GEOGRAPHIC ACCESSIBILITY AND RISK OF HOSPITALIZATION AND MORTALITY AMONG PATIENTS WITH CHRONIC RESPIRATORY DISEASES

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Abstract

Spatial differences exist in hospitalization and mortality among patients with Chronic Obstructive Pulmonary Disease (COPD) and asthma. **Objective**: Examine the association between geographic accessibility, hospitalization, and mortality among COPD and asthma patients in Newfoundland and Labrador (NL). **Methods**: A retrospective cohort of adults diagnosed with COPD and asthma were followed from diagnosis until hospitalization, death or end of the study. Geographic accessibility was defined using accessibility-remoteness index. Multivariate and geospatial analyses were performed. **Result**: We identified 44876 (43.8% inaccessible) COPD patients and 28316 asthma patients (37.4% inaccessible). Living in inaccessible areas increased hospitalization incidence for COPD (OR=2.57, 95% CI 1.54-4.25, P<0.00136) and asthma (OR=12.38, 95% CI:6.28-24.46, P<0.001). Mortality was associated with geographic accessibility only for COPD (OR=10.73, 95% CI; 2.27-44.77, P=0.002). COPD hospitalization (MI=0.034, p<0.03), mortality (MI=0.047, p<0.011) and asthma hospitalization (MI=0.065, p<0.001) were spatially autocorrelated. **Conclusion:** Living with chronic respiratory diseases in NL' remote areas increases risk of hospitalization.

Acknowledgements

I would like to acknowledge my supervisor, Dr. Shabnam Asghari. I still remember the very first interview I had with Shabnam. Now looking back at more than two years ago, I am honored that she chose me as her graduate student. This thesis would have not been possible without her guidance and dedication. During these two years, she was more than a supervisor for me, and I cannot appreciate her enough.

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List of Abbreviations

ACSC: Ambulatory Care-Sensitive Condition

AMI: Acute Myocardial Infarction

A-R: Accessibility-Remoteness

CCDSS: Canadian Chronic Surveillance System

CCHS: Canadian Community Health Survey

CCS: Census Consolidated subdivision

CDMS: Clinical Database Management System

COPD: Chronic Obstructive Pulmonary Disorder

EPR-3: Expert Panel Report 3

FEV_1: Forced Expiratory Volume

FVC: Forced Vital Capacity

ICD-10: Classification of Diseases and related health problems (ICD) 10th revision

ICD-9: Classification of Diseases and related health problems (ICD) 9th revision

IHD: Ischemic Heart Disease

IQR: Interquartile Range

LMI: Local Moran's Index

MCP: Medical Care Plan

MS: NLCHI Mortality System

NL: Newfoundland and Labrador

NLCHI: Newfoundland and Labrador Centre for Health Information

NLSA: Newfoundland and Labrador Statistics Agency

OR: Odds Ratio

PY: Person-year

RR: Relative Risk

WHO: World Health Organization

Chapter 1: Introduction and Overview

1.1. Problem Statement

Hundreds of millions of people deal with chronic respiratory diseases. According to the World Health Organization (WHO), chronic respiratory diseases are diseases affecting airways and other structures of lungs [1]. Chronic Obstructive Pulmonary Disorder (COPD) and asthma are two of the most prevalent of their kind, even though these two diseases are preventable and manageable [2].

The prevalence of COPD and asthma are increasing in most regions of the world [3][4]. With the aging population, the number of patients who are affected by these conditions, and subsequently, the number of deaths will increase [5]. Moreover, most of the patients living with chronic respiratory diseases have poor access to healthcare services [6].

COPD is one of the major reasons of mortality and morbidity. In the United States, COPD is recognized as one of the most expensive chronic diseases, the majority of it is due to hospitalizations. Both medical costs and indirect medical costs of asthma are considerable [7]. According to literature, the main direct costs are due to hospitalization and medication of asthma patients [8]. The Annual deaths of asthma are estimated to be about 250000 in the world. These rates vary in the different parts of the world [7].

Although the mortality and hospitalization of COPD and asthma are high, they are preventable. With proper management, and treatment, exacerbation of these diseases can be prevented, and consequently hospitalization and mortality will decrease.

Inequity exists in hospitalization and mortality of patients living with COPD and asthma. One of the main factors which contributes to this inequity is the geographic differences. The literature on the geographical differences of asthma and COPD hospitalization and mortality is limited. Outside of a small number of non-generalizable research projects. Previous studies have failed to address the impacts of geographic accessibility on hospitalization and mortality among chronic respiratory disease patients.

To our knowledge, this is the first study in Newfoundland and Labrador (NL) which examines the effect of geographic accessibility on hospitalization and mortality among chronic respiratory disease patients. The results of this study will help policy makers recognize the current situation of asthma and COPD hospitalization in the province, it will also assist in the provision of healthcare regarding these issues in NL.

In this thesis, we begin by explaining the concepts of COPD, asthma, geography differences, and the objectives of the study. In the second chapter, we focus on COPD hospitalization and mortality. In the third chapter, the effect of geographic accessibility of asthma hospitalization and mortality will be investigated. The final chapter presents a summary of the results and conclusion.

1.1. What is COPD?

COPD is a disease in which airflow obstruction is present due to emphysema, chronic bronchitis or small airway diseases. This airway obstruction gradually progresses; however, it can be partially reversible, and it can coexist with airway hyperreactivity [9]. Emphysema is described when the lung alveoli are enlarged or destroyed, and Chronic bronchitis is characterized for a chronic condition by phlegm and chronic coughing, and small airway diseases which refer to a condition with narrowed small bronchioles. Airflow obstruction is usually determined using a spirometry test. During the spirometry test, the volume of air exhaled within the first second (Forced Expiratory Volume [FEV_1]) and total volume of air exhaled (Forced Vital Capacity [FVC]) will be measured. Patients with airflow obstruction, associated with COPD have lower FEV_1/FVC ratio [10].

Three hundred twenty-eight million people of which 168 million are men, and 160 million are women, are affected by COPD in both developing and developed countries [6]. This disease is the fifth leading cause of death in the world [11]. It is predicted that it will be the third leading cause of death by the year 2020 [12]. In Newfoundland and Labrador, COPD makes up 3.4 percent of hospital admission. According to Statistics Canada, in 2014, 4.9% (15,280 people) of NL population were living with COPD. [25].

1.2. COPD Exacerbation and Hospitalization

COPD exacerbation is defined as an event that is characterized by a change in the patient's baseline symptoms such as dyspnea, cough or sputum. Exacerbation is different from daily variations and may require a medication different from the patient's routine medication [13]. COPD exacerbation contributes to the progression of the disease [10]. Age, severity of emphysema, history of asthma, and systemic inflammation are risk factors of hospital admission due to exacerbation for COPD patients [14]. COPD exacerbation can be triggered by other risk factors including heart failure, pollution, allergen, sedative. Among them, respiratory infection is known as the main factor of COPD exacerbation [15].

COPD hospitalization is caused by exacerbation, and respiratory failure. Previous clinical population studies of COPD patients indicate that COPD exacerbation commonly lead to hospitalizations. This increases the likelihood of hospital readmission and mortality.

1.3. Geographic Differences of COPD Hospitalization and Mortality

A very few studies have investigated the geographic variation in hospitalization of COPD patients. These studies mostly investigate rural-urban differences that exist in spatial disparity of COPD.

One study in Victoria, Australia assessed the geographic variation of COPD admission rates between rural and urban areas. The purpose of the study was to identify areas which require public health intervention to improve access to healthcare services. The results indicate that admission rates were higher in rural Victoria when compared to urban Victoria (rate ratio of 1.29, 95% CI: 1.11-1.51). A significant association was seen between the remoteness of area and hospitalization rates [16].

In another investigation from New Zealand the distribution of hospitalization regarding age, socio-economic status, length of stay, and ethnicity were studied over a 5-year period. The results showed a higher admission rate in rural areas. Their result indicates the need for intervention to provide equal public health services for COPD patients [17].

Another study in the United States assessed whether COPD related mortality is higher in rural and remote areas. This study was a retrospective cohort, conducted in 129 acute Care Veteran Affairs hospitals. The primary outcome of this study was mortality 30 days after admission. The results indicate higher mortality in patients who live in remote and rural areas in comparison to urban areas (5% vs. 3.8, p=0.002). Patients who live in isolated rural areas are prone to exacerbation and mortality. The results helped policy makers identify the needs of different regions and attempt to narrow the gaps [18].

1.4. What is Asthma?

Asthma is "a chronic inflammatory disorder of the airways in which many cells play a role, including mast cells and eosinophils. In susceptible individuals, this inflammation causes symptoms that are usually associated with widespread but variable airflow obstruction that is often reversible, either spontaneously or with treatment, and causes an associated increase in airway responsiveness to a variety of stimuli" [19]. Unlike COPD, asthma affects both adults and children. Approximately 300 million people suffer from asthma worldwide [20]. In Canada, 13% of the population deals with asthma.

1.5. Asthma Exacerbation and Hospitalization

Expert Panel Report 3 (EPR-3) defines asthma exacerbation as "acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, and chest tightness—or some combination of these symptoms" [21]. In clinical trials acute exacerbation of asthma is defined as "the need for treatment with systemic corticosteroids, hospital admission or emergency treatment for worsening asthma, or a decrease in morning peak flow >25% baseline on two consecutive days" [20]. The main cause of asthma exacerbation is respiratory infection due to rhinoviruses. Asthma patients that have a history of hospitalization from exacerbation are in a higher risk of future exacerbation. Previous research shows that hospital admission due to asthma exacerbation is related to the severity of the disease. The study shows from asthma patients with 3 or more exacerbations per years, 5% was considered as mild, 13% moderate, and 54% as severe [22]. The risk of recurrent exacerbations is higher among women, obese individuals, patients with obstructive sleep apnoea, chronic sinusitis, gastroesophageal reflux, or respiratory infections [23].

Death as a result of asthma exacerbation is not common. It is highly preventable and mainly due to poor healthcare services. There is a higher risk of mortality due to asthma exacerbation for: women, obese individuals, elderly, smokers, asthma patients noncompliant with medications, and a previous near-fatal attack [23].

1.6. Geographic Differences of Asthma Hospitalization and Mortality

Geographic variation exists in asthma hospitalization and mortality. One study identified disparity in different neighbourhoods of New York city. This study suggests access to healthcare facilities, health literacy, and community status have significant impacts on these differences.

Another study in Canada analyzed rural-urban differences of asthma hospitalizations in Saskatchewan between 1970 and 1989. The authors suggest that higher hospital admission rates in rural areas of Saskatchewan may be due to grain farming which is the main occupation in those areas. In addition, rural residents with mild asthma are more likely to get hospitalized, as the greater distance to hospitals makes it difficult to return home before complete treatment [24].

As previous research indicates geographical inequality exists in COPD and asthma hospitalization and mortality. This could be due to the existence of inequity in access to health care services geographically. In rural areas, it is expected that access to the health services will be lower, which partially can justify the findings of the previous researches.

1.7. Thesis Objective

The overall objective of this study is to identify the spatial disparity that exists in hospitalization, and mortality of the patients with chronic respiratory diseases (i.e. COPD, and Asthma) in Newfoundland and Labrador. More specifically we aim to assess:

1) Effects of the place of residence on hospitalization of COPD patients older than 35 years old
2) Effects of the place of residence on mortality of COPD patients older than 35 years old
3) Effects of the place of residence on hospitalization of asthma patients older than 20 years old
4) Effect of the place of residence on mortality of asthma patients older than 20 years old

1.8. Research Questions

1) In adults older than 35 (by gender, by age) diagnosed with COPD in Newfoundland and Labrador between 1995 and 2014, does accessibility of the place of residence affect hospitalization?
2) In adults older than 35 (by gender, by age) diagnosed with COPD in Newfoundland and Labrador between 1995 and 2014, does accessibility of the place of residence affect mortality?
3) In adults older than 20 (by gender, by age) diagnosed with asthma in Newfoundland and Labrador between 1995 and 2014, does accessibility of the place of residence affect hospitalization?

4) In adults older than 20 (by gender, by age) diagnosed with asthma in Newfoundland and Labrador between 1995 and 2014, does accessibility of the place of residence affect mortality?

1.9. Co-authorship statement

Chapter 2 of this thesis has been submitted to the journal of Health & Place and it is under review, and Chapter 3 has been submitted to the journal of Respiratory Medicine and it is under review. This research is a collaborative work. I would like to acknowledge the contribution of co-authors. Dr. Shabnam Asghari, my MSc supervisor, contributed with her guidance in all aspects of the study including, research proposal, study design, data provision, and writing. Dr. Alvin Simms contributed instrumental comments on the manuscripts and spatial analysis. Dr. Masoud Mahdavian with his guidance, and comments on the medical aspects of this study. Oliver Hurley assisted with technical aspects and geographic information system software.

1.10. References

[1] J. Bousquet, R. Dahl, and N. Khaltaev, "Global alliance against chronic respiratory diseases," *Allergy*, vol. 62, no. 3, pp. 216–223, Feb. 2007.

[2] A. G. Chuchalin, N. Khaltaev, N. S. Antonov, D.V. Galkin, L. G. Manakov, P. Antonini, M. Murphy, A. G. Solodovnikov, J. Bousquet, M. H. Pereira, I. V. Demko., "Chronic respiratory diseases and risk factors in 12 regions of the Russian Federation," *Int. J. Chron. Obstruct. Pulmon. Dis.*, vol. 9, pp. 963–974,

2014.

[3] D. M. Mannino, “COPD: Epidemiology, prevalence, morbidity and mortality, and disease heterogeneity,” *Chest*, vol. 121, no. 5, p. 121S–126S, May 2002.

[4] B. Lundbäck, H. Backman, J. Lötvall, and E. Rönmark, “Is asthma prevalence still increasing?,” *Expert Rev. Respir. Med.*, vol. 10, no. 1, pp. 39–51, Jan. 2016.

[5] P. Burney, D. Jarvis, and R. Perez-Padilla, “The global burden of chronic respiratory disease in adults,” *Int. J. Tuberc. Lung Dis.*, vol. 19, no. 1, pp. 10–20, Jan. 2015.

[6] N. Aït-Khaled, D. Enarson, and J. Bousquet, “Chronic respiratory diseases in developing countries: the burden and strategies for prevention and management,” *Bull. World Health Organ.*, vol. 79, pp. 971–979, 2001.

[7] World Health Organization, “Global surveillance, prevention and control of chronic respiratory diseases, a comprehensive approach,” 2007.

[8] K. Bahadori, M.M. Doyle-Waters, C. Marra, L. Lynd, K. Alasaly, J. Swiston, J. M. FitzGerald., “Economic burden of asthma: a systematic review,” *BMC Pulm. Med.*, vol. 9, no. 1, p. 24, Dec. 2009.

[9] ATS ERS, “Standard for the diagnosis and management of patients with COPD,” *Crit. Care Med.*, pp. 212–315, 2004.

[10] J. Loscalzo, A. S. Fauci, S. L. Hauser, J. L. Jameson; D. L. Kasper; D L Longo, *Harrison’s principles of internal medicine*. McGraw-Hill Education, 2017.

[11] R. A. Pauwels, *K. F. Rabe.*, “Burden and clinical features of chronic obstructive pulmonary disease (COPD).,” *Lancet (London, England)*, vol. 364, no. 9434, pp. 613–20, 2002.

[12] L. Schirnhofer, B. Lamprecht, W. M. Vollmer, M. J. Allison, M. Studnicka, R.

L. Jensen, A. S. Buist.., “COPD prevalence in Salzburg, Austria,” *Chest*, vol. 131, no. 1, pp. 29–36, Jan. 2007.

[13] L. A. Mandell, R. G. Wunderink, A. Anzueto, J. G. Bartlett, G. D. Campbell, N. C. Dean, SF. Dowell, T. M. File, D. M. Musher, M. S. Niederman, A. Torres, C. G. Whitney, “Infectious diseases society of America/American thoracic society consensus guidelines on the management of community-acquired pneumonia in adults,” *Clin. Infect. Dis.*, vol. 44, no. Supplement_2, pp. S27–S72, Mar. 2007.

[14] H. Müllerova, D. J. Maselli, N. Locantore, J. Vestbo, J. R. Hurst, J. A. Wedzicha, P. Bakke, A. Agusti, A. Anzueto, “Hospitalized exacerbations of COPD: Risk Factors and outcomes in the ECLIPSE cohort,” *Chest*, vol. 147, no. 4, pp. 999–1007, Apr. 2015.

[15] A. Anzueto, S. Sethi, and F. J. Martinez, “Exacerbations of Chronic Obstructive Pulmonary Disease,” *Proc. Am. Thorac. Soc.*, vol. 4, no. 7, pp. 554–564, 2007.

[16] Z. Ansari, D. Dunt, and S. C. Dharmage, “Variations in hospitalizations for chronic obstructive pulmonary disease in rural and urban Victoria, Australia.,” *Respirology*, vol. 12, no. 6, pp. 874–80, 2007.

[17] R. J. Milne and R. Beasley, “Hospital admissions for chronic obstructive pulmonary disease in New Zealand.,” *N. Z. Med. J.*, vol. 128, no. 1408, pp. 23–35, Jan. 2015.

[18] T. E. Abrams, M. Vaughan-Sarrazin, V. S. Fan, and P. J. Kaboli, “Geographic isolation and the risk for chronic obstructive pulmonary disease–related mortality,” *Ann. Intern. Med.*, vol. 155, no. 2, p. 80, Jul. 2011.

[19] I. Asher and N. Pearce, “Global burden of asthma among children.,” *Int. J. Tuberc. Lung Dis.*, vol. 18, no. 11, pp. 1269–78, 2014.

[20] R. H. Dougherty and J. V Fahy, “Acute exacerbations of asthma: epidemiology, biology and the exacerbation-prone phenotype.,” *Clin. Exp. Allergy*, vol. 39, no. 2, pp. 193–202, Feb. 2009.

[21] G. Morosco and J. Kiley, “Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma,” Nov. 2007.

[22] W. C. Moore, E. R. Bleecker, D. Curran-Everett, S. C. Erzurum, B. T. Ameredes, L. Bacharier, W. J. Calhoun, M. Castro, K. F. Chung, M. P. Clark, R. A. Dweik, A. M. Fitzpatrick, B. Gaston, M. Hew, I. Hussain, N. N. Jarjour, E. Israel, B. D. Levy, J. R. Murphy, S. P. Peters, W. G. Teague, D. A. Meyers, W. W. Busse, S. E. Wenzel., “Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute’s Severe Asthma Research Program,” *J. Allergy Clin. Immunol.*, vol. 119, no. 2, pp. 405–413, Feb. 2007.

[23] D. J. Jackson, A. Sykes, P. Mallia, and S. L. Johnston, “Asthma exacerbations: Origin, effect, and prevention,” *J. Allergy Clin. Immunol.*, vol. 128, no. 6, pp. 1165–1174, Dec. 2011.

[24] A. Senthilselvan, “Trends and rural-urban differences in asthma hospitalizations in Saskatchewan 1970-1989,” *Can. Respir. J.*, vol. 1, no. 4, pp. 229–234, 1994.

Chapter 2: Geographic Accessibility and Risk of Hospitalization and Mortality among COPD Patients

2.1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is the fifth leading global cause of morbidity [1], and it is predicted that it will be the third leading cause of death by the year 2020 [2]. COPD has a significant impact on healthcare costs, primarily due to acute exacerbations requiring hospital admission [3]. Preventing COPD hospitalization is a focus in COPD management as the risk of readmission and mortality is higher in patients hospitalized for COPD exacerbation [3]. Even though COPD is recognized as an Ambulatory Care-Sensitive Condition (ACSC) and hospital admissions are avoidable through proper use of primary health care services and early management. COPD is still the primary cause of admission and readmission to hospitals among the ambulatory Care Sensitive Conditions (ACSC) [4][5].

Identifying the factors that influence hospitalization is essential to COPD management and has significant healthcare implications [3]. Previous studies suggest that the health outcomes of patients living with COPD are worse in rural and remote areas [6]. More recent evidence suggests that as the rurality of a patient's residence increases the rate of COPD hospitalization also increases, this could indicate the inequity of primary healthcare in rural areas [7].

There is little information available to conclude that the level of geographic accessibility to healthcare facilities is a predictor of hospitalization rate for COPD patients. A study in Australia argues that a strong predictor of COPD hospitalization is the degree of remoteness of patient's place of residence [7]. The study also showed

COPD admission rates were higher in rural areas (rate ratio of 1.29, 95% CI: 1.11-1.51) of Australia [7]. A retrospective cohort study in the United States found higher COPD mortality rates in rural and remote areas (5% vs. 3.8%, $P<0.002$) [6]. They concluded patients who live in isolated rural areas are prone to exacerbation and mortality [6]. The previous studies are limited to their geography, and their results are not generalizable. For instance, country specific uniqueness was observed when comparing the results of studies which looked to determine the level of rural-urban differences in health status and mortality between Canada and Australia [8].

