Spatial analysis and determinants of asthma health and health services use outcomes in Ontario

by

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A thesis submitted to the

Faculty of Graduate and Postdoctoral Studies

in partial fulfillment of the requirements for the

MSc. degree in Geography

Department of Geography

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ABSTRACT

This thesis explores the spatial patterns and determinants of asthma prevalence and health services use (ICD-10 codes J45, J46) for the total population (all ages and both sexes combined) of the province of Ontario, Canada, between 2003 and 2013. Asthma is characterized by high health services use and reduced quality of life for asthma sufferers, representing a considerable burden on individuals, society and the health care system. While recent evidence suggests increasing asthma prevalence in Ontario, little research has been done to understand the identified spatial variability of this disease. Using population-based, ecological-level data and refined spatial analysis techniques, this research aims to explore the spatial patterns of asthma prevalence and health services use in Ontario, and examine the contribution of potential risk factors including air pollution, pollen, deprivation, physician supply and rurality. Results indicated considerable spatial variability in asthma outcomes across Ontario. Similar patterns were found between asthma prevalence and physician visits; clusters of high rates were generally found in southern urban/suburban areas, and clusters of low rates were mainly identified in most northern and southern rural areas. Conversely, clusters of high rates of ED visits and hospitalizations were found in most northern and southern rural areas, whereas clusters of low rates were found in south urban/suburban areas near Toronto. Findings from the spatial regression analysis indicated that while rurality was negatively associated with asthma prevalence and physician visits, it was positively associated with ED visits. Moreover, positive associations were also found between material deprivation and asthma prevalence and ED visits, and between NO_2 and asthma physician visits. This research contributes to a better understanding of area characteristics that influence asthma

disparities, which can help develop better, locally relevant public health strategies aimed at reducing the burden of asthma in Ontario. Further, it demonstrates the importance of using a population-based framework and spatial analysis approaches, which take into account the spatial nature of asthma morbidity and their determinants.

RÉSUMÉ

Cette thèse explore la configuration spatiale et les déterminants de la prévalence de l'asthme et l’utilisation des soins de santé (codes CIM-10 J45, J46) pour toute la population (tous âges et genres confondus) dans la province de l'Ontario, au Canada, entre 2003 et 2013. L'asthme est une cause importante d’utilisation des services de santé et d’une qualité de vie réduite pour les personnes atteintes, représentant un fardeau considérable pour les individus, la société et le système de santé. Malgré l’évidence d’une croissance de la prévalence de l'asthme en Ontario, peu de recherches ont été faites pour mieux comprendre la variation spatiale de cette maladie. Par l'utilisation de données sur les populations au niveau écologique et des techniques d'analyse spatiale raffinées, cette recherche vise à explorer la configuration spatiale de la prévalence de l’asthme et l’utilisation des services de santé en Ontario, et à examiner la contribution des facteurs de risque, tel que la pollution de l'air, le pollen, la privation matérielle, le nombre de médecins et la ruralité. Les résultats indiquent une répartition spatiale considérable de l'asthme en Ontario. Les mesures de prévalence et des visites médicales ont montré des tendances similaires; les taux élevés ont généralement été observés dans les zones urbaines / suburbaines du Sud, alors que les faibles taux ont été identifiés dans la plupart des régions du Nord et les régions rurales du Sud. Par contre, les tendances spatiales des hospitalisations et visites aux urgences ont présenté des taux élevés dans la plupart des zones rurales du nord et du sud, alors que les faibles taux ont été trouvés dans les zones urbaines / suburbaines au Sud près de Toronto. Les résultats de la régression spatiale ont montré que la ruralité était négativement associée aux visites médicales et à la prévalence de l'asthme, mais positivement associée aux visites aux urgences. De plus, des

associations positives ont également été trouvées entre la privation matérielle et la prévalence de l'asthme et les visites aux urgences, et entre NO_2 et les visites médicales. Cette recherche contribue à une meilleure compréhension des caractéristiques spatiales qui influencent les disparités géographiques de l'asthme, ce qui peut contribuer au développement de meilleures stratégies de santé publique, pertinents au niveau local, visant à réduire le fardeau de l'asthme en Ontario. Aussi, cette recherche démontre l'importance de l'utilisation de techniques d'analyses spatiales et d'un cadre de recherche basé sur les populations, permettant de prendre en compte la nature spatiale de cette maladie et de ses determinants.

ACKNOWLEDGEMENTS

First, I would like to thank my supervisor, Dr. Eric Crighton, who allowed me to work on this project and provided me with invaluable support and advice during my Masters' thesis. I am grateful for your time and patience when revising this thesis, for sharing your knowledge and wisdom, and for always finding a solution to every problem.

I would also like to thank my committee members and co-authors for their help and involvement. Thank you, Dr. Mike Sawada, for your flexibility and for always being available to answer my questions. I also owe many thanks to Dr. Kevin Brand, for all the hours spent teaching me Bayesian analysis and for always being so accommodating. Further, this work would not have been successful without the guidance of Dr. Teresa To and Dr. Eric Lavigne, who gave me data access and took the time to discuss and provide suggestions on the direction of this thesis.

Many thanks to staff at the Geography department for welcoming and assisting me with all the administrative tasks. To the HEALab community, Kathy Watson-Leblanc, Jing Feng, Rosalind Ragetlie, Jacob Sammon, Reiko Obokata, Karine Saboui, many thanks for the positive environment, thesis revisions, and moral support you have provided during these past couple of years. I really appreciate the friendships, laughs, food and experiences we have shared; I have learned so much from every one of you.

Most importantly, I would like to thank my family (mom, dad, and Lio) for keeping me grounded, giving me strength, and supporting me during moments of doubts and stress. Despite the fact that we are far apart, you constantly reminded me that I am not alone. This work would not have been possible without your support.

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PREFACE

This thesis follows the article format and is composed of one research paper being prepared for publication. The introduction and objectives are described in Chapter 1. The summary and conclusion are described in Chapter 3. The research paper for this thesis is written as a standalone paper, and as such, it contains informations that has already been mentioned in other chapters. It is as follows:

Chapter 2:

Ouedraogo A.M.C., Crighton E.J., Sawada M., Brand K. An exploration of the spatial patterns and determinants of asthma prevalence and health services use in Ontario using a Bayesian approach. (In preparation for submission to the *International Journal of Health Geographics).*

The first author and Master's candidate conducted the research, which consisted of conducting a literature review, analyzing the data and writing the manuscript drafts. Co-author and supervisor, Dr. Eric Crighton, provided guidance in the initial conceptualization and direction of the project, provided input and editorial advice in the writing of the manuscript. Co-authors, Dr. Micheal Sawada and Dr. Kevin Brand, helped develop the methodology and provided input and advice on the manuscript.

CHAPTER 1

Introduction

1.1 Background

Asthma is the most common chronic respiratory disease in Canada, affecting people of all ages. It is also a leading cause of hospitalizations and reduced quality of life for asthma sufferers, representing a burden not only on individuals, but also on society and health care system (Ismaila et al., 2013, To et al., 2007b, To et al., 2010a). In Ontario, recent evidence suggests that asthma prevalence has been increasing for the past 20 years, which contributes to an urgent need to better understand factors that determine the development and exacerbation of asthma (Gershon et al., 2010b, To et al., 2013b). Although asthma etiology is not fully understood, risk factors commonly identified in the literature include genetic predisposition, infections, diet, second-hand smoke, air pollution exposures and, co-morbidities such as allergic rhinitis and pneumonia (e.g. Chen et al., 2006, Haby et al., 2001, Subbarao et al., 2009, Huss et al., 2001). While the literature provides important insight into individual level behavioural and biological mechanisms, it does not adequately explain the significant spatial variability in asthma outcomes that have been identified elsewhere (e.g. Crighton et al., 2012, Lajoie et al., 2004, To et al., 2007a). Also, the contribution of broad socioeconomic and environmental determinants, which have been found to be associated with asthma (Burra et al., 2009, Crighton et al., 2010, Gwynn, 2004, Thakur et al., 2013), is not well understood. The goal of this research is to better understand the geographical variation of asthma outcomes and the factors that determine this variation by conducting a population-based, ecological level analysis of asthma outcomes in Ontario, using a Bayesian spatial modeling approach. Findings can be expected to inform the development of improved, more locally relevant public health strategies, which take socioeconomic, health care and environmental characteristics into account.

Asthma is the most common chronic respiratory disease in Canada, affecting approximately 3 million individuals and accounting for about 80% of the chronic respiratory disease cases (Ismaila et al., 2013, To et al., 2007b, To et al., 2010a). Recent studies suggest that asthma prevalence rates have been increasing in Canada and in Ontario for the past 20 years (Chen et al., 2005, Gershon et al., 2010a, To et al., 2013b). Asthma is generally associated with airflow obstruction in the lungs; symptoms include wheezing, coughing, chest tightness or difficulty breating, which can range from mild to severe, and in some cases be life-threatening (Canadian Lung Association, 2003). Due to its association with various comorbidities, asthma is a major cause of health services use, contributing to about 10% of all children's hospital admissions and about 146,000 emergency department (ED) visits per year. This causes direct health care expenditures ranging annually between $366 and $647 per patient and significantly reduced quality of life for asthma sufferers due to work absenteeism, productivity loss, travel time to health care services, etc. (Ismaila et al., 2013, Public Health Agency of Canada, 2007). Despite better management of the disease within the health care system, many questions remain regarding the factors that contribute to asthma development and exacerbation.

1.2 Spatial variation of asthma outcomes

With improvements in quality and access to spatial and health data in Canada and elsewhere, there is a growing body of research on the geographical variation of asthma health services use, such as hospitalizations and ED visits. For example, a recent Canadian study identified spatial trends in asthma hospital visits in Manitoba, wherein clusters of high rates were noted in north-central areas of the province (Torabi, 2014). Significant spatial variation of ED visits was also found in Quebec, with higher rates seen in urban and low socioeconomic areas (Lajoie et al., 2004). In Ontario, considerable geographical variation was also documented for asthma ED visits (Lougheed et al., 2006) and hospitalizations (To et al., 2004). While these studies demonstrate the spatial variability in asthma outcomes, they are limited by the fact that hospitalizations and emergency visits represent only the most severe cases and the degree to which this disease is being managed in the community. For example, high rates of asthma related hospitalizations or ED visits in a given community may represent poor asthma management within that community rather than high asthma prevalence. There are also a number of challenges associated with using administrative health data, including choice of case definition, possibility of missclassification bias and underrepresentation of cases. For instance, this data may vary with diagnostic resources or availability of services (e.g. prevalence may be underdiagnosed in unserviced areas). It is therefore important to look beyond one type of health care use to better understand the disease burden (Gershon et al., 2010a, Yiannakoulias et al., 2009).

Despite the challenges, health administrative data are increasingly being used to estimate prevalence. For example, To et al. (2007) investigated the spatial patterns of asthma prevalence across 14 Local Health Integration Networks (LHINs) areas in Ontario, which was generated by linking different types of health services databases using a validated case definition, i.e. at least one asthma outpatient claim within a two-year period and/or at least one asthma hospitalization. They found a 1.6-fold variation, with the highest rates in southern areas and the lowest rates in northern areas. While this study included the investigation of spatial patterns of most asthma cases, the use of large area units may have masked significant geographical variations. Addressing this concern, Crighton et al. (2012) examined prevalence using the same case definition but smaller area units across Ontario. Here significant and more detailed spatial patterns were identified, with clusters of high rates seen in many south urban and industrial areas of the province and clusters of low rates were seen in the most northern and rural areas of the province, in addition to some urban/suburban areas. Authors proposed several hypotheses to explain the findings, including air pollution or allergen exposures, socioeconomic factors and access to health services and medications. These relationships however, were not explicitly examined, which leaves an important gap in our understanding of factors that determine the identified spatial patterns.

1.3 Determinants of asthma outcomes

Commonly identified asthma risk factors in the literature include: genetic predisposition; infections; diet; second-hand smoke; age and sex; and various co-morbidities (e.g. allergic rhinitis, COPD, pneumonia) (Ledford and Lockey, 2013, Chen et al., 2006, Haby et al., 2001, Subbarao et al., 2009, Huss et al., 2001). While these determinants provide insights into the individual-level behavioural and biological/genetic mechanisms, they do not consider the many broad socioeconomic, environmental and health care factors that may generate disparities within and between populations (Evans and Stoddart, 1990, Wilkinson and Marmot, 2003, Wright and Fisher, 2003).

Due to the inherent geographic nature of asthma outcomes, there is growing recognition of mechanisms that contribute to the spatial distribution of asthma outcomes. Several Canadian and international studies have identified significant associations between asthma outcomes and a range of socioeconomic characteristics, typically finding higher asthma prevalence and health services use among those who are low income, low education, ethnic minorities and living in poor quality housing (Arif et al., 2003, Gwynn, 2004, Thakur et al., 2013, Gong et al., 2014). Other studies have found significant associations between disease development and exacerbation and community cohesion, access to services, social capital and psychosocial stress (Burra et al., 2009, Chen et al., 2007, Shankardass et al., 2007, Wright and Fisher, 2003).

Many Canadian studies have also reported low asthma prevalence in rural and remote areas, which could be explained by reduced case detection due to poor access to health care or reduced exposure to air pollution in these areas (Gao et al., 2008, Lawson et al., 2011b, Senthilselvan et al., 2003, Crighton et al., 2010). Others have suggested that this also could be due to protective environmental factors associated with living on a farm during early childhood, which has been shown to reduce the likelihood of developing asthma (Ernst and Cormier, 2000, Masley et al., 2000, Portengen et al., 2002).

There is also growing evidence of an indirect impact of climate change on asthma via complex interaction with socioeconomic and environmental processes (Beggs and Bambrick, 2005, Cecchi et al., 2010, Davis et al., 2003, McMichael et al., 2006, Wardekker et al., 2012). For example, the combination of climate change and air pollution may modify the production, dispersion and content of allergens in an area, leading to increased risk of developing asthma for populations living in these areas. Also, the effect of climate change on asthma outcomes may be influenced by adaptive socioeconomic factors (e.g. ability to buy air conditioners), health care access and public awareness. Despite the strong evidence of the aggravating effect of climate change on asthma, the complex processes by which this occurs make the association difficult to understand and assess.

Access to health services, education and medications have also been found to be important determinants of asthma outcomes. Evidence suggests that improved access to health care services and medications may improve asthma management, thus reducing risks of emergency services utilization (Clark et al., 2013, Garvey et al., 2014, Guttmann et al., 2010, Coleman et al., 2009) and mortality (Macinko et al., 2003). In Clark et al.'s study (2013), the effect of interventions aimed at improving the quality of health care services was investigated in 6 US low income communities. Findings revealed that asthma hospitalizations, emergency visits and physician urgent care visits decreased in communities that received the interventions, when compared with ones that did not. While broad and diverse determinants of asthma have been identified in the literature, most of studies do not use spatial analysis, and therefore do not adequately explain spatial variability in asthma outcomes.

