DIABETES AND EARLY AND LATE DIAGNOSIS IN NEWFOUNDLAND AND LABRADOR

By

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Abstract

The primary objective of this research was to examine diabetes with a focus on the timing of its diagnosis, the factors associated with diabetes, risk of mortality and hospitalization outcomes, and the diagnosis, treatment and management in Newfoundland and Labrador. Administrative data were used to develop definitions of early and late diabetes diagnosis based on when various complications and comorbidities developed. This dissertation is comprised of three studies. The first study aimed to describe factors associated with diabetes, a late diabetes diagnosis, and whether these factors are different for males and females. The second study compared risk of mortality and hospitalizations for males and females with and without diabetes and those diagnosed early and late with diabetes. The third study aimed to describe how family physicians diagnose, treat and manage type 2 diabetes and to identify if there were any differences in how male and female family physicians diagnose, treat and manage those with type 2 diabetes.

The findings indicate that different factors are associated with a diabetes diagnosis and its timing in males and females. Females living in a rural area, receiving social assistance, having poor self perceived health and considering most days stressful appear to have the greatest risk for developing diabetes. Females with lower education levels are less likely to be diagnosed late with diabetes compared to females with a higher level of education. Females with diabetes have a greater risk of mortality than males with diabetes and cardiovascular disease has a greater negative impact on females with diabetes than on males, especially when females are diagnosed at a later stage. Finally, the majority of family physicians in this province have patients with complications present when diagnosed with diabetes. Even though family physicians have positive attitudes toward diabetes management, risk factors for diabetes complications are not

monitored optimally. Male and female family physicians were similar in their diagnosis, treatment and management practices and in their attitudes toward diabetes.

In conclusion, certain risk factors appear to impact males and females differently and more research is needed on the timing of diagnosis and how males and females develop diabetes. Different management strategies could be considered for males and females and those diagnosed at different stages with diabetes. Family physicians should monitor risk factors for diabetes complications more closely in an attempt to manage progression of the disease.

Dedication

I dedicate this dissertation to my daughter, Harriet. Thank you for inspiring me to complete this work and for providing me with endless joy and laughter.

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List of Abbreviations

HbA1C	Glycated Hemoglobin
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AMI	Acute Myocardial Infarction
BMI	Body Mass Index
CCDSS	Canadian Chronic Disease Surveillance System
CCHS	Canadian Community Health Survey
CCI	Charlson Comorbidity Index
CDA	Canadian Diabetes Association
CDMS	Clinical Database Management System
CHD	Coronary Heart Disease
CI	Confidence Interval
CPG	Clinical Practice Guidelines
CVD	Cardiovascular Disease
DREAM	Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication
FPG	Fasting Plasma Glucose
GDM	Gestational Diabetes Mellitus
HR	Hazard Ratio
ICD	International Classification of Disease
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance

MCP	Medical Care Plan
NLCHI	Newfoundland and Labrador Centre for Health Information
PG	Plasma glucose
PH	Proportional Hazards
OR	Odds Ratio
OGTT	Oral Glucose Tolerance Test
RCT	Randomized Controlled Trial
SES	Socioeconomic Status
STOP-NIDDM	Study to Prevent Non Insulin Dependent Diabetes
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial

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Co-Authorship Statement

This thesis work resulted in two published manuscripts:

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Madonna Roche conceptualized the studies, acquired the data, performed data analysis, interpreted the results and wrote the manuscript. Peizhong Peter Wang contributed to data analysis plan, discussion and reviewed/edited the manuscripts.

CHAPTER 1 Introduction

1.1 Purpose

The primary objective of this research was to examine diabetes with a focus on the timing of its diagnosis. The factors associated with diabetes, risk of mortality and hospitalization outcomes, and the diagnosis, treatment and management in Newfoundland and Labrador was also examined.

1.2 Organization of Dissertation

This dissertation is organized into five chapters. Chapter 1 provides an introduction, research objectives and literature review. Due to the breadth and depth associated with diabetes epidemiology research, my literature review had to be selective and addresses only areas that are closely related to my research objectives. This chapter also presents the rationale for examining early and late diagnosis of diabetes. In Chapter 2, the factors associated with a diabetes diagnosis, a late diabetes diagnosis, and whether these factors are different for males and females in Newfoundland and Labrador are examined. In Chapter 3, sex differences in outcomes for individuals with and without diabetes and patients diagnosed early and late with diabetes are described. Chapter 4 presents how family physicians diagnose, treat and manage type 2 diabetes. Finally, Chapter 5 presents a general discussion of findings presented in the previous chapters, recommendations for future research, and concluding statements.

1.3 Diabetes Mellitus

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia (high blood sugar) resulting from impaired insulin secretion, impaired effectiveness of insulin action or both.

Basically, diabetes is a condition in which the body does not produce enough insulin or does not properly use insulin. The hormone insulin is needed to take glucose from the blood and move it into the body's cells where it is used as energy. There are four main types of diabetes including type 1, type 2, gestational diabetes and other specific types [1, 2].

Type 1 diabetes is an autoimmune disorder that occurs when the pancreas produces little or no insulin. The beta cells in the pancreas are the insulin-producing cells and in type 1 diabetes the beta cells are attacked by the body's defence system and as a result produce little or no insulin. The reason why this occurs is not fully understood. This type of diabetes is most commonly diagnosed in children and adolescents and accounts for about 5-10% of people with diabetes. Due to the beta cell destruction, people with type 1 diabetes need injections of insulin every day to control the levels of glucose in their blood[1, 2].

Type 2 diabetes is a metabolic disorder that usually begins with insulin resistance, in which the pancreas does not produce sufficient insulin or the insulin is not metabolized properly. Type 2 diabetes, accounting for approximately 90-95% of diabetes cases, typically develops in people over 40 years of age but can also occur in children, particularly in obese adolescents. In contrast to type 1 diabetes, people with type 2 diabetes do not necessarily need insulin therapy. Blood glucose levels can be controlled with proper diet and exercise; however, insulin may be needed to control hyperglycemia if diet and lifestyle interventions are not effective[1, 2].

Gestational diabetes mellitus (GDM) is a condition that develops in pregnancy involving glucose intolerance in varying degrees of severity. GDM carries risks to both mother and infant. Women who have had GDM are at a higher risk of developing type 2 diabetes later in life compared to women who have not had GDM. Also, children born to mothers with GDM may have higher birth weights and are more likely to be delivered via caesarean section than babies

born to mothers without GDM. These babies are also at a higher risk of having low blood sugar levels after birth and high levels of insulin in the blood. They are also more likely to become obese and develop glucose intolerance later in life[1, 2].

There are other specific types of diabetes which are relatively uncommon and include forms resulting from genetic syndromes, defects in beta cell function or insulin action, infections and/or drug induction[1, 2].

1.4 Natural History of Type 2 Diabetes

The maintenance of normal blood glucose levels involves three main processes, insulin secretion, stimulation of glucose uptake, and suppression of hepatic glucose production. The hormone insulin is required to move glucose from the blood into the body's cells to maintain normal plasma glucose levels. Under normal conditions, plasma glucose levels are maintained within a narrow range. Initially, an increase in plasma glucose concentrations occurs after glucose has been ingested. Insulin is then released by the pancreas in response to the increase in plasma glucose. Both hyperinsulinemia (increased levels of insulin in the blood) and hyperglycemia (increased levels of glucose in the blood) stimulate glucose uptake by splanchnic (liver and gut) and peripheral tissues (primarily muscle) and suppress glucose production by the liver[3, 4].

Type 2 diabetes is characterized by hyperglycemia, insulin resistance, impaired insulin secretion and an increase in glucose production by the liver. The natural history of type 2 diabetes begins with insulin resistance which is the decreased ability of the body to respond to the effects of insulin, resulting in hyperglycemia or high blood glucose[5]. As insulin resistance progresses, the pancreatic beta cells increase insulin secretion in an attempt to compensate for the decreased responsiveness to insulin and maintain normal glucose tolerance. In these early

stages elevated insulin levels will be present[6]. This compensation is successful at first and can keep plasma glucose levels within a normal range for up to several years[7]. After some time, impaired insulin secretion occurs when beta cell functioning decreases and the pancreas is no longer able to produce the required amounts of insulin. Beta cell dysfunction is more serious than insulin resistance. With beta cell dysfunction, insulin secretion is impaired whereas with insulin resistance, insulin may still be produced. Hepatic glucose production also occurs when the beta cells produce increased amounts of insulin to compensate for insulin resistance. The increased hepatic glucose production is secondary in the sequence of events that lead to type 2 diabetes but is thought to be the main cause of fasting hyperglycemia[6, 8]. It is uncertain whether insulin resistance or impaired insulin secretion initiates the development of type 2 diabetes; however, both defects must be present before an individual progresses to impaired glucose tolerance[3]. Essentially, type 2 diabetes involves two main physiological defects, impaired insulin secretion and insulin resistance, which together cause the individual to progress from normal glucose tolerance to impaired glucose tolerance and then eventually onto type 2 diabetes[4, 6].

A long asymptomatic phase and a gradual onset are very common with type 2 diabetes. Previous research has shown that hyperglycemia may be present for more than 20 years[9] and type 2 diabetes can be present for up to 12 years before being diagnosed[10, 11]. Long term hyperglycemia is associated with a progressive decline in beta cell functioning with a loss of about 4% per year. It is estimated that the loss of beta cell function begins about 12 years before diagnosis[12] and at the time of diagnosis, beta cell functioning is reduced to between 50 and 80% of normal and continues to decrease with the duration of type 2 diabetes[13, 14].

Individuals with type 2 diabetes often develop a number of chronic microvascular and macrovascular complications. Common microvascular complications include retinopathy,

nephropathy, neuropathy while common macrovascular complications include coronary artery disease, cardiovascular disease, peripheral vascular disease, myocardial infarction and stroke. As type 2 diabetes can be present for a long time before being diagnosed, patients with diabetes can have complications at the time of initial diagnosis. It has been estimated that 2-39% of newly diagnosed patients experience retinopathy, 8-18% nephropathy, 5-13% neuropathy and 8% cardiovascular disease[15].

Hypertension is a common cormorbidity in individuals with diabetes, occurring in 75% of type 2 diabetes patients. As a result, hypertension is an important risk factor for mortality and cardiovascular events in individuals with diabetes. When present, hypertension accelerates the course of microvascular and macrovascular complications. The risk of mortality due to cardiovascular events is increased in individuals with diabetes compared to those without diabetes and in hypertensive diabetes patients this risk is even higher[16].

1.5 Diagnostic Criteria

A fasting plasma glucose (FPG) test, casual plasma glucose (PG) test, a 2 hour plasma glucose in a 75 gram oral glucose tolerance test (OGTT) or glycated hemoglobin (HbA1C) can be used to positively diagnose a person with diabetes. The FPG test is a blood test that is performed to measure the level of glucose in the blood plasma after the person has fasted for 8 hours. The casual PG test is a blood test that is performed at any time of day without regard to when the last meal was consumed. The 2hPG in a 75-g OGTT test is performed after a person has fasted for 8 hours. Individuals are given a 75-g glucose drink and 2 hours later the glucose level is determined. HbA1C refers to glycated hemoglobin. This is measured to determine the average plasma glucose concentration over a period of 2-3 months[2].

Table 1.1 shows the plasma glucose levels required for the diagnosis of diabetes, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). The term 'prediabetes' is used to describe individuals with plasma glucose levels just below the threshold for diabetes. These individuals are classified as having IFG or IGT[1, 2]. IFG is defined as high blood glucose levels after a period of fasting while individuals with IGT have high blood glucose levels after eating[17]. Clinically, IFG and IGT represent a similar point along the continuum between normal glucose tolerance and type 2 diabetes and both can be used to identify those at risk for developing type 2 diabetes[18]. While those with IFG or IGT are at risk for developing type 2 diabetes, not all individuals with elevated plasma glucose levels will go on to develop the disease. It is estimated that in about one third of individuals with IGT, blood glucose levels will return to normal within a few years[19].

The Canadian Diabetes Association 2013 guidelines recommend routine screening for type 2 diabetes using an FPG, casual plasma glucose, 2 hour plasma glucose in 75 g OGTT or HbA1C test and this should be performed every 3 years in individuals 40 years of age and older or those considered to be at high risk[2]. In contrast, in 2012 the Canadian Task Force on Preventive Health Care recommends not routinely screening adults at low to moderate risk. It recommends routine screening for adults at high risk every 3-5 years and recommends annual screening for adults at very high risk[20]. Both the Canadian Diabetes Association clinical practice guidelines and the Canadian Task Force on Preventive Health Care recommend a HbA1C value of 6.5% or greater as the threshold for diagnosing diabetes. Also, both leave the decision of which test to use to diagnose diabetes to the discretion of the physician and suggest that an abnormal level may require repeat testing to confirm a diagnosis of diabetes[2, 20].

Table 1.1: Plasma Glucose Levels for Diagnosis of IFG, IGT and Diabetes

	FPG (mmol/L)	2hPG in a 75-g OGTT (mmol/L)	HbA1C (%)
IFG	6.1-6.9		
IGT		7.8-11.0	
Prediabetes			6.0-6.4
Diabetes	≥ 7.0	≥ 11.1	≥ 6.5

Source: Canadian Diabetes Association, Clinical Practice Guidelines, 2013

It would not be cost-effective to provide mass screening for diabetes since the prevalence of the disease in the general population is low. Individuals at high risk include those with a first-degree relative with type 2 diabetes and members of certain ethnic groups (Aboriginal, Hispanic, African, Asian or South Asian decent). In addition, having a history of prediabetes, gestational diabetes or having given birth to a baby that weighted more than 9 pounds are risk factors for type 2 diabetes. Being overweight or obese, having high blood pressure, high cholesterol or having microvascular and marcrovascular health complications associated with diabetes are also risk factors for type 2 diabetes. Having been diagnosed with polycystic ovary syndrome, acanthosis nigricans (skin pigmentation disorder), psychiatric disorders (bipolar, depression, schizophrenia) and HIV also places an individual at higher risk for developing type 2 diabetes. Finally, being prescribed a glucocorticoid medication, atypical antipsychotics and HAART (highly active antiretroviral therapy) are risk factors for type 2 diabetes[2].

1.6 Epidemiology of Type 2 Diabetes

1.6.1 Prevalence

The prevalence rate measures the proportion of people in a population who have the disease at a point in time[21]. The worldwide prevalence of diabetes has risen dramatically over the past two decades. According to the most recent global diabetes estimates, the number of people aged 20-79 years with diabetes will be 382 million in 2013, 80% of whom will be from low and middle-income countries. This number is expected to increase by 55% to 592 million by 2035. In terms of gender differences, more men than women have diabetes (198 million and 184 million, respectively). However, this difference is expected to increase to 15 million by 2035 with 303 million men being diagnosed with diabetes compared to 288 million women. With respect to age, almost half of those with diabetes are between 40 and 59 years of age and it is expected that this age group will continue to have the largest prevalence into 2035[17, 22]. With increasing globalization, lifestyles in low- and middle- income countries often include unhealthy diets, obesity, inadequate physical activity and unhealthy habits. These unhealthy lifestyles are resulting in increasing numbers of non-communicable disease such as diabetes[23, 24].

In the United States, the number of people with diabetes has increased from 5.6 million in 1980 to 20.9 million in 2011, and the age-adjusted prevalence of diabetes has increased from 2.8% to 6.4%. Between 1980 and 1998, the age-adjusted prevalence of persons with diabetes was similar for males and females. However, in 1999, the percentage for males with diabetes began to increase faster than the percentage of females with diabetes. By 2011, more males than females had diabetes, 6.9% compared to 5.9%, respectively. From 1980 to 2011, the percentage of the population with diabetes increased in all age-groups. Those aged 65-74 years had the

highest percentage, followed by those aged 75 or older. In 2011, 21.8% of those 65-74 years of age had diabetes, which was 13 times higher than those 45 years of age and younger (1.6%)[25].

In Canada, the crude prevalence of diagnosed diabetes was 6.8% in 2008/09, which represents almost 2.4 million people living with diabetes. The age-standardized prevalence of diabetes for individuals aged 1 year and older increased by 70% between 1998/99 and 2008/09. The aging Canadian population and the increased survival of individuals with diabetes have contributed to the increased prevalence over the last ten years. Prevalence of diabetes increases with age and therefore is much lower in children and adolescents compared to adults. Prevalence begins to increase sharply after age 40, peaks in the 75-79 year age group and then begins to decline. In terms of gender differences, in 2008/09, more males than females had diabetes, 7.2% versus 6.4% respectively. Newfoundland and Labrador had the highest age-standardized prevalence of diagnosed diabetes in the country at 6.5% in 2008/09. The eastern provinces including Newfoundland and Labrador, Nova Scotia, and New Brunswick had a higher prevalence of diabetes compared to the western Canadian provinces of Alberta, British Columbia, and Saskatchewan[26].

1.6.2 Incidence

The incidence rate is the number of new cases of a disease that occur over period of time in a population at risk for developing the disease[21]. From 1980 to 2011, the age-adjusted incidence increased from 3.5 to 7.6 per 1,000 population in the United States. In 2011, the age-adjusted incidence of diabetes was similar for males and females (7.7 versus 7.5 per 1,000 population, respectively). From 1980 to 2011, the incidence of diabetes has increased in all age-

groups. For adults aged 65–79 years, the incidence of diabetes has significantly increased from 6.9 per 1,000 population in 1980 to 15.4 in 2011[25].

In Canada, the crude incidence rate of diabetes for individuals aged 1 year and older was 6.3 per 1,000 population in 2008/09. The incidence rate is much lower in children and adolescents compared to adults. Incidence rates increase steadily after age 40, peak in the 70-74 age group and then start to decrease. The crude incidence rate for males was higher than the rate for females aged 1 year and older in 2008/09, 6.8 per 1,000 versus 5.7 per 1,000 respectively. Between 1998/99 and 2008/09, there was an overall increase in age-standardized incidence rates of diabetes. However, only certain age groups contributed to this increase (children 1-19 years of age and adults aged 30-49 years). Since 2006/07, incidence rates appear to be decreasing; however, additional years of data are required to determine if this is an aberration or a longer term trend[26].

1.6.3 Undiagnosed Type 2 Diabetes

Worldwide there are an estimated 175 million people who are living with undiagnosed diabetes[17, 22]. In Canada, the current prevalence of diabetes is likely a significant underestimation mainly due to large numbers of undiagnosed cases of diabetes. Based on data from the 2007-2009 Canadian Health Measures Survey, 0.9% of the Canadian population aged six years and older has undiagnosed diabetes. This represents about 20% of all diabetes cases[26].

1.7 Prevention of Type 2 Diabetes

Both the incidence and prevalence of type 2 diabetes are increasing worldwide and those diagnosed with type 2 diabetes are also surviving longer. As a result, the risk of progressing onto

serious complications is increased. The potential however, does exist to prevent or at least delay the onset of type 2 diabetes. Several studies have examined the potential for both lifestyle and pharmacologic interventions in adults to prevent and/or delay the onset of diabetes. The Da Qing Impaired Glucose Tolerance and Diabetes Study was the first randomized study to show that lifestyle interventions could reduce the incidence of diabetes. In this study, individuals with impaired glucose tolerance (IGT) were randomized to a control group or one of three treatment groups: dietary intervention, an exercise intervention, or a combination of both. The results showed a significant decrease in the incidence of diabetes in individuals with IGT. The incidence of diabetes at 6 years was 67.7% in the control group, 43.8% in the diet group, 41.1% in the exercise group, and 46.0% in the diet-plus-exercise group. The diet, exercise, and diet-plus-exercise group had a 31%, 46% and 42% reduction in risk of diabetes over 6 years, respectively[27].

Similar findings have been observed in the Finnish Diabetes Prevention Study. In this study, 522 overweight adults with IGT were randomly assigned to a control or lifestyle intervention group and were followed for a mean of 3.2 years. The control group was given general information about a healthy diet and exercise while the intervention group received personalized diet counselling and were encouraged to undertake 30 minutes of aerobic exercise and resistance training per day. The incidence of diabetes after 4 years was 11% in the intervention group and 23% in the control group. The risk reduction for diabetes was found to be 58% for the intervention group. The results also suggest that losing as little as 5% of body weight can greatly reduce the risk of progressing from IGT to diabetes[28].

In another lifestyle intervention trial, 458 Japanese males with IGT were randomly assigned to either a standard intervention (control group) or an intensive intervention and

followed for 4 years. Subjects in the control and intervention group were told to maintain a BMI of less than 24 kg/m^2 and less than 22 kg/m^2, respectively, through diet and exercise. The intervention group also received detailed instructions on lifestyle every 3-4 months. The results showed that the incidence of diabetes was 9.3% in the control group and 3.0% in the intervention group. The risk of diabetes was reduced by 67.4% in the intensive treatment group. In addition, individuals who lost weight had a reduced risk of developing diabetes and had improved glucose tolerance[29].

In addition to lifestyle intervention studies, there have been several pharmacological intervention studies. The Diabetes Prevention Program compared the effectiveness of lifestyle interventions to the effectiveness of a common diabetes medication in 3234 people with IGT. Subjects were randomly assigned to a placebo group, Metformin group (850 mg twice daily), or an intensive lifestyle modification group. The lifestyle modification group had goals of at least a 7% weight loss and at least 150 minutes of physical activity per week. After an average follow-up period of 2.8 years, the incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, Metformin, and lifestyle group, respectively. The risk of diabetes was reduced by 58% in the lifestyle intervention group, and 31% in the Metformin group, compared with the placebo group. These results suggest that while both lifestyle changes and Metformin can reduce the incidence of diabetes, lifestyle changes can be more effective than Metformin in preventing diabetes[30]. A systematic review and meta-analysis also found that the use of Metformin in individuals with prediabetes (IGT or IFG) decreases the likelihood that prediabetes will progress to diabetes[31].

The Study to Prevent Non Insulin Dependent Diabetes Mellitus (STOP-NIDDM) trial evaluated the effect of Acarbose in reducing the risk of type 2 diabetes in individuals with IGT.

Participants were randomly assigned to a placebo group or Acarbose group (100mg three times daily). After a mean follow-up of 3.3 years, a 25% reduction in the risk of progression to diabetes was observed in the Acarbose treated group compared with the placebo group[32].

Additionally, the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial randomized 5269 individuals with IGT and/or fasting plasma glucose to receive Rosiglitazone (8 mg daily) or placebo. In this trial, the primary outcome was the development of diabetes or death and a secondary outcome was regression to normal glycemia. At the end of the study, 11.6% of individuals given Rosiglitazone and 26.0% given placebo developed the primary composite outcome. Treatment with Rosiglitazone resulted in a 60% in reduction in diabetes or death compared to placebo. Also, 50.5% of those receiving Rosiglitazone became normal glycemic compared to 30.3% of those in the placebo group[33].

Results from randomized controlled trials (RCT) have found that the risk of microvascular complications can be reduced with intensive glucose control; however, the effect on macrovascular complications have been less clear. The UK Prospective Diabetes Study (UKPDS), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), Action to Control Cardiovascular Risk in Diabetes (ACCORD), and Veterans Affairs Diabetes Trial (VADT) are randomized controlled trials that have been conducted to compare the effect of intensive glucose control versus standard glucose control on microvascular and macrovascular complications in patients with diabetes. These trials found that CVD events can be reduced with intensive glucose control; however, no significant effect on CVD mortality or all-cause mortality was found[34-38].

Results from the UKPDS have shown that intensive blood glucose control reduces the risk of microvascular complications. In this study, 3867 newly diagnosed patients with type 2

diabetes were randomly assigned to either an intensive treatment group (with a Sulphonylurea or with insulin), or a conventional treatment group with diet. The results showed that the intensive treatment group had a 25% reduction in the risk of microvascular complications over a 10-year period[34].

The UKPDS also examined whether intensive glucose control with Metformin reduces the risk of microvascular and macrovascular complications in overweight patients with newly diagnosed type 2 diabetes. Patients were randomly assigned to an intensive treatment group (with Metformin) or a conventional treatment group. Patients treated with Metformin, compared with the conventional treatment group, had a 32% lower risk of developing any diabetes-related endpoint (microvascular and macrovascular complications), a 42% lower risk for diabetes-related mortality, and a 36% lower risk for all-cause mortality[35].

The ADVANCE trial randomly assigned 11,140 patients type 2 diabetes to either a standard glucose control group or an intensive glucose control group (with Gliclazide, plus other drugs as needed, to achieve HbA1C of 6.5% or less). Compared with standard control, intensive glucose control significantly reduced the incidence of major microvascular events (nephropathy or retinopathy) but not the incidence of macrovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke)[36].

In the VADT trial, 1791 military veterans were randomly assigned to receive either intensive or standard glucose control. The median follow up time was 5.6 years. The results showed no significant difference between the two groups in the incidence of macrovascular events or microvascular complications, with the exception of albuminuria progression[37].

The ACCORD trial attempted to determine whether intensive therapy (targeting HbA1C below 6.0%) would reduce the rate of macrovascular events (nonfatal myocardial infarction,

nonfatal stroke, or death from cardiovascular causes) compared to standard therapy (targeting HbA1C levels from 7.0 to 7.9%) in individuals with type 2 diabetes and either cardiovascular disease or cardiovascular risk factors. Unfortunately, this trial was terminated early due to the higher mortality of individuals in the intensive group compared with the standard therapy group[38].

The results from the ACCORD trial suggest that intensive glucose control may cause adverse outcomes in some patients since the ACCORD trial was stopped early due to higher mortality in the intensive glucose control group compared to the standard control group[38]. In addition, the ADVANCE, ACCORD, VADT and UKPDS trials showed higher rates of hypoglycemic episodes and weight gain in the group that was treated more intensively[34, 36-38]. A recent meta-analysis of RCT's found that intensive glucose lowering treatments did not significantly affect all-cause and CVD mortality. The risk of hypoglycemia was more than twice as high in the intensive treatment group compared to the standard treatment group and the authors concluded that the harm associated with hypoglycemia may offset any potential benefits of intense glucose control[39]. Alternatively, the UKPDS 10-year post-trial follow-up found that significant reduction in microvascular risk persisted, and significant reductions in myocardial infarction and all-cause mortality were seen in the intensive-control group during follow-up. The authors used the term 'legacy effect' to describe the continued benefit of intensive treatment[40]. Also, when patients were intensively treated with Metformin in the UKPDS, Metformin did not induce weight gain and was associated with less episodes of hypoglycaemia than sulphonylurea or insulin therapy[35]. Patients in the ADVANCE, VADT and ACCORD trials had diabetes for a number of years before entering the trial, whereas patients in the UKPDS where newly diagnosed. This could suggest that the same HbA1C target and treatment plan should not be

applied to all patients with diabetes. Perhaps the focus should not only be on glucose control but on all CVD risk factors. The Canadian Diabetes Association Clinical Practice Guidelines provide recommended targets for glycemic control and suggest that treatment strategies should be individualized with consideration given to presence of risk factors[2]. Early and aggressive treatment has been suggested for patients that are newly diagnosed and do not have a history of CVD while less aggressive treatment may be suitable for older patients with a longer duration and a history of CVD[41].

1.8 Research Objectives

The objectives of this dissertation are:

1) To use administrative data to develop a case definition of early and late diabetes diagnosis based on when comorbidities or complications develop.
2) To identify factors associated with a diabetes diagnosis and a late diabetes diagnosis and to investigate whether these factors are different for males and females.
3) To examine sex differences in all-cause and cardiovascular mortality and hospitalization for individuals with and without diabetes and patients diagnosed with diabetes early and late.
4) To describe how family physicians diagnose, treat and manage type 2 diabetes and to identify if there were any differences in how male and female family physicians diagnose, treat and manage those with type 2 diabetes.

1.9 Rationale for Examining Early and Late Diabetes Diagnosis

Worldwide, there are approximately 382 million people with diabetes and it is estimated that 592 million will be affected by 2035. Type 2 diabetes is a progressive disorder that often has a gradual onset and a long asymptomatic phase. About 175 million people are unaware they have the disease[17, 22]. Insulin resistance and beta-cell dysfunction are largely responsible for the development of diabetes and its related complications and both are present very early in the natural history of diabetes[42]. Hyperglycemia may be present for more than 20 years[9] and type 2 diabetes can be present for up to 12 years before being diagnosed[10, 11].

Symptoms of diabetes are often not present or may develop slowly and may not be noticed for years. Symptoms such as fatigue, frequent urination and excessive thirst are often ignored or can often be attributed to less serious conditions. Singh et al.[43] investigated the nature and duration of symptoms at presentation for diabetes patients and found that 40% had symptoms for more than 12 months prior to diagnosis. These people either failed to recognise these as diabetes symptoms or did not feel they were serious enough to follow up with a physician. Jackson et al.[44] examined the general public's knowledge of diabetes and found that fewer than one in 20 could name thirst and frequent urination as symptoms. However, advertising campaigns have been found to raise awareness of the symptoms of diabetes[45].

