Rural – Urban Disparities in Diabetes Diagnosis and Outcomes in Newfoundland and Labrador

By

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ABSTRACT

Newfoundland and Labrador (NL) has the highest prevalence of type 2 diabetes in Canada. Rural populations often lack adequate access to primary care services, which are critical for providing quality diabetes care. To assess diabetes diagnosis and outcomes among rural and urban populations, a population-based, retrospective cohort study of residents NL, Canada, with diagnosed diabetes aged $\geq$ 20 years old, was performed using an administrative database. The study population included was 17,796 subjects. Diabetes was classified as a complex case if comorbidities were already present at diagnosis. The provincial mortality database was used to determine mortality. The presence of complications/comorbidities was derived from patient billing data collected by the provincial medical care plan during the study period. Patients were geo-referenced using 6 digit postal code. Different levels of analysis were performed. Individual level analysis, including bivariate and multivariate analyses using STATA. Geospatial analysis inclduing visualization and community level analysis using ArcMap-GIS 10.2.. The individual-level model showed that complex cases (OR: 1.23, 95% CI: 1.19-1.28) and mortality (OR: 1.11, 95%CI: 1.07-1.16) were more likely in rural areas. The community-level model found that complex cases were more likely in rural areas (b=18.09, p< .0.05), while no relation was found between mortality and living in remote areas (b=3.53, p= 0.531). This project identified higher prevalence of complex cases in rural areas. This study suggests geographic differences should be taken into account for making better health-related decisions in diabetes care and management.

Keywords: Spatial Epidemiology, Geography, Diabetes, Newfoundland and Labrador, Remoteness, Accessibility, Rurality, Mortality, Morbidity, Healthcare Utilization.

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List of Abbreviations

DM: Diabetes Mellitus

T2 DM: Type 2 Diabetes Mellitus

CVD: Cardiovascular Disease

RF: Renal Failure

CDA: The Canadian Diabetes Association

NDSS: National Diabetes Surveillance System

NL: Newfoundland and Labrador

GP: General Practitioner

FM: Family Physician

SP: Specialist

HCF: Healthcare Facility

MCP: Medicare Plan

NLCHI: Newfoundland and Labrador Center for Health Information

A-R Index: Accessibility Remoteness Index

CCDSS: Canadian Chronic Disease Survillence System

ADA: American Diabetes Association

AD: Alzheimer's disease

WHO: World Health Organization

CDS: The Canadian Diabetes Strategy

NLSA: Newfoundland and Labrador Statistics Agency

CDMS: Clinical Database Management System

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CHAPTER 1: INTRODUCTION

1.1 What Is Diabetes?

Diabetes Mellitus (DM), is among the most common, costly, and preventable chronic diseases, results from either the cells of our body being unable to generate enough insulin or cannot use insulin efficiently[1]. A person with diabetes does not move glucose into the cells properly, which leads to its circulating in the blood causing damaging body tissues over time, resulting in disabling and life-threatening health complications[1].

Type 2-diabetes (T2 DM) is the most common type of diabetes in adult populations[2.] The number of patients living with type 2 diabetes mellitus is rapidly increasing worldwide. This increase may be due to economic expansion, age, dietetic changes, reduced physical activity, and other changes in lifestyle[2].

1.2 Diabetes Complications

The most severe issue related to type 2 diabetes is that many people remain unaware of their illness for a long time. This lack of awareness usually happens because it may take year for diabetic symptoms to appear or for the condition to be diagnosed, during this time excess blood sugar may be damaging the body. Diabetic patients usually are diagnosed when complications from diabetes have already developed[3]. Diabetes is a leading cause of several serious complications and comorbidities such as cardiovascular disease, blindness; kidney failure (RF), and lower-limb amputation or developing infections. There are two kinds of diabetic injurious: macrovascular comorbidites (coronary artery disease, peripheral arterial disease and stroke) and microvascular comorbidities (diabetic nephropathy, neuropathy and retinopathy) [2, 3].

1.2.1 Microvascular Complications of Diabetes

Diabetic retinopathy can be considered one of the most common microvascular complications of diabetes that may develop as much as seven years before the diagnosis of T2 DM[4, 5]. It is the reason for almost 10,000 new cases of blindness every year, in the United States alone[4].

Diabetic nephropathy is considered one of the main causes of renal failure. The previous studies showed that 7% of patients with type 2-diabetes might already have microalbuminuria, a marker for kidney disease, at the time of diagnosis with diabetes[4, 5].

Diabetic neuropathy is recognized by the American Diabetes Association (ADA) as "the presence of symptoms and signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes."[4].

Diabetic foot: diabetic patients may develop damage to nerves and blood vessels, which lead to some different foot problems. These problems result in infection and ulceration, which increase a person's risk of amputation[4, 6].

Alzheimer's disease: New research defined a direct relationship between sugar imbalance and Alzheimer's disease (AD) [7,8,9]. Type 2-diabetes doubled the risk of a patient having dementia and patients on insulin had four times the risk[9,10,11]. A study by

Hisayama in 1995[8] found that the relative risk (RR) of Alzheimer's disease in diabetic patients was 2.18 (95%CI: 1.97-4.9) and 2.77 of vascular dementia (95%CI: 2.59-2.97)[8]. An advanced study from the same study group (2011) showed that the RR of Alzheimer's disease was 2.05 (95%CI: 1.18-3.57) in diabetic patients and 1.82 for vascular dementia (95%CI: 1.89-3.71)[9]. The Rochester study in 1997[10] reported differences in the risk of Alzheimer's disease based on gender. This study found that the RR for AD was 2.27 for men (95%CI: 1.55-3.31) and 1.37 for women (95%CI: 1.94-2.01)[10]. The study by Rotterdam in 1999 showed that the RR for Alzheimer's disease was 1.9(95%CI: 1.2-3.1) in diabetic patients [11.] Since type 2-diabetes is still under-diagnosed and AD may be associated with hyperglycemia, so more attention should be drawn to early diagnosis of diabetes[7,8,9,10,11].

1.2.2 Macrovascular Complications of Diabetes

Cardiovascular disease: Diabetes increases the risk of cardiovascular disease (CVD), which is the leading cause of mortality in people with either type 1 or type 2-diabetes[4]. Diabetes is also strong independent risk factor for developing stroke and cerebrovascular disease, increasing risk by 150–400%[4].

1.3 The Global Burden of Disease

The world became the center of an epidemic of diabetes, which can produce an intolerable burden on quality of life worldwide and affect the health care system if unchecked will over the succeeding generation[5]. All types of diabetes are rapidly increasing particularly type 2 diabetes[5]. According to the findings of the International

Diabetes Federation, it is estimated that 382 million people worldwide (or 8.3% of adults) have diabetes[5,6]. About 80% of these diabetic patients live in low- and middle-income countries[5]. If these trends continue, some 592 million people, or one adult in 10, will have diabetes, by 2035[5]. The World Health Organization (WHO) predicts similar results for the worldwide increase in diabetes: over 180 million people all over the world have diabetes, and the number may become double by 2030[5, 6].

The Western Pacific has more diabetic populations with more than 138 million people affected[5] while the North American and the Caribbean region have the second-highest relative prevalence of diabetes[5]. An increase in predicted the total number of diabetic patients in North America and the Caribbean between 2014 and 2035[6]. An estimated 36.8 million diabetic people live in the area now, and by 2035, the number is expected to increase to 50.4 million[5, 6].

1.4 Diabetes in Canada

The Government of Canada identified that diabetes is a complex health problem and a national challenge[12]. According to diabetes statistics in Canada in 2015, the estimated prevalence in Canada was 3.4 million patients (9.3%), and it is expected to increase to 5 million (44%) by 2025[12,13].

The most recent statistics in Canada disclosed that diabetic patients are three times more likely to be hospitalized with the cardiovascular disease, tweleve times more liable to be hospitalized due to renal failure and over 20 times are more likely to be hospitalized for a non-traumatic lower limb amputation, compared to the general population [12, 13].

The Canadian Diabetes Strategy (CDS) was formed in 1999 with an original funding of $115 million for five years, for prevention and management of type 2 diabetes and its complications. CDS's strategy emphases health promotion and chronic disease prevention by reducing diabetes risks for Canadians who are at high risk and supports early discovery and controlling of chronic diseases[13, 14]. The direct treatment costs for people with diabetes in Canada had been estimated $400 million annually for hospital care and prescription drugs[9]. Also, there are costs for treating complications and for physician care, costs borne by patients, and indirect costs such as premature death, disability, and care-giving[14].

1.4.1 Diabetes in Newfoundland and Labrador

Accoroding to the Canadian Diabetes Association (CDA) and National Diabetes Surveillance System (NDSS), the Province of Newfoundland and Labrador (NL) has the highest prevalence of diabetes (for all ages) in Canada, estimated at 9.3% for 2010 and which is expected to increase to 14.4% by 2020[15]. By 2020, it is anticipated that 73,000 persons in the province will have diabetes, up from 47,000 individuals in 2010[15]. The estimated diabetes prevalence by 2015 was 60,200 (11.9%), and is expected to be 84,500 (16.6%) by 2025[15]. Previous studies in Newfoundland and Labrador showed that males and females diagnosed late with diabetes had an increased risk of CVD mortality, other associated causes of mortality and hospitalizations compared to those without diabetes[15, 16].

1.5 Urban/Rural Difference in Diabetes Diagnosis and Outcomes

Diabetes Mellitus, especially Type 2_diabetes, is considered a major health concern in rural communities in low- and middle-income countries[17,18]. Although, there are more people with diabetes living in urban (246 million) than in rural (136 million) areas, the numbers for the countryside areas are on the increase[5, 6].

Because rural populations suffer a higher financial and chronic burden from diabetes, they constitute an important public health target group as they lack the infrastructure to sustain the processes needed to improve healthcare outcomes among persons living with diabetes[17,18]. Rural populations often lack adequate access to primary care and specialty care services, which are critical for providing quality diabetes care. Rural adults who are less-educated, are more likely to report low incomes, lack health insurance, travel further for care and are correspondingly more likely to report deferring care due to cost than urban adults[17, 18, 19].

1.6 Problem Statement

Epidemiological studies show an increased rate of type 2-diabetes worldwide. The statistics show that every 10 seconds two people develop diabetes and someone dies from diabetes-related causes[19, 20]. As the diabetic population continues to increase, providing the necessary care for diabetic patients becomes progressively significant to reduce the related morbidity and mortality.

A big challenge with type 2 diabetes is detecting the disease early to prevent complications from developing. Previous studies found that about 183 million people, or half of those who have diabetes, are unaware they have the disease[19, 21]. Additionally, type 2 diabetes can be present for 9-12 years before being diagnosed, which lead to the presence of complications at the time of diagnosis[21].

On the other hand, no country can diagnose every person that has diabetes. For example, in sub-Saharan Africa, where incomes are often lacking, and governments may not list screening for diabetes, the proportion of individuals with diabetes who are undiagnosed is as high as 90%[5]. Even in developed countries, nearly one-third of people with diabetes are undiagnosed[5].

According to Statistics Canada, in 2008/09, Newfoundland and Labrador, Nova Scotia, and Ontario had the highest prevalence of diagnosed diabetes[12]. Of the three, the Province of Newfoundland and Labrador has the highest prevalence of diabetes (for all ages) in Canada[12].

In recent years, there has been substantial attention to the geographic characteristics of the public health, mainly in the areas of the global health and community development. Previous studies recognized a difference between urban and rural health care facilities related to access to care and utilization of healthcare services[22, 23]. These studies also showed the difference between urban and rural health care services associated with cost and geographic distribution of providers and services[22, 23, 24]. Studies that focused on the rural populations noted difficulties in providing care for patients with diabetes; however, results are confined to a small area and do not produce globally representative evaluations on differences in diabetes care among rural populations[17, 18].

Previous studies revealed mixed findings for urban/rural differences in diabetes diagnosis and outcomes. Some studies suggest that people living in rural and remote regions have diabetic complications percentage between 10% and 70% higher than those living in the major cities, and proprotion of diabetes-related hospitalization and mortality rise with the increasing remoteness of residence[22, 23, 24]. Others show a high prevalence of diabetes among urban inhabitants[25, 26, 27].

This study focuses on diabetes diagnosis and outcomes (complications and mortality) but not from a geographical aspect (rural and urban areas). To our knowledge, this is the first study in NL using a GIS approach to identify the variances between rural and urban areas and if these differences have an effect on diabetes diagnosis and outcomes. Identifying potential individual risk factors and rural/urban factors affecting diabetes in NL could help inform intervention strategies to decrease the possibility of diabetes and its complications in at-risk populations. Consequently, it can help decision-makers better to understand the geographic variations in diabetes diagnosis and management.

CHAPTER 2: LITERATURE REVIEW

To identify relevant articles about rural and urban disparities in diabetes diagnosis, complications and mortality, a systematic literature search was performed. This search used electronic databases including PUBMED, EMBASE, COCHRANE and CINHAL.

The initial search comprised the following MESH terms: Diabetes Mellitus, Rural Population, Rural Health Services, Rural Health, Urban Health Services, Urban Health, Urban Population, Health Disparities, Primary Care, Diabetes Complication, Morbidity, Mortality, and Diabetes Outcomes.

Analyzing the title and abstract of each paper retrieved from the initial literature search to identify potentially eligible studies. All articles that did not meet the inclusion criteria were excluded. The full text of the remaining papers was obtained for further examination.

The following number of articles, published between 1950 and 2015, from the different electronic database were identified: 430 related articles from PubMed; 200 related articles from CINHAL, 75 articles from COCHRANE and 90 related articles from EMBASE. All of these items were saved to Refworks and placed them in individual folders. When the relevant articles were identified, they were put in a newly created folder. Of the 795 articles, 300 records related to our research question were identified.

The next step was screening the 300 related articles and focusing on the articles that were published over the last five years and related to type 2 Diabetes (DM). Additionally, the articles those were readily accessible through MUN's library database without the need of subscription services were only included. Once the screening process was finished, 250 articles were excluded from the initial 300.

Consequently, 12 articles published during the past five years related to the objective of this study, disparities in rural and urban areas in diabetes diagnosis, complications and mortality, were identified. The selected articles follow the eligibility criteria, as shown in figure 1.

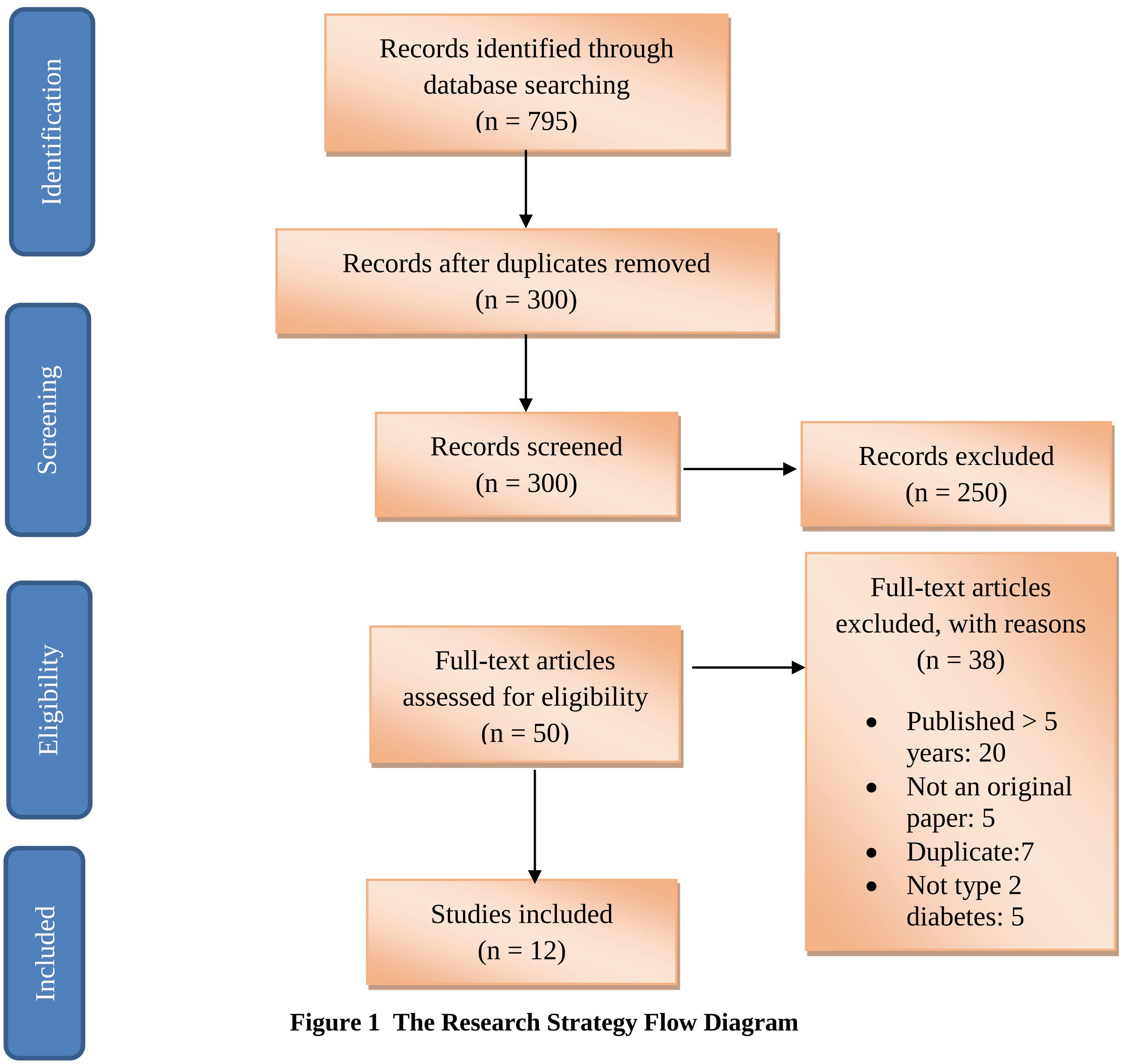


Figure 1 The Research Strategy Flow Diagram

These articles from different regions and countries showed mixed findings for urban/rural differences in diabetes diagnosis and outcomes. Some studies show a high prevalence of diabetes and its related complications in the rural areas with less adequate care; others show a high prevalence of diabetes among urban inhabitants. All potentially eligible studies were considered for review. Table 15 of appendix shows a summary of findings relevant to a rural/urban difference in diabetes diagnosis and outcomes.

