PROFILE OF CANADIAN ADULTS WITH TYPE 2 DIABETES MELLITUS AND FACTORS ASSOCIATED WITH DIABETES-RELATED COMPLICATIONS

PROFILE OF CANADIAN ADULTS WITH TYPE 2 DIABETES MELLITUS AND FACTORS ASSOCIATED WITH DIABETES-RELATED COMPLICATIONS

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ABSTRACT

Objectives: To describe the profile of Canadian adults with type 2 diabetes mellitus (T2DM), examine the prevalence of diabetes-related complications and investigate the factors associated with having common diabetes-related complications.

Methods: Self-reported data from Statistics Canada's 2011 Survey on Living with Chronic Diseases in Canada (SLCDC) – Diabetes component were available to describe the prevalence of T2DM, related complications and co-morbidities. Associations with diabetes-related complications were evaluated using logistic regression models. Survey weights and bootstrapping resampling method were applied to account for the complex survey design.

Results: 2,341 T2DM respondents (weighted Canadian population estimate n=1,365,165) had a mean age of 62.9 years and diabetes duration of 10.6 years. The prevalence of diabetes-related complications and comorbidities were high: eye (34.0%), foot or leg (24.4%), cardiovascular (22.6%), renal (15.7%), neuropathy (10.8%), hypertension (68.4%) and high cholesterol (67.2%). Factors associated with diabetes-related complications were: Eye: $\geq$ 65 years of age (odds ratio [OR] 3.7, 95% CI 2.4 – 5.5, p=<0.0001); household income $\leq$ $29,999 (OR 1.9, 95% CI 1.1 – 3.2, p=0.01), diabetes duration $\geq$ 10 years (OR 2.3, 95% CI 1.6 – 3.5, p<0.001), cardiovascular complications (OR 1.8, 95% CI 1.1 – 2.9, p=0.01). Renal: duration of diabetes 6 – 9 years (OR 3.0, 95% CI 1.4 – 6.3, p=0.02), duration of diabetes $\geq$ 10 years (OR 2.1, 95% CI 1.1 – 3.9, p=0.04) Cardiovascular: male sex (OR 1.9, 95% CI 1.3 – 2.7, p=0.0006), eye complication (OR 1.9, 95% CI 1.2 – 3.0, p=0.007), foot or leg complication (OR 2.0, 95% CI 1.3 – 3.0, p=0.002). Foot or leg: cardiovascular complication (OR 2.0, 95% CI 1.4 – 3.1, p=0.0006). Neuropathy: household income $30,000 - $59,999 (OR 2.1, 95% CI 1.2 – 3.9, p=0.03); duration of diabetes $\geq$10 years (OR 1.9, 95% CI 1.1 – 3.8, p=0.01), foot or leg complication (OR 7.0, 95% CI 4.1 – 11.8, p<0.0001), eye complication (OR 2.0, 95% CI 1.1 – 3.7, p=0.006).

Conclusions: The presence of diabetes-related complications among Canadians with T2DM is multifactorial.

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CHAPTER 1: INTRODUCTION

1.1 Diabetes Mellitus

Diabetes mellitus is a chronic, progressive metabolic disease in which the body is either unable to sufficiently produce insulin or inadequately use the insulin it produces. Insulin, a hormone secreted by beta cells in the pancreas, enables the cells of the body to absorb sugar from the bloodstream and use it as an energy source that controls the amount of glucose in the blood.[1] The body requires adequate delivery of glucose to the tissues of the body. If left uncontrolled, diabetes results in consistently high blood sugar levels, a condition known as hyperglycemia. The progressive injurious direct and indirect effects of hyperglycemia on the human vascular tree leads to the development of multiple long-term diabetes-related complications.[2] In Canada, approximately two thirds of Canadians living with diabetes reported having at least one diabetes-related complication diagnosed by a health care professional.[6]

Although all types of diabetes are characterized by the body's inability to maintain appropriate glycemic levels, each type differs in their causes, treatments and complications. Type 1 diabetes, also known as juvenile diabetes or insulin-dependent diabetes is generally diagnosed prior to late adolescence. This accounts for less than 10% of all disease cases. It is thought that this type of diabetes is an autoimmune disease in which the body's immune system attacks and destroys insulin-producing cells of the pancreas, leaving the individual dependent on an external source of insulin. Type 2 diabetes mellitus (T2DM) is commonly referred to as non-insulin dependent diabetes

mellitus, a metabolic disorder that occurs when the pancreas is not able to produce enough insulin. This accounts approximately 90% of all disease cases. Individuals are often diagnosed during later adulthood and are not typically insulin dependent during the early stages of the disease. The body does not adequately use the insulin that is produced by the pancreas, or the pancreas is unable to produce sufficient amounts of insulin. This type of diabetes is attributed to several factors including lifestyle, environmental, and genetic factors. The risk is substantially higher among people who are overweight or obese, physically inactive and of certain ethnic populations. Individuals with pre-diabetes are at an increased risk for developing T2DM. Individuals diagnosed with pre-diabetes may not go on to develop diabetes, however the risk of developing it significantly increases. Studies suggest that changes in lifestyle, including diet, physical activity and weight management, can delay or stop the progression from pre-diabetes to diabetes.[3, 4, 5] Gestational diabetes is a specific type that is diagnosed in females when hyperglycemia develops during pregnancy. This accounts for approximately 3% to 5% of all successful pregnancies. In most cases, elevated glycemic levels will disappear following delivery, however females diagnosed with gestational diabetes are at an increased risk of developing T2DM in the future. There are other types of diabetes that are associated with genetic defects, other conditions, infections and medication use that are generally uncommon. These types of diabetes affect the body's inability to produce or respond to insulin resulting in hyperglycemia.

1.2 Epidemiology in Canada

Diabetes and the associated macrovascular and microvascular complications are a growing public health problem in Canada and worldwide. In 2009, approximately 2.4

million (6.8%) Canadians were living with diabetes according to the Canadian Chronic Disease Surveillance System.[6] Estimates suggest that the number of Canadians living with diabetes will reach 3.7 million by 2018-2019. These estimates were obtained from population based administrative data from every province and territory to assess the burden of this chronic disease. T2DM is one of the fastest growing chronic diseases in Canada with more than 60,000 new cases annually. It is estimated that approximately 90% or 2 million Canadian adults diagnosed with diabetes have T2DM.[2] In general, the proportion of individuals diagnosed with diabetes generally increases with age. It is therefore not surprising that one in six people over the age of 65 years suffers from this chronic condition.[2] Moreover, individuals from lower income groups are twice as likely to have diabetes as those individuals in the highest income groups.[2]

The prevalence of diabetes is expected to increase considerably in Canada. Estimates suggest that the prevalence of diabetes in 2025 will increase to 5 million or 12.1% of the Canadian population.[7] An increase in the prevalence and rate of diabetes will subsequently lead to the increase in rates of both macrovascular and microvascular diabetes-related complications. Diabetes is the seventh leading cause of mortality in Canada. Although diabetes can be managed effectively through various treatment regimens, this chronic disease has a large economic burden on the Canadian health care system. The cost of diabetes on the healthcare system was estimated to be $11.7 billion in 2010. By 2020, the costs associated with diabetes are expected to rise to $16 billion per year.[8,9]

1.3 Diabetes-related complications

Although there are several multi-faceted interventions and treatment regimens available to manage diabetes, this chronic condition can lead to a number of short-term and long-term complications. A complication can be defined as an adverse event or end result of a disease that occurs after the diagnosis of a particular disease.[232] Complications can be endpoints or intermediate steps in the pathway from an exposure to an endpoint. Therefore, they are considered separate from comorbidities. A comorbidity is considered a pre-existing condition that exists before the time of diagnosis of a disease. Comorbidities can occur in the same patient simultaneously or sequentially. It can imply interactions between the illnesses that affect the course and prognosis of both the disease and the comorbidity.[232] Short-term complications of diabetes include infection; slow wound healing and diabetic ketoacidosis. Such conditions arise due to chronic hyperglycemia or from the use of insulin leading to hypoglycemia. Long-term diabetes-related complications arise from chronic hyperglycemia, leading to the irreversible damage of large and small blood vessels in the body ultimately affecting the functionality of major organs. Possible biochemical mechanisms include the activation of protein kinase C (PCK), increased oxygen stress, polyol pathway and the formation of glycation end products.[10]

Diabetes-related complications can be categorized into macrovascular complications (cardiovascular and cerebrovascular diseases) and microvascular complications (diabetic retinopathy, renal and neuropathy). Macrovascular complications arise due to damage to large blood vessels, whereas microvascular complications arise due to damage to small blood vessels.[11] Diabetes-related complications are attributed to

increased morbidity and mortality among individuals living with diabetes.[3] These complications contribute significantly to reduced quality of life, work limitations, and increased risk of death; they also greatly increase the demand for health care resources and add to the costs of diabetes for society.[11] However, advancements in treatment of T2DM and its related complications lead to a longer lifespan for individuals living with diabetes.

The association between hyperglycemia and diabetes-related complications are well established. Complications arise from chronic hyperglycemia leading to damage to macrovascular and microvascular vessels in the body. The long-term damage of chronic hyperglycemia affects the functionality of major organs including the eyes, kidneys, cardiovascular and nervous systems. Landmark studies have demonstrated that both macrovascular and microvascular complications can be significantly reduced with appropriate management and control of blood glucose levels, lipid levels and blood pressure in adults with T2DM. [12, 13, 14,15]

Breakthrough studies have demonstrated that T2DM is associated with a 2 to 4 fold higher risk for developing cardiovascular disease.[16, 17] In addition, the mortality rate due to heart disease is two to four times higher among individuals with diabetes compared to those without diabetes. In Canada, cardiovascular disease is the most commonly reported comorbidity with diabetes and is the most common cause of death in individuals with T2DM.[18, 19, 20] Alarmingly, estimates suggest that cardiovascular disease causes 65% of mortality in individuals with diabetes.[21] An assessment of the impact of

cardiovascular disease and diabetes suggest that there would be a 10% global decrease in the rate of acute myocardial infarction among males and a 19% global decrease among females if diabetes were to be eradicated from the world population.[12]

Diabetic retinopathy is a microvascular complication affecting the peripheral retina and the macula and is the leading cause of visual impairment and blindness in individuals with diabetes worldwide.[6] Diabetic retinopathy can range in severity from nonproliferative, background retinopathy to severely proliferative.[22] Nonproliferative retinopathy has features of small hemorrhages in the middle layers of the retina. Small vascular dilations in the retina can also occur, called microaneurysms. Proliferative retinopathy involves the abnormal growth and formation of new blood vessels on the surface of the retina. The progression of proliferation can lead to blindness through hemorrhages and tractal retinal detachment.[23, 24, 25]

Data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy demonstrated that individuals who were diagnosed with diabetes before the age of 30 years and take insulin have a 71% prevalence of diabetic retinopathy of which, 11% progress to develop proliferative diabetic retinopathy. The majority of these individuals had type 1 diabetes.[26] On the other hand, individuals with older onset of diabetes after the age of 30 and not taking insulin have the lowest prevalence of diabetic retinopathy at 39% and only 3% of these individuals progress to proliferative diabetic retinopathy. Pooled analyses from population-based studies that examined the global prevalence of diabetic retinopathy estimated that there are approximately 93 million individuals worldwide with diabetic retinopathy.[27] Of those, 17 million individuals have proliferative

diabetic retinopathy, 21 million individuals have diabetic macular edema and 28 million have vision-threatening diabetic retinopathy. In the Canadian population, it was estimated in 2006 that approximately 500,000 Canadians suffered from some form of diabetic retinopathy, diabetic macular edema or both and approximately 6000 individuals were blind due to retinopathy complications.[28]

Diabetic neuropathy is characterized by the presence of symptoms of peripheral nerve dysfunction in people with diabetes after excluding other causes. Injury to the peripheral nerves from hyperglycemia over an extended period of time can lead to damage to the peripheral nerves. [29] This complication can affect both the somatic and autonomic nervous systems. Some symptoms that are associated with nerve damage include pain, tingling, burning and numbness. Most neuropathies are asymptomatic, making it difficult to diagnose and manage. Chronic numbness and the inability to perceive pain are manifestations of peripheral neuropathy. Furthermore, peripheral neuropathies eventually lead to a number of impairments and daily activity limitations. The gradual disease progression of this complication ultimately leads to foot ulceration and subsequent lower-extremity amputation.[30, 31] Neuropathy resulting from diabetes is estimated to affect up to 70% of people with diabetes if mild to severe forms of nervous system damage are included. The prevalence of this complication varies depending on the definition used. Various studies have observed variable trends in the prevalence in the presence of diabetic neuropathy among individuals with diabetes ranging between 30% to 50%.[32, 33, 34, 35, 36]

Diabetic foot and lower extremity complications resulting in amputation are caused by nerve damage and decreased blood flow caused by peripheral vascular disease coupled with foot deformity and peripheral edema.[37] In general, diabetic foot deformity results from abnormal mechanical loading of the foot including repetitive pressure applied to the plantar aspect of the foot during walking. Foot structure changes can be caused by diabetic peripheral neuropathy, affecting foot function ultimately leading to increased plantar foot pressure. This is known to be a predictive risk factor for the development of diabetic foot ulceration.[38] Changes to the foot structure, as well as dryness of the surrounding skin leading to excessive callus formation all contributing to the changes in the foot caused by diabetes and peripheral neuropathy. Individuals with these complications typically do not feel injuries to the lower extremity because of nerve damage. Healing once an injury has occurred is compromised by decreased blood flow to the limbs. Ulcers and bone infections are the most common reasons for amputation. An active foot ulcer precedes approximately 85% of lower extremity amputations.[38]

The prevalence of diabetic foot complications varies considerably as a consequence of different diagnostic criteria used as well as population and regional differences.[39] Estimates suggest that the prevalence of individuals with diabetes who go on to develop foot ulcers is up to 25% while those affected with amputation is approximately 2%.[40, 41] In 2009, Canadian adults diagnosed with diabetes were approximately 20 times more likely to be hospitalized with non-traumatic lower limb amputations compared to those without diabetes.[42] Diabetes is the major cause of non-traumatic amputation among Western countries; rates are as much as 15 times higher than in the non-diabetic population.[42]

Diabetic nephropathy is the leading cause of end-stage renal disease worldwide accounting for approximately 50% of cases in the developed world.[43] This complication is a progressive kidney disease caused by damage to the capillaries in the kidneys' glomeruli. As with other microvascular complications, diabetic nephropathy results when hyperglycemia damages the blood vessels that filter blood in the kidneys. Progressive damage of the kidneys lead to compromised kidney function resulting in kidney failure and end stage renal disease requiring dialysis or kidney transplant. Early detection of renal impairment in individuals with diabetes is critical for delaying the progression of renal disease. As a result, several markers are used to screen for the development and progression of renal impairment.[44] Diabetic nephropathy is defined as persistent albuminuria (increased albumin levels in the urine >300 mg/d or >200 μg/min) confirmed on at least 2 occasions 3-6 months apart, proteinuria >500 mg in 24 hours, a progressive decline in the glomerular filtration rate (GFR) and elevated arterial blood pressure.[45]

It is estimated that approximately 7% of individuals diagnosed with T2DM already have microalbuminuria.[46, 47] A landmark T2DM study demonstrated that the incidence of microalbuminuria was 2% in individuals diagnosed with T2DM. The 10-year prevalence of microalbuminuria after diagnosis of T2DM was reported to be 25%.[13, 14] Reported rates of complications due to renal disease among individuals with diabetes are alarming. Estimates suggest that T2DM was the primary cause of 34% of new cases of end-stage renal disease in 2009 in Canada, creating a large demand for renal replacement therapy in the forms of dialysis or kidney transplant.[48,49]

Although a large burden of disease persists due to the increase in the prevalence of diabetes, data from the National Health Interview Survey, the National Hospital Discharge Survey and the U.S. National Vital Statistics System in the United States report a substantial decline in the prevalence of diabetes-related complications between 1990 and 2010. [50] The largest declines were seen in cardiovascular complications, specifically in acute myocardial infarction, followed by stroke and amputations. Similar trends in the decline of diabetes-related complications were also observed in Canada.[51] In Europe, a reduced incidence of amputations was also observed among individuals with diabetes.[52, 53] Changes in the prevalence of diabetes related complications are suggested to be attributed to the advancements in clinical care, improvements in the health care system and health promotion efforts directed at individuals with T2DM. Rates of several complications among individuals have stabilized and decreased over recent years, however, the increase in the number of individuals affected with diabetes is thought to precede a rise in the number of individuals affected by the diabetes-related complications.[54]

1.4 Summary and rationale

T2DM and its associated complications are a growing public health concern worldwide and in the Canadian population. The existing body of literature illustrates high variability and inconsistencies regarding the estimates of prevalence of diabetes and the associated macrovascular and microvascular complications. The myriad of studies that report the prevalence of diabetes-related complications consists of various study methodologies, differences in study populations and variability in the classification and

confirmation of diagnoses consequently making it difficult to compare and estimate the prevalence of diabetes-related complications within studies and various geographical populations.

