conditions (120). This hypothesis is supported with the findings from several studies (121–123). Another pathway that has been proposed is the 'hygiene hypothesis' where exposure to greenness during early childhood strengthens the immune system and reduces the risk of atopic allergic outcomes (121,124).

1.3.2 Epidemiological studies of greenness and asthma

Canadian studies

Sbihi et al. (14) undertook a 10-year follow-up study that included approximately 65,000 children born between 1999 and 2002 in Vancouver, British Columbia. Incident cases of asthma were identified by linking the administrative health data of mothers to childhood asthma diagnoses captured with the provincial universal health insurance program. For each identified case of childhood asthma, five controls were randomly selected from provincial health administration data after matching by age and sex. Conditional logistic regression was used to characterize the association between greenness and the incidence of asthma. Analyses were done separately to examine associations between greenness and incident asthma for those diagnosed up to 5 years of age, and those diagnosed between 6 and 10 years of age. The investigators modelled the NDVI and used a buffer of 100 m around the residential address lived in during the perinatal period. The reported associations between greenness and incident asthma were adjusted for a number of covariates including birth weight, maternal education, household income (neighbourhood level), parity, distance to the nearest park, gestational period, and maternal age at delivery. An interquartile range increase in the NDVI (IQR=0.11) was associated with 4% reduced odds (OR=0.96, 95% CI: 0.93-0.99) of incident asthma among those less than 5 years of age. This risk estimate was not adjusted for residential measures of ambient air pollution. Nevertheless, this inverse association was stronger in models that adjusted for air pollution (OR=0.67, 95% CI: 0.47-0.93). This inverse association was slightly stronger among children born to mothers with low educational attainment (OR = 0.92; 95% CI, 0.86-0.97). In contrast, neighbourhood-level

household income did not modify associations between greenness and asthma. There was no association between greenness and incident asthma among those between the ages of 6 to 10. Specifically, the odds ratios of incident asthma in relation to an IQR increase in greenness was 1.00 (95% CI, 0.90-1.11).

This same research team published a subsequent analysis that extended this study period through 2016 (125). The aim of this latter paper was to model asthma trajectories of these same 65,000 children and assess how exposure to air pollution and greenness was related to the incident trajectories of transient asthma, early-onset chronic asthma, and late-onset chronic asthma. Incident cases of asthma were identified from provincial health administration data. Overall, they concluded that "greenness was not associated with any of the asthma trajectories". Strengths of this study include a population-based cohort design, large sample size, and a 10 year follow-up. . Weaknesses of the study included a lack of residential histories to model changes in exposures during follow-up, and to evaluate risk differences between exposures received during pregnancy and after birth.

International studies

Several international studies have explored associations between greenness and the development of asthma and allergy-related symptoms among those less than 18 years of age. A review of these studies, in chronological order, is provided in this section.

Lovasi et al. (11) in 2013, conducted a population-based birth cohort study to investigate the relationship between residential tree canopy, and the prevalence of childhood asthma. This study included 549 African American and Dominican children

who lived in socially deprived neighbourhoods, in New York City, US. The prevalence of physician-diagnosed asthma was determined by self-reported survey data provided by the parents when their child was 5 and 7 years of age. Tree canopy, at a circular buffer distance of 250m from participants' residence at the time of birth, was determined by using LiDAR data. The risk estimates were adjusted for a series of variables including sex, age, ethnicity, maternal asthma, parity, cigarette smoke, population density, sociodemographic status, traffic volume, and nearby parkland percentage. The authors found that an 8% increase in tree canopy coverage increased the prevalence of asthma (RR: 1.17; 95% CI 1.02-1.33) for those 7 years of age. A similar relative risk estimate for those 5 years of age was 1.11 (95% CI 0.85-1.45). Strengths of this study include the high-resolution LiDAR to characterize urban tree canopies, and the ability to adjust for several risk factors. The survey instrument used to identify incident childhood asthma had previously been validated. However, the study may have limited generalizability as the study population was restricted to African American, and Dominican families who lived in low-income areas of New York City.

More recently, Dadvand et al. (126) reported findings from a cross-sectional study of greenness and prevalent asthma. This study collected data from 3,178 children, aged 9-12, who lived in Sabadell, Spain. Prevalent asthma was determined using the ISAAC survey instrument (127), and the questionnaire also collected information on other asthma risk factors. The NDVI, based on the place of residence at the time of the survey was conducted, was modelled. Four residentially-based buffer distances (100m, 250m, 500m, 1000m) were considered. Measures of association were adjusted for a number of factors including sex, age, exposure to environmental tobacco smoke at home, older siblings,

type of school (public vs. private), parental education, and parental history of asthma. They found no association between an IQR increase in the NDVI and current asthma at buffers of 100 m and 250 m with odds ratios of 1.00 (0.82-1.21), and 1.00 (0.78-1.27), respectively. Similarly, no statistically significant associations were observed for 500m and 1000m buffer distances. An important limitation of this study was the cross-sectional design and potential for participation bias and reliance on prevalent asthma outcomes.

Andrusaityte et al. (12) used a cross-sectional study nested within a cohort study to investigate associations between greenness and asthma among children 4 to 6 years of age in Kaunas, Lithuania (2016). They analyzed data from pregnant women who were recruited into a newborn's cohort study in 2007-2009, and had not moved during follow-up. The study included 112 asthmatic children identified using parental responses to the ISAAC questionnaire, while 1,377 children were classified as non-asthmatic. Greenness was measured with the mean NDVI at 100, 300 and 500 m buffer areas from each child's residence during pregnancy. The study also collected data on distance to parks. Information for a series of confounders was collected from the survey, including mother's age at childbirth, maternal education, parental asthma, maternal smoking during pregnancy, breastfeeding, antibiotic use during the first year of life, keeping a cat in the past 12 months, living in a flat, yearly mean of ambient $PM_{2.5}$ and NO_2 were adjusted. An IQR increase in the 100 m NDVI was found to increase the odds of asthma by 43% (OR=1.43; 95% CI: 1.10-1.85). The authors found no statistically significant association with asthma according to distance between the participant's residence and the nearest park.

Feng and Astell-Burt (16) conducted a cross-sectional study on 4,447 Australian children to examine residential green space asthma prevalence among children aged 6 to 7. Greenness was measured by the percentage of land identified as "parkland" and this exposure was classified into three categories: < 20%, 20% – 40%, and > 40% designations. A diagnosis of 'affirmative' asthma was determined by triangulation of parental responses to 3 questions: physician diagnosis, asthma medication in the past 12 months, or wheezing for at least one week in the past 12 months. The study considered air pollution concentration by asking participants about their perceptions of traffic volume near their residences. The authors found no association between greenness and asthma for those unexposed to heavy traffic. However, they reported associations between heavy traffic and asthma were weaker for participants who lived in areas with greater (> 40%) green space coverage (OR: 0.32, 95% CI: 0.12-0.84). The use of the objectively defined measure of greenness is a strength of this study. In addition, their definition of an 'affirmative asthma' case considered physician-diagnosed asthma, the presence of wheeze, and whether asthma medications were used. While they explored the joint impacts of air pollution and greenness on asthma prevalence, their use of a 'perceived' traffic measure was somewhat limited as it may be prone to reporting bias. As with many other studies on this topic, this study relied on a cross-sectional study design and a prevalent measure of asthma. This design has limited ability to inform on causal relationships.

Tischer et al. (15) examined associations between residential greenness and several health outcomes including wheezing, asthma, and allergic rhinitis in a cohort of Spanish children. This study included 2,472 children and incident respiratory outcomes

up to four years of age were ascertained through physician diagnosis. The authors modelled two measures of urban greenness. The first was a dichotomous measure of proximity to greenness (≤300 m *versus* >300 m) that was determined using an urban atlas. The second relied on the NDVI within a 300m radius of residence at the time of birth, and after the child had attained four years of age. This study adjusted for a series of potential confounders including biological sex, maternal education, maternal allergy, breastfeeding, household pets, maternal smoking during pregnancy, SHS, sociodemographic status, and air pollution. Overall, proximity to green space was not associated with asthma in children. Similarly, residential surrounding greenness (NDVI) was not significantly associated with asthma. Strengths of the study included the longitudinal study design, while on the other hand, the measures of associations were limited as the precision of the measures of association was poor.

Donovan et al. (17) reported on associations between greenness and incident asthma in a New Zealand birth cohort of approximately 50,000 individuals who were followed for up to 18 years. Incident cases of asthma were identified by using prescription drug billings, and hospital visit diagnoses. The mean NDVI across a child's life course and the mean lifetime number of natural land-cover types was determined using meshblock areas. A 'meshblock area' is the smallest geographic census unit in New Zealand. The study considered a large number of confounding variables, including roadway proximity, air pollution, ethnicity, gender, birth outcomes, parents' occupation, parents' education, parents' smoking status, antibiotic use, number of siblings, meshblock size and birth order. They found that those who lived in greener areas were less likely to develop asthma. Specifically, a one standard deviation (s.d.) increase in the mean lifetime

residential NDVI was associated with a 6.0% (95% CI: 1.9-9.9%) reduction in incident asthma. Similar strengths of associations between greenness and asthma were observed among those diagnosed before the age of two and those who were older. In addition, vegetation diversity was associated with a reduced risk of childhood asthma. Specifically, a one s.d. increase in the mean lifetime number of different natural land-cover types in a child's residential meshblock was associated with a 6.7% (95% CI: 1.5%-11.5%) reduction in incident asthma. The strength of the association was similar across different levels of sociodemographic status. This study also evaluated differences in the strength of the association by sex and found no variation between boys and girls. The longitudinal design of this study and the relatively large sample size are strengths of this study. Although, they defined incident asthma based on prescriptions and hospital diagnoses which has some advantages over the use of self-reported data, some cases could be influenced by cultural issues and access to healthcare.

A cross-sectional study by Eldeirawi et al. (18) assessed associations between greenness and asthma in 1,915 Mexican American children who lived in Chicago's inner-city in 2004 and 2005. Self-administered questionnaires completed by the parents were used to identify prevalent asthma and other behavioural and sociodemographic variables. The NDVI measure of greenness was linked to the place of residence at the time of the interview. The authors found that the association between NDVI within a 100 m buffer of and asthma incidence was modified by whether there were cigarette smokers in the household. Specifically, in non-smoking homes at the time of child's birth, a one IQR increase in residential surrounding greenness was not associated with the lifetime prevalence of childhood asthma (aOR: 1.08; 95% CI: 0.82-1.42). In contrast, the

corresponding odds ratio of asthma in smoking homes at the time of child's birth was 0.53 (95% CI: 0.31-0.92). Similar associations were observed with other NDVI buffer distances. A weakness of the study is the cross-sectional design which is unable to provide insights on the timing of exposure and disease onset, the lack of data on residential history, and information about proportion of time spent indoors or outdoors.

Hsieh and colleagues (13) undertook a matched case-control study in Taiwan on this topic. The study included approximately 7,040 subjects younger than 18 years old who were recruited between 2001 and 2013. Cases and controls were 1:1 matched by age, sex, and by the year of diagnosis of the asthma case. The NDVI at the place of residence for asthma and control subjects was measured and assigned based on the year of diagnosis of asthma (for case) or matched year (for control). The odds ratios calculated to describe associations between greenness and asthma were adjusted for urbanicity, number of healthcare visits, area levels of income, and air pollution. Conditional logistic regression analyses found a positive association between greenness and asthma in preschool children by the increase in surrounding green spaces. The OR was 1.33 (95% CI 1.11-1.60) for the fourth quintile (61-80%) compared to the lowest quintile (0-20%). However, exposure to the highest greenness quintile (81-100%) compared to the lowest quintile (0-20%) was not significantly associated with asthmatic status (OR: 1.09; 95% CI: 0.88-1.34). Due to the lack of personal information, the authors were unable to adjust for relevant confounders. The study had the advantage of having a large number of participants and an objectively determined measure of asthma.

Li et al. (20) conducted a cross-sectional study on residential greenness health effects in Suzhou, China. The study included approximately 5,700 middle school students

(12 to 15) between 2014 and 2015. For each home address, the distance to the nearest park and NDVI values at different distance buffers (100m, 200m, 500m, 1000m) were calculated at the time of survey. The child's age and sex, parental education, and parental history of asthma were considered as adjustment factors. The authors found an increased risk of asthma and other respiratory conditions among those who lived closer to parks. Specifically, those who lived in the fourth quartile (farthest away from the park (>1348 m)) had an odds ratio of current asthma of 0.58 (95% CI: 0.35-0.99), and an odds ratio of ever asthma of 0.70 (95% CI: 0.50-0.96) when compared to those in the nearest quartile (<600 m). In addition, this study stratified analyses by sex and SES based on father's education in association with quartiles of distance from a park and asthma. The direction of the association was the same in men and women with odds ratios of (OR: 0.76, 95% CI: 0.50-1.14) and (OR: 0.62, 95% CI: 0.38-1.01), respectively for the highest NDVI quartile compared to lowest. Also, the direction of association in lower education and higher education was similar, and no statistical significance was observed. The study was unable to assess associations for early life exposures and similar to other studies, the cross-sectional nature of the study is limited for making causal inferences.