1.4 Spatial approaches to understanding asthma spatial patterns

There are many methodologies employed in health geography and spatial epidemiology to describe and analyze the geographical variations in aggregated health outcomes, in relation to socioeconomic, behavioural, biological and environmental risk factors. These include descriptive analysis and spatial regression analysis (Elliott and Wartenberg, 2004, Gatrell and Elliott, 2009, Waller and Carlin, 2010, Elliott, 2000). The main challenges associated with these conventional spatial approaches include unstable risk estimates due to small population sizes, overdispersion in count data, spatial random effects. Alternative Bayesian approaches are increasingly being used in the literature, as they provide a flexible framework for parameter and risk estimation, which addresses these issues.

1.4.1 Descriptive analysis

Descriptive methods in spatial epidemiology typically consist in an exploration of the geographical variation of disease rates. This is usually done by estimating and mapping disease rates across areas, or by quantitatively investigating the existence of spatial/temporal patterns via cluster analysis or disease surveillance (i.e. systematic routine collection and analysis of health outcomes) (Elliott and Wartenberg, 2004, Gatrell and Elliott, 2009). For example, descriptive spatial studies typically use maps of age- and/or sex-standardized rates to visualize and describe the geographical variation of asthma outcomes across administrative units, such as public health boundaries (e.g. Crighton et al., 2012, Lajoie et al., 2004, To et al., 2007a). While these descriptive methods are useful for generating hypotheses about potential risk factors influencing the spatial patterns found, they do not investigate these associations and are often limited by the large variability in disease rates as a result of small population sizes in sparsely populated areas.

1.4.2 Spatial regression analysis

When investigating the association between risk factors and area-level health outcomes, one important consideration which is not always addressed in spatial studies is the need to take into account spatial dependence in the data, which is characterized by the dependence between variable values in nearby areas (Elliott and Wartenberg, 2004, Gatrell and Elliott, 2009). If spatial dependence in spatial data is ignored, it can lead to biased regression parameter estimates, underestimated standard errors and incorrect inferences about relationships (Mohebbi et al., 2011). Spatial regression models can be used to address this issue. The most common frequentist spatial regression models include spatial lag or error models, geographically weighted regressions and linear mixed models; the choice of which should be used depends on the spatial structure of the data (i.e. spatial weight matrix) and the way in which this spatial structure is incorporated or controlled for in the model (Elliot et al., 2000, Gatrell and Elliott, 2009). Despite the fact that these spatial models control for spatial dependence, they are restricted by the spatial structure formulation, which is only available for linear models. In the analysis of health outcomes, counts of disease cases are usually collected, requiring the need for Poisson regression models. In these models, along with spatial dependence, overdispersion typically occurs (i.e. when variance is greater than mean), which violates its assumption of equal mean and variance. Generalized linear mixed models (GLMMs) have been proposed to accommodate for non-linear models with spatial dependence and overdispersion, however parameter estimation based on a frequentist framework have been found to be challenging to use due to complex integration computations (McCulloch et al., 2008, Torabi, 2012).

1.4.3 Bayesian approaches to disease mapping and spatial regression

Due to the limitations in frequentist approaches, as well as recent developments in computational power and readily available software such as WINBUGS or R that facilitate parameter estimation via iterative sampling techniques, there is a growing interest in the implementation of spatial and Bayesian hierarchical modeling approaches to analyse spatial health data (Best et al., 2005, Bell and Broemeling, 2000, Clayton and Bernardinelli, 1992). The main advantage of the Bayesian modeling framework is its flexibility in incorporating spatial dependence, which may account for overdispersion (in count data) and unmeasured confounders in spatial regression analyses, thus providing unbiased parameter estimates. They also allow smoothing of disease rates over space, by borrowing information from neighbouring areas, which reduces variability in the data due to small numbers and in turn, may result in more reliable risk estimates (Richardson et al., 2004, MacNab, 2004, Elliott, 2000). While Bayesian spatial modeling is increasingly being used by health researchers to examine spatial patterns, predict high-risk areas and create informative maps (Holowaty et al., 2010, Nandram et al., 2000, Torabi, 2014), few studies have used this approach to examine respiratory disease morbidity, and to my knowledge, this approach has not been used within the context of asthma morbidity in

Ontario. Recognizing the importance of accounting for issues related to spatial and ecological contexts, this study uses a Bayesian hierarchical approach to investigate the contribution of ecological risk factors to the spatial patterns of asthma outcomes.

1.5 Conceptual framework

This research adopts a population health perspective to address the research objectives. In Evans and Stoddart's (1990) determinants of health framework, the role of a broad range of factors in generating differences in health status is highlighted, in that genetic endowment, the physical environment and the social environment interact with each other and influence individuals' behavioural and biological responses to causal agents. This conceptual framework demonstrates the complexity and inter-relatedness of broad population health determinants, rather than the effect of individual factors at an individual level. For example, people from positive social environments, such as those with strong social networks, stable family structure, and high income or education level, may be more likely to have better health behaviours or status, resulting in better health outcomes compared to people from negative social environments. They may also be more likely to live in better neighbourhoods (e.g. safe, smoke/drug-free, access to transportation) and have better access to health care services. The physical environment may also impact on people's health via exposure to toxic substances, poor housing conditions, proximity to health care services, etc. In addition, strong health care systems may improve life expectancy and disease burden. One limitation of Evan and Stoddart's conceptual framework is that it does not overtly acknowledge the geographical nature of health outcomes or broad health determinants.

The importance of space in generating health disparities has been highlighted when trying to understand the determinants of health and identify areas and populations at-risk (Wilkinson and Marmot, 2003, Wright and Subramanian, 2007). Therefore, the framework developed for this study (Figure 1.1) builds on Evans and Stoddart's framework as well as the previously discussed literature on the determinants of asthma, by incorporating a spatial component. While all determinants of health are important, the focus of this analysis will be on: (1) socioeconomic factors such as material deprivation or ethnic concentration; (2) physical environment such as air pollution exposure, pollen concentration; (3) health care access such as primary physician supply per capita and urban/rural areas. In this study, the urban/rural factor could be considered a measure of health care access since distance or travel time to health care centers varies with urban or rural locations. However, it could also be interpreted as a characteristic of the physical or socioeconomic environment. It is hypothesized that the geographical distribution of asthma prevalence and health services use rates across Ontario is not random, and that the variation is influenced by ecological socioeconomic, environmental and health care risk factors, which also vary over space and interact with one another.

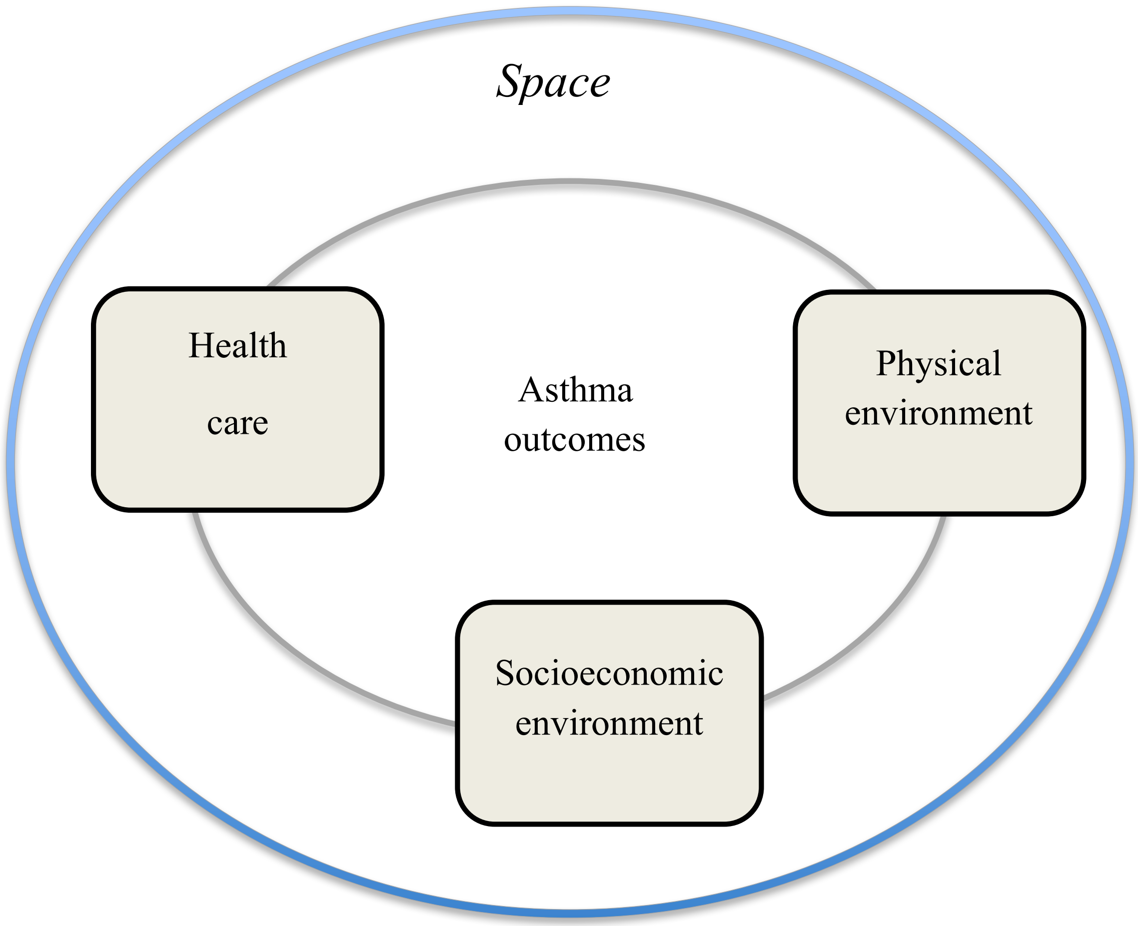

Figure 1.1 Conceptual framework of health care, physical and socioeconomic determinants of asthma outcomes

1.6 Objectives

The goal of this research is to better understand the complex relationships between asthma determinants and spatial patterns of asthma morbidity by conducting a population-based, ecological-level analysis of asthma outcomes in Ontario (both sexes and all ages included). This study uses asthma prevalence and health services use data, aggregated over Ontario sub-Local Health Integration Network (sub-LHIN) areas (n=141) and covering the years 2003 to 2013, to examine spatial patterns of asthma. A range of socioeconomic, health care and environmental factors is used to explain these patterns. To do this, descriptive analysis and a Bayesian spatial modeling approach is employed. Specifically, the objectives of this research are to:

1. Examine the spatial patterns of asthma prevalence, and health services use rates in Ontario; and,
2. Investigate the relationships between these spatial patterns and socioeconomic, health care access and environmental factors.

1.7 Organization of thesis

This thesis is organized into 3 chapters, including this introductory chapter. Chapter 2 is a manuscript that addresses the above objectives and is being prepared for submission to the *International Journal of Health Geographics*. The chapter explores the spatial variation of asthma prevalence, physician visits and ED visits standardized rates in Ontario, by examining maps of their geographic distribution at the sub-LHIN level, over an aggregated time period of 2003 to 2013 (objective 1). In addition, Bayesian spatial regression analyses are used to examine the relationship between asthma outcomes and broad socioeconomic, environmental and health care determinants including material deprivation, degree of rurality, pollen level, pollution exposure, relative humidity and physician access per capita (objective 2). Chapter 3 summarizes major findings from this research and presents additional findings that were not discussed in Chapter 2. Within this chapter, the contributions from the study are also detailed, as well as the limitations and future research directions.

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CHAPTER 2

An exploration of the spatial patterns and determinants of asthma prevalence and health services use in Ontario using a Bayesian approach

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In preparation for submission to: *International Journal of Health Geographics*

Abstract

Asthma is the most common chronic respiratory disease in Canada and as such, places a significant burden on society and the health care system. While evidence suggests that asthma prevalence has been increasing in Ontario, little is known about the spatial variability of asthma outcomes across the province or how broad socioeconomic, environmental or health care factors may contribute to this variability. To address this, we employed a population-based, ecological level study design at the Ontario sub-Local Health Integration Network (sub-LHIN) level (n=141). Asthma prevalence and health services use rates were obtained from a provincial cohort of asthma patients between 2003-2013. Bayesian spatial regression analyses were conducted to examine the relationships between asthma outcomes and explanatory variables including air pollution, pollen, deprivation, physician supply and rurality. Significant spatial variation in asthma outcomes were found across Ontario, with clusters of high rates of prevalence and physician visits generally located in southern urban/suburban areas, whereas clusters of low rates were found in northern and rural areas. Opposite patterns were found for ED visits and hospitalizations. The Bayesian spatial model results indicated that while rurality was negatively associated with asthma prevalence and physician visits, it was positively associated with ED visits. Moreover positive associations were found between material deprivation and asthma prevalence and ED visits, and between NO_2 and asthma physician visits. These findings contribute to a greater understanding of the spatial patterns of asthma in Ontario and can be expected to inform the development of improved, more locally relevant public health strategies.

2.1 Introduction

Asthma accounts for about 80% of all chronic respiratory diseases in Canada, affecting people of all ages (Ismaila et al., 2013, To et al., 2007a, To et al., 2010b). It is a leading cause of hospitalizations and reduced quality of life for asthma sufferers, representing a burden on society and the health care system (To et al., 2007a). In Ontario, recent evidence suggests that average prevalence has been increasing since 1996, which contributes to an urgent need to better understand factors that determines the development and exacerbation of asthma (Gershon et al., 2010b, To et al., 2013b). Commonly identified individual risk factors include genetic predisposition, infections, diet, second-hand smoke, indoor/outdoor air pollution exposures (e.g. Chen et al., 2006, Haby et al., 2001, Subbarao et al., 2009, Huss et al., 2001). Little is known however, about the spatial variability of asthma outcomes identified in the literature (e.g. Crighton et al., 2012, Lajoie et al., 2004, To et al., 2007a), or the potential role of broader socioeconomic and environmental area characteristics, which have been shown to be associated with asthma outcomes (Burra et al., 2009, Crighton et al., 2010, Gwynn, 2004, Thakur et al., 2013). This study aims to better understand the spatial patterns of asthma prevalence and health services use and the factors that determine these patterns by conducting a population-based, ecological analysis of asthma outcomes in Ontario, using a Bayesian spatial approach. Findings can be expected to inform the development of improved, more locally relevant public health strategies, which take into account socioeconomic and environmental characteristics of populations. The present study adds to evidence from previous analyses of the spatial patterns of asthma outcomes in Ontario

(Crighton et al., 2012, To et al., 2007a), by refining the spatial modeling approach used and examining potential ecological-level factors that may explain these variations.