Lack of knowledge of diabetes symptoms can be a factor in the late diagnosis of the disease. However, it is not only knowledge of symptoms that can affect the timing of diagnosis. It is also important that the public understand that diabetes is a serious condition. Lamont et al.[46] examined the perceived seriousness of diabetes and the implications these perceptions may have in practice. The perceptions that general practitioners, nurses and patients held were explored using interviews and focus groups to determine if type 2 diabetes is perceived to be serious and if

this perception influences screening. A difference of opinion was found between health professionals and patients regarding the seriousness of diabetes. Three frameworks were found to influence perceptions of the seriousness of diabetes, the medical framework, the political framework and the personal framework. Within the medical framework, diabetes was perceived to be more serious when intense medical intervention was required. The political framework viewed seriousness in terms of national priorities, early detection and financial investments. In general, diabetes was not thought to be as politically attractive as diseases such as cancer. The personal framework suggests that perceptions of seriousness are determined by attitudes, knowledge and experiences of diabetes. The authors suggested that the lack of knowledge about diabetes and patients' beliefs that it is not a serious condition may help to explain the lack of motivation that some people have to comply with lifestyle interventions recommended to control diabetes[46].

As type 2 diabetes can be present for a long time before being diagnosed, patients with diabetes can have complications at the time of initial diagnosis[15]. On average a person has diabetes for about 5 or 6 years before complications develop[47]. As the number of people with diabetes increases it is important to study both early and late diabetes diagnosis. Effective and active early management is of utmost importance if good control of diabetes is to be reached and late complications prevented. Randomized control trials have suggested that diet and exercise can prevent or delay the progression from impaired glucose tolerance to diabetes[27, 28]. Intensive lifestyle interventions have been found to be more effective than metformin[30] and intensive blood glucose control has been shown to reduce diabetes related microvascular complications[34,35].

Since research from randomized control trials has shown that early diagnosis and treatment is beneficial, this thesis will examine how to define early and late diabetes diagnosis; what factors are associated with diabetes diagnosis and a late diabetes diagnosis and does this differ for males and females; mortality and hospitalization outcomes for males and females with diabetes and whether these are associated with the time of diagnosis; and, how male and female family physicians diagnose, treat and manage type 2 diabetes.

1.9.1 Defining Early and Late Diabetes Diagnosis

For the purposes of this thesis, individuals with diabetes were classified as being diagnosed 'early' or 'late' depending on when diabetes related comorbidities or complications developed. Individuals early on in the disease course would not be expected to have any diabetes related comorbidities or complications around the time of their case date. On the contrary, a late diagnosed diabetes patient would likely be experiencing conditions related to diabetes around the time of diagnosis. Since type 2 diabetes can be present for 9 to 12 years before being diagnosed, complications are often present at the time of diagnosis[10]. Insulin resistance and beta-cell dysfunction are largely responsible for the development of diabetes and its related complications and both are present very early in the natural history of diabetes[42]. The progression of diabetes from pre-diabetes to complications is different for each patient. In some individuals complications may develop at lower glucose concentrations or during increases in glucose rather than after thresholds for a diagnosis are reached and remain consistent[48]. In fact, diabetes may be initially detected at the same time diabetes complications are being diagnosed[49]. For instance, the UKPDS found that 50% of patients had diabetes related tissue damage at the time of diagnosis[50].

A case definition of 'early' and 'late' diagnosis of diabetes was developed based on when various comorbidities or complications developed. A series of definitions ranging from specific to very broad (6 months to 2 years, before/after diagnosis) were developed and sample sizes were assessed (Table 1.2). Incident diabetes cases in the Canadian Chronic Disease Surveillance System (CCDSS) with a diabetes case date between Jan. 1, 1998 and Dec. 31, 2005 were identified and the early and late case definition was applied. Also, incident diabetes cases in the CCDSS with diabetes case date between Jan. 1, 1998 and Dec. 31, 2005 and a Canadian Community Health Survey (CCHS) interview date within same timeframe were identified and the early and late case definition was applied. Since there was little change in the sample distribution across definitions, the range of 6 months before and after diagnosis was used to define early and late diabetes diagnosis. In addition, an internal medicine physician was consulted and agreed that the definition of 6 months before and after diagnosis was reasonable.

Administrative data were used to identify individuals diagnosed early and late with diabetes. The Canadian Chronic Diseases Surveillance System (CCDSS) was used to identify records for those with diabetes. These records were linked to the Medical Care Plan (MCP) Fee-For-Service Physician Claims Database and the Clinical Database Management System (CDMS) data. Those data were used to determine when hospital and physician visits for diabetes related comorbidities or complications occurred and these were compared to the diabetes case dates. Incident diabetes patients without any diabetes related comorbidities or complications within 6 months before or after the diabetes case date were classified as being early diagnosed while those with a late diagnosis were defined as incident diabetes patients with at least one diabetes related comorbidity or complication within 6 months before or after diagnosis.

Table 1.2: Sample Size Distribution by Definitions of Early and Late Diabetes Diagnosis

Definitions	CCDSS[1]		CCHS[2]	
	Early	Late	Early	Late
Up to the case date	15741	7028	304	123
At the time of case date	19037	3462	372	55
6 months before or after case date	17188	5581	328	99
1 year prior to case date	18289	4480	353	74
1 year after case date	16800	5969	321	106
1 year before or after case date	16146	6623	307	120
2 years prior to case date	17592	5177	342	85
2 years after case date	15714	7055	306	121
2 years before or after case date	14701	8068	287	140

[1] Incident diabetes cases in the CCDSS with a diabetes case date between Jan. 1, 1998 and Dec. 31, 2005.
[2] Incident diabetes cases in the CCDSS with diabetes case date between Jan. 1, 1998 and Dec. 31, 2005 and a CCHS interview date within same timeframe.

The diabetes related conditions that were used to define early and late status are listed in Appendix A. In an effort to capture all late diagnosed cases of diabetes, a broad range of comorbidities and complications were included in the case definition. The term 'comorbidity' is used to describe a condition that is present at the time of diagnosis of the index disease (main condition being studied). On the other hand, 'complications' are conditions occurring after diagnosis of the index disease.[51]

The date an individual is identified as having diabetes in the CCDSS is not the date that diabetes developed. Type 2 diabetes can be present for up to 12 years before being diagnosed[10, 11] and on average an individual has diabetes for about 5 or 6 years before complications develop[47]. Using administrative data, it was not possible to identify what is a comorbidity and what is a complication of diabetes since it is not possible to determine when diabetes developed, only when it was diagnosed. As a result, all possible comorbidities and complications of diabetes were included in the definition of early and late diagnosis.

1.10 Rationale for Examining Factors Associated with a Diabetes Diagnosis and a Late Diabetes Diagnosis for Males and Females

Overweight and obesity are one of the most important risk factors for type 2 diabetes. In 2013, 29.4% of the population of Newfoundland and Labrador (NL) self-reported being obese. NL has the highest rate of obesity in the country. Overweight and obesity combined affect 69.2% of the NL population. In Canada more males self-reported being obese than females, 20.1% versus 17.4%, respectively. However, in NL more females than males self-reported being obese, 30.9% versus 27.9%[52].

Overweight and obesity account for a major proportion of diabetes. The median body mass index (BMI) for Canadians with diabetes is 29 kg/m^2 and 75.6% of individuals with diabetes are overweight or obese[26]. Hart et al.[53] examined the relationship between BMI and the development of diabetes in middle aged adults. Age-adjusted odds ratios for overweight men were 2.73 (95% CI 2.05-3.64) and 7.26 (95% CI 5.26-10.04) for obese men, compared with the normal weight group. The age-adjusted odds ratios for women were 2.54 (95% CI 1.95-3.31) in the overweight group and 5.82 (95% CI 4.41-7.68) in the obese group, compared to the normal weight group. Similarly, Jiang et al.[54] also investigated the relationship between excess weight and diabetes. Compared to the normal weight group, age-adjusted odds ratios for overweight and obese men were 1.7 (95% CI 1.3-2.1) and 3.5 (95% CI 2.8-4.4), respectively. For women the age-adjusted odds ratios for overweight were 2.0 (95% CI 1.6-2.6) and 6.3 (95% CI 5.0-7.9) for obese, compared to the normal weight group. While both Hart et al.[53] and Jiang et al.[54] found that odds ratios increased with increasing BMI, odds ratios were higher for women than men in the Jiang et al.[54] study and lower in the Hart et al.[53] study.

Physical inactivity is another important risk factor for diabetes since the incidence of diabetes decreases with increasing physical activity[55]. In 2013, 52.4% of the NL population reported being physically inactive. This was one of the highest rates in the country, second only to Nunavut at 52.6%. In NL more females are physically inactive than males, 54.1% versus 50.5%, respectively. Randomized control trials have shown that physical activity combined with dietary changes can reduce the risk of type 2 diabetes in high risk individuals[27-30]. Jeon et al.[56] conducted a systematic review to determine the association between physical activity of moderate intensity and risk of type 2 diabetes. Compared with sedentary, the risk of diabetes was reduced by 31% for moderate physical activity.

Cigarette smoking also increases the risk of developing diabetes. Foy et al.[57] investigated the association between smoking and incidence of diabetes in US adults using data from the Insulin Resistance Atherosclerosis Study. Individuals, free of diabetes at baseline, were classified as never, former, and current smokers and followed for 5 years to determine the incidence of diabetes. After adjusting for covariates, current smokers had an increased risk of diabetes than never smokers (OR=2.66, 95% CI 1.49-4.77). However, former smokers did not have an increased risk of diabetes compared to never smokers (OR=1.31, 95% CI 0.82-2.09). In addition, Will et al.[58] conducted a systematic review and meta-analysis of studies exploring the association between active smoking and the incidence of type 2 diabetes. The results showed a dose-response relationship between smoking and diabetes. The association was greater for heavy smokers (RR=1.61, 95% CI 1.43-1.80) than light smokers (RR=1.29, 95% CI 1.13-1.48). Compared to nonsmokers, the risk of diabetes was 1.44 (95% CI 1.31-1.58) for active smokers, which was higher than the risk for former smokers (RR=1.23, 95% CI 1.14-1.33). In 2012, 19.7% of the NL population reported being current smokers. This was one of the highest rates in

the country, with the territories having the highest smoking rates. In NL more 23.1% of males are smokers compared to 16.5% of females[59].

Factors such as education, income and socioeconomic status have been found to be inversely associated with diabetes. Sacerdote et al.[60] examined the association between education level and risk of type 2 diabetes. Compared with individuals with a high education level, those with a low education level had a higher risk of diabetes (HR=1.77, 95% CI 1.69-1.85). In a Canadian study, Lysy et al.[61] compared the incidence of diabetes in neighborhood income quintiles. The results show a significantly higher incidence of diabetes in lower income groups and diabetes incidence decreased with increasing income quintiles. Agardh et al.[62] conducted a systematic review and meta-analysis to investigate the association between incidence of type 2 diabetes and socio-economic position (measured by education level, occupation, and income). They found that the risk of diabetes is increased in low socio-economic position groups compared to high socio-economic position groups.

Identifying risk factors for diabetes is important as individuals at risk can be identified and screened. Early detection of diabetes is important since appropriate management strategies can be implemented. If diabetes is to be diagnosed as early as possible it is important to study the factors associated with a diabetes diagnosis. This chapter will assess the demographic, lifestyle and socioeconomic characteristics of individuals diagnosed with diabetes. Since previous research has not explored the characteristics of patients diagnosed with diabetes before and after complications develop, these factors will also be examined in this chapter. Since diabetes tends to affect males more than females[26] and females with diabetes tend to have poorer outcomes than males[63-72], sex differences will also be examined in this chapter.

1.11 Rationale for Examining Mortality and Hospitalization Outcomes for Males and Females with Diabetes and Those Diagnosed Early and Late

Diabetes is a major cause of premature death and individuals with diabetes are almost twice as likely to die from any cause compared to those without diabetes[73-75]. In addition, individuals with diabetes could have their life expectancy decreased by about 5-10 years compared to those without diabetes[76].

Declines in mortality rates in individuals with and without diabetes have been observed in both Canada and the United States. Lipscombe et al.[77] reported that between 1995 and 2005 the adjusted mortality rate decreased by 25% in people with diabetes in Ontario, Canada. Tierney et al.[78] found that the overall mortality rate decreased 35% among those with diabetes between 1997 and 2002. Thomas et al.[79] found that mortality rates for those with type 2 diabetes decreased by 13.8% between 1970 and 1994. However, this decrease was much lower than the decrease observed in individuals without diabetes at 21.4%. Other studies have observed declining mortality rates for men only and suggest that mortality rates in women have actually increased over time[80, 81]. Gregg et al.[80] found that for individuals with diabetes, the all-cause mortality rate did not change between 1971 to 1986 and 1988 to 2000. When the data was analyzed for men and women separately, mortality rates decreased among men with diabetes but not among women with diabetes. Gu et al.[81] also reported sex differences in mortality from all-causes, heart disease and ischemic heart disease with rates declining for men between 1971 and 1993 and increasing for women.

Cardiovascular disease (CVD) is the most common comorbidity associated with diabetes, and with 50% of those with diabetes dying of CVD, it is the most common cause of death[17]. Acute myocardial infarction (AMI) and stroke are other common comorbidities

associated with diabetes. Individuals with diabetes have an increased risk of all-cause mortality and morbidity related to CVD, AMI and stroke compared to individuals without diabetes[70-72,82].

While studies have consistently found that individuals with diabetes have a higher risk of mortality and hospitalizations compared to those without diabetes, results have been inconsistent when comparing males and females. Most studies have found that females with diabetes have a greater risk of mortality and hospitalizations than males with diabetes[66-69, 71, 72]. Two previous meta-analyses found that diabetes is a stronger risk factor for CVD mortality in females than in males; however, studies which did not adjust for major CVD risk factors were included in these meta-analyses[63, 65]. A meta-analysis conducted by Kanaya et al.[83], which included studies that controlled for CVD risk factors, found that the risk for CHD mortality, non-fatal myocardial infarction, and CVD associated with diabetes were not significantly different among males and females. Other studies have found that males with diabetes are at a higher risk for coronary heart disease[84] and stroke[85] than females with diabetes.

Not only does Newfoundland and Labrador (NL) have the highest age-standardized prevalence of diabetes in Canada[26], this province also has some of the highest age-standardized mortality rates and hospitalization rates for CVD, AMI and stroke in the country[86, 87]. As a result, this chapter will examine all-cause and cardiovascular mortality and hospitalization outcomes for individuals with and without diabetes. Since previous research has not explored mortality and morbidity outcomes for patients diagnosed with diabetes before or after complications develop, this chapter will also examine all-cause and cardiovascular mortality and hospitalization outcomes for patients diagnosed with diabetes early and late. In addition, since previous research has been inconsistent when comparing outcomes for males and females with and without diabetes, sex differences in outcomes will also be included in this chapter.

1.12 Rationale for Examining the Diagnosis, Treatment and Management of Diabetes

Type 2 diabetes is a progressive disorder, which often has a gradual onset and a long asymptomatic phase. As a result, hyperglycemia can be present for many years[9] and type 2 diabetes can be present for up to 12 years before being clinically diagnosed[10, 11]. Diabetes is a complex condition and the development of diabetes related complications presents an immense challenge for family physicians. Primary care providers often consider diabetes as harder to treat compared to other conditions like hypertension and angina. Larme et al.[88] explored the notion that attitudes may impede physician adherence to standards of care. Physicians were asked to rate the treatment of diabetes in comparison to other conditions. The results show that physicians rated diabetes as harder to treat than hypertension and angina.

Symptoms of diabetes are variable and are not present for all patients. Some can develop slowly and therefore may not be noticed for years. Also, symptoms are often considered insignificant or can be attributed to less serious conditions[43, 89]. At the time of diagnosis, many patients have experienced symptoms of diabetes for the 12 months prior to being diagnosed[43]. The Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD) examined prevalence of diabetes symptoms and their association with diabetes diagnosis. SHIELD found that 56% of type 2 diabetes patients experienced one or more diabetes related symptom in the previous 12 months before their diagnosis. Frequent urination and increased fatigue were the most frequently reported symptoms[90]. The general public's knowledge of diabetes symptoms is poor and they are often not aware of common diabetes symptoms such as thirst and frequent urination[44]. As a result, it is essential that family physicians identify individuals at risk for diabetes and screen for the disease. O'Connor et al.[91] found that 39% of patients with undiagnosed diabetes had diabetes-related symptoms at the time of diagnosis. In

addition, 57% of patients received their diagnosis during planned visits, while 43% received their diagnosis visits for acute care.

Family physicians have an opportunity to detect undiagnosed type 2 diabetes and impaired glucose tolerance (IGT) in patients presenting for routine care. The Diabetes Screening in Canada study (DIASCAN) found that 2.2% of patients had undiagnosed diabetes and 3.5% had IGT. Early detection of diabetes is important since appropriate management strategies can be implemented, especially for patients who have not yet developed complications[92]. Previous research has found that primary care provider attitudes about diabetes impact how patients view the disease[93]. Physician attitudes toward diabetes management may be more important than knowledge of the disease[94]. The reaction and attitude of physicians at the time of diagnosis are important factors that influence the perceived seriousness of the disease and the patients' compliance to treatment[95]. Compliance to treatment is essential for patients to prevent or delay diabetes complications. Since family physicians are crucial to identifying and caring for individuals with diabetes, this chapter aimed to describe how family physicians diagnose, treat and manage type 2 diabetes.

Previous research has found that female physicians are more likely to provide preventive services and counselling than male physicians[96, 97]. Berthold et al.[98] examined the effect physician gender on the quality of type 2 diabetes care. The results suggest that female physicians may provide better quality of diabetes care than male physicians. Patients of female physicians had lower mean fasting plasma glucose concentrations and HbA1C values compared to patients of male physicians. The proportion of patients achieving target values of HbA1C was also significantly higher in patients of female physicians. Also, mean LDL cholesterol concentrations were lower in the patients of female physicians and the proportion of patients

achieving LDL cholesterol target values was higher in patients of female physicians compared to patients of male physicians. Similarly, mean systolic and diastolic blood pressure values were lower in patients treated by female physicians and the proportion of patients achieving target blood pressure values were significantly higher in patients of female physicians compared to patients treated by male physicians[98].

Kim et al.[99] also examined the association between physician gender and quality of care. They concluded that patients of female physicians received similar quality of care compared to patients of male physicians. However, patients of female physicians were slightly more likely to have their lipid and HbA1C levels measured over 12 months and were more likely to have lower LDL levels than patients of male physicians. A secondary objective of this chapter is to determine if there were any differences in how male and female family physicians diagnose, treat and manage those with type 2 diabetes.

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CHAPTER 2 Factors Associated with a Diabetes Diagnosis and Late Diabetes Diagnosis for Males and Females

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2.1 Abstract

Objectives: To examine the factors associated with diabetes, a late diabetes diagnosis, and whether these factors are different for males and females.

Methods: Cross-sectional study including 7,101 individuals aged ≥25 years in Newfoundland and Labrador, Canada (466 with diabetes; 332 diagnosed late). Logistic regression analysis was used to determine the factors associated with a diabetes diagnosis and late diabetes diagnosis.

Results: For males, overweight/obesity (OR=1.35, 95% CI 1.06-1.72) was positively associated with diabetes while being a regular/occasional drinker (OR=0.53, 95% CI 0.32-0.88) was inversely associated with diabetes. Living in a rural area (OR=1.47, 95% CI 1.01-2.15), receiving social assistance (OR=2.80, 95% CI 1.52-5.15), having poor self perceived health (OR=2.06, 95% CI 1.32-3.21), and considering most days stressful (OR=1.45, 95% CI 1.01-2.10) were positively associated with diabetes for females. No factors were significantly associated with a late diabetes diagnosis for males. Having a low level of formal education (OR=0.33, 95% CI 0.11-0.99) was inversely associated with a late diabetes diagnosis for females.

Conclusions: The majority of individuals diagnosed with diabetes are diagnosed in the later stages of the disease. Certain risk factors appear to impact males and females differently and more research is needed on the timing of diagnosis and how males and females develop diabetes. These risk factors could be used to diagnose diabetes earlier in both males and females.

2.2 Introduction

Worldwide, there are approximately 382 million people with diabetes and it is estimated that 592 million will be affected by 2035[1, 2]. In Canada, the crude prevalence of diabetes was 6.8% in 2008/09, with more men having diabetes than women (7.2% versus 6.4%)[3].

A challenge with diabetes is diagnosing the disease early in an effort to prevent progression to complications. About 175 million people, or half of those who have diabetes, are unaware they have the disease[1, 2]. Type 2 diabetes can be present for 9 to 12 years before being diagnosed and, as a result, complications are often present at the time of diagnosis[4]. However, the potential does exit to prevent or at least delay the onset of type 2 diabetes as several randomized control trials have shown that both lifestyle and pharmacologic interventions in adults are effective[5-8]. In addition to preventing diabetes, it is also possible to reduce diabetes related microvascular complications through intensive blood glucose control[8, 9].

In most countries, even though females have lower mortality rates than males, they experience poorer health[10, 11]. Diabetes tends to affect males more than females since more males are diagnosed with diabetes[3]. In addition, males are diagnosed at lower body mass index (BMI) levels than females[12]. Even though more males are living with diabetes, females with diabetes have a greater risk of mortality and hospitalization[16-19, 21,22].

Various factors are associated with diabetes including older age, overweight or obesity, physical inactivity, marital status, smoking, lower education and low income[1, 3]. Early detection of diabetes is important since appropriate management strategies can be implemented. As the rates of diabetes increase it is important to study the factors associated with late diagnosis of diabetes and whether these determinants differ for males and females.

2.2.1 Conceptual Framework

The conceptual framework used in this study was based on that developed by Hertzman, Frank and Evans[23]. Using the model developed by Evans and Stoddart[24], Hertzman, Frank and Evans proposed a framework that describes differences in health status between or among populations. Their conceptual model is presented as a three dimensional cube with each axis of the cube representing dimensions for studying the heterogeneities in health status: i) stages of the life cycle; ii) subpopulation partitions; and, iii) sources of heterogeneity. Each of these dimensions is further divided into various levels[23].

The stages of the life cycle dimension focuses on age and periods in individuals' lives when they may become vulnerable to disease. The four time periods within this dimension are perinatal (preterm to 1 year); misadventure (1-44 years of age); chronic disease (45-74 years of age); and, senescense (75+ years of age)[23].

The subpopulation partitions dimension describes characteristics of the population where differences in health status may be observed. Populations can be partitioned by socioeconomic status, ethnicity/migration, geography, sex, and special populations. Special populations involve individuals who share a special characteristic that is related to health status differentials. An example of a special population would be vegetarians as they usually have good health[23].

Sources of heterogeneity are mechanisms that operate across different subpopulation partitions and stages of the life cycle. The sources of heterogeneity in the framework developed by Hertzman, Frank and Evans include reverse causality, differential susceptibility, individual lifestyle, physical and social environments, and differential access to/response to health care services[23].

2.2.2 Research Objectives

The objectives of this study are to examine the factors associated with diabetes and whether these factors differ for males and females. In addition, the factors associated with a late diabetes diagnosis will be explored and whether these factors differ for males and females.

Our hypothesis is that the factors associated with diabetes will be similar to the factors associated with a late diagnosis. Also, the factors associated with diabetes will be different for males and females. The factors associated with a late diagnosis will also differ for males and females.

2.3 Methods

2.3.1 Study Design and Data Sources

This cross-sectional study utilized administrative and survey data in Newfoundland and Labrador (NL), Canada. Databases included were: (i) the Newfoundland and Labrador component of the Canadian Chronic Disease Surveillance System (CCDSS), 1998-2005; ii) the Canadian Community Health Survey (CCHS), 2000/01, 2003, 2005; (iii) the Clinical Database Management System (CDMS), 1997-2006; and, (iv) the Medical Care Plan (MCP) Fee-For-Service Physician Claims Database, 1997-2006.

The Canadian Chronic Diseases Surveillance System (CCDSS) is a network of provincial and territorial chronic disease surveillance systems that compile administrative health care data and send aggregate anonymous data to the Public Health Agency of Canada for national analyses. The information from which the CCDSS is composed includes the provincial health insurance registry, hospital discharge records, and fee-for-service physician claims. The CCDSS uses a nationally validated case definition to identify diabetes cases. The case definition used for

the CCDSS has 86% sensitivity and 98% specificity for identifying individuals who had diabetes recorded in their primary care charts[25]. To be considered a diabetes case in the CCDSS, an individual must have met either of the following criteria: 1) had one hospital discharge with a diagnosis of diabetes, or 2) two medical services records with diagnosis of diabetes not more than two years apart. Once included in the CCDSS, cases remain there until a record of their death is received or they move out of the province. The CCDSS diabetes case definition excludes women with gestational diabetes. Also, it is not possible to distinguish between type 1 and type 2 diabetes.

The CCHS is a national cross-sectional survey conducted by Statistics Canada which collects information related to health determinants, health status and health system utilization for 130,000 Canadians. Three cycles of the CCHS (2000/01, 2003, 2005) were combined to increase the sample size and to decrease variation in the estimates[26].

The CDMS is the provincial hospital separation database that captures demographic, clinical and interventional information for patients admitted to all acute health care facilities and surgical day care in the province of NL. The MCP system contains information related to services provided by fee-for-service physicians under the NL provincial Medical Care Plan.

2.3.2 Diabetes and Early and Late Diagnosis Status

The dependant variables used in this study were diabetes status and early and late diabetes diagnosis status. CCHS respondents aged 25 years and older in Newfoundland and Labrador, who consented to share their data, were linked to the CCDSS via MCP number (provincial health insurance number) to verify their diabetes status according to the CCDSS case definition. All incident diabetes cases, as determined through the CCDSS, comprised the

diabetes study sample. A three year clearance period, in which an individual did not have a hospital admission or physician visit with a diabetes code, was used to identify incident diabetes cases. Previous studies have used between three and five years for clearance periods[25,27-28], and while five years is preferred[28], three years was used in this study to increase sample size. Individuals not diagnosed with diabetes at age 25 years or older, who participated in the CCHS, and who consented to share their data were eligible for the non-diabetes group. These cases were linked to the CCDSS via MCP number to verify whether or not they had diabetes according to the CCDSS case definition. The study population included individuals aged 25 years and older. Type 2 diabetes usually develops after the age of 40[1]; however, in an effort to increase the sample size, age 25 years and older was used.

Individuals with diabetes were classified as being diagnosed 'early' or 'late' depending on when diabetes related comorbidities or complications developed. The assumption was made that individuals early on in the disease course would not have any diabetes related comorbidities or complications around the time of their case date. On the contrary, a late diagnosed diabetes patient would likely have conditions related to diabetes around the time they were diagnosed. To classify individuals diagnosed early and late, records for those with diabetes were linked to the MCP and CDMS data to identify when hospital and physician visits for diabetes related comorbidities or complications occurred and these were compared to the diabetes case dates. Incident diabetes patients without any diabetes related comorbidities or complications within 6 months before or after the diabetes case date were classified as early diagnosed while those with a late diagnosis were defined as incident diabetes patients with at least one diabetes related comorbidities or complication within 6 months before or after diagnosis. The diabetes related conditions that were used to define early and late status are listed in Appendix A. This method

will identify comorbidities and complications identified through healthcare services covered by MCP; however, conditions identified through healthcare services not covered by MCP will not be captured.

2.3.3 Covariates

A number of independent variables were explored in this study and were identified using the framework developed by Hertzman, Frank and Evans[23] as a guide. Using this framework, the variables of interest are grouped together under three domains: i) stages of the life cycle, ii) subpopulation partitions, and iii) sources of heterogeneity.

Variables included under the stages of the life cycle domain include age and high blood pressure. The subpopulation partition variables included sex, level of education, region of residence, and receives social assistance. Low education was defined as less than secondary or completed only secondary education while high education was defined as some post-secondary education or completed post-secondary education. Urban region of residence was defined in the CCHS as an area with a population concentration of 1,000 or more and a population density of 400 or more per square kilometre based on census counts.

Finally, the sources of heterogeneity variables include self perceived health (Excellent/very good/good, fair/poor), body mass index (BMI), leisure time physical activity (active/moderately active, inactive), smoking status (former smoker/never smoked, occasionally/daily smoker), alcohol consumption (former/non-drinker, regular/occasional drinker), marital status, life stress (most days considered stressful/not stressful), sense of community belonging, employed in the past 12 months, exposed to second hand smoke at home, self perceived unmet health care needs and access to a regular medical doctor. BMI was

calculated from self-reported height and weight and classified as normal ($18.5 \leq BMI \geq 24.9$ kg/m^2) and overweight/obese ($BMI \geq 25$ kg/m^2). Physical activity level was derived from total energy expenditure during leisure time, which uses the frequency and duration of respondents' reported leisure time activities in the previous 3 months. Individuals who were married or common law were classified as partnered while individuals who were single, widowed, separated or divorced were classified unpartnered.