Morbidity and quality of life for the old diabetic patients who are living in urban and rural areas

Dos Santos et al. 2013[26] showed that the prevalence of diabetes in Brazil is higher among urban people (3.99%) than in rural populations (2.97%). The elderly urban residents stated a greater number of comorbidities and more vision problems and heart problems compared to the rural older people. The author found that that the elderly DM patients in the rural regions usually presented better socio-demographic situations, a lower frequency of morbidity and better quality of life scores than the residents of the urban area.

Another study by Hye Y. et al. in 2010[25] identified that the prevalence of T2DM in the Korean population was significantly higher in urban (14.5%, P<0.000) than in rural (8.6%) residents. However, subjects with a family history of T2DM in the agricultural region had a higher risk of T2DM (P<0.000) compared with those in the urban areas.

These articles showed higher prevalence of diabetes in urban areas than rural areas in Brazil and Korea (developing countries).

Rural–urban differences in the prevalence of diabetes and heart diseases

O'Connor et al. in 2012[28] found that the rural locations had the higher prevalence of diabetes and CVD. Those chronic diseases aggravated the well-established lack of primary care providers in rural cities. It includes more difficulty obtaining health insurance and longer distances to reach health care services. As a result of that medical deficiency, populations of rural states in the USA had access to about half of the number of general physicians compared to residents of urban locations.

By performing some statistical analysis, the author examined the basic prevalence of diabetes and CVD, which were 8.6% ($P < 0.001$) and 38.8% ($P < 0.001$) higher among populations living in rural regions versus urban regions, respectively. Thus, persons living in rural areas in the USA were more likely to be diagnosed with diabetes than persons living in urban areas; they were also more likely to be diagnosed with coronary heart disease.

Another study in the United States by Cheryl et al. in 2011[29] found that rural veterans were more likely to check regularly their feet (74% versus 68%; $P<0.004$). In contrast, urban veterans were more likely to perform blood sugar testing at least once daily (63% versus 59%; $P< 0.000$). On the other hand, the study results showed that rural veterans had less access to care, higher exposure to travel obstacles, lower health-related quality of life, and a higher prevalence and poorer control of physical health complications. So the authors concluded that those residing in rural areas would be limited in their access to formal clinical services compared to their urban counterparts.

Quality performance programs have not been designed and implemented with consideration of the additional challenges in access, practice characteristics, and resources faced by rural physicians. Therefore, rural doctors are less likely to participate in performance reporting, and national averages set by urban practice patterns may not reflect the diabetes care quality in rural settings.

These articles from the United States showed higher prevalence of diabetes in rural areas than urban areas with providing more qualified care for diabetic patients in urban places.

Rural-urban disparities in the management and health issues of chronic diseases

A study in Quebec (Canada) in the early 2000s by Vanasse A et al.[30] stated that nearly 66% of the Quebec inhabitants live in a metropolitan area (CMA), and 12% of them live in a small town (CA). Besides, this study found that no rural–urban difference was noticed in the incidence emerged across the three chronic diseases (atherosclerosis, osteoporosis, and diabetes). But the first observation is that the proportion of MI was greater in small towns (CA) and weak metropolitan influenced zones (MIZ) compared with metropolitan areas (CMA) while there was no clear trend in the proprotion of diabetes among rural–urban areas. But, a clinically and statistically significant smaller risk of diabetes was observed in moderate MIZ (statistically ($P < 0.01$) and clinically significant risk ($RR \geq 1.2$ or $RR \leq 0.83$) as compared with the risk in a census metropolitan areas. The results from this study stated a significantly higher mortality for atherosclerosis and diabetes, in non-metropolitan areas with the highest proprotion found in remote regions (weak and no MIZ), $P < 0.001$.

This is a Canadian study on rural-urban disparities in management of the chronic diseases, and this study showed high prevalence of diabetes mellitus, atherosclerosis and osteoporosis in rural areas.

Risk elements and co-morbidities of diabetes among adults in rural regions

A study by Dyck et al. in 2013[31] showed that unadjusted diabetes prevalence was similar among Saskatchewan's agricultural regions and was significantly higher among non-farm compared to farm inhabitants. Overall, 10.7% of non-farm inhabitants and 6.9% of rural residents stated that they received a diagnosis of diabetes from their physicians ($p<0.001$). The study suggested that rural Saskatchewan had higher diabetes prevalence for people living in non-farm places with 7.3% compared to 5.1% among those living on farms.

An American study by Nathan et al. in 2010[19] showed that a higher percentage of rural persons reported diabetes among all racial/ethnic classifications compared to urban persons (9.0 vs. 7.7%). On the other hand, rural individuals with diabetes were more likely to report not seeing a doctor due to an absence of health insurance, and less liable to report participating in Diabetes Self-Management Education (DSME) than urban persons. The percentage of rural residents indicates an annual dilated eye examination (69.1%) was significantly lower than urban individuals with diabetes (72.4%; P = 0<006). So, rural people living with diabetes were more likely to have retinopathy (25.8%) than 22.0% of urban residents (OR 1.21; $P < 0.007$).

There are only two studies in Newfoundland and Labrador by Roche et al. the first study, published in 2013[16] assessed the sex differences in all-cause and cardiovascular mortality and hospitalization for individuals with and without diabetes. Additionally, the study evaluated whether or not patients with diabetes were diagnosed early and late[16]. In this study, males and females with diabetes were more likely to die and to be hospitalized than males and females without diabetes (P< 0.01). During hospitalization, individuals with diabetes remained longer than individuals without diabetes for both males (6.4 and 5.6 days; P< 0.01) and females (7.0 and 5.5 days; P< 0.01). Males with and without diabetes had greater risk of all-cause mortality and CVD hospitalizations than females. Diagnosis of diabetes on the late stage was positively associated with CVD mortality (Hazard ratio (HR) 6.54 [95% CI: 4.80– 8.91]) and CVD hospitalizations (HR: 5.22 [95% CI: 4.31–6.33]) among females. Compared to their male counterparts, females were also at a significantly higher risk of incurring longer hospital stay (HR: 3.44, [95% CI: 2.47–4.79] and: HR: 3.33, [95% CI: 2.80–3.95]).

The second study by Roche et al. in 2014[21] examined factors associated not only with a diabetes diagnosis but also with late diabetes diagnosis for males and females[21]. The results of this study showed that men and women with diabetes were older, more likely to live in a rural area and have less education than those without diabetes (P < 0.01). The results of this study also displayed that resident in rural areas (HR: 1.47; 95% CI: 1.01-2.15), getting social care (HR, 2.80; 95% CI: 1.52-5.15), lacking of health awareness (HR: 2.06; 95% CI: 1.32-3.21) and stress (HR: 1.45; 95% CI: 1.01-2.10) were associated with diabetes among females.

These four articles (three from Canada and one from United States) showed high prevalence of diabetes in rural and less accessible areas associated with diagnosis of diabetes in late stages. Late diagnosis of diabetes lead to long hospitlization with high mortality proportion.

Elements of urbanization which are most associated with diabetes

Attard et al. in December 2012[27] showed that the prevalence of type 2 diabetes in China had become more than doubled from approximately 3% in 1994 to 7–10% in 2008. It was the reason for considering China is a home to more than 1.3 billion people and contained one-fifth of the world's population. Urbanization might impact diabetes prevalence through increased time involved in sedentary lifestyle manners and more ingesting of animal products, high-fat foods, and highly handled foods.

This study examined diabetes prevalence across low, medium and high zones of urbanization. The results showed the highest prevalence of diabetes is in highly urbanized areas. Besides, diabetes prevalence differed by sex ($p<0.001$, $\chi 2$ test); with a higher mean prevalence through all levels of urbanization in men (8.7% [SE 0.5]) vs. women (6.7% [0.4]). High vs. low urbanization was related to and near twofold higher diabetes prevalence (men OR: 2.02, 95% CI: 1.47- 2.78; women OR: 1.94, 95% CI: 1.35- 2.79) after adjusting for individual-level factors and accounting for a gathering at the community and province levels[27].

"When populations grow, the population of a place may turn from a city into nearby areas, this is called urbanization"[27]. This study form China showed that the urbanization plays a big role in increasing the prevalence of diabetes in China by increasing the time of sedentary life.

Rehospitalization proportions among rural Medicare beneficiaries with diabetes

A study by Kevin et al. in 2012[32] found that around 20% of Medicare beneficiaries with diabetes in Columbia discharged from a hospitalization had a subsequent readmission within 30 days, with only 10% of intended readmissions. The authors discovered that 12.9% of rural patients went for follow-up physician visit within 30 days compared to 14.9% of urban. Having a doctor visit within 30 days of discharge was a positive predictor of having a readmission (OR: 2.24, 95% CI: 1.95-2.57). Consequently, residents of remote rural counties were less likely to have a readmission (OR: 0.74, 95% CI: 0.57-0.95)[32].

The article showed that people in rural areas have less adequate care including a physician visit which affected the hospitalization risk in case of advanced cases with diabetic complications[32]. The authors suggested characteristics and relative factors that were influencing rural residents and placed them in risk for improper care. These factors included geographic distance, lack of transportation, higher poverty levels, insufficient or disjointed health care infrastructure, and a lack of other resources[32].

Spatial analysis and correlates of county-level diabetes

The medical geography is an important "new" area of health research that is a fusion between geography and medicine by dealing with the geographic features of health and healthcare. The aim of this new field of health research is improving the empathetic of the various influences which affect the health of inhabitants and the individuals. It is also called health geographic.

A study by Hipp JA et al. in 2015[33] found a significant spatial clustering of county-level diabetes prevalence in the United States ($p < 0.001$). The proportion of the population that were living below the federal poverty level and percentage non-white people were related to diabetes in some regions. The authors mentioned that poverty line, physical inactivity, and walking or cycling to work were each significantly related to county-level diabetes prevalence[33].

Another study by Chris G. et al.[34] found that there was a clustering of DM prevalence in the central core of the City of Winnipeg. This cluster associated with a larger Aboriginal population, low education, family low income, single parent families, high unemployment, poor housing stock, high crime rates and high levels of smoking. Significant Moran's I values ($P<0.001$) confirmed this visual impression for all values[34].

Geographical methodologies offer chances to associate individuals with characteristics of their local setting and to assess spatial modeling of health outcomes[34]. Geographic information systems can help to connect aspects of where we are living with our health consequences and skills and have been working in several advanced studies of diabetes diagnosis and outcomes[34, 35].

On the other hand, we could not find any articles in Newfoundland and Labrador that are related to disparities in diabetes diagnosis and outcomes from a **geographical view**. This study will assess the differences in diabetes diagnosis, mortality and complications among rural and urban areas by performing the statistical and geospatial analysis.

CHAPTER 3: METHODOLOGY

Ethics: The study protocol was approved for ethics by Newfoundland and Labrador Health Research Ethics Board (HREB) - reference number (15.140)

3.1) Research Question and Objective

3.1.1) Research Question

1) In adults age 20 and older in NL, does place of residence (rural vs. urban) affect the likelihood that a patient newly diagnosed with diabetes will have complications and comorbidities* at the time of diabetes diagnosis?

* A patient newly diagnosed with diabetes who has diabetic complications or comorbidities will be referred to as a complex case.

2) In adults age 20 and older in NL, does place of residence (rural vs. urban) affect the likelihood of developing complications and/or comorbidities and death after the diagnosis of diabetes?

3.1.2) Research Objective

1) Assess disparities in rural and urban areas and their effect on the development of a complex case (patients with complications and comorbidities at the time of diabetes diagnosis) in adults age 20 years and older in NL.

2) Assess presence of disparities in rural and urban area and their effect on outcomes related to diabetes (morality, morbidity) five years after getting diagnosed with diabetes mellitus in adults age 20 years and older in NL.

3.2) Hypotheses

1a) Ho: Getting diagnosed as a complex case for adults aged 20 years and older in Newfoundland and Labrador is not associated with place of residence (rural/urban).

2a) Ha: Getting diagnosed as a complex case for adults aged 20 years and older in Newfoundland and Labrador is associated with living in rural area.

1b) Ho: Diabetes outcomes (complications, mortality) in urban areas is not different from the outcomes in rural area among adults aged 20 years and older five years after getting diagnosed with diabetes mellitus in Newfoundland and Labrador.

2b) Ha: Diabetes outcomes (complications, mortality) in urban areas are different from the outcomes in rural area among adults aged 20 years and older five years after getting diagnosed with diabetes mellitus in Newfoundland and Labrador.

3.3) Study Population

All adults 20 years and older from NL who were in the Canadian Chronic Disease Surveillance System and who developed diabetes between 1998 and 2003 were included in the cohort. Pregnant women with diabetes were excluded from the study. At the time of entry into the cohort, the presence of diabetic complications or and co-morbidities were assessed. The individuals in the cohort were then followed from the date of diagnosis for five years or until their death. Diabetic complications and comorbidities were assessed during the follow-up period.

3.4) Data Sources

This retrospective cohort study utilized administrative data in Newfoundland and Labrador, Canada. Databases included were: (1)The Canadian Chronic Disease Surveillance System (CCDSS), 1998-2008; (2) the Clinical Database Management System (CDMS), 1998-2008 and (3) the Medical Care Plan (MCP) Fee-For-Service Physician Claims Database, 1998-2008.

The CCDSS is a co-operative network of provincial and regional surveillance systems and uses an authorized case definition to detect persons with diabetes (ICD-9 Code 250).

The MCP system contains information related to services provided by fee-for-service physicians under the provincial Medical Care Plan (MCP).

The CDMS is the provincial hospital departure records that release demographic, clinical and interventional data for patients admitted to all acute health care services and surgical day care in NL.

The resulting database is linked by NLCHI (a trusted third party for health data in this province) with demographic and social data generated from the Census and Statistics Canada annual mortality data files.

3.5) Data Preparation

The data collected by NLCHI went through data cleaning using STATA 13 before it was ready for ArcGIS incorporation. Among some of the more important changes applied to the database was reshaping (from long to wide) which used de-identified patient numbers and fiscal year as both of the primaries. Variables were also created for further exploration of the dataset, such as complex diagnosis which was defined using the number of health complications. A patient with one or more complications at the time of diabetes diagnosis was considered to be a complex patient. Those complications included stroke, CVDs, renal failure and amputation. Other variables included the age at the time of diagnosis, the number of visits to a specialist or general physician, and the number of hospital separations.

Once the data was cleaned, it was transferred to a file type that can be used by ArcGIS. Once in ArcGIS, relational joins were made between postal code points, the file which contains all of the spatial data attributed to each unique postal code.