With improvements in quality and access to health and spatial data in Canada and elsewhere, we are increasingly seeing research that is examining the spatial variability of asthma outcomes (Lajoie et al., 2004, Lougheed et al., 2006, Li and Newcomb, 2009). Recent Ontario studies have used health administrative databases to estimate prevalence at the population level by linking multiple databases of different types of health services use (Crighton et al., 2012, To et al., 2007a, To et al., 2013a). For example, Crighton et al. (2012) identified significant spatial patterns in asthma prevalence across Ontario. Clusters of high rates were seen in many south urban and industrial areas of the province whereas clusters of low rates were found in the most northern and rural areas of the province, as well in some urban/suburban areas. While authors proposed several hypotheses to explain the findings, including air pollution, allergen concentrations, socioeconomic and access to medications and health services, these relationships were not explicitly examined. This leaves an important gap in our understanding of factors that determine the spatial patterns identified.

Due to the inherent geographic nature of environmental, socioeconomic and health care access factors, there is growing recognition of their potential contribution to the spatial patterns of asthma in Canada. There is a vast international body of literature on the association between asthma outcomes and socioeconomic status (SES); most of them have found higher asthma prevalence and health services use in groups identified as low income, low education, ethnic minorities and people living in poor housing conditions (Chen et al., 2007, Gwynn, 2004, Thakur et al., 2013). Many recent Canadian studies have also reported low asthma prevalence in rural or remote areas (Gao et al., 2008, Lawson et al., 2011b, Senthilselvan et al., 2003, Crighton et al., 2010), and farming environments (Ernst and Cormier, 2000, Masley et al., 2000), which could be explained by reduced case detection due to poor access to health care in these areas or protective environmental characteristics. While these studies demonstrate the important role of neighbourhood characteristics, which may improve the allocation of health care ressources, they do not use spatial analyses, and therefore do not adequately explain the spatial patterns of asthma outcomes.

Most spatial studies providing some explanations of the spatial variation of health outcomes, do not address several important considerations related to spatial and ecological contexts, including variability in the data due to small population sizes, overdispersion in count data, unmeasured confounders and spatial autocorrelation, which is characterized by the dependence between variable values in nearby areas. Due to recent developments in computational power that facilitate parameter estimation and address these previously mentioned issues, Bayesian spatial modeling approaches are increasingly being used to investigate the spatial patterns of area-level health outcomes (Best et al., 2005, Clements et al., 2006). The main advantage of the Bayesian modeling framework is its flexibility in incorporating spatial dependence, which may account for overdispersion (in count data) and unmeasured confounders in spatial regression analyses, thus providing unbiased parameter estimates. They also allow smoothing of disease rates over space, by borrowing information from neighbouring areas, which reduces variability in the data and in turn, may result in more reliable risk estimates (Richardson et al., 2004, MacNab, 2004, Elliott, 2000). There is a growing interest in using Bayesian spatial models in disease mapping, especially when dealing with small population sizes, to examine the underlying spatial patterns, predict high-risk areas and create informative maps (e.g. Nandram et al., 2000, Torabi, 2014, Holowaty et al., 2010). While these models can also be used to investigate associations between possible ecological risk factors and various health outcomes (MacNab, 2004, Madsen et al., 2015, Zhu et al., 2006), they have not been used to explain asthma morbidity in Ontario to our knowledge.

In an effort to improve our understanding of the spatial patterns of asthma in Ontario and address some of the limitations of previous studies, this paper employs a Bayesian approach to investigate the role of ecological level environmental, socioeconomic and health care factors.

2.2 Data and methods

2.2.1 Study area and population

We conducted a retrospective, population-based, ecological level study to assess the spatial variation of asthma outcomes in the province of Ontario, Canada. Ontario is the most populated province in Canada with approximately 13.6 million residents (Statistics Canada, 2014) distributed between sparsely populated northern and rural southern areas and densely populated urban southern areas. For the purpose of public health and health care planning, the province has been divided into 14 Local Health Integration Network (LHIN) administrative areas boundaries by the Health analytics branch of the Ministry of Health and Long-Term Care. LHIN administrative areas have been further sub-divided into 141 areas (sub-LHINs) for more refined planning. These 141 sub-LHINs will be used as the geographic units of analysis in this research (Figure 2.1).

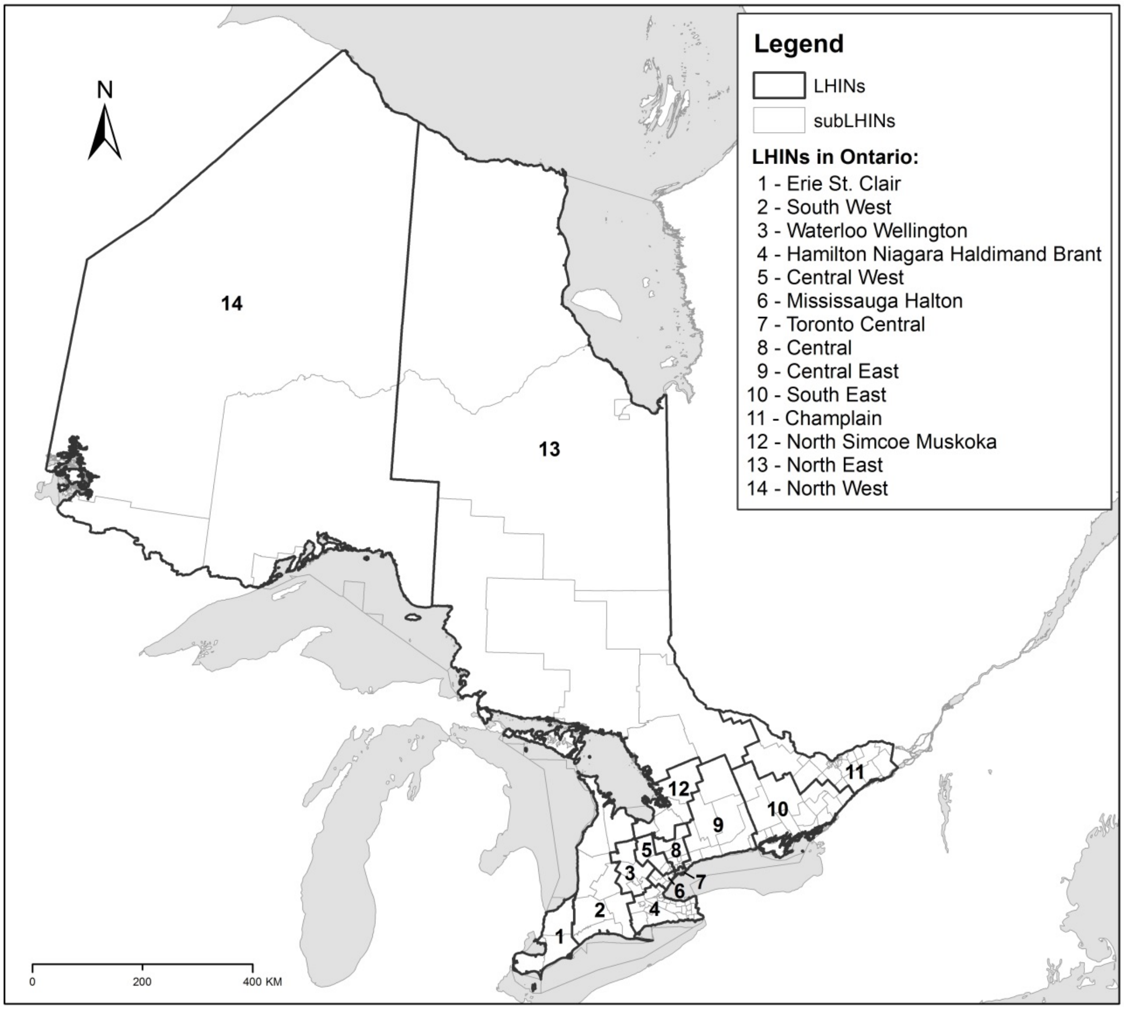

Figure 2.1 Study area, Ontario LHINs and sub-LHINs (*source: Crighton et al., 2012*)

2.2.2 Asthma outcomes

A total of four asthma outcome variables were examined in this research including prevalence, physician visits, ED visits and hospitalizations for diagnosed asthma. These outcomes were obtained from a validated asthma cohort that contains data available for all Ontario residents aged 0 to 99 with an asthma diagnosis, covering the years 2003 to 2013. This data is housed and maintained by the Institute for Clinical and Evaluative Sciences (ICES), Toronto, ON[1]. The asthma cohort was derived from the following administrative health databases: (1) Ontario Health Insurance Plan (OHIP) database, which contains information on billings for physician services; (2) Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), which contains information on hospitalizations in Canada; (3) National Ambulatory Care Reporting System (NACRS), which contains data on emergency room visits; and (4) Registered Persons Database (RPDB), which contains personal information of individuals registered for OHIP such as age, gender, health card number, etc. The validated case definition used to identify asthma cases was any individual who had at least one hospitalization and/or two or more outpatient claims within a two-year period for diagnosed asthma (International Classification of Diseases ICD-10 codes: J45, J46). This definition has been used in previous studies (Crighton et al., 2012, Gershon et al., 2010a, To et al., 2013a) and has been found to have 89% sensitivity and 72% specificity in children (ages under 18) and 84% sensitivity and 76% specificity in adults (18 years and over) (Gershon et al., 2009, To et al., 2006). Due to the evidence that asthma may remit but not resolve (Gershon et al., 2012, Gershon et al., 2010a, To et al., 2007b), identified individuals with

[1] ICES is a non-profit research institute providing population-based health research in Ontario and secured access to Ontario's health related data. Data was accessed from their Ottawa, ON satellite site.

diagnosed asthma remained in the cohort until death or relocation outside the province. Physician visits were identified as one visit for asthma per physician per day per patient and extracted from OHIP. ED visits were extracted from CIHI-NACRS with asthma as the primary diagnosis and hospitalizations were extracted from CIHI-DAD with asthma as one of the discharge diagnoses.

For each asthma outcome, indirectly standardized morbidity ratios (SMRs) were calculated using the Ontario population data by sub-LHIN. Age and sex stratified population counts were obtained from ICES and were estimated using weighted 2009 RPDB data, 2006 Ministry of Health population data at primary sub-LHIN level and Statistics Canada census population estimates at LHIN level from 2003 to 2013.

2.2.3 Explanatory variables

A total of 12 ecological risk factors were first examined to investigate the determinants of the spatial variation of asthma outcomes. These variables were obtained from various sources (Table 2.1). First, the 2006 census-based and geographically derived Ontario marginalization index (ON-Marg) was used to provide information on marginalization and health inequalities between populations and areas of Ontario (Matheson et al., 2011). This index contains four dimensions of marginalization, including material deprivation, residential instability, ethnic concentration and dependency. These are expressed in factor scores created from a principle component factor analysis, with lower scores indicating least marginalized areas and higher scores indicating most marginalized areas. Also, an indicator of physician supply was obtained from ICES Physician database (IPDB). Data from this database was used to calculate the number of family physicians and general practitioners actively practicing in Ontario per 10,000 persons in 2008, the study period's mid-point. Third, a rurality index derived from the Rurality Index for Ontario (RIO), which provides a measure of the degree of rurality and underserviced areas, was obtained from the Association of Ontario Health Centre (AOHC). The original RIO variable is expressed in a score ranging from 0 to 100 for each census subdivisions (CSD) in Ontario and exclude about 200 areas including those with small populations and Indian reserves and settlements (Kralj, 2009). The modified rurality index was produced for each sub-LHIN area to account for missing data; it categorizes rurality into six area categories ranging from less rural to more rural areas. Details can be obtained elsewhere (Steps to Equity, 2013).

Environmental exposure spatial data was obtained from 3 different sources. Ontario pollen counts from mid-March to mid-October and covering a 5-year period (2006-2011) were obtained from Aerobiology Inc. This data is based on 7 pollen-sampling stations across Ontario, collecting daily concentrations from various types of pollen including grasses, trees and weeds. Average total pollen concentration maps for the period 2006-2011, at 10km resolution, were produced using an inverse distance weighting (IDW) technique. Recognizing the limited number of stations and lack of data in some northern areas, interpretation of results from these data should be done with caution. In addition, postal code level pollution variables were obtained from Health Canada. These included satellite-derived long-term estimates for annual concentration of fine particulate matter air pollution (PM2.5) for the period of 1998-2006, as well as average 2006 Nitrogen dioxide land-use regression (NO_2-LUR) model estimates (Crouse et al., 2015, van Donkelaar et al., 2015, Hystad et al., 2011, Hystad et al., 2015). Finally, climate normals gridded layers for mean annual precipitation, mean annual temperature and relative humidity, at 1 km resolution, were obtained from AdaptWest spatial database for conservation planning in North America. Average exposure estimates in each sub-LHIN were extracted using in ArcGIS version 10.2.

A multicollinearity analysis was conducted to examine and reduce linear correlation between explanatory variables, which may mask the true relationships among variables. Continuous variables were standardized by subtracting the mean and dividing by standard deviations. A Spearman's rho correlation matrix was produced to examine correlations between variables and a Variance Inflation Factor (VIF) analysis using a step-wise deletion process was used to remove some variables in order to reduce multicollinearity. There were six remaining explanatory variables included in the models, which were: physician supply per capita; material deprivation index; rurality index; nitrogen dioxide (NO_2); relative humidity (RH); and, total pollen concentration.

Table 2.1 Description of candidate explanatory variables

Variable	Description	Data source
Socioeconomic environment		
Material deprivation	% no high school graduation, lone parent families, government transfers, unemployment, low income, homes needing major repairs (score)	ON-Marg
Residential instability	% people living alone, youth, persons per dwelling, apartments, married, owner-occupied house, residential mobility in past 5 years (score)	ON-Marg
Ethnic concentration	% recent immigrants and visible minorities (score)	ON-Marg
Dependency	% seniors, ratio of population ages 0–14 and 65+ to population ages 15–64, labour force participation (score)	ON-Marg
Health care access		
Physician supply	Number of family physicians (FP) and general practitioners (GP) per 10,000 persons	IPDB
Rurality	Rurality Index for Ontario (area type)	AOHC
Physical environment		
Pollen	Average maps of total pollen concentration for the period 2006-2011 (p/m3)	Aerobiology In
PM2.5	Annual concentration of fine particulate matter air pollution: 1998-2006 (ug/m3)	Health Canada
NO_2	Average 2006 Nitrogen dioxide (NO_2) concentration (ppb)	Health Canada
Precipitation	Average annual precipitation over 1981-2010 period (mm)	AdaptWest
Temperature	Average annual temperature over 1981-2010 period (°C)	AdaptWest
Relative humidity	Average annual relative humidity over 1981-2010 period (%)	AdaptWest

ON-Marg: Ontario Marginalization index; IPDB: ICES Physician database; AOHC: Association of Ontario Health Centre

2.2.3 Analysis

The analysis in this study follows spatial analysis methodologies for area-level health data (Brunsdon and Comber, 2015, Elliott, 2000, Elliott and Wartenberg, 2004) as well as Bayesian spatial modeling techniques (Best et al., 2005, Gelman, 2004, Lee, 2013). The first step consisted of examining summary statistics and maps of asthma SMRs. Global spatial autocorrelation indicator, Moran's I, was computed using queen's contiguity matrix (i.e. sharing any common boundaries) (Moran, 1950). In addition, Local Indicator of Spatial Autocorrelation (LISA) analysis was conducted to detect the location of clusters of high/low rates, according to k-nearest neighbours (k=4). Different adjacency definitions were explored (e.g. k=6 and 8) but no notable differences were found in the clusters. Significance levels were based on conditional Monte Carlo simulations with 999 permutations to correct for the multiple testing problem due to simultaneous tests for clustering occur at each location (Anselin, 1995). The last step consisted of conducting non-spatial and spatial regression models to examine the contribution of potential ecological risk factors and adjust for spatial dependence. Maps were created using ArcGIS (version 10.2) and all statistical modeling were performed using R-studio (R version 3.1.2).