More recently, Zeng et al. (19) published findings from a large population-based cross-sectional study. Unlike many other studies that used a residentially- based measure of greenness, this study modelled school-based measures. Prevalent cases of asthma were identified using a self-reported questionnaire in 59754 schoolchildren who were between the ages of 6 and 14 and who resided in seven northeast cities in China. Green space around schools was estimated using the NDVI, as well as the SAVI at buffers from 30 to 1000m. The study adjusted for a series of potential confounders including age, gender,

parental education, family income, breastfeeding status, low birth weight, preterm, residential area, SHS, mould in-home, and home coal usage. They found that a 0.1-unit increase in NDVI, within 1000m of the children's school location, was associated with a reduced odds of prevalent asthma (OR: 0.81, 95% CI: 0.76-0.87). Similar associations were observed for other buffered distances and for the SAVI 1000m (OR: 0.79, 95%CI: 0.72-0.85). However, these associations were weakened after adjusting for air pollution. Strengths of the study included a large study population two different measures of greenness. However, the cross-sectional design and self-reported questionnaires for outcome information and covariates were the limitations.

1.3.4 Summary of the Literature

In summary, the evidence from past studies of residential greenness and incident asthma has produced inconsistent findings. On the basis of statistical significance, of the 12 papers identified in this review, two studies reported that surrounding greenness was associated with an increased risk of asthma, and four reported inverse associations. Nearly all of the studies used the NDVI to measure residential greenness and typically, for buffer distances of between 100 and 300m. Other greenness measures considered included distance to parks, tree canopy, and the SAVI.

The majority of studies (7 out of 13) used a cross-sectional design which is limited for drawing causal inferences. Cross-sectional studies rely on prevalent outcomes, and therefore, pose challenges for understanding the timing of the relationship between exposure on disease onset. Longitudinal studies or case-control studies offer distinct advantages for characterizing the timing of the relationship between exposure and disease onset.

Most of the studies of greenness and asthma attempted to control for the potential confounding influence of air pollution. Relatively few studies have evaluated whether air pollution modifies the association between greenness and incident asthma, although findings from one study suggest this may occur (19). There was some, but limited evidence, that greenness confers a reduced risk of developing asthma among those of lower SES. Additionally, some studies reported findings that the strength of the association between greenness and asthma varied across a number of factors including biological sex of the child, maternal age at delivery, and maternal smoking. Finally, findings from the cohort studies, which are capable of evaluating associations between timing of exposure and onset of asthma, produced inconsistent findings based on the period of exposure.

1.4 Study Rationale

Based on the findings in published epidemiological literature, it remains unclear whether residential proximity to greenness in urban areas increases the risk of developing childhood asthma. Findings from the epidemiological studies have been inconsistent in terms of the strength of the association between greenness and asthma. Differences in the reported findings may be due to several factors, including study design, control for other risk factors, small sample sizes, short follow-up period, or the use of different measures of greenness or even buffer distances. Most studies used a cross-sectional design that modelled greenness and health outcomes at the same point in time. The use of a longitudinal study design, capable of identifying incident asthma outcomes is preferred to inform on possible causal associations (128). Cohort studies are better capable of modelling the timing of the exposure in relation to the clinical onset of asthma.

The research presented in this thesis addresses important research gaps by making use of a longitudinal study design while considering both skyview and streetview based measures of greenness, and indeed different buffer distances. Additionally, it uses a study population that includes a large number of participants that allows for the examination of variations between greenness and incident asthma by the period of exposure, biological sex, and socio-economic status. Finally, the study is capable of accounting for the potential confounding influence of air pollution.

2.0 Thesis Objectives

The primary objective of this research was to characterize associations between residential surrounding greenness and incident asthma in children, up to 12 years of age, in urban areas in Ontario. This research question was investigated by using a population-based retrospective cohort study design. Two measures of greenness were used to address this research question, namely, a streetview (GVI) and a skyview (NDVI) measure. This research also investigated variations in the associations between greenness and incident asthma by the timing of the exposure. Three time periods were considered: pregnancy, the first year of life, and time-weighted average exposure during childhood.

The secondary objectives of this research were to evaluate whether associations between residential surrounding greenness and incident asthma varied by:

- Age of the child,
- The biological sex of the child,
- Maternal characteristics (i.e., history of asthma, maternal age at delivery, and smoking during pregnancy),
- Season of birth (i.e., fall, spring, summer, winter),
- And the socio-demographic status of the neighbourhood of the child (based on median area-level household income).

3.0 Methods

This study used Ontario administrative health data to create a population-based retrospective birth cohort. This cohort relied on data collected from the Better Outcomes Registry & Network (BORN) Information System that collects information for births in all hospitals and midwife-attended home births in Ontario health (129). At the time of analysis, BORN included birth data from 2006 through the end of 2014. This dataset has been estimated to capture at least 99% of all live and still-born births since 2006 (130).

The BORN Information System dataset is managed and continually updated by the Institute for Clinical Evaluative Sciences (ICES) (https://www.ices.on.ca). This dataset draws on a number of provincial health administrative datasets. Record linkage across these datasets allows for the construction of a longitudinal history of health endpoints for Ontario residents. It also allows for risk factor data from mothers to be linked to birth outcomes, and health trajectories of children to be modelled.

In this section, the study population is described as is the methodology used to assign residentially-based greenness measures. This section also describes other covariates that were available in the datasets, and finally, the statistical methods used to derive measures of association.

3.1 Study Population

The study population includes all live-born singleton infants in Ontario, Canada that were born between April 1, 2006, to March 31, 2013. In total, there were 982,131 infants. Mother-infant-pair data were available from the BORN Information System (129).

Information on the residential history of the mother-infant pairs was obtained by linking data from the Registered Persons Data Base (RPDB) to the BORN database (Figure 3). This database captures the six-character postal codes of each individual's (mother and child) place of residence over time. Further, this database tracks intra-provincial changes in residence during pregnancy, and the child's vital status during follow-up. This database captures postal code changes for all Ontario residents with a health insurance number which has been reported to the Ministry of Health. Postal codes and addresses may additionally be updated within the RPDB voluntarily upon interaction with the healthcare system or upon health care card renewal every five years (131,132).

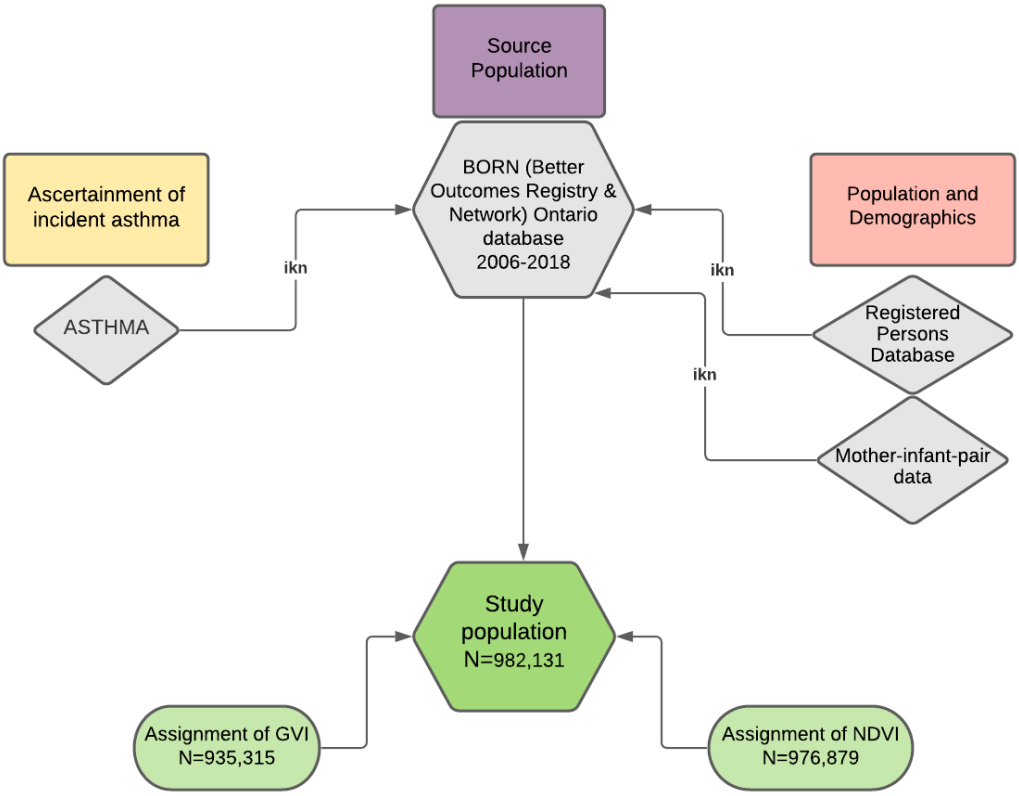
A number of exclusion criteria were applied when creating the analytic file. Specifically, infants were excluded from analysis if their date of birth was missing, had an invalid encrypted health card number, lacked biological sex at birth data, had no valid residential address information, or did not live in urban areas (the second digit of the 6 character postal code was zero). The exclusion criteria applied in these analyses are the same as those used in a previous analysis of this datasets that characterized associations between air pollution and childhood asthma (24,133).

3.2 Ascertainment of Incident Asthma

Newly diagnosed, or incident, cases of asthma were identified using the Ontario ASTHMA cohort database (134). ASTHMA is a population-based database that identifies Ontario residents with asthma, and subsequent to diagnosis, continues to track their health status. This database allowed for the identification of both incident asthma diagnoses among children, as well as previous asthma diagnoses in their mothers (135).

The ASTHMA dataset contains asthma-related data that were linked to the BORN dataset using encoded identifiers (Figure 3). Linkage was done to births occurring from 2006 onwards. Asthma was ascertained from the time of birth until the end of follow-up which was the earliest of (i) the child attained 12 years of age, or (ii) March 31, 2018. Children were classified as having asthma if they had at least two primary care visit claims for asthma in two consecutive years or at least one hospitalization for asthma (136). This case definition has been shown to have 89% sensitivity and 72% specificity in children (aged 0-17 years) (137). These interactions with the health care system using the International Classification for Diseases (ICD) 10^{th} revision code of J45 (136). For the purposes of survival analyses, children diagnosed with asthma were right censored at the time of diagnosis.

Figure 3: Databases used to create the individual-level records in the longitudinal analysis file



ICES key number (IKN): encrypted health card number; Source: ICES (https://datadictionary.ices.on.ca)

Table 1: Variables extracted from Ontario administrative health datasets and used in analysis

Databases	Variable(s)	Form of variables
ASTHMA: Ontario Asthma dataset		
	Diagnosis of incident asthma	Binary (y/n)
	Date of diagnosis	Date
	Maternal history of asthma	Binary (y/n)
BORN: Better Outcomes Registry and Network		
	Date of infant birth	Date
	Gestation weeks at delivery	Continuous
	Birth weight	Continuous
	ICES key number	Categorical
	Mother's age at delivery	Categorical
	Mother's ICES key number	Categorical
	Multiple birth status	Categorical
	Stillbirth status	Categorical
	Sex of the infant	Categorical
	Parity	Categorical
	Maternal smoking status	Categorical (y/n/missing)
	Maternal intention to breastfeed	Categorical (y/n/missing)
RPDB: Registered Persons Database		
	Mother's 6-digit postal code at delivery[a]	Character
	Child's residence 6-digit postal code [b]	Character
	Death status of newborn	Date
ONMARG: Ontario Marginalization Index[c]		
	Median household income during pregnancy	Continuous
	Instability during pregnancy	Continuous
	Deprivation during pregnancy	Continuous
	Dependency during pregnancy	Continuous
	Ethnic concentration during pregnancy	Continuous

[a]Used to assign greenspace exposures during pregnancy
[b]Used to explain possible changes in the place of residence in the province during childhood
[c]Used to adjust for neighborhood sociodemographic status confounding

3.3 Exposure to Greenness

Individual-level measures of greenness were assigned to the geolocation of the child's place of residence. These measures were assigned on a year-by-year basis from estimated date of conception until the earliest date of asthma diagnosis, or end of follow-up. The geographical coordinates of the infant's place of residence in urban areas were determined using six-character postal codes. The centroid of the postal code was used as the geolocation. In urban areas, six-character postal codes typically correspond to dwelling on one side of a street, between two intersecting streets, or sometimes one apartment building. Therefore, they have high spatial resolution in urban areas. In contrast, in rural areas, a six-character postal code can cover a large land area, sometimes an entire town. For these reasons, this study restricted characterizing associations between greenness and asthma to urban areas. As discussed in the last section, these postal codes were obtained from the Registered Persons Database (RPDB) (138).