3.6) Study Design - Strategy and Frameworks

This study was a cohort study. In this cohort study all subjects had the same potential length of follow-up without any losses. Additionally, this was a population-based, retrospective cohort study of adults 20 years and older diagnosed with diabetes, using health administrative databases from 1998 to 2008 in Newfoundland and Labrador (NL), Canada. The individuals in the cohort were followed from the date of diagnosis until either their death or the end of the study (2008).

The individuals included in the cohort were those people diagnosed with diabetes between 1998 and 2003, and then five years of follow-up for each patient were identified starting from the date of his/her diagnosis. For example, if the year of the diagnosis was 1998, he/she was followed until 2003 for a total of five years. If a patient had been diagnosed with diabetes in 2003, he/she was followed up until 2008 for a total of five years. Through those five years of follow-up, we recorded the following events: the number of the complications and/or comorbidities which this patient had, the number of visits to family doctors and specialists, the number of hospitalizations through the five years period of study, and the year of death if it happened during the study period.

3.7) Research Variables

3.7.1) Diabetes Mellitus

The Canadian Chronic Disease Surveillance System (CCDSS) is a cooperative system of provincial and regional surveillance systems and uses a nationally authorized case definition to detect persons with diabetes (ICD-9 Code 250). According to CCDSS, a diabetic case definition is required one hospitalization or two or more physician claims with a diagnosis of diabetes during a 2-year period[36]. Cases remain in the CCDSS until receiving a record of their death or leaving the province. This case definition has a sensitivity of 86% and a specificity of 98% for detecting population who had diabetes. To find the incident cases of diabetes, a clearance period of 3 years was applied to the above-mentioned definition[37]. The CCDSS diabetes case definition excludes women with gestational diabetes.

3.7.2) Dependant Variables:

3.7.2.1) Complications and/or Comorbidities at the Time of Diagnosis (Categorical Variable)

Diabetes in this study was classified as a complex case depending on the presence of comorbidities and diabetes-related complications at the time of diagnosis. Individuals diagnosed early did not have any comorbidities/diabetes-related complications at the time of their case dates. Patients without any comorbidity or diabetes-related complications within one year before or after the diabetes case date were classified as not having any complications at the time of diagnosis, whereas those with any comorbidity or diabetes-related complications at the time of diagnosis were defined as complex cases.

To identify complex cases of diabetes, patients' records were linked to the Medical Care Plan and Clinical Database Management System data. Using this linkage, any records of comorbidities and/or diabetes-related complications were identified and compared with the diabetes case dates.

3.7.2.2) Diabetes Outcomes

3.7.2.2.1) Complications and/ or Comorbidities During the Study Period

3.7.2.2.1.1) Type of Diabetic Complications and Comorbidities (Categorical Variable)

Like any other chronic disease that primarily affects middle-aged and older individuals, type 2 diabetes is usually complicated by other medical conditions. The diabetes related conditions that were used to define diabetes complications in this study are listed in Table 1. Diabetes complications and/ or comorbidities in this study were defined as any records of diabetes-related comorbidities/complications occurred during the study period. All patients diagnosed with diabetes were followed until the end of the study and any records of comorbidities and/or complications during the study period were identified.

Table 1: Diabetes Related Conditions Used to Define Diabetes Complications in This Study[16]

CONDITIONS	ICD-9-CODES	ICD-10-CA CODES
Cardiovascular Disease	390-448	100-178
Ischemic Heart Disease	410-414	120-125
Acute Myocardial Infarction	410	121-122
Heart Failure	428	150
Acute Renal Failure	584	
Renal Disease	585-586	N18-N19
Lower Limb Amputation	96.11-96.12	1VC93LA
Retinopathy	362	H35
Atherosclerosis	440	
Amyloidosis	277.3	E85

All patients regardless of whether they were a complex or non-complex case were followed until the end of the study for any additional records of comorbidities and/or diabetes-related complications that may have occurred after getting diagnosis with diabetes (Cardiovascular disease, Renal disease, Diabetic foot or Stroke).

3.7.2.2.1.2) Number of Complications

The numbers of complications and/or comorbidities during the study period were classified into: 0 = no complications at all, 1 = only one complication present, 2 = two complications present and 3 = 3 or more complications present.

3.7.2.2.2) Mortality (Categorical Variable)

Mortality was defined as a record of death that occurred during the study period. Mortality was defined as a categorical variable; patients were classified as alive or dead during the study period. All patients diagnosed with diabetes were followed until the end of the study and records of death were identified in our database during the study period.

3.7.3) Covariates/ Control Variables:

3.7.3.1) Demographic Variables

Sex (Categorical Variable) and Age (Categorical Variable)

This study focused on male and female patient age 20 years and older who had been identified in the CCDSS as having been diagnosed with diabetes between 1998 and 2003.

The patients were categorized into the following four age groups at the year of diagnosis, according to Canadian Diabetes Association (CDA) screening guidelines, at the time of diagnosis with diabetes: 20 – 39 years; 40 – 49 years; 50 – 59 years; 60 – 69 years and 70 years or more.

3.7.3.2) Utilization of Healthcare Services

Records of MCP Fee-For- Service Physician Claims and hospital discharges were used to identify the number of hospital, physician and specialist visits during the study period.

Healthcare utilization in this study were considered as categorical variables in the database and included outpatient services (visits with general practitioners and specialists) and inpatient services (hospitalization and length of stay).

Using an approach suggested by Donald E. Fetterolf based on statistical outliers and healthcare providers opinions on the number of regular visits with healthcare system[38]; the number of the visits was classified as follows:

a) **Physician Visits** were defined as the number of physician visits (General Practitioner and Specialists) per year among people during the five-year follow-up. Then by taking the mean of physician visits during five-year follow-up, these visits were categorized into the following groups:

Service Accessibility	Visits per year
Non User	No Visits
Access to Physician	One Visit
Regular Visit	2 – 6 Visits
High User	7 -12 Visits
Extreme User	≥ 13 Visits

b) **Hospitalization** was defined as the number of hospitalizations per year during the five-year follow-up. Hospitalization was categorized as:

Yes: there was one or more hospitalization

No: the patient had never been hospitalized

c) **Length of stay at hospital** was defined as the number of days spent in the hospital per year during the five-year follow-up. This variable was considered as a continuous variable.

3.7.3.3) Rural/ Urban Areas

To be able to reflect the geographical realities of Newfoundland and Labrador, we assessed different classifications for rural/urban areas using alternative spatial models. Using the six digits postal code (categorical variable), we georeferenced the study population for identification of rural/urban differences and compare groups. Additionally for detect rural/ urban access to health care facility, six digit postal code was used to identify rural/urban distance from healthcare services.

Several alternative definitions of “rural” are available for national level policy analysis in Canada. Different definitions generated a different number of “rural” people. Even if the number of “rural” people was the same, different people were classified as “rural” within each definition.

a) **Census Rural Area** is defined as residents who are living outside the spaces of 1,000 people or more, or residents living outside places with densities of 400 or more people per square kilometer[39].

b) **Rural and small town(s)** is (are) defined as the population living in cities and metropolises outside of the commuting zone centers with 10,000 people or more[39].

c) **Rural communities** are defined as the population in communities with densities less than 150 people per square kilometer[39].

d) **Non-Metropolitan Regions** are defined as a population existing outside of areas with major urban settlements of 50,000 or more people. Non-metropolitan areas contain urban settlements with less than 50,000 people and areas with no urban settlements ("urban settlements" are known as places with 2,500 or more of populations) [39].

e) **Rural Postal Codes** are defined as areas serviced by rural way transfer from a post office. "0" in the second location of a postal code means a "rural" postal code (also referred to as "rural" forward sortation area ("rural" FSA)). This method of defining an area as "rural" is no longer valid in New Brunswick and some parts of Quebec[39].

f) **Agricultural Land Proportion** is another definition for rural/urban areas. Urban areas have a low proportion of agricultural land compared to rural areas[39].

g) **The Accessibility-Remoteness (A-R) index:** the accessibility is an important factor in providing facilities to the overall community. Based on this, the Newfoundland and Labrador Statistics Agency (NLSA) established the A–R index to classify societies within the province according to the ease of access to government and community services[40]. Communities with the highest accessibility are the regions with government service centers and a health care center. On the other hand, very remote communities are isolated and must utilize transports to get to regional and provincial service centers. According to NLSA, only a small percentage (2.6%) of the total population is located in remote and very remote areas. Moreover, according to this index, 83.9% live in accessible and highly accessible localities[40].

According to the A-R index, each community was assigned a continuous numeric value that ranged from 0 to 1. The A-R index value was then partitioned into six classifications, ranging from ‘Highly Accessibility’ to ‘Very Remote’, as shown in Table 2.

Table 2: Accessibility-Remoteness Classifications[40]

Classification	Access to Goods and Services	Percentage of total 2011 Population
Highly Accessible	Unrestricted	68.3%
Accessible	Some Restriction	15.6%
Somewhat Accessible	Considerable Restriction	8.6%
Moderately Remote	Significant Restriction	4.9%
Remote	Very Restricted	1.5%
Very Remote	Little / No Access	1.2%

From a geographical perspective, classification of accessibility is defined as the road distance between an origin community and a set of services. As this road distance plays a great role on the chances of contact between people and these services, accessibility is a necessary variable in establishing new rural-urban classification. The highest accessible zones can be considered as urban centers while the lower accessible communities are an example of rural zones[40].

In the individual level analysis, the continues measure for the A-R index values were used while in the community level analysis a fuzzy set model was used for visualization analysis. Using a fuzzy set, we were able to have varying degrees of membership applied to the remoteness index that varied from highly accessible to extremely remote. We found that somewhat accessible (remote index value = 0.329) was a good cut-off point for remoteness, so we divided each remoteness score by that number; we made sure that anything above remote index value did not exceed one. This meant that communities that were closer to being accessible (i.e. 0.328) were not classified as being remote since it is more likely that travel time to services for a given community with a score closer to the cut-off are more similar to somewhat accessible communities than to extremely remote areas. After creating a histogram of the fuzzy set, we found that the 50th percentile reflected the urban or more accessible population while anything above reflected the rural or more remote population. We used this information to create our two subsets of data to be able to compare rural and urban populations at the community level analysis. This comparison is an important one since urban and rural populations were found to behave differently in other studies. Our first subset would include highly accessible to somewhat accessible communities (fuzzy remoteness < 0.5), while the other would include somewhat accessible to extremely remote communities (fuzzy remoteness > 0.5).

A GIS approach to define urban/rural area

Using GIS we combined a transformed different maps into a set of polygons (such as a community or a census subdivision), lines (such as streets, highways or rivers), and points (such as a healthcare facility). The diabetes data were also georeferenced using postal codes and linked to the correct polygons, line, or point. To identify the urban/rural area reflecting the realities of the geographies in Newfoundland and Labrador, we entered the aforementioned classification as different layers in GIS. NL Stats Agency Local Areas (Sometimes referred to as Neighborhoods) were used for the analysis.

3.8) Data Analysis

Different levels of analysis were performed. Individual level analysis, including bivariate and multivariate analyses, was used to show rural/urban differences in diabetes diagnosis, complications and demographic characteristics by using STATA software.

The logistic regression was employed to model the relationship between a dependent variable (complex case, mortality and complications) and an independent variable (rural/urban) adjusting for other crucial covariates (sex, age and health care utilization). The created model, based on the logistic regression, enabled us to look at the significance of the relationships (between dependent and independent variable) and allowed us to examining the effect of several (possibly related) variables simultaneously.

The odds ratio (OR) produced by logistic regression, "represents the odds that an outcome happened given a particular exposure, compared to the odds of the outcome happening in the absence of that exposure". The OR is a measure of the association between exposure and an outcome (living in the rural/urban areas and the diabetic complications and mortality) with adjusting other crucial variables (sex, the age of the patients and healthcare utilization). When a logistic regression is calculated, the exponential function of the regression coefficient (eb1) is the odds ratio associated with a one-unit increase in the exposure.

Furthermore, calculating the p-value determined if there is any significant relationship between the dependent and independent variables. By rejecting the null hypothesis (H0: exposure and outcome are independent) where p-value was less than 0.05, it was straightforward to detect the significant relationships and vice versa.

A variety of community and environmental factors are involved in the development of chronic disease, which goes beyond the concept of personal choice. For that reason, understanding diabetes diagnosis and outcomes (mortality, complications and comorbidities) from an ecological perspective provides opportunities to focus on the environmental and social impacts and develops a more precise model of how population health factors might interact with the individual characteristics to produce variations in diabetes diagnosis and outcomes.

Consequently, we conducted another two levels of geospatial analysis: visualization and community level analysis. The individuals were geo-referenced using the six-digit postal code and assigned to neighborhood and community. ArcMap-GIS 10.2 software package was used to produce choropleth maps, perform descriptive and geospatial analysis for diabetes diagnosis and outcomes in Newfoundland and Labrador. NL Stats Agency Local

Areas (Sometimes referred to as Neighborhoods) were used for the analysis. The shape files mappigs for the polygons came from the federal, provincial governments as well as the NL stats agency through Memorial University: a. NL Base map: provincial, b. Remoteness index: provincial, c. Hospital locations and roads: provincial, d. Local Areas: NL Stats Agency, e. Postal codes: federal, f. Every other level of geography (ie. CSD, DA, etc.): federal. The results of this study identified the location of the highest proportion of complications at the time of diagnosis, and if there was any association between place of residence and presence of diabetes outcomes. Kappa statistics were used to show the level of agreement between the different definition of rurality across Newfoundland and Labrador.

The data for this province formed a sufficiently large sample size to allow for community level geospatial analysis. The geospatial analysis involves the collection, integration, manipulation and presentation of digital maps, GPS, satellite imagery and geocoded data. The outcomes of this type of geographic analysis are described regarding absolute or relative locations, street order or postal code.

The first stage of spatial data analysis included mapping the distribution of diabetes diagnosis and outcomes by the community. Phase two included the use of two spatial statistics to determine spatial clustering (global Moran's I and local Moran's I). Global Moran's I statistic is a global measure of spatial autocorrelation, a geographical phenomenon that can test whether community diabetes diagnosis and outcomes values are randomly distributed or whether neighboring values tend to be more similar than non-neighbouring[42]. Moran's I shows the power of spatial autocorrelation on a scale extending from +1 to -1. A rate of +1 specifies positive spatial autocorrelation where high values are close to other high values. On the other hand, a value of -1 signifies negative spatial autocorrelation where high values tend to be near low values. A value of zero specifies no spatial autocorrelation, or that the data are randomly distributed within the geographical boundary of the study area [43, 44].

The local Moran I statistic detects whether or where local clustering occurs; this cannot be provided by the global Moran's I statistic[42]. The local Moran's I identify individual clusters or small regions of clusters that may not be obvious within the global pattern[42,43]. A cluster and outlier analysis tool in a geographic information system (GIS) was used to analyze the local Moran's I statistic and associated Z-score. This tool examines whether the homogeneity (or heterogeneity) in values between a community and its neighboring communities are greater than what would be expected by chance[44,45,46]. Community with a high Moran's I statistic indicates that its values are close in magnitude to the nearby community's diabetes diagnosis and outcomes values[47, 48,49]. A small Moran's I statistic shows an 'outlier' where the diabetic diagnosis and outcomes of a community are dissimilar to the neighboring values[49, 50,51].

The ordinary least square (OLS) multivariate regression model was performed to show the linear association between diabetes diagnosis and outcomes and rural/remoteness areas in the province[51,52]. The goal of this "global model" is to verify the positive relationship found in previous part of the studies. In this study, the first OLS model used percent of complex cases in the community as the dependent variable and average remoteness index score, cumulative incidence at the community level, the average age at the time of diagnosis and percentage of regular family medicine utilization as independent variables.

The second OLS model used the percent of mortality in the community as the dependent variable and average remoteness index score, percentage of complications and comorbidities at the time of diagnosis at the community level, the mean age at diagnosis and percentage of hospitalization at the community level as independent variables.

CHAPTER 4: DESCRIPTIVE RESULTS

This retrospective cohort study used administrative data from Newfoundland and Labrador, Canada. The study population from 1998 to 2003 included 20,292 patients. The sample size was reduced through the exclusion of 104 patients due to blank postal code entries and 2,392 invalid postal code entries → the total study population after excluding patients based on postal code errors was 17,796 persons.