In the Canadian context, self-reported data that is collected by Statistics Canada from the Canadian Community Health Survey (CCHS) differ substantially when compared to the information collected by the Canadian Chronic Disease Surveillance System (CCDSS).[55] The CCDSS collects information through linked administrative databases from every province and territory, The Public Health Agency of Canada affirms that although each data source and methodology is both reliable and valid, any single source may underestimate or overestimate the prevalence rates and recent trends of diagnosed diabetes in Canada.[1] The prevalence of diabetes-related complications may vary considerably due to variation in criteria and classification for diagnosis, and population characteristics, , making direct comparisons between studies challenging. This becomes important when attempting to measure the trends in epidemiology of diabetes and the impact of associated diabetes-related complications among Canadians. Furthermore, it is known that self-reported health survey data tends to underestimate the actual estimate of disease in the population.[12] Of note, however large-scale self-reported health surveys such as the National Population Health Survey (NPHS) and the CCHS may provide useful and accessible health data as it provides a national-level representation of the Canadian population that is real word evidence. It should be noted that several studies have used Statistics Canada data to document the prevalence of

diabetes, explore inequities between gender, socioeconomic status, and lifestyle behaviors as well as health care utilization. [56, 57, 58, 59, 60, 61]

To date, there are limited studies examining the profile of Canadians with T2DM and the factors associated with diabetes-related complications in Canadians using a cross sectional national population health survey. The objective of this thesis is to contribute to the current body of diabetes literature using self-reported data from Statistics Canada's Canadian Community Health Survey (CCHS) and the Survey on Living with Chronic Conditions in Canada Diabetes Mellitus Component (SLCDC-DM). This study will provide a national picture of self-reported diabetes and associated complications by characterizing and examining the profile of Canadians with T2DM. Furthermore, this study will investigate the associated factors for diabetes-related complications using cross sectional survey data sources.

1.5 Research Objectives

1. To characterize the profile of adults living with self-reported type 2 diabetes in Canada.
2. To examine the prevalence of self-reported diabetes-related complications among Canadians with type 2 diabetes.
3. To determine and investigate the factors associated with five categorized diabetes-related complications using logistic regression techniques.

The following research question is posed:

What is the profile of Canadian adults with type 2 diabetes and what are the factors associated with having a diabetes-related complication among Canadian adults with type 2 diabetes?

CHAPTER 2: LITERATURE REVIEW

A comprehensive review of the literature was conducted to identify the factors associated with the most common diabetes-related complications including eye, cardiovascular, renal, neuropathy and foot and leg complications in the current literature. The findings from the literature review partially contributed to the development of the five diabetes-related complications multivariate regression models.

2.1 Search strategy

A review of the literature was performed by a graduate student (KC) using a peer reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) and EMBASE (1980-). Websites of professional associations and other specialized databases were searched to identify grey literature. In addition, hand searching the reference lists of included articles, relevant articles and related systematic reviews as well as literature reviews were performed.

The search strategy was comprised of controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings) and keywords. The main search concepts included key words such as: "type 2 diabetes", "diabetes-related complications", "diabetic retinopathy", "diabetic neuropathy", "diabetic foot", "diabetic cardiomyopathy", "diabetic nephropathy" and "risk factor". See Appendix 1 for the full search strategy. The literature search was restricted to a publication date of January 2000.. The initial search was performed on July 27 2015 and an updated search was

performed on September 30 2016. Methodological filters were applied to limit retrieval to the human population and to the English language.

2.2 Eligibility criteria

Eligibility assessment was performed by one reviewer (KC). The titles and abstracts of all the potentially relevant publications were screened. Studies were excluded if they were not written in the English Language. Furthermore, case reports, commentaries, letters to editors, and editorial papers were excluded. Qualitative studies were excluded for the literature review, but were flagged for further information for this thesis. The following inclusion criteria were applied: the main findings of the publication pertained to risk factors of diabetes-related complications and quantitative statistics reported. Following title and abstract screening, full texts of selected articles were reviewed. The same inclusion/exclusion criteria were applied to the full text screening. The following data was abstracted from each publication: year of publication, country in which the study was conducted, study design, study population, length of follow-up period, the primary and relevant outcomes (i.e., diabetes complications) and factors associated with the outcome.

2.3 Search Results

When all keyword search terms were combined, there were 7,383 hits. Following the removal of duplicate articles, 3,167 potentially relevant articles were eligible for title and abstract screening. Of these, 399 articles met the inclusion criteria for full-text review. After reviewing the full-text articles, 147 articles were deemed eligible for

inclusion. See Figure 1 for the flow diagram of the different phases of the literature review, and the number of records identified, included and excluded.

Publications originated from the United States, Canada, South America, Europe, Asia, Africa, and Australia. The length of study follow-up for prospective studies ranged from 1 year to 26 years. The age range of the sample population was between 27 years to 72 years. Table 1 summarizes the study characteristics of the included studies. Table 2 summarizes the risk factors associated with the major T2DM complications found in the current literature.

2.4 Main Findings

2.4.1 Risk factors for eye complications

Studies suggest that the risk of developing diabetic retinopathy may be related to a number of factors including hyperglycemia, increasing age, diabetes duration, hypertension, obesity, ethnicity, sex, socioeconomic status and lifestyle factors including smoking and alcohol consumption. A definitive association between the development of diabetic retinopathy and the severity of hyperglycemia in individuals with diabetes has been established.[13, 14, 27, 64, 65, 66, 72, 74, 75, 78, 79, 80, 82] Studies have also established that a longer duration of diabetes plays a role in the development of eye complications including diabetic retinopathy.[13, 14, 27, 58, 62, 64, 65, 66, 72, 74, 75, 78, 79, 80, 82 88] A longer duration of diabetes is thought to be associated with poor control of glucose levels overtime.

Elevated blood pressure has shown to be another risk factor for developing diabetic retinopathy.[13, 14, 63, 64, 65 66, 67 68. 69,70] Given this association, various studies have

also demonstrated that controlling hypertension may reduce the onset of diabetic retinopathy as well as slow the progression of an existing diabetic retinopathy complication.[71, 72, 73, 74, 75] Studies have also demonstrated that a higher BMI and obesity are associated with the presence of eye complications.[74, 75, 76, 77]

Diabetic retinopathy susceptibility may vary considerably among different ethnic groups. A pooled analysis of individual data from population-based studies around the world observed the prevalence of diabetic retinopathy is highest among African Americans and lowest among Asians.[27] As well, diabetic retinopathy was found to be ten times higher in sub-Saharan African populations than that reported in recent European studies.[78] A multi-ethnic Asian population of Chinese, Malays and Indians study found that race was not found to be associated with diabetic retinopathy, however the associations of major risk factors with diabetic retinopathy were similar among the three ethnic groups including duration of diabetes and hyperglycemia.[79] In Canada, high prevalence rates of T2DM appear to exist in native Canadian communities.[80] Similar findings were observed among Latino Americans with Native American ancestry in the United States.[81] This suggests that ethnic origin may increase an individual's risk of eye complications such as diabetic retinopathy and it is important for the identification of specific population targets to prevention and intervention for the development of diabetic retinopathy. Studies suggest that older age is associated with the prevalence of diabetic retinopathy.[27, 70, 82] Considering the increasing proportion of the aging population globally, age as a risk factor for developing diabetic retinopathy have significant

implications for those who are likely to develop and require treatment for diabetic retinopathy in the future.

It appears that the role of sex in the development and progression of diabetic retinopathy varies considerably depending on the population being studied, suggesting that other factors may play a role in the development and progression of this complication. Studies suggest that males may be more likely to develop diabetic retinopathy. [63, 71] However, in contrast, the presence of diabetic retinopathy was found to be higher in females than males in some populations [73, 82, 58]

A review of the literature and conceptual framework by Brown and colleagues suggests that lower socioeconomic status, as measured by household income, education, employment, occupation or residing in particular underprivileged areas may be associated with an increased risk for diabetic eye complications as well as other microvascular complications. [83] A recent Canadian study examining the association between socioeconomic factors and visual impairment among patients with diabetes demonstrated similar findings such that that there are socioeconomic differences among individuals with reported diabetes related eye complications.[58] Findings from this study suggest that lower income and education level may be associated with visual impairment among those suffering from T2DM. Additionally, similar findings regarding economic position and eye complications were observed in other countries whereby lower education and lower income were found to be predictors associated with eye complications among T2DM individuals. [84 85, 86]

Lifestyle factors such as alcohol consumption and smoking have been shown to be associated with an increased risk for having diabetic retinopathy and other eye complications. [84, 87] However, other studies suggest that smoking may not be associated with having diabetic retinopathy. [63, 82]

2.4.2 Risk factors for renal complications

Diabetic nephropathy is one of the most devastating complications of diabetes, resulting in end stage renal disease. The main risk factors for the prevalence and progression of renal complications include diabetes duration, increasing age, hyperglycemia, hypertension, ethnicity, and lifestyle factors such as smoking and alcohol consumption. Studies have demonstrated strong associations between glucose control, as measured by hemoglobin A1C, and the risk of developing diabetic nephropathy.[88, 89, 90, 92, 102] Elevated glucose levels are known to contribute to the risk of renal dysfunction among individuals with T2DM. In addition, studies have shown a strong association between the development and progression of diabetic nephropathy and the duration of diabetes in individuals with T2DM.[47, 90, 91, 97, 100, 101,118] There is also evidence to suggest that elevated blood pressure and hypertension is an important risk factor for the development of diabetic nephropathy. [92, 93, 97, 94, 95, 96] It appears that there is some benefit to prevent diabetic nephropathy with treatment with antihypertensive drugs.[94, 95, 96, , 97, 128]

Ethnic differences and diabetic nephropathy as well as end stage renal disease have been well described in the literature. Compared to a Caucasian population, the prevalence of diabetic renal failure has been shown to be between two to threefold times

greater in the black population and Hispanic population, two-fold greater among Asians and up to 18-fold greater among the Aboriginal or Native communities. [98] Similarly, there exist racial and ethnic differences in the prevalence of microalbuminuria between Caucasians and Asians, Hispanics and blacks.[99, 100, 101, 102,103]

As well, the relationship between lifestyle factors such as smoking and the development of renal complications has been investigated. Cigarette smoking has been shown to be associated with the progression of nephropathy. This factor is associated with poorer glycemic control and an increased risk of renal complications among T2DM individuals.[104, 105, 106] Another lifestyle factor, alcohol consumption, has been shown to be inversely associated with renal complications among individuals with T2DM.[107] Those with moderate alcohol consumption had a significantly decreased risk of chronic kidney disease compared with those who did not consume alcohol, suggesting that alcohol use may have positive effects among individuals with T2DM. It also appears that there may be an association between lower education and the development of renal complications among individuals with T2DM. [107]

2.4.3 Risk factors for cardiovascular complications

Cardiovascular disease is a serious but often preventable complication of T2DM. There are several established risk factors for developing cardiovascular disease among individual with diabetes including hyperglycemia, duration of diabetes, hypertension, obesity, increasing age, sex, race, socioeconomic status, and lifestyle such as smoking status and alcohol consumption. Among individuals with T2DM, it has been established that poor control of glycosylated hemoglobin is significantly associated with increased

risk for cardiovascular complications.[108, 109, 119, 124, 125, 128, 131, 136, 142] A longer duration of diabetes was also found to be associated with the development of cardiovascular complication. [109, 123, 127, 128, 133, 134] Older age among T2DM individuals is also considered a risk factor for the development of cardiovascular complications. [123, 126, 128, 129,133]

In addition, evidence demonstrates that elevated blood pressure is a common comorbidity among individuals with T2DM and may play a role in developing cardiovascular complications.[13, 110 ,111, 112, 113, 114, 115, 116, 117, 118, 119, 126] As well, there is evidence to suggest that obesity is a risk factor for increased cardiovascular disease. [108,111, 112, 113 , 115, 126] Obesity was found to be associated with a 2-fold higher risk of coronary heart disease after adjustment for other variables including hypertension, serum cholesterol and familial history of myocardial infarction.

Sex has been well established as a factor for increased risk for cardiovascular disease among individuals with T2DM. Studies have demonstrated that women are at an increased risk for cardiovascular complications compared to men. [114, 115, 116,117, 118, 119, 125] On the other hand, other studies have demonstrated that males are at an increase risk for cardiovascular complications compared to females. [111, 123, 126] However, it is important to note that there is some evidence that suggests sex does not necessarily influence cardiovascular outcomes among diabetics. [120] A study prospectively analysed community-dwelling individuals in the United States to examine sex differences in the association of diabetes with cardiovascular disease including congestive heart failure and coronary heart disease and found that sex did not change the cardiovascular risk

associated with diabetes among adults. A similar finding was found in a large retrospective study in a Chinese population. [128]

As well, racial differences may play a role in the risk for developing cardiovascular complications. Studies suggest that the risk of cardiovascular complications among individuals with T2DM may be higher in individuals with African or Hispanic descent compared to Caucasians.[121, 122, 123, 124] However, some reports suggest that race does not play a role in the development of cardiovascular complication. [120]

It appears that cardiovascular risk factors such as obesity, sedentary lifestyle, and high levels of cholesterol are much more prevalent among those from a lower socio-economic status.[121, 122, 123, 125] This suggests that individuals with lower socioeconomic status have a higher prevalence of cardiovascular complications.