A cross sectional study using the Canadian Community Health Survey's (CCHS) data from the 10 Canadian provinces found inequity in access to healthcare services between rural and urban areas [9]. In Newfoundland and Labrador (NL), COPD makes up 3.4 percent of all hospital admissions in 2013-2014 [10]. In order to reduce and prevent COPD hospitalizations and mortality, effective health policies should be implemented. This requires a better understanding of the distribution of those living with COPD and identifying areas that could benefit the most from increased resource allocation or a change in the provision of healthcare services. To our knowledge this is the first study in NL investigating the association between patient's place of residence and COPD hospitalization and mortality among adults. This study aims to determine whether the risk of hospitalization and mortality is higher among COPD patients who live in inaccessible areas. Our study hypothesis is that COPD hospitalization and mortality is higher among patients who live in areas with lower geographic accessibility to healthcare services.

2.2. Methods

This study uses a retrospective cohort design which considers all adults older than 35 years in NL. It includes all patients who are diagnosed after 1995 in the province. Patients are followed from the date of diagnosis until the occurrence of the outcome, their death or the end of the study period (2014) whichever came first.

2.2.1. Data Sources

We used a population-based dataset which includes all individuals who received any healthcare services between 1995 to 2014 in Newfoundland and Labrador, containing more than 600,000 records. The dataset was provided by Newfoundland and Labrador Centre for Health Information (NLCHI) and developed by linking the following databases:

1) the Canadian Chronic Surveillance System (CCDSS) database, which is a collaborative network of surveillance systems of provinces supported by the Public Health Agency of Canada [11].

2) Clinical Database Management System (CDMS) database which is related to in-patients services and surgical day care services from acute care facilities [12].

3) Medical Care Plan (MCP) Fee-For-Service Physician Claims Database [13].

4) NLCHI Mortality System (MS) providing information about all the deaths within the province [14].

The dataset includes information about patient characteristics, number of physician and specialist visits, number of hospitalizations, and number of comorbidities according to validated CCDSS case definitions for chronic diseases using the International Classification of Diseases and related health problems (ICD) 9th and 10th revision [7].

2.2.2. Ethics and Consent

This study was granted ethics approval with reference number 20161500 from the Health Research Ethics Board in Newfoundland and Labrador.

2.2.3. COPD Case Definition

We used the CCDSS case definition of COPD to select patients for our analysis [15]. Our COPD case definition considered individuals 35 years or older, who are registered under the NL provincial health insurance plan. To be considered as a COPD case, individual should either have had a hospitalization visit that resulted in a COPD diagnosis based on ICD-9, or ICD-10 codes (491; 492; 496 in ICD-9, J41; J42; J43; J44 in ICD-10), or a physician visit with a COPD diagnosis (491; 492; 496 in ICD-9). This case-definition algorithm has been validated for the provinces of Ontario with a sensitivity of 85%, and specificity of 78% [16].

2.2.4. Geographic Accessibility

Our main exposure is living in remote and inaccessible areas. Accessibility refers to the road distance between the place of residence and the specific public services. We used Accessibility-Remoteness (A-R) index in order to geographically classify areas across the province and to create categorical classes which ranged from highly accessible to extremely remote. The A-R index was developed by the Newfoundland and Labrador Statistics Agency (NLSA) as a tool to classify the province's communities. The index categorizes the areas based on accessibility to government and community services including primary and secondary health centres, pharmacies, dental clinics, high schools, and supermarkets. The index is a geographical approach defining accessibility based on distances between region or community centroids and community services. It concentrates on the fact that distance hinders the interaction between people and these services. In general, areas with the highest accessibility are regional centres with high numbers of governmental services in close proximity, such as health centres, while communities with the lowest accessibility are characterized as being extremely remote, requiring the use of a ferry or plane to reach regional centres [17].

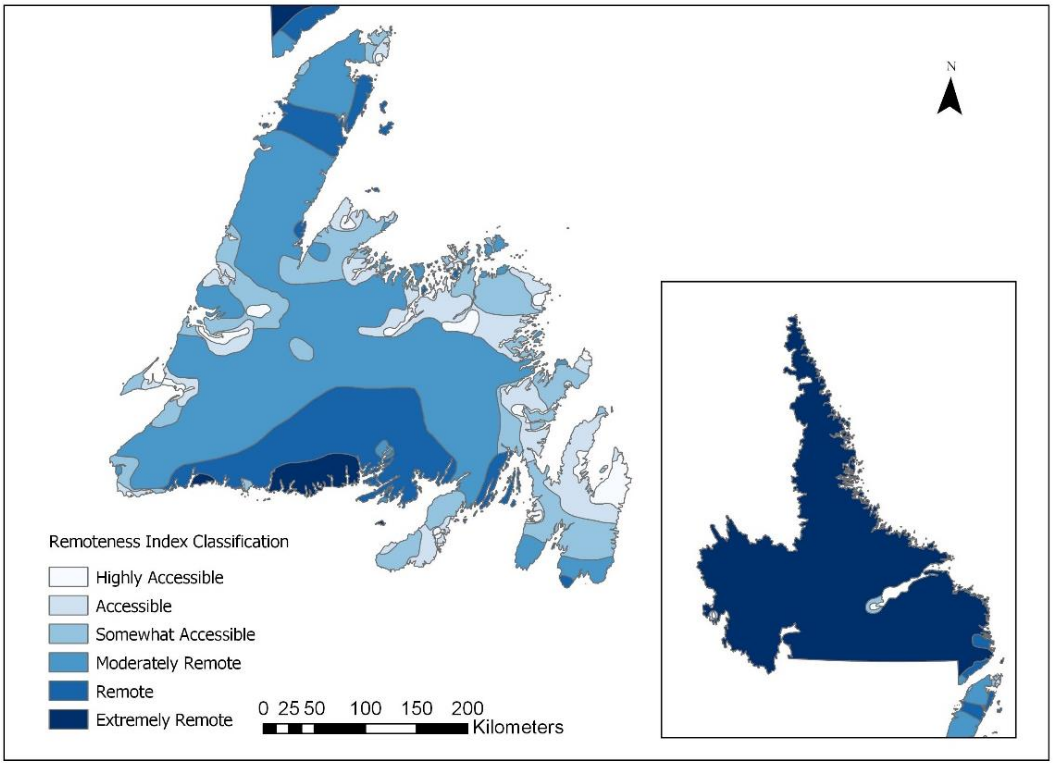

Figure 2.1. Classification of the province of Newfoundland and Labrador based on A-R

Our analysis used the NLSA A-R index as the underlying framework to determine the range of accessibility which attributes to both rural and urban classes. As illustrated in figure 2.1, the index categorizes regions of the province across the following six categories: highly accessible, accessible, somewhat accessible, moderately remote, and extremely remote areas. We categorized all six categories into two previously defined classes: accessible and inaccessible. For individual level analysis, we used the continuous A-R index scores which were assigned to each patient by spatially joining their postal codes to the regions depicted in figure 2.1. Community level analysis considered discrete classes developed through fuzzy set model. Fuzzy set model enabled us to assign varying degrees of membership for accessibility based on A-R index scores. Somewhat accessible (remote index value = 0.329) was identified as an appropriate cut off point for remoteness. The index score of 0.329 was used as a cut-off point where all index scores were divided by this number. Any values close to that index score approaching a value of 1 was considered as a part of the "accessible" community class. This allowed for the assignment of membership for index scores that fell into A-R index classes below "somewhat accessible". After creating the histogram of the transformed fuzzy index scores, we concluded that the 50th percentile would be a good cut-off to assign membership across "accessible" and "inaccessible" classes where anything above would be deemed "accessible" and anything below is "inaccessible" [18]. We used these two subsets of the results of the fuzzy model for the descriptive and community level analysis.

2.2.5. Outcome

The primary outcome of this study is hospitalization. Hospitalization is a dichotomous (yes or no) variable, and it is an incidence case which describes if the person had any hospitalization record, planned or unplanned, during the observation period. We measured hospitalization as any hospitalization per person-year at risk.

The second outcome is annual hospitalization rate, it is a numerical variable indicating the number of hospitalizations for each patient per year during the follow up period and measured per person-year at risk. The third outcome is mortality, another binary variable that indicates whether the person is alive during the study period.

2.2.6. Covariates

The variables at the patient level were collected and derived from the list of variables consisting of: sex, age at the time of diagnosis, number of comorbidities before their first hospitalization, total number of comorbidities recorded during the study period, and number of physician and specialist visits during the study period.

Patient comorbidities were identified using CCDSS algorithms and ICD-9/ICD-10 codes including diabetes, hypertension, asthma, ischemic heart disease (IHD), acute myocardial infarction (AMI), and heart failure. For the purposes of descriptive analysis and the development of regression models, patients were categorized based on the number of comorbidities (0, 1, 2, ≥3). Individuals were placed into 10-year age groups based on the time they were diagnosed [19].

For analysing where the dependent variable was hospitalization, total number of visits with family physicians, pulmonologists, internists, and other specialists from the date of diagnosis to the first admission to hospital, and total number of comorbidities before the first a patient's first hospitalization were considered. For analyses of hospitalization rate and mortality, the following exploratory variable were used: total number of visits with family physicians and specialists during the follow-up period, and total number of comorbidities.

2.2.7. Analysis

2.2.7.1. Individual Level Analysis

Descriptive analysis was performed to describe the characteristics of the study population at baseline. Bivariate analyses were performed to assess the differences between inaccessible and accessible areas.

We assessed the association between COPD hospitalization, and place of residence (inaccessible versus accessible) using binomial regression. The outcome variable is hospitalization (yes or no), and the main exposure variable is geographic accessibility, measured by A-R index. The result was adjusted for the number of comorbidities, gender, age, and physician and specialist visits. A stepwise approach was used to select variables that produced the best fit model (smaller Akaike information criterion (AIC)). The model with the variables, "visit with specialists" and "visits with family physicians" was found to have a better fit compared to the model including "visits with pulmonologists", "visits with internists", and "visits with other specialists" separately. Therefore, for this study we used the variables "visit with family physicians" and "visit with specialists" as co-varieties in the model. To account for the difference in duration for each patient's follow-up period, the model was fitted with a generalized linear model with "Complementary log-log function" and an offset term as log of follow-up (person-year at risk) [20], [21], [22], [23]. Person-year (PY) was calculated for each patient, and it was defined as the number of years from COPD diagnosis until first admission to hospital (if hospitalized), death or end of the study (if not hospitalized). A similar approach was used where we assessed the association between geographic accessibility and mortality.

The association between geographic accessibility and hospitalization rate was assessed by developing a regression model. Performing the Poisson model, the ratio of residual deviance and residual degree of freedom was greater than one, and over dispersion was suspected. Using overdispersion test by Cameron and Trivedi [24] indicated overdispersion exists in the data selected for analysis ($P<0.05$), therefore the model was fitted using negative binomial instead of Poisson regression.

The log of follow-up was added as an offset term to the model to control for differences in follow-up periods present in patient records. The result was adjusted for the number of comorbidities, gender, age, general physician visits, and specialist visits. In the analysis, an alpha of 0.05 was considered as the cut off point for specifying statistical significance. All statistical analyses were conducted using R studio Version 1.1.383 [25].

2.2.7.2. Spatial Analysis

The distribution of hospitalization, annual hospitalization rate, and mortality are visualized at the local areas level. Local areas are based on Census Consolidated subdivision (CCS) which is a spatial level between census division and census subdivision [26]. To find out if any clusters exist in the spatial distribution of outcomes, a geospatial analysis was conducted using shapefiles provided by the NLSA. To identify spatial clusters, a spatial autocorrelation tool (Global Moran's I and Anselin Local Moran's I) was applied to summarize and geolocate data. If spatial autocorrelation was detected, either globally and/or locally, an ordinary least squares regression was used to find the best model that predicts COPD hospitalization and mortality at the community level. Anselin Local Moran's I helps to find clusters and outliers. Cluster refers to when a feature has neighbors with a similar high or low value. That feature is a part of the cluster, and the level of significant is at 95% confidence interval. On the other hand, outlier refers to when a feature had neighbours with dissimilar value. For instance, the feature's value is high, while its neighbors' values are low, this is called high-low outlier.

Regression residuals were mapped and tested for autocorrelation which indicates whether spatial dependencies exist. The predictor variables were selected from the following variables: average A-R index score, percentage of female population with COPD, average age at time of diagnosis, percentage of COPD patients with comorbidities, average number of family physician visits, and specialist visits during the follow-up period at the community level. Using a stepwise approach, the explanatory predictors (p-value<0.1) were selected and the best-fitted model was developed.

2.3. Results

There were 52,158 patients who were identified as being diagnosed with COPD based on our case definition. As the place of residence was the focus of this study, patients with missing residential postal codes (14% of all records) were removed. A total population of 44,876 COPD patients with 44.05% in inaccessible areas (n=19,768) were enrolled in the study and were followed from 1995 and to 2014. Figure 2.2 shows the distribution of the cumulative incidence of COPD. As seen, some areas in east and west of Newfoundland have higher cumulative incidence including Trepassey Bay (0.74), Head of Conception Bay (0.42), Bonne Bay area (0.38), Bay of Islands (0.38), and St. Mary's Bay (0.34). The results of descriptive analysis were presented in tables 2.1 and 2.2. 41.1% of COPD patients died during the study period. Mortality of COPD patients was 5.1 per 100 person-year. The total person-years at risk was 358,683 PYs. On average, COPD patients were followed 7.993 (95% CI: 7.94-8.04) years. There were approximately 3.783 (95% CI: 3.74-3.83) years between COPD diagnosis and first hospitalization. The mean age at the time of diagnosis was 63.03 [95% CI: 62.90-63.17]. The youngest COPD patient at the time of diagnosis was 35 and the oldest COPD patient at the time of diagnosis was 104. The proportion of COPD patients increased with age: the highest proportion among the 60-69 age group. Patients with no comorbidities before the first hospitalization and the whole of the study period are lower in accessible areas, 22.6% versus 24.8% and 17.8% versus 18.9%. The most common comorbidity was hypertension (65.6%) followed by ischemic heart disease (35.4%).

The results included in Table 2.3 using person-years at risk indicates that healthcare utilization is significantly impacted by the accessibility of a patient's place of residence. The hospitalization incidence among COPD patients who live in accessible areas (0.19 per PY) was higher than those in inaccessible areas (0.15 per PY) of the province ($p<0.001$). Thirty-nine-point four percent of COPD patients in inaccessible areas were readmitted within 30 days, whereas 31.5% of the patients from accessible areas were readmitted in this time period. The annual hospitalization rate for COPD patients in inaccessible areas (0.47 per PY) was significantly higher than accessible areas, 0.35 per PY ($p<0.001$).

Table 2.1. Mortality, total person-year at risk and fellow up period for patients diagnosed with COPD in NL

Mortality per 100 Person-Year	5.1
Total Person-Year at risk	358,683
Average follow up (years)	7.993 (95% CI: 7.94-8.04)
Average follow up before the first hospitalization	3.783 (95% CI: 3.74-3.83)

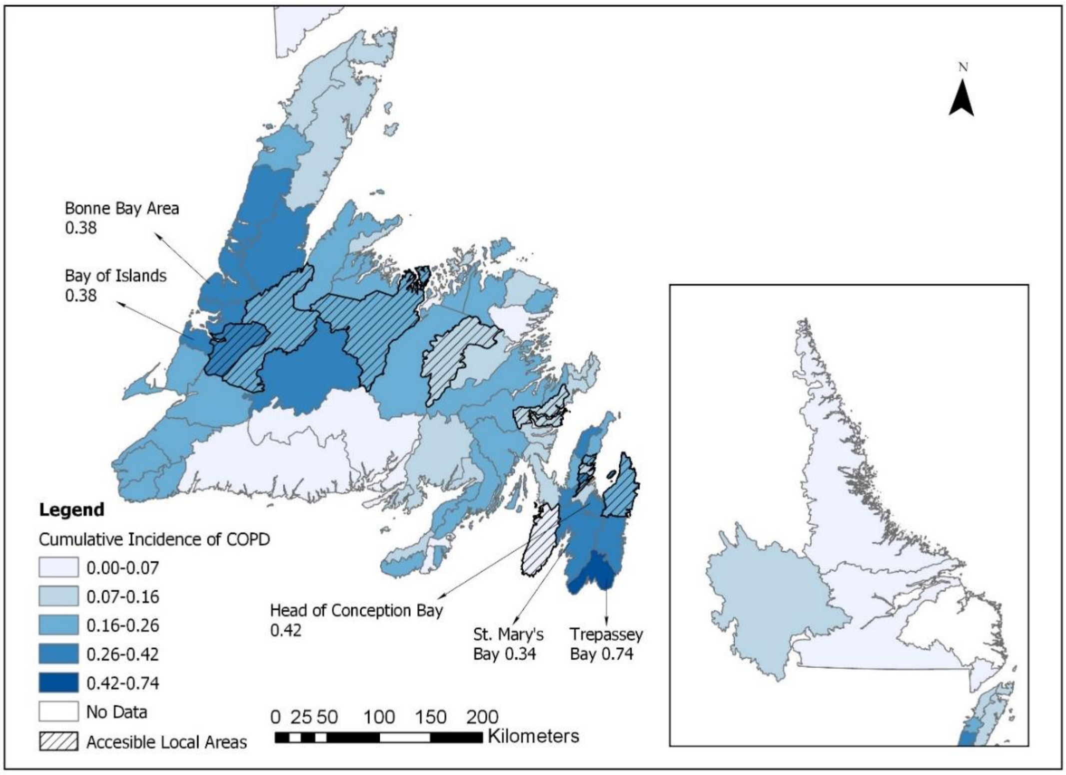

Figure 2.2. Distribution of cumulative incidence of COPD at the local area geographic level in NL

Table 2.2. Characteristics of study population according to the place of residence (N=44876)

	Inaccessible (n=19768)	Accessible(n=25108)	p-value [a]
Sex (n, %)			
Male	10940 (55.3%)	12470 (50.7%)	< 0.001
Female	8828 (44.7%)	12368 (49.3%)	
Age in years [b]			
Median (IQR)	64 (53,75)	63 (51, 74)	<0.001
Mean (SD)	62.4 (14.4)	63.84 (15.2)	
Age group (n,%)			
<40	899 (4.5%)	1778 (7%)	< 0.001
40-49	2627 (13.3%)	3900 (15.5%)	
50-59	4039 (20.4%)	4982 (19.8%)	
60-69	4772 (24.1%)	5677 (22.6%)	
70-79	4630 (23.4%)	5313 (21.1%)	
>=80	2801 (14.3%)	3458 (14%)	
Comorbidities [c] (n, %)			
Zero	6880 (34.8%)	8476 (33.7%)	0.0147

one	5940 (30%)	8083 (32.2%)	
Two	3554 (18%)	4593 (18.3%)	
Three or more	3394 (17.2%)	3956 (15.8%)	
Comorbidities [d] (n, %)			< 0.001
Zero	4908 (24.8%)	5686 (22.6%)	
One	5996 (30.3%)	8183 (32.6%)	
Two	4409 (22.3%)	5872 (23.4%)	
Three or more	4455 (22.6%)	5367 (21.4%)	
Comorbidities [e] (n, %)			< 0.001
Zero	3742 (18.9%)	4478 (17.8%)	
One	5094 (25.8%)	7127 (28.4%)	
Two	4432 (22.4%)	5705 (22.7%)	
Three or more	6500 (32.9%)	7798 (31.1 %)	
Mortality (n, %)	8373 (42.3%)	10063 (40%)	< 0.001

[a] Chi square test
[b] Age at the time of diagnosis
[c] Comorbidities at the time of diagnosis
[d] Comorbidities before the first hospitalization
[e] Comorbidities for the whole of the study period

Table 2.3. Health care utilization according to the place of residence

	Inaccessible	Accessible	p-value
Hospitalization incidence (PY)	0.19	0.15	<0.001
Annual Hospitalization rate	0.47	0.35	<0.001
Mortality	0.055	0.048	<0.001
Visit with family medicine (rate)			
Before the first hospitalization (PY)	2.69	2.94	<0.001
Total visits per year (PY)	8.11	9.85	<0.001
Visit with Specialists (rate)			
Before the first hospitalization (PY)	2.07	2.30	0.004
Total visits (PY)	6.44	7.61	<0.001
Visit with Pulmonologists and internists (rate)			
Before the first hospitalization per (PY)	0.55	0.57	0.26
Total visits (PY)	1.55	1.73	0.002

2.3.1. Geographic Remoteness and Hospitalization

2.3.1.1. Individual Level Analysis

Table 2.4 shows findings from logistic regression model on the effect of geographic accessibility on hospitalization after adjustment for age, sex, number of comorbidities, number of family medicine, and specialist visits. Patients from areas with lower accessibility were more likely to be hospitalized than those from the areas with higher accessibility (OR=2.57, 95% CI 1.54-4.25, P value=0.00136). As the result of negative binomial model is illustrated in Table 2.5 the adjusted annual hospitalizations rate increases as accessibility decreases (RR=5.05, 95% CI:3.00-8.51, P value<0.001).