4.1) Characteristic of Study Population

Of the 17,796 subjects investigated, 50.1% of patients (n= 8,923 subjects) were men and 49.9% of patients (n= 8,873 subjects) were women. As shown in Table 4, the percentage of diabetes mellitus was higher in the elderly. From 17,796 patients, 15.3% of patients (n= 2,720 subjects) were diagnosed as complex cases, which refer to the presence of complications and comorbidities at the time of diagnosis. For diabetes outcomes during the five-year follow-up period, the proprtion of mortality was 17.2% of patients (n= 3,053 subjects), while 84.7% of patients (n=15,076 subjects) did not develop any complications and/or comorbidities; 8.8% of patients (n= 1,558 subjects) developed one diabetic complication; 4.7% of patients (n= 844 subjects) developed two types of complications and 1.8% of patients (n= 318 subjects) developed three or more types of complications by the end of study period.

4.2) Utilization of Health Care Services

MCP Fee-For- Service Physician Claims and hospital claims were used to identify the number of hospitalizations, general practitioner (GP) and specialist visits during five-year follow-up. The GP visits were categorized into five groups: 6.7 % of patients (n= 1,188 subjects) that did not have any previous GP visits, 1.2 % of patients (n= 211 subjects) that had only one visit, 41.3 % of patients (n= 7,342 subjects) that had two to six visits, 34.6 % of patients (n= 6,165 subjects) that had seven to twelve visits and 16.2 % of patients (n= 2,890 subjects) that had thirteen or more visits. Specialist visits were also categorized into five groups: 3.2 % of patients (n= 561 subjects) that did not visit a specialist, 3.3 % of patients (n= 589 subjects) that had one visit, 66.9 % of patients (n= 11,918 subjects) that had two to six visits, 19.8 % of patients (n= 3,522 subjects) that had seven to twelve visits and 6.8 % patients (n= 1,206 subjects) that had thirteen or more visits.

The hospitalization was defined as the act of placing a person in a hospital as a patient. The number of the hospitalization during a five-year follow-up period was categorized into four groups: 41.2 % of patients (n= 7,330 subjects) that were not hospitalized, 3.4 % of patients (n= 602 subjects) that were hospitalized for one time, 55.4 % of patients (n= 9,858 subjects) that were hospitalized between two and six times and .03 % of patients (n= 6 subjects) that were hospitalized seven or more times. The last healthcare service considered in our analysis was the length of stay at a hospital, which was categorized into six groups: 41.5 % of patients (n= 7,384 subjects) that did not stay at the hospital, 2.6 % of patients (n= 465 subjects) that spent one day in a hospital, 38 % of patients (n= 6,760 subjects) that spent between two and six days, 11.5 % of patients (n= 2,051 subjects) that spent between seven and fourteen days, 4.6 % of patients (n= 813 subjects) that spent between fifteen and thirty days and 1.8 % of patients (n= 323 subjects) that spent more than thirty days in a hospital.

Table 3: Characteristics of Study Population During the Study Period (n=17796)

			Percentage (Total Number)
Sex			
	Men		50.1 (8,923)
Age Group			
	20 - 39		8.6 (1,537)
	40 -49		15.3 (2,719)
	50 -59		24.5 (4,362)
	60 - 69		23.4 (4,170)
	≥ 70		28.1 (5,008)
Visit with Family Physicians			
	-No visit (Nonuser)		6.7 (1,188)
	-One Visit		1.2 (211)
	-2–6 Visits (Regular user)		41.3 (7,342)
	-7–12 (High User)		34.6 (6,165)
	-≥13 (Extreme User)		16.2 (2,890)
Visit with Specialists			
	-No visit (Nonuser)		3.2 (561)
	-One Visit		3.3 (589)
	-2–6 Visits (Regular user)		66.9 (11,918)
	-7–12 (High User)		19.8 (3,522)
	-≥13 (Extreme User)		6.8 (1,206)
Hospitalization			
	NO		41.2 (7,330)
	YES	1 Time	3.4 (602)
		2-6 Times	55.4 (9,858)
		≥7 Times	.03 (6)
Hospital Length Stay			
	0		41.5 (7,384)
	1 Day		2.6 (465)
	2-6 Days		38 (6,760)
	7-14 Days		11.5 (2,051)
	15-30 Days		4.6 (813)
	>30 Days		1.8 (323)

Complications and comorbidity at time of diagnosis		15.28% (2,720)
Mortality		17.16% (3,053)
Complications and Comorbidities during 5 years follow up		
	No Complication	84.7 (15,076)
	One Complication	8.8 (1,558)
	Two Complications	4.7 (844)
	≥3Complications	1.8 (318)

Table 4 shows an increase of health care service utilization for the one year period after diabetes diagnosis compared to the one year period before the diagnosis. The mean of GP visits increased from 1.96 visits (95% CI: 1.94-1.98) one year before diagnosis to 2.18 visits (95% CI: 2.16-2.19) one year after diagnosis. That lead to an increase in the mean number of GP visits during a five-year period to 2.53 visits (95% CI: 2.51-2.54). The average of specialist (SP) visits increased from 1.38 visits (95% CI: 1.36-1.41) one year before diagnosis to 1.59 visits (95% CI: 1.57-1.61) one year after diagnosis that lead to an increase in the mean number of SP visits during a five-year period to 2.24 visits (95% CI: 2.23-2.25). Additionally, table 6 shows a slight increase in the mean number of the hospitalizations from 0.15 time one year before diagnosis (95% CI: 0.15-0.16) to 0.24 time one year after diagnosis (95% CI: 0.23-0.25) that led to an increase in the mean number of hospitalization during a five-year period to 1.14 times (95% CI: 1.13-1.16). There was also an increase in the mean of the length of stay from 0.31 days one year before diagnosis (95% CI: 0.30-0.33) to 0.51 days one year after diagnosis (95% CI: 0.51-0.53) that led to an increase in the mean number of length of stay in hospital during a five-year period to 1.405 days (95% CI: 1.31-1.42).

Table 4: Mean and 95% Confidence Interval of Healthcare Utilization of Patient Diagnosed With Diabetes One Year Before and After Diagnosis and During the 5 Year Study Period

Health Care Utilization	1-Year Period Before Diagnosis	1-Year Period After Diagnosis	During 5 Year Period / Per year
GP* Visits	1.96 (1.94-1.98)	2.18 (2.16-2.19)	2.53 (2.51-2.54)
SP* Visits	1.39 (1.37-1.40)	1.59 (1.58-1.61)	2.24 (2.23-2.25)
Hospitalizations	0.15 (0.15-0.16)	0.24 (0.23-0.25)	1.14 (1.13-1.16)
Hospital Lengthy of Stay (Days)	0.31 (0.30-0.33)	0.52 (0.50-0.54)	1.41 (1.39-1.42)

*GP: Visits with general practitioner
*SP: Visits with specialist

4.3) Place of Residence

The study population was georeferenced using six digits postal codes. To be able to reflect the realities of the geographies in Newfoundland and Labrador we assessed different classifications for rural/urban areas using alternative geographical classification. As mentioned before, there are different definitions for rural and urban areas. Table 5 shows the difference between each of the definitions regarding the percentage of the people living in both rural and urban areas for each classification scheme.

The definition of rurality according to the Newfoundland and Labrador Statistics Agency's Remoteness Index (A-R Index), classified 51.5% of NL's population as living in rural areas and 48.5% as residing in urban areas. The postal code classification for rurality (A0) classified 62.5% of NL's population as living in rural zones and 37.5% as living in urban areas. The Census Rural Area classified 39.5% of residents as living in rural regions and 60.5% as living in urban areas. The Census Metropolitan Area ranked 63.6% of residents as living in rural areas and 36.4% as living in urban zones. The

Community Zone classified 63.5% of residents as living in rural regions and 36.5% as living in urban areas. The Remoteness Index, Rural Postal Codes and Census Rural Areas all provided similar results concerning rural/urban classification and the attributed populations when compared to Census Metropolitan Area and The Community Zone classification scheme.

Table 5: Rural/ Urban Classification by Type of Geographic Classifications (N=17796)

Geography Classification Type	RURAL %	URBAN %
Remoteness Index	51.47	48.53
Rural Postal Code	62.47	37.53
Census Metropolitan Area	63.56	36.44
Census Rural Area (<1000 people in place= Rural)	39.46	60.54
Community Zone (60 Km)	63.46	36.54

Table 6 shows the measurement of an agreement between different rural and urban definitions. There was a good agreement between the A-R Index and Postal Code (Kappa: 0.76, P-value< 0.001, Percent Agreement: 85.88%), fair agreement between the A-R Index and the Census Rural Area (Kappa: 0.57, P-value <0.000, Percent Agreement : 78.47 %), fair agreement between the Postal Code and the Census Rural Area (Kappa: 0.48, P-value< 0.000, Percent Agreement: 72.85%) and a very good agreement between the Community Zone and the Census Metropolitan Area (Kappa: 0.78, P-value< 0.000, Percent Agreement : 89.7 %). As shown in table 6, there was no agreement between the following definitions of the rurality: the Census Metropolitan area and remoteness index (Kappa: -0.67, P-value < 0.000, Percent Agreement : 15.87%), the Census Metropolitan Area and the Postal Code (Kappa: -0.69, P-value < 0.000, Percent Agreement: 9.56%), the Census Rural Area and the Census Metropolitan Area (Kappa: -0.54, P-value < 0.000, Percent Agreement: 27.5%), the Community Zone and the Remoteness Index (Kappa: -0.59, P-value: < 0.000, Percent Agreement : 19.8%), the Community Zone and the Postal Code (Kappa: -0.63, P-value < 0.000, Percent Agreement : 12.8%) and the Community Zone and the Census Rural (Kappa: -0.48, P-value < 0.000, Percent Agreement : 30.3%). Based on the Kappa measurement, the postal code, and the A-R index definitions were chosen for categorizing rural and urban areas in further analysis.

Table 6: Measuring Agreement between Different Rural/Urban Definitions

	Remoteness Index (A-R index)	Rural Postal Code	Census Metropolitan	Census Rural	Community Zone
Remoteness Index					
Rural Postal Code	0.76*				
Census Metropolitan	-0.67^{NS}	-0.69^{NS}			
Census Rural	0.57*	0.48*	-0.53^{NS}		
Community Zone	-0.59^{NS}	-0.63^{NS}	0.78*	-0.48^{NS}	

*P-value <0.0001 for Kappa agreement

4.3.1) Characteristics of Study Population According to the Place of Residence

As shown in Table 7, there were 9,368 (4,589 men, 4,779 women) rural diabetic patients and 8,428 (4,334 men, 4,094 women) urban diabetic patients included in our study population. There were significantly older diabetic living in rural regions compared to those living in urban regions (60 – 69 years: 23.6% of rural patients compared to 23.2% of urban patients and ≥70 years: 30% of rural patients compared to 25.9% of urban patients, P<0.0001). Young urban patients (20 – 49 years) had a higher prevalence of diabetes compared to young rural patients (20 -39 years: 9.4% urban patients compared to 7.9 % rural patients and 40 – 49 years: 16 of urban patients compared to 14% of rural patients).

The rural patients were more likely to be non-user or low users of GP services while urban patients were more likely to be higher or extreme user of GP service than rural people as shown in Table 7. For specialist visits, the urban patients were more likely to be higher or extreme users of specialist service, while the rural residents were more to have used specialist services one times or 2 to 6 times, as shown in Table 7. The percentage of subjects who were not hospitalized during the five-year follow-up was higher in urban than rural populations. The rural subjects had a higher hospitalization proportion than urban populations. Besides a higher proportion of hospitalization for rural subjects, they also tended to have longer stays in hospitals which ranged from one to thirty days as shown in Table 7.

The percentage of diabetes complications and/ or comorbidities at the time of diagnosis was higher in rural (17.03%) compared to urban subjects (13.3%). Table 7 shows a higher percentage of mortality in rural residents (18.4%) compared to urban counterparts (15.8%). On the other hand, there was no significant difference between rural and urban patients who developed complications and/ or comorbidities during the five-year follow-up. Approximately 7.05%, of rural patients developed one diabetic complication or comorbidity while 6.5% urban patients developed one complication or comorbidity during the study period. The respective percentage of two complications or comorbidities and more than two complications or comorbidities was 4.4% of rural residents compared to 4.3% in urban patients and 5.95% of rural patients compared to 5.67% of urban residents, respectively.

Table 7: Characteristics of Study Population According To the Place of Residence During the Study Period

			RURAL % (N) (n= 9368)	URBAN % (N) (n= 8428)
Sex				
	Men		48.9 (4,589)	51.4 (4,334)
	Women		51 (4,779)	48.6 (4,094)
Age Group				
	20 - 39		7.98 (748)	9.4 (789)
	40 -49		14.3 (1,336)	16.4 (1,383)
	50 -59		24 (2,250)	25 (2,112)
	60 - 69		23.6 (2,215)	23.2 (1,955)
	≥ 70		30 (2,819)	25.97 (2,189)
Visit with Family Physicians				
	-No visit (Nonuser)		8.5 (792)	4.7 (396)
	-One Visit		1.3 (121)	1.06 (90)
	-2–6 Visits (Regular)		42 (3,934)	40.4 (3,408)
	-7–12 (High User)		32.96 (3,088)	36.5 (3,077)
	-≥13 (Extreme User)		15.3 (1,433)	17.3 (1,457)
Visit with Specialists				
	-No visit		2.95 (277)	3.4 (284)
	-One Visit		3.6 (338)	2.97 (251)
	-2–6 Visits		70 (6,560)	63.6 (5,358)
	-7–12 visits		18.3 (1,719)	21.4 (1,803)
	-≥13 visits		5.05 (474)	8.68 (732)
Hospitalization				
	NO		38.03 (3,563)	44.69 (3,767)
	YES	1 Time	3.8 (352)	2.96 (250)
		2-6 Times	58.2 (5,449)	52.3 (4,409)
		≥7 Times	0.04 (4)	0.02 (2)
Hospital Length Stay				
	0		38.3 (3,592)	44.99 (3,792)
	1 Day		2.6 (246)	2.3 (219)
	2-6 Days		39.7 (3,715)	36.1 (3,045)
	7-14 Days		12.8 (1,198)	10.1 (853)

	15-30 Days	4.89 (458)	4.2 (355)
	>30 Days	1.69 (159)	1.7 (164)
Diabetes Diagnosis			
	With Complications	17.06 (1,599)	13.3 (1,121)
	Without Complications	82.9 (7,769)	86.69 (7,307)
Mortality			
	Alive	81.6 (7,647)	84.2 (7,095)
	Dead	18.4 (1,720)	15.8 (1,333)
Complications and Comorbidities during 5 years follow up			
	No Complication	82.6 (7,740)	83.2 (7,015)
	One Complication	7.05 (661)	6.8 (571)
	Two Complications	4.4 (409)	4.3 (364)
	≥3 Complications	5.95 (558)	5.67 (478)

CHAPTER 5: INDIVIDUAL LEVEL ANALYSIS

5.1) Logistic Regression

5.1.1) Complications and Comorbidities at the Time of Diagnosis:

The logistic regression analysis was performed to assess the association between complications and comorbidities at the time of diagnosis and place of residence (rural vs. urban). By using the continuous value of the A-R index, It was observed that people who were living in very remote/ less accessible areas were more likely to be diagnosed as complex cases, where diabetic complications and/ or comorbidities presented at the time of diagnosis. The likelihood of being diagnosed as complex case was 23% higher in rural areas than in urban (Odds Ratio(OR): 1.23, P<0.000, 95% CI: 1.19-1.28). When regression analysis was performed using postal code (dichotomous variable), a significant relationship was found where living in rural areas was associated with a high ferequency of complex cases (OR: 1.13, P 0.000, 95% CI 1.03-1.25). Table 8 shows the adjusted regression model after adding age, sex and healthcare service visits as independent variables to the model.