Studies have consistently demonstrated that smoking is an important risk factor for cardiovascular complications among individuals with T2DM. Previous studies demonstrate higher incidences of cardiovascular complications in diabetic patients who were known cigarette smokers[126, 127, 128, 129, 130, 131, 132, 133, 134] However, the relationship between other lifestyle factors such as alcohol consumption and cardiovascular complications among T2DM remains uncertain. A literature review by O'Keefe and colleagues describe the relationship between alcohol and cardiovascular health as a double edge sword. [135] Data shows J-shaped associations between alcohol intake and a variety of adverse health outcomes, including coronary heart disease, diabetes,

hypertension, congestive heart failure, stroke and dementia. Light to moderate alcohol consumption is associated with cardioprotective benefits, compared to increasingly excessive consumption resulting in proportional worsening of outcomes. Light to moderate alcohol consumption suggests cardiovascular protection through improvements in insulin sensitivity and high-density lipoprotein cholesterol. Studies have demonstrated that alcohol consumption has been shown to have favorable effects on factors such as insulin resistance, inflammation and dyslipidemia. [136, 137, 138, 139, 140] Although the mechanisms by which alcohol plays a role in reducing the risk of developing cardiovascular disease is uncertain, there is evidence to suggest that there are both physiologic and genetic pathways through which alcohol may reduce the risk of cardiovascular events. [141] These findings suggest that there is an inverse association between moderate alcohol consumption and cardiovascular complications. Conversely, the role of heavy alcohol consumption on the development of cardiovascular complications have shown to have an inverse relationship between heavy alcohol consumption and the risk of cardiovascular disease among individuals with T2DM. [142, 143] The mechanisms of alcohol's effect on cardiovascular problems are complex and there exists ongoing debate regarding the role of alcohol consumption on developing cardiovascular events.

2.4.4 Risk factors for Neuropathy complications

Factors that may play a role in the development and progression of diabetic neuropathy include age, hyperglycemia, duration of diabetes, sex, obesity, and lifestyle factors such as smoking. Peripheral neuropathy is a significant long-term complication of diabetes affecting up to 50% of individuals suffering from T2DM. As with other

diabetes-related complications, previous studies have shown a relationship between the duration of diabetes and impaired fasting glucose and peripheral neuropathy. [144, 145, 146, 147, 152] Studies have observed that increasing age may be considered a risk factor for diabetic neuropathy.[148, 149, 150 , 151, 152, 154] As well, a longer duration of diabetes has shown to be associated with diabetic neuropathy. [145, 152, 146, 147, 148, 149]

Some studies observed that males experienced more neuropathy complications compared to females.[146, 151] However, there are studies that suggest that females are more likely to have a neuropathy, while another study indicates that sex does not influence the risk of neuropathy.[149, 175] There may be important correlations between obesity and neuropathy among individuals with T2DM. Studies evaluating the association of psychological factors, physical activity, quality of life and neuropathy among individuals with T2DM showed associations between the presence of obesity among those with neuropathy stemming from T2DM.[144, 153, 175] This suggests that obesity may be associated with the development of diabetic neuropathy.

Studies evaluating the impact of lifestyle factors such as cigarette smoking and alcohol consumption suggest that certain lifestyle factors may be risk factors for the development of diabetic neuropathy. Studies observed that neuropathy was less common in individuals who currently smoked compared to individuals who were former smokers.[154, 155] This suggests that a past history of smoking may have some impact on the development and progression of diabetic neuropathy. Furthermore, a recent systematic review and meta analysis of studies conducted by Clair and colleagues report that

smoking may be associated with an increased risk of diabetic neuropathy in individuals with diabetes.[156] Similarly, this study demonstrated that alcohol consumption may play a role in the worsening of diabetic neuropathy. A similar trend was observed in a study that analysed the effect of alcohol on diabetes and its related complication. It was found that minimal or single bouts of alcohol consumption do not worsen glucose tolerance and the related complications. However, excessive daily drinking worsens diabetic control and increases the prevalence of diabetic neuropathy.[157]

2.4.5 Risk factors for foot or leg risk complications

As with other diabetes-related complications, the risk for foot ulcers, amputations and gangrene have been linked to hyperglycemia, diabetes duration, hypertension, sex, ethnicity, obesity, lower socioeconomic status and lifestyle factors such as alcohol consumption. A longer duration of diabetes is a known important risk factor for foot ulceration and lower limb amputations. [158, 159, 160, 162, 166, 172, 180, 185, 186, 207] In addition, poor blood glucose control and hyperglycemia were found to be risk factors for major limb amputations above or below the knee and minor amputations of the toes or metatarsals. [36, 161, 162, 180,

A number of studies have concluded that there is an association between sex and risk for amputation among individuals with diabetic foot ulcers, particularly among males compared to females. [162, 163, 164, 156, 165, 166, 167, 168, 174, 190] Ethnicity may also play a role in developing diabetic foot complications. In a mixed population study, diabetic foot complications, including foot ulcerations and amputations, were found to be more common among those of European origin in comparison to African-Caribbean and the

Asian population.[168] In an American study, individuals with Hispanic origins were found to be at an increase risk for foot or leg complications. [190]

There also appears to be an association between hypertension and the risk of amputation among individuals with diabetic foot ulcers. [36, 169, 170, 171, 172, 206] In contrast, a number of other studies have suggested that hypertension has no significant association with diabetic foot complications.[173, 174, 175] Therefore, the association of hypertension and the risk of lower limb complications is uncertain. A systematic review and meta-analysis of case control and cohort studies aimed to investigate the predictors of foot ulcerations in patients with diabetes. [176] Obesity was identified as a predictor of foot ulcers among diabetics. Other studies also suggest that obesity may be a risk factor for the development of foot ulcers[36, 177] Interestingly, paradox findings were reported in a United States Department of Veterans Affairs Healthcare system study that evaluated the association between BMI and amputation in diabetic individuals. The results showed that a higher BMI was associated with a lower risk of lower extremity amputation and major lower extremity amputation in diabetic men.[178] The association between obesity and amputation risk in this study was inconsistent with the pattern of the observed health conditions associated with obesity. More research is needed to better understand pathophysiological mechanisms that may explain the paradoxical association between higher BMI, obesity and lower-extremity amputation.

There is a wide range of literature describing lifestyle conditions that may be a predictor of developing foot ulcerations and other foot and leg complications among

individuals with T2DM. Alcohol consumption may be an important predictor for foot complications. Daily alcohol intake was reported more frequently amongst those with foot ulcerations compared to those without this complication. [179, 180, 181] However, other studies have suggested that alcohol intake reduces the risk of foot complications or does not appear to be associated with the development of foot complications among diabetics. [182, 183, 184] These conflicting findings suggest that the role of alcohol consumption is uncertain and that more research is needed to better understand the association of alcohol and the risk of foot or leg complications among individuals with T2DM. In addition to alcohol consumption, there are studies evaluating the effect of smoking status on the development of foot complications. Smoking habits, specifically that of current and active smokers appear to be associated with the development of diabetic foot complications. [185, 186] However, there are a number of studies that report conflicting results, indicating that there is no association between smoking habits and the development of diabetic foot complications. [187, 188, 189, 190]

The impact of socio-economic status on the development of foot complications is unclear in the literature. A systematic review of studies evaluating predictive factors of diabetic ulcers report no association between education level, income and social status and outcomes of diabetic foot ulcers. [166] However, it appears that countries with a similar health care system to that of Canada have reported a positive association between poverty and deprivation and lower extremity complications among individuals with T2DM. [191, 192, 193, 194, 195] A recent Canadian study utilized the Ontario Diabetes Database to examine the interplay between low socioeconomic status as a risk factor for diabetes-related lower

extremity amputation.[162] This study reported marked socioeconomic status disparities in the risk of lower extremity amputation among patients with diabetes despite access to universal healthcare.

2.4.6 Diabetes-related complications as risk factors for other diabetes-related complications

A study conducted by Abu El-Asrar and colleagues determined the predictive value of retinopathy for the presence of other diabetic complications.[196] This study found that diabetic retinopathy significantly predicted the presence of nephropathy in individuals with diabetes. It was also suggested that the presence of neuropathy and cerebrovascular disease are predictive factors of renal complications among individuals with diabetes. Mottl and colleagues demonstrated that diabetic retinopathy is associated with a higher risk for both renal and cardiovascular complications. [197] Interestingly, this study showed that the incidence of cardiovascular and renal events were similar, regardless of the severity of diabetic retinopathy. Renal complications have also been shown to be associated with diabetic retinopathy in individuals with T2DM. A case controlled study demonstrated that microalbuminuria was shown to be associated with diabetic retinopathy and could be considered a reliable marker of retinopathy.[198]

It appears that a significant proportion of diabetics with end stage renal disease have pre-existing cardiovascular disease at the initiation of dialysis, as demonstrated by the high prevalence of cardiovascular disease, including coronary artery disease, heart failure, stroke, and peripheral vascular disease.[199, 200, 201] Individuals with T2DM who approach renal dysfunction and end stage renal disease requiring dialysis are subjected to a number of cardiovascular risk factors and suffer considerably from various

cardiovascular complications. [202] A recent large nationwide study in Taiwan with 648,851 patients investigated the interaction of diabetes and end stage renal disease on the risk of cardiovascular events. This study demonstrated that individuals with renal complications have an increased risk for cardiovascular events.[203] The risk of cardiovascular-related incidences was significantly noted in the presence of renal dysfunction among diabetes after stratification by age and sex. The risk for myocardial infarction and stroke were especially high in this particular population.

Additionally, the presence of other diabetes-related complications have proven to be an important predictor for neuropathy. In a European study, the presence of diabetic retinopathy, as well as diabetic nephropathy, among individuals with diabetes was correlated to the risk of developing neuropathy.[145] Similar findings were found in two Japanese populations. [143, 152] Other studies have also demonstrated associations between various diabetic complications. The presence of other diabetic complications including neuropathy, renal dysfunction, peripheral neuropathy and cardiovascular complications may be independent predictors for the risk for developing foot ulcers and subsequent lower limb amputation.[204, 205, 206, 207,] Despite evidence that suggest that certain diabetic-related complications may be predictors for foot ulcerations and amputation, there are conflicting results from other studies that challenge these findings. Other studies have demonstrate the presence of other diabetes-related complications, such as neuropathy are not significant predictors for amputation. [177, 208, 209] Inconsistent findings regarding the presence of other diabetes-related complications make it challenging to understand the predictors of diabetic foot and leg complications.

2.5 Key Message and Conclusions

The objective of this literature review was to identify previous studies that have evaluated factors associated with diabetes-related complication. The findings from this literature review helped inform the potential variables to explore for factors associated with diabetes-related complications. A review of the literature describes various risk factors that may be associated with diabetes-related complications. In general, the most common risk factors of diabetes-related complications include: hyperglycemia, a longer duration of diabetes, increasing age, ethnicity, sex, socioeconomic status, lifestyle factors including smoking, and the presence of other comorbidities including hypertension, obesity as well as other diabetes-related complications. Overall, light to moderate alcohol consumption was found to be a protective measure for developing diabetes-related complications. It is important to note that several variables in the present study and those measured and defined in previous studies may be measured and defined differently. The variation of factors identified emphasizes the need for further research on the factors associated with diabetes-related complications. The findings from this literature search have identified potential variables to investigate factors that are associated with having a diabetes related complication for the analysis of the CCHS and SLCDC-DM in the following Methods Chapter.

CHAPTER 3: METHODS

This chapter describes the dataset, outcome measures, variables and methods used for analyses in this study. The information about the survey design and methodology used has been collected from a combination of user guides provided by Statistics Canada. This research study was carried out at the Statistics Canada Research Data Centre (RDC) at McMaster University.

3.1 Data sources

3.1.1 Canadian Community Health Survey

The Canadian Community Health Survey (CCHS) is a cross-sectional national population health survey that has been conducted annually since 2007. Previously, the CCHS was conducted biennially from 2001 to 2005. The main objective of the CCHS is to gather health-related data at the provincial levels of geography (health region or combined health regions). [211] This survey collects information related to health status, health care utilization and health determinants for the Canadian population.[211] The survey relies on a large sample of respondents and is designed to provide reliable estimates at the health region level. The CCHS aims to support health surveillance programs by providing health data at the national, provincial and intra-provincial levels. This national survey is a single data source for health research on small populations as well as rare characteristics and becomes a flexible survey instrument that includes a rapid response option to address emerging issues related to the health of the population. [211]

The CCHS covers the population 12 years of age and over living in the ten provinces and three territories. For the purposes of this study, adults, 20 years of age and older were analysed. The CCHS excludes full time members of the Canadian Forces and

residents of First Nations Reserves and other Aboriginal settlements, Crown lands, institutions, three territories and in the Quebec health regions of Région du Nunavik and Région des Terres-Cries-de-la-Baie-James. Altogether, these exclusions represent less than 3% of the overall Canadian population. In the north, the CCHS covers 92% of the targeted population in the Yukon and 96% in the Northwest Territories and 71% in Nunavut. [211]

The CCHS questions are designed for computer-assisted interviewing (CAI). When the questions were developed, the logical flow into and out of the questions was programmed such as the type of answer required, the minimum and maximum values, online edits associated with the question and instructions on what to do in the event an item had a non-response. The survey is comprised of three content components including the common content, the optional content and the rapid response content. The common content is collected from all survey respondents. The optional content satisfies the need for data for specific health regions. The rapid response component is offered to specific organizations interested in national estimates of emerging issues related to the population's health. [211]

3.1.2 Survey on Living with Chronic Diseases in Canada

The Survey on Living with Chronic Diseases in Canada (SLCDC) is a cross-sectional survey that is sponsored by the Public Health Agency of Canada (PHAC) developed with the purpose of providing information on the impact of chronic disease on individuals, as well as how individuals with chronic diseases manage their health condition.[210] The SLCDC takes place every two years, with two chronic diseases covered

in each survey cycle. In 2011, the SLCDC focused on diabetes mellitus, asthma and chronic obstructive pulmonary disease. The SLCDC surveys respondents about a number of issues about chronic health conditions including the diagnosis of a chronic health condition, the type of care received by health care professionals, medication use and self-management of their conditions. This survey allows researchers to assess the impact of chronic health conditions on quality of life, to provide more information on how individuals manage their chronic health conditions, to identify specific behaviours that may influence disease outcomes and to identify particular barriers to self-management of chronic health conditions.[210] The SLCDC diabetes mellitus component (DM) respondents were 20 years of age or older, living in private dwellings in the 10 Canadian provinces. Similar to the CCHS, SLCDC-DM excluded members of the Canadian Forces and residents of First Nations Reserves, Crown lands, institutions and three territories. PHAC was granted access under the terms of data sharing agreements.[210]

3.2 Sampling design

The 2011 SLCDC-DM utilized the 2010 CCHS to select the sample. Specifically, the SLCDC-DM employed a two-phase design in which the first phase was the CCHS sample and the second phase was the SLCDC-DM sample.The following is a description of the CCHS sampling frame. To determine reliable estimates for all health regions, a sample of 65,000 respondents is required on an annual basis. A multi-state sample allocation strategy is employed to ensure equal importance to the health regions and provinces. First, the sample is allocated among the provinces according to the size of their respective populations and the number of health regions within the province. Second, each provincial sample is allocated among its health regions proportionally to the

square root of the population within each health region. The CCHS employs the following three sampling frames to select the sample of households: an area frame, a list frame of telephone numbers and a random digit dialling (RDD) sampling frame. The following is a detailed description of the sampling frames used. [211]

The area frame is designed for the Labour Force Survey (LFS). This complex sampling design employs a two stage stratified design in which each stratum is comprised of clusters. The LFS selects clusters using a sampling method with a probability proportional to size. The final sample is then chosen using a systematic sampling of dwellings within the cluster. LFS clusters are then stratified by health regions. Once this is done, a sample of clusters and dwellings are selected within each health region. [211] The list frame is comprised of telephone numbers that are updated every six months. This is stratified by health regions and postal codes to match health regions to the telephone numbers. The telephone numbers are then selected using a random sampling process within each health region. [211] RDD sampling frame employs the working banks technique. Here, 100 number banks with at least one valid residential telephone number are selected. The banks are then grouped into RDD strata to include the health region areas. In each stratum, a 100 number bank is randomly selected and a number between 00 and 99 is randomly generated to create an actual telephone number. This procedure is repeated until the sample size is achieved.[211] Following the selection of the dwelling or telephone number sample, a member in each household is selected. This decision is made at the time of contact for data collection. All members of the household are listed and a person aged 12 years or over is automatically selected using various selection

probabilities based on age and household composition. [211] The 2010 CCHS survey comprised of 117 health regions. 46.5% of the sample was derived from area frame, 1% of the sample was derived from RDD and 52.2% were derived from list frame.