2.3.4 Data Linkage

The linkage of the CCHS to the CCDSS and other administrative databases was completed in five steps. Step one involved linking the 2000/01, 2003 and 2005 CCHS share files and link files together. The share files contain all variables and all records of CCHS respondents who agreed to share their data with Statistic Canada's partners including the provincial and territorial health departments, Health Canada and the Public Health Agency of Canada. Personal identifiers were removed from the share files. The link file contains MCP numbers, names and dates of birth. Individuals who did not give permission to have their information linked and who were under 25 at the time of interview were removed from the share file. The share files and link files were linked using the household ID and person ID variables.

Step two involved linking the CCHS files to the MCP master file using the MCP number. This was done to verify the MCP number provided in the link file. For individuals with a missing or invalid MCP number in the link file, a unique ID was created using the first four characters of surname and given name and the date of birth. This unique ID was then linked to the MCP master file. Any record with a missing or invalid MCP number was excluded.

Step three involved linking the CCHS files to the CCDSS via MCP number. The CCDSS file was used to identify individuals aged 25 years and older who were diagnosed with diabetes. Individuals who reported that they had diabetes for more than a year were considered non-incident cases and excluded.

In step four, the three CCHS cycles were combined to form the CCHS combined file. An individual could have been surveyed in more than one CCHS cycle. When this occurred, answers in the most recent cycle were kept and the duplicates were removed. The final CCHS file resulted in 7,101 records.

Finally, the CDMS and MCP data were linked to the final CCHS file via provincial health insurance number to identify those diagnosed early and late with diabetes. To determine this, physician visits and hospital admission data from the MCP and CDMS data were used to identify when hospital and physician visits for diabetes related comorbidities or complications occurred and these were compared to the diabetes case dates. A detailed data linkage procedure can be found in Appendix B.

2.3.5 Statistical Analysis

Characteristics of the study population are presented as weighted percentages and compared between individuals with and without diabetes and those diagnosed early and late with diabetes using chi-square tests and t-tests. To determine the factors associated with a diabetes diagnosis and late diabetes diagnosis, logistic regression analysis was used to calculate odds ratios (OR). Coefficients of variation and 95% confidence intervals (CI) were estimated using Statistics Canada's Bootvar program. The Bootvar program uses sampling weights to produce variance estimates, which is necessary to account for the multistage cluster survey design of the

CCHS[29]. Analyses were conducted separately for males and females. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC) software.

2.3.6 Ethical Considerations

This study was approved by the Health Research Ethics Authority (HREA) at Memorial University of Newfoundland (Appendix C), the research ethics board responsible for reviewing research on human subjects in Newfoundland and Labrador. Approval to access data from the Newfoundland and Labrador Centre for Health Information was approved by the Centre's Secondary Uses Committee (Appendix D).

2.4 Results

The study sample consisted of 7,101 individuals, with a mean age of 48.4 years (SD, 14.8 years). Forty eight percent of the sample were male and 52% were female. Characteristics of the study sample by diabetes status and sex are presented in Table 2.1. Overall, 6.7% of the study sample had diabetes; 7.6% of males had diabetes compared to 5.9% of females. Males and females with diabetes were more likely to be older, live in a rural area and have less education than those without diabetes ($p<0.01$). Females with diabetes were more likely to receive social assistance compared to females without diabetes ($p<0.01$), whereas no difference was found for males. Males and females with diabetes were more likely to be overweight/obese and physically inactive compared to those without diabetes ($p<0.01$). Males without diabetes were more likely to be smokers compared to males with diabetes ($p<0.01$), while females had similar smoking rates regardless of diabetes status.

Table 2.1: Characteristics of the study sample by diabetes status and sex

	Males (n=3,144)			Females (n=3,957)			Total (n=7,101)		
	Diabetes (n=224)	No Diabetes (n=2,920)	p value[1]	Diabetes (n=242)	No Diabetes (n=3,715)	p value[1]	Diabetes (n=466)	No Diabetes (n=6,635)	p value[1]
Age (years), mean (SD)	58.9 (12.7)	47.5 (14.3)	< 0.01	59.2 (12.1)	47.8 (14.9)	< 0.01	59.1 (12.5)	47.6 (14.6)	< 0.01
Has High Blood Pressure, % (n)	43.5% (92)	16.3% (536)	< 0.01	46.3% (127)	19.6% (850)	< 0.01	44.8% (219)	18.0% (2,808)	< 0.01
Female, % (n)	--	--	--	--	--	--	6.7% (242)	93.3% (3,715)	< 0.01
Low Education, % (n)	54.8% (133)	42.8% (1,314)	< 0.01	65.9% (169)	44.8% (1,801)	< 0.01	59.9% (302)	43.9% (3,115)	< 0.01
Rural Place of Residence, % (n)	43.3% (93)	41.1% (1,259)	< 0.01	44.4% (106)	37.0% (1,459)	< 0.01	43.8% (199)	38.9% (2,718)	< 0.01
Receives Social Assistance, % (n)	F	6.4% (193)	0.517	16.8% (31)[E]	8.6% (332)	< 0.01	11.1% (43)[E]	7.6% (525)	< 0.01
Poor/Fair Self Perceived Health, % (n)	29.0% (63)[E]	12.0% (398)	< 0.01	30.8% (71)	11.0% (445)	< 0.01	29.8% (134)	11.5% (843)	< 0.01
Body Mass Index (BMI), % (n)									
Normal[2]	14.8% (44)[E]	30.0% (882)	< 0.01	20.3% (50)	43.5% (176)	< 0.01	17.3% (94)	37.0% (2,348)	< 0.01
Overweight[3]/Obese[4]	85.2% (178)	70.0% (2,012)		79.7% (176)	56.5% (2,080)		82.7% (354)	63.0% (4,092)	
Physical Activity, % (n)									
Active/Moderately	32.6% (67)[E]	44.4% (1,225)	< 0.01	25.4% (64)	35.8% (1,331)	< 0.01	29.2% (131)	39.8% (2,556)	< 0.01
Inactive	67.4% (140)	55.6% (1,583)		74.6% (176)	64.2% (2,352)		70.8% (316)	60.2% (3,935)	
Daily/Occasional Smoker, % (n)	13.3% (36)[E]	28.5% (867)	< 0.01	24.8% (52)	25.6% (970)	0.090	18.5% (88)	27.0% (1,837)	< 0.01
Regular/Occasional Drinker, % (n)	70.3% (157)	85.2% (2,438)	< 0.01	52.8% (118)	75.1% (2,658)	< 0.01	62.3% (275)	79.9 % (5,096)	< 0.01
Life Stress, % (n)									
Not Stressful	48.1% (117)	43.6% (1,361)	< 0.01	35.4% (104)	38.7% (1,501)	< 0.01	42.3% (221)	41.0% (2,862)	< 0.01
Stressful	51.9% (106)	56.4% (1,554)		64.6% (138)	61.3% (2,213)		57.7% (244)	59.0% (3,767)	
Marital Status, % (n)									
Partnered	83.5% (170)	81.3% (2,185)	< 0.01	64.3% (129)	73.8% (2,474)	< 0.01	74.7% (299)	77.4% (4,659)	< 0.01
Unpartnered	16.5% (54)[E]	18.7% (733)		35.7% (113)	26.2% (1,241)		25.3% (167)	22.6% (1,974)	< 0.01
Weak Sense of Belonging, % (n)	20.0% (38)[E]	20.1% (512)	0.785	20.2% (48)[E]	21.5% (727)	0.006	20.1% (86)	20.9% (1,239)	< 0.01
Unemployed in the last 12 months, % (n)	41.3% (90)	21.6% (673)	< 0.01	65.8% (148)	35.8% (1,324)	< 0.01	53.0% (238)	29.1% (1,997)	< 0.01
Exposed to Second Hand Smoke at Home, % (n)	12.8% (21)[E]	20.5% (389)	< 0.01	25.9% (31)[E]	22.3% (526)	< 0.01	18.4% (52)[E]	21.5% (915)	< 0.01
Self Perceived Unmet Health Care	10.8% (24)[E]	10.7% (306)	0.763	11.0% (28)[E]	13.0% (482)	< 0.01	10.9% (52)[E]	11.9% (788)	< 0.01

Needs, % (n)									
Has Regular Medical Doctor, % (n)	94.2% (206)	82.3% (2,248)	< 0.01	96.3% (231)	89.8% (3,201)	< 0.01	95.2% (437)	86.2% (5,449)	< 0.01

[1]Significance level $p < 0.05$; [2]BMI = 18.5-24.9; [3]BMI = 25.0-29.9; [4]BMI = ≥ 30.0; % = weighted percentages; n = unweighted numbers; Data with a coefficient of variation (CV) from 16.6% to 33.3% are identified as follows: (E) use with caution; Data with a coefficient of variation (CV) greater than 33.3% were suppressed due to extreme sampling variability and are identified as follows: (F) too unreliable to be published.

Characteristics of the diabetes sample by early and late diagnosis status and sex are presented in Table 2.2. For individuals with diabetes, 25.8% were diagnosed early and 74.2% were diagnosed late. For males, 21.1% were diagnosed with diabetes early and 78.9% were diagnosed late, whereas 31.5% of females were diagnosed with diabetes early and 68.5% were diagnosed late. Both males and females diagnosed late with diabetes were older than those diagnosed early ($p<0.01$). 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. Similarly, 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 inactive compared to females diagnosed early ($p<0.01$). Physical activity level for males was similar for those diagnosed early and late with diabetes.

Table 2.2: Characteristics of the study sample by early and late diabetes diagnosis status and sex

	Males (n=224)			Females (n=242)			Total (n=466)		
	Early (n=58)	Late (n=166)	p value[1]	Early (n=76)	Late (n=176)	p value[1]	Early (n = 134)	Late (n = 332)	p value[1]
Age (years), mean (SD)	56.1 (11.3)	59.7 (13.0)	< 0.01	56.7 (13.2)	60.4 (11.4)	< 0.01	56.4 (12.4)	60.0 (12.3)	< 0.01
Female, % (n)	--	--		--	--		31.5% (76)	68.5% (166)	< 0.01
Low Education, % (n)	52.6% (33)[E]	55.4% (100)	0.022	76.8% (56)	60.9% (113)	< 0.01	66.1% (89)	57.7% (213)	< 0.01
Rural Place of Residence, % (n)	31.9% (17)[E]	46.3% (76)	< 0.01	45.6% (37)[E]	43.9% (69)	0.147	39.5% (54)[E]	45.3% (145)	< 0.01
Receives Social Assistance, % (n)	F	F		F	15.5% (22)[E]		F	10.9% (33)[E]	0.249
Poor/Fair Self Perceived Health, % (n)	22.2% (12)[E]	30.8% (51)[E]	< 0.01	26.0% (19)[E]	33.0% (52)[E]	< 0.01	24.3% (31)[E]	31.8% (103)	< 0.01
Body Mass Index (BMI), % (n)									
Normal[2]	18.8% (12)[E]	13.7% (32)[E]	< 0.01	21.3% (14)[E]	19.8% (36)[E]	0.113	20.2% (26)[E]	16.3% (68)	< 0.01
Overweight[3]/Obese[4]	81.2% (45)[E]	86.3% (133)		78.7% (57)	80.2% (119)		79.8% (102)	83.7% (252)	
Physical Activity, % (n)									
Active/Moderately	32.7% (20)[E]	32.6% (47)[E]	0.912	31.6% (22)[E]	22.6% (42)[E]	< 0.01	32.1% (42)[E]	28.1% (89)	< 0.01
Inactive	67.3% (36)[E]	67.4% (104)		68.4% (54)	77.4% (122)		67.9% (90)	71.9% (226)	
Daily/Occasional Smoker, % (n)	22.9% (15)[E]	10.7% (21)[E]	< 0.01	32.3% (23)[E]	21.3% (29)[E]	< 0.01	28.2% (38)[E]	15.2% (50)[E]	< 0.01
Regular/Occasional Drinker, % (n)	81.4% (44)[E]	67.3% (113)	< 0.01	57.0% (42)[E]	50.9% (76)	< 0.01	67.9% (86)	60.4% (189)	< 0.01
Life Stress, % (n)									
Not Stressful	40.6% (29)[E]	50.1% (88)	< 0.01	31.7% (28)[E]	37.1% (76)	< 0.01	35.7% (57)	44.7% (164)	< 0.01
Stressful	59.4% (29)[E]	49.9% (77)		68.3% (48)[E]	62.9% (90)		64.3% (77)	55.3% (167)	
Marital Status, % (n)									
Partnered	88.1% (43)	82.2% (127)	< 0.01	67.5% (47)[E]	62.7% (82)	< 0.01	76.7% (90)	74.0% (209)	< 0.01
Unpartnered	11.9% (15)[E]	17.8% (39)[E]		32.5% (29)[E]	37.3% (84)		23.3% (44)[E]	26.0% (123)	
Weak Sense of Belonging, % (n)	F	F		23.9% (18)[E]	18.5% (30)[E]		19.7% (27)[E]	20.3% (59)	0.439
Unemployed in the last 12 months, % (n)	36.4% (20)[E]	42.8% (70)	< 0.01	63.0% (44)[E]	67.1% (104)	< 0.01	51.5% (64)	53.6% (174)	0.018
Exposed to Second Hand Smoke at Home, % (n)	F	10.5% (15)[E]		25.6% (13)[E]	26.0% (18)[E]	0.787	24.1% (19)[E]	16.5% (33)[E]	< 0.01
Self Perceived Unmet Health Care Needs, % (n)	F	9.5% (15)[E]		14.4% (11)[E]	9.5% (17)[E]	< 0.01	15.1% (20)[E]	9.5% (32)[E]	< 0.01
Has Regular Medical Doctor, % (n)	96.1% (54)	93.7% (152)	< 0.01	98.4% (73)	95.4% (158)	< 0.01	97.4% (127)	94.4% (310)	< 0.01

[1]Significance level $p < 0.05$; [2]BMI = 18.5-24.9; [3]BMI = 25.0-29.9; [4]BMI = ≥ 30.0; % = weighted percentages; n = unweighted numbers; Data with a coefficient of variation (CV) from 16.6% to 33.3% are identified as follows: (E) use with caution; Data with a coefficient of variation (CV) greater than 33.3% were suppressed due to extreme sampling variability and are identified as follows: (F) too unreliable to be published.

Adjusted odds ratios (OR) and 95% confidence intervals (CI) for factors associated with diabetes are presented in Table 2.3. High blood pressure was positively associated with having diabetes for both males (OR=1.81, 95% CI 1.15-2.85) and females (OR=1.58, 95% CI 1.03-2.42). Being unemployed in the last 12 months and not having a regular doctor were inversely associated with diabetes for both males and females. For males only, being overweight or obese (OR=1.35, 95% CI 1.06-1.72) was positively associated with diabetes while being a regular or occasional drinker (OR=0.53, 95% CI 0.32-0.88) was inversely associated with diabetes. In contrast, living in a rural area (OR=1.47, 95% CI 1.01-2.15), receiving social assistance (OR=2.80, 95% CI 1.52-5.15), having poor self perceived health (OR=2.06, 95% CI 1.32-3.21), and considering most days stressful (OR=1.45, 95% CI 1.01-2.10) were positively associated with diabetes for females.

Adjusted ORs and 95% CIs for factors associated with a late diabetes diagnosis are presented in Table 2.4. 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. No other factors were significantly associated with a late diabetes diagnosis in females.

Table 2.3: Adjusted Odds Ratios (OR) and 95% confidence intervals (CI) for factors associated with diabetes

	Males	Females	Total
	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Age	1.07 (1.04-1.09)**	1.07 (1.05-1.09)**	1.07 (1.05-1.08)**
Sex			
Male	--	--	1.00
Female	--	--	0.68 (0.51-0.91)*
High Blood Pressure			
Yes	1.81 (1.15-2.85)**	1.58 (1.03-2.42)*	1.70 (1.24-2.34)**
No	1.00	1.00	1.00
Education			
High	1.00	1.00	1.00
Low	0.99 (0.64-1.55)	1.11 (0.71-1.73)	1.04 (0.78-1.40)
Region			
Urban	1.00	1.00	1.00
Rural	0.94 (0.88-1.54)	1.47 (1.01-2.15)*	1.14 (0.86-1.52)
Social Assistance			
Yes	0.80 (0.27-2.34)	2.80 (1.52-5.15)**	1.93 (1.15-3.23)*
No	1.00	1.00	1.00
Self Perceived Health			
Good/Very Good/Excellent	1.00	1.00	1.00
Poor/Fair	1.68 (0.92-3.07)	2.06 (1.32-3.21)**	1.80 (1.25-2.60)**
Body Mass Index (BMI)			
Normal	1.00	1.00	1.00
Overweight/Obese	1.35 (1.06-1.72)*	1.10 (0.98-1.22)	1.17 (1.07-1.28)**
Physical Activity			
Active/Moderately Active	1.00	1.00	1.00
Inactive	1.52 (0.98-2.37)	1.12 (0.71-1.75)	1.32 (0.95-1.81)
Smoking Status			
Non Smoker	1.00	1.00	1.00
Daily/Occasional	0.60 (0.33-1.08)	1.12 (0.68-1.86)	0.83 (0.58-1.18)
Drinking Status			
Former/Non Drinker	1.00	1.00	1.00
Regular/Occasional	0.53 (0.32-0.88)*	0.71 (0.48-1.06)	0.61 (0.44-0.85)**
Life Stress			
Not Stressful	1.00	1.00	1.00
Stressful	1.08 (0.74-1.59)	1.45 (1.01-2.10)*	1.25 (0.96-1.67)
Marital Status			
Partnered	1.00	1.00	1.00
Unpartnered	0.89 (0.55-1.44)	0.97 (0.64-1.46)	0.93 (0.68-1.26)
Sense of Belonging			
Strong	1.00	1.00	1.00
Weak	1.19 (0.72-1.98)	0.97 (0.62-1.52)	1.09 (0.78-1.52)
Employed in the last 12 months			
Yes	1.00	1.00	1.00
No	0.75 (0.64-0.88)**	0.77 (0.68-0.88)**	0.76 (0.68-0.84)**
Exposed to Second Hand Smoke			

Yes	1.04 (0.93-1.16)	1.08 (0.99-1.19)	1.06 (0.99-1.14)
No	1.00	1.00	1.00
Self Perceived Unmet Health Care Needs			
Yes	1.09 (0.54-2.21)	0.88 (0.52-1.48)	0.95 (0.61-1.46)
No	1.00	1.00	1.00
Has a Regular Medical Doctor			
Yes	1.00	1.00	1.00
No	0.50 (0.25-0.99)**	0.30 (0.11-0.83)*	0.40 (0.24-0.67)**

-- Odds Ratios not calculated for these indicators; **p<0.01; *p<0.05

Table 2.4: Adjusted Odds Ratios (OR) and 95% confidence intervals (CI) for factors associated with a late diabetes diagnosis

	Males	Females	Total
	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Age	1.02 (0.98-1.07)	1.04 (0.98-1.09)	1.02 (0.99-1.06)
Sex			
Male	--	--	1.00
Female	--	--	0.65 (0.37-1.14)
Education			
High	1.00	1.00	1.00
Low	0.71 (0.28-1.84)	0.33 (0.11-0.99)*	0.49 (0.25-0.94)*
Region			
Urban	1.00	1.00	1.00
Rural	1.84 (0.64-5.28)	1.05 (0.46-2.39)	1.32 (0.70-2.47)
Self Perceived Health			
Good/Very Good/Excellent	1.00	1.00	1.00
Poor/Fair	2.33 (0.73-7.46)	1.13 (0.44-2.87)	1.66 (0.87-3.16)
Body Mass Index (BMI)			
Normal	1.00	1.00	1.00
Overweight/Obese	2.14 (0.62-7.35)	0.99 (0.36-2.71)	1.30 (0.59-2.85)
Physical Activity			
Active/Moderately Active	1.00	1.00	1.00
Inactive	1.19 (0.47-2.99)	1.38 (0.57-3.34)	1.26 (0.69-2.33)
Smoking Status			
Non Smoker	1.00	1.00	1.00
Daily/Occasional	0.46 (0.12-1.70)	0.72 (0.26-1.99)	0.64 (0.29-1.42)
Drinking Status			
Former/Non Drinker	1.00	1.00	1.00
Regular/Occasional	0.47 (0.16-1.35)	0.78 (0.32-1.95)	0.68 (0.37-1.24)
Life Stress			
Not Stressful	1.00	1.00	1.00
Stressful	0.62 (0.23-1.64)	0.92 (0.37-2.32)	0.79 (0.41-1.52)
Marital Status			
Partnered	1.00	1.00	1.00
Unpartnered	1.58 (0.42-6.02)	0.98 (0.38-2.53)	1.10 (0.51-2.35)
Employed in the last 12 months			
Yes	1.00	1.00	1.00
No	0.94 (0.55-1.63)	0.92 (0.64-1.34)	0.96 (0.73-1.26)
Exposed to Second Hand Smoke			
Yes	--	--	0.99 (0.84-1.16)
No	--	--	1.00
Self Perceived Unmet Health Care Needs			
Yes	--	--	0.47 (0.21-1.05)
No	--	--	1.00
Has a Regular Medial Doctor			
Yes	--	--	1.00

No (1)	--	--	2.18 (0.36-13.07)

-- Odds Ratios not calculated for these indicators; **p<0.01; *p<0.05

2.5 Discussion

This study found that for males and females, high blood pressure was positively associated with diabetes. This finding is consistent with Meisinger et al.[30] who also found that hypertension was strongly associated with diabetes in both males and females. This study also found males and females who do not have a regular doctor are less likely to be diagnosed with diabetes than those who do. This could be due to the fact that those who have a doctor have an increased opportunity to discuss symptoms and to be screened for diabetes.

Being overweight or obese was associated with diabetes for males only in this study. Similarly, Njolstad et al.[31] also found that BMI was positively associated with diabetes and, after controlling for other factors, BMI was a stronger predictor in men. Previous research has found that men are diagnosed at lower BMI levels than females, which suggests that males may be more susceptible to diabetes than females[12]. In addition, it has been suggested that abdominal fat is associated with higher risk of diabetes and males usually carry weight in their abdominal region while females tend to carry weight in their hips and thighs[32].

For males only, being a regular or occasional drinker was inversely associated with diabetes. A U-shaped relationship has been found between diabetes risk and alcohol consumption[33, 34]. A meta-analysis conducted in 2005 found that moderate alcohol consumption is associated with a 30% reduced risk of type 2 diabetes in males and females[33]. The findings of this study are consistent with a recent study by Rasouli et al.[35] which found that moderate alcohol consumption is protective for type 2 diabetes in males

but not in females. The authors suggest that females could be more sensitive to the negative effects of alcohol compared to males or that females are more likely than males to underreport their alcohol intake.

This study found that living in a rural area was associated with diabetes for females only. The prevalence of diabetes is higher for individuals living in rural areas compared to urban areas[36, 37]. In general, diabetes prevalence is higher in males than females[3]. Johnson et al.[38] found diabetes prevalence was highest in rural men; however, mortality rates declined slightly for rural men and did not change for rural women between 1995 and 2006. Individuals living in rural areas are also more likely than urban residents to visit an emergency room or be admitted to hospital for the management of diabetes[39]. These findings highlight the differences in diabetes outcomes for individuals living in rural areas, especially females.

Receiving social assistance was associated with diabetes for females only in this study. Lysy et al.[40] found that diabetes risk is higher for lower income groups compared to higher income groups. In addition, risk was higher for lower income females compared to males. Dinca-Panaitescu et al.[36] also found an association between diabetes and income for both males and females, and the odds ratios were higher for females.

Having poor self-perceived health was positively associated with diabetes for females only. Unden et al.[41] also found that females with diabetes reported having a worse health situation than males, and were more likely to rate their health as poor compared to males. They conclude that diabetes may be experienced differently for males and females. In addition, Badawi et al.[42] also found that females were less likely to rate their health as excellent compared with males. They also found that self-rated health was significantly

associated with diabetes complications. One explanation for the discrepancy is that men and women use different information when making assessments about their health. Women have been found to base their health ratings on both serious and mild diseases, while men base them on serious illness only[43].

Previous research has also found that stress increases the risk of diabetes[44, 45]. The present study found that considering most days stressful was positively associated with diabetes for females but not for males. In addition, being unemployed in the last 12 months was inversely associated with diabetes for both males and females. This is interesting since work stress has been found to increase the risk of diabetes for females while the risk in men was decreased by high work demands[46].

This study found that females with a low education level, defined as less than secondary or completed secondary education, were less likely to be diagnosed late with diabetes compared to those with a higher level of education. Research investigating the association between early and late diabetes diagnosis and educational attainment has not been previously explored; however, research has been conducted on education level as a risk factor for diabetes. Most research suggests that individuals with a low level of education have a higher risk of diabetes and that the association is stronger in females[47-49]. However, Chien et al.[50] found that higher education levels were significantly associated with developing pre-diabetes or type 2 diabetes and this finding was significant for females only.

When comparing literature from other conditions, Sobrino-Vegas et al.[51] found that females with a high education level were more likely to have a delayed HIV diagnosis than those with a low education level. The opposite was observed in males. The authors

suggested that females with low education levels and males believe they are at higher risk for HIV as do their health care providers. As a result, they are offered routine HIV testing more than females with high education levels. HIV and diabetes are very different conditions since HIV is associated with social stigma and discrimination. However, previous research has found that patients with low education levels have more consultation time spent on physical examination and nutritional counselling compared to higher educated patients[52]. In addition, Piette et al.[53] examined general communication processes and diabetes-specific communication. Patients with lower education levels reported better general and diabetes-specific communication than patients with higher education levels. Health care providers may spend more time counselling patients that they perceive are in need of extra attention or explanation. Physicians may pay particular attention to individuals with lower education levels in an effort to diagnose diabetes earlier and since females visit their doctors more than males[54], females with lower education levels may be diagnosed with diabetes earlier than females with higher education levels or males.

Another possible explanation is that demands on an individuals' time may negatively affect his/her health. Adults with diabetes who are the primary caregivers for children or the elderly may not have time to obtain health care for themselves[55]. Females are usually the primary care givers for their families and often have to balance their families' needs with caring for an aging or sick relative and working outside the home. When asked the reasons for delaying or going without care, one in five women state that lack of time is a barrier[56].

The risk factors identified in this study could be used by physicians to diagnose diabetes earlier in both males and females. Also, the findings from this study could also be

used by policy makers. For males, lifestyle factors appear to be associated with diabetes. However, for females, disadvantages such as living in a rural area, receiving social assistance, having poor self perceived health and considering most days stressful is positively associated with diabetes. This information could be helpful when developing policies and strategies.

2.5.1 Limitations

There are several limitations that need to be addressed. Firstly, this was a cross-sectional study and therefore not as strong as a cohort or intervention study. Secondly, the covariates in this study are based on self-reported responses from the CCHS. Self-reported information can be affected by recall bias and social desirability bias. In addition, the CCDSS diabetes case definition does not differentiate between type 1 and type 2 diabetes. However, since most adults are diagnosed with type 2 diabetes[1], it is unlikely to have a major impact on the results. Furthermore, the CCDSS diabetes case definition uses physician claims data. In Newfoundland and Labrador, approximately one-third of the province's physicians are paid on a salary basis and these physicians are not required to submit medical claims so information on these visits is not captured. As a result, the sample of diabetes cases may be less than the true number of incident cases. In addition, some misclassification could have occurred as individuals with diabetes could have been classified as not having diabetes because a salaried physician provided most of their care.

Also, early and late diabetes diagnosis was determined by linking records for those with diabetes to the MCP and CDMS data to identify when hospital and physician visits for diabetes related comorbidities or complications occurred and these were compared to the

diabetes case dates. The range of 6 months before and after diagnosis was used to define early and late diabetes diagnosis. Some misclassification could have occurred as comorbidities or complications could have developed outside the 6 month range. Conditions such as cardiovascular disease, stroke, and coronary artery disease have similar risk factors as diabetes and could be diagnosed at the same time or before diabetes is diagnosed. Since many definitions of early and late diabetes diagnosis were tested and there was little change in the sample distribution across definitions, we feel that the range of 6 months before or after diagnosis is a good definition of early and late diabetes diagnosis. However, more research into when comorbidities and complications of diabetes develop is needed.

In addition, the definition of early and late depends on conditions identified through healthcare services covered by MCP. Conditions identified through healthcare services not covered by MCP could not be captured. Optometry services are not covered under MCP, therefore retinopathy would not be captured unless it was included in the CDMS data. Also, the list of conditions used in the early and late case definition is extensive. Many of these conditions could have been due to conditions other than diabetes. For example, it is possible that for conditions such as renal disease, amyloidosis, hyperlipidemia, optic nerve problems, polyneuropathies, facial nerve disorders, inflammatory polyneuropathy, radiculopathy, and a number of others may not be due to complications of diabetes. Conditions such as hypertension may also be present prior to the onset of diabetes. For the CCHS cohort, hypertension was the condition that defined a late diagnosis in 30.4% of cases. Misclassification bias is a possibility and future research should aim to not only test different case definitions of early and late diabetes diagnosis but also to include fewer

conditions in the definitions. Finally, even though the problem of small sample sizes is reduced by combining CCHS cycles, it is not completely eliminated.