Table 8: Logistic Regression for Complications and/ or Comorbidity at Diagnosis

Variable		Odds Ratio	Standard Error	P > z	95 % CI
1) A-R Index 2) Postal Code		1.23 1.13	.022 .06	0.000 .000	1.19-1.28 1.03-1.25
Female		.69	.689	0.000	.63-.76
Age Group	**40-49**	3.98	.91	0.000	2.54-6.23
	50-59	6.39	1.39	0.000	4.17-9.79
	60-69	8.66	1.87	0.000	5.67-13.21
	≥70	15.21	3.26	0.000	10.01-23.11
FM visits	**1**	1.02	.21	0.911	.68-1.51
	2-6	.83	.067	0.02	.71-.97
	7-12	.43	.037	0.000	.36-.51
	≥13	.45	.043	0.000	.37- .54
SP visits	**1**	.91	.212	0.692	.58-1.44
	2-6	.69	.117	0.031	.49-.97
	7-12	.82	.138	0.233	.59-1.13
	≥13	1.22	.216	0.263	.86-1.71
Hospitalization	**1**	74.72	594.177	0.000	154.41-3541.9
	2-6	531.97	423.211	0.000	112.3-2519.7
	≥7	2110.91	2588.55	0.000	192.4-23155.86
Length Stay	**1**	.76	.299	0.493	.35-1.65
	2-6	1.4	.518	0.324	.70-2.92
	7-15 **16-30**	2.59 2.59	.945 1.09	0.009 0.004	1.26-5.31 1.4-6.11
	>30	4.12	1.567	0.000	1.9-8.76

The results within the enclosed rectangle are from two logistic regression models: 1) model using Postal Code and the variables included in the model to adjust (data was shown in the table. 2) The results from the second logistic regression model using A-R index using the same variables (data was not shown in the table)

5.1.2) Mortality

Additionally, the logistic regression analysis was performed to assess the association between the mortality and place of residence among patients diagnosed with diabetes mellitus. Presence of complications/ comorbidities at the time of diagnosis (complex cases) was significantly associated with higher mortality (OR: 2.27, P < 0.0001, 95% CI: 1.83 – 2.25). For the A-R index analysis, the results showed that the mortality was 1.11 times higher in rural areas than in urban areas (OR: 1.11, P< 0.000, 95% CI: 1.07-1.16) and for the postal code analysis, the results showed that the mortality was 1.19 times higher in rural areas than in urban areas (OR: 1.19, P <0.000, 95% CI: 1.11-1.29). Table 9 shows the adjusted regression model after adding age, sex and health care service visits as independent variables to the model.

Table 9: Logistic Regression for Diabetes Mortality

Mortality		Odds Ratio	Standard Error	P > z	95 % CI
1) A-R Index **2) Postal Code**		**1.11** **1.19**	**.022** **.004**	**0.000** **0.000**	**1.07-1.16** **1.1-1.29**
Complications and comorbidity at diagnosis		2.27	.111	0.000	1.83-2.25
Female		.82	.04	0.000	.73-.89
Age Group	**40-49**	0.04	.007	0.011	.02-.05
	50-59	.06	.007	0.000	.05-.08
	60-69	.13	.009	0.000	.11-.15
	≥70	.27	0.15	0.000	.24-.31
FM visits	**1**	1.73	.362	0.010	1.14-2.6
	2-6	1.33	.1139	0.001	1.12-1.58
	7-12	.55	.049	0.000	.46-.66

	≥13	.42	.042	0.000	.35-.52
SP visits	**1**	.85	.166	0.418	.58-1.25
	2-6	.65	.09	0.002	.49-.85
	7-12	.48	.07	0.000	.36-.64
	≥13	.59	.09	0.001	.44-.82
Hospitalization	**1**	7.72	2.74	0.000	3.85-15.47
	2-6	6.63	2.25	0.000	3.42-12.87
	≥7	16.14	16.7	0.006	2.24-116.1
Length Stay	**1**	.41	.155	0.018	.19-.86
	2-6	.72	.24	0.317	.37-1.38
	7-15	2.24	.769	0.017	1.15-4.3
	16-30	3.93	1.377	0.000	1.99-7.73
	>30	3.91	1.44	0.000	1.93-7.91

The results in enclosed rectangle are from two logistic regression models: 1) model using Postal Code and the variables included in the model to adjust (data was shown in the table. 2) The results from the second logistic regression model using A-R index using the same variables (data was not shown in the table)

5.1.3) Diabetes Complications and Comorbidities During Study Period

As shown in table 10 for the logistic regression analysis, the presence of complex cases was associated with increased development of complications and/ or comorbidities during the study period (OR: 3.73, P <0.0001, 95% CI: 3.34-4.17). For the A-R index and the postal code analysis, the results did not show any effect of remoteness areas on developing complications and/ or comorbidities after five years follow-up (OR: 1.02, P> 0.18, 95% CI: .99-1.06) and (OR: 1.05, P >0.29, 95% CI: .96-1.16), respectively. Table 10 showed the adjusted regression model after adding age, sex and health care service visits as independent variables to the model.

Table 10: Logistic Regression for Diabetes Complications and Comorbidities during Study Period

Complications			Odds Ratio	Standard Error	P > z	95 % CI
1) A-R Index 2) Postal Code			1.02 1.05	.019 .05	0.18 0.29	.99-1.06 .96-1.16
Complications and comorbidity at diagnosis			3.73	.212	0.000	3.337- 4.17
Female			.635	.03	0.000	.58 - .69
Age Group	40-49		4.33	.812	0.000	2.99-6.25
	50-59		6.5	1.17	0.000	4.57-9.2
	60-69		7.39	1.32	0.000	5.2-10.5
	≥70		5.29	.94	0.000	3.7-7.5
FM visits	1		.55	.157	0.036	.3-.96
	2-6		.93	.09	0.468	.76-1.12
	7-12		2.4	.24	0.000	2.01-2.94
	≥13		3.5	.36	0.000	2.88-4.3
SP visits	1		.09	.032	0.000	.04-.18
	2-6		.36	.058	0.000	.26-.49
	7-12		.81	.13	0.196	.59-1.1
	≥13		1.5	.25	0.014	1.08-2.1
Hospitalization	1		124.7	123.7	0.000	17.8-871.1
	2-6		117.4	115.8	0.000	16.9-811.7
	≥7		215.6	325.2	0.000	11.2-4142.8
Length Stay	1		6.8	4.9	0.007	1.6-27.7
	2-6		7.02	4.96	0.006	1.75-28.09
	7-15		7.3	5.2	0.005	1.8-29.3
	16-30		5.05	3.6	0.023	1.25-20.4
	>30		5.3	3.8	0.020	1.29-21.8

The results in enclosed rectangle are from two logistic regression models: 1) model using Postal Code and the variables included in the model to adjust (data was shown in the table. 2) The results from the second logistic regression model using A-R index using the same variables (data was not shown in the table)

CHAPTER 6: SPATIAL AND COMMUNITY LEVEL ANALYSIS

Although traditional interference and prevention efforts to reduce diabetes complications and comorbidities have focused on individual factors, a variety of community and environmental factors are involved in the development of chronic disease, which goes beyond the concept of personal choice[50]. In recent times, there has been a shift toward understanding diabetes diagnosis and outcomes (mortality, complications and comorbidities) from an ecological perspective[48, 49]. This wider perception provides opportunities to focus on the environmental and social impacts and to develop a more precise model of how population health factors might interact with the individual characteristics to produce variations in diabetes diagnosis and outcomes[50, 51]. Geographical methodologies provide opportunities to associate people with features of their local environment and to assess the spatial patterning of health outcomes such as diabetes diagnosis and outcomes.

6.1) Diabetes Cumulative Incidence:

We used the ESRI ArcGIS software to create a map of diabetes cumulative incidence at the community level from 1998 to 2003, as shown in Figure 2.

The map showed high cumulative incidence of diabetes in remote or less accessible areas while it started to be lower incidence with being inhabitant in urban or more accessible areas.

According to the accessibility remoteness index (A-R), the Northeast Avalon area was considered to be an accessible local area while its diabetes cumulative incidence was 2.5%. Likewise, the Grand-Falls Point Leamington and Dear Lake Cormack were deemed to be accessible local areas and their cumulative diabetes incidence were 3.6% and 1.2% respectively. The Placentia Bay North West was seen as a remote (less accessible) area according to A-R index and its diabetes cumulative incidence was 12.2%. The Crabbes River area was one of the least accessible local areas in the province and resulted in an 8.3% incidence of diabetes.

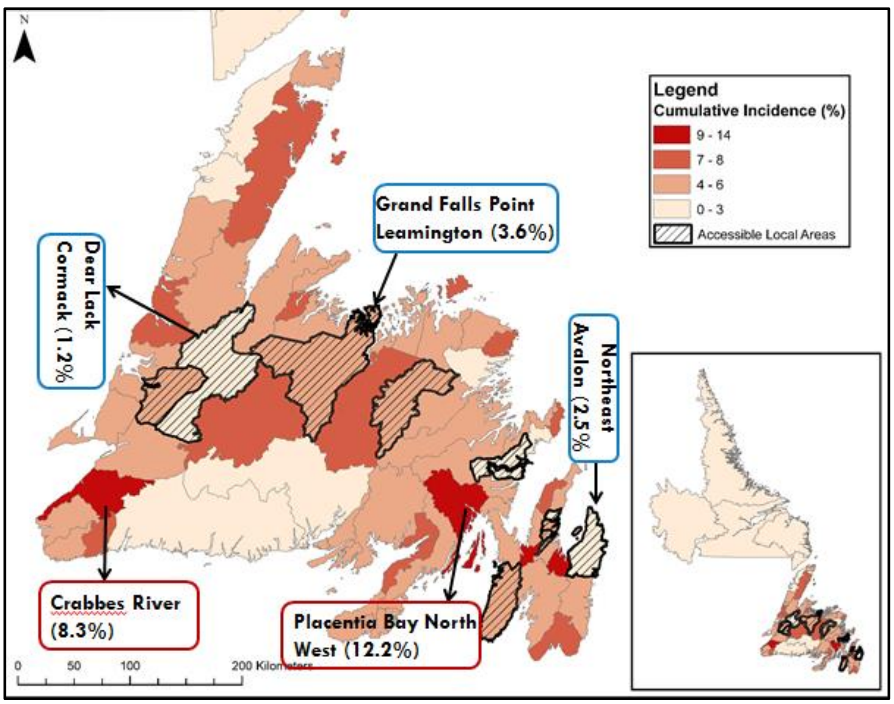


Figure 2: Diabetes Cumulative Incidence at Community Level 1998-2003

6.2) Diabetes Complications and Comorbidities at the Time of Diagnosis

Figure 3 shows the distribution of diabetic patients diagnosed with complications and comorbidities from 1998 to 2003. The results showed a higher percentage of complex cases (diabetic patients diagnosed with comorbidities/complications) in remote areas with less accessibility as shown in the Belle Bay area with a proportion of 30.7% and the Strait of Belle Isle with 39.4%. Both areas were considered to be rural or remote areas according to the A-R index classification. However, the accessible local areas had a lower percentage of complex cases as indicated by the Northeast Avalon area (13%) and the Grand Falls Point Leamington area (8.6%).

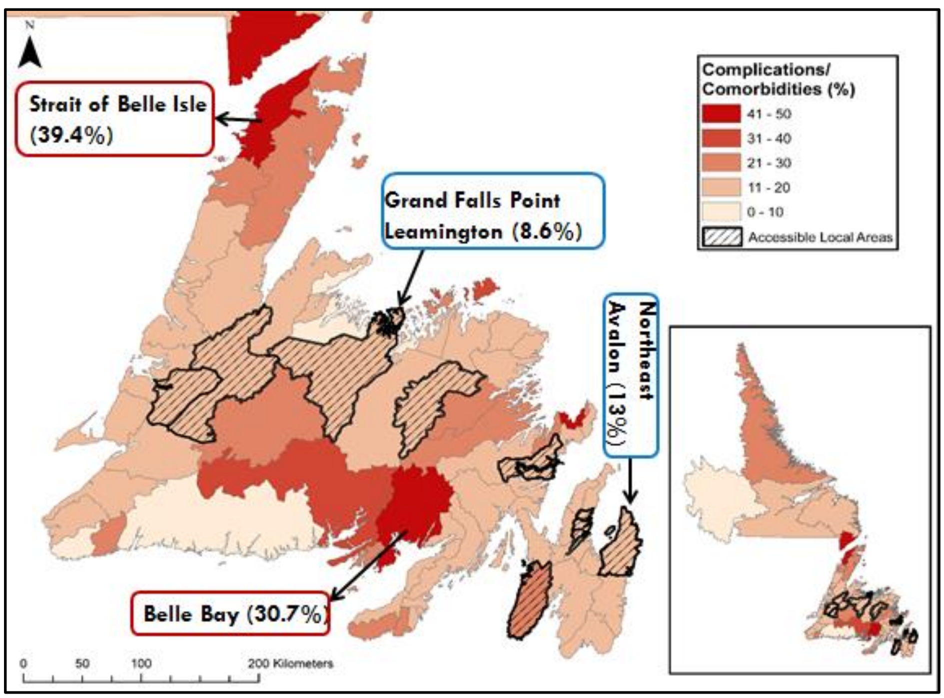
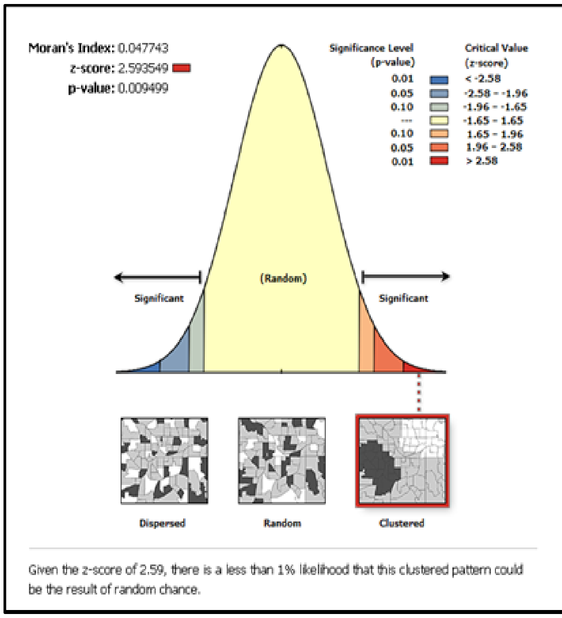


Figure 3: Distribution of Diabetic Patients Diagnosed With Complications/Comorbidities 1998-2003

6.2.1) Spatial Analysis

<u>The Spatial Autocorrelation (Moran's I)</u>

The global Moran's I values (figure 4) for diabetic patients complications and/or comorbidities at the time of diagnosis showed a non-random pattern and positive spatial autocorrelation with a Moran's I of 0.05 and P- value< 0.0095. The z-score of 2.59 indicated that there was less than 1% likelihood that this clustered pattern could be the result of randomness.



Global Moran's I Summary Table

Variable	Late Diagnosis
Moran's Index	0.0477
Expected Index	-0.0128
Variance	0.0005
z-score	2.5935
p-value	0.0095

Figure 4: Diagnosed With Complications/Comorbidities: Spatial Autocorrelation Results

<u>Anselin Local Moran's I</u>

Anselin local Moran's I (cluster – outlier) map (figure 5) for those diagnosed with complications and comorbidities demonstrated hot spots (High – High cluster) of complex cases in the Pinware River area with 48.9% (P<0.000), Strait of Belle Isle with

48.97% (P<0.000), Roddickton area with 27.8% (P<0.003) and Hermitage Bay with 33% (P<0.02). According to the A-R index classification, those areas were considered less accessible (remote). However, in the Goosebay area there was only 14% (P<0.013) of complex cases and the map showed it as a low – high outlier.