The SLCDC-DM employs a two-phase design in which the first phase is the CCHS sample and the second phase is the SLCDC-DM sample. As mentioned previously, the CCHS sample is selected from multiple frames. To have reliable estimates at the national level by age group and sex, CCHS respondents were stratified by condition, age group and sex. Furthermore, it was decided that respondents would only receive one questionnaire to reduce the response burden even if the individual reported more than one condition (e.g., both asthma and diabetes). As a result, individuals who reported having two conditions were randomly assigned to the specific questionnaire that corresponded to one of their condition. Sample allocation was performed by age and sex groups in proportion to the number of 2010 CCHS respondents for each condition. Proxy respondents and those who did not agree to share or link their CCHS data were excluded.

3.3 Data Collection

The CCHS data collection employs a number of CAI. Interviews are administered in two separate forms depending on the type of sampling frame employed. Computer-assisted personal interviewing (CAPI) is conducted in person and households are typically selected using the time frame method. Field interviewers are trained to establish first contact with each potential dwelling. Computer-assisted telephone interviewing (CATI) is conducted over the telephone following the selection of households from telephone and RDD frames. Respondents selected English, French or any other preferred

language to complete the interview. A wide range of languages was available to remove language as a barrier to conducting interviews. If necessary, respondents were transferred to an interviewer with the language competency needed to complete the interview. The Statistics Act protected respondents' personal information and confidentiality.[212] CAI allows the interviewers to conduct custom interviews according to the respondents' individual survey responses and demographics. Furthermore, the interviewers were notified immediately if responses are considered to be out of range during the completion of the survey. The response is flagged and must be corrected in order to continue on with the questionnaire. This feature ensures the validity of the responses and allows for consistent and accurate answers throughout the entire interview.

Data collection for the SLCDC-DM took place in October and November 2010 and continued in March and April of 2011. The questions posed in the SLCDC-DM were designed for CAI, similar to the CCHS. As described previously, the logical flow into and out of the questions were programmed. The types of answers required were specified and the minimum and maximum values were provided. Online edits associated with the question and what to do in the event of non-responses were also provided. Respondents were interviewed using the CATI system, as described previously in the CCHS description.[210]

3.4 Estimation and weighting

Statistics Canada's weighted records were applied to adjust point estimates to reflect the Canadian population 20 years old and older who live in private dwellings. To account for sampling design, bootstrap re-sampling method was used to estimate

coefficients of variation and 95% confidence intervals.[213] The bootstrap re-sampling method used in the CCHS involves the selection of simple random samples known as replicates, and the calculation of the variation between the estimates from replicate to replicate. In each stratum, a simple random sample of (n-1) of the n clusters is selected with replacement to form a replicate. In each replicate, the survey weight for each record in the (n-1) selected clusters is recalculated. These weights are then post-stratified according to demographic information in the same way as the sampling design weights in order to obtain the final bootstrap weights. The entire process is repeated B times, where B is large. The CCHS typically uses B=500, to produce 500 bootstrap weights. [211]

Survey weights were incorporated into the calculations to ensure that the data was representative of the Canadian population. That is, each respondent to the SLCDC in the sample represents beside himself or herself, several other individuals not in the sample. For example, in a random 2% sample of the population, each individual in the sample represents 50 individuals in the population. A weighting phase calculates for each record, what this particular number is. Survey weights must be incorporated in the calculations to ensure that estimates produced from the SLCDC-DM are representative of the surveyed population and not just the sample itself. The weight corresponds to the number of individuals in the population that are represented by the respondent. A survey weight is given to each individual included in the final sample. Thus, the weight corresponds to the number of individuals in the population that are represented by the respondent.[210]

A number of weighting strategies were employed for weight adjustment for sample weight. These include: proxy-link adjustment, selection criteria adjustment, out-

of-scope in SLCDC-DM adjustment, non-response in SLCDC-DM adjustment, share-link adjustment, windsorization and lastly, post-stratification. A brief description of each strategy is described below. For more information, please refer to the SLCDC-DM user guide weighting section.[210] Proxy link adjustment drops the CCHS units in the territories since they were not part of the target population. Also, some CCHS respondents were excluded from the SLCDC if individuals did not agree to link their 2010 CCHS information and if a proxy completed the CCHS survey. Selection criteria adjustment adjusts for the fact that respondents only received one questionnaire even if they reported having multiple health conditions. For example, if an individual reported diabetes and asthma, he or she was randomly assigned to either the asthma component or the diabetes component and not both.[210]

The 2011 SLCDC-DM weight variable name is WTSX_S, which represents the SLCDC-DM sampling weight. For any respondent, the sampling weight can be interpreted as the number of people the respondent represents in the population. Statistics Canada weighted records were applied to all point estimates to reflect the Canadian population. [210]

3.5 Data quality and non-responses

Given that this study used a large database of information, we predicted that there may be missing data entries. Therefore, it was decided *a priori*, that multiple imputation, a statistical technique for analyzing incomplete data sets, would be performed if necessary to account for missing data entries.[214] Following the analysis of the data, it was

determined that partial nonresponse, in which a respondent chooses to not answer one or several questions in the CCHS, was not a major issue during data collection. Nevertheless, some imputation methods were used for certain modules in the annual content to ensure data quality. [211] Data is imputed from the "nearest neighbour" derived from a distance function. For modules that are entirely self-reported or where imputation is not possible, partial responses are coded as missing values. For complete nonresponses and to reduce the risk of nonresponse bias, that is, bias that results when respondents differ in meaningful ways from nonrespondents, data collection is adjusted for with proper weighting with strategies developed by Statistics Canada and by increasing the sample size during the data collection process. In doing so, the number of nonresponders is limited in the sample size. [211]

3.6 Ethical Considerations

This study used CCHS and SLCDC-DM microdata files stored in Statistics Canada RDC. A confidentiality oath required by Statistics Canada was completed for each researcher involved in this project. Furthermore, data was kept on a secure server and entry into the RDC was restricted to key card access only. All analyses were computed using master data files and were screened and vetted by a Research Analyst at the McMaster University Research Data Centre before being released for publication. All vetted data was stripped of personal identifying information. This research study did not require a review by the Research Ethics Board (REB) as secondary analysis; using Statistics Canada data does not require an REB review. Further consent from respondents was not required.

3.7 Measures

3.7.1 Diabetes

Individuals were identified as having diabetes if they reported that a health care professional had diagnosed them with diabetes in the CCHS. Specifically, the term "diabetes" indicates that an individual has self-reported a physician diagnosis of diabetes of either type 1 or type 2 by answering "yes" to the question at the time of survey completion: "Do you have diabetes?". Individuals who reported a diagnosis of diabetes were invited to complete the 2011 SLCDC. In the SLCDC-DM, respondents were asked to confirm the diagnosis of diabetes by a health care professional as well as the type of diabetes that they have. This module was also used to screen out women whose only diagnosis of diabetes occurred during pregnancy. In the confirmation of diabetes diagnosis module, a follow-up question was also asked if the respondents indicated that they do not have diabetes to help determine why there was a discrepancy between what was reported in the CCHS and in the SLCDC-DM. It should be noted that even if the respondent indicated that they did not have diabetes because the condition is controlled by medication or lifestyle changes, the respondent continued with the survey. This is because the survey was specifically interested in the experiences of individuals who can control their condition through medication or lifestyle change. The specific questions were posed: "Do you have diabetes that has been diagnosed by a health professional?" and "Have you ever been diagnosed with diabetes?". Respondents who reported, "yes" to both questions were included. Respondents who stated, "Diabetes was never diagnosed by a health professional" were excluded. Individuals were identified as having T2DM by

posing the question "What kind of diabetes do you have?". Individuals who responded to "type 2 diabetes (also known as adult onset diabetes)" were included in the analysis.

3.7.2 Diabetes-related complications

The SLCDC-DM was used to describe the complications and profile of the study sample. The diabetes complication module asks about health conditions and complications that are associated with diabetes. Respondents must have had the condition diagnosed by a health care professional. The number of complications suffered by a respondent is thought to be an indication of how severe or well controlled their diabetes is. [210] The following five complications were evaluated: 1) eye complications, 2) renal complications, 3) cardiovascular complications, 4) foot or leg complications 5) neuropathy complications. To determine the presence or absence of complications, respondents were asked the following questions:

1) Eye Complications: "Have you ever had any of the following conditions diagnosed by a health professional?"
    a. Diabetic eye disease or diabetic retinopathy? Yes or No
    b. Partial or complete blindness? (Only if the respondent answered yes to diabetic eye disease or diabetic retinopathy) Yes or No
    c. Cataracts? Yes or No
    d. Glaucoma? Yes or No
2) Renal Complications: "Have you ever had any of the following conditions diagnosed by a health professional?"
    a. Protein in your urine? Yes or No
    b. Kidney failure? Yes or No

3) Cardiovascular Complications: "Have you ever had any of the following conditions diagnosed by a health professional?"
    a. Heart disease (for example, angina, heart attack)? Yes or No
    b. Stroke or mini-stroke? Yes or No
4) Neuropathy Complication: "Have you ever had any of the following conditions diagnosed by a health professional?"
    a. Nerve damage or neuropathy? Yes or No
5) Feet or Leg Complication: "Have you ever had any of the following conditions diagnosed by a health professional?"
    a. Poor circulation in the feet or legs? Yes or No
    b. Foot or leg ulcers or infection? Yes or No
    c. Gangrene and/or amputation? (Only if the respondent answered yes to foot or leg ulcers or infection) Yes or No

The outcome variable of the presence of each diabetes-related complication at the time of the completion of the survey is binary (i.e., has complication or does not have complication). From the diabetes complication module, five categories of complications were categorized and defined as follows: 1) eye (including diabetic eye disease, retinopathy, partial or complete blindness, cataracts and glaucoma, 2) renal (including protein in urine or kidney failure), 3) cardiovascular (including heart disease, stroke/mini stroke), 4) neuropathy (including nerve damage or neuropathy) and 5) foot or leg (including poor circulation in feet or legs, foot or leg ulcers/infection, and gangrene/amputation). It is important to note that these complications could have

occurred before the diagnosis of T2DM. Furthermore, respondents could have reported more than one complication within the defined categorized complication. For example, a respondent could have reported diabetic eye disease or retinopathy and cataracts, but the "eye complication" for this respondent was only counted once.

3.7.3 Comorbidities

To describe the comorbidities that may be associated with diabetes-related complications, the Medication Use module in the SLCDC-DM was utilized. In the Medication Use module, respondents were asked about prescription medications taken to control blood pressure and blood cholesterol. In the present study, the assumption was made that an individual who is being treated for high blood pressure is taking medication to control high blood pressure. Similarly, the assumption was made that an individual who is being treated for high cholesterol takes medication to control high cholesterol. To determine the presence of hypertension (high blood pressure), respondents were asked, "Do you currently take prescription medications to control high blood pressure?" Those who answered "yes", were assumed to have been diagnosed with high blood pressure and subsequently treated for high blood pressure. To determine the presence of high blood cholesterol levels, respondents were asked, "Currently, do you take prescription medications to control your blood cholesterol levels?" Those who answered "yes", were assumed to have been diagnosed with high blood cholesterol and subsequently treated for high blood cholesterol.

Height and weight were self-reported in the height and weight module of the CCHS. Respondents were asked to report their exact height and weight. From these

measurements, BMI was calculated and categorized into the following categories of BMI: Underweight (<18.5 kg/m^2), normal weight (18.5 kg/m^2 – 24.9 kg/ m^2), overweight (25 kg/ m^2 – 29.9 kg/ m^2) and obese: class I - III (greater or equal to 30 kg/ m^2). According to Health Canada, this BMI classification system can be used as a screening tool to identify weight-related health risks at the individual and population levels. The following health risks are associated with each of the BMI categories for adults aged 18 and over: Normal weight = least health risk, Underweight and overweight = increased health risk, obese class I – III = high health risk to extremely high health risk. It is important to note that at the population level, the BMI classification system can be used to compare body weight patterns and related health risks between populations to establish certain trends in body weight patterns. However, it is also noted that this classification system should be interpreted with caution at the individual level because the health risk associated with each BMI category can vary considerably between individuals. For instance, adults may be naturally very lean or muscular.[215] To explore the association of BMI among individuals with T2DM in the current study, BMI was categorized as not obese, (combining underweight, normal weight, and overweight), and obese.

3.7.4 Covariates

There have been a number of proposed frameworks in the literature that describe a number of associated factors that contribute to an increased risk for developing diabetes-related complications. The literature review section of this thesis described common factors that may contribute to having diabetes-related complications and were used to inform the selection of variables for developing the diabetes-related complication models. As well, variables in the CCHS and SLCDC-DM were identified to inform the

selection of variables for developing the diabetes-related complication models. It is important to note that the selection of variables were limited to what was available in the CCHS and SLCDC-DM.