Table 2.4. Effects of geographic accessibility on hospitalization among COPD patients

Predictor	OR	95% CI	P-value
AR INDEX [a]	**2.57**	**1.54-4.25**	**0.00136**
Comorbidity [b, c]			
One	1.00	0.94-1.05	0.91
Two	1.19	1.12-1.26	<0.001
Three or more	2.12	2.00-2.25	<0.001
Sex Female	0.85	0.83-0.87	<0.001
Age 40-49 [d, e]	1.18	1.07-1.31	0.00242
Age 50-59	1.81	1.65-1.99	<0.001
Age 60-69	2.83	2.58-3.10	<0.001
Age 70-79	4.72	4.30-5.18	<0.001
Age >=80	5.47	4.97-6.03	<0.001
AR INDEX: comorbidity=1	0.70	0.52-0.93	0.02352
AR INDEX: comorbidity=2	0.71	0.51-0.97	004936
AR INDEX: comorbidity>=3	0.37	0.27-0.52	<0.001
AR INDEX: age 40-49 [c]	1.42	0.79-2.55	0.29658
AR INDEX: age 50-59	1.13	0.65-1.99	0.69522
AR INDEX: age 60-69	1.75	1.01-3.03	0.07545
AR INDEX: age 70-79	1.91	1.10-3.34	0.04028
AR INDEX: age >=80	2.79	1.57-4.97	0.00187

[a] Accessibility Remoteness Index
[b] Comorbidities before the first hospitalization
[c] Patients with no comorbidities are the reference group.
[d] Age 30-39 is used as the reference group.
[e] Age at the time of diagnosis

Table 2.5. Effects of geographic accessibility on annual hospitalization rate among COPD patients

Predictor	RR	95% CI	P-value
AR INDEX [a]	**5.05**	**3.00-8.51**	**<0.001**
Comorbidity [b]			
One	1.11	1.05-1.18	<0.001
Two	1.42	1.33-1.51	<0.001
Three or more	2.21	2.08-2.35	<0.001
Sex Female	0.87	0.83-0.90	<0.001
Age 40-49 [c, d]	1.15	1.05-1.27	0.002
Age 50-59	1.60	1.46-1.75	< 0.001
Age 60-69	2.39	2.18-2.62	<0.001
Age 70-79	3.55	3.24-3.88	< 0.001
Age >=80	4.50	4.09-4.95	< 0.001
Family Medicine visits [e]	1.0074	1.0072-1.0077	< 0.001
Specialist visits [f]	0.9970	0.9969-0.9972	< 0.001
AR INDEX: comorbidity=1	0.92	0.67-1.25	0.56
AR INDEX: comorbidity=2	0.81	0.58-1.12	0.19
AR INDEX: comorbidity>=3	0.70	0.52-0.95	0.019
AR INDEX: Female	0.82	0.65-1.98	0.028
AR INDEX: age 40-49 [d]	1.27	0.72-2.21	0.40
AR INDEX: age 50-59	1.35	0.79-2.31	0.25
AR INDEX: age 60-69	1.82	1.07-3.08	0.02
AR INDEX: age 70-79	2.04	1.19-3.46	0.007
AR INDEX: age >=80	2.34	1.34-4.10	0.002

[a] Accessibility Remoteness Index
[b] Number of comorbidities patients have until the end of study period
[c] Age at the time of diagnosis
[d] Age 30-39 is used as the reference group.
[e] The family medicine visits for the whole study period.
[f] The specialist visits for the whole study period.

2.3.1.2. Spatial Analysis

Cumulative incidence of hospitalizations among COPD patients by Local Area is presented in figure 2.3. Labrador North (0.98), Pinware River (0.96), Belle Bay (0.92), and Roddikton (0.91) were found to have the highest cumulative incidence of hospitalizations. The result of the global Moran's I test points out a significantly small amount of (p-value <0.03) spatial autocorrelation at the significance level of 0.05. The Moran's I index was 0.034 with a Z score of 2.21 (table 2.6), indicating overall positive autocorrelation with a less than 1% chance that the clustered pattern observed was due to randomness. Anselin's Local Moran's I (LMI) identified local areas in the Grandfalls-Windsor region including Grandfalls-Point Leamington area (p-value<0.014, LMI=0.00061) and other local areas in the Avalon Peninsula including Northeast Avalon (p-value<0.008, LMI=0.000221) as low-low clusters (figure 2.4). These areas have a lower cumulative incidence of hospitalizations as illustrated in figure 2.3 and relatively higher accessibility (figure 2.1). At the community level, a model which considered average age, average A-R index score, and percentage of total female in our study population produced the highest level of fitness (R^2=0.52) in terms of the ability to predict the cumulative incidence of hospitalizations. The adjusted R^2 was 0.49, which shows the model explains approximately 49% of the variability in the dependent variable. The effect of A-R index was positive and significant (p<0.001). This indicates that at the community level, an increase in remoteness is significantly associated with an increase in the cumulative incidence of hospitalizations. The analysis of standard residuals did not show any spatial autocorrelation (Moran's I= 0.026, p = 0.1). The standard residuals of the over-prediction (>2.5 standard deviations) and under-prediction (<-2.5 standard deviation) at the local area level were not clustered. This provides evidence that while modelling at the community level, adjusting for spatial dependencies will not produce better model fitness in terms of predicting the cumulative incidence of hospitalizations of COPD patients.

Table 2.6. Results of Global Moran's I test on cumulative incidence of hospitalization and annual hospitalization rate among COPD patients

Variable	Cumulative incidence of hospitalizations
Moran's Index	0.034
Z-score	2.21
p-value	0.07
Variable	Annual hospitalization rate
Moran's Index	0.14
Z-score	6.48
p-value	P<0.001

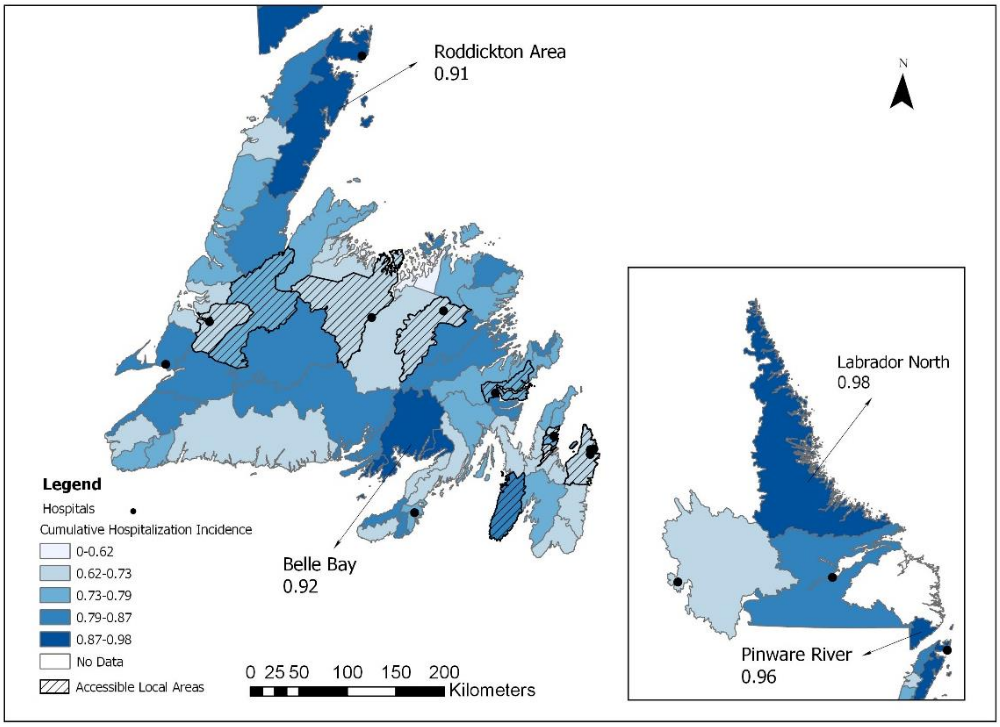

Figure 2.3. Distribution of cumulative hospitalization incidence at local area level 1995-2014

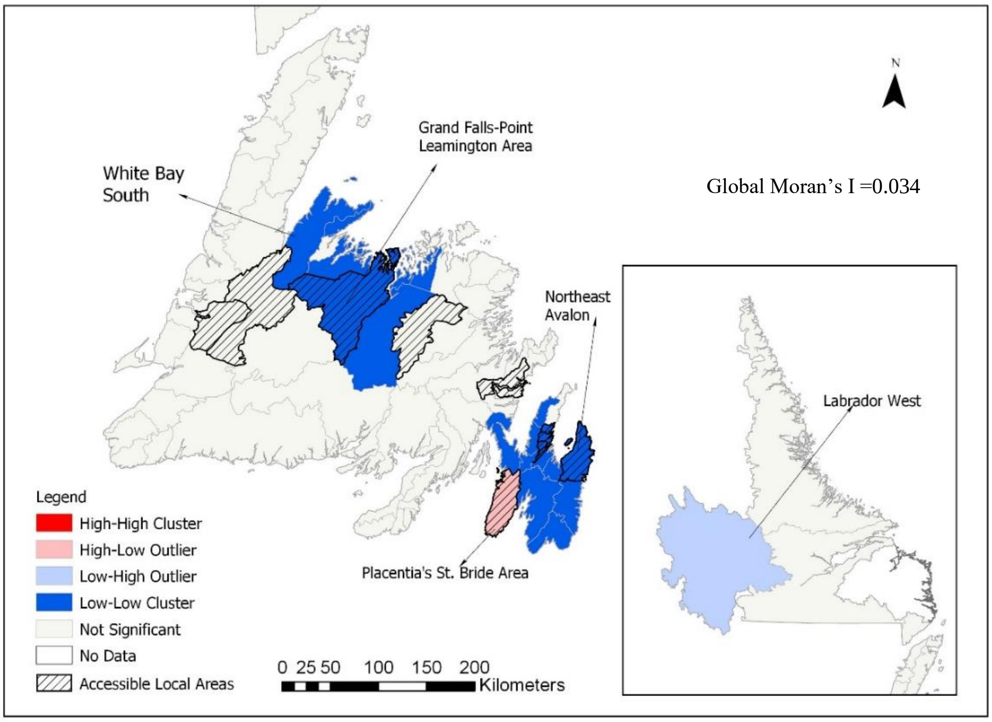

Figure 2.4. Outlier and clusters of cumulative hospitalization incidence at local area level 1995-2014

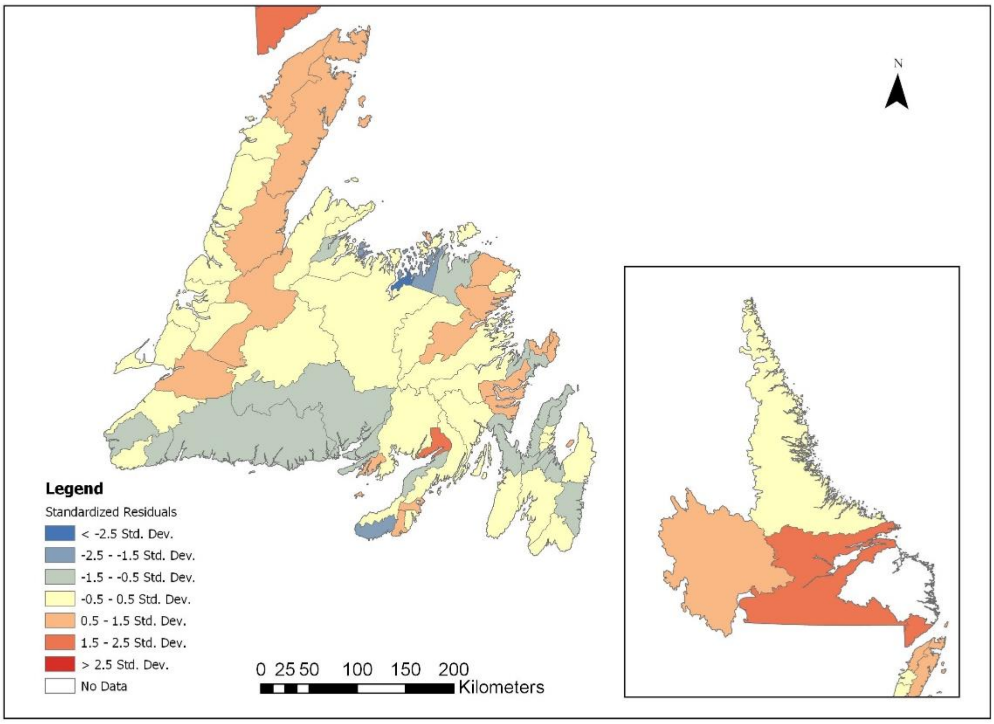

Figure 2.5. Standard residuals of regression-adjusted hospitalization incidence at local area level

Results from the annual hospitalization rate analysis also indicated a clustered pattern with Moran's I index score of 0.14 and a Z score of 6.48 (p-value <0.001). Anselin's Local Moran's I identified central and eastern Avalon Peninsula areas including Northeast Avalon (p-value<0.002, LMI=0.000288), and Grand Falls-Point Leamington Area (p-value<0.022, LMI=0.000041) as low-low clusters or cold spots. The northern peninsula of the island and the southern tip of Labrador which includes the Strait of Belle Isle (p-value<0.046, LMI=0.000086), Roddickton (p-value<0.04, LMI=0.000091), Hawks' Bay-Port aux Choix (p-value<0.042, LMI=0.000016), Quirpon-Cook's Harbour (p-value<0.04, LMI=0.000057), and Pinware River (p-value<0.026, LMI=0.000066) as high-high clusters or hot spots (figure 2.7). From figure 2.6 we observe that cold spot areas have the lowest annual hospitalization rates and are mostly accessible or moderately remote. Hot spots were found in moderately remote to extremely remote areas. The results indicate not all the variability found in annual hospitalization rate across local areas can be justified by the A-R index alone. At the community level, the ordinary least squares regression model with the best fit (R^2=0.60) included average age, average A-R index score, percentage of total female population, average number of comorbidities, and average number of family medicine visits. The model demonstrated that an increase in A-R index (decrease in accessibility), increase annual hospitalization rate at the local level (Coefficient=1.6, p-value <0.05). The residuals from this OLS model were depicted at the local area level (figure 2.8). At the global level, the standard residuals were also not found to be spatially autocorrelated (global Moran's I = -0.003, p-value = 0.68) indicating a pattern that is not significantly different from random.

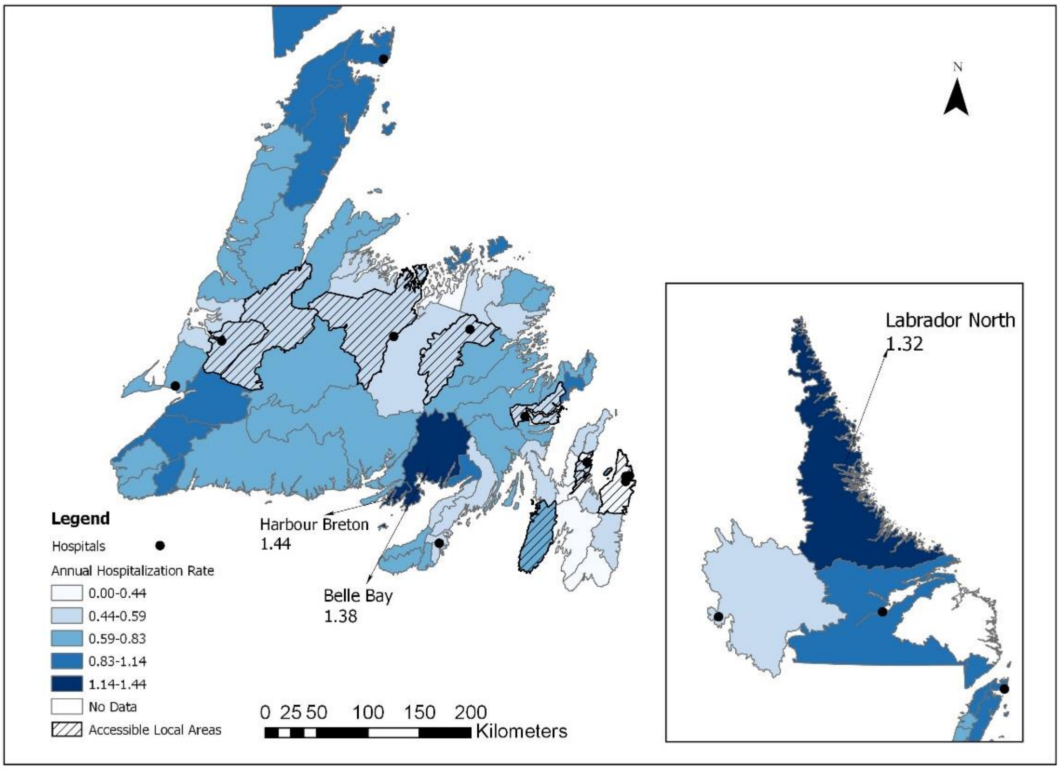

Figure 2.6. Distribution of annual hospitalization rate at area local level (1995-2014)

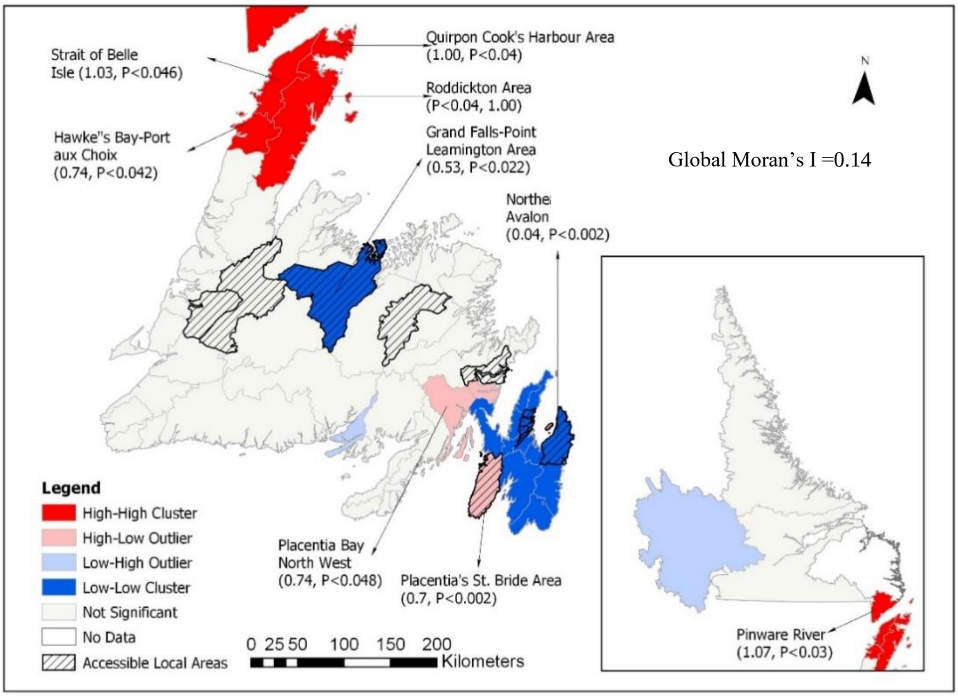

Figure 2.7. Outlier and clusters of annual hospitalization rate at local area level

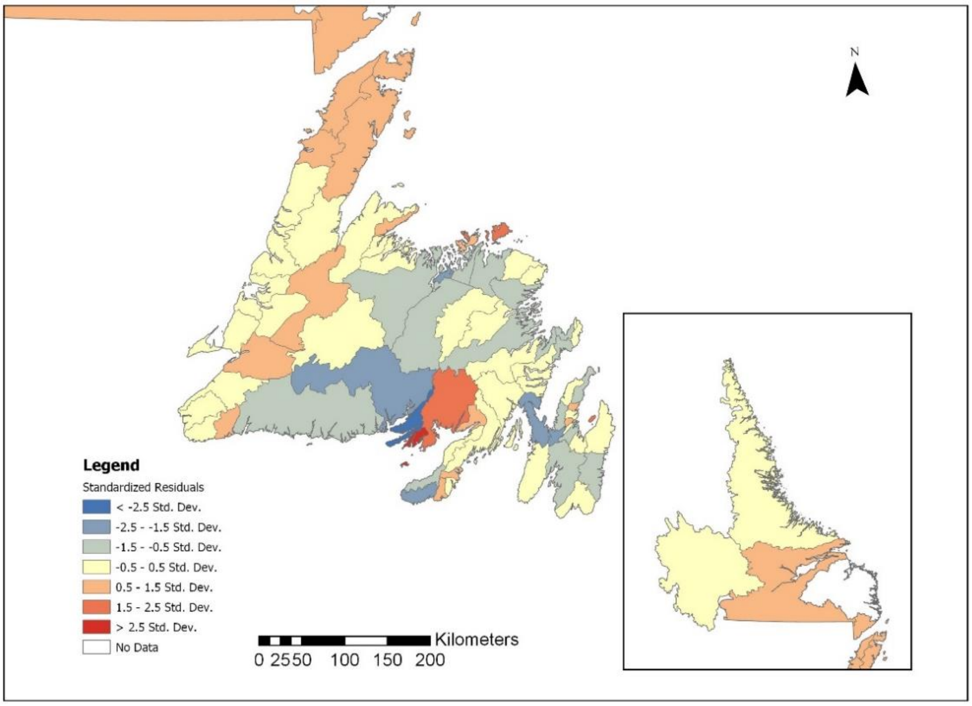

Figure 2.8. Standard residuals of regression – Adjusted annual hospitalization rate at local area level

2.3.2. Geographic Remoteness and Mortality

2.3.2.1. Individual Level Analysis

Table 2.7. represents the results of the regression model that was adjusted for patient comorbidities, sex, age, number of family medicine and specialist visits. Patients living with COPD in less accessible and remote areas were found to have a higher risk of death compared to those living in more accessible areas (OR=10.73, 95% CI; 2.27-44.77, P=0.002).