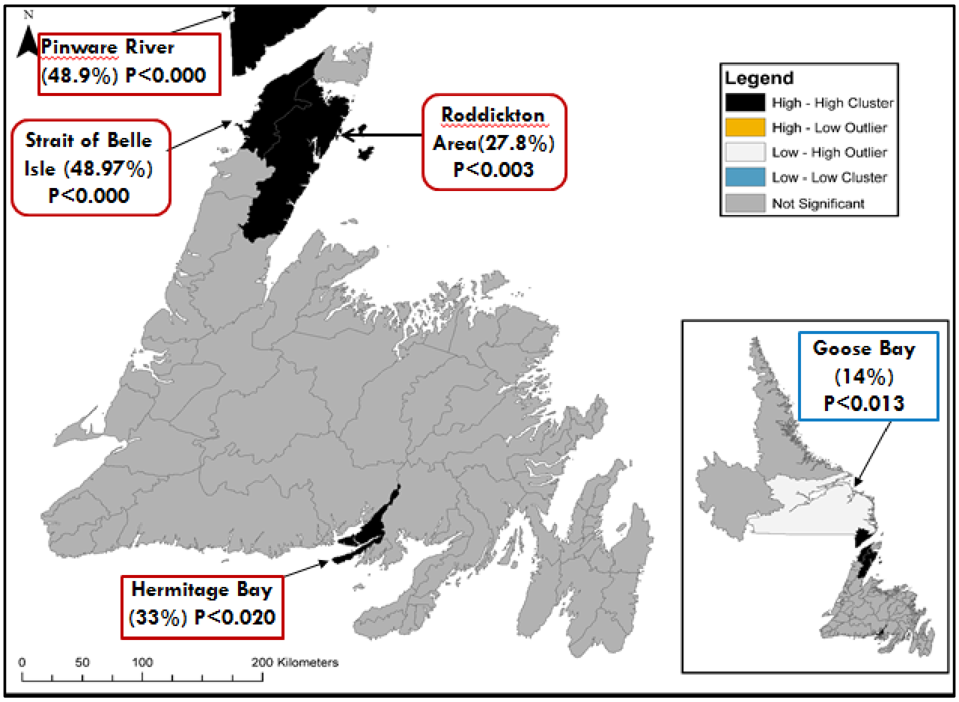


Figure 5: Diagnosed With Complications/Comorbidities Anselin Local Moran's I (Cluster-Outlier) Map

6.2.2) Community Level Model

<u>Model identification and fitness</u>

An iterative stepwise approach was used to determine the best-fitted model to predict diagnosis with complications. By adding and removing some variables and after conducting several trials, the model to predict the diagnosis with complications and comorbidities in terms of its relationships to explanatory variables included: the average remoteness index score, the cumulative incidence at community level, the average age at time of diagnosis and the percentage of regular family medicine utilization at community level, as shown in Table 11, 12.

By assessing model performance in Table 11, we determined the best fitted model we could derive through the previously mentioned explanatory variables. Our best fitted model had a **Multiple R-Squared** of 0.66 and **Adjusted R- Squared** of 0.64, where the adjusted R-Squared for model complexity (number of variables) as it related to the data and the model (explanatory variables modeled using linear regression) and explained approximately 64 percent of the variation in the dependent variable (complications and comorbidities at the time of diagnosis).

Both the **Joint F-Statistic** and **Joint Wald Statistic** are measures of overall model statistical significance and were measured to be 35.63 and 92.23 respectively with a p-value (probability) smaller than 0.001 which indicated a statistically significant model.

The Koenker (BP) Statistic (Koenker's studentized Bruesch-Pagan statistic) is a tool to detect whether the explanatory variables in the model have a reliable relationship to the dependent variable both in geographic space and in data space. The Koenker p-value reveals how likely it is that the associations being modeled are constant across the entire study area. It was measured 16.6 with a p-value (probability) smaller than 0.001, which indicated statistically significant and the relationships did vary across the study area and were, therefore, nonstationary.

The Jarque-Bera statistic was 2.19 with a p-value (probability) larger than 0.001 for a 95 percent confidence level, meaning the residuals were normally distributed, which indicated that this model was not biased.

Table 11: Ordinary Least Squares Regression & Residual Spatial Autocorrelation Results – Diagnosis with Complications

Diagnostic Name	Diagnostic Value
AICc	495.12
R^2	0.66
Adjusted R^2	0.64
Joint F-Statistic	35.63*
Wald Statistic	92.23*
Koenker (Breusch-Pagan) Statistic	16.61*
Jarque-Bera Statistic	2.19^{NS}

*Significant (<0.001)
^{NS}Not Significant

Over and under predictions for an accurately identified regression model were randomly distributed to examine the model residuals. As shown in figure 6, the over-prediction (>2.5 standard deviations) and under-prediction areas (<-2.5 standard deviation) were not clustered, which provided evidence for a good model for predictions with no missing crucial variables. On the other hand, Figure 7 showed spatial autocorrelation results for the residuals with Moran's Index 0.013 and P-value= 0.2667, which were not statistically significant indicating a tendency toward randomness. Given a Z score of 1.11, the pattern did not appear to be significantly different from the pattern of randomness.

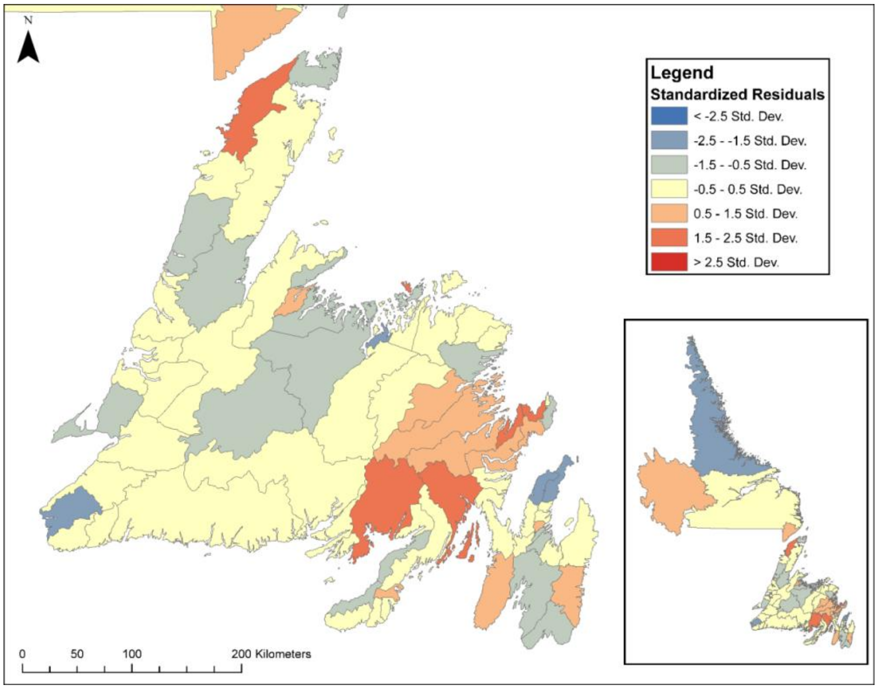
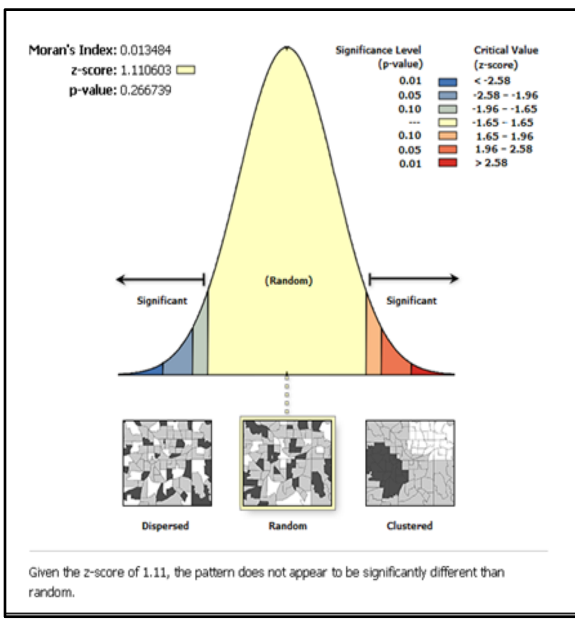


Figure 6: Ordinary Least Squares Regression Map – Diagnosis with Complications



Global Moran's I Summary Table

Variable	Late Diagnosis
Moran's Index	0.0134
Expected Index	-0.0128
Variance	0.0006
z-score	1.1106
p-value	0.2667

Figure 7: Ordinary Least Squares Regression & Residual Spatial Autocorrelation Results – Diagnosis with Complications

Ordinary least squares regression model for complications at the time of diagnosis

Table 12 shows a positive relationship between complications at the time of diagnosis and the average remoteness index score (coefficient 18.09, $P < 0.014$) as well as the average age at the time of diagnosis (coefficient 1.63, $P < 0.000$) at the community level. There was an increase in the percentage of complications at the time of diagnosis, which was associated with both of increasing the remoteness scores (living in very remote (rural) areas) and increasing average age at diagnosis. Also, there was a negative relationship between the percentage of complications at the time of diagnosis and the following indicators: cumulative incidence of diabetes at the community level (coefficient -0.64, $P < 0.046$) and percentage of regular family physician visits in the community (coefficient -0.25, $P < 0.000$). A high percentage of regular family physician visits of low cumulative incidence was associated with a low percentage of complications at diagnosis at the community level.

Table 12: Ordinary Least Squares Regression Model– Diagnosis with Complications

Variable	Coefficient	Standard Error	T Statistics	Probability
Intercept	-74.05	14.41	-5.14	0.000
Average Remoteness Index Score	18.09	7.22	2.51	0.014
Cumulative Incidence of diabetes at Community Level	-0.64	0.31	-2.03	0.046
Average Age at Diagnosis	1.63	0.22	7.47	0.000
Percentage of Regular Visit with Family Physicians	-0.25	0.07	-3.51	0.000

Diagnosed with Complications/Comorbidities = -74 + 18 Remoteness Index - 0.64 Cumulative Incidence + 1.63 Age at Diagnosis - 0.25 Regular Visit with Family Physician

6.3) Mortality Proportion for Diabetic Patients During The Five-Year Study Period

Figure 8 shows the distribution of mortality among diabetic patients during the five-year study period. There was a higher percentage of mortality in remote areas with less accessibility as exemplified by the following local areas: Strait of Belle Isle area (33.3%), Buchans area (31.8%), Bay d'Espoir area (28.8%) and Roddick-ton area (27.2%) of mortality percentage. These local areas with high percentage of mortality were deemed to be remote or rural according to the A-R index classification. With that in mind, the accessible local areas had lower percentage of complex cases as indicated by the Northeast Avalon area (15.2%) and Grand Falls Point Leamington areas (17.2%).

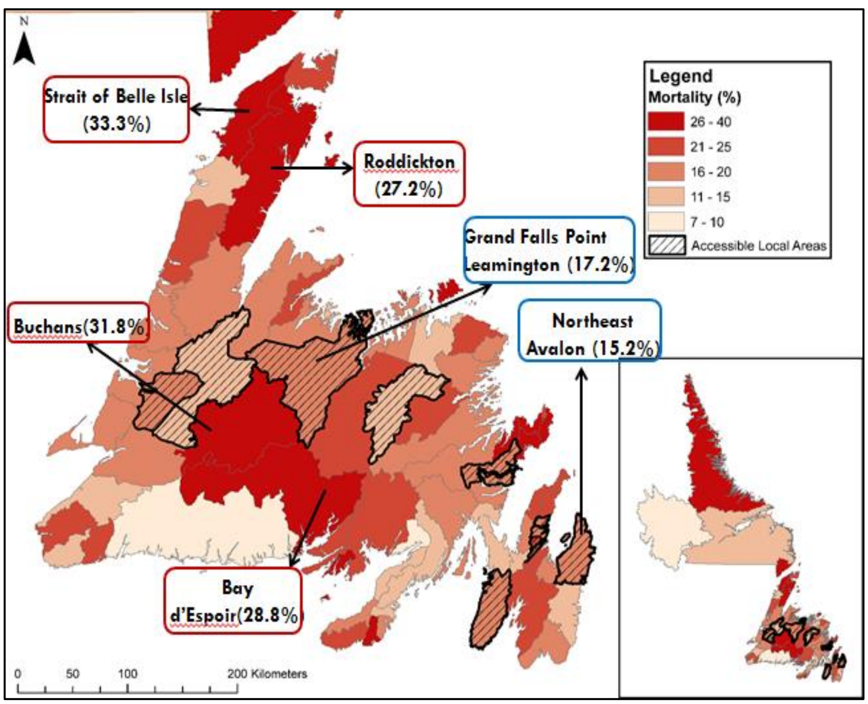


Figure 8: Distribution of Mortality for Diabetic Patients during 5 Year Study Period

6.3.1) Spatial Analysis

The Spatial Autocorrelation (Moran's I)

The spatial autocorrelation model (figure 9) for mortality during the five-year study period showed clustered values and positive spatial autocorrelation with Moran's I = 0.0556 and P- value< 0.0038. The z-score of 2.89 indicated there was less than 1% likelihood that this clustered pattern could be the result of random.

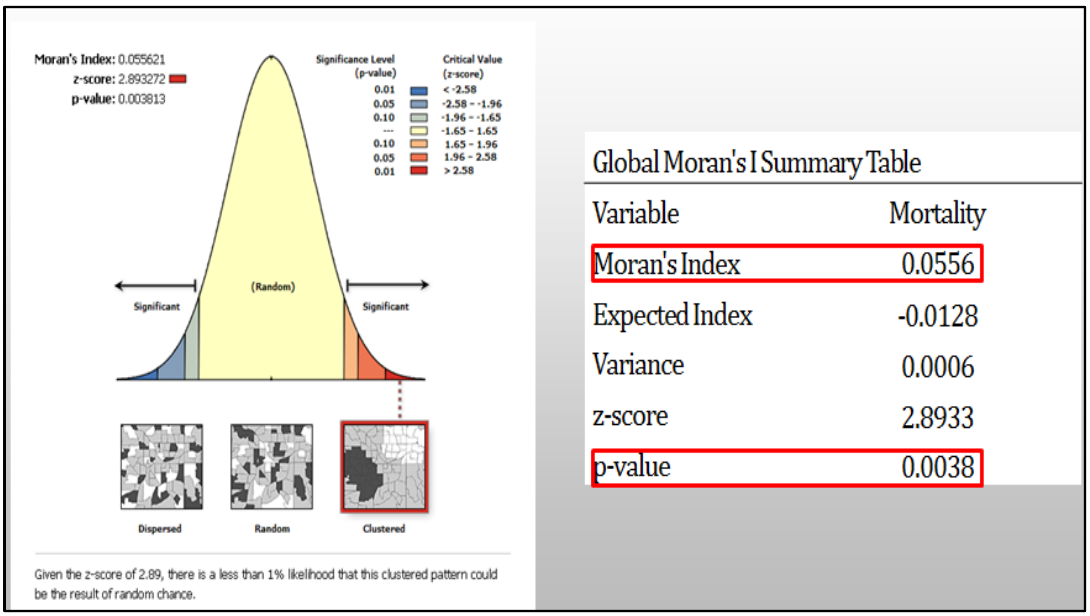


Figure 9: Mortality during Five Year Study Period: Spatial Autocorrelation Results

Anselin Local Moran's I

Anselin local Moran's I (cluster – outlier) map for mortality during the five years showed hot spots (High – High cluster) of mortality in the following areas: the Pinware River area with 26% (P<0.034), the Strait of Belle Isle with 33.3% (P<0.012) and the combination area of Catalina area, Trinity Bay and Black Head Bay with 25 - 40% (P<0.003) mortality. According to the A-R index classification, those areas were considered to be less accessible (remote) areas. The Buchans area which had a 32% (P<0.039) mortality and Labrador North which had a 30% (P<0.001) mortality were classified as being high - low outliers, while the Terrence Ville area was found to be in a low – low cluster with a 9% (P<0.039) mortality. (Figure 10)

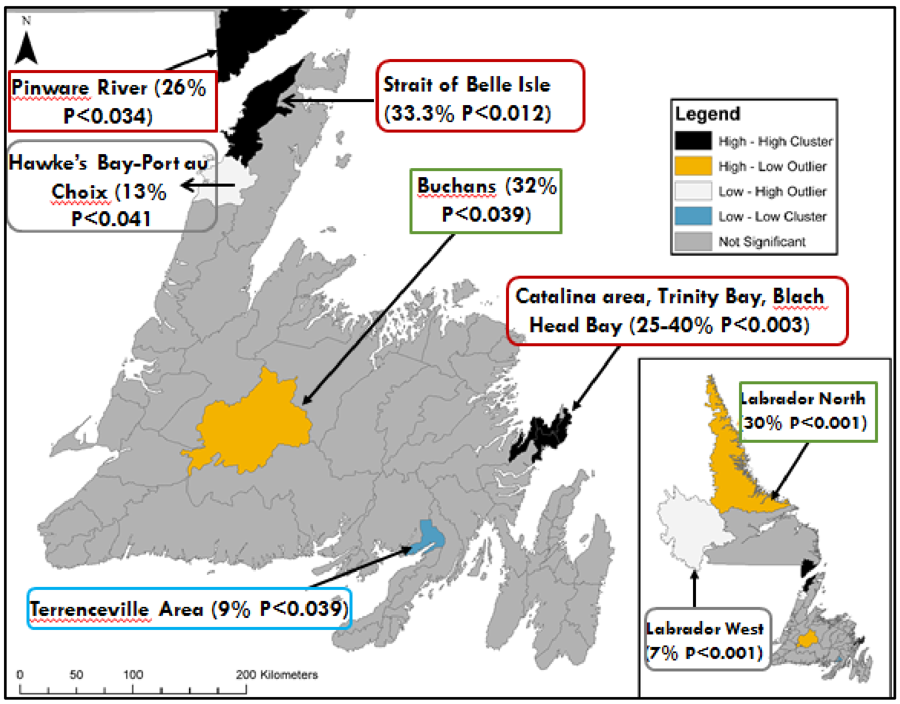


Figure 10: Patient Mortality Anselin Local Moran's I (Cluster-Outlier) Map

6.3.2) Community Level Model

<u>Model identification and fitness</u>

An iterative stepwise approach was used to determine the best-fitted model for predicting diabetes mortality. By adding and removing variables and after conducting several trials the best fitted model to predict diabetes mortality probability in terms of its relationships to explanatory variables included: average remoteness index score, percentage of complications and comorbidities at the time of diagnosis at the community level, the average age at diagnosis and the percentage of hospitalization at the community level. (Table 13, 14)

By assessing model performance (Table 13), the best fitted resulted in a **Multiple R-Squared** of 0.61 which represented the proportion of variation in the dependent variable explained by the model and **Adjusted R- Squared** of 0.59 which explained approximately 59 percent of the variation in the dependent variable (diabetic mortality).