The NDVI was the primary measure of greenness exposure in this study. The NDVI values are continuous measures between -1 and 1. In this study, we modelled a maximum value of the NDVI and therefore, all these values were positive. The yearly NDVI values were based on an average of readings taken about every 16 days (using the orbit pattern of the satellites) (139). From these measures, the maximum of the NDVI value for the growing season (May 1st to August 31st) was calculated annually from 2005 to 2018, excluding 2012. The NDVI was constructed within a circular buffer of 250 m from the children's residence for the following time periods: during pregnancy, the first year of life, and a time-weighted average exposure from birth until the end of follow-up (24). A 250m buffer was chosen as this distance is typically assessed in other

epidemiological studies that have modelled the NDVI. For the exposure period during pregnancy, greenness was estimated as a time weighted average of consecutive years were weight correspond to the number of months pregnant in adjacent years (138). To calculate time-varying exposures during childhood, the exposure estimate for the first two years of life was calculated by averaging exposures in the first and second year. Similarly, a time-weighted average was also created to represent exposure throughout childhood (up to age 12).

The Green View Index (GVI) was also modelled. This measure was derived by the Canadian Urban Environmental Health Research Consortium (CANUE) (www.canue.ca) and made available for these analyses (140–142). This measure of greenness was constructed from Google Street View (GSV) images using deep learning techniques (111). This analysis considered two different ways to measure GVI. The first method is a segmented based technique that determines green objects in the image and is used to derive the measure and output a single value across the image (110). The second method is a pixel-based technique which determines the proportion of green pixels in each image (111). The GVI were constructed from six images, taken at the same point in time, for each postal code. These images have been 'stitched' together to allow for the generation of a measure of greenness. These images cover all directions from a set geographical coordinate and are used to create a full panorama image (110). GSV images cover a 360-degree horizontal environment and a 180-degree vertical outline (110). The GVI values were based on images that were taken between 2006 and 2017. The GVI values were assigned to the centroid of the residential postal code at the time of birth.

3.4 Air pollution

This study dataset also included ambient concentrations of air pollution, specifically, NO_2 and $PM_{2.5}$. These exposure estimates were also linked to the place of residence of this study population. Similar to greenness, air pollution exposure measures were created for pregnancy, the first year of life, and a time-weighted average throughout childhood.

For $PM_{2.5}$, an overall mean exposure was obtained from monthly satellite imaging between 2006 and 2018 (143). These estimates were derived at a spatial resolution of 1×1 km at the centroid of residential postal codes. The 1 km optimal estimate aerosol optical depth satellite retrieval method related to $PM_{2.5}$ was developed and adjusted with ground-based $PM_{2.5}$ monitors using Geographically Weighted Regression (GWR) to resolve the bias in the entire North American region (144). These monthly estimates were averaged to create an overall exposure during pregnancy and were calculated for each year of follow-up. For instance, a child's exposure to $PM_{2.5}$ during first year of life included all monthly averages for the 12 months following their date of birth, then the child's exposure in year two of life included the running average of the first year and second year and so on for all years until the end of follow-up.

NO_2 exposures were obtained from a national exposure surface that was created using a Land Use Regression (LUR) model (145). This model was developed using data from National Air Pollution Surveillance monitoring data (http://www.ec.gc.ca/rnspa-naps/) (146), road lengths within 10 km, an area of industrial land use within 2 km, mean rainfall of summer, and satellite NO_2 from 2005 to 2018 (147). The resulting LUR NO_2 surface was available for each year of follow-up. Time dependent measures of exposure

measures for NO_2 were derived using the same methodology as for greenness, and $PM_{2.5}$. The national NO_2 surface only provided annual values and therefore, a temporal adjustment was applied to capture monthly data of NO_2. These monthly average ambient concentrations of NO_2 estimates were collected from the National Air Pollution Surveillance network (148). Estimates of monthly average were used to create overall exposure during pregnancy.

3.5 Other individual-level Covariates

The linked datasets contain data for several asthma risk factors, and their potential or modifying roles were evaluated. These factors included: maternal age at delivery (< 20, 20-34, ≥ 35 years, or missing), the biological sex of the infant, and parity (0, 1, ≥ 2). Using the month of birth, each infant birth was classified into the following season of birth categories: winter (January to March), spring (April to June), summer (July to September) and fall (October to December). Other variables in the linked dataset included maternal intention to breastfeed (yes, no), maternal cigarette smoking status (yes, no), maternal history of asthma, gestational age (in weeks), and birthweight (Table **1**).

3.6 Contextual Variables

The analyses also considered the Ontario Marginalization (ON-Marg) Index (149) which is a measure of contextual/neighbourhood-level socioeconomic status (SES). The ON-Marg variables include median household income during pregnancy, instability during pregnancy (people who experience high rates of family or housing instability), deprivation during pregnancy (connected to poverty such as quality of housing, and educational attainment), dependency during pregnancy (people who don't have income

from employment), and ethnic concentration during pregnancy (high ethnic area include people of recent immigrants and people belonging to a 'visible minority' group) (150). These variables were modelled as a continuous variable which was taken from Canadian census dissemination area data from the closest census year (i.e., 2006, 2011, or 2016), and are available at ONMARG dataset in ICES (Table 1).

3.7 Statistical analyses

The first step of the analysis was to perform descriptive analysis to examine the frequency distributions of the greenness measures, asthma outcomes, and other risk factors. The outliers were identified and converted into missing data. For instance, data values of -9,999 for GVI were converted to missing in the dataset. Analyses were also done to examine how these distributions differ between infants with and without asthma. Pearson and Spearman correlation coefficients were calculated to quantify the magnitude and direction of the linear association between the greenness and air pollution measures.

3.7.1 Survival Analysis

Due to the longitudinal nature of the data, survival analysis was used to characterize the association between greenness and the incidence of childhood asthma. The age of the child in days, from the date of birth, was used as the time axis in the survival model. The Cox proportional model (151) is commonly used to describe associations between an exposure of interest and incident outcomes and has the advantage of being able to control for the potential confounding influence of other risk factors. The general form of the proportional hazards model is as follows:

$$h_i(t) = \exp(\beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p)\, h_0(t) \qquad \text{Equation (3)}$$

Where, t is survival time, $h_0(t)$ is baseline hazard function, β_p = Cox regression model coefficients variable, and x_p = a vector of explanatory variables including greenness. This model is capable of describing the exposure-response curve between greenness and asthma while adjusting for the influence of the explanatory variables. A key underlying assumption of the Cox proportional hazards is that the ratio of the hazards is constant over the follow-up time, and similarly, the hazard associated with the other variable is also constant over time. The Cox model also assumes that the relationship between the log hazard and each covariate is linear and that the observations (different infants) are independent.

As this study modelled a time-dependent covariate, namely, a measure of greenness that could change during follow-up, an extended Cox model was used (152). Basically, an extended Cox model compares the hazard of an event between exposure levels at each event time and re-evaluates the hazard rate for each person based on their exposure level at that time. The extended Cox model is as follows:

$$h(t, X(t)) = h_o(t) \exp\left[\sum_{b=1}^{p} \beta_b X_b + \sum_{b=1}^{p} \delta_b X_b g_b(t)\right] \qquad \text{Equation (4)}$$

Where we have $X_b(t)=X_b.g_b(t)$ and the δ_b is Cox regression model coefficients for a time-dependent covariate (greenness), X_b is a covariate that has no time dependency, and the time function for covariate-b is defined as $g_b(t)$, β_b = Cox regression model coefficients variable and p is the number of covariates (151).

By definition, a confounding variable must be associated with both outcome and exposure but not to the causal pathway (153). Following adjustment for the confounder the magnitude of the association between exposure and outcome changes (153). In this study, to identify possible confounding variables, univariate Cox proportional hazards models were fit to evaluate the association between each variable and incident asthma to identify factors that are associated with the outcome under study. Formally, this involved estimating the hazard ratio and assessing statistical significance. Statistical significance was assessed using the Chi-Square test statistic. Those variables that were associated with outcome (p-value <0.05) were included in adjustment factors in the models. The extended Cox proportional hazards models were also fitted to estimate the risk of childhood asthma incidence in relation to measures of greenness. Separate models were fitted to describe associations between greenness and incident asthma based on exposure to NDVI during pregnancy, first year of life, and over childhood and exposure to segment based and pixel based of GVI. Follow-up time was measured as each children's age in days from birth until death, the incidence of asthma in children, ineligibility for provincial health insurance, or end of follow-up (i.e., March 31st, 2018). These models were fitted to adjust for relevant confounding variables in different time periods exposure to NDVI and different measure of GVI.

The indicators of green space, NDVI and GVI, were each modelled as both categorical (i.e., quartiles) and continuous measures. Modelling the continuous measure of NDVI and GVI as a linear function was done to estimate the hazard ratio in relation to an increase in the interquartile range (IQR) of green space. Modelling the categorical measure of NDVI and GVI was done to estimate the hazard ratio in relation to an

increase in the level of green space, and also to evaluate whether associations between these measures and asthma were consistent with linearity.

Stratified analyses were undertaken to assess variations in the associations between greenness and incident asthma by age, season of birth, sociodemographic status, and maternal characteristics. NDVI was categorized in quartiles for this analysis. These stratified models were fitted to adjust for relevant confounding variables (excluding selected variable as modifier) for different time periods exposure to NDVI (whole pregnancy, 1st year of life, and average exposure during childhood).

All statistical analyses were performed using SAS software, version 9.4 (154).

3.8 Ethics

This study was approved by the Research Ethics Board (REB) of Health Canada and the Public Health Agency of Canada. The approval was granted on June 29, 2020, and the file number was REB 2019-005H. The ICES also reviewed and approved the study.

4.0 Results

In total, there were 982,131 singleton live births between April 1, 2006, and March 31, 2013 (Table 2). During the follow-up (April 1, 2006, and March 31, 2018) 161,436 of these children (16.4%) developed asthma. Lower birthweight was associated with an increased risk of asthma. Specifically, the cumulative incidence of asthma among those less than 2500g was (23.6%) whereas, in children greater than 2500g, the cumulative incidence of asthma was (16.1%). Furthermore, children with asthma were more likely to have mothers with a history of asthma (19.4% versus 12.8%). Of all identified incident cases of asthma, 60% of them occurred in boys (Table 2). Children with asthma more frequently belonged to families who lived in more deprived areas (26.7% versus 24.6% for less deprived areas) and areas with high levels of ethnic concentrations (31.5% versus 19.4%for areas with lower ethnic concentrations) (Table **3**). In our study population, nearly one of four (24.3%) diagnosed with asthma were diagnosed in the first year of life. The average age of asthma diagnosis in our cohort was 2.1 years. This young age at diagnosis is due to the fact that our dataset only included births between 2006 and 2013 and follow-up ended on March 31, 2018 (Figure 4).

The value of the interquartile range (IQR) for the NDVI for the 250 m buffer was 0.1, for segmented GVI was 10.6, and for pixel-based GVI the IQR was 5.88 during the first year of life (Table 4). The average exposure to residential greenness during the first year of life for NDVI was 0.70, and the average segmented and pixel based GVI at the time of birth was 14.21 and 6.90 (Table 4).

There were negative correlations between NDVI and air pollution exposure $PM_{2.5}$ ($r=-0.20$) and NO_2 ($r=-0.31$) during the first year of life. $PM_{2.5}$ was positively correlated

with NO_2 during the first year of life (r=0.58) (Table 5), and the same correlation was observed with NO_2 during childhood exposure (r=0.58) [data not shown]. Furthermore, the results of Spearman correlation were approximately the same as Pierson correlation.