Table 3 summarizes the variables created to explore factors associated with each diabetes-related complication. In addition, other diabetes-related complications that may have associations with the presence of a specific complication were included as variables. Covariates included binary, ordinal, categorical and continuous variables. Non-modifiable factors including sex, age, race/ethnicity, years living with diabetes as well as modifiable factors such as level of education, household income, lifestyle factors such as smoking status, alcohol consumption, comorbidities such as obesity (defined by BMI), high blood pressure and high blood cholesterol were grouped into defined categories. Categorical variables with two levels were entered directly into each complication model. For categorical variables with more than two levels, the variable was transformed into two levels by creating dummy variables to create dichotomous variables. For continuous variables including age and years living with diabetes, categorical variables were also created for the analyses to explore the associations of categorized age groups and categorized years living with diabetes groups. When constructing each diabetes-related complication model, separate models had age and years living with diabetes entering the model as continuous variables and as categorical variables. When the continuous variables were explored in the univariate and multivariate analyses, the results suggested that age and years living with diabetes had no difference on the presence of each diabetes- related complication (i.e., odds ratio of 1.0). This was consistent across all five

diabetes-related complication models. Since this finding did not appear to be logical, considering the findings in the literature review that diabetes-related complications are associated with increasing age and a longer diabetes duration, the age and years living with diabetes variables were explored further. In logistic regression analysis, a continuous variable looks at the change in the odds for one unit change, which may not be considered meaningful. For continuous variables, logistic regression assumes that predictors are linearly related to the log odds of the outcome. This assumption is known as linearity of the logit.[233] If this assumption is violated, logistic regression underestimates the strength of the association and rejects the association; that is being not significant (not rejecting the null hypothesis) where it should be significant. Thus, a solution is to categorize the distribution of the continuous variable into clinically different categories. Therefore, in separate univariate and multivariate logistic regression complication models, age and years living with diabetes entered the model as categorical variables. These variables were categorized according to clinically different categories (age groups [< 65 years, ≥ 65 years] and years living with diabetes groups [≤5 years, 6 – 9 years, ≥ 10 years]). This resulted in findings that appeared to be logical and consistent with evidence in the literature: age and a longer duration are associated with having diabetes related complication. Therefore, the logistic regression analyses presented in the results section of this thesis include categorical variables for age and years living with diabetes. There were a low number of Aboriginal citizens who responded to the CCHS and SLCDC-DM (n = 79) because Aboriginals living on reserves were excluded from partaking in the survey. Therefore, the Aboriginal status variable was not included in the univariate and multivariate regression analyses as the Aboriginals living off of the

reserves may not be considered representative of the Canadian Aboriginal population. All variables were categorized considering Statistics Canada's requirement of a minimum sample size in each variable category. To ensure participant confidentiality and to avoid spurious or data error, all output and results derived from the analysis produced unweighted groups of no less than 5 respondents.

3.8 Statistical analyses

Statistical Analysis System (SAS Institute Inc. Cary, NC, USA), version 9.4 was used to perform all statistical analyses. The survey weights provided by Statistics Canada were used for all analyses to account for the complex survey design, sample selection, adjustments for nonresponses and post-stratification as described previously. To characterize the profile of adults living with self-reported T2DM in Canada, descriptive statistics, weighted frequencies and percentages were calculated to describe the patient socio-demographic information. Descriptive statistics, weighted frequencies as well as percentages were calculated to describe the complication and comorbidity profile of the Canadian population. Finally, logistic regression models were built to describe the relationship between variables and having a diabetes-related complication.

3.8.1 Logistic regression

A common statistical method for analysing a dataset in which there is more than one independent variable that can determine an outcome is logistic regression. The goal of logistic regression is to determine the best fitting model to describe the relationship between the dichotomous characteristic of interest (dependent variable), and the set of independent (explanatory or predictor) variables. The outcome is measured with a

dichotomous variable (i.e. there are only two possible outcomes). In this study, the dependent variable is dichotomous, that is, having a diabetes-related complication, denoted as yes or no. Logistic regression analyses generate coefficients to predict a logit transformation of the probability of the presence of outcome of interest. This measures the effect of an independent variable on the dependent variable in terms of the independent variable predicting the response outcome.[216]

Logistic regression can involve multiple predictors, each simultaneously controlled for others. However, the results may be difficult to interpret because logistic regression coefficient (*b* values) is not in the metric of proportions of probabilities. As an alternative, each coefficient indicates how the log of adds of an outcome are increased by a one point increase in the predictor. While the log of odds may not be easily interpretable, these coefficients are exponentiated, changing the metric from log odds to odds. As well, exponentiating changes the resulting coefficient exp*(b),* to a ratio rather than an increment. The resulting odds ratios (OR) are then multiplicative and in the metric of odds in contrast to linear regression coefficients. [217]

There is a direct relationship between the odds ratio and the coefficient. The logit is defined as the log base *e* (log) of the odds, *p* is the probability of success and *q* is the probability of failure:

logit(p)= log(odds) = log(p/q)

Logistic regression uses the logit as the response variable:

logit(p) = a + bX

or

$$\log(p/q) = a + bX$$

The coefficients in logistic regression are in terms of the log odds. The coefficient infers that one unit change in the independent variable results in a unit change in the log of odds. To express the coefficient as an odds ratio, the log is removed by raising *e* to the power of the logistic coefficient.[218]

$$p/q = e^{a+bX}$$

The regression coefficients can be transformed into an odds ratio for practical purposes, by raising e to the power of the logistic coefficient. The odds ratio represents the constant effect of the predictor on the likelihood that the outcome will occur.

$$OR = e^{b}$$

3.8.2 Model development

For each independent variable identified, a univariate logistic regression analysis was performed to investigate factors associated with each defined complication. A multivariable logistic regression analysis was then performed for each complication to investigate the association of different factors for the presence of a diabetes-related complication. The selection of variables was based on empirical as well as statistical significance. It was determined *a priori* that age and diabetes duration (years living with diabetes) would be included in the final model for each categorized diabetes-related complication model. Independent variables were selected based on factors of diabetes related complications described in the literature review conducted in Chapter 2 of this thesis and what was available in the CCHS and SLCDC-DM. A decision to keep a

variable in the model considered the clinical or statistical significance.[219] There may be clinical and relevant variables that may enter the model regardless of statistical significance, which may control for confounding. The advantage of this purposeful selection method may be useful when investigating risk factor modeling and not just prediction.[220] Thus, variables selected include non-modifiable factors that are generally considered demographic factors including sex, race as well as modifiable factors including educational attainment and socio-economic factors as well as lifestyle factors including alcohol consumption and smoking status. Finally, the presence of other diabetes- related complications were observed to be associated with specific diabetes-related complications and therefore were included in the models.

The best model should have variables that produce less bias and the most precise estimates. As a check to explore estimate parameters for effect and to select the best regression models, the automated procedure selection score method in SAS was applied to determine the best subset selection of variables for each diabetes-related complication model. This technique uses the branch-and- bound algorithm of Furnival and Wilson to identify the best subset of useful covariates. This allows one to select the number of models for each model size with the highest likelihood score (chi-square) statistics for all possible model sizes containing all the explanatory effects.[221] The selection score method displays the best models with the highest score chi-squares containing the effects. It was determined that the model with the highest likelihood (chi square) was a model with all explanatory variables included. The process was performed for all five diabetes-related complication models. The selection of variables considered the theoretical significance

of each variable and not only relied on the automatic selection performed by the statistical software. Given that there are several predictor variables that may be associated with having a diabetes-related complication, and that a model with all explanatory variables produced the highest chi square value, all covariates were included in the initial multivariate logistic regression models to explore possible interactions and associations.

The PROC SURVEYLOGISTIC procedure was applied to the final univariate and multivariate logistic regression models. This procedure fits logistic regression models for discrete response survey data by the method of maximum likelihood. The PROC SURVEYLOGISTIC procedure incorporates complex survey sample designs, such as those used in the CCHS and SLCDC-DM, to make statistical inferences. Variances of the regression parameters and odds ratios are computed using replication and resampling methods to estimate sampling errors of estimators based on complex survey designs.[222] The survey weights provided by Statistics Canada and bootstrapping resampling methods were also applied to the final complication models to account for the complex survey designs in the CCHS and SCLDC-DM. The results from the univariate and multivariate regression analyses are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was determined for all logistic regressions at $p < 0.05$.

3.8.3 Multicollinearity

Given that there were several independent explanatory variables that could be highly correlated, the threat of collinearity, or multicollinearity was investigated. Multicolliniarty arises when variables that measure the same outcome are present in a regression model. This causes problems in estimating regression coefficients by inflating

the standard errors of the coefficient. To detect multicollinearity in each complication model, the variance of inflation factor function test (VIF) in SAS was employed. The VIF measures the inflation in the variances of parameter estimates due to collinearities that exist among the independent variables.

CHAPTER 4: RESULTS

This section describes the overall T2DM sample characteristics. The prevalence of T2DM and the associated diabetes-related complications are described. Additionally, odds ratios for each identified variable will be described for each complication. Unless stated otherwise, all estimates reported are weighted to reflect the Canadian population.

4.1 Type 2 diabetes mellitus sample characteristics

The following descriptions pertain to those individuals who self-reported a diagnosis of T2DM in the SLCDC. Among the 2,933 SLCDC respondents who knew their diabetes type, 2,341 individuals reported having T2DM diagnosed by a health care professional excluding diabetes related to pregnancy (n=7). This accounts for 80% of the respondents to the SLCDC diabetes component. This represented an estimated total population of 1,365,165 individuals with T2DM in Canada. The majority of respondents were male, with a mean age of 62.9 years, white, with a household income over $60,000 and with post-secondary education. The estimated mean time since diagnosis of diabetes was 10.6 years. Table 4 summarizes the general characteristics of the respondents to the SLCDC-DM and the estimated Canadian population.

Approximately 86% of individuals with T2DM reported taking some kind of medication to control their diabetes. Of these individuals approximately 86% reported taking pills to control their blood sugars and 25% of individuals required insulin injections to control their blood sugars at some point when diagnosed with T2DM. In terms of comorbidities estimates, approximately 68% of individuals with T2DM

indicated that they were prescribed medication to control high blood pressure and high cholesterol. Among those who self-reported height and weight, calculated BMIs revealed that approximately 44% of respondents were obese.

4.2 Type 2 diabetes mellitus related complications

Table 5 summarizes the prevalence of each specific eye, renal, cardiovascular, foot or leg and neuropathy complication among individuals with T2DM. Eye complications were the most prevalent among T2DM respondents comprising one third of the reported complications. Approximately one quarter of T2DM respondents reported a foot or leg complication. Over 20% of the respondents reported having a cardiovascular complication diagnosed by a health care professional. 16% of the T2DM respondents reported having a renal complication and 11% of the T2DM respondents reporting having a neuropathy complication diagnosed by a health care professional. Among males, 16% reported that a health care professional diagnosed them with erectile dysfunction.

4.3 Factors associated with diabetes-related complications: Univariate and Multivariate Logistic Regression Analyses Results

Odds ratios (the likelihood of having a diabetes-related complication) were generated for each complication according to the defined variables found in Table 3. The results of the univariate and multivariate logistic regression analyses for each complication are summarized in Tables 6 to 10.

4.3.1 Eye complication

Table 6 summarizes the variables associated with having an eye complication. Univariate analyses revealed that the following variables significantly increased the likelihood of having an eye complication: ≥ 65 years of age, living with diabetes ≥10 years, a household income ≤$29,999 per annum, and less than secondary school education. The presence other diabetes-related complications including cardiovascular complications and foot or leg complications increased the likelihood of having an eye complication. The following variables significantly decreased the likelihood of having an eye complication: male sex, secondary school education, consuming 1 to 7 alcoholic beverages per week, as well as taking medication for high blood pressure and taking medication for high cholesterol. Individuals with neuropathy were less likely to have an eye complication.

In the multivariate model, ≥ 65 years of age, living with diabetes ≥ 10 years, having a household income of less than $29,999 per annum, and having a cardiovascular complication were factors significantly associated with having an eye complication. Individuals ≥ 65 years of age were more than 3 times more likely (OR 3.7, 95% CI 2.4 – 5.5, $p<0.0001$) to have an eye complication. Individuals living with diabetes ≥ 10 years were more than 2 times likely to have an eye complication (OR 2.3, 95% CI 1.6 – 3.5, $p<0.0001$). Individuals with a household income of less than $29,999 per annum were almost 2 times more likely (OR 1.9, 95% CI 1.1 – 3.2, $p =0.01$) to have an eye complication. Individuals with a cardiovascular complication were almost 2 times more likely (1.8, 95% CI 1.1 – 2.9, $p=0.01$) to have an eye complication. Males were less likely (OR 0.6 95% CI 0.4 – 0.9, $p=0.008$) to have an eye complication. Individuals with a

neuropathy complication were less likely (0.5 95% CI 03– 0.9, p=0.03) to have an eye complication.

4.3.2 Renal complication

Table 7 summarizes the variables associated with having a renal complication. Univariate analyses revealed that the following variables significantly increased the likelihood of having a renal complication: the presence of a cardiovascular complication or a foot or leg complication. Individuals with neuropathy were significantly less likely to have a renal complication.

The multivariate model demonstrated that individuals living with diabetes between 6 to 9 years were 3 times more likely to have a renal complication (OR 3.0, 95% CI 1.4 – 6.3, p=0.02). A similar trend was seen for individuals with duration of diabetes greater than 10 years (OR 2.1, 95% CI 1.1 – 3.9, p=0.04). No significant variables were found to be associated with a decreased likelihood of having a renal complication.

4.3.3 Cardiovascular complication

Table 8 summarizes the variables associated with having a cardiovascular complication. Univariate analyses revealed that the following variables were found to significantly increase the likelihood of having a cardiovascular complication: male sex, ≥ 65 years of age, living with diabetes ≥ 10 years, household income ≥$29,999per annum, less than secondary school education, the presence of an eye complication, the presence renal complication, and the presence a foot or leg complication. The following variables were found to significantly decrease the likelihood of having a cardiovascular

complication: living with diabetes for 6 to 9 years, having a higher level of education (secondary school/post secondary school education), consuming 1 to 3 alcoholic beverages per month, taking blood pressure medication, taking medication to control high cholesterol, and the presence of a neuropathy complication.

In the multivariate model, male sex, having eye complication and having a foot or leg complication were factors significantly associated with having a cardiovascular complication. Males were almost 2 times more likely (OR 1.9, 95% CI 1.3 – 2.7, p=0.0006) to have a cardiovascular complication. Individuals with an eye complication were almost 2 times more likely (OR 1.9, 95% CI 1.2 – 3.0, p=0.007) to have a cardiovascular complication. Individuals with a foot or leg complication were 2 times more likely (OR 2.0, 95% CI, 1.3 – 3.0, p=0.002) to have a cardiovascular complication. Taking medication to control high cholesterol had a protective effect on having a cardiovascular complication, as these individuals were less likely to have a cardiovascular complication (OR 0.6, 95% CI 0.3 – 0.9, p=0.01). Individuals living with diabetes for 6 to 9 years were less likely (OR 0.5, 95% CI 0.3 – 0.9, p=0.005) to have a cardiovascular complication. Notably, individuals living with diabetes $\geq$ 10 years were 1.1 times more likely (OR 1.1, 95% CI 0.7 – 1.8, p=0.05) to have a cardiovascular complication, however this result was not statistically significant.

4.3.4 Foot or Leg complication

Table 9 summarizes the variables associated with a foot or leg complication. Univariate analyses revealed that the following variables were found to significantly increase the likelihood of having a foot or leg complication: living with diabetes $\geq$ 10

years, having a cardiovascular complication, having a renal complication, or having an eye complication. The following variables were found to significantly decrease the likelihood of having a foot or leg complication: living with diabetes between 6 to 9 years, consuming 1 to 7 alcoholic drinks per week, taking blood pressure medication, having a neuropathy complication.

The multivariate model demonstrated that individuals with a cardiovascular complication were 2 times more likely to have a foot or leg complication (OR 2.0, 95% CI 1.4 – 3.1, p=0.0006). Interestingly, individuals with neuropathy were less likely (OR 0.1, 95% CI 0.07 – 0.2, p<0.0001) to have a foot or leg complication.