2.6 Conclusion

In conclusion, the results of this study suggest that different factors are associated with diabetes for males and females. The majority of individuals diagnosed with diabetes are diagnosed in the later stages of the disease. Certain risk factors appear to impact males and females differently and more research is needed on the timing of diagnosis and how males and females develop diabetes. These risk factors could be used to diagnose diabetes earlier in both males and females.

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CHAPTER 3 Sex Differences in All-Cause and Cardiovascular Mortality and Hospitalization for Individuals With and Without Diabetes and Patients Diagnosed Early and Late With Diabetes

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3.1 Abstract

Objective: To compare risk of all-cause, cardiovascular disease (CVD), acute myocardial infarction (AMI) and stroke mortality and hospitalizations for males and females with and without diabetes and those diagnosed early and late with diabetes.

Methods: Population-based retrospective cohort study including 73,783 individuals aged ≥25 years in Newfoundland and Labrador, Canada (15,152 with diabetes; 9,517 diagnosed late).

Results: Males and females with diabetes had an increased risk of all-cause, CVD and AMI mortality and CVD hospitalizations compared to individuals without diabetes and the risk was stronger in females than in males. For females, risk of all-cause mortality (HR=1.85, 95% CI 1.74-1.96) and CVD hospitalizations (HR=2.57, 95% CI 2.24-2.94) was significantly higher compared to their male counterparts (HR=1.59, 95% CI 1.51-1.69 and HR=1.92, 95% CI 1.72-2.14, respectively). Females diagnosed late had an increased risk of CVD mortality (HR=6.54, 95% CI 4.80-8.91) and CVD hospitalizations (HR=5.22, 95% CI 4.31-6.33) compared to females without diabetes and both were significantly higher compared to their male counterparts (HR=3.44, 95% CI 2.47-4.79 and HR=3.33, 95% CI 2.80-3.95, respectively).

Conclusions: Females with diabetes have a greater risk of mortality than males with diabetes. CVD has a greater impact on females with diabetes than males, especially when

diagnosed at a later stage. Different management strategies could be considered for males and females and those diagnosed early and late with diabetes.

3.2 Introduction

Diabetes has become a health problem of increasing significance in the past two decades. The number of individuals with diabetes will increase to 592 million by 2035[1,2]. In the United States, the number of people with diabetes tripled from 5.6 million in 1980 to 17.4 million in 2007[3]. In Canada, almost 2.4 million people aged 1 and older were diagnosed with diabetes in 2008/09. The age-standardized prevalence of diabetes increased by 70% from 3.3% in 1998/99 to 5.6% in 2008/09 while the age-standardized incidence rate has been slightly increasing[4].

Diagnosing diabetes early is a challenge since many individuals who meet the criteria are often asymptomatic. About 175 million people, or half of those who have diabetes, are unaware they have the disease[1,2]. Furthermore, type 2 diabetes can be present for 9 to 12 years before being diagnosed and, as a result, complications are often present at the time of diagnosis[5]. Insulin resistance and beta-cell dysfunction are largely responsible for the development of diabetes and its related complications and both are present very early in the natural history of diabetes[6]. However, the potential does exist to prevent or at least delay the onset of type 2 diabetes as several randomized control trials have shown that both lifestyle and pharmacologic interventions in adults are effective[7-10]. In addition to preventing diabetes, it is also possible to reduce diabetes related microvascular complications through intensive blood glucose control. Results from the United Kingdom Prospective Diabetes Study (UKPDS) have shown that intensive blood glucose control reduces diabetes related microvascular complications[10,11].

Diabetes is a major cause of premature death and is associated with a 2-fold increase in mortality[12-14]. Individuals with type 2 diabetes could have their life

expectancy decreased by about 5-10 years compared to those without diabetes[15]. Cardiovascular disease (CVD) is the most common comorbidity associated with diabetes, and with 50% of those with diabetes dying of CVD it is the most common cause of death[1]. Acute myocardial infarction (AMI) and stroke are other common comorbidities associated with diabetes. Individuals with diabetes have an increased risk of all-cause mortality and morbidity related to CVD, AMI and stroke compared to individuals without diabetes[16-19].

While studies have consistently found that individuals with diabetes have a higher risk of mortality and hospitalizations compared to those without diabetes [12, 17-19], results have been inconsistent when comparing males and females. Most studies have found that females with diabetes have a greater risk of mortality and hospitalizations than males with diabetes[17, 19-24]. Two previous meta-analyses found that diabetes is a stronger risk factor for CVD mortality in females than in males; however, studies which did not adjust for major CVD risk factors were included in these meta-analyses[25,26]. A meta-analysis conducted by Kanaya et al.[27], which included studies that controlled for CVD risk factors, found that the risk for CHD mortality, non-fatal MI, and CVD associated with diabetes were not significantly different among males and females. Also, other studies have found that males with diabetes are at a higher risk for CHD[28] and stroke than females with diabetes[28,29].

Not only does Newfoundland and Labrador (NL) have the highest age-standardized prevalence of diabetes in Canada[4], the age-standardized mortality and hospitalization rates for CVD, AMI and stroke are some of the highest in the country[30-31]. A better

understanding of mortality and hospitalizations associated with diabetes in both males and females is important to support diabetes prevention and management.

3.2.1 Conceptual Framework

The conceptual framework used in this study was based on the behavioural model of health service utilization[32]. In this model, environmental factors (health care system and external environment), population characteristics and health behaviours interact to influence health service utilization. Three categories of determinants are used to describe population characteristics, 1) predisposing, 2) enabling, and 3) need. Predisposing factors are individual characteristics that influence the use of health services and include demographic, social structure, health beliefs, genetic factors and psychological characteristics. Enabling factors are those that assist or prevent an individual from using health services. Resources specific to individuals and their families as well as the attributes of the community in which they reside are enabling factors. Examples of enabling factors include income, insurance coverage and urban/rural region of residence. Need factors can be described as the reason why an individual would seek health care. Specifically, the medical reason/condition present or the health status of the individual as they perceive it or as evaluated by a health professional. Need factors are often the most important predictor of health service utilization[32].

The behavioral model of health service utilization has been widely used in research related to health service utilization[33-39]. The extensive use of the Andersen model to guide research demonstrates the model's flexibility. Since the model is a framework used to

guide analysis, variables to use are not stipulated[40] allowing researchers to modify the model and add variables.

The behavioral model of health service utilization was revised to provide the conceptual framework used to examine outcomes associated with diabetes for males and females (Figure 3.1). In this study, the predisposing variables consist of age and sex while the enabling factor is urban/rural region of residence. Need factors include the presence of diabetes and related co-morbidities while the outcomes of interest are hospital separations and mortality.

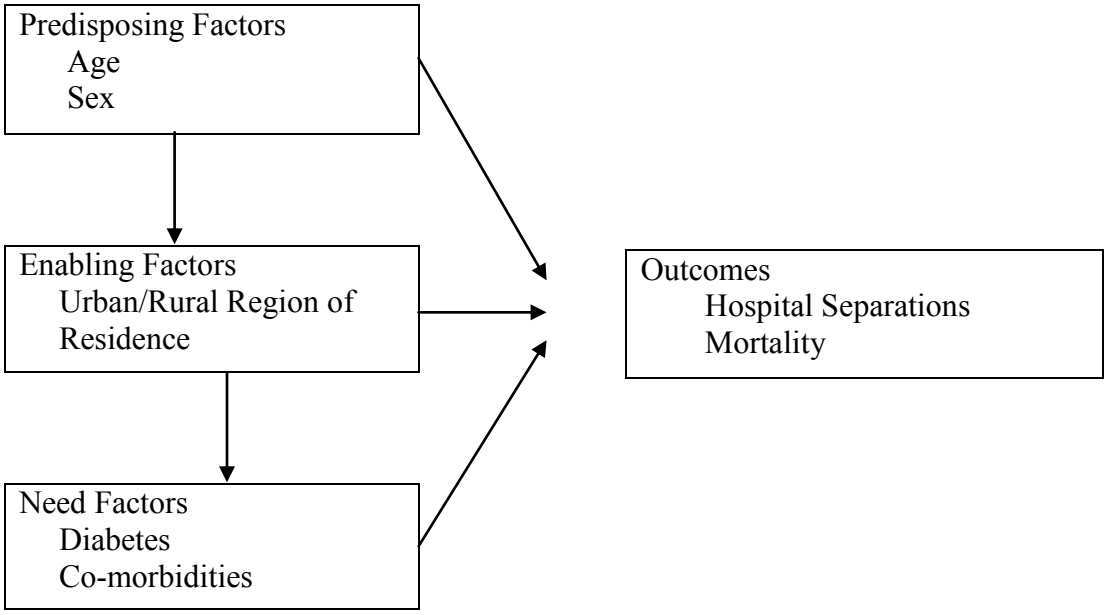


Figure 3.1: Revised Behavioral Model of Health Service Utilization to Examine Outcomes Associated with Diabetes for Males and Females

3.2.2 Research Objectives

The objectives of this study are 1) to compare the risk of all-cause, CVD, AMI, and stroke mortality and hospitalizations for males and females with and without diabetes, and 2) to assess and compare the risk of outcomes for males and females that did not have complications present at the time of diagnosis (early diagnosis) and for those that had complications at the time of diagnosis (late diagnosis). Our hypothesis is that risk of all-cause, CVD, AMI, and stroke mortality and hospitalizations will be higher for individuals with diabetes compared to those without diabetes. Risk of these outcomes will also be higher for individuals diagnosed early and late with diabetes compared to those without diabetes. In addition, we hypothesize that females will have a higher risk of these outcomes than males.

3.3 Methods

3.3.1 Study Design and Data Sources

This study was a population based retrospective cohort using administrative databases in Newfoundland and Labrador (NL). Databases included were: 1) Canadian Chronic Diseases Surveillance System (CCDSS) which uses provincial health insurance registries, hospital discharge records, and fee-for-service physician claims to identify individuals with diabetes; 2) the Clinical Database Management System (CDMS) which contains hospital separation data; 3) the Medical Care Plan (MCP) fee-for-service physician claims database which contains billing claims for fee-for-service physicians in NL; 4) the Newfoundland and Labrador Centre for Health Information (NLCHI) Mortality System, and 5) Statistics Canada Annual Mortality Data Files.

The Canadian Chronic Diseases Surveillance System (CCDSS) is a network of provincial and territorial chronic disease surveillance systems that compile administrative health care data relating to diabetes and send aggregate anonymous data to the Public Health Agency of Canada for national analyses. The information from which the CCDSS is composed includes the provincial health insurance registry, hospital discharge records, and fee-for-service physician claims. The CCDSS uses a nationally validated case definition to identify diabetes cases. The case definition used for the CCDSS has 86% sensitivity and 98% specificity for identifying individuals who had diabetes recorded in their primary care charts[41]. To be considered a diabetes case in the CCDSS, an individual must have met either of the following criteria: 1) had one hospital discharge with a diagnosis of diabetes or 2) two medical services records with diagnosis of diabetes not more than two years apart. Once included in the CCDSS, cases remain there until a record of their death is received or they move out of the province. The CCDSS diabetes case definition excludes women with gestational diabetes and cannot distinguish between type 1 and type 2 diabetes.

The CDMS is the provincial hospital separation database that captures demographic, clinical and interventional information for patients admitted to all acute health care facilities and surgical day care in the province of NL. The MCP system contains information related to services provided by fee-for-service physicians under the NL provincial Medical Care Plan.

The NLCHI Mortality System contains data extracted from provincial death notifications including demographics, health insurance number and conditions surrounding each death. Data are available since 1991. Conditions and/or diseases present at death are recorded but there is no indication of which of these leads directly to death (i.e. the

underlying cause of death). Diagnoses associated with the death are captured based on the International Classification of Disease (ICD), versions nine (1995/96 to 2000/2001) and ten (2001/02 to 2007/08).

The Statistics Canada Annual Mortality Data Files are a compilation of data from provincial and territorial offices of vital statistics that are submitted annually to Statistics Canada and contain data on deaths in Canada. Data are available since 1993. Diagnoses associated with the death are captured based on the International Classification of Disease (ICD), versions nine (1995/96 to 2000/2001) and ten (2001/02 to 2007/08). While data contained in the NLCHI Mortality system is more current, Statistics Canada Annual Mortality Data Files include the underlying cause of death.

3.3.2 Diabetes and early and late diagnosis status

The exposed group included all residents of Newfoundland and Labrador aged 25 years and older identified in the CCDSS as having a diabetes diagnosis between April 1, 1998 and March 31, 2003. The study entry date for the exposed group was the diabetes case date, which is defined as the latest date of hospital admission or the later of the two physician claims that contribute to the CCDSS case definition. A three year clearance period, in which an individual did not have a hospital admission or physician visit with a diabetes code, was used to identify incident diabetes cases. Previous studies have used between three and five years for clearance periods[41-43], and while five years is preferred[43], three years was used in this study to increase sample size.

Individuals with diabetes were classified as being diagnosed ‘early’ or ‘late’ depending on when diabetes related comorbidities or complications developed. Individuals

early on in the disease course would not be expected to have any diabetes related comorbidities or complications around the time of their case date. On the contrary, a late diagnosed diabetes patient would likely already have conditions related to diabetes around the time of diagnosis. To classify individuals diagnosed early and late, records for those with diabetes were linked to the MCP and CDMS data to identify when hospital and physician visits for diabetes related comorbidities or complications occurred and these were compared to the diabetes case dates. Incident diabetes patients without any diabetes related comorbidities or complications within 6 months before or after the diabetes case date were classified as early diagnosed while those with a late diagnosis were defined as incident diabetes patients with at least one diabetes related comorbidity or complication within 6 months before or after diagnosis. The diabetes related conditions that were used to define early and late status are listed in Appendix A. This method will identify comorbidities and complications identified through healthcare services covered by MCP; however, conditions identified through healthcare services not covered will not be captured.

Residents of Newfoundland and Labrador aged 25 years and older who had at least one hospitalization or fee-for-service physician visit between April 1, 1998 and March 31, 2003 and were not identified in the CCDSS as having diabetes were eligible to be included in the unexposed group. Using frequency matching by sex and 5-year age groups, each exposed individual was matched to four randomly selected individuals without diabetes.

The exposed and unexposed groups included individuals aged 25 years and older. Type 2 diabetes usually develops after the age of 40[1]; however, in an effort to increase the sample size, age 25 years and older was used.

3.3.3 Data Linkage

The linkage of the CCDSS data to the other databases was completed in seven steps. Step one involved identifying the exposed group (diabetes cases). Individuals diagnosed with diabetes between April 1, 1998 and Mar. 31, 2003 were identified and extracted from the CCDSS. Even though the CCDSS has information from January 1, 1995 to March 31, 1998, data from this time period was excluded to help ensure only newly diagnosed cases of diabetes were included (only individuals diagnosed with diabetes after March 31, 1998).

In step two, the early and late definitions were applied to determine which individuals with diabetes were classified as having an early or late diagnosis. This was achieved by linking diabetes cases to the MCP and CDMS data. Diabetes case dates were then compared to dates of hospital admissions and physician visits for diabetes related complications.

In step three, the unexposed group was identified (individuals without diabetes). The CCDSS was linked to the MCP and CDMS data to identify individuals aged 25 years and older who were not present in the CCDSS. Using frequency matching by sex and 5-year age groups, each exposed individual was matched to four randomly selected individuals without diabetes.

Step four involved linking to the MCP and CDMS data to determine if individuals with diabetes and those without diabetes were admitted to hospital or had physician visits for the outcomes of interest between January 1, 1995 and March 31, 1998. In step five, the file containing the diabetes and non-diabetes cases was linked to the MCP and CDMS to identify comorbidities using the Charlson Comorbidity Index (CCI). The CDMS data was

also used to identify hospital separations and length of stay for each individual in the study sample between April 1, 1998 and March 31, 2008.

In step six, the data were linked to NLCHI Mortality System (1998 to 2008) and Statistics Canada Annual Mortality Data Files (1998 to 2007) to capture those who had died. Finally, the data were linked to the neighbourhood socioeconomic status (SES) database to derive an SES score for each individual. This database contains an SES score that was developed by Audas, Cirtwill, and O'Keefe (2007)[44]. This score is based on social and economic variables, including employment, education, and income from the 2001 census. The SES score ranges from -24.0 to +24.0, with -24.0 representing the poorest and +24.0 representing the richest.

3.3.4 Outcomes and Follow-up

The outcomes of interest were mortality and hospitalizations due to all-causes, CVD (ICD-9 390-459; ICD-10-CA I00-I99), AMI (ICD-9 410; ICD-10-CA I21-I22), and stroke (ICD-9 430-436; ICD-10-CA I60-I64). The reference group used included individuals without diabetes for all analyses. Each outcome was assessed separately. Individuals who had a hospital admission or physician visit for CVD between January 1, 1995 and March 31, 1998 were excluded from the CVD analysis. Similar exclusions were made for the AMI and stroke analysis. For hospitalizations and all-cause mortality reported in this study, individuals were followed until March 31, 2008 (December 31, 2007 for cause specific mortality) or until one of two exit events: death or moved out of province. For the hospitalization analysis, hospitalization was also included as an exit event. For cause-specific outcomes, all other hospitalizations were censored. For example, for the

CVD hospitalization analysis, non-CVD hospitalizations were censored. The exposed and unexposed cohorts entered the study between April 1, 1998 and March 31, 2003 and followed until March 31, 2008 (December 31, 2007 for cause specific mortality). This allowed for a minimum follow-up period of five years, for those entering the study in 2003, and a maximum follow-up period of 10 years, for those entering the study in 1998.

Individuals who died prior to their study entry date were identified by linking to the NLCHI Mortality System and the Statistics Canada Annual Mortality Data Files and excluded.

3.3.5 Covariates

Region of residence, comorbidities and socioeconomic status (SES) were considered covariates in the analysis. An urban place of residence was defined as an area with 5,000 inhabitants or more while a rural place of residence was defined as an area with less than 5,000 inhabitants. This definition was used in an effort to define communities as urban and rural so they would match the urban and rural communities in the Canadian Community Health Survey (CCHS). Urban region of residence is defined in the CCHS as an area with a population concentration of 1,000 or more and a population density of 400 or more per square kilometre based on census counts. For this study, population estimates were identified for each standard geographical classification (SGC). SGC's with a population greater than or equal to 5,000 was defined as urban and compared to the CCHS classification. Similar comparisons were made for rural communities. Approximately 5.5% (4,040) of the study subjects did not have information on place of residence. The most commonly occurring category was assigned to the missing cases.

Comorbidities at baseline were estimated using the Charlson Comorbidity Index (CCI)[45]. The CCI is one of the most frequently used indexes that controls for comorbid conditions. Comorbidities were identified through diagnosis codes in the CDMS and MCP data and a comorbidity score, representing severity of illness, was assigned to each individual. The CCI was initially developed to predict in-hospital and 1-year mortality[43]; however, it has since been adapted for use with administrative data using ICD-9 and ICD-10-CA codes and has been shown to perform well[46, 47].

The neighbourhood SES database was used to derive an SES score for each individual. This database contains an SES score for each postal code in NL. This score is based on social and economic variables, including employment, education, and income from the 2001 census. The SES score ranges from -24.0 to +24.0, with -24.0 representing the poorest and +24.0 representing the richest. Approximately 3.2% (2,338) of the study subjects did not have information on SES so values were imputed using the median value imputation method. SES scores were divided into 5 quintiles with the first quintile representing the lowest SES group and the 5th quintile representing the highest SES group.

3.3.6 Statistical Analysis

Characteristics of the study population are presented as means and proportions and stratified by sex, diabetes status and early versus late diabetes diagnosis status. Chi-square tests were used for categorical variables and t-tests were used for continuous variables. In the mortality analysis, person-time was calculated from study entry date to date of death, termination of health insurance coverage or December 31, 2007. In the hospitalization analysis, all-cause, CVD, AMI, and stroke hospitalizations were assessed separately. For

all-cause hospitalizations, the person-time was calculated from study entry date to date of first hospital admission for any cause, termination of health insurance coverage, date of death or March 31, 2008. For the CVD hospitalizations, date of first CVD hospital admission was used. Likewise for AMI and stroke hospitalizations, date of first AMI hospital admission and stroke hospitalization were used, respectively.

Kaplan-Meier curves were constructed for each outcome and log rank tests were used to test the difference between the survival curves for those with and without diabetes and those diagnosed early and late. Cox proportional hazard models were used to calculate hazard ratios (HR) with 95% confidence intervals. The main assumption of the Cox proportional hazard model is the proportional hazards (PH) assumption, which assumes the HR is constant over time. When the PH assumption was not met, an extended Cox model with an interaction term between survival time and the variable failing the PH assumption was applied[48]. Interaction terms for diabetes and sex, early diagnosis and sex, and late diagnosis and sex were tested by the likelihood ratio test. When interactions were not significant, the analysis was not stratified by sex. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC) software.

3.3.7 Ethical Considerations

This study was approved by the Health Research Ethics Authority (HREA), the research ethics board responsible for reviewing research on human subjects in Newfoundland and Labrador (Appendix C). Approval to access data from the Newfoundland and Labrador Centre for Health Information was approved by the Centre's Secondary Uses Committee (Appendix D).

3.4 Results

The study sample consisted of 73,783 individuals; mean age at baseline was 60.1 years (SD=14.3). There were almost equal numbers of males and females, 37,790 (51.2%) and 35,993 (48.8%), respectively. About half (53.9%) of the study sample lived in a rural area. Over the ten-year study period, 11,385 (15.4%) individuals died and the mean age at death was 77.9 years (SD=11.0).

Characteristics of the study sample by diabetes status are presented in Table 3.1. For males, 20.5% (n=7,751) had diabetes while 20.6% (n=7,401) of females had diabetes. The mean age at baseline was similar for males and females with and without diabetes. More males without diabetes lived in a rural area compared to males with diabetes ($p<0.01$). However, more females with diabetes lived in a rural area compared to females without diabetes ($p<0.01$). Both males and females with diabetes where more likely to die, be younger at death and be admitted to hospital than those without diabetes ($p<0.01$). When admitted to hospital, females with diabetes had a longer mean length of stay compared to females without diabetes (7.0 and 5.5, $p<0.01$, respectively). Males with diabetes also had a longer length of stay compared to males without diabetes (6.4 and 5.6, $p<0.01$, respectively).

Characteristics of the diabetes sample by early and late diagnosis status are presented in Table 3.2. Both males and females diagnosed late with diabetes were significantly older at the time of diagnosis than those diagnosed early ($p<0.01$). Males and females diagnosed late with diabetes were more likely to be deceased at the end of the study period compared to those diagnosed early ($p<0.01$). Those diagnosed early were younger at death compared to those diagnosed late ($p<0.01$). During the study period, when

Table 3.1: Characteristics of the study sample stratified by diabetes status for males and females

	Males (n = 37,790)			Females (n = 35,993)			Total (n = 73,783)		
	No Diabetes (n = 30,039)	Diabetes (n = 7,751)	p-value[1]	No Diabetes (n = 28,592)	Diabetes (n = 7,401)	p-value[1]	No Diabetes (n = 58,631)	Diabetes (n = 15,152)	p-value[1]
Mean Age at baseline (yrs)	59.4 (SD=13.4)	59.2 (SD=13.4)	0.289	60.9 (SD=15.1)	60.6 (SD=15.2)	0.109	60.1 (SD=14.3)	59.9 (SD=14.3)	0.059
% Residing in Rural area	53.6% (16,913)	50.4% (3,906)	<0.01	52.5% (15,007)	52.4% (3,879)	0.646	54.6% (31,984)	51.4% (7,785)	<0.01
% Deceased at Study End	14.5% (4,360)	23.8% (1,842)	<0.01	12.1% (3,471)	23.1% (1,712)	<0.01	13.4% (7,831)	23.5% (3,554)	<0.01
Mean Age at Death (yrs)	76.5 (SD=10.2)	74.1 (SD=11.0)	<0.01	81.3 (SD=10.7)	78.3 (SD=11.2)	<0.01	78.7 (SD=10.7)	76.1 (SD=11.3)	<0.01
CCI									
0	96.6% (29,017)	95.5% (7,406)	<0.01	97.3% (27,825)	96.0% (7,107)	<0.01	96.9% (56,842)	95.8% (14,513)	<0.01
1-2	2.6% (781)	3.4% (265)		2.1% (612)	3.1% (226)		2.4% (1,393)	3.2% (491)	
3+	0.8% (241)	1.0% (80)		0.5% (155)	0.9% (68)		0.7% (396)	1.0% (148)	
SES quintile									
1 (lowest)	20.5% (6,154)	18.6% (1,442)	<0.01	19.2% (5,486)	22.8% (1,687)	<0.01	19.9% (11,640)	20.7% (3,129)	<0.01
2	20.2% (6,079)	21.0% (1,625)		19.4% (5,539)	20.8% (1,536)		19.8% (11,618)	20.9% (3,161)	
3	20.0% (6,012)	19.3% (1,498)		20.2% (5,784)	20.1% (1,488)		20.1% (11,796)	19.7% (2,986)	
4	19.7% (5,930)	21.0% (1,631)		20.0% (5,712)	19.2% (1,424)		19.9% (11,642)	20.2% (3,055)	
5 (highest)	19.5% (5,864)	20.1% (1,555)		21.2% (6,071)	17.1% (1,266)		20.4% (11,935)	18.6% (2,821)	
Hospitalizations									
All-Cause	58.5% (17,576)	72.3% (5,602)	<0.01	59.5% (17,012)	74.6% (5,518)	<0.01	59.0% (34,588)	73.4% (11,120)	<0.01
CVD	17.5% (5,261)	28.9% (2,238)	<0.01	12.3% (3,517)	22.9% (1,694)	<0.01	15.0% (8,778)	26.0% (3,932)	<0.01
AMI	6.0% (1,055)	8.6% (479)	<0.01	3.4% (584)	6.1% (335)	<0.01	4.7% (1,639)	7.3% (814)	<0.01
Stroke	3.9% (694)	5.4% (302)	<0.01	3.0% (507)	4.8% (267)	<0.01	3.5% (1,201)	5.1% (569)	<0.01
Mean Length of Stay (days)									
All-Cause	5.6 (SD=14.5)	6.4 (SD=15.2)	<0.01	5.5 (SD=14.6)	7.0 (SD=17.4)	<0.01	5.6 (SD=14.5)	6.7 (SD=16.4)	<0.01
CVD	8.7 (SD=16.4)	9.9 (SD=32.3)	0.102	9.5 (SD=20.6)	10.0 (SD=18.4)	0.305	9.1 (SD=18.3)	10.0 (SD=27.1)	0.020
AMI	9.9 (SD=12.2)	9.2 (SD=8.3)	0.251	11.1 (SD=17.2)	11.8 (SD=17.4)	0.595	10.3 (SD=14.2)	10.2 (SD=12.9)	0.882
Stroke	25.8 (SD=39.5)	20.8 (SD=30.3)	0.054	17.8 (SD=27.3)	24.3 (SD=84.2)	0.191	21.2 (SD=33.3)	22.7 (SD=64.7)	0.519

[1] Significance level = 0.05

Table 3.2: Characteristics of the study sample stratified by early and late diabetes diagnosis status for males and females

	Males (n = 7,751)			Females (n = 7,401)			Total (n = 15,152)		
	Early (n =3,034)	Late (n = 4,717)	p-value[1]	Early (n=2,601)	Late (n=4,800)	p-value[1]	Early (n=5,635)	Late (n=9,517)	p-value[1]
Mean Age at baseline (yrs)	53.9 (SD=12.8)	62.6 (SD=12.7)	<0.01	53.6 (SD=14.7)	64.4 (SD=14.0)	<0.01	53.7 (SD=13.7)	63.5 (SD=13.4)	<0.01
% Residing in Rural area	55.5% (1,684)	53.7% (2,535)	0.128	55.6% (1,447)	56.4% (2,708)	0.516	55.6% (3,131)	55.1% (5,243)	0.572
% Deceased at Study End	13.2% (401)	30.5% (1,441)	<0.01	11.7% (305)	29.3% (1,407)	<0.01	12.5% (706)	29.9% (2,848)	<0.01
Mean Age at Death (yrs)	70.7 (SD=12.5)	75.0 (SD=10.4)	<0.01	76.3 (SD=12.6)	78.7 (SD=10.8)	0.002	73.1 (SD=12.8)	76.8 (SD=10.8)	<0.01
CCI									
0	98.1% (2,977)	94.4% (8,987)	<0.01	98.0% (2,549)	95.0% (4,558)	<0.01	98.1% (5,526)	94.4% (8,987)	<0.01
1-2	1.7% (51)	4.2% (396)		1.7% (44)	3.8% (182)		1.7% (95)	4.2% (396)	
3+	0.2% (6)	1.6% (74)		0.3% (8)	1.3% (60)		0.2% (14)	1.4% (134)	
SES quintile									
1 (lowest)	18.6% (565)	18.6% (877)	<0.01	23.3% (606)	18.6% (877)	<0.01	20.8% (1,171)	20.6% (1,958)	<0.01
2	20.6% (624)	21.2% (1,001)		19.8% (516)	21.2% (1,001)		20.2% (1,140)	21.2% (2,021)	
3	20.6% (624)	18.5% (874)		19.4% (504)	18.5% (874)		20.0% (1,128)	19.5% (1,858)	
4	21.2% (644)	20.9% (987)		20.3% (527)	20.9% (987)		20.8% (1,171)	19.8% (1,884)	
5 (highest)	19.0% (577)	20.7% (978)		17.2% (448)	20.7% (987)		18.2% (1,025)	18.9% (1,796)	
Hospitalizations									
All-Cause	64.6% (1,960)	77.2% (3,642)	<0.01	69.1% (1,798)	77.5% (3,720)	<0.01	66.7% (3,758)	77.4% (7,362)	<0.01
CVD	17.7% (538)	36.0% (1,700)	<0.01	13.8% (360)	27.8% (1,334)	<0.01	15.9% (898)	31.9% (3,034)	<0.01
AMI	7.4% (144)	9.2% (335)	0.018	3.3% (60)	7.4% (275)	<0.01	5.4% (204)	8.3% (610)	<0.01
Stroke	2.9% (57)	6.7% (245)	<0.01	2.6% (47)	5.9% (220)	<0.01	2.8% (104)	6.3% (465)	<0.01
Mean Length of Stay (days)									
All-Cause	4.9 (SD=10.3)	7.2 (SD=17.2)	<0.01	5.1 (SD=13.3)	8.0 (SD=19.0)	<0.01	5.0 (SD=11.9)	7.6 (SD=18.2)	<0.01
CVD	8.2 (SD=22.1)	10.4 (SD=35.0)	0.148	7.5 (SD=13.4)	10.9 (SD=19.6)	<0.01	7.9 (SD=18.9)	10.6 (SD=29.1)	0.001
AMI	9.2 (SD=7.8)	9.2 (SD=8.5)	0.992	8.1 (SD=6.0)	12.6 (SD=18.9)	0.001	8.9 (SD=7.3)	14.3 (SD=16.4)	0.017
Stroke	21.2 (SD=62.9)	25.1 (SD=88.5)	0.754	24.2 (SD=35.0)	20.1 (SD=29.2)	0.458	22.5 (SD=52.0)	22.7 (SD=67.2)	0.979

[1] Significance level = 0.05

considering hospitalizations for all causes males and females with a late diabetes diagnosis were more likely to be hospitalized ($p<0.01$) and have a longer length of hospital stay compared to those diagnosed early ($p<0.01$).