4.1 Risk factors and childhood asthma associations

The univariate associations between the risk factors and childhood asthma are presented in Table 8. Girls had a 32% reduced risk of incident asthma relative to boys (HR: 0.68; 95%CI: 0.67-0.69). Children whose mothers had a history of asthma had an elevated risk of being asthmatic when compared to those whose mothers had no such history (HR: 1.57; 95%CI: 1.55-1.59). Furthermore, infants with birthweight in excess of 2500g had a reduced risk of asthma relative to those with birthweight <2500 g (HR: 0.62 95%CI: 0.60-0.63) (Table 8). Children who live in more affluent areas (household income >83,308 $/year) were at a heightened risk of asthma when compared to those of lower household incomes areas (household income ≤46589 $/year) (HR: 1.07; 95% CI: 1.06-1.09) (Table 9). In all exposure periods, ambient air pollution concentrations were associated with an increased risk of asthma. An interquartile range increase exposure to $PM_{2.5}$ and NO_2 during childhood increased the risk of asthma by 11% (HR: 1.11 95% CI:1.10-1.12) and 36% (HR: 1.36 95% CI:1.35-1.37) respectively, after adjusting for sex, and birth year) (Table 10)

4.2 Greenness and childhood asthma associations

The associations between an IQR increase exposure to NDVI over different periods and different measurements of GVI (segmented and pixel based) on childhood asthma incidence are presented in Table 11. In an unadjusted model, an IQR in NDVI,

based on a 250m buffer, was inversely associated with asthma in all three exposure periods. Following adjustment for several covariates, the hazard ratios between NDVI and asthma were somewhat attenuated but suggested reduced risks in all three exposure periods. Finally, following adjustment for ambient concentrations of NO_2, the inverse associations in all three exposure periods disappeared. The corresponding risk estimate for a 0.08 IQR increase in the NDVI was 0.99 (95% CI 0.99-1.01) for exposures during childhood. Similarly, the risk estimates for an IQR increase in the segmented and pixel based GVI were essentially null (HR: 0.99; 95% CI: 0.98-0.99) and (HR: 0.98; 95% CI: 0.97-0.99), respectively (Table 11).

The associations between the NDVI quartile (250m buffer) over specific periods and different measurements of the GVI quartile (segmented and pixel based) on childhood asthma incidence are presented in Table 12. The exposure to the highest quartile residential greenness was associated with reduced risk of childhood asthma over different times and different measures of GVI before adjustment for air pollution concentrations. However, these associations were weakened after adjustment for ambient concentrations of NO_2 which was almost null in all three exposure periods. The hazard ratio for the highest NDVI quartile during childhood was 0.97 (95% CI 0.96-0.99) and was the same for segmented GVI measurement (Table 12).

4.3 Stratified analyses of greenness and childhood asthma across select covariates

Tables 13 to 19 contain the findings of stratified analyses of the associations between greenness and incident asthma for selected characteristics. Hazard ratios for the three exposure periods have been presented across the following categorical variables:

age of the child, biological sex at birth, maternal history of asthma, smoking status during pregnancy, maternal age at birth, season of birth, and neighbourhood median household income in tables 13 to 19 respectively.

There was little evidence of an association between greenness and incident childhood asthma among those who were diagnosed before the age of six (Table 13). In contrast, children who lived in the uppermost quartile of greenness (based on exposure during childhood) had a 14% decreased risk (HR=0.86, 95% CI: 0.79-0.93) of asthma when compared to those in the lowest quartile. Greenness was not associated with the incident of asthma in either boys or girls, with similar risk estimates observed for each sex (Table 14). The findings from the stratified analysis suggest that there were no substantial differences in the measures of association between greenness and incident asthma based on maternal history of asthma (Table 15), smoking status during pregnancy (Table 16), maternal age at birth (Table 17), or neighbourhood median household income (Table 19).

Analyses revealed that the association between greenness and incident asthma varied across the four seasons of birth (Table 18). For all three exposure periods considered, greenness was inversely associated with a reduced risk of asthma for children born in the spring and summer seasons. Specifically, those children in the highest quartile of NDVI during childhood exposure relative to the lowest quartile with the hazard ratios of 0.84 (95% CI: 0.81-0.87) and 0.88 (95% CI: 0.85-0.91) respectively. Furthermore, there were positive associations for children born in the fall and winter seasons. The corresponding hazard ratio for children born in fall was 1.10 (95% CI: 1.07-1.14), and for children born in winter was 1.09 (95% CI: 1.05-1.13) (Table 18).

Table 2: Sociodemographic characteristics and mean NDVI of study participants with and without asthma select characteristics in Ontario urban areas between April 1, 2006, to March 31, 2018.

Characteristic	Children		Children with asthma		Children without asthma		NDVI [a]	
	N	%	N	%	N	%	Mean	SD
Total	**982,131**	**100**	**161,436**	**16.4**	**820,695**	**83.6**	**0.701**	**0.08**
Sex at birth								
Male	504,158	51.3	96,703	59.9	407,455	49.6	0.701	0.08
Female	477,973	48.7	64,733	40.1	413,240	50.3	0.701	0.08
Calendar period of birth								
2006-2009	479,402	48.8	90,650	56.1	388,752	47.4	0.686	0.08
2010-2013	502,729	51.2	70,786	43.8	431,943	52.6	0.716	0.08
Parity								
0	440,854	44.9	74,232	45.9	366,622	44.7	0.701	0.08
1	352,001	35.8	58,513	36.2	293,488	35.7	0.701	0.08
2 or more	189,273	19.3	28,690	17.8	160,583	19.6	0.701	0.08
Intention to breastfeed								
Yes	606,204	61.7	106,560	66.0	499,644	60.9	0.686	0.08
No	64,951	6.6	11,502	7.1	53,449	6.5	0.687	0.08
Missing	310,976	31.6	43,374	26.9	267,602	32.6	0.734	0.08
Maternal asthma								
Yes	136,515	13.9	31,293	19.4	105,222	12.8	0.706	0.08
No	845,616	86.1	130,143	80.6	715,473	87.2	0.701	0.08
Season of birth								
Oct-Dec	246,686	25.1	41,500	25.7	205,186	25.0	0.699	0.08
Apr-June	247,689	25.2	39,569	24.5	208,120	25.4	0.702	0.08
July-Sep	259,381	26.4	43,039	26.6	216,342	26.4	0.699	0.08
Jan- Mar	228,375	23.2	37,328	23.1	191,047	23.3	0.704	0.08
Gestational age (weeks)								
<28	3,058	0.3	874	0.5	2,184	0.3	0.682	0.09
28-32	7,566	0.8	2,366	1.5	5,200	0.6	0.697	0.08
≥33	971,507	98.9	158,196	98.0	813,311	99.1	0.701	0.08
Birthweight (g)								
<2500	46,362	4.7	10,950	6.8	35,412	4.3	0.696	0.08
≥2500	935,769	95.3	150,486	93.2	785,283	95.7	0.702	0.08
Maternal age (years)								
15-19	32,573	3.3	5,180	3.2	27,393	3.3	0.699	0.08
20-34	738,295	75.2	120,266	74.5	618,029	75.3	0.702	0.08
35-54	211,263	21.5	35,990	22.3	175,273	21.4	0.701	0.08
Maternal smoking status during pregnancy								
Yes	80,112	8.2	13,634	8.4	66,478	8.1	0.691	0.08
No	598,326	60.9	105,815	65.5	492,511	60.0	0.686	0.08
Missing	303,693	30.9	41,987	26.0	261,706	31.9	0.734	0.08

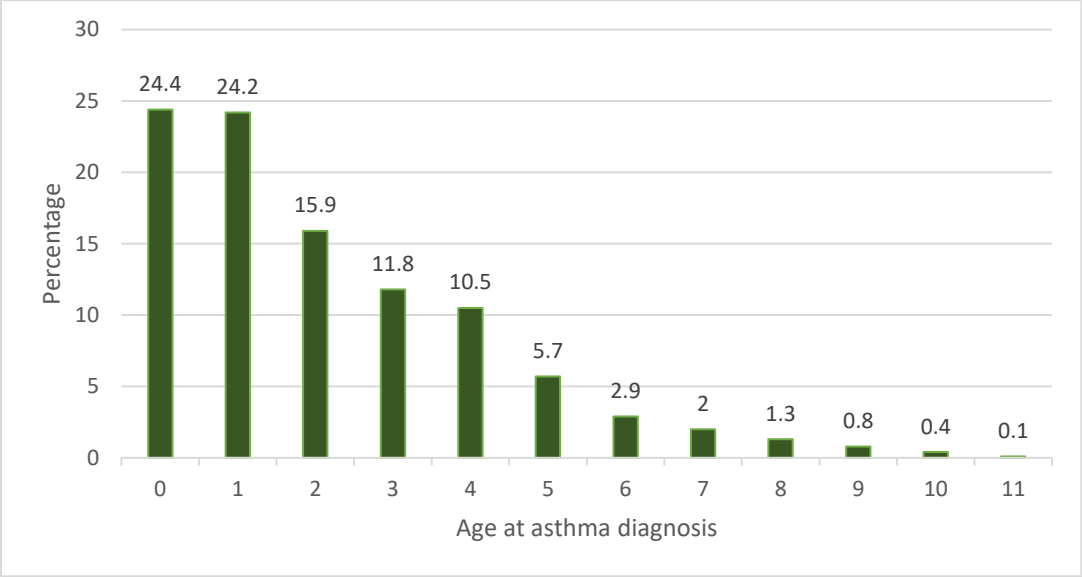
[a] Based on annual greenness estimates within 250 m circular buffer from the centroid of their postal code.

Table 3: Neighbourhood-based sociodemographic characteristics of study participants with and without asthma based on 2006 dissemination area census data

Sociodemographic status	Children		Children with asthma		Children without asthma		NDVI [a]	
	N	%	N	%	N	%	Mean	SD
Median Household Income								
Quartile 1 (lowest)	243,456	25.0	39,391	24.6	204.065	25.1	0.695	0.08
Quartile 2	243,624	25.0	37,865	23.6	205,759	25.3	0.703	0.08
Quartile 3	242,940	24.9	40,322	25.1	202,618	24.9	0.703	0.08
Quartile 4 (highest)	244,097	25.1	42,745	26.7	201,352	24.7	0.703	0.08
Dependency Factor Score								
Quartile 1 (least dependent)	241,612	25.0	42,567	26.7	199,045	24.7	0.693	0.08
Quartile 2	241,667	25.0	42,550	26.6	199,117	24.7	0.698	0.08
Quartile 3	241,643	25.0	38,295	24.0	203,348	25.2	0.704	0.08
Quartile 4 (most dependent)	241,657	25.0	36,195	22.7	205,462	25.4	0.709	0.07
Deprivation Factor Score								
Quartile 1 (least deprived)	241,645	25.0	40,139	25.1	201,506	25.0	0.703	0.08
Quartile 2	241,639	25.0	39,854	25.0	201,785	25.0	0.706	0.08
Quartile 3	241,653	25.0	39,068	24.5	202,585	25.1	0.704	0.07
Quartile 4 (most deprived)	241,642	25.0	40,546	25.4	201,096	24.9	0.692	0.08
Ethnic Concentration Factor Score								
Quartile 1 (least concentrated)	241,663	25.0	30,978	19.4	210,685	26.1	0.722	0.07
Quartile 2	241,630	25.0	36,054	22.6	205,576	25.5	0.706	0.07
Quartile 3	241,652	25.0	42,358	26.5	199,294	24.7	0.692	0.08
Quartile 4 (most concentrated)	241,634	25.0	50,217	31.5	191,417	23.7	0.685	0.08
Instability Factor Score								
Quartile 1 (stable)	241,631	25.0	43,267	27.1	198,364	24.6	0.702	0.08
Quartile 2	241,662	25.0	38,568	24.2	203,095	25.2	0.710	0.08
Quartile 3	241,637	25.0	37,904	23.7	203,733	25.2	0.703	0.07
Quartile 4 (unstable)	241,649	25.0	39,869	25.0	201,780	25.0	0.689	0.08

[a] Based on annual greenness estimates within 250 m circular buffer from the centroid of their postal code

Figure 4: Frequency distribution of the age at asthma diagnosis[a] among Ontario singleton births in urban areas between 2006 and 2013



[a] Incident cases of asthma were determined through December 31, 2018

Table 4: Descriptive statistics of residential surrounding greenness (NDVI and GVI) for different exposure periods, in Ontario urban areas between 2006 and 2018

Greenness measure	Exposure period	Births	Min	25th P	Median	Mean	75th P	Max	SD	IQR
NDVI [a]										
	Pregnancy	975,894	0.08	0.66	0.71	0.70	0.75	1.00	0.08	0.09
	First year of life	976,879	0.08	0.66	0.71	0.70	0.76	1.00	0.08	0.10
	Average during childhood	976,879	0.08	0.66	0.71	0.70	0.76	1.00	0.08	0.10
GVI [b]										
Segmented	At birth	935,315	0.00	7.99	12.24	14.21	18.33	93.19	8.83	10.34
Pixel Based	At birth	935,315	0.00	3.27	5.61	6.90	9.15	71.00	5.33	5.88

SD, standard deviation. IQR, interquartile range. P, percentile

[a] Normalized Difference Vegetation Index (NDVI) is based on annual maximum greenness estimates within 250 m circular buffer from the centroid of the residential postal code.