Non-spatial models

Non-spatial regression models for asthma prevalence, physician visits and ED visits were conducted to examine the geographical relationships with chosen explanatory variables. Asthma hospitalizations were not modeled due to the variable's similarities in spatial patterns with ED visits. A multicollinearity analysis was first conducted to examine and reduce the linear correlation between explanatory variables, which may mask the true relationships among variables. A Poisson log-linear model was used to model observed numbers Y_i and the age and sex-adjusted expected numbers E_i (i.e. offset) for each area i:

$$Y_i|E_i, r_i \sim \text{Poisson}(r_i E_i) \text{ for } i = 1,\ldots,n \qquad (1)$$

$$\log(r_i) = \beta_0 + x_i^T\beta + E_i$$

Where:

r_i is the relative risk for asthma outcome in sub-LHIN area i, i=1,…,n (n=141)

β_0 is the intercept

β is the regression parameters

x_i^T values of the explanatory variables matrix $X=(x_1^T, \ldots, x_n^T)^T$, for area i

This model is commonly used with this type of outcome data (i.e. counts). P-values were significant at the 5% level. Overdispersion was adjusted for using quasi-poisson regressions.

Spatial Bayesian models

When analyzing areal data, there is typically some remaining spatial autocorrelation in the model residuals after accounting for known covariates, which violates the assumptions of independence in Poisson regressions. To account for this issue, spatially autocorrelated random effects can be modeled by Conditional Autoregressive (CAR) priors, by borrowing information from neighbouring areas (Besag et al., 1991). To do this, Bayesian spatial models were implemented through generalized linear mixed models (GLMM) for area data. The first stage of the models specified a likehood model, representing the distribution of observed and expected asthma counts in each area i. In the second stage, a Leroux CAR prior, which was found to efficiently adjust for overdispersion and spatial autocorrelation (Lee, 2011, Leroux et al., 2000), was chosen to model the spatial random effect. The same explanatory variables were accounted for in this analysis. The Bayesian spatial models were fitted using a hierarchical approach:

1) Level 1: likelihood model

$Y_i|E_i,r_i \sim$ Poisson (r_iE_i) for i = 1,…,n (n=141) (2)

$\log(r_i) = \beta_0 + x_i^T\beta + E_i + \varphi_i$

Where:

r_I, E_i, Y_i, β_0, x_i^T, and β are specified as above,

φ_i is the spatial random effect of sub-LHIN area i, i=1,…,n (n=141).

2) Level 2: spatial autocorrelation prior

The spatial random effect was specified using the Leroux CAR prior:

$$\varphi_i \sim \mathrm{N}\left(\frac{\rho\sum_{j-1}^{n} w_{ij}\,\varphi_j}{\rho\sum_{j-1}^{n} w_{ij}+1-\rho}\ ,\frac{\tau^2}{\rho\sum_{j-1}^{n} w_{ij}+1-\rho}\right) \quad (3)$$

$\tau^2 \sim$ Inverse-Gamma (a=0.001; b=0.001)

$\rho \sim$ Uniform (0,1)

Where,

φ_j is the random effect of neighbouring areas

w_{ij} is the adjacency matrix parameter, with w_{ij}=1 if areas i and j share a common border and w_{ij}=0 otherwise

ρ is the spatial autocorrelation parameter; $\rho=1$ indicates a strong spatial autocorrelation and $\rho=0$ indicates independence

τ^2 is the variance parameter, representing the random variation not accounted by the explanatory variables

For Bayesian spatial models, inference is based on Markov Chain Monte-Carlo (MCMC) simulations of a single chain, using a combination of Gibbs and Metropolis sampling methods. Model parameters (i.e. posterior medians) were estimated using 1,000,000 iterations, 250,000 burn-in iterations. Parameters were significant if their 95% credible interval did not include zero. Model performance was evaluated by plotting parameter samples to visually check for convergence, as well as by performing Geweke convergence diagnostics tests (Plummer et al., 2006, Plummer et al., 2015, Gelman, 2004). We also examined whether any spatial autocorrelation remained in the data by examining model residuals and conducting Moran's I tests. Spatial models were implemented using CarBayes package (Lee, 2013) in R-studio (R version 3.1.2).

2.3 Results

In Ontario, there were 1,818,971 prevalent cases of asthma (141.09 per 1000) identified during the study period, with 641,065 physicians visits (352.43 per 1000), 41,304 ED visits (22.71 per 1000) and 13,635 hospitalizations (7.50 per 1000) (Table 2.2). Rates varied in the total population (all ages and both sexes combined), with the highest variability found in ED visits (CV= 54%) and hospitalizations (CV= 44%), when compared with physician visits (CV= 23%) and prevalence (CV= 18%). Similarities in the spatial patterns were found between ED visits and hospitalizations. As a result, asthma hospitalizations were only explored (see Appendix A), but not further analyzed.

Table 2.2 Crude rates and variability asthma prevalence, physician visits, ED visits and hospitalizations for total population by sub-LHIN, for Ontario population, 2003-2013[2]

	Provincial level		Sub-LHIN level crude rates				
	Counts	Crude Rate (per 1000)	Min	Mean	Max	sd	CV* (%)
Prevalence	1,818,971	141.09	58.38	140.71	278.56	24.85	17.66
Physician visits	641,065	352.43	151.34	311.01	517.05	72.85	23.42
ED visits	41,304	22.71	8.71	28.39	76.65	15.38	54.17
Hospitalizations	13,635	7.50	3.78	7.76	38.50	3.39	43.69

**CV: coefficient of variation*

Maps of SMRs and LISA results for asthma prevalence, physician visits, ED visits and hospitalizations revealed considerable and distinct spatial patterns across Ontario sub-LHINs (Figures 2.2, 2.3, 2.4 and Appendix A). A 4.9-fold variation was found in asthma prevalence across Ontario, with the highest SMRs in southeastern areas of the province (Champlain LHINs), areas near Toronto, and southwestern areas near Sarnia

[2] Prevalence is per 1000 Ontario residents, and HSU is per 1000 resident with asthma.

and Windsor (Erie St. Clair LHIN), and the lowest SMRs were found in the most northern (North East and North West LHINs) and rural southern areas (e.g. South West and South East LHINs). The spatial patterns of asthma physician visits were similar to prevalence, with a 3.4-fold variation between the highest SMRs in the Toronto and Ottawa urban areas, as well as near Sarnia and Windsor, and the lowest SMRs in the North and rural South. Conversely, the spatial patterns of asthma ED visits and hospitalizations had opposite patterns. Highest SMRs were seen in the north and rural south of the province, whereas lowest SMRs were in and around the cities of Toronto and Ottawa, representing the largest variations across the province (9 and 9.6-fold for ED visits and hospitalizations, respectively).

Global Moran's I tests indicated the presence of moderate but statistically significant spatial autocorrelation (prevalence: I= 0.40; physician visits: I= 0.64; ED visits: I= 0.52; hospitalizations: I=0.30; all pseudo p-values< 0.05), indicating that asthma outcomes are not randomly distributed over space. Several significant clusters of high SMRs for asthma prevalence were located in suburban areas northeast and west of Toronto (e.g. Central East, Central West LHINs) and rural areas near Ottawa (Champlain LHINs), whereas clusters of low SMRs were located in the North (North East and North West LHINs) and rural South (South West and Waterloo Wellington LHINs). Two clusters of high SMRs for asthma physician visits were identified in the Toronto and Ottawa areas, whereas several clusters of low SMRs were found northern (North East and North West LHINs), rural southeastern (e.g. Central East and South East LHINs) and southwestern areas (e.g. South West and Waterloo Wellington LHINs). For ED visits, large clusters of high SMRs were identified in most northern (North East and North West LHINs), rural southwestern and eastern areas (e.g. South West and South East LHINs), whereas two clusters of low SMRs were found in areas near Toronto (e.g. Central and Hamilton Niagara Haldimand Brant (HNHB) LHINs) and Ottawa. Similar patterns were found for asthma hospitalizations (see Appendix A).

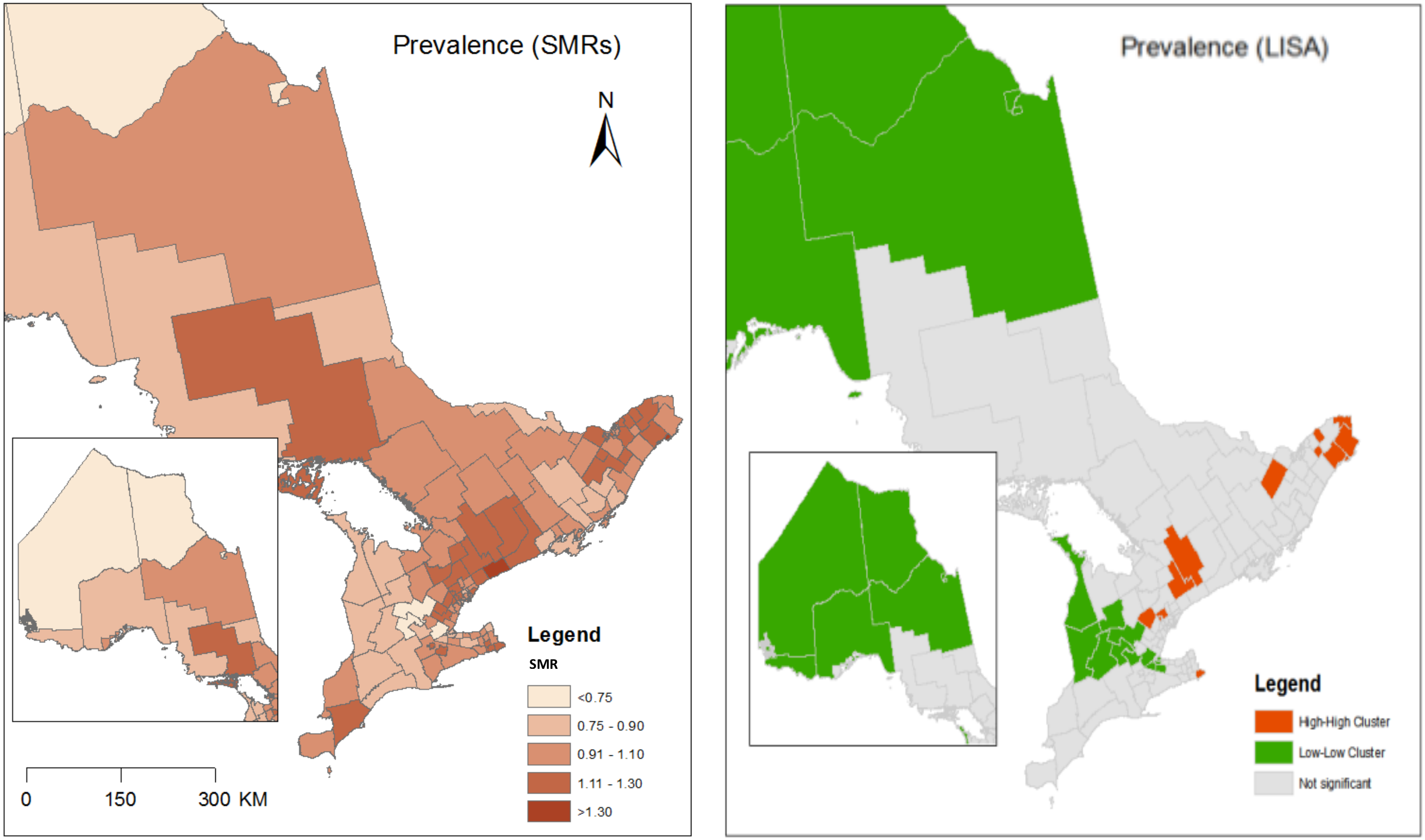

Figure 2.2 Standardized morbidity ratios (SMRs) and Local Indicators of Spatial Autocorrelation (LISA) of asthma prevalence for total population in Ontario, 2003-2013