4.3.5 Neuropathy complication

Table 10 summarizes the variables associated with neuropathy. Univariate analyses revealed that the following variables were found to significantly increase the likelihood of having a neuropathy complication: living with diabetes $\geq$ 10 years, household income between $30,000 and $59,999 per annum, having a cardiovascular complication, having a renal complication, having an eye complication, or having a foot or leg complication. Individuals who consumed 1 to 7 alcoholic beverages per week were less likely to have a neuropathy complication.

In the multivariate model, living with diabetes $\geq$ 10 years, a household income of $30,000 - $59,999 per annum, having an eye complication and a foot or leg complication were factors most significantly associated with the presence of a neuropathy complication. Individuals living with diabetes $\geq$ 10 years were almost 2 times more likely

to have a neuropathy complication (OR 1.9, 95% CI 1.1 – 3.8, p=0.01). Individuals who had a household income between $30,000 and $59,999 per annum were more than 2 times likely (OR 2.1, 95% CI 1.2 – 3.9, p=0.03) to have a neuropathy complication. Individuals with a foot or leg complication were 7 times more likely (OR 7.0, 95% CI 4.1 – 11.8, p<0.0001) to have a neuropathy complication. Individuals with an eye complication were 2 times more likely (OR 2.0, 95% CI 1.1 – 3.7, p=0.006) to have a neuropathy complication. Interestingly, individuals with less than secondary school education were less likely (OR 0.4, 95% CI 0.2 – 0.8, p=0.01) to have a neuropathy complication.

To evaluate the explained variance for the multivariate logistic models for each diabetes-related complication, pseudo-r^2 (for logistic distribution) [223] were calculated as follows: eye complication of $R^2 = 0.24$, renal complication of $R^2 = 0.04$, cardiovascular complication of $R^2 = 0.3$, foot or leg complication of $R^2 = 0.1$, and neuropathy complication of $R^2 = 0.08$. R-squared values can range from 0 to 1. In general, a value closer to 0 indicates no predictive value on the outcome and a higher value closer to 1 explains the variation in the outcome. Although the pseudo r-squared measures of the complication models are considered low, suggesting no predictive value on the outcome, it is important to acknowledge that there were statistically significant variables in each of the diabetes-related models. The variance of inflation factor function test measured inflation in variance of parameter estimates due to collinearities. It was established that the degree of collinearity was acceptable for each variable in each of the regression models and therefore, no variables were omitted from the models.

CHAPTER 5: DISCUSSION & CONCLUSION

The aims of this thesis were to describe the prevalence of Canadians diagnosed with T2DM, describe this population and investigate factors associated with having diabetes-related complications in Canada. This chapter will begin with an overview of the study results and a discussion of the results in comparison to the current body of literature. Lastly, a summary of the study's strengths, limitations, implications and conclusions will be discussed.

5.1 Summary of findings

5.1.1 Diabetes and diabetes-related complications

In 2010, 6.4% of Canadians reported having diabetes according to the responses to the CCHS. Among those that were invited to respond to the SLCDC survey, approximately 80% of the respondents reported having a diagnosis of T2DM. The Canadian Diabetes Association estimates that 90% of diabetes mellitus cases are T2DM.[224] The percentage of individuals with T2DM in the current study is slightly lower than the Canadian Diabetes Association estimate for several possible reasons. First, there may be an underestimation of self-reported T2DM in the current study. As mentioned previously, large health surveys are limited by self-reporting bias when sampling a large proportion of the population. This may be much more common when reporting chronic diseases such as diabetes. Therefore, results from the CCHS and SLCDC may be more indicative of self-reported or self-perceived health status among a large Canadian sample. Secondly, all individuals who reported a diagnosis of diabetes in the CCHS were not invited to respond to the SLCDC-DM. As mentioned previously in the methodology

section of this thesis, respondents received only one questionnaire to reduce the response burden even if the individual reported more than one chronic condition in the CCHS. For example, an individual who reported a diagnosis of both asthma and diabetes was randomly assigned to only one specific questionnaire that corresponded to one of their conditions. The individual was not asked to complete both questionnaires.

The most common diabetes-related complications among respondents with T2DM were eye complications, followed by foot or leg complications, cardiovascular complications, renal complications and neuropathy complication, respectively. The prevalence of diabetes-related complications in this study was high. Specifically, 34% of individuals reported an eye complication. When compared to estimates in the literature, this finding is similar to the estimates that suggest that up to 40% of individuals with T2DM may experience some kind of diabetic eye complication as described in the literature review of this thesis. [25, 26, 27] Approximately 16% of individuals with T2DM reported having a renal complication. As mentioned previously, studies suggest that the prevalence of renal complications among individuals with T2DM range from 7% to up to 25%. [13, 14, 46, 47] The findings from the present study are in the lower range when compared to findings in previous studies. Cardiovascular complications was prevalent among Canadians with T2DM estimated at approximately 22%, a finding that is similar to the estimates in the literature that suggest approximately 20% of individuals with T2DM suffers from some form of cardiovascular complication. [225, 226, 227] The prevalence of foot or leg complications reported was close to 25% in the present study. Previous findings suggest that the prevalence of foot or leg complications can range from 2% to up

to 25% depending on the type and severity of the complication.[40, 41] Finally, approximately 11% of individuals with T2DM reported suffering from neuropathy. This is lower than the estimated prevalence in the current literature. Previous studies report that neuropathy complications could range between 30% and 50% among individuals with T2DM depending on the type and severity of this particular complication. [32, 33, 34, 35, 36]

The existing body of literature illustrates high variability regarding the estimates of prevalence of diabetes and the associated macrovascular and microvascular complications. This may be due to the differences in study methodologies, study populations and variability in the classification and confirmation of respective diagnoses. As a result, it may be difficult to compare and estimate the prevalence of diabetes-related complications within studies and various populations. The present study aimed to describe the estimates of prevalence of T2DM and its related complication using the SLCDC-DM as well as investigate the factors associated with diabetes-related complications in Canada. To our knowledge, this is the first study that has used Statistics Canada SLCDC-DM to estimate the factors associated with diabetes-related complications. For a meaningful understanding of trends in epidemiology of T2DM and its related complications in the Canadian setting, future research should focus on examining T2DM and the related complications extensively in a prospective Canadian population study.

5.1.2 Factors associated with diabetes-related complications

This study found that known risk factors were associated with having common diabetes-related complications in a sample of Canadians with T2DM. Univariate analysis

revealed that a longer duration of diabetes generally increased the likelihood of having each diabetes-related complication. Similarly, the multivariate regression models for eye, renal, and neuropathy complications demonstrated that a longer duration of diabetes is significantly associated with having diabetes related complications. A similar trend was found for the cardiovascular complication and foot or leg complication models, however this finding was not statistically significant. This aligns with previous findings that confirm that the longer duration of diabetes results in developing various diabetes-related complications as identified in the literature review. Specifically, the present study revealed that having diabetes for longer than 10 years significantly increased an individual's likelihood of having a diabetes-related complication. This finding confirms that chronic elevated blood glucose levels over a long period of time leads to multiple complications in individuals with T2DM as described in the literature review in Chapter 2.

The literature review in Chapter 2 suggests that age is a factor for developing diabetes-related complications. In the present study, age was investigated as a possible factor for having a diabetes-related complication. In the univariate analyses, being 65 years of age or older was associated with an increased likelihood of having an eye, cardiovascular and foot or leg complication. The multivariate analyses revealed that being greater than 65 years of age increases the likelihood of having an eye complication. It appears that age may increase the risk of cardiovascular complications among individuals with T2DM, however this was not a statistically significant finding. Interestingly, this study found that being 65 years or older decreased the likelihood of

having a renal complication, a foot or leg complication or a neuropathy complication. A possible explanation for these unexpected findings is that approximately 55% of respondents were less than 65 years of age and therefore, it is possible that individuals under the age of 65 may have reported these particular complications. However, this theory was not specifically analysed in this study and could not be verified. Although these are unexpected findings, given that older age is associated with the development of diabetes-related complications, it is important to note that these findings were not considered statistically significant.

The literature review in Chapter 2 suggests that race, as a factor for developing diabetes-related complications is uncertain. In this study, the majority (85%) of respondents reported to be white. Race was not determined to be a significant factor for having any of the five categorized diabetes-related complication. However, the trend was that non-whites were more likely to have a renal or foot or leg complication compared to whites. In contrast, non-whites were less likely to have an eye complication, a cardiovascular complication or a neuropathy complication. The results from this study demonstrate the uncertainty of the impact of race on having a diabetes related complication. Given that Canada is a multiethnic country, further research should be conducted to explore the association of specific ethnic backgrounds and diabetes related complications in the Canadian population.

In general, socioeconomic status, often characterized by annual household income as well as level of education attained, is associated with having a diabetes-related

complication. In this study, approximately half of respondents reported a household income of less than $60,000 per annum. This study demonstrated a significant finding that individuals with a lower household income were more likely to have an eye complication and a neuropathy complication. Although the association between household income and other diabetes related complication associations were not found to be statistically significant, the general trend found in the present study is in line with the current literature: Those with a lower household income are more likely to have a diabetes-related complication.

Approximately one quarter of respondents reported that the highest level of education attained was less than secondary school education. The association of level of educational attainment and having a diabetes-related complication was investigated in the present study, and results demonstrated that the association between education level and having any diabetes-related complication was not statistically significant. This study found that a lower level of education (less than secondary school education) made no difference in having an eye complication or cardiovascular complication. A lower level of education appears to decrease the likelihood of having a renal complication, and a neuropathy complication. However, individuals with less than secondary school education were more likely to have a foot or leg complication.

The association of smoking status and diabetes-related complications was investigated in this study. Approximately 67% of respondents reported a history of smoking. Although findings from the present study were not statistically significant, the

results suggest that the association between smoking status and having a diabetes-related complication is uncertain. Being a current smoker had no difference on having an eye complication. In contrast, being a current smoker increased the likelihood of having a renal or cardiovascular or neuropathy complication, and decreased the likelihood of having a foot or leg complication. Former smokers were more likely to have an eye complication, or a cardiovascular complication or a neuropathy complication. In comparison, former smokers were less likely to have a renal complication or a foot or leg complication.

Approximately 68% of respondents reported light to moderate alcohol consumption on a monthly or weekly basis. In the current study, alcohol consumption (i.e., 1 to 3 drinks per month or 1 to 7 drinks per week) generally had had a protective effect on having a diabetes-related complication, such that consuming alcohol decreased one's likelihood of having a diabetes-related complication. This supports the findings of previous studies discussed in the literature review that suggest that light to moderate alcohol intake has an inverse relationship with developing diabetes related complications. [137, 139, 140, 141, 142, 143, 156]

Obesity was investigated as a factor for having diabetes related complications. In this study, more than 40% of respondents reported to be obese as measured by BMI. Although the associations for this variable were not statistically significant, this study demonstrated the general trend that obesity increases the likelihood of having a diabetes related complication. The exception to this trend was for eye complications whereby

being obese decreased the likelihood of having this complication. Notably, obesity was associated with an increased likelihood of having a cardiovascular complication. Although this finding was not considered statistically significant, this finding supports previous findings of the impact of obesity on the development of cardiovascular complications in individuals with T2DM. Complications such as stroke and high blood pressure are comorbidities that result from obesity and other symptoms of the metabolic syndrome.

In terms of specific diabetes-related complications, this study found that known risk factors such as older age were associated with an increased likelihood of an eye complication. Individuals greater than 65 years of age are almost 4 times more likely to have diabetes-related eye complication. These findings align with other epidemiologic studies, which suggest that risk for eye complications such as diabetic retinopathy, cataracts and glaucoma increases in prevalence and severity in diabetics who are older. [27, 82] As mentioned previously, findings from the present study also confirm that there is a socioeconomic health gradient with respect to eye complications. Individuals with a household income less than $29,999 per annum were almost 2 times more likely to have an eye complication. In general, lower income has been associated with visual impairments and complications regardless of a diagnosis of diabetes. The findings from the literature search in Chapter 2 suggest that socioeconomic status may have an impact on the risk for diabetes eye complications. [58, 80, 81] Findings from this study support previous research regarding income as a risk factor or predictor of visual complications among individuals with diabetes. In addition, independent of socioeconomic factors,

findings from this study suggest that having other comorbidities such as other diabetes-related complications including cardiovascular complications may be associated with a greater likelihood of an individual having an eye complication. The role of sex in the development and progression of eye complications varies depending on the population being studied. There is some evidence that suggests males are more likely to develop visual impairments, however some studies have contradicted this finding and have reported that females are more likely to suffer from visual impairments as described in the literature review. [58, 63, 73, 82] This uncertainty suggests that the presence of eye complications are multifactorial. In the present study, males were less likely to have an eye complication. Considering that these factors were shown to be associated with having an eye complication in the Canadian setting, health care providers of patients with T2DM should consider age, duration of diabetes, the presence of cardiovascular disease, and socioeconomic status as possible factors associated with eye complications.

A small number of individuals reported renal complications in this study (n=327), and presumably investigating factors for this particular complication was limited by the sample size. Respondents were asked whether or not a health professional had diagnosed them with having protein in their urine. Since this parameter is a clinical marker for renal dysfunction, a respondent may not be aware of the significance of this particular diagnosis as it is related to renal complications due to diabetes, and therefore may become under-reported in the SLCDC-DM. Additionally, the prevalence of kidney failure in this sample was approximately 4.7%, a finding much lower than the reported 34% of end stage renal failure due to diabetes as noted in a previous Canadian Institute of Health

Information report.[48] Findings from the Canadian Institute of Health Information report were derived from a variety of data sources including data from hospital dialysis programs, regional transplant programs, organ procurement organizations and kidney dialysis services. These sources may better estimate the prevalence of end stage renal failure compared to self-reported kidney complications in the SLCDC-DM. The renal complication model demonstrated that living with diabetes for 6 to 9 years or greater than 10 years increases the likelihood of having a renal complication.

Cerebrovascular disease and heart disease complications were reported among respondents. Individuals with an eye complication were 2 times more likely to also have a cardiovascular complication. This finding aligns with previous research suggesting that retinopathy and other visual impairments can predict other diabetic complications, including cardiovascular complications.[199, 200, 201, 202, 203] Individuals who took medication to control high cholesterol were less likely to have a cardiovascular complication, a statistically significant finding. Similarly, individuals who took medication to control blood pressure were less likely to have a cardiovascular complication, however this association was not statistically significant. This is to be expected with taking medication to control hypertension or high cholesterol, as taking medication should have a protective effect on developing cardiovascular complications. In the present study, males were almost 2 times more likely to have a cardiovascular complication, compared to the findings in the literature review that suggests females with T2DM are more likely to experience a cardiovascular complication. [116, 117, 118, 119, 120] Although the association between duration of diabetes and having a cardiovascular complication was approaching

statistical significance (p=0.05), the trend in the present study demonstrated living with diabetes for more than 10 years increases an individual's risk of having a cardiovascular complication. Considering that these factors that may be associated with having a cardiovascular complication in the Canadian setting, health care providers of patients with T2DM should consider male sex, and screening for the presence of eye complications and foot or leg complications.