Table 2.7. Effects of geographic accessibility on mortality among patients with COPD

Predictor	OR	95% CI	P-value
AR INDEX [a]	**11.25**	**2.34-47.97**	**0.002**
Comorbidity [b, c]			
One	0.93	0.85-1.01	0.11
Two	1.16	1.06-1.27	0.002
Three or more	1.79	1.65-1.95	< 0.001
Sex Female	0.77	0.73-0.81	< 0.001
Age 40-49 [d, e]	2.85	2.07-3.98	< 0.001

Age 50-59	7.97	5.90-10.94	< 0.001
Age 60-69	20.48	15.23-27.96	< 0.001
Age 70-79	46.78	34.81-63.84	< 0.001
Age >=80	108.85	80.91-1.49	< 0.001
Family Medicine visits [f]	0.9936	0.9933-0.9939	< 0.001
Specialist visits [g]	1.0007	1.0005-1.0009	< 0.001
AR INDEX: comorbidity=1	0.75	0.48-1.19	0.26
AR INDEX: comorbidity=2	0.74	0.47-1.16	0.23
AR INDEX: comorbidity>=3	0.65	0.43-00.99	0.06
AR INDEX: Female	0.62	0.47-00.82	0.002
AR INDEX: age 40-49 [e]	0.16	0.03-0.90	0.03
AR INDEX: age 50-59	0.09	0.02-0.45	0.003
AR INDEX: age 60-69	0.1	0.02-0.49	0.004
AR INDEX: age 70-79	0.09	0.02-0.47	0.003
AR INDEX: age >=80	0.11	0.02-0.53	0.005

[a] Accessibility Remoteness Index
[b] Number of comorbidities patients have until the end of study period
[c] Patients with no comorbidities is the reference group.
[d] Age at the time of diagnosis
[e] Age 30-39 class is used as the reference group.
[f] The family medicine visits for the whole study period.
[g] The specialist visits for the whole study period.

2.3.2.2. Spatial Analysis

The distribution of Mortality of COPD patients who died during the study period by local area is visualized in figure 2.9. The local areas of Alexandre Bay (0.63), Trinity (0.62), Bay d'Espoir (0.60), Bonavista area (0.60), St. George's area (0.59), and Labrador North (0.55) were found to have higher mortality. The results from spatial autocorrelation analysis of mortality among COPD patients revealed significant low clustering with a Moran's I index of 0.047, and Z score of 2.52 (p-value=0.011). Local level analysis found the White Bay South area as a low-low cluster (p-value=0.05, LMI= 0.000014), and the Black Head Bay (p-value=0.006, LMI=0.000153) and Southern Bay areas (p-value=0.024, LMI=0.00018) as high-high clusters (figure 2.10). Mortality hotspots were found to be occurring in "somewhat accessible" and "accessible" A-R index classified areas. The predictors that led to the best-fitted models at the community level were average age, and average number of specialist visits, average A-R index of place of residence (P=0.002). No OLS residual clustering was observed at the local level (figure 2.11), indicating no spatial dependencies while a global Moran's I test uncovered a non-random distribution of residuals across the province (Moran's I = 0.03, p-value=0.08).

Table 2.8. Results of Global Moran's I test on mortality among COPD patients

Variable	Mortality
Moran's Index	0.047
Z-score	2.52
p-value	0.011

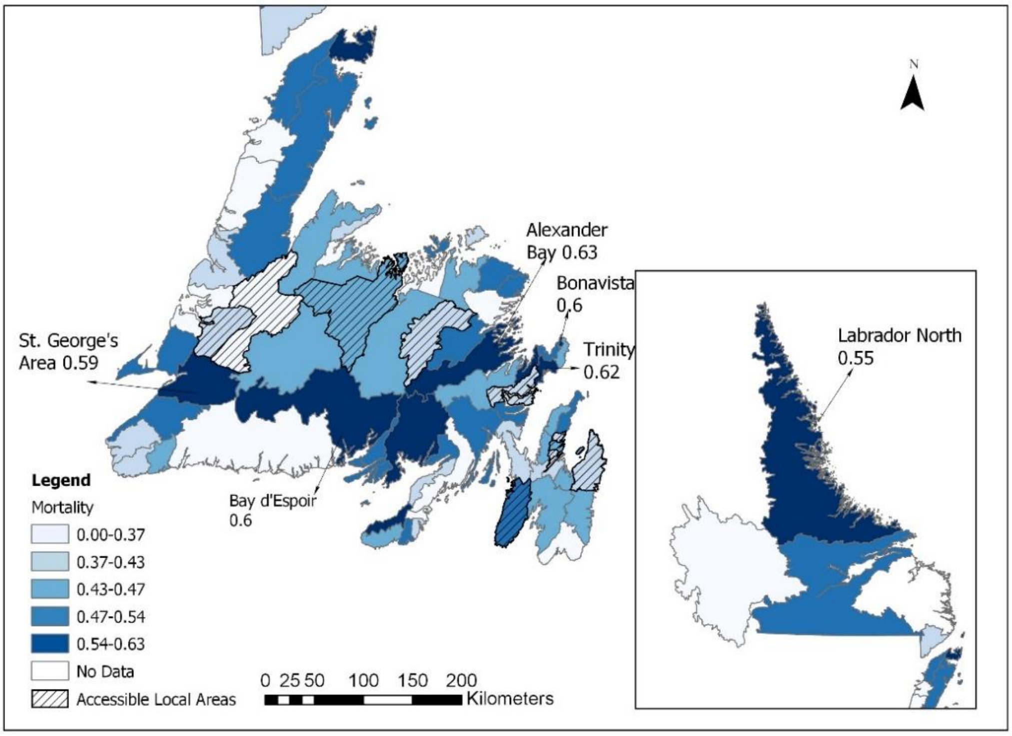

Figure 2.9. Distribution of mortality at local area level 1995-2014

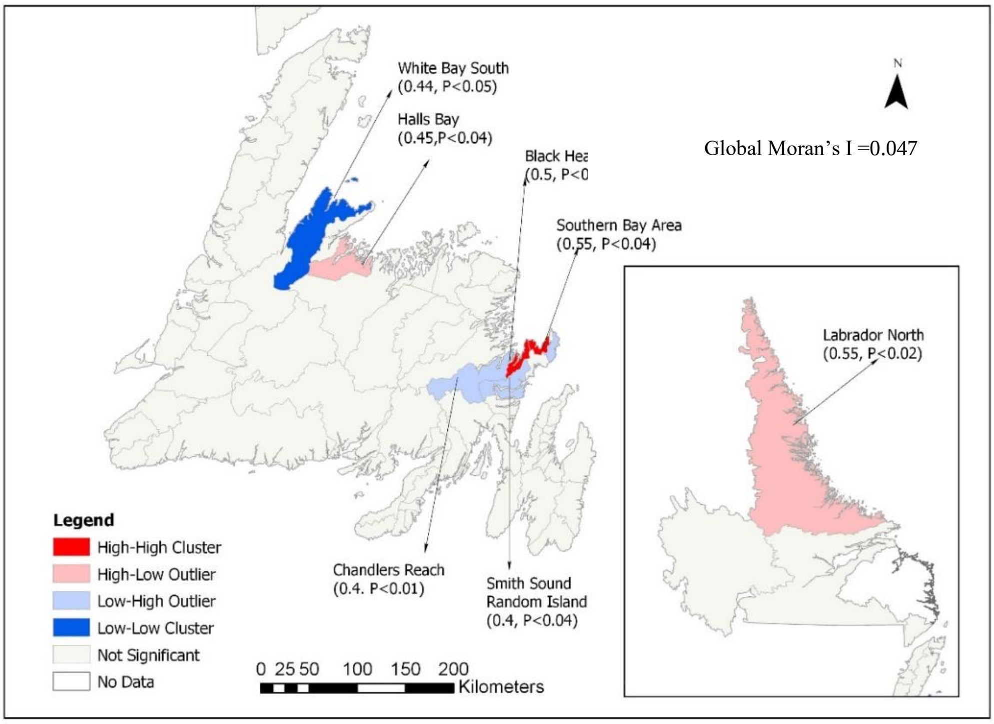

Figure 2.10. Outlier and clusters of mortality at local area level

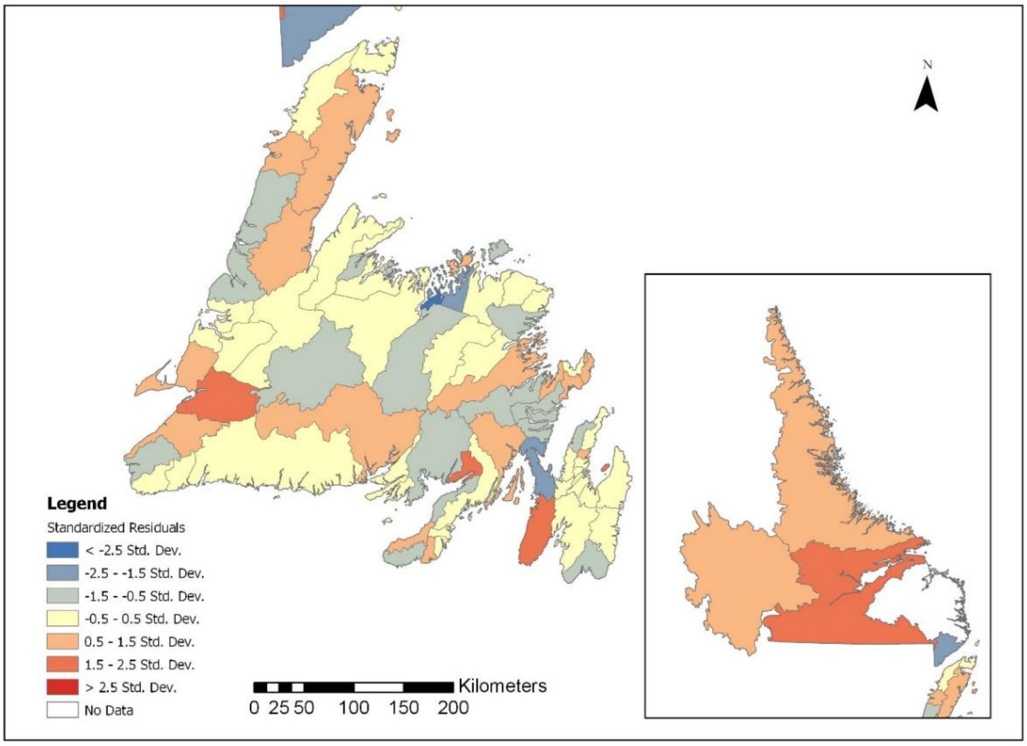

Figure 2.11. Standard residuals of regression – Adjusted mortality at the community level

2.4. Discussion and Conclusion

2.4.1. Main Findings of the Study

Our study shows COPD patients from remote and less accessible areas are more prone to hospitalization and mortality. As the degree of remoteness of an area increases, so does the likelihood a COPD related hospitalization. A similar pattern was observed for mortality of COPD patients.

The findings from our study are consistent with previous studies regarding the positive association between the degree of remoteness of an area and COPD hospitalization and mortality [6] [7]. Although there is no consistency in defining rural or remote in the literature [27]. To identify remoteness and rurality we used a definition standardized for NL[17]. Our analyses included multivariate modelling for individual and community level as well as spatial analysis.

Analysis of the annual hospitalizations rates showed hot spots in more remote areas of the province while cold spots were more likely to occur in more accessible areas. One may say these cold spots and hot spots cannot be explained purely by A-R index classification; for example, the difference could be due to underlying systemic issues such as inequity in access to the healthcare services especially primary healthcare. Using multivariate analysis controlling for healthcare utilization factors did not change the result of our study. In all of these models, COPD hospitalization and mortality were associated with the degree of remoteness even after controlling for the number of visits with primary care physicians and specialists. However, we did not have data allowing us to examine differences in the type of treatment options and availability of COPD related expenditures among these areas.

Although this study sheds light on the association between geographic accessibility and risk of hospitalization and mortality, the underlying reasons for this pattern is still unknown. Further studies are recommended to identify the role of smoking on these differences. Researchers could also look in more details for health status of the patients and the type of the services they receive. This information is vital in identifying the necessary steps that regional health authorities or individuals should take to reduce this risk.

2.4.2. Limitations

The result of this study should be interpreted in light of its limitations; This is a retrospective cohort study using secondary data. The secondary data in this study may have suffered data quality issues.

Some risk factors of COPD hospitalization and mortality were not included in the dataset such as: socioeconomic status and type of medication prescribed to the patient. We were not able to control for smoking since there was no information in our datasets. Smoking is a well-known contributor to the increased risk of developing COPD and other life-threatening comorbidities and complications.

We did not have information to differentiate planned and unplanned hospital admission nor were we able to identify the cause of hospital admission or cause of death. These factors may influence our results, as some of the hospital admissions or deaths may be unrelated to COPD.

A-R index is not based on health authority’s level, and we do not have the information at this level, therefore we could not conduct the analysis at this level.

In our study, cases were identified using ICD-9 and ICD-10 codes, therefore our result relies heavily upon the accuracy of the COPD case definition algorithm. The data for this study came from hospital discharge and physician claims data. In NL, salary-based physicians (approximately 30 percent of the total pool of active practicing physicians in the province) are not obligated or expected to submit medical fee claims, therefore the number of COPD patients might have been underestimated.

2.4.3. Conclusion

In order to solve complex population health problems, it is important to identify communities and regions that may require emergent attention. After controlling for physician visits, we found that COPD patients who live in inaccessible and remote areas are at a greater risk of hospitalization and mortality in Newfoundland and Labrador. Although limited by the data this study provides evidence for health planners in resource allocation and in designing targeted interventions to address the healthcare needs of COPD patients living in remote and rural regions of the province.

2.5. References

[1] R. A. Pauwels, K. F. Rabe., “Burden and clinical features of chronic obstructive pulmonary disease (COPD).,” *Lancet (London, England)*, vol. 364, no. 9434, pp. 613–20, 2002.

[2] L. Schirnhofer, B. Lamprecht, W. M. Vollmer, M. J. Allison, M. Studnicka, R. L. Jensen, A. S. Buist., “COPD prevalence in Salzburg, Austria,” *Chest*, vol. 131, no. 1, pp. 29–36, Jan. 2007.

[3] D. J. Maselli and A. Anzueto, “The need to further understand who gets hospitalized for a COPD exacerbation,” *Multidiscip. Respir. Med.*, vol. 7, no. 1, p. 7, Dec. 2012.

[4] T. Dang-Tan, S. Zhang, R. V. Tavares, M. Stutz, A. S. Ismaila, J. Vaillancourt, D. Corriveau, R. H. Stanford, X. Lin, G. A. Nadeau, A. Simidchiev, D. Parsons, and J. S. Sampalis, “The burden of illness related to chronic obstructive pulmonary disease exacerbations in Québec, Canada,” *Can. Respir. J.*, vol. 2017, pp. 1–10, Jun. 2017.

[5] Canadian Institute for Health Information, “COPD in Alberta: examining the characteristics and health care use of high users,” Ottawa, ON, 2017.

[6] T. E. Abrams, M. Vaughan-Sarrazin, V. S. Fan, and P. J. Kaboli, “Geographic Isolation and the Risk for Chronic Obstructive Pulmonary Disease–Related Mortality,” *Ann. Intern. Med.*, vol. 155, no. 2, p. 80, Jul. 2011.

[7] Z. Ansari, D. Dunt, and S. C. Dharmage, “Variations in hospitalizations for chronic obstructive pulmonary disease in rural and urban Victoria, Australia.,” *Respirology*, vol. 12, no. 6, pp. 874–80, 2007.

[8] R. W. Pong, M. DesMeules, and C. Lagacé, “Rural-urban disparities in health: How does Canada fare and how does Canada compare with Australia?,” *Aust. J. Rural Health*, vol. 17, no. 1, pp. 58–64, Feb. 2009.

[9] L. M. Sibley and J. P. Weiner, “An evaluation of access to health care services along the rural-urban continuum in Canada,” *BMC Health Serv. Res.*, vol. 11, no. 1, p. 20, Dec. 2011.

[10] Canadian Institute for Health Information, “Inpatient Hospitalizations, Surgeries and Childbirth Indicators,” Ottawa, 2015.

[11] L. Lix and K. Reimer, "The Canadian chronic disease surveillance system: A distributed surveillance model," *Online J. Public Health Inform.*, vol. 9, no. 1, May 2017.

[12] Newfoundland and Labrador Centre for Health Information, "Clinical Database Management System (CDMS) data users guide v.1.0," St. John's, NL, 2014.

[13] Canadian Institute for Health Information, "National physician database data release, 2015-2016," Ottawa, ON, 2017.

[14] Newfoundland and Labrador Centre for Health Information, "NLCHI mortality system data user guide August 2017 v.1.0," St. John's, NL, 2017.

[15] A. Feely, L. M. Lix, and K. Reimer, "Estimating multimorbidity prevalence with the Canadian Chronic Disease Surveillance System.," *Heal. Promot. chronic Dis. Prev. Canada Res. policy Pract.*, vol. 37, no. 7, pp. 215–222, Jul. 2017.

[16] A. S. Gershon, C. Wang, J. Guan, J. Vasilevska-Ristovska, L. Cicutto, and T. To, "Identifying individuals with physcian diagnosed COPD in health administrative databases.," *COPD*, vol. 6, no. 5, pp. 388–94, Oct. 2009.

[17] Newfoundland and Labrador Statistics Agency, "Accessibility-Remoteness (A-R) index summary paper," 2014.

[18] O. Hurley, "Health selective migration analysis of diabetes patients living in Newfoundland and Labrador," Memorial University of Newfoundland, 2014.

[19] The Canadian Chronic Disease Surveillance System, "Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Canada, 2018," 2018.

[20] N. Alexander, "Can studies where subjects have different follow-up times be analysed through binomial regression?," *Mem. Inst. Oswaldo Cruz*, vol. 106,

no. 5, p. 639; discussion 639, Aug. 2011.

[21] R. H. Gray, M.J. Wawer, R. Brookmeyer, N. K. Sewankambo, F. Wabwire-Mangen, T. Lutalo, X. Li, T. VanCott, T. C. Quinn, Rakai Project team., “Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda,” *Lancet*, vol. 357, no. 9263, pp. 1149–1153, Apr. 2001.

[22] D. Collett, *Modelling Binary Data*. Boston, MA: Springer US, 1991.

[23] E. Vittinghoff, D. V. Glidden, S. C. Shiboski, and C. E. McCulloch, *Regression Methods in Biostatistics*, Second. Boston: Springer, 2012.

[24] A. C. Cameron and P. K. Trivedi, “Regression-based tests for overdispersion in the Poisson model,” *J. Econom.*, vol. 46, no. 3, pp. 347–364, Dec. 1990.

[25] Rs. Team, “RStudio: integrated development for R.” RStudio, Inc, Boston, MA, 2016.

[26] W. Locke, “Review of economic and employment data from the community accounts dataset,” 2016.

[27] L. G. Hart, E. H. Larson, and D. M. Lishner, “Rural definitions for health policy and research.,” *Am. J. Public Health*, vol. 95, no. 7, pp. 1149–55, Jul. 2005.