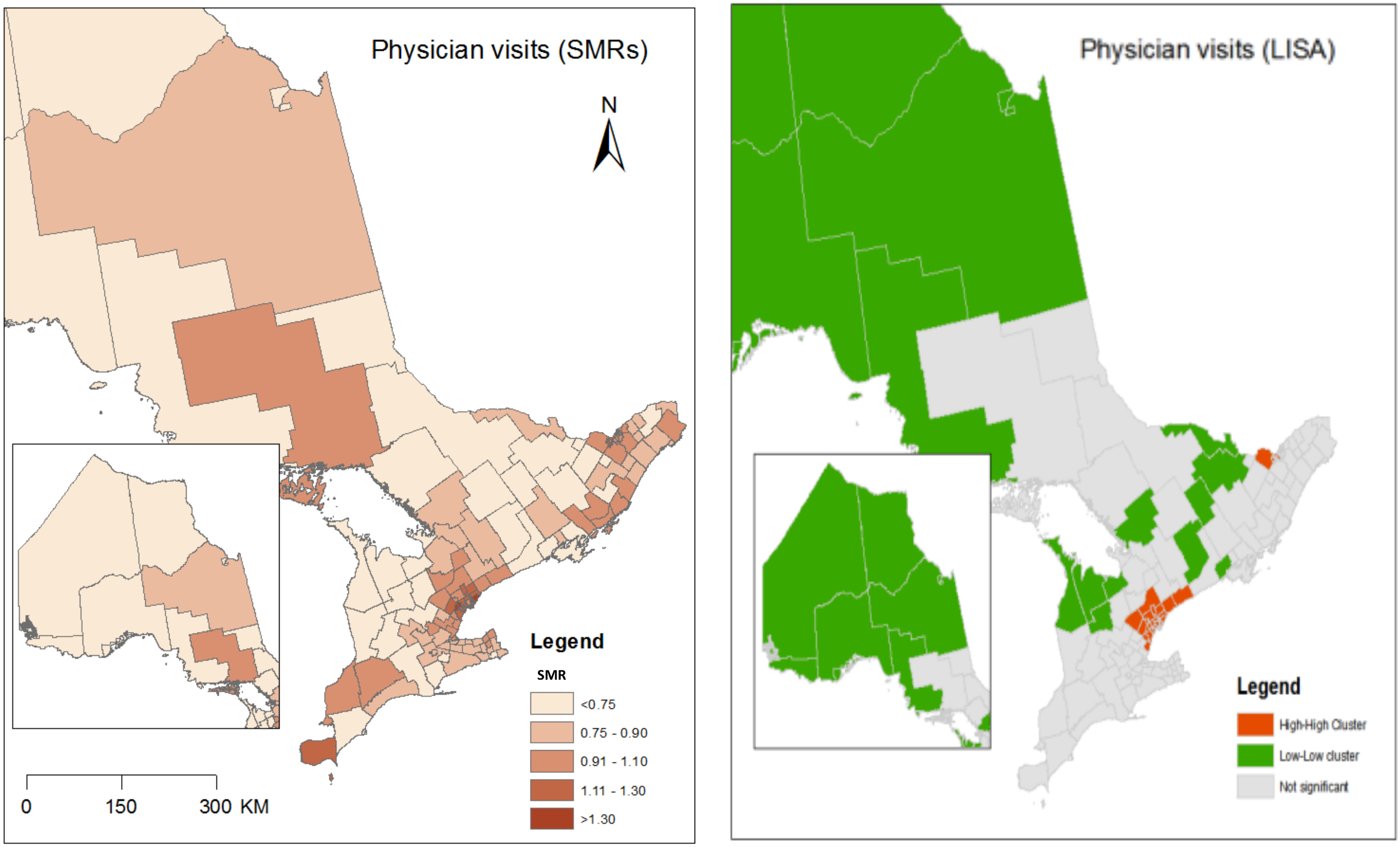

Figure 2.3 Standardized morbidity ratios (SMRs) and local Local Indicators of Spatial Autocorrelation (LISA) of physician visits for asthma for total population in Ontario, 2003-2013

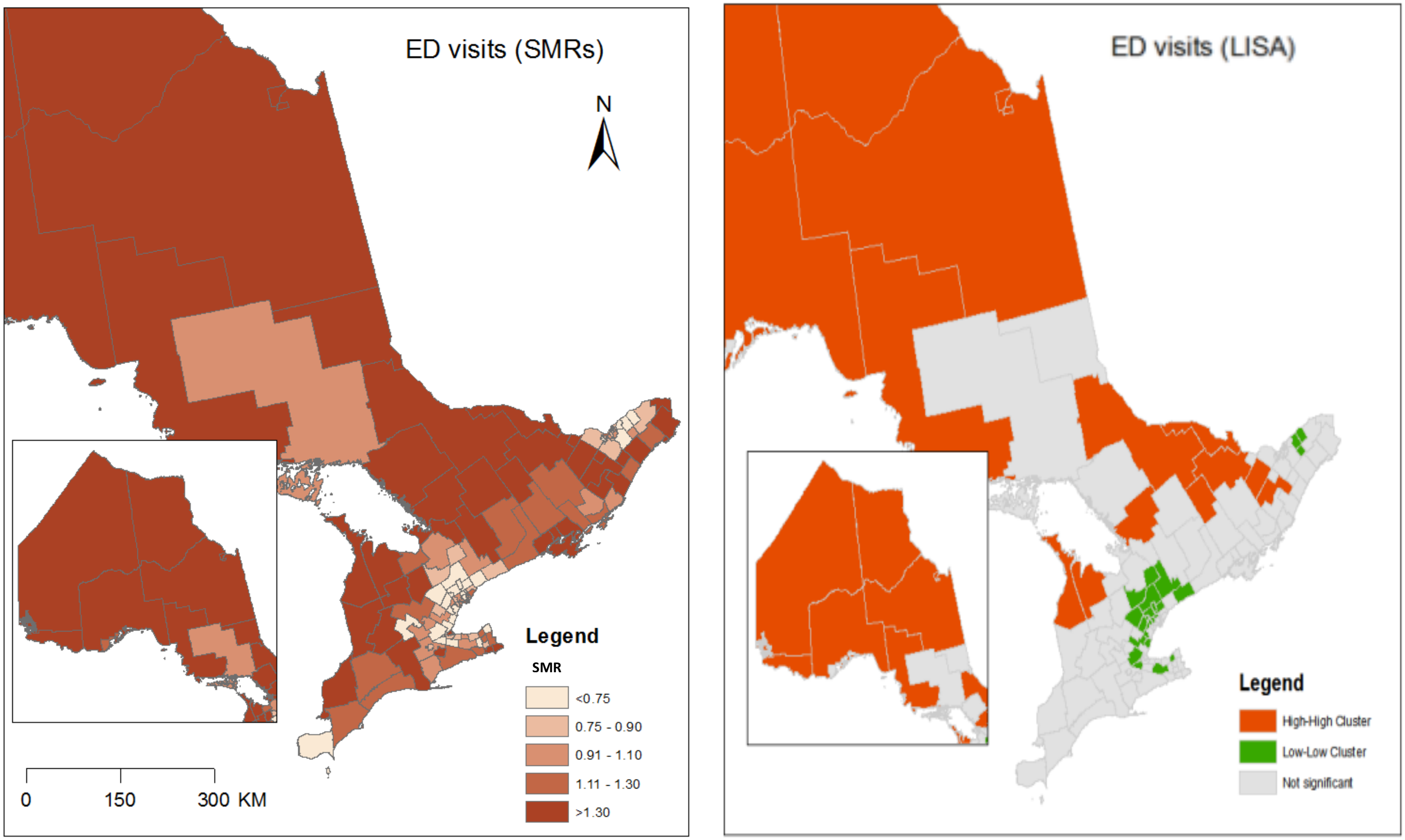

Figure 2.4 Standardized morbidity ratios (SMRs) and Local Indicators of Spatial Autocorrelation (LISA) of ED visits for asthma for total population in Ontario, 2003-2013

Tables 2.3, 2.4 and 2.5 show the results of non-spatial and spatial regression models for asthma prevalence, physician visits and ED visits. In the non-spatial models, most explanatory variables were significant, whereas after adjusting for overdispersion in each model, wider confidence intervals and loss of parameters significance were observed.

Bayesian spatial models accounted for spatial dependence in all the models; both spatial variation coefficients ($\tau 2$ and ρ) were significant. For prevalence, the spatial correlation parameter (ρ=0.773) indicated that spatial random effects modeled about 77% of the spatial autocorrelation. Significant but more moderate spatial autocorrelation was modeled by the spatial random effects for the other outcomes (i.e. 59% for physician visits and 41% for ED visits). Global Moran's I tests and residual maps (Appendix B) also confirmed that no significant spatial autocorrelation remained in the spatial models.

Spatial regression results revealed that material deprivation, rurality and NO_2 had significant effects on the different asthma outcomes. For asthma prevalence (Table 2.3), significant associations were limited to material deprivation and rurality. While asthma prevalence was positively related to deprivation (RR = 1.073; 95% CI: 1.015, 1.139), it was inversely associated with rurality (RR = 0.949, 95% CI: 0.922, 0.982). In other words, when deprivation score increases by 1 unit, asthma prevalence increases by 7.3%. In the case of rurality, a 1 unit increase is associated with 5.1% decrease (i.e. 1 - 0.949 = 0.051) in asthma prevalence. In the physician visits model (Table 2.4), after accounting for spatial dependence, significant associations were found with rurality and NO_2. While physician visits for asthma was negatively related to rurality (RR = 0.927, 95% CI: 0.900, 0.955), it was positively associated with NO_2 (RR = 1.112, CI: 1.037, 1.191). In other words, when rurality increases by 1 unit, physician visits decreases by 7.3%, whereas when NO_2 increases by 1 unit, physician visits increases by 11.2%. For ED visits (Table 2.5), after accounting for spatial dependence, significant positive relationships were found with deprivation (RR = 1.530, 95% CI: 1.351, 1.731) and rurality (RR = 1.149, 95% CI: 1.083, 1.217), whereas negative associations were found with NO_2 (RR = 0.858; 95% CI: 0.767, 0.960). In other words, when deprivation and rurality increase by 1-unit, ED visits increases by 53% and 14.9%, respectively. In the case of NO_2, a 1-unit increase is associated with a 14.2% decrease in ED visits.

Table 2.3 Summary statistics of regression parameters for non-spatial and spatial regression models for asthma prevalence

Non-Spatial								Spatial		
	No adjustment for overdispersion				Adjustment for overdispersion					
	RR	2.5% CI	97.5% CI	p-value	2.5% CI	97.5% CI	p-value	RR	2.5% CI	97.5% CI
Intercept	1.125	1.121	1.130	<0.001	1.057	1.198	<0.001	**1.123**	**1.038**	**1.201**
Deprivation index	1.033	1.029	1.036	<0.001	0.981	1.087	0.225	**1.073**	**1.015**	**1.139**
Rurality (RIO)	0.945	0.943	0.946	<0.001	0.919	0.971	<0.001	**0.949**	**0.922**	**0.982**
Relative humidity	0.960	0.958	0.963	<0.001	0.923	0.998	0.043	0.976	0.916	1.047
Physian supply	0.959	0.957	0.961	<0.001	0.931	0.989	0.009	0.981	0.960	1.004
NO_2	0.987	0.985	0.989	<0.001	0.957	1.018	0.406	0.924	0.847	1.008
total pollen	1.000	0.998	1.000	0.815	0.973	1.027	0.988	1.010	0.958	1.088
	Estimate							Estimate	2.5% CI	97.5% CI
Dispersion parameter	232.568									
Spatial variation, τ2								**0.056**	**0.041**	**0.075**
Spatial correlation, ρ								**0.773**	**0.488**	**0.959**

Table 2.4 Summary statistics of regression parameters for non-spatial and spatial regression models for asthma physician visits

Non-Spatial								Spatial		
	No adjustment for overdispersion				Adjustment for overdispersion					
	RR	2.5% CI	97.5% CI	p-value	2.5% CI	97.5% CI	p-value	RR	2.5% CI	97.5% CI
Intercept	1.064	1.055	1.071	<0.001	1.007	1.123	0.028	**1.025**	**0.954**	**1.098**
Deprivation index	1.009	1.004	1.015	<0.001	0.969	1.051	0.649	1.006	0.948	1.068
Rurality (RIO)	0.915	0.912	0.919	<0.001	0.892	0.939	<0.001	**0.927**	**0.900**	**0.955**
Relative humidity	0.934	0.930	0.938	<0.001	0.901	0.968	<0.001	0.971	0.913	1.029
Physian supply	0.976	0.973	0.979	<0.001	0.953	1.000	0.048	0.993	0.967	1.020
NO_2	1.131	1.127	1.135	<0.001	1.103	1.161	<0.001	**1.112**	**1.037**	**1.191**
total pollen	1.051	1.048	1.054	<0.001	1.027	1.077	<0.001	1.026	0.944	1.094
	Estimate							Estimate	2.5% CI	97.5% CI
Dispersion parameter	62.100									
Spatial variation, $\tau 2$								**0.040**	**0.026**	**0.060**
Spatial correlation, ρ								**0.590**	**0.283**	**0.905**

Table 2.5 Summary statistics of regression parameters for non-spatial and spatial regression models for asthma ED visits

Non-Spatial								Spatial		
	No adjustment for overdispersion				Adjustment for overdispersion					
	RR	2.5% CI	97.5% CI	p-value	2.5% CI	97.5% CI	p-value	RR	2.5% CI	97.5% CI
Intercept	0.826	0.806	0.847	<0.001	0.745	0.916	<0.001	0.887	0.770	1.017
Deprivation index	1.556	1.520	1.590	<0.001	1.416	1.709	<0.001	**1.530**	**1.351**	**1.731**
Rurality (RIO)	1.198	1.186	1.210	<0.001	1.149	1.251	<0.001	**1.149**	**1.083**	**1.217**
Relative humidity	1.120	1.104	1.135	<0.001	1.054	1.189	<0.001	1.035	0.912	1.163
Physian supply	1.078	1.065	1.092	<0.001	1.023	1.137	0.005	1.053	0.992	1.115
NO_2	0.847	0.835	0.858	<0.001	0.800	0.896	<0.001	**0.858**	**0.767**	**0.960**
total pollen	0.915	0.905	0.925	<0.001	0.872	0.960	<0.001	0.940	0.832	1.055
	Estimate							Estimate	2.5% CI	97.5% CI
Dispersion parameter	17.299									
Spatial variation, $\tau 2$								**0.158**	**0.101**	**0.245**
Spatial correlation, ρ								**0.413**	**0.157**	**0.763**

Important findings from the spatial regression models are summarized in Figures 2.5, 2.6 and 2.7, which show the effect of each significant variable across the different asthma outcomes. While material deprivation positively affected the spatial patterns of asthma prevalence and ED visits, it did not influence physician visits patterns. Rurality however, significantly affected the spatial patterns of all 3 asthma outcomes, indicating a negative association with asthma prevalence and physician visits, but a positive association with ED visits. For NO_2, a negative association is found with the spatial patterns of asthma ED visits, while a positive association is found with physician visits. No significant relationship was found with asthma prevalence.