Interaction terms for diabetes and sex, early diagnosis and sex, and late diagnosis and sex were tested by the likelihood ratio test. P-values for sex interactions are shown in Table 3.3. When interactions were not significant, the analysis was not stratified by sex. For example, the interaction terms for diabetes and sex were not significant for stroke mortality, all-cause hospitalization, AMI hospitalization or stroke hospitalization. Therefore, for these outcomes, the analysis was not stratified by sex and was analyzed for males and females combined.

Rates and hazard ratios (HR) for mortality and hospitalizations by sex and diabetes status are shown in Table 3.4. Males with and without diabetes have higher rates of all-cause mortality and CVD hospitalizations than females. For CVD and AMI mortality, males without diabetes have higher rates than females; however, females have higher rates when diabetes is present. After adjusting for place of residence, SES and CCI, both males and females with diabetes had an increased risk of dying of all-causes and dying and being hospitalized for CVD and AMI when compared to males and females without diabetes. The positive association between diabetes and all-cause mortality, CVD mortality and AMI mortality was stronger in females than in males. Not only was diabetes positively associated with all-cause mortality (HR=1.85, 95% CI 1.74-1.96), and CVD hospitalizations (HR=2.57, 95% CI 2.24-2.94), for females, the risk was significantly higher compared to their male counterparts (HR=1.59, 95% CI 1.51-1.69 and HR=1.92, 95% CI 1.72-2.14 respectively).

Table 3.3: P-value for sex interaction by diabetes and early and late diabetes diagnosis

	P-value for sex interaction		
	Diabetes versus No Diabetes	Early versus No Diabetes	Late versus No Diabetes
All-Cause Mortality	<0.0001**	0.0142*	0.0006**
CVD Mortality	0.0002**	0.0332*	0.0214*
AMI Mortality	0.0204*	0.0319*	0.1273
Stroke Mortality	0.7819	0.0243*	0.4548
All-Cause Hospitalization	0.6586	0.0001**	0.0026**
CVD Hospitalization	<0.0001**	0.0177*	0.0004**
AMI Hospitalization	0.0767	0.2002	0.0044**
Stroke Hospitalization	0.1001	0.1327	0.2613

**p<0.01
*p<0.05

Table 3.4: Mortality and Hospitalization Rates and Adjusted Hazard Ratios (HR)[1] by diabetes status and sex

	Males		Females		Total	
	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes
All-Cause Mortality						
Rate per 10,000 (n)	375.0 (1,842)	214.7 (4,360)	361.0 (1,712)	177.5 (3,471)	368.1 (3,554)	196.5 (7,831)
Unadjusted HR (95% CI)	1.74 (1.65-1.84)**	1.00 (reference)	2.03 (1.91-2.15)**	1.00 (reference)	--	--
Adjusted HR (95% CI)	1.59 (1.51-1.69)**	1.00 (reference)	1.85 (1.74-1.96)**	1.00 (reference)	--	--
CVD Mortality						
Rate per 10,000 (n)	52.5 (82)	35.7 (386)	64.3 (77)	24.7 (238)	57.6 (159)	30.5 (624)
Unadjusted HR (95% CI)	1.46 (1.15-1.85)**	1.00 (reference)	2.60 (2.01-3.36)**	1.00 (reference)	--	--
Adjusted HR (95% CI)	1.50 (1.15-1.90)**	1.00 (reference)	2.45 (1.89-3.17)**	1.00 (reference)	--	--
AMI Mortality						
Rate per 10,000 (n)	27.9 (127)	17.2 (330)	28.9 (130)	12.8 (239)	28.4 (257)	15.0 (569)
Unadjusted HR (95% CI)	1.62 (1.32-1.99)**	1.00 (reference)	2.25 (1.82-2.79)**	1.00 (reference)	--	--
Adjusted HR (95% CI)	1.48 (1.19-1.83)**	1.00 (reference)	1.96 (1.57-2.44)**	1.00 (reference)	--	--
Stroke Mortality						
Rate per 10,000 (n)	17.0 (78)	9.7 (187)	21.0 (93)	11.7 (216)	18.9 (171)	10.7 (403)
Unadjusted HR (95% CI)	--	--	--	--	1.77 (1.48-2.12)**	1.00 (reference)
Adjusted HR (95% CI)	--	--	--	--	1.62 (1.35-1.94)**	1.00 (reference)
All-Cause Hospitalization						
Rate per 1,000 (n)	242.9 (5,602)	140.5 (17,576)	255.1 (5,518)	145.7 (17,012)	248.8 (11,120)	143.0 (34,588)
Unadjusted HR (95% CI)	--	--	--	--	1.64 (1.60-1.67)**	1.00 (reference)
Adjusted HR (95% CI)	--	--	--	--	1.61 (1.58-1.64)**	1.00 (reference)
CVD Hospitalization						
Rate per 1,000 (n)	28.5 (418)	15.0 (1,603)	24.1 (277)	9.0 (871)	26.6 (695)	12.1 (2,474)
Unadjusted HR (95% CI)	2.91 (2.39-3.56)**	1.00 (reference)	4.61 (3.57-5.94)**	1.00 (reference)	--	--
Adjusted HR (95% CI)	1.92 (1.72-2.14)**	1.00 (reference)	2.57 (2.24-2.94)**	1.00 (reference)	--	--
AMI Hospitalization						
Rate per 1,000 (n)	9.3 (425)	5.0 (985)	6.5 (297)	2.9 (553)	7.9 (722)	4.0 (1,538)
Unadjusted HR (95% CI)	--	--	--	--	1.57 (1.44-1.72)	1.00 (reference)
Adjusted HR (95% CI)	--	--	--	--	1.61 (1.48-1.75)**	1.00 (reference)
Stroke Hospitalization						

Rate per 1,000 (n)	5.7 (265)	3.1 (608)	5.2 (236)	2.3 (445)	5.5 (501)	2.7 (1,053)
Unadjusted HR (95% CI)	--	--	--	--	1.58 (1.42-1.76)**	1.00 (reference)
Adjusted HR (95% CI)	--	--	--	--	1.31 (1.17-1.46)**	1.00 (reference)

Note: Missing HRs indicate lack of significant group by sex interaction

[1] Adjusted for region of residence, SES quintile and CCI.

*p<0.05

**p<0.01

Rates and hazard ratios (HR) for mortality and hospitalizations by sex and early and late diabetes diagnosis status are shown in Table 3.5. The reference group used included individuals without diabetes for all analyses. An early diagnosis does not appear to have an impact on all-cause, CVD, AMI or stroke mortality. However, the hospitalization results suggest that an early diagnosis does increase the risk of all-cause, CVD, and AMI hospitalizations compared to individuals without diabetes. After adjusting for covariates, males diagnosed late with diabetes had an increased risk of all-cause and CVD mortality and hospitalizations compared to males without diabetes. Similar findings were found for females. Not only was a late diabetes diagnosis positively associated with CVD mortality (HR=6.54, 95% CI 4.80-8.91) and CVD hospitalizations (HR=5.22, 95% CI 4.31-6.33) for females, the risk was significantly higher compared to their male counterparts (HR=3.44, 95% CI 2.47-4.79 and HR=3.33, 95% CI 2.80-3.95, respectively).

Table 3.5: Mortality and Hospitalization Rates and Adjusted Hazard Ratios (HR) [1] by early and late diabetes diagnosis status and sex

	Males		Females		Total	
	Early[2]	Late[2]	Early[2]	Late[2]	Early[2]	Late[2]
All-Cause Mortality						
Rate per 10,000 (n)	192.4 (401)	509.4 (1,441)	169.8 (305)	477.5 (1,407)	182.0 (706)	493.1 (2,848)
Unadjusted HR (95% CI)	--	2.37 (2.23-2.52)**	--	2.68 (2.52-2.85)**	0.92 (0.85-0.99)*	--
Adjusted HR (95% CI)	--	2.09 (1.97-2.23)**	--	2.38 (2.23-2.53)**	0.91 (0.84-0.98)*	--
CVD Mortality						
Rate per 10,000 (n)	34.7 (43)	120.0 (39)	30.5 (28)	175.1 (49)	32.9 (71)	145.5 (88)
Unadjusted HR (95% CI)	--	3.39 (2.44-4.71)**	--	7.14 (5.25-9.71)**	1.07 (0.84-1.37)	--
Adjusted HR (95% CI)	--	3.44 (2.47-4.79)**	--	6.54 (4.80-8.91)**	0.99 (0.77-1.28)	--
AMI Mortality						
Rate per 10,000 (n)	9.0 (18)	42.7 (109)	12.1 (21)	39.5 (109)	10.4 (39)	41.0 (218)
Unadjusted HR (95% CI)	--	--	--	--	0.70 (0.50-0.96)*	2.72 (2.33-3.18)*
Adjusted HR (95% CI)	--	--	--	--	0.70 (0.51-0.97)*	2.34 (1.98-2.76)*
Stroke Mortality						
Rate per 10,000 (n)	4.5 (9)	26.6 (69)	12.2 (21)	26.5 (72)	8.1 (30)	26.5 (141)
Unadjusted HR (95% CI)	--	--	--	--	0.75 (0.52-1.09)	2.49 (2.06-3.02)**
Adjusted HR (95% CI)	--	--	--	--	0.74 (0.51-1.08)	2.21 (1.81-2.70)**
All-Cause Hospitalization						
Rate per 1,000 (n)	168.8 (1,960)	318.0 (3,642)	193.9 (1,798)	301.1 (3,720)	179.9 (3,758)	309.3 (7,362)
Unadjusted HR (95% CI)	1.18 (1.13-1.24)**	2.05 (1.98-2.12)**	1.30 (1.23-1.36)**	1.91 (1.84-1.98)**	--	--
Adjusted HR (95% CI)	1.17 (1.11-1.23)**	1.89 (1.81-1.95)**	1.26 (1.20-1.32)**	1.75 (1.69-1.82)**	--	--
CVD Hospitalization						
Rate per 1,000 (n)	23.4 (277)	49.6 (141)	16.8 (151)	50.5 (126)	20.5 (428)	50.0 (267)
Unadjusted HR (95% CI)	--	3.34 (2.81-3.96)**	--	5.73 (4.76-6.91)**	1.70 (1.53-1.88)**	--
Adjusted HR (95% CI)	--	3.33 (2.80-3.95)**	--	5.22 (4.31-6.33)**	1.64 (1.48-1.82)**	--
AMI Hospitalization						
Rate per 1,000 (n)	7.0 (142)	11.1 (283)	3.3 (59)	8.5 (238)	5.3 (201)	9.8 (521)

Unadjusted HR (95% CI)	--	1.63 (1.43-1.86)**	--	2.24 (1.93-2.61)**	1.14 (0.99-1.32)	--
Adjusted HR (95% CI)	--	1.64 (1.44-1.88)**	--	2.15 (1.85-2.51)**	1.27 (1.09-1.48)**	--
Stroke Hospitalization						
Rate per 1,000 (n)	2.6 (53)	8.1 (212)	2.6 (46)	6.9 (190)	2.6 (99)	7.5 (402)
Unadjusted HR (95% CI)	--	--	--	--	0.82 (0.67-1.01)	2.05 (1.82-2.29)**
Adjusted HR (95% CI)	--	--	--	--	0.95 (0.78-1.17)	1.98 (1.76-2.23)**

Note: Missing HRs indicate lack of significant group by sex interaction

[1] Adjusted for region of residence, SES quintile and CCI.

[2] The reference group used included individuals without diabetes.

*p<0.05

**p<0.01

Kaplan-Meier curves and log rank tests show that males and females without diabetes had lower risks of all-cause mortality ($p<0.01$; Figure 3.2 and 3.3) and CVD hospitalizations ($p<0.01$; Figure 3.4 and 3.5) compared to males and females with diabetes. When comparing individuals diagnosed late with diabetes to those without diabetes, Kaplan-Meier curves and log rank tests show that males and females without diabetes had lower risks of CVD mortality ($p<0.01$; Figure 3.6 and 3.7) and CVD hospitalizations ($p<0.01$; Figure 3.8 and 3.9) compared to males and females diagnosed late with diabetes.

Figure 3.2: Kaplan-Meier curves for all-cause mortality among males with and without diabetes

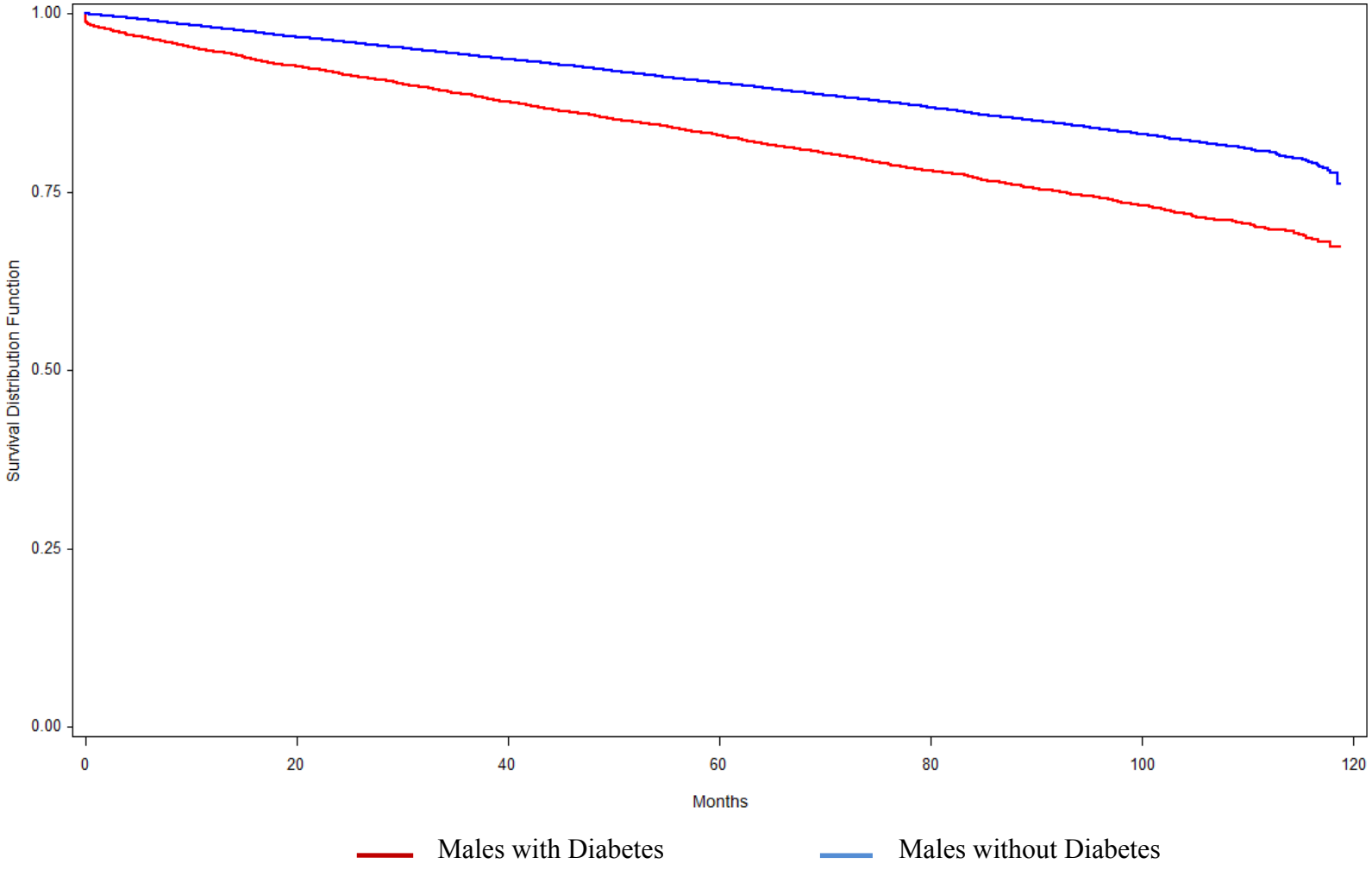


Figure 3.3: Kaplan-Meier curves for all-cause mortality among females with and without diabetes

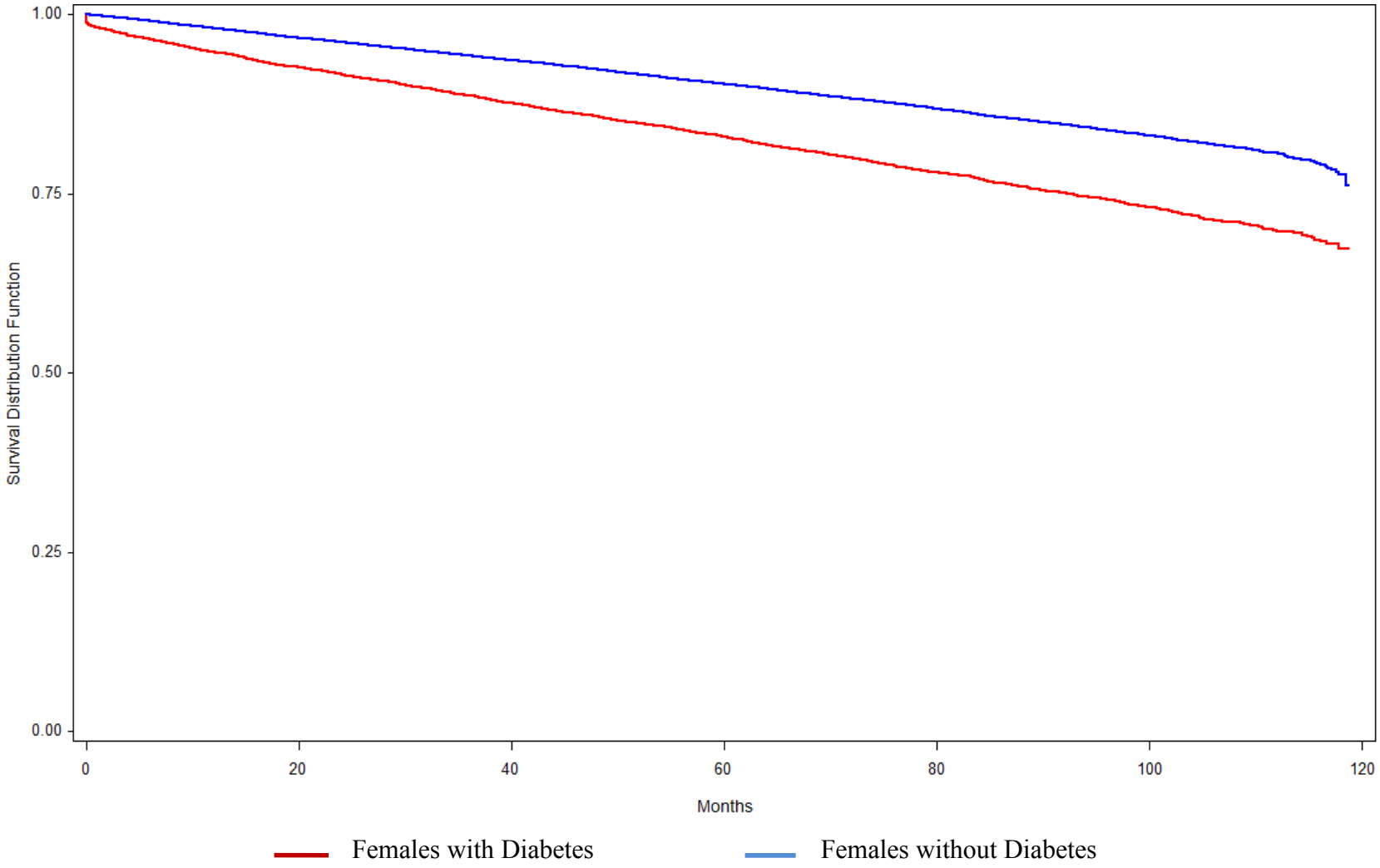


Figure 3.4: Kaplan-Meier curves for CVD hospitalizations among males with and without diabetes

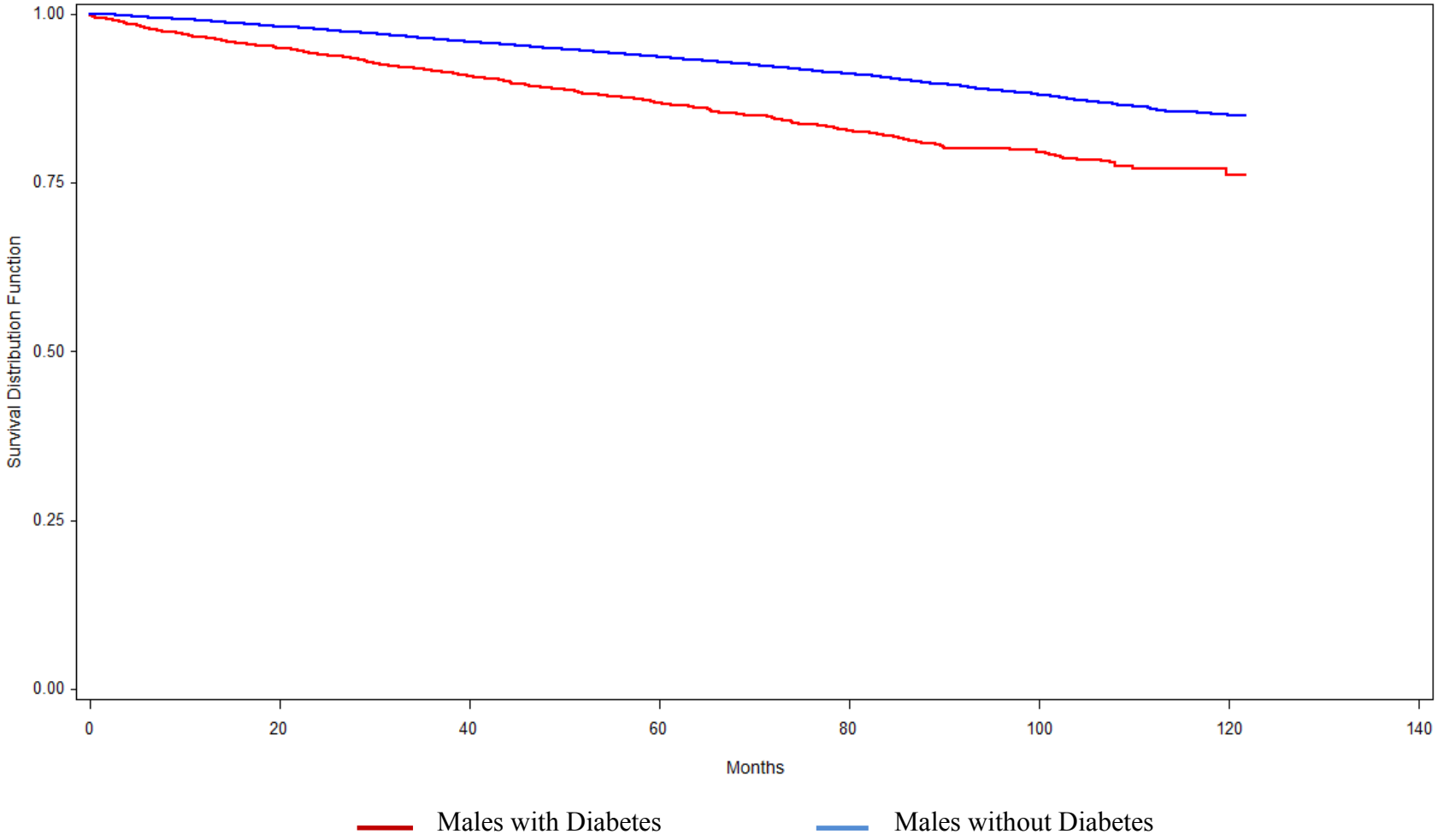


Figure 3.5: Kaplan-Meier curves for CVD hospitalizations among females with and without diabetes

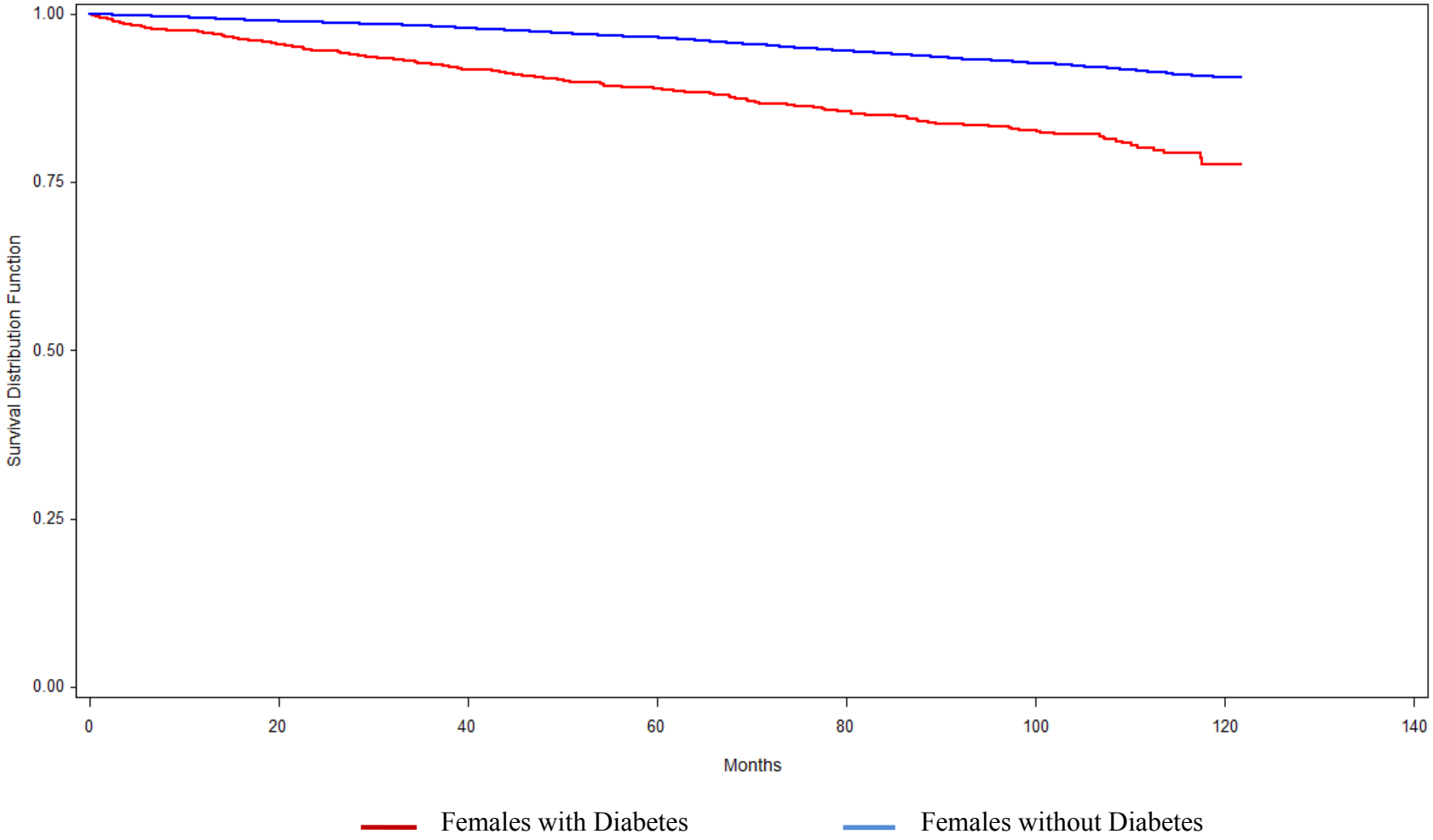


Figure 3.6: Kaplan-Meier curves for CVD mortality among males diagnosed late with diabetes and males without diabetes