[b] Green View Index (GVI)

Table 5: Pearson correlation coefficients between measures of greenness and ambient concentrations of NO_2 and $PM_{2.5}$ during the child's first year of life, in Ontario urban areas between 2006 and 2018

	GVI [a]		NDVI [b]	NO_2 (ppb)	$PM_{2.5}$ ($\mu g/m^3$)
	Segmented	Pixel			
GVI					
Segmented	1.00				
Pixel Based	0.71	1.00			
NDVI	0.16	0.12	1.00		
NO_2 (ppb)	-0.09	-0.08	-0.31	1.00	
$PM_{2.5}$ ($\mu g/m^3$)	0.01	0.08	-0.20	0.58	1.00

[a] Based on their postal code at the time of birth.
[b] Based on annual greenness estimates within 250 m circular buffer from the centroid of their annual residential postal code.

Table 6: Pearson correlation coefficients between measures of greenness (NDVI) and ambient concentrations of NO_2 during different exposure time periods, in Ontario urban areas between 2006 and 2018

	NDVI			NO_2 (ppb)		
	Pregnancy average	Child's 1st year	Average during childhood	Pregnancy average	Child's 1st year	Average during childhood
NDVI [a]						
Pregnancy average	1.00					
Child's 1st year	0.88	1.00				
Average during childhood	0.88	1.00	1.00			
NO_2 (ppb)						
Pregnancy average	-0.30	-0.30	-0.30	1.00		
Child's 1st year	-0.28	-0.29	-0.29	0.95	1.00	
Average during childhood	-0.28	-0.29	-0.29	0.95	1.00	1.00

[a] Based on annual greenness estimates within 250 m circular buffer from the centroid of their annual residential postal code.

Table 7: Pearson correlation coefficients between measures of greenness (NDVI) and ambient concentrations of $PM_{2.5}$ during different exposure time periods, in Ontario urban areas between 2006 and 2018

	NDVI			$PM_{2.5}$ ($\mu g/m^3$)		
	Pregnancy average	Child's 1st year	Average during childhood	Pregnancy average	Child's 1st year	Average during childhood
NDVI						
Pregnancy average	1.00					
Child's 1st year	0.88	1.00				
Average during childhood	0.88	1.00	1.00			
$PM_{2.5}$ ($\mu g/m^3$)						
Pregnancy average	-0.20	-0.18	-0.18	1.00		
Child's 1st year	-0.17	-0.19	-0.19	0.80	1.00	
Average during childhood	-0.17	-0.19	-0.19	0.80	1.00	1.00

[a] Based on annual greenness estimates within 250 m circular buffer from the centroid of their annual residential postal code.

Table 8: Unadjusted hazard ratios (HRs) for selected characteristics in relation to incident asthma in Ontario urban areas between 2006 and 2018

Characteristic	Levels	Asthma cases	HR	HR (95% CI)
Sex at birth				
	Male	96,703	1.0	
	Female	64,733	0.68	0.67-0.69
Calendar period of birth				
	2006-2009	90,650	1.00	
	2010-2013	70,786	0.84	0.83-0.85
Maternal asthma				
	No	130,143	1.00	
	Yes	31,293	1.57	1.55-1.59
Parity				
	0	74,232	1.00	
	1	58,513	0.99	0.98-1.01
	⩾ 2	28,690	0.91	0.89-0.92
Intention to breastfeed				
	No	11,502	1.00	
	Yes	106,560	0.98	0.96-0.99
Maternal smoking status during pregnancy				
	No	105,815	1.00	
	Yes	13,634	0.97	0.95-0.99
Maternal age years at delivery				
	15 - 19	5,180	1.00	
	20 - 34	120,266	1.02	0.99-1.05
	35 - 54	35,990	1.07	1.04-1.10
Season of birth				
	Oct - Dec	41,500	1.00	
	Apr - June	39,569	1.02	1.01-1.04
	July - Sept	43,039	0.95	0.94-0.97
	Jan - Mar	37,328	0.99	0.98-1.01
Gestational age (weeks)				
	≥33	158,196	1.00	
	28 – 32	2,366	2.23	2.14-2.32
	<28	874	3.40	3.18-3.63
Birthweight (g)				
	≥2500	147,180	1.00	
	<2500	14,256	1.62	1.59-1.65

Table 9: Unadjusted hazard ratios between contextual measures of sociodemographic status and incident of childhood asthma in Ontario urban areas between 2006 and 2018

sociodemographic status [#]	Levels	Asthma cases	HR	HR (95% CI)
Median Household Income				
Quartile 1 (lowest)	0 to 46,589	39,391	1.0*	
Quartile 2	46,590 to 64,853	37,865	0.95	0.94-0.96
Quartile 3	64,854 to 83,308	40,322	1.02	1.01-1.03
Quartile 4 (highest)	83,309 to 551,293	42,745	1.07	1.06-1.09
Dependency Factor Score				
Quartile 1 (least dependent)	-2.75 to -0.82	42,567	1.0*	
Quartile 2	-0.82 to -0.43	42,550	0.99	0.98-1.01
Quartile 3	-0.43 to 0.09	38,295	0.89	0.88-0.90
Quartile 4 (most dependent)	0.09 to 11.97	36,195	0.84	0.82-0.85
Deprivation Factor Score				
Quartile 1 (least deprived)	-2.47 to -0.86	40,139	1.0*	
Quartile 2	-0.86 to -0.35	39,854	0.99	0.98-1.01
Quartile 3	-0.35 to 0.34	39,068	0.98	0.96-0.99
Quartile 4 (most deprived)	0.34 to 6.60	40,546	1.02	1.01-1.04
Ethnic Concentration Factor Score				
Quartile 1 (least concentrated)	-2.10 to -0.39	30,978	1.0*	
Quartile 2	-0.39 to 0.26	36,054	1.18	1.16-1.20
Quartile 3	0.26 to 1.50	42,358	1.40	1.38-1.42
Quartile 4 (most concentrated)	1.50 to 7.42	50,217	1.70	1.67-1.73
Instability Factor Score				
Quartile 1 (stable)	-2.27 to -0.83	43,267	1.0*	
Quartile 2	-0.83 to -0.42	38,568	0.88	0.87-0.89
Quartile 3	-0.42 to 0.48	37,904	0.87	0.85-0.88
Quartile 4 (unstable)	0.48 to 4.74	39,869	0.93	0.91-0.94

* Reference category

[#] Contextual sociodemogprahic characteristics were obtained from the 2006 Canadian census

Table 10: Hazard Ratios (HR) and 95% confidence intervals (95% CI) of incident asthma in relation to an interquartile range increase in NO_2 and $PM_{2.5}$ in Ontario urban areas between 2006 and 2018

Air pollutant	Exposure period	IQR	Asthma cases	Model 1	Model 2
$PM_{2.5}$					
	Entire pregnancy	2.41	160,897	1.12 (1.11,1.13)	1.08 (1.07,1.09)
	First year of life	2.31	158,446	1.14 (1.13,1.15)	1.13 (1.12,1.14)
	Average during childhood	2.06	161,044	1.13 (1.12,1.14)	1.11 (1.10,1.12)
NO_2					
	Entire pregnancy	9.14	154,184	1.31 (1.30,1.32)	1.29 (1.28,1.30)
	First year of life	7.57	147,784	1.39 (1.38,1.40)	1.37 (1.36,1.38)
	Average during childhood	7.82	154,826	1.38 (1.37,1.39)	1.36 (1.35,1.37)

Model 1: Unadjusted model
Model 2: Adjusted for birth of year and sex at birth.

Table 11: Hazard Ratios (HR) and 95% confidence intervals (95% CI) of incident asthma in relation to an interquartile range increase in the NDVI (250m buffer) over specific periods and GVI in Ontario urban areas between 2006 and 2018

Greenness measure	Exposure period	IQR	Model 1	Model 2	Model 3	Model 4	Model 5
NDVI							
	Entire pregnancy	0.10	0.91 (0.90,0.92)	0.92 (0.91, 0.93)	0.92 (0.91, 0.93)	0.94 (0.93, 0.95)	0.99 (0.98, 0.99)
	First year of life	0.09	0.93 (0.92,0.93)	0.94 (0.94, 0.95)	0.94 (0.93, 0.95)	0.97 (0.96, 0.97)	1.00 (0.99,1.01)
	Average during childhood	0.08	0.91 (0.91,0.92)	0.93 (0.92, 0.94)	0. 93 (0.92, 0.94)	0.96 (0.95, 0.96)	0.99 (0.99,1.01)
GVI							
Segmented	At birth	10.34	0.94 (0.94, 0.95)	0.94 (0.94, 0.95)	0. 94 (0.93, 0.95)	0.98 (0.97, 0.99)	0.99 (0.98, 0.99)
Pixel Based	At birth	5.88	0.95 (0.94, 0.95)	0.95 (0.94, 0.95)	0. 94 (0.94, 0.95)	0.97 (0.97, 0.98)	0.98 (0.97, 0.99)

Model 1: Unadjusted model
Model 2: Adjusted for birth of year and sex at birth.
Model 3: Adjusted for all the factors included in model 2, as well as parity, breastfeeding status at the time of discharge, maternal smoking during pregnancy, season of birth, gestational age, birthweight, and maternal history of asthma.
Model 4: Adjusted for all the factors in model 3, as well as SES of neighbourhood during pregnancy (median income, dependency, ethnic concentration).
Model 5: Adjusted for all the factors in model 4 additionally adjusted for air pollution exposure (NO_2 at first year of life).

Table 12: Hazard ratios (HR) and 95% confidence intervals (95% CI) of incident asthma in relation to an increase in the quartile of the NDVI (250m buffer) over specific periods and GVI in Ontario urban areas between 2006 and 2018

Greenness		Model 1	Model 2	Model 3	Model 4	Model 5
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
NDVI						
Entire pregnancy	Lowest quartile (0. 08 – 0.65)	1.0	1.0	1.0	1.0	1.0
	Second quartile (0.66 – 0.71)	0.94 (0.93,0.96)	0.94 (0.93, 0.96)	0.94 (0.93, 0.95)	0.97 (0.96, 0.99)	1.00 (0.98, 1.02)
	Third quartile (0.72 – 0.75)	0.91 (0.90,0.93)	0.92 (0.90, 0.93)	0.91 (0.90, 0.92)	0.96 (0.95, 0.98)	1.01 (0.99, 1.03)
	Highest quartile (0.76 – 1.00)	0.82 (0.81,0.83)	0.84 (0.83, 0.86)	0.84 (0.83, 0.85)	0.92 (0.90, 0.93)	0.98 (0.97, 0.99)
First year of life	Lowest quartile (0. 08 – 0.69)	1.00	1.00	1.0	1.0	1.0
	Second quartile (0.70 – 0.74)	0.96 (0.94,0.97)	0.96 (0.95, 0.97)	0.96(0.95, 0.97)	0.99 (0.97, 1.01)	1.03 (1.02, 1.05)
	Third quartile (0.75 – 0.78)	0.90 (0.88,0.91)	0.92 (0.91, 0.93)	0.92 (0.90, 0.93)	0.96 (0.95, 0.98)	1.03 (1.01, 1.04)
	Highest quartile (0.79 – 1.00)	0.81 (0.80,0.83)	0.86 (0.84, 0.87)	0.86 (0.84, 0.87)	0.90 (0.89, 0.92)	0.99 (0.97, 1.01)
Average during childhood	Lowest quartile (0. 08 – 0.68)	1.0	1.0	1.0	1.0	1.0
	Second quartile (0.69 – 0.72)	0.96 (0.94,0.97)	0.96 (0.94, 0.97)	0.95(0.94, 0.97)	0.99 (0.97, 1.01)	1.02 (1.01,1.04)
	Third quartile (0.73 – 0.76)	0.89 (0.88,0.91)	0.91 (0.89, 0.92)	0.90 (0.89, 0.92)	0.97 (0.95, 0.98)	1.02 (1.01,1.04)
	Highest quartile (0.77 – 1.00)	0.78 (0.77,0.79)	0.82 (0.81, 0.84)	0.82 (0.81, 0.83)	0.90 (0.89, 0.92)	0.97 (0.96,0.99)
GVI						
Segmented	Lowest quartile (0. 00 – 7.98)	1.0	1.0	1.0	1.0	1.0
	Second quartile (7.99 – 12.31)	1.01 (0.99, 1.02)	1.00 (0.99, 1.02)	1.00 (0.99, 1.02)	1.01 (0.99, 1.02)	1.03 (1.02, 1.05)
	Third quartile (12.32 – 18.58)	0.97 (0.96, 0.99)	0.97 (0.96, 0.99)	0.96 (0.95, 0.98)	0.99 (0.98, 1.01)	1.01 (0.99, 1.02)
	Highest quartile (18.59-93.19)	0.90 (0.88, 0.91)	0.89 (0.88, 0.90)	0.88 (0.87, 0.90)	0.96 (0.95, 0.98)	0.97 (0.96, 0.99)
Pixel Based	Lowest quartile (0.00 – 3.34)	1.0	1.0	1.0	1.0	1.0
	Second quartile (3.35 – 5.70)	1.01 (1.00, 1.03)	1.01 (1.00, 1.03)	1.01 (1.00, 1.03)	1.01 (0.99, 1.02)	1.03 (1.01, 1.04)
	Third quartile (5.71 – 9.31)	0.98 (0.97, 0.99)	0.98 (0.96, 0.99)	0.97 (0.96, 0.99)	0.98 (0.97, 0.99)	1.01 (0.99, 1.02)
	Highest quartile (9.32 – 71.00)	0.89 (0.88, 0.90)	0.89 (0.87, 0.90)	0.88 (0.87, 0.90)	0.94 (0.93, 0.96)	0.96 (0.95, 0.98)