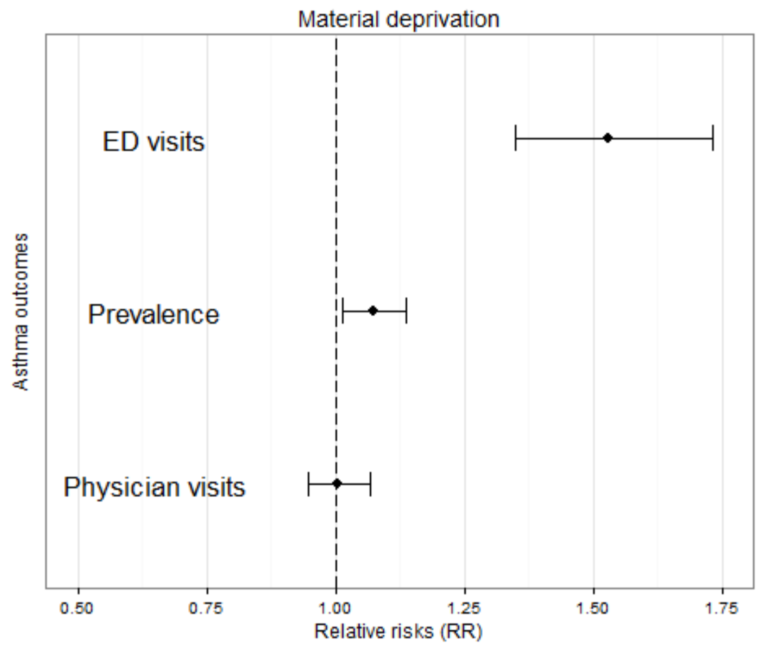

Figure 2.5 Relative Risks (RRs) for material deprivation by asthma outcomes

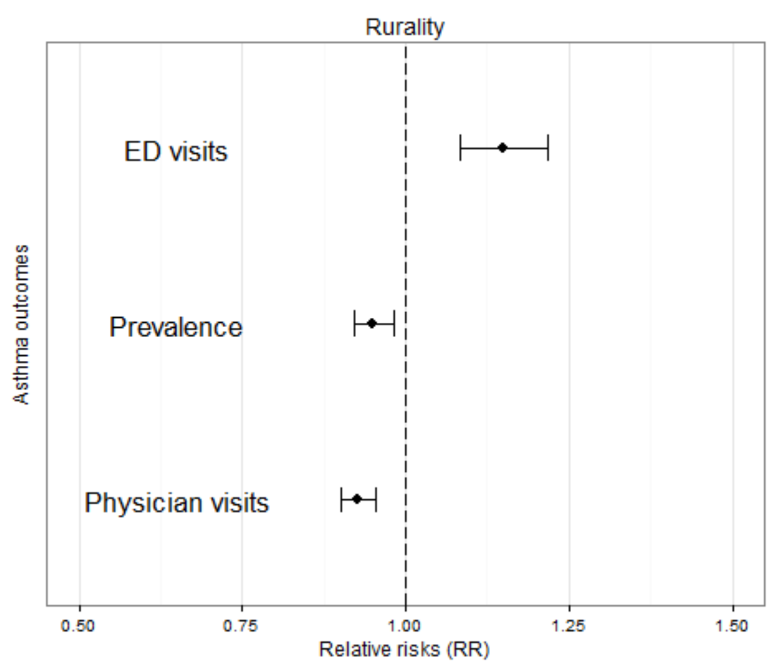

Figure 2.6 Relative Risks (RRs) for rurality by asthma outcomes

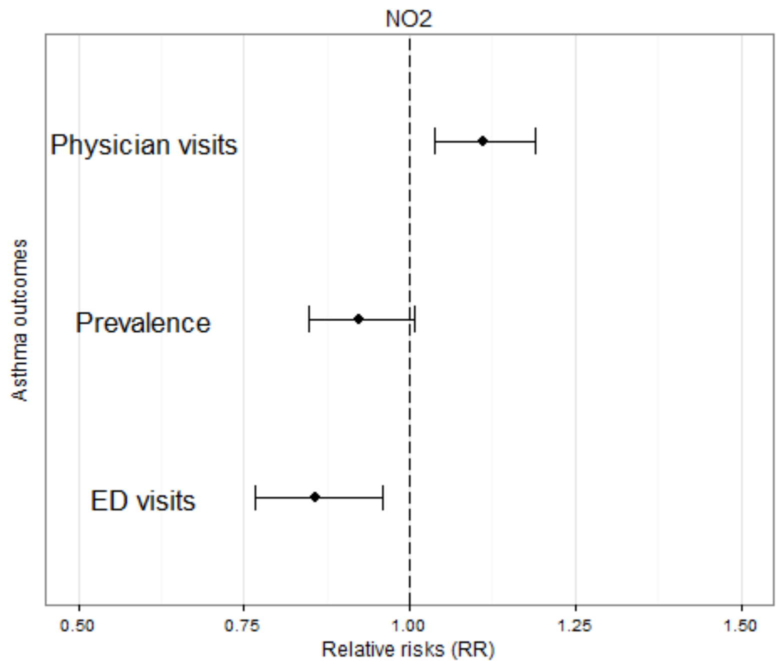

Figure 2.7 Relative Risks (RRs) for NO_2 by asthma outcomes

2.4 Discussion

The goal of this study was to examine the spatial patterns of prevalence and health services use for physician diagnosed asthma, and to better understand the role of ecological determinants in explaining these patterns. Significant spatial patterns in asthma outcomes were found across Ontario. For asthma prevalence, clusters of high SMRs were found in suburban areas near Toronto and in rural areas near Ottawa, whereas clusters of low SMRs were located in the north and rural south of the province. It is likely that these patterns are driven by physician visits patterns since the physician visits map indicated similar patterns; two clusters of high SMRs were found in the Toronto and Ottawa areas, whereas clusters of low SMRs were located in northern and rural south areas of the province. In addition, high asthma rates in the Toronto area could also be explained by exposure to environmental factors. Conversely, the variation of asthma ED visits and hospitalizations showed the opposite pattern; large clusters of high rates were found in most northern and rural areas in the south of the province, whereas two clusters of low SMRs were found in areas near Toronto. Similar urban/rural patterns have been reported in previous Ontario studies examining asthma and other respiratory diseases outcomes such as COPD and pneumonia (Crighton et al., 2012, To et al., 2007a, Crighton et al., 2015, Jaakkimainen, 2006) suggesting that related factors may be at play in determining them.

Consistent with the descriptive spatial analysis, our models revealed that rurality was negatively associated with asthma prevalence and physician visits, but positively associated with ED visits. Higher asthma prevalence in urban areas compared to rural areas has been reported in other Canadian studies (Lawson et al., 2011a, To et al., 2010b, Wong and Chow, 2008, Crighton et al., 2010). In these studies, the patterns are explained by an increased likelihood of diagnosis due to better access and more regular contact with primary care physicians in urban areas, combined with urban risks factor including higher levels of outdoor air pollution. A further potential explanation can be found in the hygiene hypothesis which posits that increased early life exposure to germs (e.g. from farm environment, large family households) is associated with reduced likelihood of developing asthma (Ernst and Cormier, 2000, Masley et al., 2000, Portengen et al., 2002). In contrast, higher ED visit rates for asthma in rural, northern or remote areas in Ontario may be explained by reduced access to primary health care, resulting in poorer management resulting in more severe reactions and reliance on emergency services (Ministry of Health and Long-Term Care, 2010).

Material deprivation was positively associated with asthma prevalence and even more strongly associated with ED visits. This is consistent with findings commonly reported in the literature which suggests higher asthma morbidity among people with low SES (Crighton et al., 2010, Gwynn, 2004, Li and Newcomb, 2009, Shankardass et al., 2007, Sin et al., 2003). These findings suggests that despite universal access to health care in Canada, people with low SES still face many access barriers that create a negative impact on their health outcomes, including costs of asthma medications and lack of reliable transportion. Moreover, the strong association found between material deprivation and ED visits may reflect poor asthma management in lower SES groups, in that increased use of emergency health services suggests symptom exacerbations, which are often caused by inadequate asthma control and/or irregular physician visits.

While both PM2.5 and NO_2 pollution variables were examined in the preliminary multicollinearity analysis (results not shown), only NO_2 was found to be significantly associated with asthma outcomes, and therefore included in the models. NO_2 variable was positively associated with asthma physician visits but negatively associated with asthma ED visits. In the case of physician visits, findings are consistent with the literature since many studies have reported a positive effect of exposure to ambient air pollutants, including NO_2, particulate matter (PM), ozone (O_3) and carbon oxides (CO), on asthma exacerbations and increased use of health services (Lavigne et al., 2012, To et al., 2013a, Lin et al., 2005, Villeneuve et al., 2007). The negative relationship to ED visits is inconsistent with the literature and may be explained by the fact that the NO_2 exposure variable may not be accurately capturing air pollution exposures or that it is perhaps confounded by some other factors not included in the model. In fact, the NO_2-LUR model estimates used in this study were reported to be more accurate in urban areas due to the locations of satellite monitors, resulting in overpredictions in rural areas (Hystad et al., 2011). Better air pollutant measures and the effect of other air pollutants, such as O_3 or CO, should be further examined.

It is also worth noting that a number of variables examined here were not significant in the models despite evidence of their effects in the literature. While our previous findings suggest that better access to primary care may explain higher prevalence rates in urban areas, the physician supply variable was not significantly associated with any asthma outcome. Several studies have reported that better access to primary care physicians and specialists is associated with better asthma management and reduced likelihood of patients experiencing severe symptoms that require emergency care, hospitalizations (Clark et al., 2013, Garvey et al., 2014, Guttmann et al., 2010) or death (Macinko et al., 2003). Possible explanations for our findings could be that the physician supply variable does not adequately measure health care access or that the scale and spatial configuration of area units may confound the 'true' variability – for example, the variable used in this study does not take into account physician supply in neighbour areas, mobility of patients across geographic areas, etc. (Guagliardo, 2004, Pong and Pitblado, 2005). The pollen variable in this study was also not significantly associated with any asthma outcome. Although the effect of aeroallergen exposure on asthma symptoms exacerbation (Darrow et al., 2012, DellaValle et al., 2012, Villeneuve et al., 2006) and development (Harley et al., 2009, Kihlstrom et al., 2003) has been shown in the literature, the spatial patterns of pollen exposure are still not well understood due to several measurement issues including taxon-sensitive patterns, unmeasured confounders, limited number of monitoring sites, etc. (Weinberger et al., 2015, Cecchi, 2013). In this study, non-significant results may be explained by the fact that pollen estimates are based on a small number of sampling stations across the province, resulting in inaccurate estimates in areas farther away from these stations, particularly more rural and northern areas.

There are a few limitations to this research that should be discussed. Firstly, the ecological study design used here does not allow us to make inferences about the determinants of asthma at the individual level. It does however, provide contextual explanations for understanding outcomes across geographies, which has useful implications for the development of public health strategies and interventions (Macintyre and Ellaway, 2000). Secondly, the modifiable areal unit problem (MAUP) may cause different results within different spatial scales and zones (Openshaw, 1984). Alternate levels of aggregation could be examined to reduce this issue; however, this is challenging due to data availability and sparse population data in larger areas. Thirdly, while the asthma prevalence measure used here has been validated and shown to have good sensitivity and specificity for diagnosed cases (Gershon et al., 2009, To et al., 2006), less severe cases may go undiagnosed, particularly in rural and northern areas due to poorer access to primary care and diagnostic services. Fourthly, since rurality, a proxy for health care access, was significantly associated with all asthma outcomes, further analysis should control for physician accessibility in the models. In addition, the influence of temperature extremes should be examined due to the extreme gradient in Ontario. Finally, although clusters of high/low risks were identified and spatial models accounted for spatial dependence, different adjacency formulations should be further examined. There may also be a number of unknown or unmeasured ecological risk factors that were not accounted for in this study, including other measures of SES and environmental exposure.

2.5 Conclusion

With the increasing asthma prevalence and spatial disparities in Canada, there is an urgent need to better understand the role of contextual socioeconomic, environmental and health care factors on the development and exacerbation of asthma. This research highlights the utility of large and sophisticated health administrative databases for asthma identification and surveillance in the entire population. Also, the use of a Bayesian spatial approach provided a sophisticated and flexible framework, which facilitated the adjustment for confounders and spatial dependence in the data, and a better understanding of the relationships between asthma outcomes and ecological risk factors. Results demonstrated the presence of significant spatial patterns in asthma outcomes across Ontario, which were mainly explained by material deprivation, rurality and air pollution. These findings can inform the development of better, locally relevant public health strategies directed towards improving access to health care in rural/northern areas and the health outcomes of people with low SES. Further research should consider the use of multilevel analysis techniques to better understand the role of both individual and ecological level determinants of asthma. Spatio-temporal trends and time-dependent risk factors should also be examined for a more comprehensive understanding of asthma morbidity and trends. Lastly, further investigations should consider better exposure variables and unmeasured confounders such as second-hand smoke exposures, housing conditions, physician accessibility among others.

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CHAPTER 3

Summary and Conclusion

3.1 Introduction

This research used a retrospective, population-based, ecological level study design and Bayesian spatial modeling to better understand the role of ecological risk factors in explaining the spatial patterns of asthma outcomes (ICD-10 codes J45, J46) for the total population in Ontario, aggregated over a 10 year period. This research was conducted for several reasons. Firstly, as a major cause of morbidity and health services use in Canada, asthma represents a significant burden on individuals, society and the health care system (Ismaila et al., 2013, To et al., 2007a). Secondly, there is strong evidence of increasing asthma prevalence in Ontario and in Canada over the past 20 years (Chen et al., 2005, Gershon et al., 2010a, To et al., 2013b) and thus, an urgency to better understand the factors that contribute to asthma morbidity. Thirdly, while most evidence on asthma risk factors provide insights into individual-level biological or behavioural/lifestyle mechanisms (e.g. infections, diet, second-hand smoke), little is known about the spatial variability of asthma outcomes, relative to broad socioeconomic, environmental and health care determinants. Lastly, many spatial studies investigating potential associations between asthma outcomes and risk factors do not address several important methodological considerations related to spatial and ecological contexts, including reliable risk and parameter estimation, accounting for confounders and spatial autocorrelation. Despite the increasing use of refined spatial methods that address these issues, such as Bayesian spatial modeling, rarely have studies used these methods to investigate determinants of asthma in general, and more particularly within the context of Ontario. Considering these issues, this research addressed the following objectives:

1. Explore the spatial patterns of asthma prevalence and health services use rates (emergency department (ED) visits and physician visits) in Ontario; and,
2. Investigate the relationships between these asthma outcomes and socioeconomic, health care access and environmental factors.

3.2 Summary of findings

<u>3.2.1 Objective 1: Spatial patterns of asthma rates</u>

A descriptive analysis indicated the presence of significant spatial variation in asthma prevalence, physician visits and ED visits rates across Ontario. Hospitalizations rates were also explored (see Appendix A), but not modeled due to similarities in their spatial patterns with asthma ED visits. Maps of SMRs for asthma prevalence and physician visits revealed generally similar spatial patterns. The highest SMRs were seen in southern areas in and around Toronto and Ottawa, as well as near Sarnia and Windsor, whereas the lowest SMRs were mainly found in the north and rural south of the province. Spatial patterns of asthma ED visits were opposite, with the highest SMRs in most northern and rural south areas, and the lowest SMRs in south urban/suburban areas near Toronto and Ottawa. Similar urban/rural patterns have been reported in previous Ontario studies examining asthma and other respiratory diseases outcomes such as COPD and pneumonia (Crighton et al., 2012, To et al., 2007a, Crighton et al., 2015, Jaakkimainen, 2006), suggesting that related factors may be at play in determining these patterns.