Both the **Joint F-Statistic** and **Joint Wald Statistic** measured 28.46 and 94.74 respectively with a p-value (probability) smaller than 0.001, which indicated a statistically significant model.

The Koenker (BP) Statistic (Koenker's studentized Bruesch-Pagan statistic) was measured 10.28 with a p-value (probability) smaller than 0.001, which indicated statistically significant and the relationships did vary across the study area and were, therefore, nonstationary.

The Jarque-Bera statistic was 4.67 with a p-value (probability) larger than 0.001 for a 95 percent confidence level, meaning the residuals were normally distributed, which indicated that this model was not biased.

Table 13: Ordinary Least Squares Regression & Residual Spatial Autocorrelation Results – Mortality

Diagnostic Name	Diagnostic Value
AICc	449.69
R^2	0.61
Adjusted R^2	0.59
Joint F-Statistic	28.46*
Wald Statistic	94.74*
Koenker (Breusch-Pagan) Statistic	10.28*
Jarque-Bera Statistic	4.67^{NS}

*Significant (<0.001) ^{NS} Not Significant

Over and under predictions for an appropriately identified regression model was randomly distributed for examining the model residuals. As shown in figure 11, the over-prediction (>2.5 standard deviations) and under-prediction areas (<-2.5 standard deviation) which indicated that it was not a good model for diabetes mortality predictions. Additionally, figure 12, showed spatial autocorrelation results for the residuals with Moran's Index I = 0.0725 and P-value< 0.0003, which indicated a tendency toward clustering and presented a non-random spatial pattern. The z-score of 3.59 indicated there was less than 1% likelihood that this clustered pattern could be the result of randomness.

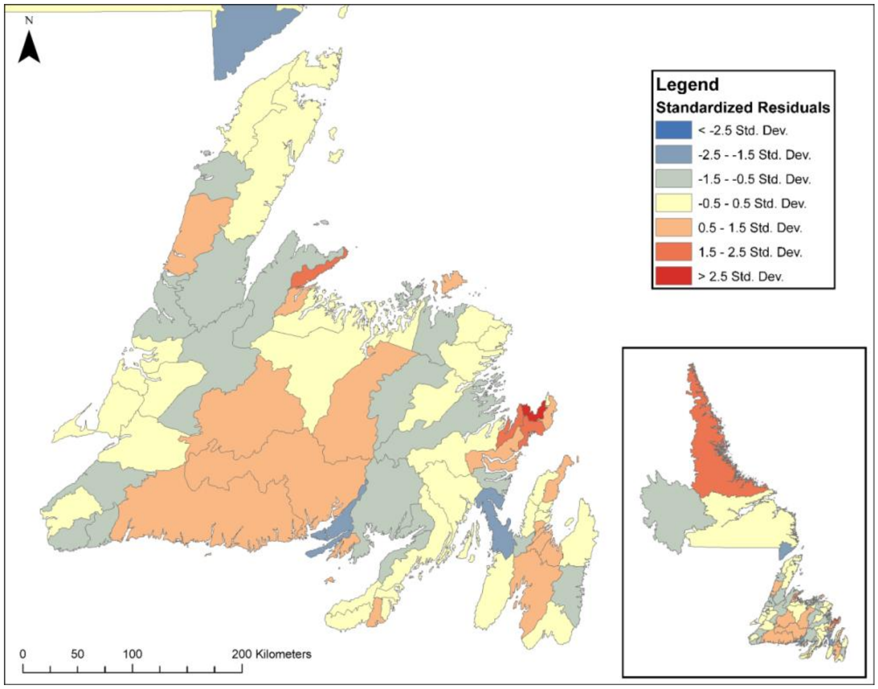
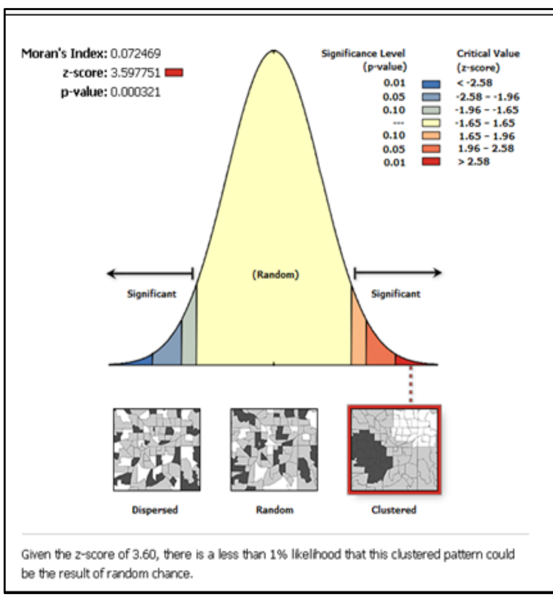


Figure 11: Ordinary Least Squares Regression Map – Mortality



Global Moran's I Summary Table

Variable	Mortality
Moran's Index	0.0725
Expected Index	-0.0128
Variance	0.0006
z-score	3.5978
p-value	0.0003

Figure 12: Ordinary Least Squares Regression & Residual Spatial Autocorrelation Results – Mortality

Ordinary least squares regression model for mortality after five -year follow up

Table 14 shows, positive relationships between the diabetic mortality and both complications at the time of diagnosis (coefficient 0.18, P< 0.046) and the average age at the time of diagnosis (coefficient 0.94, P< 0.000) at the community level. There was no significant association between mortality proportion and both the average remoteness index score (coefficient 3.53, P= 0.531) and percentage of hospitalization at the community level (coefficient 0.21, P= 0.091).

Table 14: Ordinary Least Squares Regression & Residual Spatial Autocorrelation Results – Mortality

Variable	Coefficient	Standard Error	T-Statistics	Probability
Intercept	-43.57	12.11	-3.60	0.001
Average Remoteness Index Score	3.53	5.62	0.62	0.531
Percentage of Complications at time diagnosis at the Community Level	0.18	0.09	2.02	0.046
Average Age at Diagnosis	0.94	0.21	4.52	0.000
Percentage of Hospitalization at Community Level	0.21	0.12	1.71	0.091

6.4) Diabetic Complications and Comorbidities During the Study Period

Figure 13 showed the distribution of diabetic patients that developed complications and comorbidities during the five-year study period and illustrated a higher percentage of complications and comorbidities in remote areas, as indicated by local areas such as the Hermitage Bay area (25.5%), the Belle Bay area which (27%) and the Hawke's Bay Port Au Choix area (23.7%). These local areas were all classified as being remote or rural areas according to the A-R index classification. More accessible local areas had lower percnetages of patients developing complications and/or comorbidities during the study period, as indicated by the Northeast Avalon area (17%) and the Grand Falls Point Leamington area (13.5%).

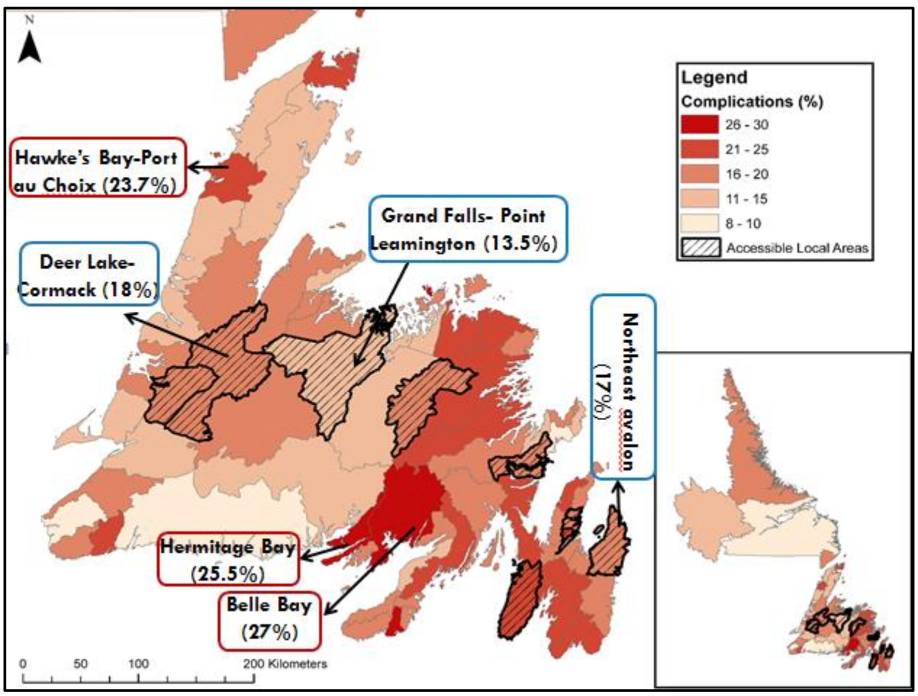


Figure 13: Distribution of Diabetic Patients That Developed Complications during Five Years Study Period

6.4.1) Spatial Analysis

<u>The Spatial Autocorrelation (Moran's I)</u>

The spatial autocorrelation model (figure 14) which analyzed complications and/or comorbidities during the five-year study period showed a low and non-significant Moran's I index (Moran's I= 0.0088 and P- value= 0.3617). Given the Z-score of 0.19, the pattern did not appear to be significantly different from the pattern of randomness. The result from the spatial analysis showed that there was no spatial autocorrelation between diabetes complications and comorbidities and its associated spatial features (Local Areas) during the study period.

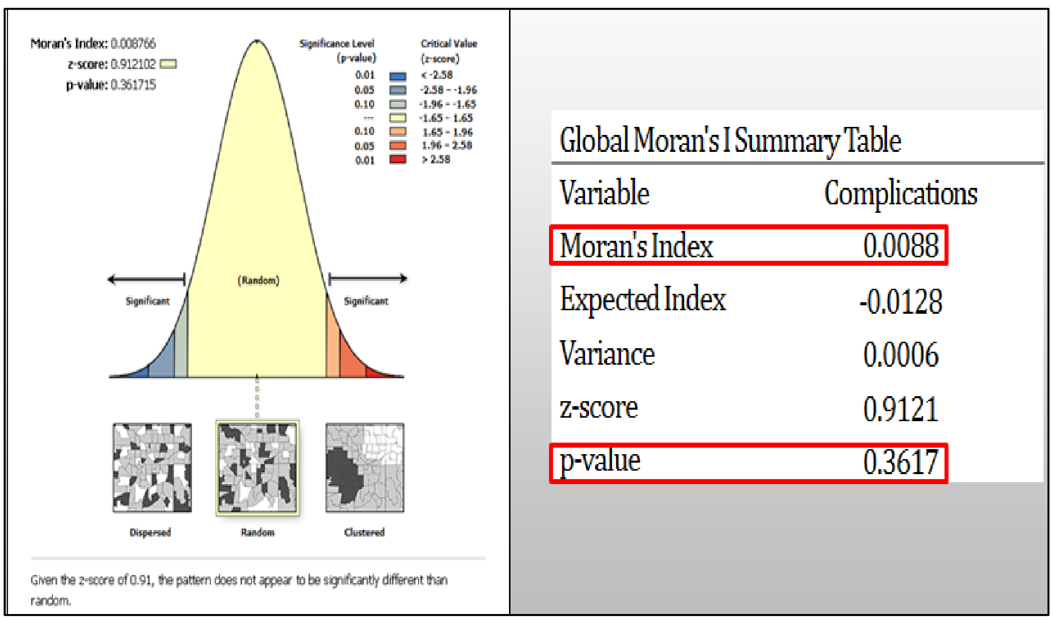


Figure 14: Complications/Comorbidities during Five Year Study Period: Spatial Autocorrelation Results

6.4.2) Community Level Model

We did not perform any further geospatial analysis or OLS regression model as there was no spatial autocorrelation between diabetes complications and comorbidities and its associated spatial features (Local Areas) during the study period, according to the Global Moran's I model.

CHAPTER 7: DISCUSSION AND CONCLUSION

This thesis aimed to assess the presence of disparities between rural and urban areas and to analyze the effect of geographic variation on diabetes diagnosis and outcomes (mortality, comorbidities and/or complications) in adults age 20 and older in NL after a five-year follow-up. This thesis illustrated the impact of rural-urban difference in demographic factors (sex and age) and health care utilization on diabetes outcomes factors (visits with specialists, family physicians, and hospitalization). This chapter initiates with an overview of the study results and how they compare to the current body of rural – urban disparities in diabetes research. A summary of the present study's strengths, limitations, implications, and conclusions are described.

7.1) Overview of The Findings

This study focused on diabetes diagnosis and outcomes (complications, comorbidities, and mortality) but from a geographical aspect (rural and urban areas). The first question which the study tried to answer was: in adults age 20 years and older in NL, does where people live (rural vs. urban) affect the probability of complex cases (patients with complications and comorbidities at the time of diabetes diagnosis)? The second question was: in adults age 20 and older in NL, does where people live (rural vs. urban) affect their likelihood of death& developing complications/ co-morbidities and death after the diagnosis of diabetes?

According to the individual level analysis, spatial and community level analysis, a positive relationship existed between complications and/or comorbidities at the time of diagnosis and where one lived: people who lived in remote/ less accessible areas in NL were more likely to be diagnosed as a complex patient [OR: 1.23, P<0.000, 95% CI: 1.19-1.28). Higher percentage of complex cases in remote areas with less accessibility (30 – 50%) comparing to (8 -10%) of complex cases in accessible areas. Remote/less accessible areas mean increase distance from community services and accessibility to health care services like hospital, clinics or laboratories.The early detection of diabetes can result in timely treatment and the prevention of complications. These results agree with what others found. For example, Roche et al. concluded that males diagnosed late with diabetes were more likely to live in a rural area[16]. O'Connor et al. found that the rural locations had the higher prevalence of diabetes and CVD, which aggravated the well-established lack of primary care providers in rural areas and also to more difficulty obtaining health insurance and longer distances to reach health care services[29].

After adjustment, the models for some crucial variables showed significant relationships between complex diagnosis and the different age groups and the number visits to the family physician. This finding agrees with the study from South Carolina, which concluded rural areas have less adequate care including physician visits which subsequently affect frequency of hospitalization for diabetic complications[19]. An American study by Salanitro et al[53] of rural primary care practices showed that physician-level performance was significantly related to patients' age and insulin use as well as difficulties with self-testing and keeping appointments. This study also concluded that rural patients confront barriers in self-testing and appointment keeping.

Our second hypothesis was that diabetes outcomes (complications, mortality) in urban areas were different from the outcomes in rural areas among adults aged 20 years and older five years after getting diagnosed with diabetes mellitus in NL. The logistic regression model, spatial and community level analysis didn't find any significant association between complications and/ or comorbidities during the five-year study period and living in remote or rural areas (OR: 1.02, P> 0.18, 95% CI: .988-1.06). After adjustment the models for some crucial variables, we observed that a diabetic patient who was diagnosed as a complex case was more likely to develop more complications and/ or comorbidities during the five-year follow-up. Complications and/ or comorbidities through the five-year follow-up were higher among the patients aged 60 to 69 years old and also with more visits for a family physician.