Model 1: Unadjusted model
Model 2: Adjusted for birth of year and sex at birth.
Model 3: Adjusted for all the factors included in model 2, as well as parity, breastfeeding status at the time of discharge, maternal smoking during pregnancy, season of birth, gestational age, birth weight, and maternal history of asthma.
Model 4: Adjusted for all the factors in model 3, as well as SES of the neighbourhood during pregnancy (median income, dependency, ethnic concentration).
Model 5: Adjusted for all the factors in model 4 additionally adjusted for air pollution exposure (NO_2 at the first year of life).

Table 13: Adjusted hazard ratios (HR) and 95% confidence intervals (95%CI) of incident asthma in relation to an increase in the quartile of the NDVI (250m buffer) over specific periods, stratified by age of child.

		≤ 6 years of age		7 – 12 years of age	
NDVI		**Asthma Cases**	**HR (95% CI)**	**Asthma Cases**	**HR (95% CI)**
Entire pregnancy					
	Lowest quartile (0. 08 – 0.65)	40,257	1.0*	2,191	1.0*
	Second quartile (0.66 – 0.71)	35,686	0.99 (0.98, 1.02)	1,798	0.98 (0.911, 1.05)
	Third quartile (0.72 – 0.75)	36,965	1.01 (0.99, 1.03)	1,719	0.95 (0.887, 1.02)
	Highest quartile (0.76 – 1.00)	40,347	0.97 (0.95, 0.99)	1,418	0.94 (0.875, 1.02)
First year of life					
	Lowest quartile (0. 08 – 0.69)	46,325	1.0*	1,311	1.0*
	Second quartile (0.70 – 0.74)	48,288	1.03 (1.01, 1.04)	1,582	0.98 (0.90, 1.07)
	Third quartile (0.75 – 0.78)	33,816	1.01 (0.99, 1.03)	1,765	0.99 (0.91,1.08)
	Highest quartile (0.79 – 1.00)	24,912	0.98 (0.96, 1.00)	2,474	0.96 (0.88, 1.04)
Average during childhood					
	Lowest quartile (0. 08 – 0.68)	43,149	1.0*	1,499	1.0*
	Second quartile (0.69 – 0.72)	43,243	1.02 (1.01, 1.04)	2,199	0.97 (0.90, 1.05)
	Third quartile (0.73 – 0.76)	38,859	1.02 (1.00,1.03)	2,326	0.94 (0.88,1.02)
	Highest quartile (0.77 – 1.00)	28,473	0.97 (0.96, 0.99)	1,161	**0.86** (0.79, 0.95)

* Reference category

Hazard ratios were adjusted for birth of year, sex at birth, parity, breastfeeding status at the time of discharge, maternal smoking during pregnancy, season of birth, gestational age, birthweight, and maternal history of asthma, SES of neighbourhood during pregnancy (median income, dependency, ethnic concentration), air pollution exposure (NO_2 at first year of life).

Table 14: Adjusted hazard ratios (HR) and 95% confidence intervals (95%CI) of incident asthma in relation to an increase in the quartile of the NDVI (250m buffer) over specific periods, stratified by biological sex at birth

		Males		Females	
NDVI		**Asthma Cases**	**HR (95% CI)**	**Asthma Cases**	**HR (95% CI)**
Entire pregnancy					
	Lowest quartile (0. 08 – 0.65)	25,449	1.0*	16,999	1.0*
	Second quartile (0.66 – 0.71)	22,343	0.99 (0.97, 1.01)	15,141	1.01 (0.98, 1.03)
	Third quartile (0.72 – 0.75)	23,178	1.01 (0.99, 1.03)	15,506	1.02 (0.99, 1.04)
	Highest quartile (0.76 – 1.00)	25,110	0.98 (0.96, 1.00)	16,655	0.98 (0.96, 1.01)
First year of life					
	Lowest quartile (0. 08 – 0.69)	28,900	1.0*	18,736	1.0*
	Second quartile (0.70 – 0.74)	30,015	1.03 (1.01, 1.05)	19,855	1.04 (1.02, 1.06)
	Third quartile (0.75 – 0.78)	21,199	1.02 (1.00, 1.04)	14,382	1.04 (1.01, 1.06)
	Highest quartile (0.79 – 1.00)	16,022	0.98 (0.96, 1.01)	11,364	1.00 (0.97, 1.03)
Average during childhood					
	Lowest quartile (0. 08 – 0.68)	26,988	1.0*	17,660	1.0*
	Second quartile (0.69 – 0.72)	27,120	1.02 (1.00, 1.04)	18,322	1.02 (1.00, 1.05)
	Third quartile (0.73 – 0.76)	24,649	1.03 (1.01, 1.05)	16,536	1.02 (1.00, 1.05)
	Highest quartile (0.77 – 1.00)	17,635	0.97 (0.95, 0.99)	11,999	0.98 (0.96, 1.01)

* Reference category

Adjusted for birth of year, age, parity, breastfeeding status at the time of discharge, maternal smoking during pregnancy, season of birth, gestational age, birthweight, and maternal history of asthma, SES of neighbourhood during pregnancy (median income, dependency, ethnic concentration), air pollution exposure (NO_2 at first year of life).

Table 15: Adjusted hazard ratios (HR) and 95% confidence intervals (95%CI) of incident asthma in relation to an increase in the quartile of the NDVI (250m buffer) over specific periods, stratified by maternal history of asthma

		Maternal history of asthma			
		No		Yes	
NDVI		Asthma Cases	HR (95% CI)	Asthma Cases	HR (95% CI)
Entire pregnancy					
	Lowest quartile (0. 08 – 0.65)	34,823	1.0*	7,625	1.0*
	Second quartile (0.66 – 0.71)	30,355	0.99 (0.98, 1.02)	7,129	1.01 (0.98, 1.05)
	Third quartile (0.72 – 0.75)	31,047	1.01 (0.99, 1.03)	7,637	1.02 (0.99, 1.06)
	Highest quartile (0.76 – 1.00)	33,060	0.98 (0.96, 0.99)	8,705	0.99 (0.95, 1.02)
First year of life					
	Lowest quartile (0. 08 – 0.69)	39,092	1.0*	8,544	1.0*
	Second quartile (0.70 – 0.74)	40,003	1.02 (1.01, 1.04)	9,867	1.07 (1.04, 1.11)
	Third quartile (0.75 – 0.78)	28,447	1.02 (1.01, 1.04)	7,134	1.05 (1.02, 1.09)
	Highest quartile (0.79 – 1.00)	21,819	0.98 (0.96, 1.01)	5,567	1.02 (0.98, 1.06)
Average during childhood					
	Lowest quartile (0. 08 – 0.68)	36,739	1.0*	7,909	1.0*
	Second quartile (0.69 – 0.72)	36,726	1.02 (1.00, 1.03)	8,716	1.05 (1.02, 1.09)
	Third quartile (0.73 – 0.76)	32,802	1.01 (0.99, 1.03)	8,383	1.07 (1.03, 1.10)
	Highest quartile (0.77 – 1.00)	23,447	0.97 (0.95, 0.99)	6,187	0.99 (0.96, 1.04)

* Reference category

Adjusted for birth of year, sex at birth, parity, breastfeeding status at the time of discharge, maternal smoking during pregnancy, season of birth, gestational age, birthweight, and maternal age at delivery, SES of neighbourhood during pregnancy (median income, dependency, ethnic concentration), air pollution exposure (NO_2 at first year of life).

Table 16: Adjusted hazard ratios (HR) and 95% confidence intervals (95%CI) of incident asthma in relation to an increase in the quartile of the NDVI (250m buffer) over specific periods, stratified by maternal smoking status during pregnancy

		Smoker		Non-smoker	
NDVI		**Asthma Cases**	**HR (95% CI)**	**Asthma Cases**	**HR (95% CI)**
Entire pregnancy					
	Lowest quartile (0. 08 – 0.65)	6,899	1.0*	3,571	1.0*
	Second quartile (0.66 – 0.71)	6,972	0.99 (0.95, 1.02)	3,559	1.06 (1.01, 1.12)
	Third quartile (0.72 – 0.75)	8,734	1.02 (0.99, 1.06)	3,515	1.02 (0.97, 1.08)
	Highest quartile (0.76 – 1.00)	19,124	1.01 (0.97, 1.04)	2,896	1.05 (1.00, 1.11)
First year of life					
	Lowest quartile (0. 08 – 0.69)	8,831	1.0*	4,192	1.0*
	Second quartile (0.70 – 0.74)	10,991	1.04 (1.01, 1.07)	4,622	1.05 (1.01, 1.10)
	Third quartile (0.75 – 0.78)	10,720	1.05 (1.01, 1.08)	2,955	1.07 (1.02, 1.13)
	Highest quartile (0.79 – 1.00)	11,188	1.00 (0.97, 1.04)	1,789	1.00 (0.94, 1.06)
Average during childhood					
	Lowest quartile (0. 08 – 0.68)	7,181	1.0*	3,823	1.0*
	Second quartile (0.69 – 0.72)	8,537	1.02 (0.99, 1.06)	4,380	1.06 (1.01, 1.11)
	Third quartile (0.73 – 0.76)	10,840	1.05 (1.01, 1.08)	3,713	1.08 (1.03, 1.14)
	Highest quartile (0.77 – 1.00)	15,300	1.01 (0.98, 1.05)	1,671	1.03 (0.96, 1.09)

* Reference category

Adjusted for birth of year, sex at birth, parity, breastfeeding status at the time of discharge, maternal age at delivery season of birth, gestational age, birthweight, and maternal history of asthma, SES of neighbourhood during pregnancy (median income, dependency, ethnic concentration), air pollution exposure (NO_2 at first year of life).