Global Moran's I tests indicated the presence of moderate but statistically significant spatial autocorrelation (prevalence: I= 0.40; physician visits: I= 0.64; ED visits: I= 0.52; hospitalizations: I=0.30; pseudo p-values< 0.05), indicating that asthma outcomes are not randomly distributed over space. LISA analysis for asthma prevalence revealed significant clusters of high SMRs in suburban areas northeast and west of Toronto and in some rural areas near Ottawa, whereas clusters of low SMRs were located in the north and rural south of the province. It is likely that these patterns are driven by physician visits patterns since the physician visits map indicated similar patterns; two clusters of high SMRs were found in the Toronto and Ottawa areas, whereas clusters of low SMRs were located in northern and rural south areas of the province. In addition, high asthma rates in the Toronto area could also be explained by exposure to environmental factors. Conversely, the variation of asthma ED visits and hospitalizations showed the opposite pattern; large clusters of high rates were found in most northern and rural areas in the south of the province, whereas two clusters of low SMRs were found in areas near Toronto.

3.2.2 Objective 2: Determinants of asthma spatial patterns

Non-spatial and spatial regression models were used to investigate the influence of ecological risk factors on the spatial patterns of asthma outcomes. The conceptual framework of broad determinants of asthma presented in Chapter 1 (see Figure 1.1 and Table 2.1) was used to inform the selection of explanatory variables, and a number of variables were removed due to concerns about multicollinearity. There were 6 remaining explanatory variables, which were: material deprivation; rurality; relative humidity;

physician supply; NO_2 and pollen levels. While non-spatial models adjusted for the measured explanatory variables and overdispersion, which occurs when the variability in the data is larger than expected, model residuals indicated that some spatial autocorrelation remained in the data, which means that spatial regressions should be conducted.

Bayesian spatial models accounted for significant spatial dependence in all the models; the spatial random effects modeled about 77% of the spatial autocorrelation in asthma prevalence, 59% in physician visits and 41% in ED visits. Further, Moran's I tests (p-values > 0.05) and maps of residuals (Appendix B) confirmed that no statically significant spatial autocorrelation was left in the spatial models, indicating that the models successfully explained the spatial patterns in the data. Long chains (i.e. number of iterations) were used to ensure convergence. In addition, plots of parameters samples and Geweke diagnostics were examined to confirm that the chains had reached convergence.

Important findings from our spatial analysis revealed that variables representing the social environment (i.e. material deprivation), access to health care (i.e. rurality) and physical environment (i.e. NO_2 exposure) made the largest contribution, which demonstrate the important role of these broad determinants in the generation of asthma patterns (Wright and Fisher, 2003). Specifically, rurality was positively associated with asthma prevalence and physician visits, which may be explained by an increased likelihood of diagnosis due to better access and more regular contact with primary care physicians in urban areas, combined with urban risks factors including higher levels of outdoor air pollution (Lawson et al., 2011a, To et al., 2010b, Wong and Chow, 2008, Crighton et al., 2010). A further possible explanation is the exposure to farming environment during childhood, which has been found to reduce the likelihood of developing asthma (Ernst and Cormier, 2000, Masley et al., 2000, Portengen et al., 2002). In contrast, the negative association between rurality and asthma ED visit rates may be explained by reduced access to primary health care, resulting in a greater reliance on emergency services for asthma management (Ministry of Health and Long-Term Care, 2010).

Material deprivation was positively associated with asthma prevalence and even more strongly associated with ED visits. This is consistent with findings commonly reported in the literature, suggesting higher asthma outcomes in low SES or more deprived groups (Crighton et al., 2010, Gwynn, 2004, Li and Newcomb, 2009, Shankardass et al., 2007, Sin et al., 2003). This suggests that despite a system of universal health care in Canada, people with low SES still face many barriers that create a negative impact on their health outcomes, including costs of asthma medications and lack of reliable transportation. Moreover, the strong association found with ED visits here may reflect poorer asthma management in lower SES groups, since increased use of this emergency health services suggests symptom exacerbations, which are often caused by inadequate asthma control and/or irregular physician visits.

With regards to air pollution, NO_2 was found to be positively associated with asthma physician visits, but negatively associated with asthma ED visits. In the case of the ED visit results, this is inconsistent with the literature. Studies commonly report a positive relationship between traffic-related air pollutants including NO_2, particulate matter (PM), ozone (O_3) and carbon oxides (CO) and asthma exacerbations, and increased use of health services use (Lavigne et al., 2012, McConnell et al., 2006, Sahsuvaroglu et al., 2009, To et al., 2013a, Villeneuve et al., 2007). These results suggest that the NO_2 variable may not be accurately capturing air pollution exposures or that it is perhaps confounded by some other factors not included in the model. In fact, the NO_2-LUR model estimates used in this study are reported to be more accurate in urban areas due to the locations of satellite monitors, resulting in overpredictions in rural areas (Hystad et al., 2011). Alternative NO_2 measures and other pollutants, such as PM, O_3 or CO should be further examined.

3.2.3 Additional findings: predicted relative risks

Although using Bayesian methods to predict high-risk areas was not an objective in this study, maps of relative risks (RRs) by sub-LHIN after adjustment for risk factors were produced for each asthma outcome (a), and compared with maps of RRs after adjustment for both spatial dependence and risk factors (b) (Figures 3.1, 3.2 and 3.3). When compared to non-spatially adjusted risk maps, the geographical distribution of spatially adjusted RRs showed more visible or reduced patterns. For example, maps of RRs for prevalence and ED visits showed clearer spatial patterns (Figures 3.1 and 3.3), which could be explained by other unmeasured factors not included in the models. In the case of physician visits (Figure 3.2), maps indicated a considerable decrease in the range of values (all RRs below 1) and no spatial patterns were visible after accounting for both spatial dependence and risk factors. These results may suggest that the spatial patterns were largely controlled for by the model. A possible explanation could be that the presence of mostly low SMRs, as seen in the initial non-adjusted map (Figure 2.3), may have influenced the patterns founds. While accounting for both risk factors and spatial dependence between areas may enhance the visualization of spatial patterns, there is some concern that risk estimates based on Bayesian methods may over-smooth the spatial patterns, decreasing their ability to identify high risk areas. Thus, maps of smoothed risk estimates should be interpreted with caution and further analysis is required to confirm these predicted patterns (Jarup and Best, 2003, Richardson et al., 2004).

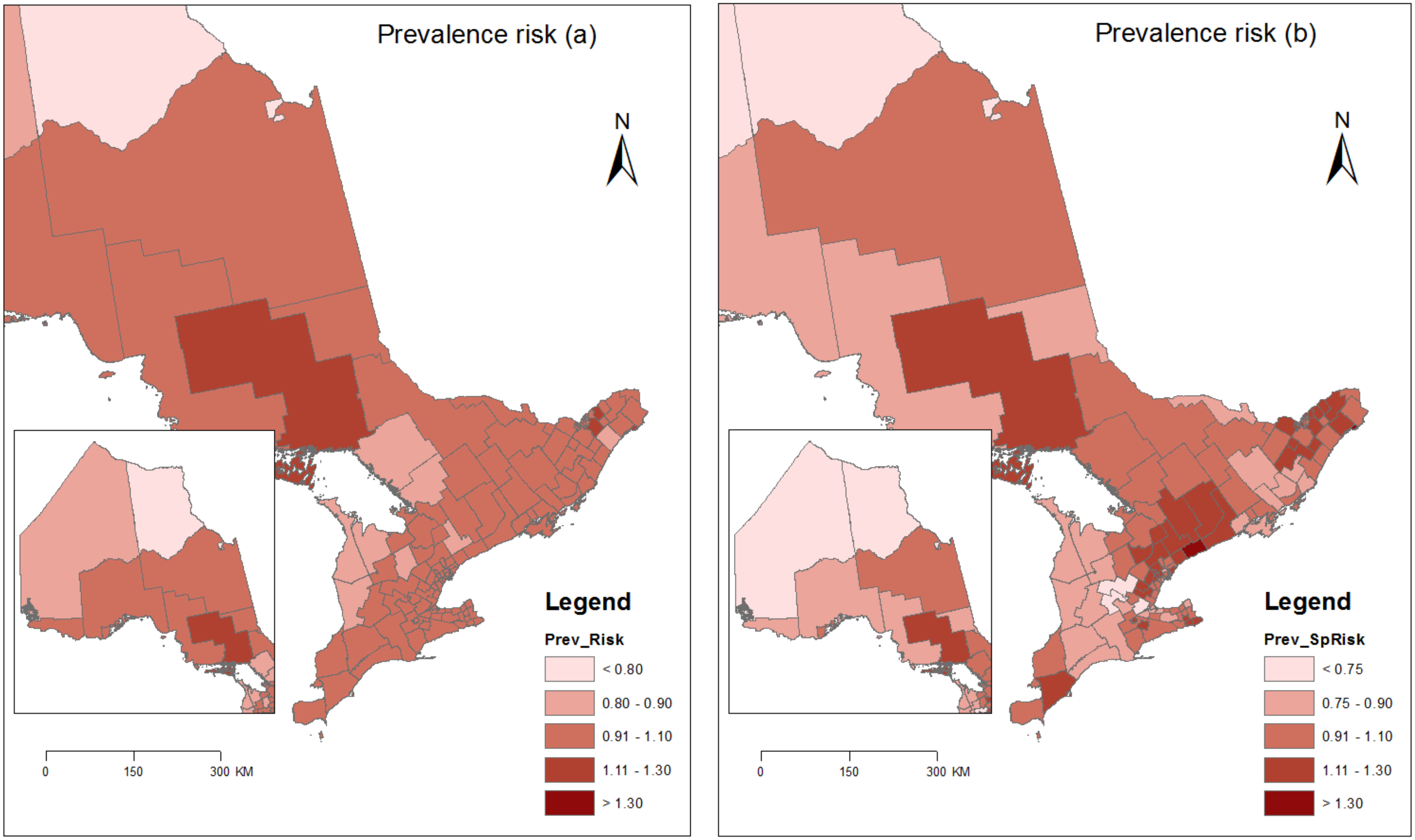

Figure 3.1 Relative risk maps showing Standardized Morbidity Ratios (SMRs) of asthma prevalence adjusted for risk factors only (a), and adjusted for both risk factors and spatial dependence (b)

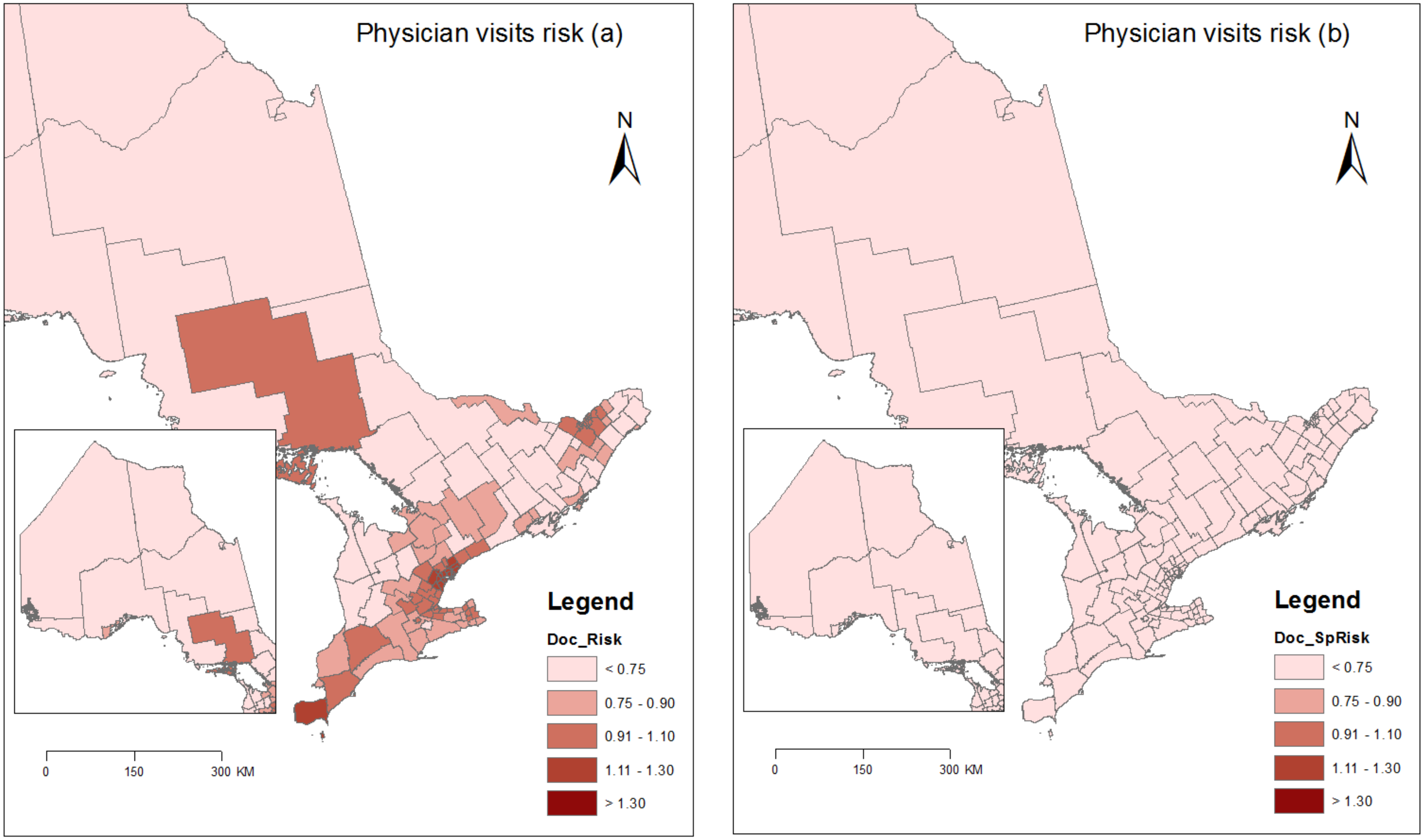

Figure 3.2 Relative risk maps showing Standardized Morbidity Ratios (SMRs) of asthma physician visits adjusted for risk factors only (a), and adjusted for both risk factors and spatial dependence (b)