A study by Krishna et al.[54] disclosed that rural diabetes self-management education (DSME) in the rural areas of Pennsylvania is an underused service and lower than one-half of this patients reported receiving any diabetes education. The lack of this service in the rural communities caused a dramatic increase in myocardial infarctions, microvascular disease, and death[54]. The American Diabetes Association recommends diabetes preventive care practices of an annual eye examination, annual foot examination by a health professional, and HbA1c testing at least twice a year[55, 56]. The other studies showed that residing in rural areas had increased the barriers to receiving these recommended care for eye and foot examinations[56, 57]. So, examining the diabetic complications and/or comorbidities may give a significant association with a rurality by adding other explanatory variables or it might need a longer period of follow-up during the study.

The logistic regression model showed that mortality increased in those patients who were diagnosed as a complex case, and these complex cases were more likely to live in remote/ less accessible areas. So the individual level model showed that there was a high risk of mortality in rural and remote areas (OR: 1.11, $P < 0.000$, 95% CI: 1.07-1.16). The spatial and the community level analysis showed positive spatial autocorrelation between spatial features and mortality with high clustering of mortality in rural and remote areas. The best-fitted OLS model for mortality prediction found a positive relationship between mortality and both complications at the time of diagnosis and the average age of diabetic patients. However, the standardized residuals from the OLS model for mortality were spatially autocorrelated and therefore globally miss-specified so that mortality could be predicted at the local level but not globally. These results agree with the study by Roche et al. who found a late diabetes diagnosis was positively associated with CVD mortality and CVD and have a longer length of hospital stay for females[16]. A study, published in 2011[58], on the variances between rural and urban health in Canada, found that those who lived in rural or remote regions had a higher mortality percentage than urban residents[58]. The mortality proprotion related to diabetes appeared to be a greater worry for women living in rural area than women in urban regions[58]. The main causes for the differences detected in rural Canadians were the limited access to health care and maintenance programs compared to Canadians living in urban places and absence of early diagnosis, where it was known that treatment will have better outcomes[58,59,60,61].

Hill criteria, suggested by English epidemiologist Sir Austin Bradford Hill[61], are a group of criteria to provide evidence of a causal relationship between a cause (in this study place of residence) and its effect (in this study diabetes diagnosis and outcomes). This study addresses some of these criteria: *Strength of association*: the odds ratio of 1.2 and the coefficient of 18 in this study propose a causal effect between living in rural areas and getting diagnosis as a complex case. *Consistency:* both the individual and community level analysis showed a high association between remote/less accessible areas and the prevalence of complex cases. Furthermore, previous studies listed a significant relationship between living in a rural area and developing complications or comorbidities at the time of diagnosis[16,21,24,28,29]. Studies also showed that people who were living in remote areas were more likely to die[16, 18, 52]. Consistent findings observed by different investigators in different places with different samples strengthened the likelihood of an effect of the remote/ less accessible areas on complex cases and mortality. *Temporality*: a cohort study using the geospatial technique to identify the place of residence at the time of diagnosis was also supportive of a causal relationship. *Analogy:* other studies for different chronic diseases showed the place of residence as an influential factor in diagnosis and outcomes[16, 22, 57, 58, 59,62]. *Coherence*: there was consistency between epidemiological and geospatial findings showing an increase the likelihood of the complex cases and the mortality in remote/ less accessible areas.

Biological gradient: the accessibility remoteness index score ranged from highly accessible to extremely remote, the individual and community level models showed that increase in remoteness leads to a greater incidence of complex cases and the mortality, which agreed with the criteria of a biological gradient.

7.2) Strength and Limitations

To our knowledge, this is the first study in NL using a GIS approach to identify differences between rural and urban regions and to define whether these variances affect diabetes diagnosis and outcomes. Additionally, using a large population-based database and performing both individual and community level analyses, was a cost-effectiveness approach to enhance the accuracy of study findings and to improve the generalizability of these conclusions.

The study does have some limitation, however. First, this was a retrospective cohort study using secondary data, so it is not as reliable as a prospective study. In our study, we used the CCDSS diabetes case definition, so we were not capable of distinguishing between type 1 and type 2 diabetes; however, this is not likely to have a major effect on the results as the study population included adult only, most of the adults have type 2 diabetes[15].

The CCDSS diabetes case definition depends on the physician claims data and hospital discharge data. In NL, one-third of the physicians in the province are paid on a salary basis, who is not obliged to submit medical claims. Consequently, the sample of diabetes cases might be less than the exact and the real number of incident cases.

This secondary analysis is representative of complications and comorbidities condition recorded in our database. In reality, hospital discharge data and physician billing are limited in the representation of some disease state including obesity, dyslipidemia and the disease condition which may be diagnosed by allied health practitioner such as retinopathy[16].

We were restricted to a cut-off point of one year when identifying complex cases as the data was available on a yearly basis not per month. Several studies empathized that comorbidities or complications that developed in individuals with diabetes could be extended from definite to very broad (6 months–2 years) before/after diagnosis[16, 21].

Additionally, secondary data does not provide information on all factors influencing diabetes diagnosis and outcomes including socioeconomic status, patient educations, patient moving or income. So, future studies can be designed using a prospective cohort study approach which can test more explanatory variables related to diabetes comorbidities.

The community level analysis is prone to an ecological fallacy, but it is less likely to be an issue in this study. Similar findings were obtained using individual-level modeling, community-level modeling and geospatial visualization.

Lastly, this study used the place of habitation at the beginning of the study period but the movement from an urban to a rural region and vice versa through the 5-year study period could have occurred.

7.3) Conclusions

Our findings indicated that at the individual level, living in a rural area affected the likelihood of complications and/ or comorbidities at the time of diagnosis. The individual level analysis showed that living in rural areas did not affect the likelihood of the complications and/ or comorbidities through the five-year follow-up; however, it showed that people who were living in a remote places were more likely to die. At the community level, the results of each model demonstrated the importance of proper conceptualization of geography and how a person's environment could influence their health outcomes. We did find that remoteness/ accessibility affected the likelihood of a complex case detection. While the diabetic patients who were living in a remote/ less accessible area were more likely to die at the local level, the OLS model was miss-specified and A-R index was not significant. So, the mortality could be predicted at the local level but not globally. Besides, the geospatial analysis did not show that residing in a remote area had any effect on complication and comorbidities through the five-year follow-up.

People in remote rural locations often face many challenges in access to healthcare services resulting in under diagnoses, and poorer health outcomes. Identifying potential individual risk factors and rural/urban factors affecting diabetes in NL could help inform intervention strategies to decrease the risk of diabetes and its complications in at-risk populations. Different aspects of statistical, geographical and epidemiological analysis were used in this study, which can help to develop a new methodology for using the medico-administrative data in NL and getting more accurate and significant results which help decision-makers better understand the geographic variations in diabetes diagnosis and management. By demonstrating diabetes diagnosis and outcomes in a geographic context, this project could help in allocating resources more efficiently to improve healthcare services including screening, diagnosis, and controlling services for diabetes.

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APPENDIX

Table 15 Summary of Findings in Studies Relevant to Rural/Urban Difference in Diabetes Diagnosis and Outcomes

Study	Country	Study Population	Study Sample Size	Study Design	Rural / Urban definition	Complications and morbidities at diagnosis	Complications	Mortality
Kevin et al, 2012	South Carolina, Columbia	At least 1 hospitalization during the year	21275	Retrospective cohort study	Rural was defined using the 2003 Urban Influence Codes (UICs). UICs of rurality were classified as "urban" while all other UICs were classified as "rural." Analysis across levels of rurality used 3 groups: "metropolitan rural" (UICs 3, 5, and 8); "small adjacent rural" (UICs 4, 6, and 7); and "remote rural" (UICs 9, 10, 11, and 12).		20% discharged from a hospitalization had a subsequent readmission within 30 days, with only 10% of these being intended readmissions. Residents of remote rural counties were also less likely to have a readmission (OR 0.74, 0.57-0.95) Follow-up physician visit within 30 days were lower in rural inhabitants, 12.9% rural compared to 14.9% urban.	
O'Connor et al, 2012	United State.	respondents using data from the US Centers for Disease Control and Prevention's (CDC's) 2008 Behavioral Risk	214,000	Cross-sectional study	Respondents were categorized by metropolitan statistical area (MSA). Respondents living in an urban area with 50,000		Prevalence rates of diabetes and CVD were 8.6% (P = 0.001) and 38.8% (P < 0.001) higher among population living in rural areas compared with urban areas,	

		Factor Surveillance System			or more inhabitants were designated as 'urban', whereas respondents living outside of an MSA were designated as 'rural.'		respectively. After controlling for risk factors, the prevalence of diabetes was lower among respondents living in rural areas [prevalence odds ratio (POR) = 0.94, P = 0.032], but the prevalence of coronary heart disease was higher (POR = 1.09, P = 0.011).	
Dos Santos et al, 2013	Brazil.	Elderly individuals with self-reported DM. Aged 60 years or more.	271 elderly individuals from urban areas and 104 from rural areas	observational and cross-sectional household survey studies	The population sample analyzed by the Center for Research in Community Health of the Triangulo Mineiro Federal University was used to define the urban population.	The mean number of morbidities within the elderly urban population (μ = 8.57) was significantly higher than that of the rural population ($\mu = 7.2$).	Females were more prevalent in both the urban (69%) and rural (65.4%) areas. The elderly urban population reported more vision problems ($\beta = 1.875$; $p = 0.019$), instances of poor circulation ($\beta = 3.189$; $p < 0.001$) and heart problems ($\beta = 2.271$; $p = 0.001$) compared to the rural population.	the elderly individuals who lived in the rural area had significantly lower QoL scores than those of the urban area in the sensory abilities ($\beta = -0.243$; p
Hye Y. et al, 2010	Korea	adults >30 year of age from urban and rural districts	1,060 from urban (189 males and 331 females) and rural districts (219 males and 321 females).	Prospective Cohort study	The characteristics of rural life were defined to represent a livelihood related to agriculture or agrarian activities, while the livelihood of urban dwellers was primarily office work.	Higher prevalence of T2DM in an urban population (14.5 %) compared to a rural population (8.6%) in Korea.	The serum HDL-C level and monthly income were significantly higher in the urban than rural population (3.95 vs 3.74 mM/L). Systolic blood pressure is high in both populations.	
Vanasse A et al, 2010	Quebec (Canada	1- patients newly hospitalized for a myocardial infarction (MI)	1- The atherosclerotic cohort included a	retrospective population-based cohort studies	According to The Statistical Area Classification (SAC) there are		For atherosclerosis and diabetes, the adjusted rates of morbidity were	No difference between rural and urban areas in the mortality

		2- patients who had suffered a fragility fracture (FF) 3-Incident cases of diabetic (DB) patients.	total of 44 806 patients 2- The cohort of patients with FFs included a total of 64 540 individuals 3- A total of 71 857 patients were newly diagnosed with diabetes between 2001 and 2002.		two categories of urban areas depending on the size of the urban core population: Census Metropolitan Areas (CMA) or metropolitan areas, with a population of at least 100 000, and Census Agglomerations (CA) or small towns, with a population between 10 000 and 99 999		significantly higher in non-metropolitan areas than in metropolitan areas with the highest rates found in remote regions	rates is observed across all three chronic diseases
Attard et al, 2012	China.	18– 90 years old.	7741 adults	Cohort study	Urbanisation was measured using an urbanisation index based on household- and community-level data representing 12 features of the community environment.	High vs low urbanisation was associated with approximate twofold higher diabetes prevalence (men OR 2.02, 95% CI 1.47, 2.78; women OR 1.94, 95% CI 1.35, 2.79). The prevalence of undiagnosed diabetes did not differ by high vs low urbanisation level (men OR 1.25, 95% CI 0.84, 1.85; women OR 1.38, 95% CI 0.88, 2.17).		
Cheryl et al, 2011	United State	veterans with type 2 diabetes determined according to US census-based metropolitan statistical area	10,570	Cohort study	The Office of Management and Budget (OMB) defines "rural" as residing in a non-metropolitan statistical area (MSA).	A lower proportion of rural patients received screening and preventive clinical services than urban patients, such as lipid profiles (74% versus 50%), eye examinations (18% versus 6%), micro albumin screening (32% versus 4%), aspirin therapy (39% versus 18%) and vaccinations (74%	Rural veterans had less access to care, higher susceptibility to travel barriers, lower health-related quality of life, and a higher prevalence and poorer control of physical health comorbidities.	

						versus 11%)		
Dyck et al, 2013	Saskatchewan	Male and Female aged 18 years or older who lived on an identified farm/non-farm location	8208	prospective cohort study	rural dwelling – residence on a farm or non-farm location (including town and self-described acreage)	Residence on farms had significantly lower diabetes prevalence than those living in non-farm locations. Diabetes prevalence in nonfarm location is 7.3% compared to 5.1% among those living on farms.	Cardiovascular disorders exhibited odds ratios (ORs) of 3.01 (hardening of the arteries) to 5.21 (high blood pressure) among people with diabetes compared to others, while tuberculosis also demonstrated a strong relationship. Cancer and chronic lung disorders displayed less striking but still largely significant associations with diabetes. Diagnosed sleep apnea and related symptoms demonstrated particularly significant associations with diabetes.	
Nathan et al, 2010	United States	18 and older self-reporting a diagnosis of diabetes	29,501	a cross-sectional analysis	Definitions of rural were based on the 2003 Urban Influence Codes (UICs) from the United States Department of Agriculture Economic Research Service. Rural counties vary in size, and may contain modest urbanized areas of less than 50,000 populations.	A lower proportion of rural than urban persons with diabetes reported a dilated eye examination (69.1 vs. 72.4%; *P* = 0.005) or a foot examination in the past year (70.6 vs. 73.7%; *P* = 0.016).	a greater proportion of rural than urban persons reported diabetic retinopathy (25.8 vs. 22.0%; *P* = 0.007) and having a foot sore taking more than four weeks to heal (13.2 vs. 11.2%; *P* = 0.036).	
Madonna et al, 2013	Newfoundland and	individuals aged 25 years or older	73,783	population-based retrospective	urban place of residence was	A late-diagnosed diabetes patient would have	Diabetes was positively associated	both males and females with

	Labrador			cohort study	defined as an area with $5,000 inhabitants, whereas a rural place of residence was defined as an area with ,5,000 inhabitants	comorbidities related to diabetes at the time of diagnosis with diabetes-related comorbidities within 6 months before or after diagnosis. Males and females with late diagnoses were significantly older at the time of diagnosis than those with early diagnoses (P< 0.01). Survival time for both males and females with early diagnoses was significantly longer than that of those with late diagnoses (P < 0.01). During the study period, males and females with late diabetes diagnoses were more likely to be hospitalized (P < 0.01) and have a longer length of hospital stay compared with those with early diagnoses (P < 0.01).	CVD hospitalizations (2.57 [2.24–2.94]) for females, and the risk was significantly higher compared with their male counterparts (1.59 [1.51–1.69] and 1.92 [1.72–2.14]). A late diabetes diagnosis was positively associated with CVD mortality (HR 6.54 [95% CI 4.80– 8.91]) and CVD hospitalizations (5.22 [4.31–6.33]) for females, and the risk was significantly higher compared with their male counterparts (3.44 [2.47–4.79] and 3.33 [2.80–3.95]).	diabetes had an increased risk of dying of all causes and being hospitalized for CVD and AMI when compared with males and females without diabetes. Diabetes was positively associated with all-cause mortality (HR 1.85 [95% CI 1.74– 1.96])
Madonna et al, 2014	Newfoundland and Labrador	individuals aged 25 years	7101	Cross-sectional study	Urban region of residence was defined in the CCHS as an area with a population concentration of 1000 or more and a population density of 400 or more per square kilometer based on census counts	Males diagnosed late with diabetes were more likely to live in a rural area compared to early diagnosed males (P < 0.01), whereas no difference was found for females. Males with late diagnoses were more likely to be overweight/obese compared to early diagnosed males (P < 0.01), while no difference was found for females. On the other hand, females with a late diabetes diagnosis were more likely to be physically	Living in a rural area (HR, 1.47; 95% CI, 1.01-2.15), receiving social assistance (HR, 2.80; 95% CI, 1.52-5.15), having poor self-perceived health (HR, 2.06; 95% CI, 1.32-3.21), and considering most days stressful (HR, 1.45; 95% CI, 1.01-2.10) were positively associated with diabetes for females.	

						inactive compared to females diagnosed early (P < 0.01). For males, no factors were significantly associated with an early or late diabetes diagnosis. However, for females, having a low education (OR, 0.33; 95% CI, 0.11-0.99) was inversely associated with a late diabetes diagnosis		