Chapter 3: Geographic Accessibility and Risk of Hospitalization and Mortality among Asthma Patients

3.1. Introduction

Asthma accounts for about 80% of chronic respiratory diseases in Canada, which makes it the most common respiratory chronic disease in this country [1]. Three million people in Canada and 235 million around the world are affected by asthma [2]. As stated by Statistics Canada, 8.1% of Canadians aged 12 and older have been diagnosed with asthma [3]. In Canada, 250 people die from Asthma annually and about 70000 emergency visits are due to an asthma attack. Economic costs of asthma are one of the highest among chronic diseases as a consequence of health care utilization [4]. Asthma is considered as an ambulatory care-sensitive condition (ACSC) which means that hospital admissions are avoidable given proper primary health care services and early management. Previous research also shows that asthma hospitalization is highly preventable when the patients have access to quality healthcare [5]. However, asthma hospitalization is still high in most countries [6]. Concerned by this trend, it has been started to evaluate healthcare further, and identify potential contributors to the severe outcome of asthma patients. Severe outcome refers to hospitalization and mortality [4][7].

Evidence suggests that there are differences in hospitalization and mortality within and between regions. A few studies found higher rates in rural areas and a few others found higher rates in urban areas [8] [9] [10] [11]. These differences are justifiable since characteristics of rural areas vary in different parts of the world.

The spatial variation in asthma outcomes could be due to many factors. In previous studies, inaccessibility to health centers was mentioned as a risk factor for asthma hospitalization, and mortality [12]. Analysis of rural-urban differences in asthma hospitalization in Saskatchewan between 1970 and 1989 showed a higher rate (RR=1.5, CI:1.38-1.84) among rural residents in comparison to urban residents in patients 35 years old and younger. The results were not different for men or women. For children and young adults under 35, the difference was only significant before the year 1984. The authors discuss that one of the causes for higher admission rates in rural areas of Saskatchewan might be due to lower accessibility to health services. Rural residents live further from hospitals in comparison to urban residents [9]. In another study of children with asthma in an urban setting, they found higher accessibility to primary health care is significantly associated with higher scheduled visits, and lower unscheduled visits to an urban pediatric emergency department [13]. A. Jones, G. Bentham, and C. Horwell found that an increase in travel time to hospitals significantly increase mortality among asthma patients. The authors concluded that an improvement in access to acute care facilities would reduce the mortality rate among asthma patients [12]. Information on geographic accessibility to healthcare services is critical for the implementation of effective policies aiming to improve healthcare for asthma patients.

In our study, by assessing the association between the degree of remoteness, and hospitalization, and mortality of asthma patients among the adult population of Newfoundland and Labrador (NL) we will be able to identify the areas in NL at higher risk, which is critical for the development of effective healthcare policies. To our knowledge, this study is the first study that assesses the impacts of the place of residence on hospitalization and mortality among adults living with asthma in NL. We hypothesize that asthma patients who live in more inaccessible areas will have a higher number of hospitalizations and mortality in comparison to patients that live in accessible areas.

3.2. Methods

3.2.1. Study Design

We conducted a retrospective cohort using medico-administrative data from 1995 to 2014. The patients were followed from diagnosis until the occurrence of study outcomes, the end of the study period (2014), or their death.

3.2.2. Data Source

The dataset for this study was retrieved from Newfoundland and Labrador health administrative data. For the purpose of this study, Newfoundland and Labrador Centre for Health Information (NLCHI), the data custodian, provided us with a de-identified database. This database was developed via linkage with the following databases: the Canadian Chronic Disease Surveillance System (CCDSS), Clinical Database Management System (CDMS), Medical Care Plan (MCP) Fee-For-Service Physician Claims Database, and NLCHI Mortality System Database (MS). CCDSS is the network of the provinces' and territories' chronic disease surveillance [14]. CDMS includes demographic and clinical information of patients who received surgical day care or healthcare services by acute care facilities within the province [15]. MCP billing database includes information about the provided care under MCP by the fee-for-service physicians [16]. MS database provides the death records within the province [17].

The dataset provides information about the characteristics, hospitalization, comorbidities, and physician visits of patients who received medical care in the province between 1995 to 2014. The database includes approximately 600,000 records.

3.2.3. Study Population

The study population are adults living with asthma in NL. To meet the inclusion criteria, the patients must be 20 or older and must be diagnosed with asthma between the years of 1995, and 2014 in Newfoundland and Labrador. The cases are identified according to the CCDSS definition. To meet the criteria of this definition, the patient must have a record of diagnosis with asthma from a hospital admission (493 in ICD-9, J45 and J46 in ICD-10) or must have records of diagnosis with asthma in two physician visits within 730 days of the first visit (401-405 in ICD-9). A sensitivity of 83.6% (95% CI: 77.1–89.1) and specificity of 76.5% (95% CI: 71.8–80.8) have been reported for this case definition in Manitoba and Ontario [18].

3.2.4. Ethics and Consent

The ethical approval's references number is 20161500, which has been received from the Health Research Ethics Board in Newfoundland and Labrador.

3.2.5. Geographic Accessibility

The primary independent variable in this study was geographic accessibility. In this study, patients are classified into two groups based on their place of residence at diagnosis. Accessibility of place of residence was evaluated based on the Accessibility Remoteness Index (A-R index), which was developed by the Newfoundland and Labrador Statistics Agency (NLSA). The areas within the province are classified based on their accessibility to governmental services such as primary and secondary health centers, pharmacies, dental clinics, high schools, and supermarkets. The index was developed with a geographical approach, which refers to the fact that road distance restricts the interaction between the users and these services. Generally, the most accessible areas within the province are regional centers which have many public services. The lowest accessible areas within the province are remote areas where the residents only have access to regional centers via ferry or plane [19].

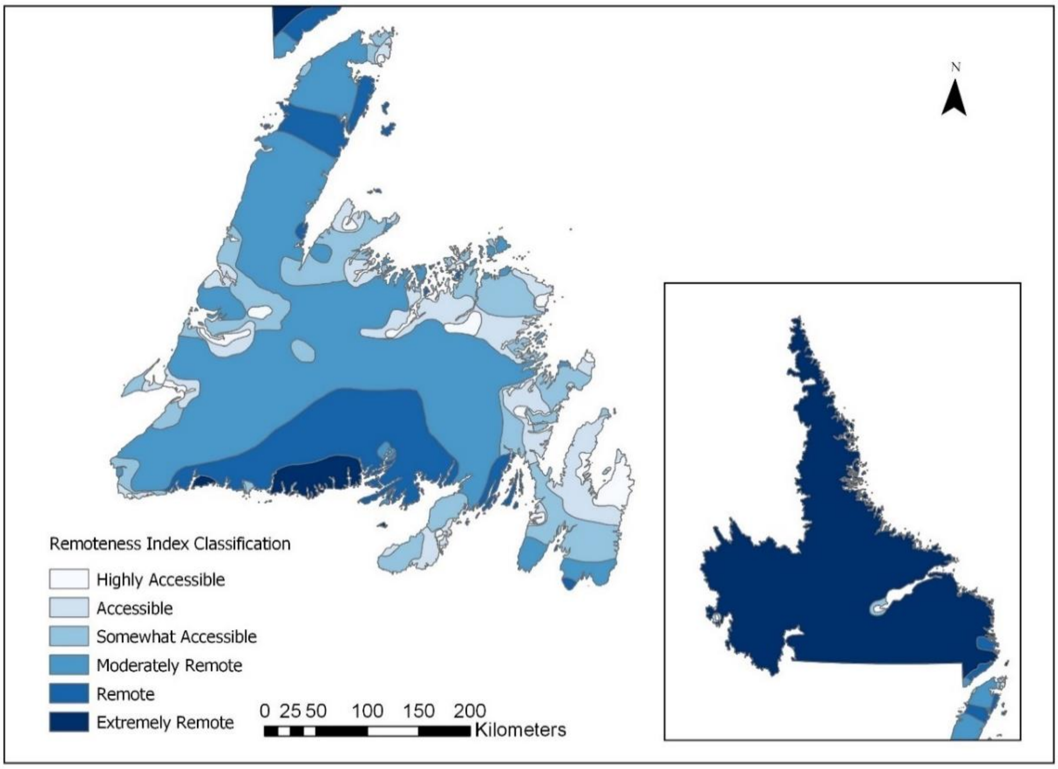

Figure 3.12. Classification of the province of Newfoundland and Labrador based on A-R index [19]

Figure 3.1 shows that the A-R index categorizes the province to the defined classes of highly accessible, accessible, somewhat accessible, moderately remote, and extremely remote areas [19].

3.2.6. Outcome

Hospitalization is the primary outcome of our study. Hospitalization is a binary (yes or no) variable. It is an incident case and it explains if the person has experienced any hospital admission, planned or unplanned during the observation period. Hospitalization was measured by person-year at risk.

Annual hospitalization rate and mortality are secondary outcomes of this study. Annual hospitalization rate is calculated based on the number of hospital admissions per person-year at risk. Mortality is a dichotomous variable and describes if the person was alive during the study period.

3.2.7. Covariates

The covariates on the individual level are sex, age at the baseline. The variable age was categorized on the basis of 10-year age groups [20]. We also collected information on the number of comorbidities, and number of physician and specialist visits during the study period.

Comorbidities include Hypertension, Chronic Obstructive Pulmonary Disease (COPD), Ischemic Heart Disease (IHD), Acute Myocardial Infarction (AMI), and Heart Failure. The comorbidities were identified based on the CCDSS method using ICD-9 and ICD-10 codes [21]. For each patient, the number of comorbidities was calculated. We classified number of comorbidities as: zero, one, two, three and more.

3.2.8. Analysis

3.2.8.1. Individual Level Analysis

We performed a descriptive analysis to describe the characteristics of the study population. Reporting the outcomes, we calculated person-year at risk for each patient.

In order to examine the differences between the inaccessible and accessible areas, bivariate analysis was performed. In the analysis, at the individual level, we used continuous A-R index, and at the local area level, we developed a fuzzy set model where we divided the areas to accessible and inaccessible [22].

The association between the place of residence and hospitalization of asthma patients was analyzed using logistic regression. The dependent variable is hospitalization, and the main independent variable is accessibility based on A-R index. The results were adjusted for sex, age, number of comorbidities, number of specialist visits and family physician visits, and interaction terms between A-R index and the other covariates. To find the optimum model a stepwise selection approach was used based on the smaller Akaike information criterion (AIC). We assessed the model's fitness based on different combinations of family physicians, internists, pulmonologists and other specialists. The model including variables family physicians and all specialists was selected as it performed better than the other models according to AIC. Since the follow-up duration was different for each patient, a generalized linear model with "Complementary log-log function" was used, and log of person-year at risk (follow-up duration) was used as the offset term [23], [24], [25], [26]. A similar approach was used to develop a logistic regression model for assessing the relationship between the place of residence and mortality.

To evaluate the association of place of residence and annual hospitalization rate, negative binomial regression was used due to the presence of overdispersion in the data (overdispersion test by Cameron and Trivedi) [27]. To control for the differences in the follow-up duration of each patient, log of follow up was used as an offset term. The model was adjusted for the number of comorbidities, gender, and age, family physician and specialist visits. Interaction terms between A-R index and other covariates were added to the model. Similarly, we used a stepwise approach to find the model with the best fit. R studio Version 1.1.383 was used for performing the statistical analysis [28].

3.2.8.2. Spatial Analysis

The distribution of the study outcomes is visualized. The natural breaks was used for the visualization. In this study, local areas were identified according to the census consolidate subdivision (CCS). Local areas are intermediate geographic levels between census division and census subdivision [29]. We had access to maps and files through Memorial University which was provided by the government of Newfoundland and Labrador and NLSA.

Using Global Moran's I test, and Anselin Local Moran's I (LMI) test, the existence of clusters were determined. In general, when the value of neighbouring features are similarly high or low, they all together make either high-high or low-low cluster. When the value of neighbors is either lower or higher, this makes high-low, or low-high outliers. If autocorrelation was observed, we developed an ordinary least square regression to identify the best model of asthma hospitalization, annual hospitalization rate, and mortality at the local area level.

The model variables which had the best fit (p-value<0.1) was selected based on an iterative stepwise approach from the following variables: average A-R index, percentage of female with Asthma, average age at the time of diagnosis, percentage asthma patients with comorbidities, percentage of physician visits, and specialist visits during the follow up period at the local area level.

3.3. Result

We identified 31613 asthma patients between 1995 and 2014. After removing the missing value for the place of residence (10.43%), we had 28316 records of patients living with asthma. The characteristics of the study population are presented in table 3.1. Cumulative incidence of asthma by local area during the study period has been depicted in figure 3.2. It is visible that areas in eastern and southern Newfoundland have a higher cumulative incidence of asthma; for instance, in Bay L'argent Area, Terrenceville Area, Placentia Bay West, Placentia Bay North, Gambo Area the cumulative incidence of asthma was 0.59, 0.29, 0.26, 0.12 respectively. The overall person-year for the study population was 323795 person-years (mean = 11.44 person-year, 95% CI: 11.37-11.55). On average the first event of hospital admission happened 9.58 years (95% CI: 9.48-9.68) after the diagnosis of asthma. The average age of patients at the baseline was 47.69 years [95% CI: 47.48 - 48.89]. The most prevalent comorbidities were Hypertension (45%) followed by COPD (31%). As shown in Table 3.2, asthma patients from less accessible areas face a higher number of hospital admissions per person-year in comparison to patients in accessible areas (0.20 versus 0.19; p<0.001). Patients from areas with higher accessibility have a higher number of family physician visits per person-year (8.03 versus 7.35, p<0.001) and higher specialist visits (5.20 versus 4.42, p<0.001) per person-year.

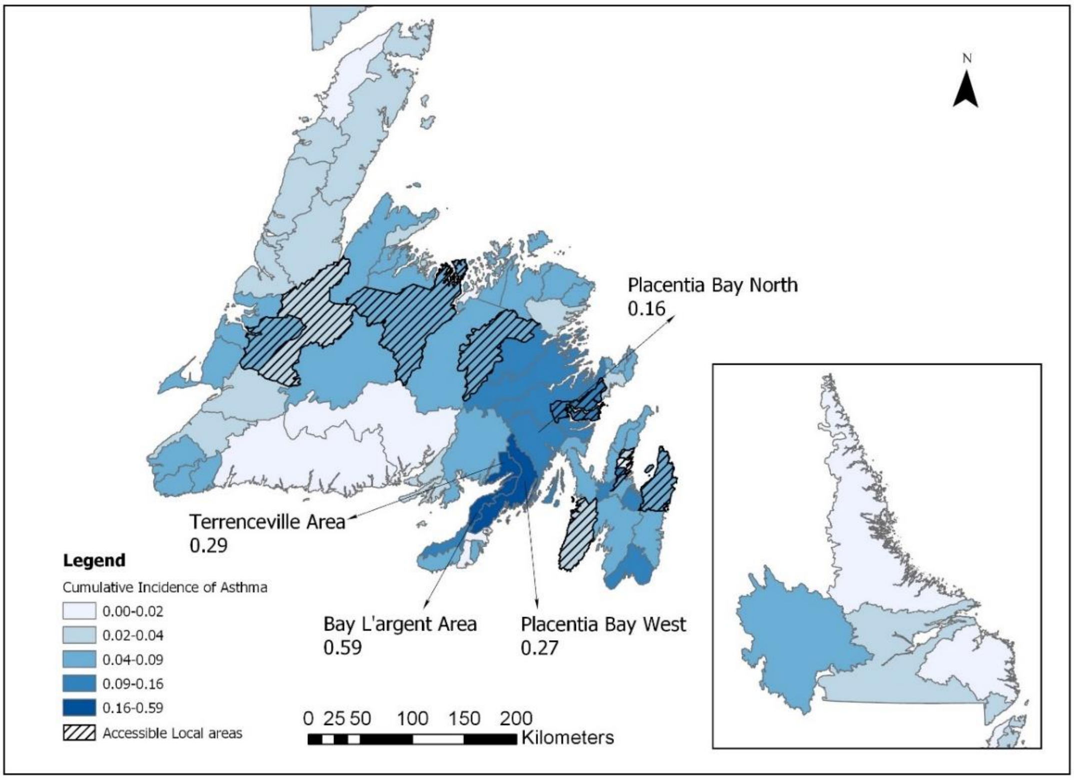

Figure 13. 1. Cumulative incidence of asthma at the local area level in NL between 1995 and 2014

Table 3.9. Characteristics of the study population according to the place of residence (N=28316)

	Inaccessible (n=10595)	Accessible (n=17721)	p-value [a]
Sex (n, %)			<0.001
Male	4172 (39.3%)	6457 (36.4%)	
Female	6423 (60.7%)	11264(63.6%)	
Age in years [b]			
Median (IQR)	49 (37, 63)	44 (32, 58)	<0.001
Mean (SD)	50.3 (18.3)	46.12 (19)	
20-29	1419 (13.4%)	3598 (20.3%)	<0.001
30-39	1754 (16.6%)	3772 (21.3%)	
40-49	2136 (20.2%)	3479 (19.6%)	
50-59	2027 (19.1%)	2696 (15.2%)	
60-69	1571 (14.8%)	1960 (11.1%)	
70-79	1115 (10.5%)	1440 (8.1%)	
>=80	573 (5.4%)	776 (4.4%)	
Comorbidities [c]			<0.001
Zero	5494 (51.9%)	10946(61.8%)	

One	2738 (25.8%)	3861 (21.8%)	
Two	1325 (12.5%)	1699 (9.6%)	
Three or more	1038 (9.8%)	1215 (4.9%)	
Comorbidities [d]			
Zero	3956 (37.3%)	8062 (45.5%)	<0.001
One	3003 (28.3%)	4828 (27.2%)	
Two	1997 (18.8%)	2725 (15.4%)	
Three or more	1639 (15.6%)	2106 (11.9%)	
Comorbidities [e]			
Zero	3161 (29.9%)	6818 (38.5%)	
One	2798 (26.4%)	4570 (25.8%)	
Two	2070 (19.5%)	2998 (16.9%)	
Three or more	2566 (24.2%)	3335 (18.8%)	
Mortality (n, %)	2226 (21%)	2922 (16.5%)	<0.001

[a] Chi square test
[b] Age at the time of diagnosis
[c] Comorbidities at the time of diagnosis
[d] Comorbidities before the first hospitalization
[e] Comorbidities for the whole of the study period

Table 3.10. Healthcare utilization according to the place of residence (N=28316)

	Inaccessible	Accessible	p-value
Hospitalization incidence (PY)	0.11	0.09	<0.001
Hospitalization rate (PY)	0.20	0.19	<0.001
Mortality (PY)	0.02	0.01	<0.001
Visit with Family Physicians (PY)			
Before the first hospitalization	2.02	2.46	0.3955
Total visits	7.35	8.03	<0.001
Visit with Pulmonologist/Internist (PY)			
Before the first hospitalization	2.3	2.8	0.1233
Total visits	0.86	1.05	0.9422
Visit with Other Specialists (PY)			
Before the first hospitalization	1.20	1.62	<0.001
Total visits	4.42	5.20	<0.001

3.3.1. Geographic Remoteness and Hospitalization

3.3.1.1. Individual Level Analysis

The results of logistic regression model (table 3.3) after adjusting for sex, age, number of comorbidities, indicated hospitalization is higher in remote and inaccessible areas. As the A-R index increases (decrease in accessibility), the likelihood of hospitalization among asthma patients increases significantly (OR=12.38, 95% CI:6.28-24.46, P<0.001).

As shown in Table 3.4, annual hospitalization rate is higher in the areas with lower accessibility after adjustment for sex, age, the number of comorbidities, and the number of family medicine and specialist visits (RR=4.74, 95% CI:3.10-7.25, P<0.001).

Table 3.11. Predictors of hospitalization among patients living with asthma in Newfoundland and Labrador

Predictor	OR	95% CI	P-value
AR INDEX [a]	**12.38**	**6.28-24.46**	**< 0.001**
Comorbidity [b, c]			
One	1.96	1.82-2.11	< 0.001
Two	5.32	4.86-5.84	< 0.001
Three or more	38.24	34.01-43.05	< 0.001
Sex Female	2.55	2.33-2.79	< 0.001
Age 30-39 [d, e]	0.69	0.61-0.78	<0.001
Age 40-49	0.42	0.37-0.48	<0.001
Age 50-59	0.62	0.53-0.71	<0.001
Age 60-69	0.98	0.82-1.17	0.83
Age 70-79	2.58	2.06-3.25	<0.001
Age >=80	1.40	1.08-1.83	<0.001
AR INDEX: Female	0.47	0.28-0.81	0.0063
AR INDEX: Age 30-39 [e]	0.66	0.29-1.49	0.32
AR INDEX: Age 40-49	1.69	0.75-3.80	0.21
AR INDEX: Age 50-59	0.51	0.22-1.20	0.12
AR INDEX: Age 60-69	0.52	0.19-1.39	0.19
AR INDEX: Age 70-79	1.07	0.30-3.90	0.92
AR INDEX: Age >=80	73.40	13.45-419-5	<0.001

[a] Accessibility remoteness index
[b] Number of Comorbidities at the time of diagnosis
[c] Patients with no comorbidities are the reference group.
[d] Age at the time of diagnosis
[e] Age 20-29 class is the reference group.