Table 17: Adjusted hazard ratios (HR) and 95% confidence intervals (95%CI) of incident asthma in relation to an increase in the quartile of the NDVI (250m buffer) over specific periods, stratified by maternal age at birth

NDVI		Maternal age (in years)					
		15-19		20-34		35-54	
		Asthma Cases	HR (95% CI)	Asthma Cases	HR (95% CI)	Asthma Cases	HR (95% CI)
Entire pregnancy							
	Lowest quartile (0. 08 – 0.65)	1,403	1.0*	31,471	1.0*	9,574	1.0*
	Second quartile (0.66 – 0.71)	1,241	0.97 (0.90, 1.05)	27,783	0.99 (0.98, 1.02)	8,460	1.02 (0.99, 1.05)
	Third quartile (0.72 – 0.75)	1,257	0.95 (0.88, 1.03)	28,921	1.01 (0.99, 1.03)	8,506	1.02 (0.99, 1.05)
	Highest quartile (0.76 – 1.00)	1,243	0.93 (0.85, 1.01)	31,283	0.98 (0.96, 0.99)	9,239	1.01 (0.98, 1.04)
First year of life							
	Lowest quartile (0. 08 – 0.69)	1,524	1.0*	35,397	1.0*	10,715	1.0*
	Second quartile (0.70 – 0.74)	1,721	1.11 (1.03, 1.20)	37,170	1.03 (1.02, 1.05)	10,979	1.02 (0.99, 1.05)
	Third quartile (0.75 – 0.78)	1,124	1.09 (1.01, 1.19)	26,553	1.03 (1.01, 1.04)	7,904	1.03 (0.99, 1.06)
	Highest quartile (0.79 – 1.00)	783	1.06 (0.97, 1.17)	20,424	0.98 (0.96, 1.00)	6,179	1.01 (0.98, 1.05)
Average during childhood							
	Lowest quartile (0. 08 – 0.68)	1,416	1.0*	33,154	1.0*	10,078	1.0*
	Second quartile (0.69 – 0.72)	1,626	1.07 (0.99, 1.15)	33,923	1.02 (1.01, 1.04)	9,893	1.02 (0.99, 1.05)
	Third quartile (0.73 – 0.76)	1,352	1.07 (0.99, 1.16)	30,645	1.02 (1.01, 1.04)	9,188	1.04 (1.01, 1.07)
	Highest quartile (0.77 – 1.00)	775	1.01 (0.92, 1.12)	22,150	0.97 (0.96, 0.99)	6,709	0.98 (0.95, 1.02)

* Reference category

Hazard ratios were adjusted for birth of year, sex at birth, parity, breastfeeding status at the time of discharge, maternal smoking during pregnancy, season of birth, gestational age, birthweight, and maternal history of asthma, SES of neighbourhood during pregnancy (median income, dependency, ethnic concentration), and air pollution exposure (NO_2 at first year of life).

Table 18: Adjusted hazard ratios (HR) and 95% confidence intervals (95%CI) of incident asthma in relation to an increase in the quartile of the NDVI (250m buffer) over specific periods, stratified by season of birth

NDVI	Oct-Dec		Apr-June		July-Sep		Jan- Mar	
	Asthma Cases	HR (95% CI)	Asthma Cases	HR (95% CI)	Asthma Cases	HR (95% CI)	Asthma Cases	HR (95% CI)
Entire pregnancy								
Lowest quartile (0. 08 – 0.65)	11,042	1.0*	10,144	1.0*	11,346	1.0*	9,916	1.0*
Second quartile (0.66 – 0.71)	9,603	1.02 (0.99, 1.06)	9,178	0.98 (0.95, 1.01)	10,013	0.97 (0.94, 0.99)	8,690	1.03 (1.00, 1.06)
Third quartile (0.72 – 0.75)	9,831	1.07 (1.04, 1.10)	9,644	0.96 (0.93, 0.99)	10,418	0.96 (0.94, 0.99)	8,791	1.05 (1.02, 1.09)
Highest quartile (0.76 – 1.00)	10,808	**1.08** (1.05, 1.12)	10,178	**0.88** (0.86, 0.91)	11,062	**0.89** (0.87, 0.92)	9,717	**1.07** (1.04, 1.11)
First year of life								
Lowest quartile (0. 08 – 0.69)	12,687	1.0*	11,496	1.0*	13,108	1.0*	10,345	1.0*
Second quartile (0.70 – 0.74)	12,898	1.08 (1.05, 1.10)	12,282	0.98 (0.95, 1.01)	13,403	0.98 (0.96, 1.01)	11,287	1.09 (1.06, 1.12)
Third quartile (0.75 – 0.78)	8,921	1.11 (1.08, 1.14)	8,750	0.91 (0.88, 0.94)	9,243	0.94 (0.91, 0.97)	8,667	1.17 (1.13, 1.20)
Highest quartile (0.79 – 1.00)	6,752	**1.12** (1.08, 1.16)	6,808	**0.85** (0.82, 0.88)	7,037	**0.90** (0.87, 0.93)	6,789	**1.10** (1.07, 1.14)
Average during childhood								
Lowest quartile (0. 08 – 0.68)	11,983	1.0*	10,681	1.0*	12,376	1.0*	9,608	1.0*
Second quartile (0.69 – 0.72)	11,658	1.05 (1.03, 1.08)	11,184	0.97 (0.94, 0.99)	12,347	0.98 (0.95, 1.00)	10,253	1.09 (1.06, 1.12)
Third quartile (0.73 – 0.76)	10,424	1.11 (1.08, 1.15)	10,229	0.92 (0.89, 0.95)	10,749	0.93 (0.90, 0.95)	9,783	1.14 (1.10, 1.17)
Highest quartile (0.77 – 1.00)	7,291	**1.10** (1.07, 1.14)	7,344	**0.84** (0.81, 0.87)	7,434	**0.88** (0.85, 0.91)	7,565	**1.09** (1.05, 1.13)

* Reference category

Hazard ratios were adjusted for birth of year, sex at birth, parity, breastfeeding status at the time of discharge, maternal smoking during pregnancy, maternal age at delivery, gestational age, birthweight, and maternal history of asthma, SES of neighbourhood during pregnancy (median income, dependency, ethnic concentration), air pollution exposure (NO_2 at first year of life).

Table 19: Adjusted hazard ratios (HR) and 95% confidence intervals (95%CI) of incident asthma in relation to an increase in the quartile of the NDVI (250m buffer) over specific periods, stratified by quartile of neighbourhood median household income

NDVI	Median neighbourhood income [#]							
	< 46,589		46,589 - 64,853		64,854 - 83,308		≤551,293	
	Asthma Cases	HR (95% CI)	Asthma Cases	HR (95% CI)	Asthma Cases	HR (95% CI)	Asthma Cases	HR (95% CI)
Entire pregnancy								
Lowest quartile (0.08 – 0.65)	11,021	1.0*	9,693	1.0*	10,978	1.0*	10,374	1.0*
Second quartile (0.66 – 0.71)	9,815	1.04 (1.00, 1.07)	9,220	1.02 (0.98, 1.05)	8,974	0.96 (0.93, 0.99)	9,244	1.00 (0.97, 1.04)
Third quartile (0.72 – 0.75)	9,603	1.08 (1.05, 1.12)	9,061	1.01 (0.97, 1.04)	9,637	0.99 (0.97, 1.03)	10,172	0.98 (0.95, 1.02)
Highest quartile (0.76 – 1.00)	9,010	1.02 (0.99, 1.05)	9,535	0.99 (0.96, 1.03)	10,713	0.98 (0.95, 1.01)	12,236	0.96 (0.93, 0.99)
First year of life								
Lowest quartile (0. 08 – 0.69)	12,272	1.0*	11,059	1.0*	12,042	1.0*	11,879	1.0*
Second quartile (0.70 – 0.74)	12,816	1.09 (1.06 ,1.12)	11,862	1.04 (1.01, 1.07)	12,260	1.01 (0.98, 1.04)	12,651	1.00 (0.97, 1.03)
Third quartile (0.75 – 0.78)	8,458	1.08 (1.05, 1.12)	8,147	1.02 (0.99, 1.05)	9,028	1.03 (0.99, 1.06)	9,714	0.99 (0.97, 1.03)
Highest quartile (0.79 – 1.00)	5,912	1.03 (0.99, 1.06)	6,453	1.00 (0.97, 1.04)	6,986	0.98 (0.95, 1.02)	7,833	0.97 (0.93, 1.00)
Average during childhood								
Lowest quartile (0. 08 – 0.68)	11,558	1.0*	10,194	1.0*	11,376	1.0*	11,138	1.0*
Second quartile (0.69 – 0.72)	11,828	1.05 (1.03, 1.08)	11,136	1.04 (1.01, 1.07)	11,039	0.99 (0.97, 1.03)	11,154	1.01 (0.99, 1.04)
Third quartile (0.73 – 0.76)	9,856	1.08 (1.05, 1.12)	9,486	1.02 (0.99, 1.05)	10,421	1.02 (0.99, 1.05)	11,180	0.99 (0.97, 1.02)
Highest quartile (0.77 – 1.00)	6,322	1.01 (0.98, 1.05)	6,803	0.98 (0.95, 1.02)	7,586	0.98 (0.95, 1.02)	8,726	0.96 (0.93, 0.99)

* Reference category

[#]Median Household Income $ (DA at Pregnancy) -2006 Census

Hazard ratios were adjusted: for birth of year, sex at birth, parity, breastfeeding status at the time of discharge, maternal smoking during pregnancy, season of birth, gestational age, birthweight, and maternal history of asthma, maternal age at delivery, air pollution exposure (NO_2 at first year of life).

5.0 Discussion

5.1 Key findings

In this cohort study, the association between living in greener neighbourhoods and the risk of developing asthma among Ontario infants was investigated using both skyview (NDVI) and streetview (GVI) measures of greenness. This study found that after adjusting for potential risk factors, especially air pollution concentrations, there was no association between exposure to greenness across different time periods and the development of asthma in children up to 12 years of age. However, this study found an inverse association between exposure to greenness during childhood and asthma among children who were diagnosed after the age of seven. The analyses also revealed that there were seasonal differences in the strength of the association, with inverse associations occurring among children who were born in spring and summer. Furthermore, this study found that there were no meaningful differences in risk across the different measures of greenness.

Some past studies that evaluated the associations between air pollution and asthma across different periods found that exposures during pregnancy were most strongly predictive of the risk of incident asthma (24,25). Contrary to the hygiene hypothesis, that assumes that exposures shortly after birth are most relevant, this study found little variation in the risk estimates for greenness across the different exposure periods. In contrast, the findings suggested that exposures after birth were most strongly related to incident asthma and could contribute to reduced rates of asthma later in childhood.

Analysis on air pollution and childhood asthma found roughly the same findings as the previous paper which was on the same population of mother-infant pairs in Ontario (24). For instance, in this thesis an interquartile range increase exposure to $PM_{2.5}$ during childhood increased the risk of asthma by 13% (HR: 1.13; 95% CI: 1.12-1.14) and by 9% in the previous paper (HR: 1.09; 95% CI: 1.08-1.11). There was a minor difference because this analysis included more births than the previous analyses (24).

These findings suggest that exposure to the NDVI based on a 250m buffer, an interquartile range increase (0.09) was associated with a 4% reduced risk of developing asthma (HR: 0.96; 95% CI: 0.95-0.96), but this estimate was attenuated after adjusting for air pollution concentrations (HR: 0.99; 95% CI: 0.99-1.01). Only two previous studies have assessed this association with and without adjusting for air pollution (14,19).

A recent cross-sectional study in China found a 0.1 unit increase of NDVI in 1000m buffer around schools decreased asthma symptoms by 19% (OR: 0.81 95% CI: 0.75-0.86) before adjusting for air pollution (19). This inverse association was weakened in models with air pollution adjustment (OR: 0.89; 95% CI: 0.80-0.99), resulting in 11% reduction in asthma symptoms. Although a similar trend was found in this thesis when adjusted for air pollution, no association was found between asthma and greenness. Nevertheless, in this thesis, the protective effect of the highest NDVI surrounding residential areas during childhood exposure was 14% stronger for children above the age of 7 (HR: 0.86; 95% CI: 0.79-95). This could be that children in this age-group are also exposed to greenness around their school environment. Evidence suggests that exposure to a more diverse microbial environment can protect against asthma development by enhancing the immune system tolerance and with children spending time in school surroundings, they are

exposed to a more diverse microbial environment (155). Furthermore, this could be due to asthma symptoms improving or resolving altogether as children age (27). Overall, the inconsistent results may have happened because of different study designs and different greenness location measurements (residential vs school base).

A 10-year follow-up study conducted in British Columbia, Canada found that exposure to neighbourhood greenness during the perinatal period was associated with reduced risk of development of asthma in children less than 5 years of age before adjusting for air pollution (per 0.11 IQR NDVI increase (OR: 0.96; 95% CI: 0.93-0.99)) (14). In contrast to our study, the protective association became stronger following adjustment for air pollution. However, they did not find any association for children between ages 6 to 10 even after adjusting for air pollution. Although these results were in line with our results for exposure during pregnancy, evidence of stronger inverse association was seen in exposure during childhood when analyses were restricted to children diagnosed at a later age (7-12). There are a number of different explanations for the possible differences. First, the study in British Columbia only observed exposure to greenness during pregnancy while this thesis had association across different exposure periods. Second, the overall findings of this thesis are largely based on asthma diagnoses in very young children where no association was observed. Other factors that could contribute to differences between the two studies include regional differences in climate and vegetation, which could contribute to differences in how children and mothers use the green spaces. Also, one study birth cohort in Euro-Siberian and Mediterranean found this association differed by region and it could be due to unknown region-specific confounding factors (15).