Individuals living with diabetes for more than 10 years were almost 2 times more likely to have a neuropathy complication. This finding is consistent with the literature that suggests a longer duration of diabetes leads to neuropathy complications among individuals with T2DM. Interestingly, this study found that individuals with neuropathy were less likely to have a foot or leg complication. A possible reason for this unexpected finding may be due to the small number of individuals who reported a neuropathy complication (n=218). Another reason for this unexpected finding may be due to the limitation of the cross-sectional study design. At the particular time point when respondents were asked to complete the survey, individuals who reported neuropathy or nerve damage may not have experienced a foot or leg complication at that time point. It is unknown whether or not an individual went on to eventually develop a foot or leg complication since there was no follow-up period in the present study. As mentioned previously in the literature review, although it is known that neuropathy may be an independent predictor for the risk for developing foot ulcers and subsequent lower limb amputations, previous research has also suggested that neuropathy is not significantly associated with the development of foot or leg complications.[37,] Specifically, studies have

demonstrated that neuropathy is not associated with lower limb amputations. [208, 209] That being said, the findings from this study demonstrate that the association between neuropathy and a foot or leg complication in this particular T2DM population is uncertain. Furthermore, this study found that individuals with eye complications were 2 times more likely to have a neuropathy complication. As well, a socioeconomic gradient was determined among individuals with neuropathy such that individuals with a household income of $30,000 - $59,999 per annum were more than 2 times more likely to have a neuropathy complication. Moderate consumption of alcohol (i.e., 1 to 7 drinks per week) demonstrated a statistically significant protective effect on having neuropathy complication. Considering that these factors may be associated with having a neuropathy complication in the Canadian setting, health care providers of patients with T2DM should consider duration of diabetes, socioeconomic status, and screen for the presence of foot or leg complications and eye complications.

This study found that having a foot or leg complication makes an individual more than 7 times more likely to have a neuropathy complication. It is known that a foot or leg complication subsequently arises from neuropathy complications. Previous studies have demonstrated that lower limb complications such as foot ulcers are a result of chronic neuropathy complications. [37] The finding in the present study that the presence of a foot or leg complication increases the likelihood of having neuropathy may have been be due to the cross-sectional design of this study. Individuals with foot or leg complications may have also experienced neuropathy complications. However, since this the SLCDC-DM survey does not prospectively follow respondents, it is unknown whether individuals had

neuropathy complications prior to the foot or leg complication. This finding highlights a limitation that the exact date or time the complication was first diagnosed is not available in the SLCDC-DM, and therefore it is difficult to predict which complication occurred first. The presence of cardiovascular complications such as stroke or heart disease increased the likelihood of having a foot or leg complication by two-fold. Considering that cardiovascular complications are associated with having a foot or leg complication in the Canadian setting, health care providers of patients with T2DM should consider screening for foot or leg complications in patients who present with cardiovascular complications.

5.2 Strengths and limitations

A major strength of this research study was the use of a population-based health survey that produced Canadian population estimates of diabetes and its related complications. A large sample size of respondents to the SLCDC with a high response rate of 81.7% limited non-response and selection biases. Altogether, this study allows for some generalizability of findings to Canadians with T2DM and its associated complications.

There are a number of limitations to be considered when interpreting the results of this study. Self-reporting biases introduce a number of limitations. It is known that self-reporting health surveys may be problematic due to the over or under-estimation, of particular measures.[228] Self-reporting bias may compromise the validity of the research conducted. For example, negative stigmas and social desirability around certain lifestyle behaviours exist, such as smoking behaviour, alcohol consumption and weight, which

may cause individuals to inaccurately report certain lifestyle behaviours when responding to health surveys. It is thought that self-reported smoking status; alcohol consumption and body weight (used to calculate BMI) may be greatly underestimated because respondents may report health-related responses in a way that they believe is socially acceptable. [229, 230] Respondents to the health surveys may have under-reported the diagnosis of particular comorbidities including other diabetes related complications that they may have experienced which may have skewed the results of this study. Survey respondents may want to respond in such a way that makes them look as good as possible. As a result, the prevalence of obesity based on self-reported data is underestimated. Moreover, the magnitude of the bias may increase over time. This is because survey respondents may tend to under-report certain behaviours that may be deemed inappropriate by an observer and may over-report behaviours that are viewed as appropriate. For instance, BMI (based on self-reported height and weight) may be under-estimated or over-estimated. We acknowledge that there are correction equations published by Statistics Canada that attempt to adjust for over-estimation or under-estimation in self-reported height and weight.[231] However, these correction factors were not applied to the self-reported data in the present study. Thus, the self-reported height and weight, and therefore obesity prevalence in the present study is likely underestimated. Applying the correction factors to the self-reported data may have produced obesity prevalence estimates that are higher than reported in the present study and may be closer to estimates derived from actual measured data.

Additionally, there were no objective measures to assess the accuracy of respondent reports from health care professionals. All questions that pertained to diabetes and reported complications were based solely on whether a respondent recalled that a health professional had diagnosed them with a particular health problem or complication. Therefore, this may have introduced the possibility of misclassifications of diagnoses of diabetes and related complications.

The cross-sectional design of this study is a limitation. This is because causal inferences or exposure and effect relationships cannot be made between various risk factors examined in this study. As such, it is impossible to establish specific causal factors that lead to the development of each diabetes-related complication because the temporal relationship between disease occurrence and exposure cannot be established. For example, evaluating associations between comorbidities and diabetes-related complications was attempted in this study. The Medication use module in the SLCDC-DM 2011 was used to estimate comorbidities. In the present study, the assumption was made that an individual who is being treated for high blood pressure or high cholesterol is taking medication to control these comorbidities. Another approach considered was the use of the CCHS 2010 self-reported comorbidities. While this approach is an option to obtain comorbidity prevalence estimates among respondents, the cross-sectional nature of the study precludes demonstrating temporality and is a limitation of the present study. Respondents to the CCHS participated in the survey in 2010, and respondents who reported a diagnosis of diabetes were then invited to complete the SLCDC-DM survey in 2011. This retrospective approach may be another option to obtain comorbidity

prevalence estimates since the comorbidities would have been reported at the time of reporting diabetes. Both approaches were considered to describe the comorbidity profile of respondents with T2D, however it is important to recognize that both approaches do not demonstrate temporality or causality, since both the exposure and outcome are assessed at the same time. Prospective studies that follow study respondents forward through time, including prospective cohort studies and interventional studies would be ideal for suggesting causation.

Furthermore, it is important to note that the specific date and time of the diagnosis of the self-reported complications could not be verified due to the design of the SLCDC-DM survey. Considering this limitation, it is plausible that some of the reported complications may have been diagnosed before the diagnosis of T2DM. It is also possible that patients may have had diabetes longer than they reported. Experiencing a complication may have been when an individual was actually diagnosed with T2DM.

Additionally, self-reported data in the SLCDC-DM does not capture clinical parameter measurements that are known to be significant risk factors for various complications including glycemic control and blood pressure. For example, hemoglobin A1C levels, a clinically relevant and significant indication of the severity of diabetes and its related complications, were not collected in the CCHS or the SLCDC-DM and therefore could not be used to explore associations. Furthermore, information on the types of medication used to control diabetes or the rates of compliance are unknown. As well, it is unknown whether the respondents had controlled diabetes.

Finally, sampling bias is considered a limitation to this study such that the generalizability of the findings may be limited to some sub-populations in Canada. Specifically, residents from First Nation reserves and the three territories were not included in this study due to the sampling design and therefore there was an under-representation of Aboriginal Canadians, a sub-population known to be at a higher risk for diabetes and its related complications. There was a low number of Aboriginals who responded to the CCHS and SLCDC-DM making up only 3% of the respondents and therefore it was considered that these individuals were not representative of the Canadian Aboriginal population. Thus, insights into the profile of Aboriginal Canadians living with T2DM and factors associated with the related complications could not be explored in this particular population. Considering these limitations, it is important to acknowledge that this study attempted to identify important associations of factors that may be linked to the prevalence of diabetes-related complications in the general Canadian population.

5.3 Conclusions

In conclusion, the present study characterized the profile of Canadians with T2DM and its related complications. In addition, this study demonstrated that factors associated with having certain diabetes-related complications are multifactorial. The results of this research can be used for future diabetes research, health surveillance and may be helpful for health care providers and decision makers to make recommendations around the prevention and management of diabetes and its related complications in the Canadian setting. Understanding the risk factors within a population is necessary for predicting trends in the prevalence and incidence of T2DM and its associated

complications. Furthermore, the identification of factors associated with diabetes-related complications may support initiatives for the prevention, early detection and management of complications by targeting certain factors that are known to impact particular complications.

The present study demonstrated that there are gaps in diabetes research in the Canadian setting. For example, further research should examine ethnic origin in the Canadian context when examining risk factors for diabetes related complications, given that certain subpopulations are known to be at an increased risk for developing diabetes as well as its related complications. Considering Statistics Canada's requirement for a minimum sample size in variable categories, it was not possible to conduct analyses for certain subpopulation groups. For instance, it was not possible to categorize non-white into specific subgroups of ethnic origins (e.g., Asian descent). As well, future Canadian studies should be inclusive of individuals with Aboriginal origins to identify risk factors that may contribute to the risk of developing diabetes and its related complications. Canadian population surveys such as the CCHS and SLCDC-DM exclude individuals living on Native reserves and the 3 territories, which significantly limits information from persons with Aboriginal origins. Hence, further studies are needed to investigate vulnerable populations at risk for developing diabetes and related complications in order to produce findings that are more generalizable to this subgroup of Canadians. Such findings would be useful for developing programs and services that target individuals at risk for developing particular diabetes-related complications. Furthermore, future studies should consider linking various provincial health databases to the CCHS and SLCDC-

DM individual respondents. This would facilitate more precise and high quality research for exploring predictors of chronic diseases such as T2DM and the related complications. As well, linking claims data to each CCHS and SLCDC-DM respondent would facilitate the ability to measure health service utilization and associated costs.

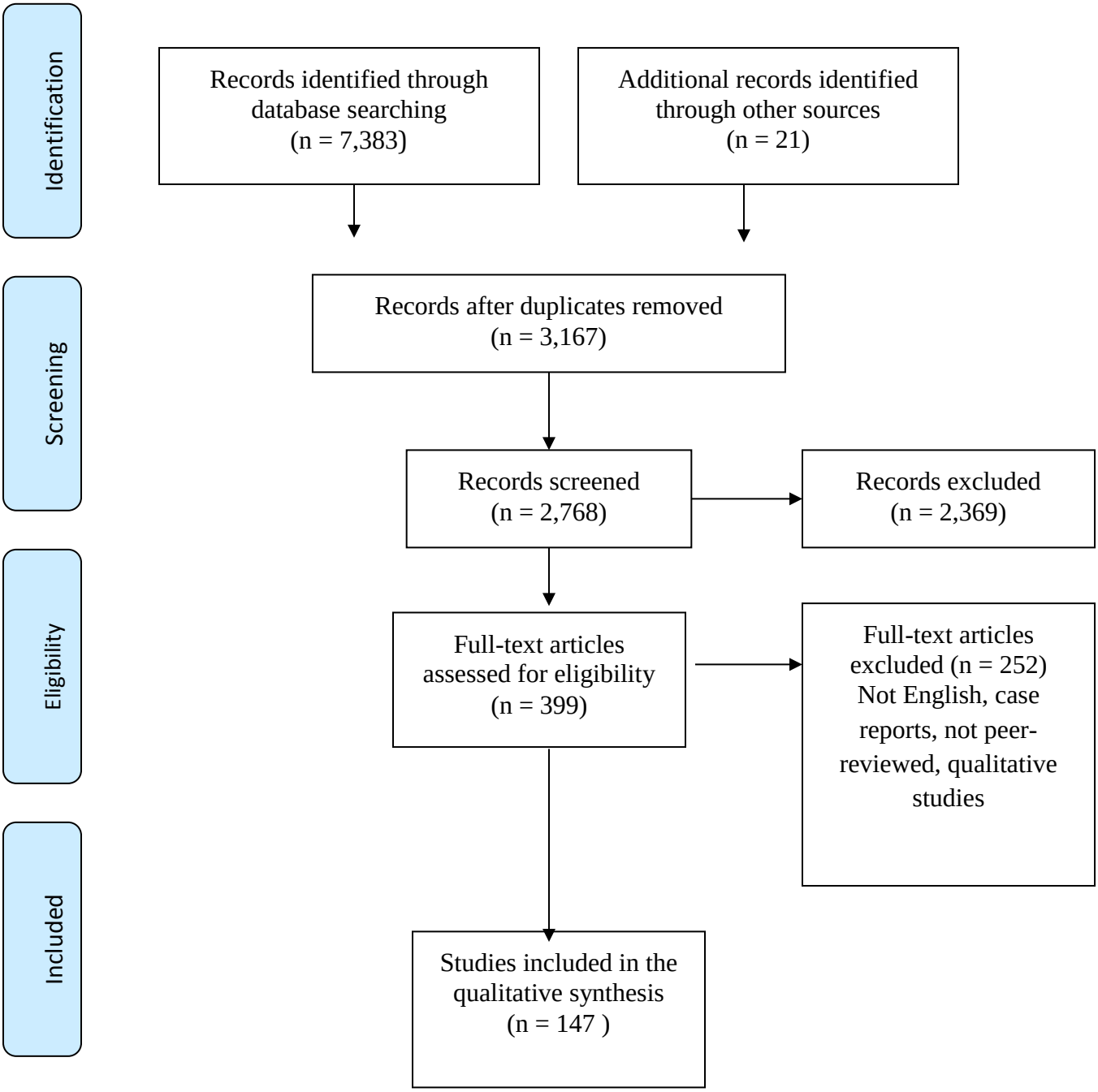
APPENDIX

Search Strategy

Results	Search Type	Actions
1	exp Diabetes Mellitus, Type 2/	94945
2	diabet*.ti.	259342
3	(DM adj (adult-onset or insulin independent or ketosis-resistant or maturity-onset or noninsulin dependent or non-insulin-dependent or slow-onset or stable or type II or type 2)).ti.	6
4	(DM2 or DM 2 or MODY or NIDDM or T2DM).ti.	2042
5	1 or 2 or 3 or 4	285390
6	Diabetes Complications/	37070
7	(diabet* adj2 complicat*).tw.	18666
8	Diabetic Retinopathy/	19759
9	(diabet* adj retinopath*).tw.	16079
10	Diabetic Neuropathies/	12640
11	(diabet* adj4 (amyotroph* or neuralgia* or neuropath* or mononeuropath* or mono-neuropath* or polyneuropath* or polyneuropath*)).tw.	11476
12	Diabetic Foot/	6423
13	((diabet* adj5 (foot or feet or ulcer*)) or charcot foot).tw.	8486
14	exp Diabetic Angiopathies/	40645
15	exp Diabetic Angiopathy/	40645
16	(diabet* adj angiopath*).tw.	688
17	Diabetic Cardiomyopathies/	691
18	Diabetic Cardiomyopathy/	691
19	(diabet* adj cardiomyopath*).tw.	1397
20	Diabetic Nephropathies/	20667

21	Diabetic Nephropathy/	20667
22	(diabet* adj nephropath*).tw.	13826
23	(diabet* adj (obesit* or obese)).tw.	2399
24	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	127130
25	risk factor.mp. or exp Risk Factors/	688830
26	5 and 24 and 25	11255
27	limit 26 to (english language and yr="2000 -Current")	7676
28	**limit 27 to humans**	**7383**