Table 3.12. Predictors of annual hospitalization rate at the individual level among asthma patients

Predictor	RR	95% CI	P value
AR INDEX [a]	**4.74**	**3.10-7.25**	**< 0.001**
Comorbidity [b, c]			
One	1.27	1.18-1.36	< 0.001
Two	1.83	1.68-1.99	< 0.001
Three or more	3.06	2.80-3.35	< 0.001
Sex Female	1.13	1.08-1.19	<0.001
Age 30-39 [d, e]	0.71	0.65-0.77	< 0.001
Age 40-49	0.57	0.52-0.62	< 0.001
Age 50-59	0.74	0.67-0.81	<0.001
Age 60-69	1.14	1.03-1.27	0.010
Age 70-79	1.84	1.65-2.06	< 0.001
Age >=80	2.49	2.18-2.85	< 0.001
Family Medicine visits [f]	0.9984	0.9982-0.9986	< 0.001
Specialist visits [g]	1.009	1.008-1.009	< 0.001
AR INDEX: Comorbidity=1	1.34	0.88-2.03	0.17
AR INDEX: Comorbidity=2	0.78	0.49-1.25	0.31
AR INDEX: Comorbidity>=3	0.80	0.49-1.31	0.37
AR INDEX: Female	0.67	0.50-0.89	0.006
AR INDEX: age 30-39 [e]	1.71	1.04-2.81	0.036
AR INDEX: age 40-49	2.36	1.40-4.00	0.001
AR INDEX: age 50-59	2.96	1.72-5.11	<0.001
AR INDEX: age 60-69	3.06	1.69-5.55	<0.001
AR INDEX: age 70-79	4.10	2.16-7.78	< 0.001
AR INDEX: age >=80	4.22	1.98-8.98	< 0.001

[a] Accessibility Remoteness index
[b] Number of Comorbidities at the time of diagnosis
[c] Patients with no comorbidities are the reference group.
[d] Age at the time of diagnosis
[e] Age 20-29 class is the reference group.
[f] Number of family medicine visits for the whole study period
[g] Number of specialist visits for the whole study period

3.3.1.2. Spatial Level Analysis

Cumulative incidence of hospitalization during the study period is depicted in figure 3.3. The highest cumulative hospitalization incidence are in Labrador east coast (1.00), Burgeo area (0.90), Pinware river (0.90), Roddicton area (0.89), Belle bay

(0.87), Buchans area (0.85), Strait of Belle Isle (0.84), St. George’s area (0.83), and Labrador north (0.83).

The Global Moran’s I test of asthma Cumulative hospitalization incidence found statistically significant spatial autocorrelation at the alpha level of 0.05 (table 3.5). According to the results (Global Moran’s I index=0.065 and Z score=3.29, P=0.001) there is less than 1% chance that this clustered pattern is due to randomness. Anselin Local Moran’s I (LMI) showed Labrador East coast (LMI=0.000136, P<0.002), Goose Bay (LMI=0.000024, P<0.002), Pinware River (LMI=0.000145, P<0.004), Roddickton Area (LMI=0.000131, P<0.026), Strait of Belle Isle (LMI=0.000144, P<0.004), Hawk’s Bay Port aux Choix (LMI=0.000068, P<0.012) as significant clusters of high value (high-high clusters). Grand Falls Point Leamington (LMI=0.000027, P<0.03), and St. Mary’s Bay (LMI=0.000062, P=0.02) as clusters of low value (low-low). As it is shown in figure 3.4, the cold spots (areas with lower Cumulative Hospitalization Incidence) are mostly in accessible regions; hot spots are in inaccessible regions.

The results from goodness of fit from ordinary least square showed that the model fit the data well (Adjusted R^2 = 0.9) and the significant variables were average A-R index, the average number of comorbidities, and percentage of female living with asthma in the community. We observed a significant association between average A-R index at the local level and cumulative hospitalization incidence (Coefficient=1.3, p-value<0.001). The residuals of the model were visualized and presented in figure 3.5. The results of global Moran’s I test did not show any significant spatial autocorrelation, and the observed pattern is due to randomness (Moran’s Index = 0.02, p-value=0.12).

Table 3.13. Global Moran's I summary on hospitalization and hospitalization rate among asthma patients

Variable	Cumulative incidence of hospitalizations
Moran's Index	0.065
Z-score	3.29
p-value	0.001
Variable	Annual hospitalization rate
Moran's Index	0.07
Z-score	3.57
p-value	0.0003

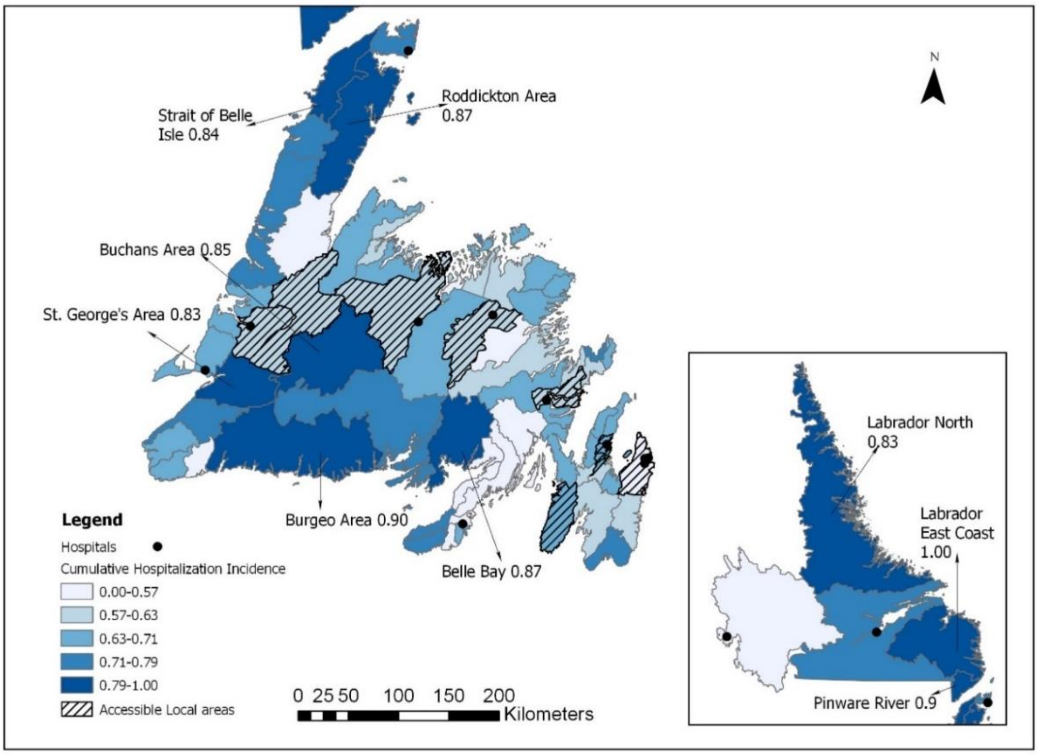

Figure 3.14. Cumulative incidence of hospitalization at the local area level in NL between 1995 and 2014

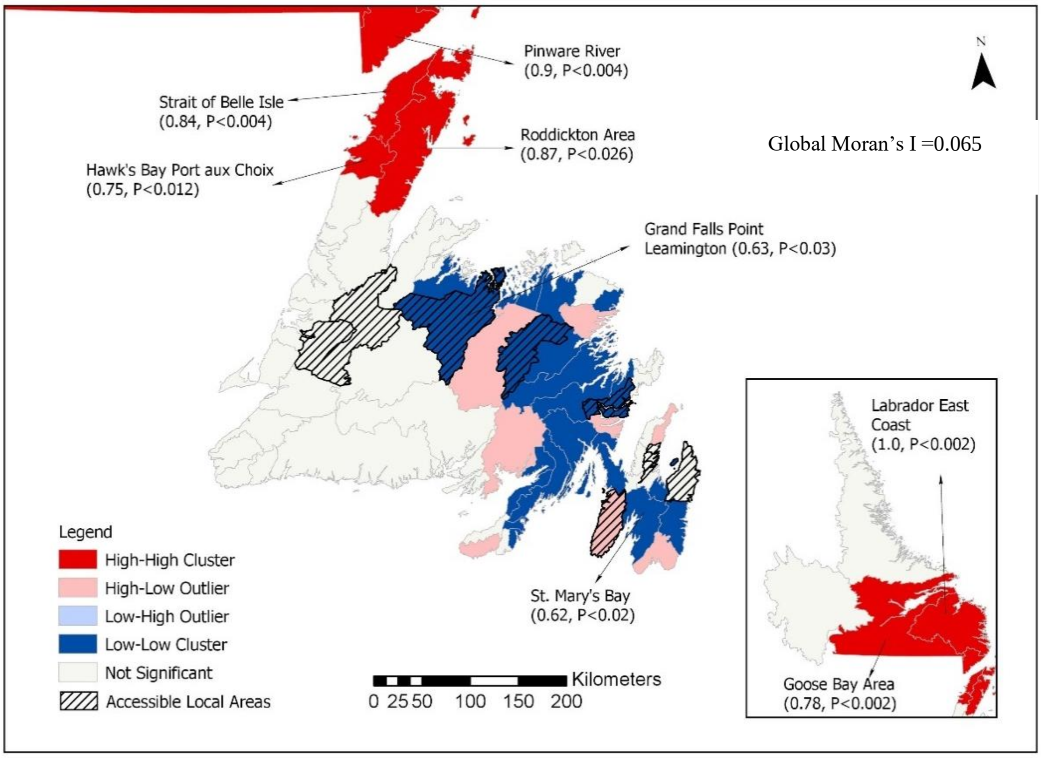

Figure 3.15. Outlier and clusters of cumulative incidence of hospitalization at the local area level

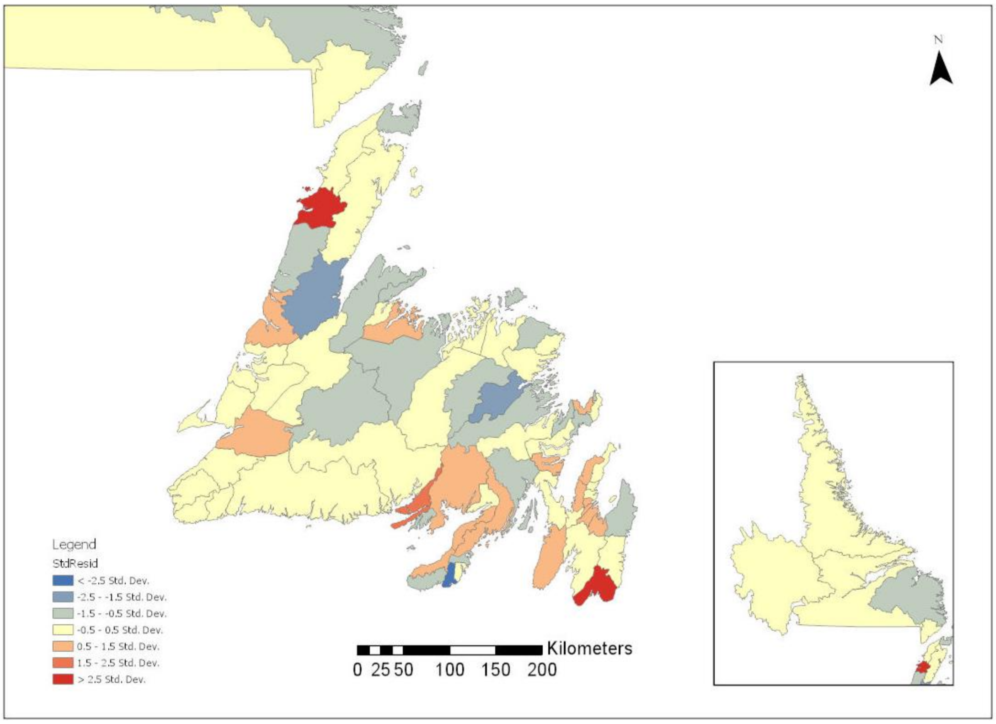

Figure 3.16 Standard residuals of ordinary least square regression- Adjusted hospitalization incidence at the local area level

Distribution of annual hospitalization rate is visualized and presented in figure 3.6. Harbour Breton area (1.2), Burgeo area (1.0), Belle Bay (0.9), Labrador north (0.9), Buchans area (0.8), Labrador east coast (0.8) are among the regions with the highest annual hospitalization rate. All of these regions are located in inaccessible areas. The Global Moran's I test found significant autocorrelation (alpha=0.05) of annual hospitalization rate (Global Moran's I index 0.07, and Z score=3.57, P=0.0003)). According to this index, there is less than 1% chance that this clustered pattern is due to randomness. Anselin Local Moran's I found Hermitage Bay as high-high cluster (P= 0.022, LMI=0.000101). Local Moran's I test also identified low-low clusters statistically significant in eastern and southeastern of NL, as it was shown in figure 3.7.

At the local level, the ordinary least square regression model with average A-R index, average age, and the average number of physician and specialist visits during the study period had the best fit (Adjusted R2 = 0.59). This model shows an increase in average A-R index at the local area level is associated with an increase in average annual hospitalization rate (P<0.001). The visualization of the residuals is presented in figure 3.8, the global Moran's I test of residuals indicated no spatial autocorrelation of residuals (Moran's I= -0.000005, p-value=0.59) and the observed pattern is not significantly different from random.

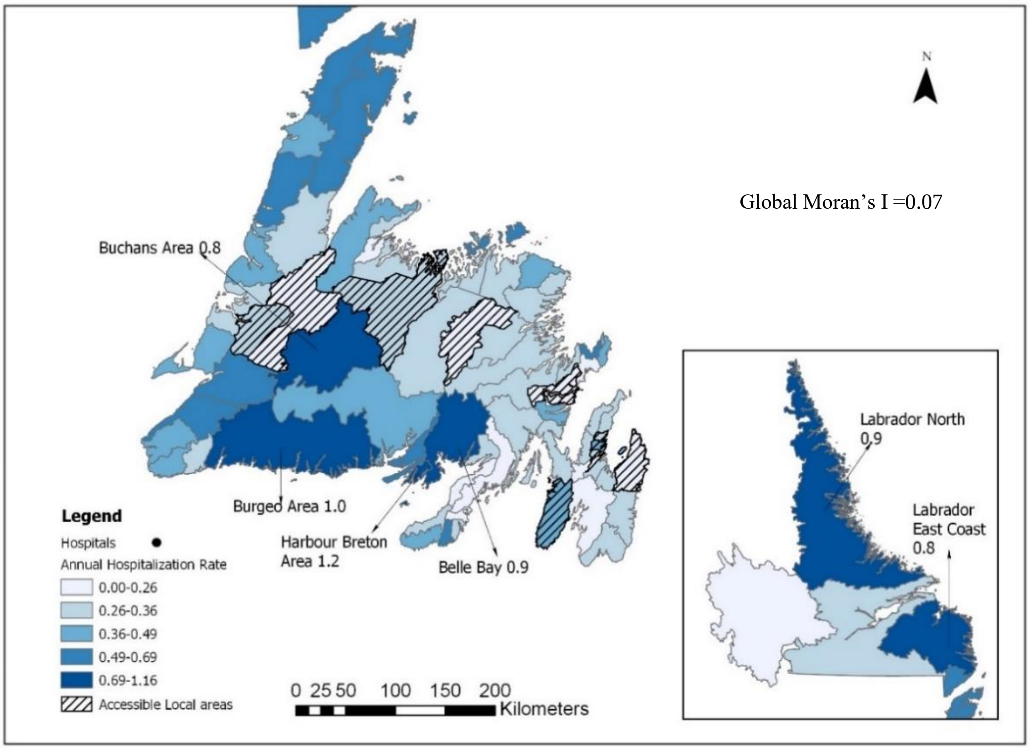

Figure 3.17 Distribution of annual hospitalization rate at the local area level

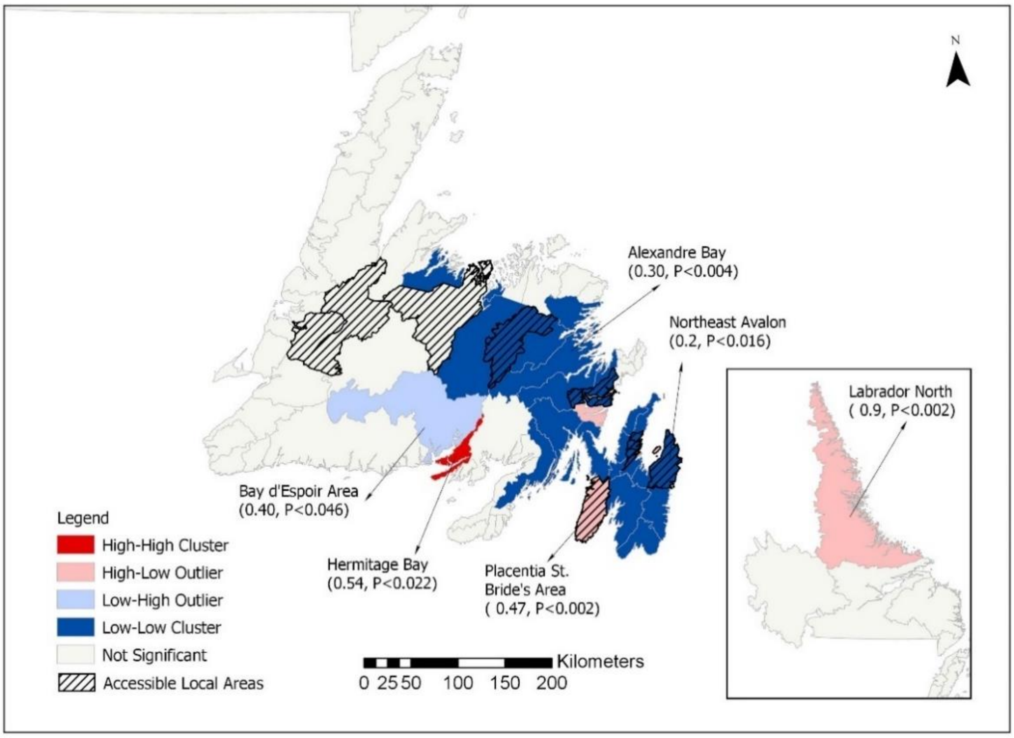

Figure 3.18 Outlier and clusters of the annual hospitalization rate at the local area

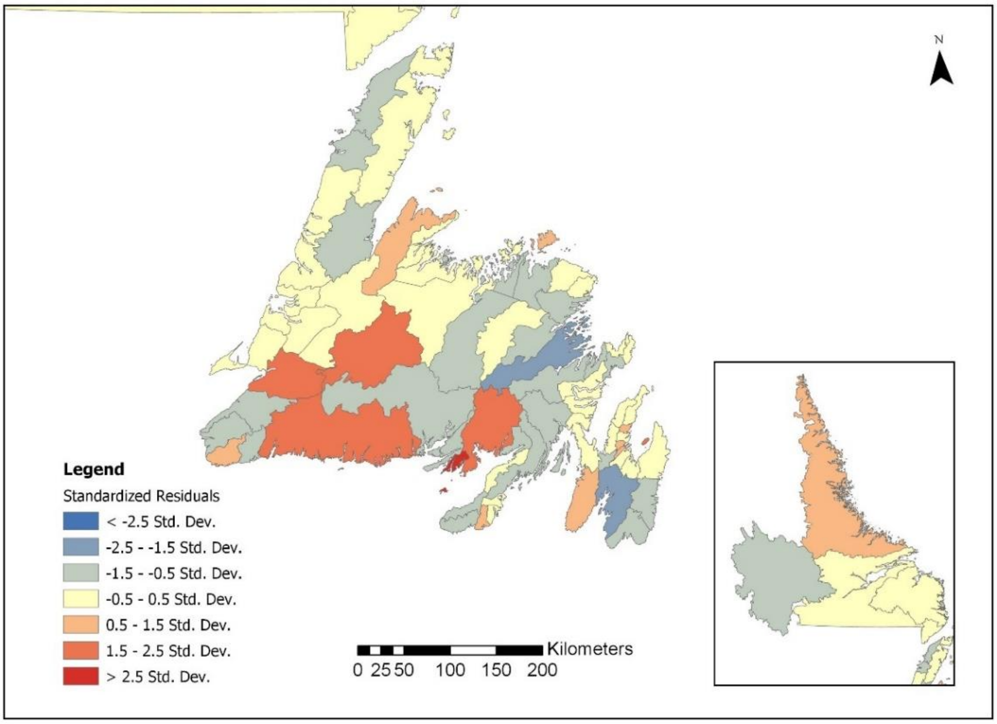

Figure 3.19 Standard residuals of ordinary least square regression – Adjusted annual hospitalization rate at the local area level

3.3.2. Geographic Remoteness and Mortality

3.3.2.1. Individual Level Analysis

The result of the adjusted logistic regression model is presented in table 3.6. Using this model, we controlled for comorbidity, sex, age, number of family medicine and specialist visits during the study period. Overall the results did not show any significant association between A-R index and mortality among asthma patients (OR=3.55, 95% CI; 0.30-32.9, P=0.29).