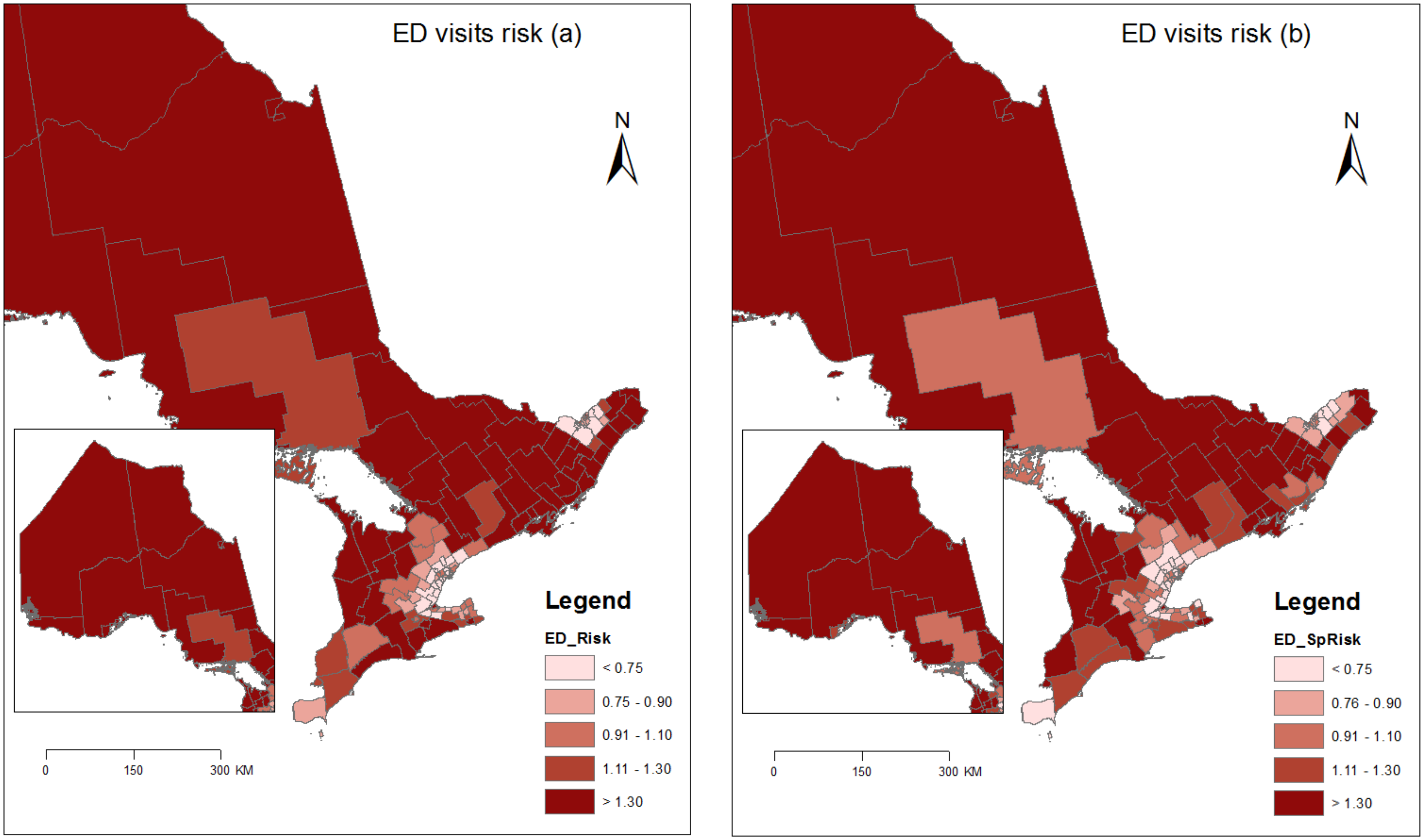

Figure 3.3 Relative risk maps showing Standardized Morbidity Ratios (SMRs) of asthma ED visits adjusted for risk factors only (a), and adjusted for both risk factors and spatial dependence (b)

3.3 Contributions

3.3.1 Theoretical contributions

This study makes important theoretical contributions to the research on asthma risk factors through the use of a population-based conceptual framework (Figure 1.1). This framework is derived from Evans and Stoddart's (1990) population health framework, which highlights the role of a broad range of interrelated factors in generating differences in health status, including biological and behavioural factors, genetic endowment, the social and physicial environment, and health care factors. The framework developed for this study also highlights the spatial nature of asthma outcomes and their determinants, which was not included in Evans and Stoddart's model, as it also plays an important role in the understanding of asthma morbidity. The significant spatial patterns found in this study demonstrated the spatial nature of asthma outcomes, which was illustrated by the framework. In addition, results from the statistical models indicated the influence of socioeconomic, environmental and health care components, which demonstrated the importance of the hypothesized relationships. While most evidence on asthma risk factors focus on important individual-level biological or behavioural/lifestyle mechanisms, this research suggests the need to also take into account more contextual factors, as they generate disparities and contribute to asthma morbidity.

3.3.2 Methodological contributions

Methodologically, this research highlights the usefulness of Bayesian spatial modeling techniques in understanding the factors contributing to the spatial patterns of asthma outcomes, while addressing several limitations related to analyzing area-level outcomes, including parameter estimation, adjustment for confounders and spatial autocorrelation. The use of a Bayesian spatial approach provided a flexible framework, which allowed for specification of contextual risks factors and spatial random effects, and in turn contributed to the generation of unbiased parameter coefficients and their significance level.

Another important advantage of Bayesian spatial modeling is its ability to smooth disease rates towards a global or local mean to reduce variability in the data and reveal the underlying spatial patterns in the data, which allows for more reliable risk estimates, more informative maps and prediction of high risk areas (Richardson et al., 2004, Best et al., 2005). This is useful when dealing with unstable risk estimates due to small population sizes. Despite some concerns that Bayesian methods may over-smooth the spatial patterns, evidence suggests that patterns identified are strongly specific, reducing the risk for false negatives (Richardson et al., 2004).

Lastly, the use of large and sophisticated health administrative databases contributed to the identification of asthma cases in the entire population and the ability to examine various types of health services use. This allows for producing generalizable and more comprehensive data, while reducing issues commonly associated with survey data, including recall bias, small sample sizes, limited population groups and areas (Gershon et al., 2010a).

3.3.3 Substantive contributions

The current study makes important substantive contributions to policies and health care programs. This research contributes to a better understanding of asthma spatial patterns and the factors that contribute to these patterns. Findings revealed the presence of significant spatial patterns across Ontario, including significant clusters of high rates for asthma prevalence and physician visits located in urban/suburban southern areas, whereas clusters of high rates of ED visits and hospitalizations were found in the north and rural south areas. These findings can be expected to inform the implementation of better, locally relevant public health strategies aimed at reducing the burden of asthma in Ontario, by taking into account the area needs and contexts.

The analysis also indicated significant relationships between asthma outcomes and contextual factors such as rurality, material deprivation and NO_2. These findings suggest that efforts should be directed towards improving the access to primary health care in rural, remote and northern communities, which will reduce the burden of high emergency health services use in these areas (Ministry of Health and Long-Term Care, 2010, Steps to Equity, 2013, To et al., 2007a). Further, results indicate that public health strategies should focus on improving the health outcomes of people with low SES, by improving access to care, education and medications, as well as reducing their exposure to environmental hazards (To et al., 2007a).

3.4 Limitations and future research directions

While this study contributes to an improved understanding of the spatial patterns of asthma in Ontario, there are a number of limitations that should also be acknowledged. First, the ecological approach used in this research does not allow for making inferences about the determinants of asthma outcomes at the individual level. It does however provide a contextual explanation by highlighting the important role of physical and social environments in generating heterogeneity between areas or population groups. As such, the results have important implications for the development of more focused and population specific public health strategies and interventions and further, generate hypotheses to inform further research in this areas (Macintyre and Ellaway, 2000). Future research should consider multilevel analysis techniques to better understand the role of individual and contextual level factors on asthma outcomes.

Second, the modifiable areal unit problem (MAUP), which occurs when results vary depending on the spatial scales and zones used, is commonly discussed in ecological and health geography studies (Openshaw, 1984). Alternate levels of aggregation could be examined to reduce this issue; however this would be challenging due to data availability and sparse population data in larger areas. Further, previously reported temporal trends of asthma morbidity (Gershon et al., 2010b, To et al., 2013b) have been lost as a result of the temporal aggregation used in this study. Given the importance of the spatial and temporal nature of asthma outcomes, future studies should consider a spatio-temporal approach by including a temporal component and time-dependent risk factors for a more comprehensive understanding of the disease.

Another potential limitation relates to the use of health administrative databases based on physician diagnoses. While the prevalence measure used in this research has been been validated and found to have a high sensitivity and specificity, and has been used in numerous studies (Crighton et al., 2012, Gershon et al., 2010a, To et al., 2013a), research to assess the extent to which underdiagnosis may occur in areas with poor health care access is required.

Further, while risk factors such as physician access and environmental exposure have been shown to be important determinants of asthma outcomes in other studies (Clark et al., 2013, Guttmann et al., 2010, Darrow et al., 2012, DellaValle et al., 2012), the limited quality of the data used here mean that the results must be interpreted with caution. In this study, since rurality, a proxy for health care access, was found to be significantly associated with all asthma outcomes, further analysis should control for physician accessibility, for example using measures based on distances or travel times. The influence of temperature extremes should also be examined due to due to large regional variations in Ontario. In addition, better pollen estimates, which take into account temporal and seasonal variations, could be incorporated in future analyses.

Lastly, although clusters of high/low risks were identified and spatial models accounted for spatial dependence, different adjacency formulations could be further examined. There may also be a number of unknown or unmeasured ecological risk factors that were not accounted for in this study, including other SES risk factors (e.g. ethnicity, smoking, housing conditions), and pollutants (e.g. PM, O_3, CO).

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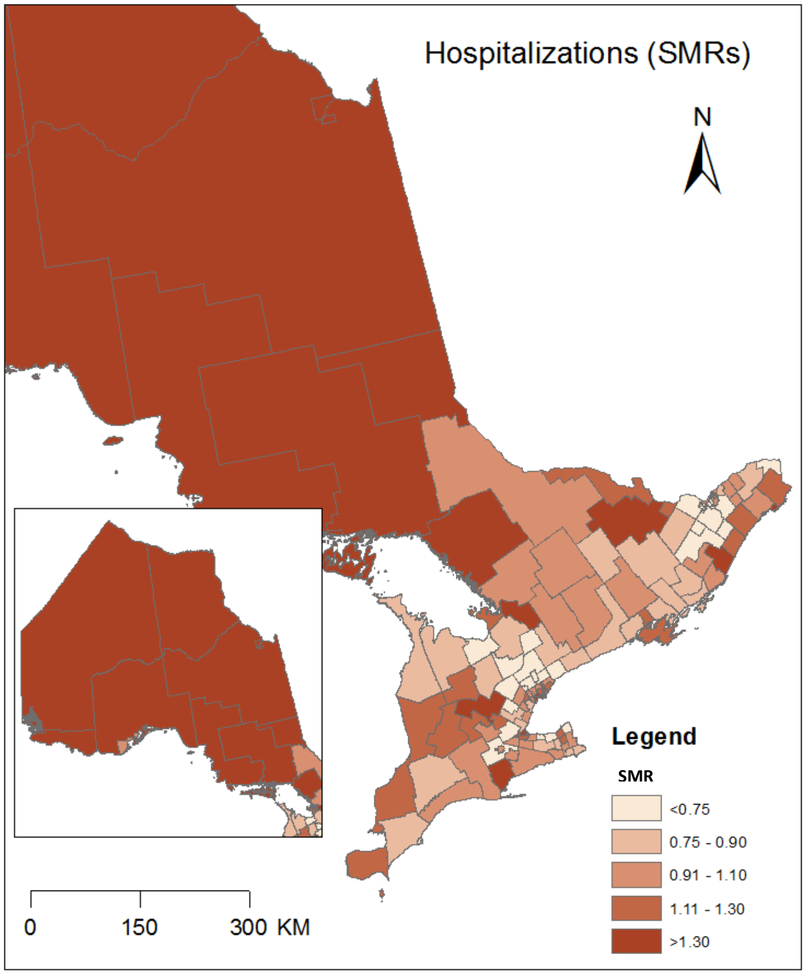
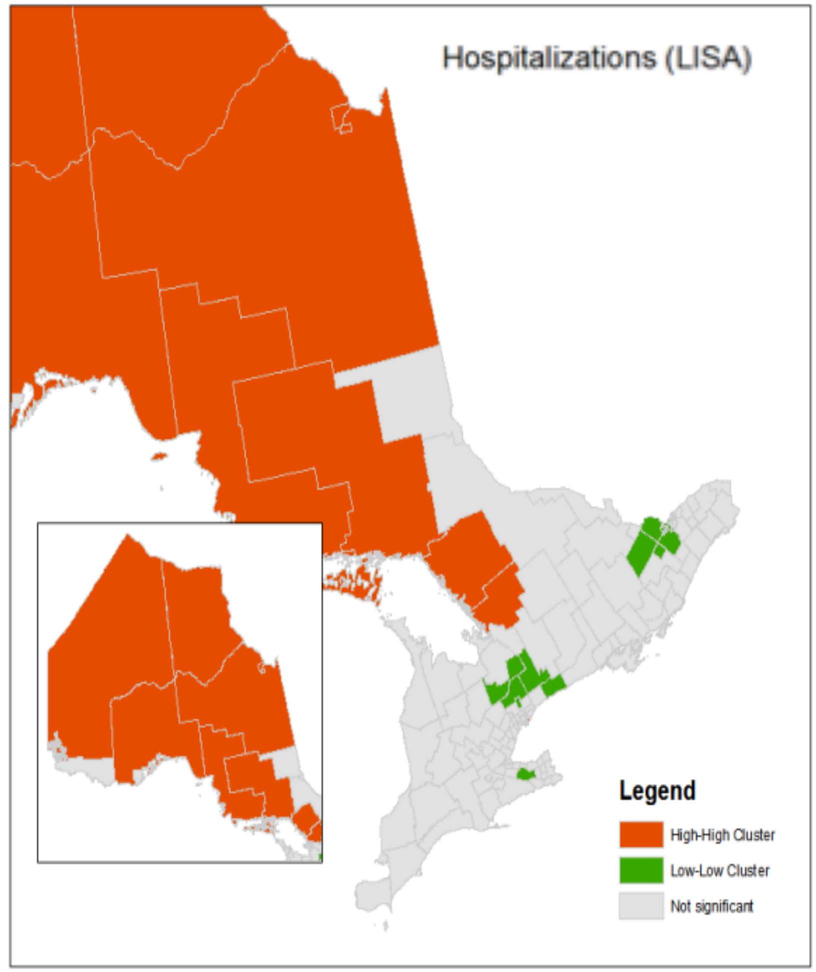
APPENDIX A

Standardized morbidity ratios (SMRs) and Local Indicators of Spatial Autocorrelation (LISA) of asthma hospitalizations for total population in Ontario, 2003-2013





APPENDIX B

1) Moran's I tests for model residuals

	Prevalence		Physician visits		ED visits	
	Non-spatial model	Spatial model	Non-spatial model	Spatial model	Non-spatial model	Spatial model
I	0.425	-0.236	0.151	-0.192	0.234	-0.111
Pseudo p-values	0.0001	1.000	0.003	1.000	0.0001	0.980

2) Residual maps of asthma prevalence, physician visits and ED visits for total population in Ontario, 2003-2013