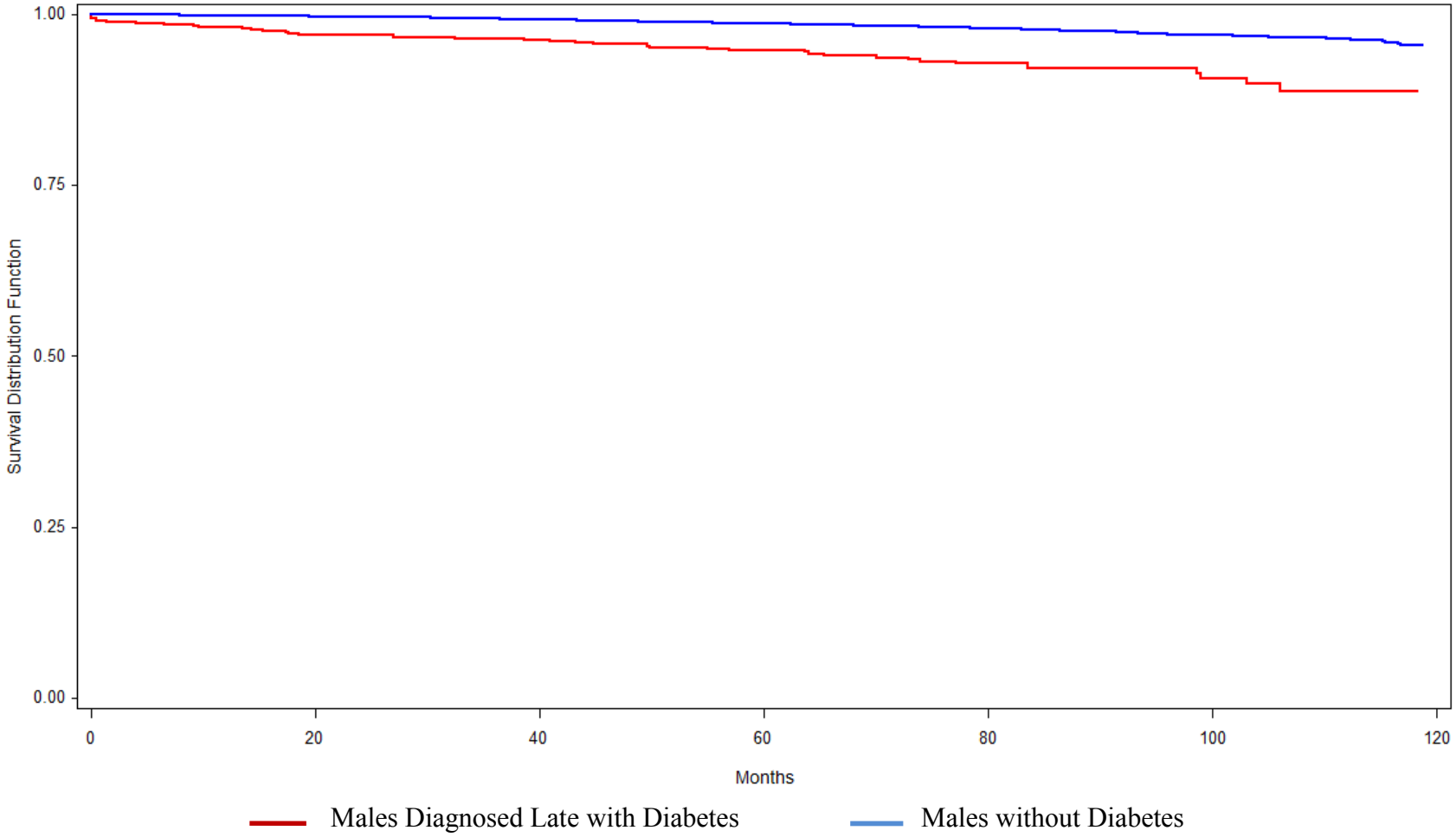


Figure 3.7: Kaplan-Meier curves for CVD mortality among females diagnosed late with diabetes and females without diabetes

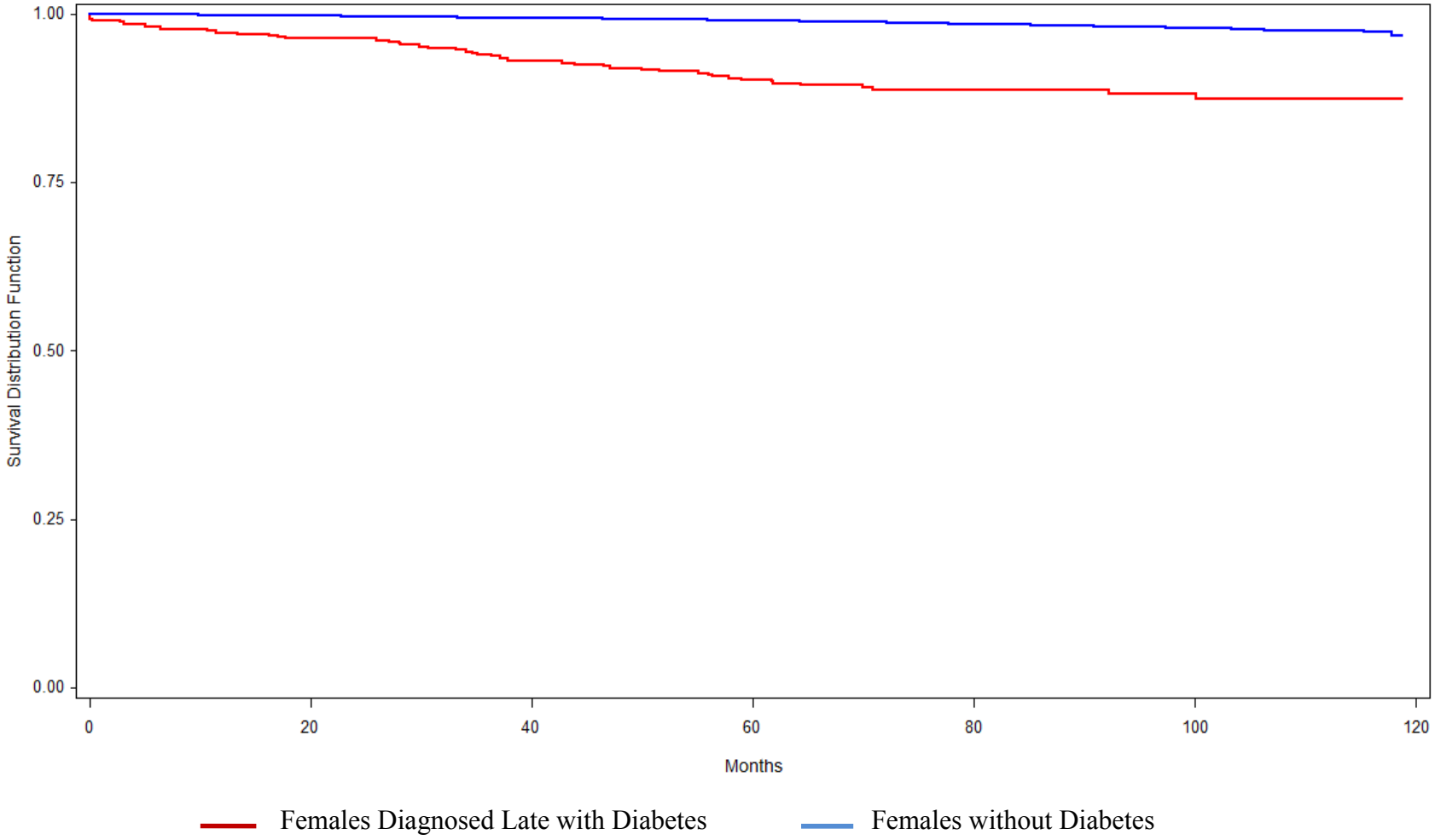


Figure 3.8: Kaplan-Meier curves for CVD hospitalizations among males diagnosed late with diabetes and males without diabetes

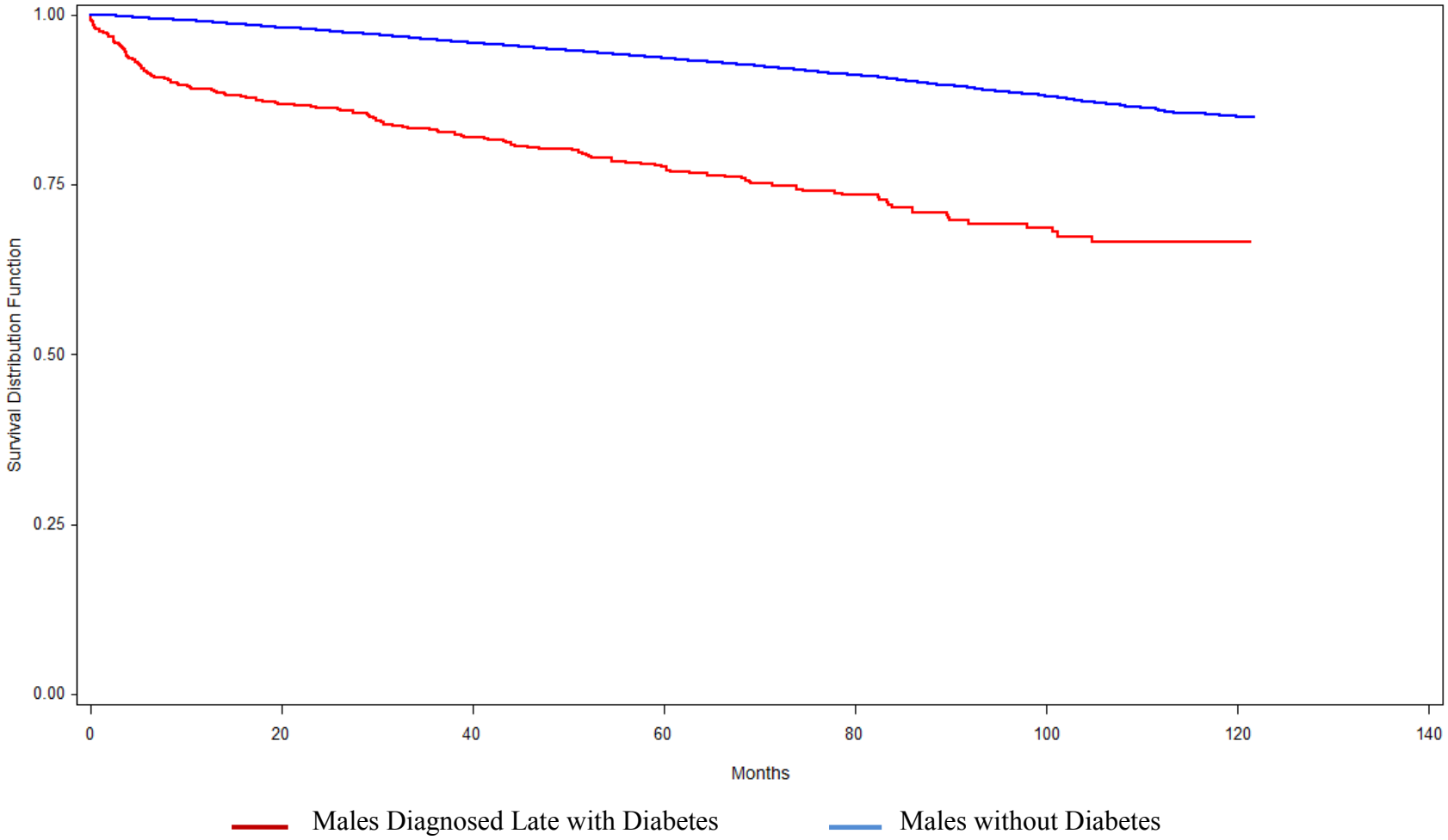
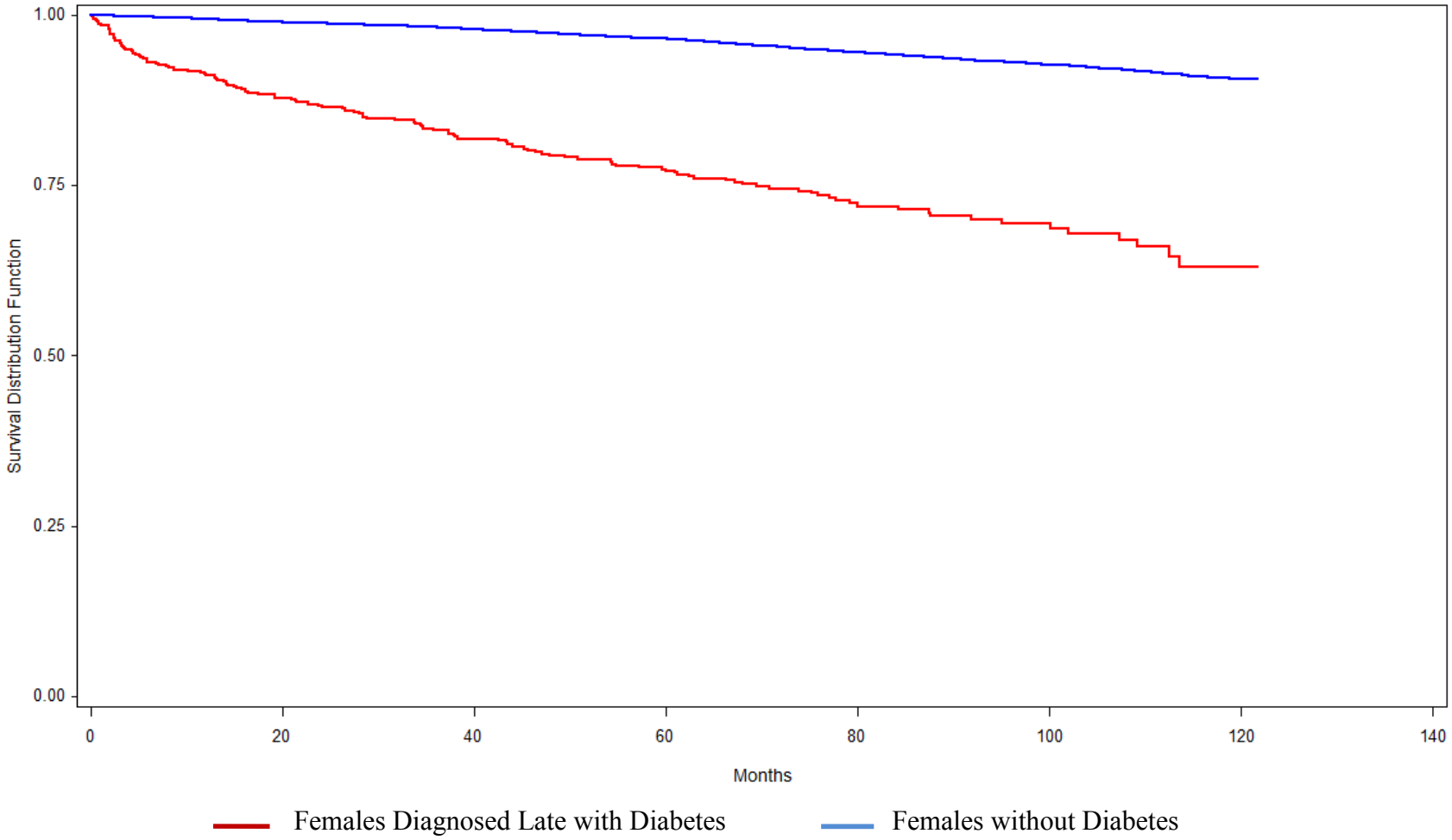


Figure 3.9: Kaplan-Meier curves for CVD hospitalizations among females diagnosed late with diabetes and females without diabetes



3.5 Discussion

In this population-based retrospective cohort study, mortality and hospitalizations for males and females with and without diabetes and those diagnosed early and late with diabetes were examined. After adjusting for covariates, not only was diabetes positively associated with all-cause mortality and CVD hospitalizations for females, the risk was significantly higher compared to their male counterparts. After adjusting for covariates, an early diagnosis does not appear to have an impact on all-cause, CVD, AMI or stroke mortality. However, the hospitalization results suggest that an early diagnosis does increase the risk of all-cause, CVD, and AMI hospitalizations compared to individuals without diabetes. Males and females diagnosed late with diabetes had an increased risk of all-cause mortality, CVD mortality, and CVD hospitalizations compared to those without diabetes. The risk of CVD mortality and hospitalizations for females diagnosed late compared to females without diabetes was significantly higher when compared to their male counterparts. While diabetes increases the risk of mortality and hospitalizations for both males and females, females are at a higher risk than males. CVD, in particular, has a greater impact on females with diabetes than males, especially when diabetes is diagnosed late.

Previous studies have also found that individuals with diabetes have an increased risk of mortality and morbidity related to all-causes, CVD, AMI, and stroke compared to individuals without diabetes[12, 17-19]. This study also found that females with diabetes had an increased risk of all-cause mortality, CVD mortality and CVD hospitalizations compared to females without diabetes and this was significantly higher compared to their male counterparts. The majority of previous studies have supported the claim that females with

diabetes are at a greater risk of mortality and morbidity than males with diabetes [12, 17, 19-24]. In addition, the results of this study show that CVD has a greater impact on females than males with diabetes.

It is not known why females with diabetes have an increased risk of mortality and hospitalizations compared to males with diabetes. More males are diagnosed with diabetes[4], and are diagnosed at lower BMI levels than females, which suggest males may be more susceptible to diabetes than females[49]. One explanation is that CVD risk factors have a stronger impact on females than males. The Strong Heart Study compared differences in diabetes risk factors in males and females aged 45-74. Differences in waist-to-hip ratio, HDL cholesterol, apolipoprotein (apo)B, apoA1, fibrinogen and LDL size between females with diabetes and those without diabetes were greater than differences for males[20]. Juutilainen et al.[23] investigated possible explanations for the stronger effect that diabetes has on the risk of coronary heart disease (CHD) in females compared to males. Risk factors in the presence of diabetes were greater in females than in males at baseline. During follow-up, these risk factors were stronger contributors to diabetes-related CHD risk in females than in males. Moreover, Homko et al.[50] examined differences in CVD risk factors and risk perception among males and females with diabetes. Although HbA1C and fasting plasma glucose levels were similar, females with diabetes had higher cholesterol levels and were less likely to meet LDL and blood pressure targets. While males and females had similar knowledge of CVD, females perceived their risk of CVD to be higher than males did. Also, females have an elevated risk of MI and stroke before they are clinically diagnosed with diabetes and it has been suggested that the risk of CVD in

females begins to increase at least 15 years before they are clinically diagnosed with diabetes[51].

Another possible explanation is that CVD risk factors are less aggressively treated in females. Females with diabetes are less likely than males to have optimal blood glucose control (HbA1C <7%), be prescribed aspirin and lipid-lowering medications and to achieve recommended blood pressure and LDL cholesterol levels[52, 53]. In addition, results from the NL Component of the Canadian Community Health Survey show that females with diabetes are less likely to be taking insulin, have their HbA1C levels tested and be prescribed aspirin and blood cholesterol medication compared to males with diabetes[54].

Barrett-Connor et al.[55] suggested that higher cardiovascular mortality risk observed in females with diabetes is a result of the larger survival advantage females have when diabetes is not present. This could explain the CVD and AMI mortality results found in this study. However, this does not explain the results for all-cause mortality and CVD hospitalizations as males had higher rates than females whether diabetes was present or not. In addition, risk of all-cause mortality and CVD hospitalizations where higher for females than males.

Results from randomized controlled trials (RCT) have found that the risk of microvascular complications can be reduced with intensive glucose control; however, the effect on macrovascular complications have been less clear[10, 11]. The UK Prospective Diabetes Study (UKPDS), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), Veterans Affairs Diabetes Trial (VADT) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) are RCT's that have been conducted to compare the effect of intensive glucose control

versus standard glucose control on CVD mortality and hospitalizations in patients with diabetes. These trials found that CVD events can be reduced with intensive glucose control; however, no significant effect on CVD mortality or all-cause mortality was found[10, 56-58].

However, the UKPDS examined whether intensive glucose control with Metformin reduces the risk of microvascular and macrovascular complications in overweight patients with newly diagnosed type 2 diabetes. Patients treated with Metformin, compared with the conventional treatment group, had a 32% lower risk of developing any diabetes-related endpoint (microvascular and macrovascular complications), a 42% lower risk for diabetes-related mortality, and a 36% lower risk for all-cause mortality[11].

Intensive glucose control however, may cause adverse outcomes in some patients. The ACCORD trial was stopped early due to higher mortality in the intensive glucose control group compared to the standard control group[57]. Also, the ADVANCE, ACCORD, VADT, and UKPDS trials showed higher rates of hypoglycemic episodes and weight gain in the group that was treated more intensively[56-58]. A recent meta-analysis of RCT's found limited benefits of intensive glucose lowering treatments on all-cause and CVD mortality, and concluded that the harm associated with hypoglycemia may offset any potential benefits of intense glucose control[59]. Alternatively, the UKPDS 10-year post-trial follow-up found that significant reduction in microvascular risk persisted, and significant reductions in myocardial infarction and all-cause mortality were seen in the intensive-control group during follow-up. The authors used the term 'legacy effect' to describe the continued benefit of intensive treatment[60]. Also, when patients were intensively treated with Metformin in the UKPDS, Metformin did not induce weight gain and was associated with less episodes of hypoglycaemia than sulphonylurea or insulin therapy[11].

Patients in the ADVANCE, VADT and ACCORD trials had diabetes for a number of years before entering the trial, whereas patients in the UKPDS where newly diagnosed. This could suggest that the same HbA1C target and treatment plan should not be applied to all patients with diabetes. Perhaps the focus should not only be on glucose control but on all CVD risk factors. The Canadian Diabetes Association Clinical Practice Guidelines provide recommended targets for glycemic control and suggest that treatment strategies should be individualized with consideration given to presence of risk factors[61]. Early and aggressive treatment has been suggested for patients that are newly diagnosed and do not have a history of CVD while less aggressive treatment may be suitable for older patients with a longer duration and a history of CVD[62]. However, this recommendation does not take into account the greater CVD risk that females with diabetes have. Perhaps a better approach would be to consider different treatment plans based on sex and timing of diabetes diagnosis.

3.5.1 Limitations

There are several strengths and limitations in this study. First of all, this was a large population-based cohort study with a long follow-up time. In addition, multiple outcomes were studied and administrative data was used to identify hospital separations and deaths. However, there are also several limitations that need to be addressed. Firstly, the CCDSS diabetes case definition does not differentiate between type 1 and type 2 diabetes. Since most individuals developing diabetes as adults will have type 2 diabetes[1] it is unlikely to have impacted the results in a major way.

Furthermore, the CCDSS diabetes case definition uses physician claims data. In Newfoundland and Labrador, one-third of the province's physicians are paid on a salary

basis[63] and these physicians are not required to submit medical claims so information on these visits is not captured. Some misclassification could have occurred as individuals with diabetes could have been classified as not having diabetes because a salaried physician provided most of their care. This also has the potential to impact findings by place of residence (urban/rural), as rural areas are largely serviced by salaried physicians. However, results from the Newfoundland and Labrador Component of the Canadian Community Health Survey show that individuals living in rural areas are less likely to have a physician visit in the last 12 months than individuals living in urban areas[64]. Also, individuals in rural areas are more likely to have a hospital admission in the last 12 months than those living in urban areas[65]. This suggests that the number of individuals with diabetes that are missed in rural areas is not substantial.

Also, early and late diabetes diagnosis was determined by linking records for those with diabetes to the MCP and CDMS data to identify when hospital and physician visits for diabetes related comorbidities or complications occurred and these were compared to the diabetes case dates. The range of 6 months before and after diagnosis was used to define early and late diabetes diagnosis. Some misclassification could have occurred as comorbidities or complications could have developed outside the 6 month range. Conditions such as cardiovascular disease, stroke, and coronary artery disease have similar risk factors as diabetes and could be diagnosed at the same time or before diabetes is diagnosed. Since many definitions of early and late diabetes diagnosis were tested and there was little change in the sample distribution across definitions, we feel that the range of 6 months before or after diagnosis is a good definition of early and late diabetes diagnosis. However, more research into when comorbidities and complications of diabetes

develop is needed. In addition, the definition of early and late depends on conditions identified through healthcare services covered by MCP. Conditions identified through healthcare services not covered by MCP could not be captured. Optometry services are not covered under MCP, therefore retinopathy would not be captured unless it was included in the CDMS data.

Also, the list of conditions used in the early and late case definition is extensive. Many of these conditions could have been due to conditions other than diabetes. For example, it is possible that for conditions such as renal disease, amyloidosis, hyperlipidemia, optic nerve problems, polyneuropathies, facial nerve disorders, inflammatory polyneuropathy, radiculopathy, and a number of others may not be due to complications of diabetes. Conditions such as hypertension may also be present prior to the onset of diabetes. For the CCDSS cohort, hypertension was the condition that defined a late diagnosis in 71.1% of cases. Misclassification bias is a possibility and future research should aim to not only test different case definitions of early and late diabetes diagnosis but also to include fewer conditions in the definitions.

Individuals hospitalized for CVD, AMI or stoke before 1994/95 cannot be identified using the existing database. However, a washout period from January 1, 1995 to March 31, 1997 was applied to exclude those that had a CVD, AMI or stroke event prior to the study start date and to help ensure that only newly diagnosed cases of diabetes were included.

Also, information on CVD risk factors was not available and thus could not be controlled for in the analysis. Finally, place of residence used in this study was the place of

residence at the beginning of the study period. Movement from a rural to an urban region and vice versa throughout the ten-year study period could have occurred.

3.6 Conclusion

In conclusion, the results of this study show that females with diabetes have a greater risk of mortality than males with diabetes. CVD has a greater impact on females than males with diabetes, especially when diagnosed at a later stage. Different management strategies could be considered for males and females and for those diagnosed early and late with diabetes.

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CHAPTER 4 Diabetes Diagnosis and Late Diabetes Diagnosis from the Family Physician Perspective

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4.1 Abstract

Objective: To describe how family physicians diagnose, treat and manage type 2 diabetes. A secondary objective was to identify if there were any differences in how male and female family physicians diagnose, treat and, manage individuals with type 2 diabetes.

Methods: A 28-item questionnaire, which included both open and closed ended questions was developed and mailed to all family physicians and general practitioners practicing in Newfoundland and Labrador (NL). Descriptive statistics were used to describe the characteristics of the survey respondents and to present results from the survey.

Results: Only 5.4% of family physicians reported that none of their patients had complications at the time of diagnosis. The majority of family physicians diagnose type 2 diabetes at an FPG (Fasting Plasma Glucose) level of 7 or greater (87.2%) and 68.5% will initiate a pharmacologic treatment at this level or greater. Only 31.3% of family physicians record a patient's weight at every visit while 91.2% checked a patient's blood pressure at every visit. The majority of family physicians reported counselling patients with type 2 diabetes on weight management (96.9%), healthy eating habits (94.4%), physical activity (98.8%) and smoking cessation (98.1%). The majority of family physicians reported screening high-risk patients for type 2 diabetes (98.1%); however, only 69.6% agreed that individuals aged 40 years and older with no risk factors should be screened for type 2 diabetes every 3 years. Male and female family physicians were similar in their diagnosis, treatment and management practices and in their attitudes toward diabetes. However, male family physicians were more likely than female family physicians to agree that HbA1C

(Glycated Hemoglobin A1C) is useful for screening (32.7% versus 16.0%, $p<0.05$) and male family physicians use HbA1C as a screening method more than female family physicians (45.9% versus 23.5%, $p<0.05$).

Conclusion: The majority of family physicians in NL have patients with complications present when they are diagnosed with diabetes. Even though family physicians have positive attitudes toward diabetes management, risk factors for diabetes complications like patient's body weights are not monitored to the extent blood pressure is. Family physicians need to monitor all risk factors for diabetes complications closely in an attempt to prevent progression to serious complications.