Table 3.14. Predictors of Mortality at the individual level

Predictor	OR	95% CI	P > z
AR INDEX [a]	**3.55**	**0.30-32.9**	**0.29**
Comorbidity [b, c]			
One	1.51	1.17-1.94	0.001
Two	2.43	1.89-3.14	< 0.001

Three or more	7.63	5.94-9.84	< 0.001
Sex Female	0.67	0.59-0.76	<0.001
Age 30-39 [d, e]	1.67	1.05-2.68	0.03
Age 40-49	4.02	2.64-6.26	< 0.001
Age 50-59	8.71	5.76-1.35	< 0.001
Age 60-69	2.78	1.83-4.29	< 0.001
Age 70-79	9.43	6.19-1.47	< 0.001
Age >=80	5.15	3.26-8.32	< 0.001
Family Medicine visits [f]	0.994	0.993-0.995	< 0.001
Specialist visits [g]	1.002	1.001-1.003	< 0.001
AR INDEX: Comorbidity=1	0.85	0.21-3.39	0.81
AR INDEX: Comorbidity=2	0.32	0.079-1.35	0.12
AR INDEX: Comorbidity>=3	0.23	0.059-0.89	0.03
AR INDEX: Female	0.50	0.24-1.03	0.06
AR INDEX: Age 30-39	1.39	0.009-24.4	0.82
AR INDEX: Age 40-49	1.10	0.024-1.03	0.94
AR INDEX: Age 50-59	0.61	0.05-8079	0.71
AR INDEX: Age 60-69	0.54	0.53-0.04	0.63
AR INDEX: Age 70-79	1.42	0.11-21.00	0.79
AR INDEX: Age >=80	0.64	0.04-11.3	0.76

[a] Accessibility Remoteness index
[b] Number of Comorbidities at the time of diagnosis
[c] Patients with no comorbidities are the reference group.
[d] Age at the time of diagnosis
[e] Age 20-29 class is the reference group.
[f] Number of family medicine visits for the whole study period
[g] Number of specialist visits for the whole study period

3.3.2.2. Spatial Level Analysis

The distribution of mortality among patients living with asthma at the local area level is visualized and presented in figure 3.9. Labrador east coast (1.00) Burgeo area (0.45), and St. George's area (0.45) has the highest mortality among asthma patients, respectively. The Global Moran's I index is 0.006973, and the Z score is 0.98 with the p-value of 0.33 (table 3.7). The results showed no geographic autocorrelation.

Table 3.15. Global Moran's I summary on mortality among asthma patients

Variable	Mortality
Moran's Index	0.006973
Z-score	0.98
p-value	0.33

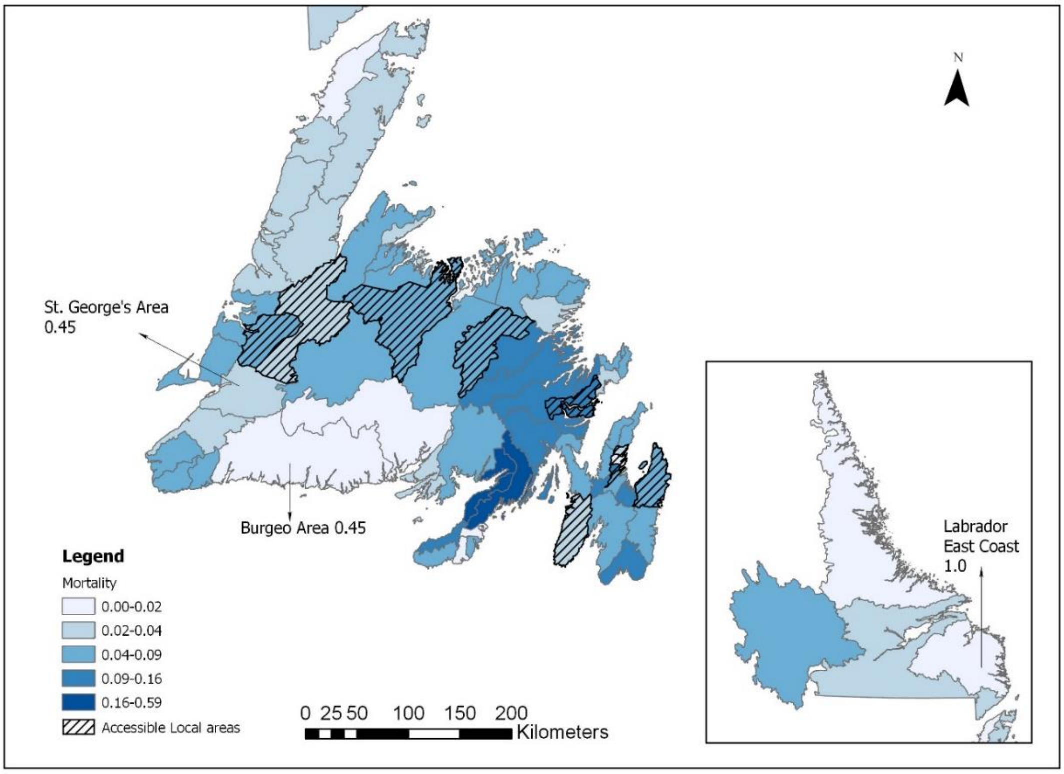

Figure 3. 20. Distribution of mortality at the local area level 1995-2014

3.4. Discussion and Conclusion

3.4.1. Main Findings of the Study

Using population-based data from two decades in NL, we conducted both individual and local area level analyses, we found geographical differences in hospitalization and annual hospitalization rate. No association was observed between the place of residence and mortality of asthma patients.

The findings of this study are in line with some studies in North America [12] [30] [31]. One study in Saskatchewan showed hospitalization rate of asthma patients was higher in rural areas [12]. Another study in Washington, found accessibility to health centres as a contributing factor to lower emergency visits of asthmatic children

[30]. In New South Wales, Australia, hospitalization rate was 51.2-69.1% and mortality rate was 3.62-42.85% higher in the rural areas versus urban areas [31].

We did not find any significant association between place of residence and mortality; however, studies in other provinces of Canada show inaccessibility is associated with higher mortality among asthma patient [12]. The finding of these studies could be affected by the geographic classification of the areas. In our study we used a classification standardized for NL, where we focus on an inaccessible-accessible continuum based on access to goods and services [19]. This index is not representative of the spectrum of geography in other regions. This also may account for the differences between studies

One may say, the observed spatial pattern in hospitalization could be due to many factors including the differences in the healthcare utilization. In our study, using both individual level and local area level analyses, hospitalization was associated with the degree of remoteness even after controlling for the number of visits with physicians and specialists.

Although the cumulative incidence of asthma was higher in more accessible areas, the hospitalization incidence was higher in less accessible areas of NL. The observed difference might be due to many factors including the differences in the availability and delivery of healthcare in these areas. Further study is recommended to identify the underlying causes of this difference.

Although our study shows asthma patients who live in remote and less accessible areas are at higher risk of hospitalization, many important research questions regarding underlying causes remained unanswered. Future studies can address the effects of smoking on the pattern we identified on this study. They could also investigate the health status of the patients and the type of care they received thoroughly.

3.4.2. Limitations

Several limitations might have impacted the results. This study uses secondary dataset, where the quality of data is always under question. We did not have information on the cause of hospital admissions or deaths, nor could we distinguish between unplanned and planned hospitalization. We did not have information on some risk factors which might affect hospitalization and mortality, including smoking and socio-economic factors. A-R index is not based on health-authority's level; therefore, we were not able to perform the analysis at this level. We used medico-administrative data and identified asthma cases using ICD-9 and ICD-10 codes. The results of this study are influenced by the accuracy of case definition algorithms. This is a longitudinal study between 1995 and 2014, we did not account for the evolution of healthcare during this time. To account for this factor, a time series analysis is recommended.

3.4.3. Conclusion

One out of four patients with asthma lives in inaccessible areas in NL. These patients are older and suffer from a higher number of comorbidities. Living in inaccessible areas is associated with higher risk of hospitalization. Identifying communities and regions at higher risk of hospitalization is essential for evidence-informed decision making and to help in resource allocation and disease management.

3.5. References

[1] A. S. Gershon, C. Wang, L. Cicutto, and T. To, “ICES Report: The burden of asthma: Can it be eased?,” *Healthc. Q.*, vol. 10, no. 1, pp. 22–24, Jan. 2007.

[2] A. S. Ismaila, A. P. Sayani, M. Marin, and Z. Su, “Clinical, economic, and humanistic burden of asthma in Canada: a systematic review,” *BMC Pulm. Med.*, vol. 13, no. 1, p. 70, Dec. 2013.

[3] “Statistics Canada,” 2014. [Online]. Available: https://www150.statcan.gc.ca/n1/pub/82-625-x/2015001/article/14179-eng.html. [Accessed: 04-Dec-2018].

[4] K. Bahadori, M.M. Doyle-Waters, C. Marra, L. Lynd, K. Alasaly, J. Swiston, J. M. FitzGerald, “Economic burden of asthma: a systematic review.,” *BMC Pulm. Med.*, vol. 9, p. 24, May 2009.

[5] D. K. Greineder, K. C. Loane, and P. Parks, “Reduction in Resource Utilization by an Asthma Outreach Program,” *Arch. Pediatr. Adolesc. Med.*, vol. 149, no. 4, p. 415, Apr. 1995.

[6] D. R. Terry, H. Nguyen, J. Kim, and M. R. Islam, “Factors contributing to COPD hospitalizations from 2010 to 2015: Variation among rural and metropolitan Australians,” *Clin. Respir. J.*, p. crj.13012, Mar. 2019.

[7] M. D. Eisner, P. P. Katz, E. H. Yelin, S. C. Shiboski, and P. D. Blanc, “Risk factors for hospitalization among adults with asthma: the influence of sociodemographic factors and asthma severity.,” *Respir. Res.*, vol. 2, no. 1, pp. 53–60, 2001.

[8] R. S. Valet, T. T. Perry, and T. V. Hartert, “Rural health disparities in asthma care and outcomes,” *J. Allergy Clin. Immunol.*, vol. 123, no. 6, pp. 1220–1225, Jun. 2009.

[9] A. Senthilselvan, “Trends and rural-urban differences in asthma hospitalizations in Saskatchewan 1970-1989,” *Can. Respir. J.*, vol. 1, no. 4, pp. 229–234, 1994.

[10] Y. Jie, Z. M. Isa, X. Jie, Z. L. Ju, and N. H. Ismail, “Urban vs. rural factors that affect adult asthma,” in *Reviews of environmental contamination and toxicology*, vol. 226, 2013, pp. 33–63.

[11] C. A. Keet, E. C. Matsui, M. C. McCormack, and R. D. Peng, “Urban residence, neighborhood poverty, race/ethnicity, and asthma morbidity among children on Medicaid.,” *J. Allergy Clin. Immunol.*, vol. 140, no. 3, pp. 822–827, Sep. 2017.

[12] A. Jones, G. Bentham, and C. Horwell, “Health service accessibility and deaths from asthma,” *Int. J. Epidemiol.*, vol. 28, no. 1, pp. 101–105, Feb. 1999.

[13] S. J. Teach, M. F. Guagliardo, E. F. Crain, R. J. McCarter, D. M. Quint, C. Shao, J. G. Joseph, “Spatial accessibility of primary care pediatric services in an urban environment: Association with asthma management and outcome,” 2006.

[14] L. Lix and K. Reimer, “The Canadian chronic disease surveillance system: A distributed surveillance model,” *Online J. Public Health Inform.*, vol. 9, no. 1, May 2017.

[15] Newfoundland and Labrador Centre for Health Information, “Clinical Database Management System (CDMS) data users guide v.1.0,” St. John’s, NL, 2014.

[16] Canadian Institute for Health Information, “National physician database data release, 2015-2016,” Ottawa, ON, 2017.

[17] Newfoundland and Labrador Centre for Health Information, “NLCHI mortality system data user guide August 2017 v.1.0,” St. John’s, NL, 2017.

[18] A. S. Gershon, C. Wang, J. Guan, J. Vasilevska-Ristovska, L. Cicutto, and T. To, “Identifying patients with physician-diagnosed asthma in health administrative databases.,” *Can. Respir. J.*, vol. 16, no. 6, pp. 183–8, 2009.

[19] Newfoundland and Labrador Statistics Agency, “Accessibility-Remoteness (A-R) index summary paper,” 2014.

[20] The Canadian Chronic Disease Surveillance System, “Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Canada, 2018,” 2018.

[21] L. Lix, J. Ayles, S. Bartholomew, C. A. Cooke, J. Ellison, V. Emond, N. Hamm, H. Hannah, S. Jean, S. LeBlanc, J. M. Paterson, C. Pelletier, K. Phillips, R. Puchtinger, K. Reimer, C. Robitaille, M. Smith, L. W. Svenson, K. Tu, L.D. VanTil, S. Waits, L. Pelletier, “The Canadian Chronic Disease Surveillance System: A model for collaborative surveillance,” *Int. J. Popul. Data Sci.*, vol. 3, no. 3, Oct. 2018.

[22] O. Hurley, “Health selective migration analysis of diabetes patients living in Newfoundland and Labrador,” Memorial University of Newfoundland, 2014.

[23] N. Alexander, “Can studies where subjects have different follow-up times be analysed through binomial regression?,” *Mem. Inst. Oswaldo Cruz*, vol. 106, no. 5, p. 639; discussion 639, Aug. 2011.

[24] R. H. Gray, M.J. Wawer, R. Brookmeyer, N. K. Sewankambo, F. Wabwire-Mangen, T. Lutalo, X. Li, T. VanCott, T. C. Quinn, Rakai Project team., “Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda,” *Lancet*, vol. 357, no. 9263, pp. 1149–1153, Apr. 2001.

[25] E. Vittinghoff, D. V. Glidden, S. C. Shiboski, and C. E. McCulloch, *Regression Methods in Biostatistics*, Second. Boston: Springer, 2012.

[26] D. Collett, *Modelling Binary Data*. Boston, MA: Springer US, 1991.

[27] A. C. Cameron and P. K. Trivedi, “Regression-based tests for overdispersion in the Poisson model,” *J. Econom.*, vol. 46, no. 3, pp. 347–364, Dec. 1990.

[28] Rs. Team, “RStudio: integrated development for R.” RStudio, Inc, Boston, MA, 2016.

[29] W. Locke, “Review of economic and employment data from the community accounts dataset,” 2016.

[30] J. Corburn, J. Osleeb, and M. Porter, “Urban asthma and the neighbourhood environment in New York City,” *Health Place*, vol. 12, no. 2, pp. 167–179, Jun. 2006.

[31] S. Tong and P. Drake, “Hospital admission and mortality differentials of asthma between urban and rural populations in New South Wales,” *Aust. J. Rural Health*, vol. 7, no. 1, pp. 18–22, Feb. 1999.

Chapter 4. Summary

COPD and asthma are two of most important respiratory chronic diseases. 328 million people deals with COPD in the world [1], and asthma affects about 300 million in the world [2]. COPD and asthma are great burdens for the world. COPD and asthma hospital admissions usually happen following exacerbation. COPD is expected to be the third leading cause of death in the world by 2030 [3]. This thesis focused on the assessment of spatial disparity of chronic respiratory diseases in Newfoundland and Labrador (NL).

Literature shows that differences exist in spatial distribution of hospitalization and mortality of COPD and asthma in various regions of the world. Previous studies mainly focused on rural-urban differences of COPD and asthma. Whereas, our study took a closer look at this disparity by making use of accessibility remoteness index. Understanding geographic differences is required for effective management of the chronic respiratory diseases. Our study focused on Newfoundland and Labrador. To the best of our knowledge this is the first study that assess the association of place of residence and respiratory chronic diseases (i.e. COPD and asthma) outcome in NL. We aimed to determine if asthma and COPD patients who live in the areas with lower accessibility experience higher hospitalization and mortality. We designed a retrospective cohort using medico-administrative data. We conducted our analyses at individual and local area levels. At the individual level we made use of logistic and negative binomial regressions to find the association between accessibility of place of residence and COPD, asthma outcomes. At the local area level, we applied Global and Local Moran's I to find spatial autocorrelation, and we performed ordinary least square regression to analyze the effect of accessibility of place of residence on COPD, and asthma outcomes at the local area level.

Overall 73 192 patients diagnosed with COPD and asthma are identified. 44 876 COPD patients, and 28 316 asthma patients were included. Approximately 43.8% of COPD patients and 37.4% asthma patients live in inaccessible areas. 9 655 patients are diagnosed with both COPD and asthma, 41% of them living in inaccessible areas. The mean age at the time of diagnosis of COPD patients and asthma patients were respectively 63.03 (±14.42), and 47.69 (±17.59).

Our results showed that after adjustment for age, sex, number of comorbidities, number of physician visits and number of specialist visits, living in places with lower accessibility areas significantly increase hospitalization incidence and annual hospitalization rate for both COPD and asthma patients. Higher likelihood of hospitalization was observed in both COPD (OR=2.57, 95% CI 1.54-4.25, P value=0.00136) and asthma patients (OR=12.38, 95% CI:6.28-24.46, P<0.001) who live in remote and inaccessible areas. COPD (RR=5.05, 95% CI:3.00-8.51, P value<0.001) and asthma patients (RR=4.74, 95% CI:3.10-7.25, P<0.001) from the areas with lower accessibility experience higher annual hospitalization rate.

Nearly 41.1% of COPD patients, and 18.2% of asthma patients died during the study period. Mortality among COPD patients and asthma patients were 5.1, and 1.6 per 100 person-year respectively. The results of our study showed COPD patients from remote and inaccessible areas were more likely to pass away (OR=10.73, 95% CI; 2.27-44.77, P=0.002). We did not find any association between mortality of asthma patients, and accessibility of place of residence (OR=3.55, 95% CI; 0.30-32.9, P=0.29).

At the local area level, we found COPD hospitalization (Moran-Index=0.034, $p<0.03$), COPD annual hospitalization rate and COPD mortality (Moran-Index I=0.047, $p<0.011$) to be spatially autocorrelated. We found spatial autocorrelation for the hospitalization (Moran-Index=0.065,$p<0.001$), and annual hospitalization rate of asthma patients (Moran-Index=0.07,$p<0.001$), but not mortality (Moran-Index=0.006973, $p=0.33$).

Using the ordinary least square regression at the local area level, we observed a significant association between accessibility of place of residence and cumulative hospitalization incidence ($P<0.001$), annual hospitalization rate ($p<0.05$), and mortality ($p=0.002$) of COPD patients. The association was also observed in cumulative hospitalization incidence ($P<0.001$), and annual hospitalization rate ($P<0.001$) of asthma patients.

Our results are in line with previous studies on hospitalization and mortality of chronic respiratory disease patients in relation to geography. For example, one study in Australia identified higher hospitalization of COPD patients in rural areas in comparison with the urban areas. A significant association was also observed between the degree of remoteness and hospitalization [4]. In the United States, COPD patients from rural and isolated areas were at higher risk of exacerbation and mortality [5]. Asthma patients in rural areas of Saskatchewan had higher hospitalization rates [6]. No association of accessibility of place of residence and mortality of asthma patients was observed in our study. However, in Australia, they found that asthma patients who have lower accessibility to the health centres experience higher mortality rates [7].

One out of three asthma patients and two out of five COPD patients in Newfoundland and Labrador live in rural areas. The results of our study indicate that asthma and COPD patients living in inaccessible areas are at higher risk of hospitalization and mortality. Identifying the regions at higher risk is necessary in order to enhance healthcare services and disease management for patients. Further studies are recommended to discover the underlying factors of these differences.

4.1. References

[1] N. Aït-Khaled, D. Enarson, and J. Bousquet, "Chronic respiratory diseases in developing countries: the burden and strategies for prevention and management," *Bull. World Health Organ.*, vol. 79, pp. 971–979, 2001.

[2] R. H. Dougherty and J. V Fahy, "Acute exacerbations of asthma: epidemiology, biology and the exacerbation-prone phenotype.," *Clin. Exp. Allergy*, vol. 39, no. 2, pp. 193–202, Feb. 2009.

[3] World Health Organization, "Global status report on noncommunicable diseases 2010," Geneva, 2011.

[4] Z. Ansari, D. Dunt, and S. C. Dharmage, "Variations in hospitalizations for chronic obstructive pulmonary disease in rural and urban Victoria, Australia.," *Respirology*, vol. 12, no. 6, pp. 874–80, 2007.

[5] T. E. Abrams, M. Vaughan-Sarrazin, V. S. Fan, and P. J. Kaboli, "Geographic isolation and the risk for chronic obstructive pulmonary Disease–related mortality," *Ann. Intern. Med.*, vol. 155, no. 2, p. 80, Jul. 2011.