The analyses of greenness and asthma in Ontario singleton birth found little evidence of an association between greenness and incident asthma, nor any evidence that this association was modified by biological sex. The hazard ratio of exposure to the highest level of NDVI compared to the lowest level during childhood in relation to asthma for males was 0.97 (95%CI: 0.95-0.99) and for females was 0.98 (95%CI: 0.96-1.01). Donovan et al. (17) also found no variation in this association between boys and girls, however, a protective effect of greenness was observed. Similarly, a Chinese study by Li et al. (20) found protective associations in both boys and girls where the benefit was slightly greater in girls. The corresponding odds ratio for both males and females were 0.76 (95% CI: 0.50-1.14) and 0.62 (95% CI: 0.38-1.01) respectively for the highest NDVI quartile compared to the lowest.

Moreover, this Ontario singleton birth cohort did not find any evidence that this association was modified across levels of sociodemographic status. The analyses did find a slightly stronger association between greenness and asthma among families that live in affluent areas (HR: 0.96 95% CI: 0.93-0.99), however, this association was still close to the null value. Elsewhere, Sbihi et al.'s analyses of children in Vancouver (14) found a stronger association for children born to mothers with low educational attainment.

In the stratified analysis by season of birth, strong negative associations between greenness and asthma were found for children born in spring and summer seasons and strong positive association was found for those born in fall and winter seasons on the exposure to the highest category of NDVI (i.e., 4th quartile) during all time periods and incidence of asthma. The corresponding hazard ratios during pregnancy for April to June was 0.88 (95% CI: 0.86-0.91), for children born between July to September was 0.89

(95% CI: 0.87-0.92), for children born between October to December was 1.08 (95% CI: 1.05-1.12), and for children born between January to March was 1.07 (95% CI: 1.04-1.11). The different hazard ratios in warm and cold seasons may be due to greenness densities and vegetation types during those seasons. Also, it could be due to a higher rate of respiratory infections during the cold seasons. Further, children born during summer do not experience high pollen counts until the next spring as infants often spend their first six months of life indoors (76). In a previous study in China, it was found that a 0.1 unit increase of $NDVI_{300}$ m in August 2010 decreased asthma symptoms by 13% (OR:0.87, 95% CI: 0.82-0.92) (19). While they found the same result for October of 2010, our study found a 10% increase in the risk of asthma incidence with exposure to the highest level of NDVI during childhood from October to December. The contradicting results may be due to geographical differences between the studies during the months of studies. Furthermore, this cross-sectional study observed exposure to greenness only in August and October at the time of the study, but it is important to consider the long-term effect of greenness in a different season of birth and their impact on asthma. This thesis suggests that children born in warmer seasons (greater greenness density) had beneficial effects of greenness later in life.

5.2 Strengths and limitations

Significant strengths of this thesis research include the large sample size, availability of skyview (NDVI) and streetview (GVI) measures of greenness exposure estimate available across a large geographical area and the ability to track residential histories over time. This longitudinal design study allows for the identification of

incident, rather than prevalent outcomes, the population-based nature of the study population is likely to have reduced risks of selection bias.

Some weaknesses of this work include the limited ability to track all children through 12 years of age. Only birth cases from 2006 to 2013 were accessible and were followed up from birth to 2018, which lead to some of the children only being followed for up to six years only. However, the number of such children is relatively small, therefore it is unlikely to introduce substantial bias. In addition, data for some important risk factors for childhood asthma development were not available such as maternal gestational weight gain or maternal obesity, and maternal medications use during pregnancy (156).

There was a limitation assessment of greenness GVI that was measured at only one point in time (at birth), nevertheless, the measure of NDVI was for different time periods exposure that showed no meaningful differences in different periods of exposure. Therefore, the GVI results at one point in time cannot be a big issue. Further, relevant measures of greenness such as biodiversity in greenness, access, and safety may not be captured by NDVI and GVI which may have been the reason that this study did not find any association.

Moreover, a limitation on asthma outcome identified based on health administrative databases may have led to some level of misclassification bias. For instance, data on asthma phenotypes and asthma severity was not available that could lead to different outcomes when exposed to greenness. However, a 10-year follow-up study in Canada used a similar physician-diagnosed asthma case ascertainment with

results in line with this thesis (14). Therefore, this provides support that "true" asthma cases were likely captured (24). Also, children less than 5 years old with wheezing symptoms from viral infections may have been misdiagnosed as having asthma (24). In addition, potential bias could have occurred in the methods used in the diagnosis of asthma that may have differed by level of greenness but were controlled by adjusting for SES factors.

5.3 Recommendations for future research

This type of research is needed as there are competing pathways whereby vegetation can either increase or reduce the risk of asthma. For example, vegetation can reduce air pollution, while it can also produce pollen (157). Therefore, further studies that incorporate features of greenness, such as type of vegetation that the mother and child are exposed to, would be of value. Further studies are needed to evaluate the relevance of the timing of exposure given that contradictory findings exist in the existing literature.

6.0 Conclusion

In conclusion, this study suggests that, overall, exposure to greenness, both streetview and skyview measures, are not strongly associated. The study did however find that exposure to greenness during childhood may reduce the risk of developing asthma for children diagnosed at a later age (after 7 years of age). This suggests that the period of exposure after birth may be relevant. These findings are relevant for urban planners and policymakers to set up a greener environment surrounding schools that could help reduce the burden of childhood asthma for school-age children.

As a final concluding remark, we would like to reiterate that the collection and analyses of the data presented in this thesis was adversely impacted by the COVID-19. This included having to transition to accessing less detailed data for some covariates from the ICES datasets as access to the on-site data lab was not possible. This is not expected to fundamentally change the findings presented herein.

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8.0 Appendices

Appendix A: Definitions and measurement of exposures and health outcomes by year of publication in past studies

AUTHOR (YEAR)	LOCATION	NUMBER OF CHILDREN	STUDY DESIGN	GREENNESS MEASURE	OUTCOME MEASUREMENT	DIRECTION OF ASSOCIATION	EXPOSURE ESTIMATE (95% CI)	ADJUSTMENT FACTORS
LOVASI, ET AL. (2013)	New York City	n = 549	Population-based birth cohort	Urban tree canopy coverage and (LiDAR) data and colour infrared aerial imagery) for address at the time of birth (250 m).	Current asthma (assessed by BQR questionnaire) at 5 and 7 years old.	The tree cover does not have a protective role in asthma	5 years 1.11 (0.85, 1.45) 7 years 1.17 (1.02, 1.33)	Sex, age, ethnicity, maternal asthma, previous birth, other previous pregnancy, Medicaid, tobacco smoke in-home, active maternal smoking, population density, poverty, parkland, and estimated traffic volume.
DADVAND ET AL. (2014)	Sabadell, Spain	n = 3178	Cross-sectional sample	NDVI at 100, 250, 500 and 1000 m areas of current residential address.	Current asthma as assessed using the ISAAC questionnaire plus having, had wheezing or having used asthma medication in the preceding 12 months	No association but 11–19% lower relative prevalence of overweight/obesity	100 m: 1.00 (0.82, 1.21) 250 m: 1.00 (0.78, 1.27) 500 m: 1.03 (0.79, 1.34) 1000 m: 1.06 (0.85, 1.32)	Sex and age, exposure to environmental tobacco smoke at home, having older siblings, type of school (public vs. private), parental education, and parental history of asthma

SBIHI ET AL. (2015)	Vancouver, Canada	n = 51,857	Nested Case-Control	Surrounding Greenness (NDVI 100 m) during the perinatal period.	1. Incident asthma during preschool-age 2. incident asthma during school years (6–10 years)	Greenness was protective of early-life asthma, but not of school-age asthma	Pre-school aged: 0.96 (0.93–0.99) School-aged reported as no association.	Maternal age at delivery, parity, breastfeeding status at discharge, birth weight, gestational period, household income, and maternal education.
ANDRUSAITYTE ET AL. (2016)	Lithuania (KANC)	n = 1489	Nested Case-Control	mean NDVI at 100, 300 and 500 m areas of exact residential address	Clinically diagnosed asthma (ISAAC) questionnaire completed by parents)	Increase of relative risk of asthma with more level of vegetation	100 m: 1.43 (1.10, 1.85) 300 m: 1.23 (0.94, 1.61) 500 m: 1.18 (0.88, 1.57)	Mother's age at childbirth, maternal education, parental asthma, maternal smoking during pregnancy, breastfeeding, antibiotic use during the first year of life, keeping a cat in the past 12 months, living in a flat, yearly mean of ambient NO2 and $PM_{2.5}$.
SBIHI ET AL. (2016)	Vancouver, Canada	n= 65,254	Population based birth cohort	Surrounding Greenness (NDVI) during the perinatal period. (Measured in 100 m areas around residential postal codes)	asthma trajectory defined based on group-based trajectory modelling (No asthma, transient, Late-Onset and Early-Onset) – risk compared to being in 'no asthma' group	Greenness was not associated with any of the asthma trajectories	Transient: 0.91 (0.80, 1.05) Late-Onset: 1.05 (0.90, 1.23) Early-Onset: 1.01 (0.81, 1.25)	Gender, parity, breastfeeding initiation, birth weight, delivery mode, maternal smoking and educational attainment, and household income

FENG AND ASTELL-BURT (2017)	Australia	n=4447	Cross-sectional	% Land use classified as "parkland", stratified into 0%–20%, 20%–40%, and > 40%	Self-report of physician diagnosis, asthma medication in the past 12 months, and wheezing for at least one week in the past 12 months	No significant association (asthma prevalence to be lower in-residence areas with larger percentages of green space)	living in high traffic and high greenness had a lower risk OR= 0.32(0.12–0.84)	Age, gender, maternal education, household income, geographic remoteness, area disadvantage and green space quantity
TISCHER ET AL. (2017)	Spain	n= 2472	birth cohort	Proximity to greenness using urban atlas map, and surrounding green spaces measured as NDVI within 300m radius of residence at birth and age 4 years.	Asthma as wheezing in past 12 months, physician diagnosis of bronchitis, allergic rhinitis in past 12 months	No statistically significant associations	For cohort (OR 1.82; CI:0.71–4.67), Euro-Siberian region (OR 2.26; CI: 0.91–5.67), and Mediterranean region (aOR 2.05; CI: 0.69–6.06)	Sex, cohort, maternal education, maternal smoking during pregnancy, any breastfeeding, the season of birth, maternal allergy, pets at home at birth, passive smoking at home at 4 years, area SES and air pollution.
DONOVAN ET AL. (2018)	New Zealand	n= 49,956	birth cohort study	Max annual NDVI per meshblock; native and nonnative land cover types.	Asthma prescriptions for inhaled corticosteroids or beta-adrenoceptor agonist (age 7-18)	Greenness was associated with a significantly lower risk of developing asthma	6.0% (1.9–9.9%) lower risk of asthma for mean lifetime NDVI	Air pollution, ethnicity, gender, birth outcomes, occupation, education, smoking status, antibiotic use, number of siblings, meshblock size and birth order

CILLUFFO ET AL. (2018)	Palermo, Italy	n=219	Cross-sectional	NDVI at 200 m around the home address on a single date during month outcomes were assessed	Parent and child report	greenness and air pollution within the urban environment are associated with respiratory/allergic	No statistically significant relationships between NDVI and wheeze) [OR = 0.98 (0.79, 1.21)]	
HSIEH ET AL. (2019)	Taiwan	n= 7040	matched case-control	(NDVI) value ≥0.4 was used as the criterion to determine the green space		The risk of incident asthma increased with increasing residential proximity to greenness		Urbanization level, frequency of healthcare visits, mean township family income, CO, NO_2, and $PM_{2.5}$
LI ET AL. (2019)	Suzhou, China	n = 5643	cross-sectional survey	distance to the nearest park and NDVI	self-reported doctor diagnoses of asthma	Increased risk of asthma and respiratory conditions among those who lived in greener areas	0.58 (95% CI: 0.35, 0.99) for current asthma and 0.70 (95% CI: 0.50, 0.96) ever asthma	Pneumonia, rhinitis, and eczema
ZENG ET AL. (2020)	China	n = 59754	Cross-sectional	(NDVI) and (SAVI) at buffers from 30 to 1000 m.	self-reported questionnaires	Greenness in all buffered sizes was negatively associated with the prevalence of asthma in schoolchildren	A 0.1-unit increase in NDVI1000m was associated with lower odds of current asthma (odds ratio: 0.81, 95% CI: 0.75, 0.86)	Age, gender, parental education, family income, breastfeeding, low birthweight, preterm, residential area, SHS, mould in home, home coal usage, and family history of asthma, PM10, and NO2