4.2 Introduction

Type 2 diabetes is a progressive disorder, which often has a gradual onset and a long asymptomatic phase. As a result, hyperglycemia can be present for many years[1] and type 2 diabetes can be present for up to 12 years before being clinically diagnosed[2, 3]. Diabetes is a complex condition and the development of diabetes related complications presents an immense challenge for family physicians. Symptoms of diabetes are variable and are not present for all patients. Some can develop slowly and therefore may not be noticed for years. Symptoms such as fatigue, frequent urination and excessive thirst are often ignored or can often be attributed to less serious conditions[4, 5].

Primary care providers often consider diabetes as harder to treat compared to other conditions like hypertension and angina[6]. Not all newly diagnosed patients will have complications at the time of diagnosis though some will. Fortunately, the potential does exit to prevent or at least delay the onset of type 2 diabetes as the findings of several randomized control trials have suggested that both lifestyle and pharmacologic interventions in adults are effective[7-10]. In addition to preventing diabetes, it is also possible to reduce diabetes related microvascular complications through intensive blood glucose control. Results from the United Kingdom Prospective Diabetes Study (UKPDS) have shown that intensive blood glucose control reduces diabetes related microvascular complications[10, 11].

Not only does Newfoundland and Labrador (NL) have the highest age-standardized prevalence of diabetes in Canada[12], the age-standardized mortality and hospitalization rates for diabetes complication such as cardiovascular disease (CVD), acute myocardial infarction (AMI) and stroke are among the highest in the country[13, 14]. Family physicians

have an opportunity to detect type 2 diabetes at the earliest possible stage and to provide appropriate management and treatment strategies in an effort to prevent serious complications. Early detection of diabetes is important since appropriate management strategies can be implemented. Therefore, it is important to identify how family physicians are diagnosing, treating, and managing type 2 diabetes.

4.2.1 Research Objectives

The main objective of this study was to describe how family physicians diagnose, treat and manage type 2 diabetes. A secondary objective was to identify if there were any differences in how male and female family physicians diagnose, treat, and manage individuals with type 2 diabetes.

4.3 Methods

4.3.1 Study Design and Study Sample

This was a descriptive cross-sectional study. Data were collected through a survey developed specifically for this study. Names and mailing addresses of all physicians practicing in NL (n=1110) were obtained from the Newfoundland and Labrador Medical Association in May 2009. Of the 1110 addresses provided, one physician's mailing address was listed as another province so he/she was excluded, leaving 1109 physician addresses. Mailing addresses were missing or incomplete for 13 physicians so they were also excluded, leaving 1096 physician addresses. Only family physicians and general practitioners were included leaving 509 physicians practicing within NL that met the inclusion criteria.

4.3.2 Questionnaire Development

Data were collected using a 28-item self-administered questionnaire, which included both open and closed ended questions. The questionnaire was developed to assess how family physicians diagnose, treat, and manage type 2 diabetes.

4.3.3 Data Collection

The survey was pilot tested with four family physicians between March 2009 and May 2009. Based on feedback, questions were deleted, reworded or reordered. A letter of information, the survey itself and a stamped return envelope were mailed to all general practitioners in the province (Appendix E). A second survey mail out was sent to all general practitioners four weeks after the first. The first mail out occurred in September 2009 and the second occurred in November 2009.

4.3.4 Statistical Analysis

Data were entered and analyzed using SPSS (SPSS Inc., Chicago IL). Descriptive statistics were used to describe the characteristics of the survey respondents and to present results from the survey. Percentages reflect the percentage of total respondents answering the survey question. Chi square tests were used to determine if sex and practice location differences existed. A significance level is $p<0.05$ was used to establish statistical significance.

4.3.5 Ethical Considerations

This study was approved by the Health Research Ethics Authority (HREA), the research ethics board responsible for reviewing research on human subjects in Newfoundland and Labrador (Appendix C). Since the surveys that were returned were anonymous this ensured the confidentiality and privacy of all study participants. All study data were stored on a secure server at the Newfoundland and Labrador Centre for Health Information.

4.4 Results

Surveys were mailed to 509 family physicians and general practitioners practicing within NL. Of the 509 surveys mailed, 26 were returned due to invalid addresses leaving a total of 483 potential respondents. A total of 161 (33.3%) surveys were completed and returned.

Demographic characteristics of the survey respondents are presented in Table 4.1. Mean age of respondents was 47.5 years (SD=10.9) and the majority of those that responded were male (68.3%). Years of practice ranged from one to 43 years with a mean of 19.4 (SD=11.9) years in practice. About half (48.5%) of family physicians had been practicing for more than 20 years with. The majority of family physicians practiced in a group setting (52.2%) while 31.7% practiced in a hospital or health centre and 10.5% in a private practice. The majority of family physicians responding practiced in an urban setting (72.3%) and were paid on a fee-for-service billing schedule (64.0%).

Table 4.1: Characteristics of Family Physician Survey Respondents and Practice Characteristics in NL

	n	%
Sex (n=161)[1]		
Male	110	68.3%
Female	51	31.7%
Number of years practicing (n=161)		
1 – 5	23	14.3%
6 – 10	30	18.6%
11 – 20	30	18.6%
> 20	78	48.5%
Type of Practice (n=161)		
Hospital/Health Centre	51	31.7%
Private	17	10.5%
Group Practice	84	52.2%
Other	9	5.6%
Practice Location (n=159)		
Rural (≤ 5,000)	44	27.7%
Urban (> 5,000)	115	72.3%
Billing Structure (n=161)[2]		
Fee-for-service	103	64.0%
Salaried academic physician	11	6.8%
Salaried community based physician	42	26.1%
Other	5	3.1%
Provide care to patients with type 2 diabetes (n=160)	156	97.5%
Involved in the Chronic Disease Management Diabetes Collaborative (n=157)	41	26.1%
Percentage of patients with type 2 diabetes (n=150)		
< 10%	36	24.0%
10 – 19	60	40.0%
20 – 49	44	29.3%
50% or more	10	6.7%
Percentage of type 2 diabetes patients with complications at diagnosis (n=147)		
0%	8	5.4%
1 – 9%	69	46.9%
10 - 24%	45	30.6%
25 - 49%	14	9.5%
50% or more	11	7.5%
Percentage of type 2 diabetes patients who receive care from a specialist (n=140)		
< 10%	52	37.1%
10 - 19%	32	22.9%
20 - 49%	34	24.3%
50% or more	22	15.7%

[1] In 2009, when this survey was conducted, 30.7% of practicing physicians in NL were female and 69.3% were male, according to the Newfoundland and Labrador Medical Association.

[2] In 2009, when this survey was conducted, 59.8% of practicing physicians in NL were paid on a fee-for-service schedule and 37.1% were salaried, according to the Newfoundland and Labrador Medical Association.

When asked if they provided care to patients with type 2 diabetes, 97.5% indicated they did and 26.1% said they were involved in the Chronic Disease Management Diabetes Collaborative. When asked what percentage of their patients had type 2 diabetes, 24.0% of Family physicians said less than 10%; 40.0% said between 10 and 19%; 29.3% said between 20 and 49%; and, 6.7% of family physicians said that 50% or more of their patients had type 2 diabetes. When asked what percentage of their patients had complications at the time of diagnosis only 5.4% of family physicians said none of their patients had complications at the time of diagnosis. Almost 47% said between 1 and 9% while 30.6% said between 10 and 24% of patients had complications at diagnosis. When asked what percentage of their type 2 diabetes patients received care from a specialist, 37.1% said that less than 10%; 22.9% said between 10% and 19%; 24.3% said between 20% and 49%; and, 15.7% said 50% or more.

The diagnosis, treatment and management practices of family physicians are shown in Table 4.2. Fasting plasma glucose (FPG) was the most frequent method used to screen patients for diabetes (98.8%) followed by 2 hr plasma glucose (2hPG) in a 75-g oral glucose tolerance test (56.9%). The majority of family physicians surveyed stated they would make a type 2 diabetes diagnosis when the FPG level is 7 or greater (87.2%). When asked about initiating a pharmacologic treatment, 68.5% would begin this treatment when the FPG level is 7 or greater while 19.6% stated waiting until the FPG level is 10 or greater. When asked what glycated hemoglobin A1C (HbA1C) is useful for, 89.4% of family physicians said blood glucose monitoring, 74.4% said treatment and 27.5% said

Table 4.2: Diagnosis, Treatment and Management Practices of Family Physicians in NL

	n (%)	%
Which screening method do you use (n=160)		
Fasting plasma glucose (FPG)	158	98.8%
Casual plasma glucose (PG)	28	17.5%
2 hr plasma glucose (2hPG) in a 75-g oral glucose tolerance test (OGTT)	91	56.9%
Glycosylated haemoglobin (HbA1C)	62	38.8%
Other[1]	7	4.3%
At what FPG level do you usually make a diagnosis of type 2 diabetes (n=156)		
6 or greater	16	10.3%
7 or greater	136	87.2%
10 or greater	4	2.6%
At what FPG level do you usually initiate a pharmacologic treatment (n=143)		
6-6.9	5	3.5%
7 or greater	98	68.5%
10 or greater	28	19.6%
Need to consider other factors	12	8.4%
Measuring Glycosylated hemoglobin (HbA1C) is useful for:		
screening (n=160)	44	27.5%
treatment (n=160)	119	74.4%
Blood glucose monitoring (n=160)	143	89.4%
Do you recommend home glucose monitoring to your type 2 diabetes patients (n=158)	157	99.4%
For patients with type 2 diabetes, do you record their weight at every visit (n=160)	50	31.3%
For patients with type 2 diabetes, do you check their blood pressure at every visit (n=159)	145	91.2%
Do you counsel patients on the following topics (n=160)		
Weight management	157	98.1%
Healthy eating habits	148	92.5%
Physical activity	156	97.5%
Smoking cessation	158	98.8%
Other[2]	18	11.3%
Do you counsel type 2 diabetes patients on the following topics (n=160)		
Weight management	155	96.9%
Healthy eating habits	151	94.4%
Physical activity	158	98.8%
Smoking cessation	157	98.1%
Other[3]	25	15.6%

[1]Other includes 2 hr PG, urinelysis and 2h postprandial ; [2]Other includes alcohol, body image, self esteem, medications, heredity, cholesterol, stress reduction, control of comorbidities;[3] Other includes alcohol, medications, diabetes complications, foot care, glucose monitoring, cholesterol, cancer screening, stress reduction.

screening. Ninety-nine percent of family physicians said they recommend home glucose monitoring to their patients.

When asked about diabetes management practices, only 31.3% of family physicians record their patient's weight at every visit while 91.2% of family physicians checked their patient's blood pressure at every visit. The majority of family physicians reported counselling patients with type 2 diabetes on weight management (96.9%), healthy eating habits (94.4%), physical activity (98.8%) and smoking cessation (98.1%).

Table 4.3 shows family physician attitudes toward diabetes screening, management and treatment practices. Almost 84% of family physicians said they always or often use the 2008 Canadian Diabetes Association's Clinical Practice Guidelines as a decision support tool. The majority of family physicians reported that they screen high-risk patients for type 2 diabetes (98.1%). While 71.1% of family physicians indicated that they refer patients to a registered dietitian, 95% said they refer type 2 diabetes patients to a registered dietitian. Only 69.6% of family physicians agreed that individuals 40 years of age and older with no risk factors should be screened for type 2 diabetes every 3 years. However, 89.4% agreed that screening high-risk patients is feasible in a day-to-day medical practice. In terms of reducing complications, 82.6% agreed that tight blood glucose control would reduce complications for the patient in the long term. In addition, 90.7% agreed that early treatment for those with impaired fasting glucose (IFG) should reduce complications in the long term.

Diagnosis, treatment and management practices of family physicians by sex are shown in Table 4.4, while family physician attitudes toward diabetes by sex are presented in Table 4.5. Male and female family physicians were similar in their diagnosis, treatment and management practices and in their attitudes toward diabetes. The only differences

found were that male family physicians were more likely than female family physicians to agree that HbA1C is useful for screening (32.7% versus 16.0%, $p<0.05$) and male family physicians use HbA1C as a screening method more than female family physicians (45.9% versus 23.5%, $p<0.05$).

Table 4.3: Family Physician Attitudes Toward Diabetes Screening, Management and Treatment Practices in NL

	Always/Often n (%)
How often do you use the 2008 Canadian Diabetes Association's Clinical Practice Guidelines as a decision support tool? (n=158)	132 (83.5%)
How often do you screen high-risk patients for type 2 diabetes? (n=159)	155 (98.1%)
How often do you refer your patients to a registered dietician? (n=159)	113 (71.1%)
How often do you refer your type 2 diabetes patients to a registered dietician? (n=159)	151 (95.0%)
	Agree n (%)
According to the 2008 CDA's Clinical Practice Guidelines, screening for type 2 diabetes should be performed every 3 years among individuals > 40 years of age with no other risk factors? (n=160)	112 (69.6%)
Screening all high-risk patients for type 2 diabetes is feasible in a day-to-day medical practice (n=160)	144 (89.4%)
Tight blood glucose control for patients with type 2 diabetes will reduce complications for the patient in the long term (n=160)	133 (82.6%)
Early treatment of patients with impaired fasting glucose (IFG) will reduce complications in the long term? (n=161)	146 (90.7%)

Table 4.4: Diagnosis, Treatment and Management Practices of Family Physicians by Sex

	n (%) Yes		
	Male Physicians (n=110)	Female Physicians (n=51)	p-value
Do you use Fasting Plasma Glucose (FPG) as a screening method?	107 (98.2%)	51 (100%)	0.330
Do you use Casual Plasma Glucose (PG) as a screening method?	21 (19.3%)	7 (13.7%)	0.390
Do you use Oral Glucose Tolerance Test (OGTT) as a screening method?	62 (56.9%)	29 (56.9%)	0.390
Do you use Glycosylated hemoglobin (HbA1C) as a screening method?	50 (45.9%)	12 (23.5%)	0.007*
Measuring HbA1C is useful for screening.	36 (32.7%)	8 (16.0%)	0.028*
Measuring HbA1C is useful for treatment.	85 (77.3%)	34 (68.0%)	0.213
Measuring HbA1C is useful for blood glucose monitoring.	97 (88.2%)	46 (92.0%)	0.468
Do you recommend home glucose monitoring?	107 (99.1%)	50 (100%)	0.495
For type 2 diabetes patients, do you record their weight at every visit?	38 (34.5%)	12 (24.0%)	0.182
For type 2 diabetes patients, do you check their blood pressure at every visit?	101 (91.8%)	44 (89.8%)	0.678
Do you counsel patients on weight management?	107 (97.3%)	50 (100%)	0.238
Do you counsel patients on healthy eating habits?	100 (90.9%)	48 (96.0%)	0.257
Do you counsel patients on physical activity?	106 (96.4%)	50 (100%)	0.172
Do you counsel patients on smoking cessation?	108 (98.2%)	50 (100%)	0.337
Do you counsel type 2 diabetes patients on weight management?	107 (97.3%)	48 (96.0%)	0.668
Do you counsel type 2 diabetes patients on healthy eating habits?	102 (92.7%)	49 (98.0%)	0.180
Do you counsel type 2 diabetes patients on physical activity?	108 (98.2%)	50 (100%)	0.337
Do you counsel type 2 diabetes patients on smoking cessation?	107 (97.3%)	50 (100%)	0.668

*$p<0.05$

Table 4.5: Sex Differences in Family Physician Attitudes Toward Diabetes

	n (%) Always/ Often		
	Male Physicians (n=110)	Female Physicians (n=51)	p-value
How often do you use the 2008 Canadian Diabetes Association's Clinical Practice Guidelines as a decision support tool?	90 (82.6%)	42 (85.7%)	0.622
How often do you screen high-risk patients for type 2 diabetes?	106 (98.1%)	49 (98.0%)	0.949
How often do you refer your patients to a registered dietician?	81 (74.3%)	32 (64.0%)	0.183
How often do you refer your type 2 diabetes patients to a registered dietician?	103 (94.5%)	48 (96.0%)	0.687
	n (%) Agree		
According to the 2008 CDA's Clinical Practice Guidelines, screening for type 2 diabetes should be performed every 3 years among individuals > 40 years of age with no other risk factors?	75 (71.4%)	37 (78.7%)	0.345
Screening all high-risk patients for type 2 diabetes is feasible in a day-to-day medical practice.	98 (92.5%)	46 (92.0%)	0.921
Tight blood glucose control for patients with type 2 diabetes will reduce complications for the patient in the long term.	92 (87.6%)	41 (89.1%)	0.792
Early treatment of patients with impaired fasting glucose (IFG) will reduce complications in the long term?	99 (92.5%)	47 (95.9%)	0.422

4.5 Discussion

The results of this study found that only 5.4% of family physicians reported that none of their patients had complications at the time of diagnosis. Most family physicians in this province have patients with complications present when they are diagnosed with diabetes. This suggests a late diagnosis since hyperglycemia can be present for many years[1] and studies have shown that type 2 diabetes can be present for up to 12 years before being clinically diagnosed[2, 3]. In addition, symptoms of diabetes are often not present or develop slowly and may not be noticed for years. Symptoms such as fatigue, frequent urination and excessive thirst are often ignored or can often be attributed to less serious conditions. Singh et al.[4] found that 40% of patients with diabetes had symptoms for more than 12 months prior to being diagnosed. Patients can often put off seeing their doctor, especially if they do not recognize the symptoms of diabetes and if they are not feeling ill. According to Koopman et al.[5], patients often attribute diabetes symptoms to other causes and are often not aware that these symptoms are related to diabetes. Also, patients have limited knowledge of diabetes symptoms prior to being diagnosed, even when they had close family members with diabetes.

However, it is not only knowledge of symptoms that can affect when a person is diagnosed but understanding that diabetes is a serious condition[15]. Murphy & Kinmonth[16] found that people with diabetes interpreted the disease in terms of avoiding short term symptoms or avoiding long term complications. Those who focused on the complications rather than the symptoms tended to believe that diabetes was a serious condition. However, those who did not have symptoms did not think diabetes was serious and described themselves as having a mild form of diabetes. Similarly, a study by Dietrich[17] found that patients who did not feel sick do not take their diabetes diagnosis serious. However, this can change once they are prescribed insulin

or develop complications. Also, patients who are diagnosed with prediabetes do not take this seriously as they often do not consider this 'real' diabetes and as a result do not adopt the proper risk reduction behaviours[18]. Educating individuals on the seriousness of diabetes could potentially result in early diagnosis and prevent the progression to complications. It is essential that family physicians encourage risk reduction behaviours.

Previous research has found that primary care provider attitudes about diabetes impact how patients view the disease[19]. The reaction and attitude of physicians at the time of diagnosis are important factors that influence the perceived seriousness of the disease and the patients' compliance to treatment[17]. Physician attitudes toward diabetes management may be more important than knowledge of the disease[20]. This is encouraging since family physicians in this province have positive attitudes toward diabetes management. This study found that the majority of family physicians refer type 2 diabetes patients to a registered dietician and feel that screening high-risk patients is feasible in a day-to-day medical practice. Also, the majority of family physicians report counselling patients and patients with type 2 diabetes on weight management, healthy eating habits, physical activity and smoking cessation. This is important since previous research has found that physician advice is associated with the reported adoption of healthy behaviours such as weight loss, physical activity, healthy eating and smoking cessation[18, 21-22].

While the majority of family physicians report they screen high-risk patients for type 2 diabetes not all agreed that individuals aged 40 years and older with no risk factors should be screened for type 2 diabetes every three years, which is recommended by the Canadian Diabetes Association's Clinical Practice Guidelines. When asked, the majority of family physicians said they use the 2008 Canadian Diabetes Association's (CDA) Clinical Practice Guidelines (CPG) as

a decision support tool. These evidence-based recommendations are published every five years to guide healthcare professionals in the prevention and management of diabetes in Canada[23].

Worrall et al.[24] evaluated family physician compliance with the CDA's guidelines in Newfoundland and Labrador and found that CPGs were generally not being followed. Adherence to some guidelines was very good while adherence to others were poor. All patients had their blood pressure checked and 83% had their weight measured at visits. This study also found that the majority of family physicians checked their patient's blood pressure at every visit; however only 31.3% of family physicians recorded their patient's weight at every visit. Since the majority of individuals with diabetes are overweight or obese, the CDA's CPGs recommend interventions in overweight and obese individuals with diabetes or those at risk for diabetes in an effort to prevent weight gain and to achieve and maintain a reduced body weight[23]. Research has shown that even losing 5% to 10% of initial body weight can improve glycemic control and cardiovascular disease risk factors[8, 9].

We found that male and female family physicians were similar in their diagnosis, treatment and management practices and in their attitudes toward diabetes. This finding is different from previous research which has found that female physicians are more likely to provide preventive services and counselling than male physicians[25-27]. Also, previous research findings suggest that female physicians may provide better quality of diabetes care than male physicians[28]. However, this study did find that male family physicians were more likely than female family physicians to agree that HbA1C is useful for screening (32.7% versus 16.0%, $p<0.05$) and male family physicians use HbA1C as a screening method more than female family physicians (45.9% versus 23.5%, $p<0.05$). This difference is not overly concerning since the 2013 CDA's CPGs allow for the diagnosis of diabetes to be made on the basis of either a fasting

plasma glucose test, HbA1C, 2-hour plasma glucose in a 75 gram oral glucose tolerance test or a random plasma glucose test. The decision of which test to use to diagnose diabetes is left to the discretion of the physician[23].

4.5.1 Limitations

The following limitations should be considered when interpreting the results of this study. A response rate of 33.3% is not high; however, this is not surprising for the physician population, given the demands on their time. Previous studies have also reported low response rates in mailed surveys to family physicians[29, 30] and it has been suggested that response rates are declining[29]. In 2009, when this survey was conducted, 30.7% of practicing physicians in NL were female and 69.3% were male[31]. This is comparable to the males and females who responded to our survey (31.7% female versus 68.3% male). Similarly, in 2009, 59.8% of practicing physicians in NL were paid on a fee-for-service schedule and 37.1% were salaried. This is also comparable to our study in which 64% of family physicians responding to the survey were fee-for-service family physicians and 32.9% were salaried[30]. Nevertheless, the results of this study may not reflect the opinions of family physicians who did not respond.

In addition, item non-response occurred in this survey as certain questions were not answered by all respondents. This is unlikely to have impacted the results in a major way as the large majority of respondents did answer most questions. Also, response bias could have affected the results as this study depended on physicians self reporting how they manage and treat their patients. Recall bias could also have affected the results since physicians would have to recall how many diabetes patients they have and what their status was at the time of diagnosis.

At the time this study was conducted the 2008 Canadian Diabetes Association clinical practice guidelines were the most recent guidelines. There are some notable differences between the 2008 guidelines and the most current guidelines. In 2013, the Canadian Diabetes Association released the 2013 clinical practice guidelines. The 2008 version did not recommend using HbA1C as a screening test[23]; however, the 2013 version has including HbA1C as a screening test in addition to FPG, casual plasma glucose and the 2 hour plasma glucose in 75 g OGTT. The 2013 Canadian Diabetes Association clinical practice guidelines recommend routine screening be performed every 3 years in individuals 40 years of age and older or those considered to be at high risk[32]. In contrast, in 2012 the Canadian Task Force on Preventive Health Care recommends not routinely screening adults at low to moderate risk. It recommends routine screening for adults at high risk every 3-5 years and recommends annual screening for adults at very high risk[33]. Both the Canadian Diabetes Association clinical practice guidelines and the Canadian Task Force on Preventive Health Care recommend an HbA1C value of 6.5% or greater as the threshold for diagnosing diabetes. Also, both leave the decision of which test to use to diagnose diabetes to the discretion of the physician and suggest that an abnormal level may require repeat testing to confirm a diagnosis of diabetes[32, 33].

4.6 Conclusion

In conclusion, the results of this study show that the majority of family physicians in this province have patients with complications present when they are diagnosed with diabetes. Family physicians have positive attitudes toward diabetes management; however, patient's body weights are not monitored to the extent blood pressure is. Male and female family physicians

were similar in their diagnosis, treatment and management practices and in their attitudes toward diabetes.

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CHAPTER 5 General Discussion and Summary

5.1 Summary of Key Findings

This thesis examined diabetes and early and late diagnosis of diabetes in the province of Newfoundland and Labrador. A review of the literature revealed that type 2 diabetes can be present for a long period of time before being diagnosed. Insulin resistance and beta-cell dysfunction are largely responsible for the development of diabetes and its related complications and both are present very early in the natural history of the disease[1]. Hyperglycemia may be present for more than 20 years[2] and type 2 diabetes can be present for up to 12 years before being diagnosed[3, 4]. As a result newly diagnosed patients can have complications at the time of diagnosis. It has been estimated that 2-39% of newly diagnosed patients have retinopathy, 8-18% have nephropathy, 5-13% have neuropathy and 8% have cardiovascular disease[5]. On average a person has diabetes for about 5 or 6 years before complications develop[6]. Randomized control trials have shown that diet and exercise can prevent or delay the progression from impaired glucose tolerance to diabetes[7, 8]. Intensive lifestyle interventions have been found to be more effective than metformin[9] and intensive blood glucose control has been shown to reduce diabetes related microvascular complications[10, 11].

The objectives of this thesis were to use administrative data to develop a case definition of early and late diabetes diagnosis based on when comorbidities or complications develop; describe what factors are associated with a diabetes diagnosis and a late diabetes diagnosis, for males and females; mortality and hospitalization outcomes for males and females with diabetes and those diagnosed early and late; and, to describe how male and female family physicians diagnose, treat, and manage type 2 diabetes. After developing a series of definitions ranging

from specific to very broad (6 months to 2 years, before/after diagnosis) sample sizes were determined and assessed. Since there was little change in the sample distribution across definitions, the range of 6 months before and after diagnosis was used to define early and late diabetes diagnosis. Administrative data were used to identify individuals diagnosed early and late with diabetes. The Canadian Chronic Diseases Surveillance System (CCDSS) was used to identify records for those with diabetes. These records were linked to the Medical Care Plan (MCP) Fee-For-Service Physician Claims Database and the Clinical Database Management System (CDMS) data. Those data were used to determine when hospital and physician visits for diabetes related comorbidities or complications occurred and these were compared to the diabetes case dates. Incident diabetes patients without any diabetes related comorbidities or complications within 6 months before or after the diabetes case date were classified as being early diagnosed while those with a late diagnosis were defined as incident diabetes patients with at least one diabetes related comorbidity or complication within 6 months before or after diagnosis.

In chapter 2 factors associated with a diabetes diagnosis and late diabetes diagnosis for males and females were examined. The results of this study suggest that different factors are associated with diabetes for males and females. For males, overweight/obesity was positively associated with diabetes while being a regular/occasional drinker was inversely associated with diabetes. Living in a rural area, receiving social assistance, having poor self perceived health, and considering most days stressful were positively associated with diabetes for females. The factors associated with a late diabetes diagnosis were also different for males and females. While no factors were significantly associated with a late diabetes diagnosis for males, having a low education was inversely associated with a late diabetes diagnosis for females.

In chapter 3 all-cause and cardiovascular mortality and hospitalizations for males and females with and without diabetes and those diagnosed early and late with diabetes were assessed. After adjusting for covariates, not only was diabetes positively associated with all-cause mortality and CVD hospitalizations for females, the risk was significantly higher compared to their male counterparts. After adjusting for covariates, an early diagnosis does not appear to have an impact on all-cause, CVD, AMI or stroke mortality. However, the hospitalization results suggest that an early diagnosis does increase the risk of all-cause, CVD, and AMI hospitalizations compared to individuals without diabetes. Males and females diagnosed late with diabetes had an increased risk of all-cause mortality, CVD mortality and CVD hospitalizations compared to those without diabetes. The risk of CVD mortality and hospitalizations for females diagnosed late compared to females without diabetes was significantly higher when compared to their male counterparts. While diabetes increases the risk of mortality and hospitalizations for both males and females, females appear to be at a higher risk than males. Our results suggested that CVD, in particular, had a greater impact on females with diabetes than males, especially when diabetes was diagnosed late.

How family physicians diagnose, treat and manage type 2 diabetes was assessed in chapter 4. A secondary objective was to identify if there were any differences in how male and female family physicians diagnose, treat and manage those with type 2 diabetes. The results of this study suggested that the majority of family physicians in this province have patients with complications when they are diagnosed with diabetes. Family physicians have positive attitudes toward diabetes management; however, patient's body weights are not monitored to the extent that blood pressure is. Male and female family physicians participating in the survey were

similar in their diagnosis, treatment and management practices and in their attitudes toward diabetes.

5.2 Recommendations for Future Research

5.2.1 Definition of Early and Late Diabetes Diagnosis

One of the objectives of this dissertation was to use administrative data to develop a case definition of early and late diabetes diagnosis based on when comorbidities or complications develop. A series of definitions ranging from specific to very broad (6 months to 2 years, before/after diagnosis) and sample sizes for each definition were developed. Since there was little change in the sample distribution across definitions, the range of 6 months before and after diagnosis was used to define early and late diabetes diagnosis. In addition, an internal medicine physician was consulted and agreed that the definition of 6 months before and after diagnosis was reasonable. Incident diabetes patients without any diabetes related comorbidities or complications within 6 months before or after the diabetes case date were classified as early diagnosed while those with a late diagnosis were defined as incident diabetes patients with at least one diabetes related comorbidity or complication within 6 months before or after diagnosis.