[6] A. Senthilselvan, "Trends and rural-urban differences in asthma hospitalizations in Saskatchewan 1970-1989," *Can. Respir. J.*, vol. 1, no. 4, pp. 229–234, 1994.

[7] S. Tong and P. Drake, "Hospital admission and mortality differentials of asthma between urban and rural populations in New South Wales," *Aust. J. Rural Health*, vol. 7, no. 1, pp. 18–22, Feb. 1999.

Chapter 5: Overall Thesis References (Alphabetical)

1. A. Anzueto, S. Sethi, and F. J. Martinez, “Exacerbations of Chronic Obstructive Pulmonary Disease,” *Proc. Am. Thorac. Soc.*, vol. 4, no. 7, pp. 554–564, 2007.

2. A. C. Cameron and P. K. Trivedi, “Regression-based tests for overdispersion in the Poisson model,” *J. Econom.*, vol. 46, no. 3, pp. 347–364, Dec. 1990.

3. A. Feely, L. M. Lix, and K. Reimer, “Estimating multimorbidity prevalence with the Canadian Chronic Disease Surveillance System.,” *Heal. Promot. chronic Dis. Prev. Canada Res. policy Pract.*, vol. 37, no. 7, pp. 215–222, Jul. 2017.

4. A. G. Chuchalin, N. Khaltaev, N. S. Antonov, D.V. Galkin, L. G. Manakov, P. Antonini, M. Murphy, A. G. Solodovnikov, J. Bousquet, M. H. Pereira, I. V. Demko., “Chronic respiratory diseases and risk factors in 12 regions of the Russian Federation,” *Int. J. Chron. Obstruct. Pulmon. Dis.*, vol. 9, pp. 963–974, 2014.

5. A. Jones, G. Bentham, and C. Horwell, “Health service accessibility and deaths from asthma,” *Int. J. Epidemiol.*, vol. 28, no. 1, pp. 101–105, Feb. 1999.

6. A. Senthilselvan, “Trends and rural-urban differences in asthma hospitalizations in Saskatchewan 1970-1989,” *Can. Respir. J.*, vol. 1, no. 4, pp. 229–234, 1994.

7. A. S. Gershon, C. Wang, J. Guan, J. Vasilevska-Ristovska, L. Cicutto, and T. To, “Identifying individuals with physcian diagnosed COPD in health administrative databases.,” *COPD*, vol. 6, no. 5, pp. 388–94, Oct. 2009.

8. A. S. Gershon, C. Wang, J. Guan, J. Vasilevska-Ristovska, L. Cicutto, and T. To, “Identifying patients with physician-diagnosed asthma in health administrative databases.,” *Can. Respir. J.*, vol. 16, no. 6, pp. 183–8, 2009.

9. A. S. Gershon, C. Wang, L. Cicutto, and T. To, “ICES Report: The burden of asthma: Can it be eased?,” *Healthc. Q.*, vol. 10, no. 1, pp. 22–24, Jan. 2007.

20. A. S. Ismaila, A. P. Sayani, M. Marin, and Z. Su, “Clinical, economic, and humanistic burden of asthma in Canada: a systematic review,” *BMC Pulm. Med.*, vol. 13, no. 1, p. 70, Dec. 2013.

11. B. Lundbäck, H. Backman, J. Lötvall, and E. Rönmark, “Is asthma prevalence still increasing?,” *Expert Rev. Respir. Med.*, vol. 10, no. 1, pp. 39–51, Jan. 2016.

12. C. A. Keet, E. C. Matsui, M. C. McCormack, and R. D. Peng, “Urban residence, neighborhood poverty, race/ethnicity, and asthma morbidity among children on Medicaid.,” *J. Allergy Clin. Immunol.*, vol. 140, no. 3, pp. 822–827, Sep. 2017.

13. Canadian Institute for Health Information, “COPD in Alberta: examining the characteristics and health care use of high users,” Ottawa, ON, 2017.

14. Canadian Institute for Health Information, “Inpatient Hospitalizations, Surgeries and Childbirth Indicat,” Ottawa, 2015.

15. Canadian Institute for Health Information, “National physician database data release, 2015-2016,” Ottawa, ON, 2017.

16. D. Collett, *Modelling Binary Data*. Boston, MA: Springer US, 1991.

17. D. K. Greineder, K. C. Loane, and P. Parks, “Reduction in Resource Utilization by an Asthma Outreach Program,” *Arch. Pediatr. Adolesc. Med.*, vol. 149, no. 4, p. 415, Apr. 1995.

18. D. J. Jackson, A. Sykes, P. Mallia, and S. L. Johnston, “Asthma exacerbations: Origin, effect, and prevention,” *J. Allergy Clin. Immunol.*, vol. 128, no. 6, pp. 1165–1174, Dec. 2011.

19. D. J. Maselli and A. Anzueto, “The need to further understand who gets

hospitalized for a COPD exacerbation," *Multidiscip. Respir. Med.*, vol. 7, no. 1, p. 7, Dec. 2012.

20. D. M. Mannino, "COPD: Epidemiology, prevalence, morbidity and mortality, and disease heterogeneity," *Chest*, vol. 121, no. 5, p. 121S–126S, May 2002.

21. D. R. Terry, H. Nguyen, J. Kim, and M. R. Islam, "Factors contributing to COPD hospitalisations from 2010 to 2015: Variation among rural and metropolitan Australians," *Clin. Respir. J.*, p. crj.13012, Mar. 2019.

22. E. Vittinghoff, D. V. Glidden, S. C. Shiboski, and C. E. McCulloch, *Regression Methods in Biostatistics*, Second. Boston: Springer, 2012.

23. G. Morosco and J. Kiley, "Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma," Nov. 2007

24. H. Müllerova, D. J. Maselli, N. Locantore, J. Vestbo, J. R. Hurst, J. A. Wedzicha, P. Bakke, A. Agusti, A. Anzueto, "Hospitalized exacerbations of COPD: Risk Factors and outcomes in the ECLIPSE cohort," *Chest*, vol. 147, no. 4, pp. 999–1007, Apr. 2015.

25. I. Asher and N. Pearce, "Global burden of asthma among children.," *Int. J. Tuberc. Lung Dis.*, vol. 18, no. 11, pp. 1269–78, 2014.

26. J. Bousquet, R. Dahl, and N. Khaltaev, "Global alliance against chronic respiratory diseases," *Allergy*, vol. 62, no. 3, pp. 216–223, Feb. 2007.

27. J. Corburn, J. Osleeb, and M. Porter, "Urban asthma and the neighbourhood environment in New York City," *Health Place*, vol. 12, no. 2, pp. 167–179, Jun. 2006.

28. J. Loscalzo, A. S. Fauci, S. L. Hauser, J. L. Jameson; D. L. Kasper; D L Longo, *Harrison's principles of internal medicine*. McGraw-Hill Education, 2017.

29. K. Bahadori, M.M. Doyle-Waters, C. Marra, L. Lynd, K. Alasaly, J. Swiston, J.

M. FitzGerald, “Economic burden of asthma: a systematic review,” *BMC Pulm. Med.*, vol. 9, no. 1, p. 24, Dec. 2009.

30. L. A. Mandell, R. G. Wunderink, A. Anzueto, J. G. Bartlett, G. D. Campbell, N. C. Dean, SF. Dowell, T. M. File, D. M. Musher, M. S. Niederman, A. Torres, C. G. Whitney, “Infectious diseases society of America/American thoracic society consensus guidelines on the management of community-acquired pneumonia in adults,” *Clin. Infect. Dis.*, vol. 44, no. Supplement_2, pp. S27–S72, Mar. 2007.

31. L. G. Hart, E. H. Larson, and D. M. Lishner, “Rural definitions for health policy and research.,” *Am. J. Public Health*, vol. 95, no. 7, pp. 1149–55, Jul. 2005.

32. L. Lix and K. Reimer, “The Canadian chronic disease surveillance system: A distributed surveillance model,” *Online J. Public Health Inform.*, vol. 9, no. 1, May 2017.

33. L. Lix, J. Ayles, S. Bartholomew, C. A. Cooke, J. Ellison, V. Emond, N. Hamm, H. Hannah, S. Jean, S. LeBlanc, J. M. Paterson, C. Pelletier, K. Phillips, R. Puchtinger, K. Reimer, C. Robitaille, M. Smith, L. W. Svenson, K. Tu, L.D. VanTil, S. Waits, L. Pelletier, “The Canadian Chronic Disease Surveillance System: A model for collaborative surveillance, “The Canadian Chronic Disease Surveillance System: A model forcollaborative surveillance,” *Int. J. Popul. Data Sci.*, vol. 3, no. 3, Oct. 2018.

34. L. M. Sibley and J. P. Weiner, “An evaluation of access to health care services along the rural-urban continuum in Canada,” *BMC Health Serv. Res.*, vol. 11, no. 1, p. 20, Dec. 2011.

35. L. Schirnhofer, B. Lamprecht, W. M. Vollmer, M. J. Allison, M. Studnicka, R. L. Jensen, A. S. Buist.., “COPD prevalence in Salzburg, Austria,” *Chest*, vol. 131, no. 1,

pp. 29–36, Jan. 2007.

36. M. D. Eisner, P. P. Katz, E. H. Yelin, S. C. Shiboski, and P. D. Blanc, “Risk factors for hospitalization among adults with asthma: the influence of sociodemographic factors and asthma severity.,” *Respir. Res.*, vol. 2, no. 1, pp. 53–60, 2001.

37. N. Aït-Khaled, D. Enarson, and J. Bousquet, “Chronic respiratory diseases in developing countries: the burden and strategies for prevention and management,” *Bull. World Health Organ.*, vol. 79, pp. 971–979, 2001.

38. N. Alexander, “Can studies where subjects have different follow-up times be analysed through binomial regression?,” *Mem. Inst. Oswaldo Cruz*, vol. 106, no. 5, p. 639; discussion 639, Aug. 2011.

39. Newfoundland and Labrador Centre for Health Information, “Clinical Database Management System (CDMS) data users guide v.1.0,” St. John’s, NL, 2014.

40. Newfoundland and Labrador Centre for Health Information, “NLCHI mortality system data user guide August 2017 v.1.0,” St. John’s, NL, 2017.

41. Newfoundland and Labrador Statistics Agency, “Accessibility-Remoteness (A-R) index summary paper,” 2014.

42. O. Hurley, “Health selective migration analysis of diabetes patients living in Newfoundland and Labrador,” Memorial University of Newfoundland, 2014.

43. P. Burney, D. Jarvis, and R. Perez-Padilla, “The global burden of chronic respiratory disease in adults,” *Int. J. Tuberc. Lung Dis.*, vol. 19, no. 1, pp. 10–20, Jan. 2015.

44. R. A. Pauwels, *K. F. Rabe.*, “Burden and clinical features of chronic obstructive pulmonary disease (COPD).,” *Lancet (London, England)*, vol. 364, no. 9434, pp. 613–

20, 2002.

45. R. H. Dougherty and J. V Fahy, “Acute exacerbations of asthma: epidemiology, biology and the exacerbation-prone phenotype.,” *Clin. Exp. Allergy*, vol. 39, no. 2, pp. 193–202, Feb. 2009.

46. R. H. Gray M.J. Wawer, R. Brookmeyer, N. K. Sewankambo, F. Wabwire-Mangen, T. Lutalo, X. Li, T. VanCott, T. C. Quinn, Rakai Project team., “Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda,” *Lancet*, vol. 357, no. 9263, pp. 1149–1153, Apr. 2001.

47. R. J. Milne and R. Beasley, “Hospital admissions for chronic obstructive pulmonary disease in New Zealand.,” *N. Z. Med. J.*, vol. 128, no. 1408, pp. 23–35, Jan. 2015.

48. Rs. Team, “RStudio: integrated development for R.” RStudio, Inc, Boston, MA, 2016.

49. R. S. Valet, T. T. Perry, and T. V. Hartert, “Rural health disparities in asthma care and outcomes,” *J. Allergy Clin. Immunol.*, vol. 123, no. 6, pp. 1220–1225, Jun. 2009.

50. R. W. Pong, M. DesMeules, and C. Lagacé, “Rural-urban disparities in health: How does Canada fare and how does Canada compare with Australia?,” *Aust. J. Rural Health*, vol. 17, no. 1, pp. 58–64, Feb. 2009.

51. S. J. Teach, M. F. Guagliardo, E. F. Crain, R. J. McCarter, D. M. Quint, C. Shao, J. G. Joseph, “Spatial accessibility of primary care pediatric services in an urban environment: Association with asthma management and outcome,” 2006.

52. “Statistics Canada,” 2014. [Online]. Available: https://www150.statcan.gc.ca/n1/pub/82-625-x/2015001/article/14179-eng.html. [Accessed: 04-Dec-2018].

53. S. Tong and P. Drake, “Hospital admission and mortality differentials of asthma between urban and rural populations in New South Wales,” *Aust. J. Rural Health*, vol. 7, no. 1, pp. 18–22, Feb. 1999.

54. T. Dang-Tan, S. Zhang, R. V. Tavares, M. Stutz, A. S. Ismaila, J. Vaillancourt, D. Corriveau, R. H. Stanford, X. Lin, G. A. Nadeau, A. Simidchiev, D. Parsons, and J. S. Sampalis, “The burden of illness related to chronic obstructive pulmonary disease exacerbations in Québec, Canada,” *Can. Respir. J.*, vol. 2017, pp. 1–10, Jun. 2017.

55. T. E. Abrams, M. Vaughan-Sarrazin, V. S. Fan, and P. J. Kaboli, “Geographic isolation and the risk for chronic obstructive pulmonary disease–related mortality,” *Ann. Intern. Med.*, vol. 155, no. 2, p. 80, Jul. 2011.

56. The Canadian Chronic Disease Surveillance System, “Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Canada, 2018,” 2018.

57. W. C. Moore, E. R. Bleecker, D. Curran-Everett, S. C. Erzurum, B. T. Ameredes, L. Bacharier, W. J. Calhoun, M. Castro, K. F. Chung, M. P. Clark, R. A. Dweik, A. M. Fitzpatrick, B. Gaston, M. Hew, I. Hussain, N. N. Jarjour, E. Israel, B. D. Levy, J. R. Murphy, S. P. Peters, W. G. Teague, D. A. Meyers, W. W. Busse, S. E. Wenzel., “Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute’s Severe Asthma Research Program,” *J. Allergy Clin. Immunol.*, vol. 119, no. 2, pp. 405–413, Feb. 2007.

58. W. Locke, “Review of economic and employment data from the community accounts dataset,” 2016.

59. World Health Organization, “Global surveillance, prevention and control of chronic respiratory diseases, a comprehensive approach,” 2007.

60. World Health Organization, “Global status report on noncommunicable diseases

2010," Geneva, 2011.

61. Y. Jie, Z. M. Isa, X. Jie, Z. L. Ju, and N. H. Ismail, "Urban vs. rural factors that affect adult asthma," in *Reviews of environmental contamination and toxicology*, vol. 226, 2013, pp. 33–63.

62. Z. Ansari, D. Dunt, and S. C. Dharmage, "Variations in hospitalizations for chronic obstructive pulmonary disease in rural and urban Victoria, Australia.," *Respirology*, vol. 12, no. 6, pp. 874–80, 2007.

Appendix

Table A1- Cumulative Hospitalization Incidence of COPD Patients

Local areas	Cumulative Hospitalization Incidence
Isthmus of Avalon	0.72
Placentia-St. Bride's Area	0.81
Heart's Delight Area	0.70
New Perlican-Winterton Area	0.77
North Shore of Conception Bay	0.78
Carbonear Area	0.70
Harbour Grace Area	0.74
Spaniard's Bay Area	0.69
Bay Roberts Area	0.62
Clarke's Beach Area	0.68
Head of Conception Bay	0.72
Bell Island	0.76
Southern Shore	0.70
Trepassey Bay	0.72
St. Mary's Bay	0.74
Whitbourne Area	0.69
Northeast Avalon	0.68
Placentia Bay West Centre	0.72
St. Lawrence Area	0.80
Lamaline Area	0.73
Fortune-Grand Bank Area	0.84
Bay L'Argent Area	0.73
Terrenceville Area	0.90
Placentia Bay North West	0.78
Belle Bay	0.91
Harbour Breton Area	0.92
Hermitage Bay	0.84
Burgeo Area	0.69
Port aux Basques Area	0.75
Rose Blanche Area	0.77
Codroy Valley	0.73
Crabbes River	0.82
St. George's Area	0.85
Stephenville-Port au Port Peninsula	0.80
Deer Lake-Cormack Area	0.76
Corner Brook-Pasadena Area	0.72
Bay of Islands	0.71
Jackson's Arm Area	0.83
Grand Falls-Point Leamington Area	0.72
Gander Area	0.73

Wesleyville Area	0.77
Greenspond Area	0.76
Alexander Bay	0.86
Chandlers Reach	0.76
Southern Bay Area	0.77
Catalina Area	0.78
Trinity, Trinity Bay Area	0.79
Smith Sound-Random Island	0.78
South West Arm Area	0.85
Gambo Area	0.84
White Bay South	0.75
Halls Bay	0.72
Pilley's Island Area	0.61
New World Island	0.80
Twillingate Island	0.89
Hamilton Sound	0.75
Straight Shore	0.80
Fogo and Change Islands	0.79
Burlington Area	0.75
King's Point Area	0.65
Bonne Bay Area	0.79
Strait of Belle Isle	0.86
Quirpon-Cook's Harbour Area	0.89
Norris Arm Area	0.70
Roddickton Area	0.90
Hawke's Bay-Port au Choix Area	0.73
Daniel's Harbour Area	0.77
Pinware River	0.96
Goose Bay Area	0.87
Labrador West	0.67
Labrador North	0.98
Buchans Area	0.81
Bay d'Espoir Area	0.80
Lewisporte Area	0.52
Notre Dame Bay South	0.61
Burin Area	0.74
Mortier Bay	0.75
Black Head Bay	0.83
Bonavista Area	0.86
Labrador East Coast	------[a]

[a] The areas with patients less than 5 are filtered.

Table A1- Cumulative Hospitalization Incidence of COPD Patients

Local areas	Cumulative Hospitalization Incidence
Isthmus of Avalon	64.36
Placentia-St. Bride's Area	70.19
Heart's Delight Area	66.10
New Perlican-Winterton Area	65.87
North Shore of Conception Bay	68.12
Carbonear Area	67.29
Harbour Grace Area	68.24
Spaniard's Bay Area	68.99
Bay Roberts Area	64.16
Clarke's Beach Area	63.41
Head of Conception Bay	65.94
Bell Island	67.19
Southern Shore	59.91
Trepassey Bay	76.32
St. Mary's Bay	62.10
Whitbourne Area	59.82
Northeast Avalon	55.66
Placentia Bay West Centre	55.07
St. Lawrence Area	------------- [a]
Lamaline Area	79.37
Fortune-Grand Bank Area	72.08
Bay L'Argent Area	55.98
Terrenceville Area	51.37
Placentia Bay North West	53.16
Belle Bay	86.79
Harbour Breton Area	71.74
Hermitage Bay	75
Burgeo Area	90.91
Port aux Basques Area	66.91
Rose Blanche Area	50
Codroy Valley	64.56
Crabbes River	76.47
St. George's Area	82.35
Stephenville-Port au Port Peninsula	70.37
Deer Lake-Cormack Area	62.03
Corner Brook-Pasadena Area	59.75
Bay of Islands	65.90
Jackson's Arm Area	55
Grand Falls-Point Leamington Area	62.89
Gander Area	57.61
Wesleyville Area	66.90
Greenspond Area	69.41
Alexander Bay	57.92

Chandlers Reach	65.28
Southern Bay Area	60.26
Catalina Area	65.62
Trinity, Trinity Bay Area	61.29
Smith Sound-Random Island	60
South West Arm Area	70
Gambo Area	52.38
White Bay South	64.29
Halls Bay	65.32
Pilley's Island Area	62.16
New World Island	70.67
Twillingate Island	72.73
Hamilton Sound	57.31
Straight Shore	65.59
Fogo and Change Islands	64.62
Burlington Area	62.86
King's Point Area	58.34
Bonne Bay Area	74.29
Strait of Belle Isle	83.88
Quirpon-Cook's Harbour Area	75.90
Norris Arm Area	69.05
Roddickton Area	88.89
Hawke's Bay-Port au Choix Area	75.38
Daniel's Harbour Area	72.55
Pinware River	90.62
Labrador East Coast	------------- [a]
Goose Bay Area	77.95
Labrador West	56.40
Labrador North	82.35
Buchans Area	85.42
Bay d'Espoir Area	73.34
Lewisporte Area	56.92
Notre Dame Bay South	59.70
Burin Area	65.80
Mortier Bay	52.63
Black Head Bay	73.08
Bonavista Area	67.54

[a] The areas with patients less than 5 are filtered.