Future research should aim to validate this definition of early and late diabetes diagnosis. Since many definitions of early and late diabetes diagnosis were tested and there was little change in the sample distribution across definitions, we feel that the range of 6 months before or after diagnosis is a good definition of early and late diabetes diagnosis. In an effort to capture all late diagnosed cases of diabetes, a broad range of comorbidities and complications were included in the case definition. The date an individual is identified as having diabetes in the CCDSS is not the date that diabetes developed. Type 2 diabetes can be present for up to 12 years before being

diagnosed[3, 4] and on average an individual has diabetes for about 5 or 6 years before complications develop[6]. Since administrative data was used to identify diabetes cases, it was not possible to identify what is a comorbidity and what is a complication of diabetes since it is not possible to determine when diabetes developed, only when it was diagnosed. As a result, all possible comorbidities and complications of diabetes were included in the definition of early and late diagnosis. Also, the list of conditions used in the early and late case definition is extensive. Many of these conditions could have been due to conditions other than diabetes. For example, it is possible that for conditions such as renal disease, amyloidosis, hyperlipidemia, optic nerve problems, polyneuropathies, facial nerve disorders, inflammatory polyneuropathy, radiculopathy, and a number of others may not be due to complications of diabetes. Conditions such as hypertension may also be present prior to the onset of diabetes. In Chapter 2, for the CCHS cohort, hypertension was the condition that defined a late diagnosis in 30.4% of cases. In Chapter 3, for the CCDSS cohort, hypertension was the condition that defined a late diagnosis in 71.1% of cases. Some misclassification is possible and therefore, it would be useful to test the case definition of early and late diabetes diagnosis using fewer comorbidities and complications. In addition, more research into when comorbidities and complications of diabetes develop is needed.

Administrative data were used to identify individuals with diabetes and to identify those diagnosed early and late. The CCDSS diabetes case definition does not differentiate between type 1 and type 2 diabetes. However, since most adults are diagnosed with type 2 diabetes[12], it is unlikely to have a major impact on the results. Furthermore, the CCDSS diabetes case definition uses the Medical Care Plan (MCP) Fee-For-Service Physician Claims Database. MCP data was also used in the definition of early and late diabetes diagnosis. Records for those with diabetes

were linked to the MCP and CDMS data to identify when hospital and physician visits for diabetes related comorbidities or complications occurred and these were compared to the diabetes case dates. In Newfoundland and Labrador, one-third of the province's physicians are paid on a salary basis and these physicians are not required to submit medical claims so information on these visits is not captured. Some misclassification could have occurred as individuals with diabetes could have been classified as not having diabetes or classified as early or late diagnosed because a salaried physician provided most of their care. Also, the definition of early and late depends on conditions identified through healthcare services covered by MCP. Conditions identified through healthcare services not covered by MCP could not be captured. Optometry services are not covered under MCP, therefore retinopathy would not be captured unless it was included in the CDMS data. Using medical charts instead of the MCP data would be a richer and more complete data source. However, the time required to review medical charts would be extensive. Once a provincial electronic medical record is developed and being used by all physicians in the province, the EMR data could then be used to validate the early and late diagnosis definition.

5.2.2 Factors Associated with a Diabetes Diagnosis and Late Diabetes Diagnosis for Males and Females

This study found that different factors are associated with the occurrence of diabetes in males and females. For males, lifestyle factors such as BMI and alcohol consumption impact whether or not they will be diagnosed with diabetes. Njolstad et al.[13] also found that BMI was positively associated with diabetes and, after controlling for other factors, BMI was a stronger predictor in men. Since men are diagnosed at lower BMI levels than females, they may be more susceptible to diabetes than females[14]. In addition, males usually carry weight in their abdominal

region and females tend to carry weight in their hips and thighs[15]. It has been suggested that abdominal fat is associated with higher risk of diabetes and this could explain the greater risk of diabetes in overweight and obese men compared to women. Similarly, Rasouli et al.[16] found that moderate alcohol consumption is protective for type 2 diabetes in males but not in females. The authors suggest that females could be more sensitive to the negative effects of alcohol compared to males or that females are more likely than males to underreport their alcohol intake.

This study found that for females, disadvantages such as living in a rural area, receiving social assistance, having poor self perceived health, and considering most days stressful were positively associated with diabetes. Previous research has also found that diabetes risk is higher for lower income groups compared to higher income groups and the risk was higher for lower income females compared to males[17, 18].

Females with diabetes report having a worse health situation than males and are more likely to rate their health as poor compared to males[19]. In addition, females are less likely to rate their health as excellent compared with males[20]. One explanation for the discrepancy is that men and women use different information when making assessments about their health. Women have been found to base their health ratings on both serious and mild diseases, while men base them on serious illness only[21].

Previous research has also found that stress increases the risk of diabetes[22, 23]. One explanation for this finding is that stress is also associated with unhealthy lifestyle behaviors, such as unhealthy eating, physical inactivity, smoking, and alcohol abuse. These factors are also risk factors for developing diabetes[24, 25].

This study also found that the factors associated with a late diabetes diagnosis were different for males and females. While no factors were significantly associated with a late

diabetes diagnosis for males, having a low education was inversely associated with a late diabetes diagnosis for females. Most research suggests that individuals with low levels of education have a higher risk of diabetes and that the association is stronger in females[26-28]. However, Chien et al.[29] found that higher education levels were significantly associated with developing pre-diabetes or type 2 diabetes and this finding was significant for females only. More research is needed on why males and females develop diabetes, when they are diagnosed, and why females are at greater risk than males.

5.2.3 Sex Differences in All-Cause and Cardiovascular Mortality and Hospitalization for Individuals With and Without Diabetes and Patients Diagnosed Early and Late With Diabetes

This study found that diabetes was positively associated with all-cause mortality and CVD hospitalizations for females and the risk was significantly higher compared to their male counterparts. Males and females diagnosed late with diabetes had an increased risk of all-cause mortality, CVD mortality and CVD hospitalizations compared to those without diabetes. The risk of CVD mortality and hospitalizations for females diagnosed late compared to females without diabetes was significantly higher when compared to their male counterparts. While diabetes increased the risk of mortality and hospitalizations for both males and females, females had a higher risk than males. CVD, in particular, had a greater impact on females with diabetes than males, especially when diabetes was diagnosed late.

Previous studies have also found that individuals with diabetes have an increased risk of mortality and morbidity related to all-causes, CVD, AMI, and stroke compared to individuals without diabetes[30-33]. In addition, previous studies also found that females with diabetes are at a greater risk of mortality and morbidity than males with diabetes[30, 31, 33-38]. It is not known why

females with diabetes had an increased risk of mortality and hospitalizations compared to males with diabetes. One explanation is that CVD risk factors have a stronger impact on females than males[39-42]. Another possible explanation is that CVD risk factors are less aggressively treated in females[43-45]. More research is needed to determine why females had a greater risk of adverse outcomes compared to males.

In terms of diabetes management the same HbA1C target and treatment plan should not be applied to all patients with diabetes. Perhaps the focus should not only be on glucose control but on all CVD risk factors. The Canadian Diabetes Association Clinical Practice Guidelines provide recommended targets for glycemic control and suggest that treatment strategies should be individualized with consideration given to presence of risk factors[46]. Early and aggressive treatment had been suggested for newly diagnosed patients without a history of CVD while less aggressive treatment may be suitable for older patients who have had diabetes for a longer period of time and who have a history of CVD[47]. However, this recommendation does not take into account the greater CVD risk that females with diabetes have. More research into whether different treatment plans based on sex and timing of diabetes diagnosis would be beneficial is needed.

5.2.4 Diabetes Diagnosis and Late Diabetes Diagnosis from the Family Physician Perspective

The results of this study suggest that the majority of family physicians in this province have patients with complications present when they are diagnosed with diabetes. Family physicians have positive attitudes toward diabetes management; however, patient's body weights are not monitored to the extent blood pressure is. Previous research in Newfoundland and

Labrador found that adherence to clinical practice guidelines such as blood pressure monitoring and weight measurement was very good[48].

This study also found that male and female family physicians were similar in their diagnosis, treatment, management practices, and in their attitudes toward diabetes. This finding is different from previous research which has found that female family physicians are more likely to provide preventive services and counselling than male family physicians[49-51] and may provide better quality of diabetes care than male physicians[52].

Since this study relied on family physicians' self reporting, response bias and recall bias would have impacted the results. Future research using medical charts to determine how family physicians diagnose, treat and manage diabetes would provide more accurate results. In addition, once a provincial electronic medical record is developed and being used by all physicians in the province, this data could also be used to assess physician practices. Future studies should also focus on management strategies for dealing with diabetes complications such as foot examinations and referrals for eye exams.

5.3 Conclusions

In conclusion, certain risk factors appear to impact males and females differently and more research is needed on how males and females develop diabetes and timing of diagnosis. Different management strategies could be considered for males and females and those diagnosed early and late with diabetes. Also, family physicians need to monitor all risk factors for diabetes complications closely in an attempt to better manage progression of the disease.

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Appendix A

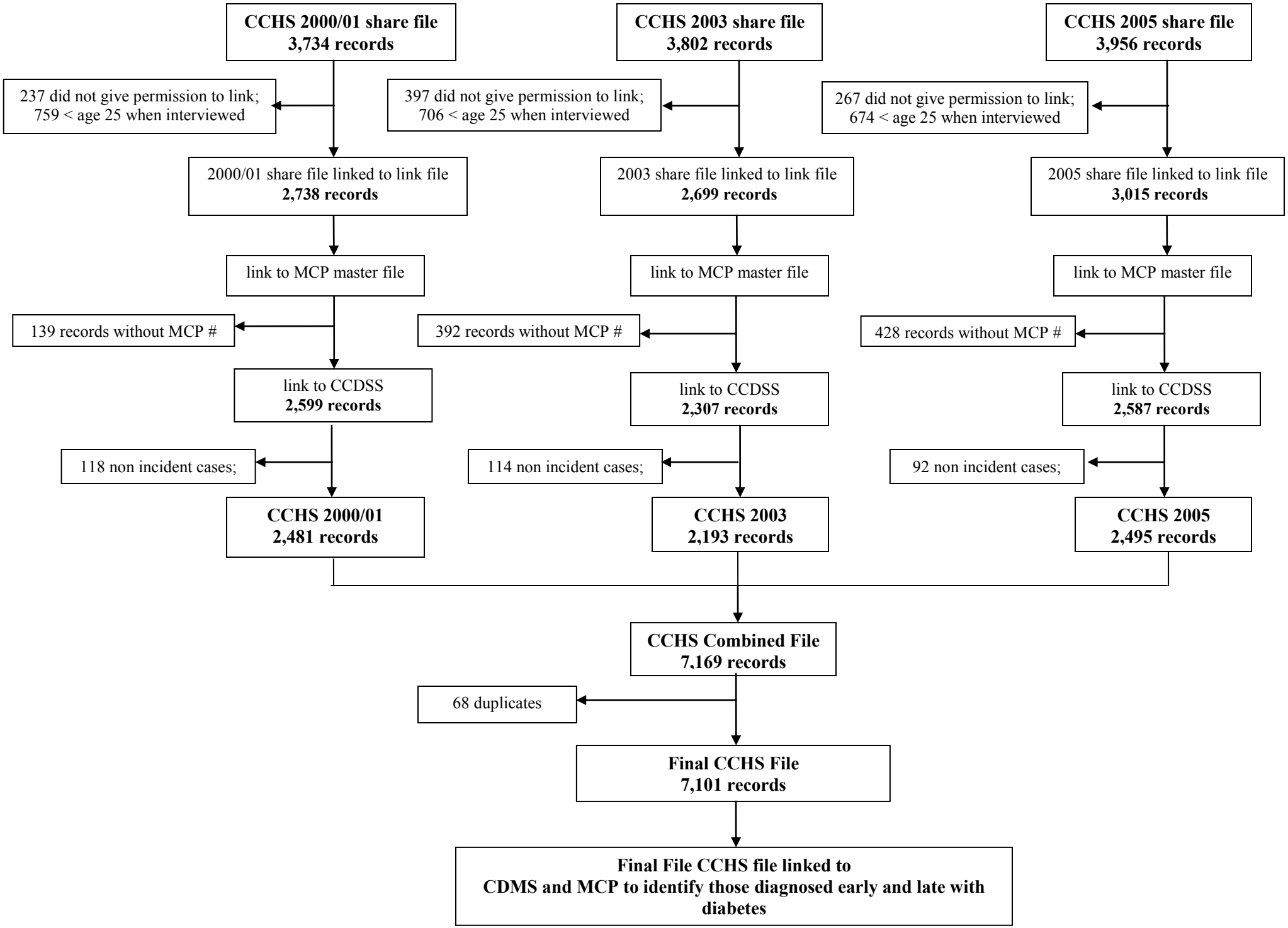
Conditions used to Identify Early and Late Diabetes Diagnoses

Conditions	ICD 9 Codes	ICD-10-CA Codes
Cardiovascular Disease	390-448	I00-I78
Ischemic Heart Disease	410-414	I20-I25
Hypertensive Disease		I10-I13, I15
Acute Myocardial Infarction	410	I21-I22
Heart Failure	428	I50
Stroke	430-438	I60-I69
Renal Disease	585-586	N18-N19
Atherosclerosis	440	
Amyloidosis	277.3	E85
Other peripheral vascular diseases	443	I73
Other and unspecified hyperlipidaemia	372.4	
Other proliferative retinopathy: poliferative vitreo-retinopathy		H35.2
Chorioretinal scars	363	H31.0
Atherosclerotic retinopathy		I70.8 H36.8
Other disorders of optic nerve and visual pathways		H47
Other retinal disorders	362	H35
Nephritis and nephropathy, not specified as acute or chronic	583	
Acute renal failure	584	
Disorder of kidney and ureter, unspecified		N28.9
Other renal tubulo-interstitial diseases		N15
Acute nephritic syndrome		N00
Unspecified nephritic syndrome		N05
Isolated proteinuria with specified morphological lesion		N06
Neuromuscular dysfunction of bladder, not elsewhere classified		N31
Other polyneuropathies		G62
Nerve root and plexus disorders	353	G54
Other mononeuropathies		G58
Mononeuropathies of lower limb		G57
Mononeuropathies of upper limb		G56
Facial nerve disorders	351	G51
Disorders of autonomic nervous system	337	G90
Inflammatory polyneuropathy		G61
Radiculopathy		M54
Mononeuritis of upper limb and mononeuritis multiplex	354	
Mononeuritis of lower limb	355	
Neuralgia, neuritis, and radiculitis, unspecified	729.2	
Lower Limb amputations	96.11, 96.12, 96.13, 96.14, 96.15, 96.2	1VC93LA, 1VG93LA, 1VQ93LA,

	1WA93LA, 1WE93LA, 1WJ93LA, 1WL93LA, 1WM93LA, 1WV59LA

Appendix B

Data Linkage Procedure for Chapter 2


CCHS 2000/01 share file
3,734 records
237 did not give permission to link;
759 < age 25 when interviewed
2000/01 share file linked to link file
2,738 records
link to MCP master file
139 records without MCP #
link to CCDSS
2,599 records
118 non incident cases;
CCHS 2000/01
2,481 records
CCHS 2003 share file
3,802 records
397 did not give permission to link;
706 < age 25 when interviewed
2003 share file linked to link file
2,699 records
link to MCP master file
392 records without MCP #
link to CCDSS
2,307 records
114 non incident cases;
CCHS 2003
2,193 records
CCHS 2005 share file
3,956 records
267 did not give permission to link;
674 < age 25 when interviewed
2005 share file linked to link file
3,015 records
link to MCP master file
428 records without MCP #
link to CCDSS
2,587 records
92 non incident cases;
CCHS 2005
2,495 records
CCHS Combined File
7,169 records
68 duplicates
Final CCHS File
7,101 records
Final File CCHS file linked to
CDMS and MCP to identify those diagnosed early and late with
diabetes

Appendix C

Health Research Ethics Authority Approval

MEMORIAL

Faculty of Medicine

Human Investigation Committee
Suite 200, 2nd Floor Bonaventure Place
95 Bonaventure Avenue
St. John's, NL Canada A1B 2X5
Tel: 709 777 6974 Fax: 709 777 8776
hic@mun.ca www.med.mun.ca/hic

ENTERED MAY 0 6 2010

SHIPPED MAY 0 6 2010

May 5, 2010

Ms. Madonna Murphy
70 O'Leary Avenue
St. John's NL A1A 2C7

Dear Ms. Murphy:

Reference #10.73

Re: Early versus Late Diagnosis of Type 2 Diabetes in Newfoundland and Labrador

Your application received an expedited review by a Sub-Committee of the Human Investigation Committee and **full approval** was granted effective **May 5, 2010**.

This approval will lapse on **May 4, 2011**. It is your responsibility to ensure that the Ethics Renewal form is forwarded to the HIC office prior to the renewal date. *The information provided in this form must be **current to the time of submission** and submitted to the HIC **not less than 30 nor more than 45 days** of the anniversary of your approval date.* The Ethics Renewal form can be downloaded from the HIC website http://www.med.mun.ca/hic/downloads/Annual%20Update%20Form.doc

The Human Investigation Committee advises THAT IF YOU DO NOT return the completed Ethics Renewal form prior to date of renewal:

- *Your ethics approval will lapse*
- *You will be required to stop research activity immediately*
- *You may not be permitted to restart the study until you reapply for and receive approval to undertake the study again*

Lapse in ethics approval may result in interruption or termination of funding

It is your responsibility to seek the necessary approval from Eastern Health, other hospital boards and/or organizations as appropriate.

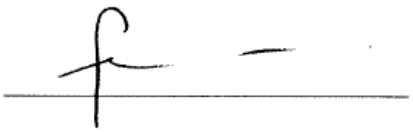
Modifications of the protocol/consent are not permitted without prior approval from the Human Investigation Committee. Implementing changes in the protocol/consent without HIC approval may result in the approval of your research study being revoked, necessitating cessation of all related research activity. Request for modification to the protocol/consent must be outlined on an amendment form (available on the HIC website) and submitted to the HIC for review.
This research ethics board (the HIC) has reviewed and approved the research protocol and

documentation as noted above for the study which is to be conducted by you as the qualified investigator named above at the specified site. This approval and the views of this Research Ethics Board have been documented in writing. In addition, please be advised that the Human Investigation Committee currently operates according to *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*; *ICH Guidance E6: Good Clinical Practice* and applicable laws and regulations. The membership of this research ethics board is constituted in compliance with the membership requirements for research ethics boards as defined by *Health Canada Food and Drug Regulations Division 5; Part C*

Notwithstanding the approval of the HIC, the primary responsibility for the ethical conduct of the investigation remains with you.

We wish you every success with your study.

Sincerely,



Fern Brunger, PhD
John D. Harnett, MD, FRCPC
Co-Chairs
Human Investigation Committee

C VP Research c/o Office of Research, MUN
VP Research c/o Patient Research Centre, Eastern Health
HIC meeting date: May 13, 2010

Appendix D

Secondary Uses Committee Approval

Centre for Health Information
Newfoundland & Labrador

70 O'Leary Avenue, St. John's, NL A1B 2C7
Telephone: 709-752-6000 • Facsimile: 709-752-6011

Registry Integrity Unit, 41 Conception Bay Highway
E. K Jerrett & Associate Building, Bay Roberts NL, A0A 1G0
Telephone: 866-279-1198 • Facsimile: 709-786-5337

October 27, 2010

Donna Murphy
Centre for Health Information
70 O'Leary Avenue
St. John's, NL A1B 2C7

Dear Donna:

This letter is to advise you that the Secondary Uses Committee of the Centre for Health Information reviewed your information request application on September 20, 2010 for the study **Early Versus Late Diagnosis of Type 2 Diabetes in NL**. Having consulted with the Secondary Uses Committee, I authorize the use of information for your project.

The use of the information outlined in your application is conditional upon the following.

- The Centre is provided evidence of ongoing ethics approval from the Human Investigation Committee of Memorial University during the lifetime of the study.
- Another employee of the Centre who is not a member of the project team links and de-identifies the information.
- Members of the project team accessing the information must not attempt to re-identify the subjects of the information.

Please coordinate with the necessary staff to arrange preparation of the information. On behalf of the Centre for Health Information, I wish your team continued success in their research.

Yours sincerely,

Paul Caines
Chief Information Officer

Cc David Morgan, Centre for Health Information
Kayla Collins, Centre for Health Information

Appendix E

Survey Materials for Chapter 4

Letter of Information

Title of Research Project: Assessing Determinants of Early versus Late Diagnosis of Type 2-Diabetes from the Patient, Physician and Policy/Decision Maker Perspective in Newfoundland and Labrador

Investigators: Kayla Collins, MSc, PhD(c), Madonna Murphy, MSc, PhD(c), Don MacDonald, MSc, PhD, Reza Alaghehbandan, MD

You have been invited to take part in a research study. It is up to you to decide whether to be in the study or not. Before you decide, you need to understand what the study is for, what risks you might take and what benefits you might receive. This letter of information explains the study.

The researchers will:

- **discuss the study with you**
- **answer your questions**
- **keep confidential any information which could identify you personally**
- **be available during the study to deal with problems and answer questions**

Introduction/Background

Diabetes is a serious chronic disease associated with multiple complications and premature death. A challenge with type 2-diabetes has always been the late diagnosis of the disease. It has been proven that type 2-diabetes can be prevented or delayed through lifestyle modifications among those at high risk of developing the disease. Early detection and management is important for good control of diabetes and to prevent late complications.

Purpose of the Research

The purpose of this study is to examine the reasons why some people are diagnosed with diabetes early when they first develop the condition, while other people are diagnosed later after they have had the condition for some time. We are examining this from three perspectives, including the patient, physician and policy/decision maker perspective. The findings of this study will be used to support public health decision-making for diabetes prevention and management.

Description of the Study Procedures

Your role in this research will involve completing and returning the enclosed survey. All of the work on this study will be carried out at the Newfoundland and Labrador Centre for Health Information.

Length of Time

It is estimated that it will take 10 minutes of your time to complete the enclosed survey.

Possible Risks or Discomforts

There are no anticipated risks or discomforts associated with your participation in this study except for the time taken to complete the survey.

Possible Benefits

You will not personally receive any benefit from participating, however, the information we will collect may help us find ways to improve care for people with diabetes.

Liability Statement

Completing and returning this survey gives us your implied consent to be in this study. It tells us that you understand the information about the research study and that you understand you are returning the survey anonymously. Since this survey will be returned anonymously there is no risk of identifying a clinic or a physician. Researchers or agencies involved in this research study still have their legal and professional responsibilities. Throughout the study, all data will be securely stored at the Newfoundland and Labrador Centre for Health Information in locked filing cabinets and password protected computer files.

Distribution of Research Findings

A final report describing the overall findings from this study will be submitted to the provincial Department of Health and Community Services, the Public Health Agency of Canada and sent to health professionals with an interest in this research. The findings of the study will be submitted for publication in academic journals and presented at health/scientific conferences. Any report produced from the study will also be made available electronically, free of charge, on the Centre's website (www.nlchi.nl.ca). If you would like a hard copy of the study summary, please contact the Principal Investigator (contact information below).

Questions

If you have any questions about taking part in this study, or need any additional information, please contact:

Kayla Collins,
Director, Research and Evaluation
Newfoundland and Labrador Centre for Health Information
(709) 752-6045
email: kayla.collins@nlchi.nl.ca

Madonna Murphy,
Manager, Research
Newfoundland and Labrador Centre for Health Information
(709) 752-6037
email: donna.murphy@nlchi.nl.ca

Or you can talk to someone who is not involved with the study at all, but can advise you on your rights as a participant in a research study. This person can be reached through:

Office of the Human Investigation Committee (HIC)
(709) 777-6974
email: hic@mun.ca

This is your copy of the Letter of Information to keep for your records

Physician Survey

Assessing Determinants of Early versus Late Diagnosis of Type 2-Diabetes from the Patient, Physician and Policy/Decision Maker Perspective in Newfoundland and Labrador

Items 1-17 relate to diagnosis and treatment of type 2-diabetes.

1. Do you provide care (screening and/or treatment) to patients with type 2-diabetes?

❑ Yes ❑ No

2. Is your practice involved in the Chronic Disease Management Diabetes Collaborative?

❑ Yes ❑ No

3. Approximately what percentage of your current patients have been diagnosed with type 2-diabetes?

_____ %

4. Approximately what percentage of your current type 2-diabetes patients have diabetes related complications at the time of diagnosis?

_____ %

5. What percentage of your patients with type 2-diabetes are required to receive care from a specialist?

_____ % ❑ Not Applicable

6. How often do you use the 2008 Canadian Diabetes Association's Clinical Practice Guidelines as a decision support tool?

❑ Always ❑ Seldom
❑ Often ❑ Never

7. How often do you screen high-risk patients for type 2-diabetes?

❑ Always ❑ Seldom ❑ Not Applicable
❑ Often ❑ Never

8. Which screening method(s) do you use (Check all that apply)?

❑ Fasting plasma glucose (FPG)
❑ Casual plasma glucose (PG)
❑ 2-hours plasma glucose (2hPG) in a 75-g oral glucose tolerance test (OGTT)
❑ Glycosylated haemoglobin (A1c)
❑ None of the above
❑ Other _____

9. At what fasting plasma glucose (FPG) level do you usually make a diagnosis of type 2-diabetes?

_____

10. At what FPG level do you usually initiate a nonpharmacologic (i.e. lifestyle) treatment?

_____

11. At what FPG level do you usually initiate a pharmacologic treatment?

_____

12. Measuring Glycosylated haemoglobin (A1c) is useful for (Check all that apply):

❑ Screening ❑ Treatment ❑ Blood glucose monitoring

13. Do you recommend home glucose monitoring to your type 2-diabetes patients?

❑ Yes ❑ No

14. For patients with type 2-diabetes, do you record their weight at every visit?

❑ Yes ❑ No

15. For patients with type 2-diabetes, do you check their blood pressure at every visit?

❑ Yes ❑ No

16. a. How often do you refer your patients to a registered dietician (where applicable)?

❑ Always ❑ Seldom ❑ Often ❑ Never

b. How often do you refer your type 2-diabetes patients to a registered dietician?

❑ Always ❑ Seldom ❑ Often ❑ Never

17. a. Where applicable, do you counsel your patients on the following topics? (Check all that apply)

❑ Weight management ❑ Physical activity ❑ Smoking cessation ❑ Healthy eating habits ❑ None of the above

❑ Other _____

b. Do you counsel your type 2-diabetes patients on the following topics? (Check all that apply)

❑ Weight management ❑ Physical activity ❑ Smoking cessation ❑ Healthy eating habits ❑ None of the above

❑ Other _____

For items 18-21please indicate the extent to which you agree/disagree with the following statements.

18. According to the 2008 CDA's Clinical Practice Guidelines, screening for type 2-diabetes should be performed every 3 years among individuals > 40 years of age with no other risk factors.

❑ Strongly disagree
❑ Somewhat disagree
❑ Neither agree nor disagree
❑ Somewhat agree
❑ Strongly agree

19. Screening all high-risk patients for type 2-diabetes is feasible in a day-to-day medical practice.

- ❑ Strongly disagree
- ❑ Somewhat disagree
- ❑ Neither agree nor disagree
- ❑ Somewhat agree
- ❑ Strongly agree

20. Tight blood glucose control for patients with type 2-diabetes will reduce complications for the patient in the long term.

- ❑ Strongly disagree
- ❑ Somewhat disagree
- ❑ Neither agree nor disagree
- ❑ Somewhat agree
- ❑ Strongly agree

21. Early treatment of patients with impaired fasting glucose (IFG) will reduce complications in the long term.

- ❑ Strongly disagree
- ❑ Somewhat disagree
- ❑ Neither agree nor disagree
- ❑ Somewhat agree
- ❑ Strongly agree

Items 22-28 are intended to help us group responses based on similar demographic characteristics. Please respond to only those items which you are comfortable with.

22. Please indicate your sex:

❑ Male ❑ Female

23. What is your month and year of birth?

_____ _____
Month Year

24. How long have you been practicing as a physician?

_____ years

25. What is your specialty? _____

26. Which of the following best describes the primary setting in which you practice?

- ❑ Hospital/Health Centre
- ❑ Group Practice
- ❑ Private
- ❑ Other (please specify) _____

27. Which of the following best describes the area in which your practice is located?

❑ Rural (≤ 5,000 inhabitants) ❑ Urban (> 5,000 inhabitants)

28. Which of the following best describes the billing structure of your practice?

- ❑ Fee for Service
- ❑ Salaried Community Based Physician
- ❑ Salaried Academic Physician
- ❑ Other (please specify) _____

Thank you for volunteering your time to participate in this study.