Figure 1: Flow diagram of study selection for the literature review



Note: Adapted from PRISMA

TABLES

Table 1: Study characteristics of included studies

Author, year, country	Study design, mean follow-up time	Study population (sample size)	Outcome	Risk factors identified
United Kingdom Prospective Diabetes Study (UKPDS) Group, 1998, England, Scotland, Northern England [14]	RCT, 10 years	Newly diagnosed patients with type II diabetes, mean age 54 (n=3867)	Microvascular complications	• Hyperglycemia, Hemoglobin A1C
United Kingdom Prospective Diabetes Study (UKPDS) Group, 1999, England, Scotland, Northern England [13]	RCT, 8.4 years	Hypertensive patients with T2DM, mean age 56 (n=1148)	Predefined clinical endpoints, risk of death related to DM, complications related to diabetes, blood pressure, retinopathy, cardiovascular complications	• Hypertension
Wirta et al, 1995, Finland [62]	Population-based controlled cross-sectional survey, 10 years	T2DM, mean age 56, (n=296)	Nephropathy, Eye complication, Neuropathy	• Duration of diabetes
Wise et al, 2011, United States [84]	Prospective cohort, 12 years	T2DM African American women, mean age 54 (n=32,570)	Eye complication	• Alcohol consumption, • smoking
Stratton et al, 2001, England, Northern Ireland, Scotland [82]	Prospective cohort, 6 years	T2DM, mean age 57 (n=1919)	Eye complication	• Hyperglycemia, • duration of diabetes, • blood pressure, • older age, • male sex • Not smoking
Saif et al, 2014, Sweden [68]	Cross sectional study	T2DM, mean age 59	Eye complication	• Hypertension

		(n=140)		
Teitelbaum et al, 2005, United States[69]	Cross sectional study	T2DM, African American, mean age 60 (n=234)	Eye complication	• Hypertension
Rahman et al, 2011, Pakistan [70]	Cross sectional study	T2DM, mean age 54 (n=200)	Eye complication	• Hypertension
Nittala et al, 2014, United States [63]	Prospective, cross-sectional case control study	T2DM, Latino American, mean age 56 (n=729)	Eye complication	• Duration of diabetes, • male sex, • insulin use, • high blood pressure • Not smoking
Olafsdottir et al, 2014, Sweden [64]	Case control	T2DM, mean age 70 (n= 263)	Eye complication	• Hyperglycemia, • hypertension, • duration of diabetes, • cholesterol
Okudaira et al, 2000, Japan [65]	Cross sectional study	T2DM, mean age 27 (n=394)	Eye complication	• Blood pressure, • hyperglycemia, • duration of diabetes
Song et al, 2011, Korea, [66]	Cross sectional study	T2DM, mean age 40 (n=2516)	Eye complication	• Hypertension, • hyperglycemia, • long duration of diabetes
Raman et al, 2011, India[67]	Case control study	T2DM, mean age 40 (n=1414)	Eye complication	• Hyperglycemia, • insulin use, • duration of diabetes, • macroalbuminuria, • male sex, • hypertension
Matthews DR et al, 2004, England, Scotland, Northern Ireland [71]	RCT, 5 years	T2DM, mean age 56 (n=1148)	Eye complication	• Hypertension, • male sex
Leske et al, 2005, Barbados [72]	Population based cohort study, 9 years	T2DM, African descent, mean age 54 (n=324)	Eye complication	• Hyperglycemia, • blood pressure, • duration of diabetes
Macky et al, 2011, Egypt [73]	Cross sectional study	T2DM, mean age 49 (n=1325)	Eye complication	• Female sex, • longer duration of diabetes,

				• hypertension, • absence of hypertension control medication
Yoshida et al, 2001, Japan [74]	Prospective cohort study, 3 years	T2DM, mean age 58 (n=787)	Eye complication	• Hyperglycemia, • duration of diabetes, • high BMI, • blood pressure
Lim et al, 2013, Korea [75]	Prospective cohort study, 2 years	T2DM, mean age 50 (n= 2164)	Eye complication	• Hyperglycemia, • high BMI, • obesity, • high lipid profiles
Kastelan et al, 2013, Croatia [76]	Cross sectional study	T2DM, mean age 68 (n=545)	Eye complication	• Obesity, high cholesterol, high blood pressure
Dirani et al, 2011, Australia[77]	Cross sectional study	T2DM, mean age 65 (n=492)	Eye complication	• Higher BMI, • obesity, • waist circumference
Burgess et al, 2014, Malawi [78]	Prospective cohort, 2 years	T2DM, sub-Saharan Africans, mean age 55 (n=357)	Eye complication	• Duration of diabetes, • hyperglycemia, • hypertension, • high cholesterol, • race (African)
Chiang et al, 2011, Chinese, Malaysia, Singapore [79]	Cross sectional study	T2DM, multi-ethnic Asian, mean age 68 (n=2919)	Eye complication	• Duration of diabetes, • hyperglycemia, • high creatinine levels • Not Race
Ross et al, 2007, Canada [80]	Prospective cohort, 3 years	T2DM, mean age NR (n= 2247)	Eye complication	• Native American ancestry, • Duration of diabetes, • hyperglycemia, • hypertension, • high cholesterol
Gao et al, 2014, United States [81]	Case control	T2DM, mean age 54 (n=944)	Eye complication	• Native American ancestry, • age, • duration of diabetes, • hyperglycemia, • hypertension

Kajiwara et al, 2014, Japan [82]	Retrospective Longitudinal, 5 years	T2DM, mean age 62 (n= 383)	Eye complication	• Female sex
Hwang et al, 2015, Canada [58]	Cross sectional study	T2DM, mean age 62 (n=2323)	Eye complication	• Socioeconomic factors, • low income, • female, • duration of diabetes
Moss et al, 1995, United States [84]	Cross sectional study	T2DM, mean age 58 (n=765)	Eye complication	• Duration of diabetes, • lower education, • lower income
Rossing et al, 2004, United States [88]	Prospective observational, 3 years	T2DM, mean age 57 (n=411)	Nephropathy	• Albuminuria, • hypertension, hyperglycemia, • hemoglobin A1C, • heavy smoking, • diabetic retinopathy
Pang et al, 2012, China [89]	Prospective Cohort, 5 years	T2DM, mean age 66 (n=3736)	Eye complication	• Hyperglycemia, • hypertension, • obesity, • diabetes duration
Parving, 2006, global: Europe, Asia, Africa, North America, Central America, South America, Oceania [90]	Cross sectional	T2DM, mean age 57 (n= 32,208)	Renal complication	• Hypertension, • ethnicity, • diabetes duration, retinopathy, • smoking
Adler 2004, England, Scotland, Northern Ireland [153]	Cross-sectional study	T2DM, mean age 52 (n=5097)	Renal complication	• Cardiovascular disease, microalbuminuria, elevated creatinine
Araki 2012, Japan [91]	Retrospective study, 4 years	T2DM, mean age 71 (n=621)	Renal complication	• Age, • female sex, • cholesterol, • Cardiovascular disease
Hypertension in Diabetes Study, 1993, England, Scotland, Northern Ireland [92]	Cross-sectional study	T2DM, mean age 52 (n=3648)	Renal complication	• Hypertension, • hyperglycemia, obesity, cardiovascular disease
Okada et al, 2012, Japan [93]	Cross sectional study	T2DM, mean age 54 (n=422)	Renal complication	• Hypertension, cardiovascular disease

Yang et al, 2011, Korea[97]	Cross-sectional study	T2DM, mean age 62 (n=3738)	Renal complication	• Male sex, diabetes duration, blood pressure
Lewis et al, 1993, Global: Asia, Europe, Central America, South America, North America [94]	RCT, 3 years	T2DM, mean age 35 (n=207)	Renal complication	• Hypertension, anti-hypertensive medication reduces risk
Brenner et al, 2001, Global: Asia, Europe, Central America, South America, North America [95]	RCT, 3 years	T2DM, mean age 50 (n=1513)	Renal complication	• Hypertension, anti-hypertensive medication reduces risk
Lewis et al 2001, Global: Asia, Europe, Central America, South America, North America [96]	RCT, 2 years	T2DM, mean age 59 (n=1715)	Renal complication	• Hypertension, anti-hypertensive medication reduces risk
Young et al, 2003, United States [98]	Longitudinal cohort study, 1 year	T2DM veterans, mean age 64 (n= 429,918)	Renal complication	• Ethnicity (African American, Native, Hispanic)
Karter et al, 2002, United States [99]	Longitudinal cohort study, 3 years	T2DM, mean age 47 (n=62, 432)	Renal complication	• Ethnicity (African American, Latino, Asian), socioeconomic factors
Pugh et al, 1995, United States [100]	Population-based incidence cohort, 3 years	T2DM, mean age 54 (n= 633)	Renal complication	• Duration of diabetes, retinopathy, proteinuria
Young et al, 2004, United States [101]	Cross sectional study	T2DM, mean age 67 (n= 44,671)	Renal complication	• Duration of diabetes, age, race
Kohler et al, 2000, United States [102]	Cross sectional study	T2DM, mean age 51 (n=1,167)	Renal complication	• Microalbuminuria, • elevated triglyeride levels, • creatinine level, • race (African American), • hypertension, • hyperglycemia
Young et al, 2005, United States [103]	Cross sectional study	T2DM, mean age 61 (n=2969)	Renal complication	• Microalbuminuria, • Race (Asian, Hispanic) • hypertension
Chaturvedi et al, 1995, Europe [104]	Cross sectional study	T2DM, mean age 34 (n=3250)	Renal complication	• Current smoking, • male sex, • former smokers

Gambaro et al, 2001, Italy[105]	Retrospective study, 3 years	T2DM, mean age 51 (n=273)	Renal complication	• Current smokers, • former smokers
Ikeda et al, 1997, Japan [106]	Cross sectional study	T2DM, men, mean age 62 (n=148)	Renal complication	• Current smokers, • former smokers
Dunkler et al, 2015, Global [107]	Observational study, 6 years	T2DM, mean age 66 (n= 6972)	Renal complication	• Education, • Lack of physical activity, • moderate alcohol consumption decreased risk
Sazlina et al, 2014, Malaysia[108]	Cross sectional study	T2DM, mean age 67 (n=10, 363)	Cardiovascular complication	• Hyperglycemia, • age, • waist circumference, • triglycerides
Schulze et al, 2004, United States [109]	Prospective case control, 7 years	T2DM women, mean age 60 (n=921)	Cardiovascular complication	• High cholesterol, hyperglycemia, • diabetes duration
Hansson et al, 1998, Global: Europe, North and South America, and Asia. [110]	RCT, 4 years	T2DM, hypertension, mean age 61 (n=18,790)	Cardiovascular complication	• Hypertension, • hypertension lowering medication decreases risk
Hubert et al, 1993, United States [111]	Prospective cohort, 26 years	Clinically free of recognizable Cardiovascular disease, T2DM, mean age 45, (n= 5209)	Cardiovascular complication	• Obesity, • male sex, • high blood pressure, • high cholesterol
Cho et al, 2002, United States [112]	Prospective cohort, 20 years	T2DM women, mean age 57 (n= 5,897)	Cardiovascular complication	• Increasing BMI, • weight gain, • obesity
Rabkin et al, 1977, Canada[113]	Prospective cohort, 26 years	Clinically free of recognizable Cardiovascular disease, Men, mean age 30 (n= 3,983)	Cardiovascular complication	• Increasing BMI, • obesity, • high blood pressure
Garcia, et al, 1974, United States [115]	Prospective cohort, 16 years	Clinically free of recognizable cardiovascular disease, T2DM mean age	Cardiovascular complication	• High lipid values, • hypertension, • obesity

		(n=5,209)		
McFarlane et al, 2005, United States[116]	Cross sectional study	T2DM, mean age 61 (n= 3,678)	Cardiovascular complication, eye complication, nephropathy	• Female sex, • hypertension • Lower risk for female for eye and nephropathy
Strom et al, 2014, United States [117]	Cross sectional study	T2DM, mean age 57 (n=680)	Cardiovascular complication	• Female sex, • hypertension
Homko et al, 2010, United States [118]	Cross sectional study	T2DM, mean age 61 (n=211}	Cardiovascular complication	• Female sex, • high cholesterol, • hypertension
Sekerija et al 2012, Croatia[119]	Cross sectional study	T2DM, mean age 64 (n= 8,775)	Cardiovascular complication	• Female sex, • high cholesterol, hypertension, • hyperglycemia
Vimalananda et al, 2014, United States [120]	Prospective cohort, 12 years	T2DM, mean age 72 (n=4817)	Cardiovascular complication	• Female sex • Race not a difference
Ma et al, 2012, United States [121]	Prospective cohort, 14 years	T2DM, mean age 45 (n= NR)	Cardiovascular complication	• Education
Saydah et al, 2013, United States[122]	Prospective cohort, 6 years	T2DM, mean age 49 (n= 6,177)	Cardiovascular complication	• Low level of education, low income
McEwan et al, 2007, United States[122]	Prospective cohort, 4 years	T2DM, mean age 61 (n=8,733)	Cardiovascular complication	• Age, • male sex, • lower income, • longer duration of diabetes, • lower BMI, • smoking, • nephropathy, • macrovascular disease
Wang et al, 2014, United States [124]	Prospective cohort, 8 years	T2DM, mean age 42 (n=27,704)	Cardiovascular complication	• Race (African American), • hyperglycemia, • hypertension, • high cholesterol
Larranaga, et al, 2005, Spain [125]	Cross sectional study	T2DM, mean age NR (n=2,985)	Cardiovascular complication	• Socioeconomic status (unemployment, education, unskilled workers, low

				standard of living), • Female sex, • obesity, • high cholesterol, • hyperglycemia
Ford et al, 1991, United States [126]	Prospective cohort, 10 years	T2DM, mean age NR (n=12,562)	Cardiovascular complication	• Age, • male sex, • severe overweight, • non-leisure-time physical inactivity
Morrish et al, 1991, United States[127]	Prospective cohort, 8 years	T2DM, mean age 46 (n= 497)	Cardiovascular complication	• High blood pressure, • duration of diabetes, • smoking, • high cholesterol
Wan et al, 2016, China [128]	Retrospective, 5 years	T2DM, mean age 47 (n=115,470)	Cardiovascular complication	• Age, • current smoking, • longer duration, • smoking, • BMI, • hyperglycemia, • high blood pressure, • high cholesterol • Sex had no difference
Nilsson et al, 2009, Sweden [129]	Longitudinal study, 5 years	T2DM, mean age 52 (n =3,087)	Cardiovascular complication	• Smoking, • age
Al-Delaimy et al, 2002, United States[130]	Prospective study, 20 years	T2DM women, mean age 62 (n=6,547)	Cardiovascular complication	• Smoking
Turner et al, 1998, United Kingdom [131]	Prospective study, 8 years	T2DM, mean age 52 (n=3,055)	Cardiovascular complication	• High cholesterol, • high triglyceride, • hemoglobin A1C, hyperglycemia, • high blood pressure, • smoking
Karim et al, 2005, United	Cross sectional study	T2DM, mean age 52	Cardiovascular	• Longer duration of diabetes,

States [133]		(n=299)	complications	• smoking
Khuwaja et al, 2004, Pakistan [134]	Cross sectional study	T2DM, mean age 54 (n=672)	Cardiovascular complications	• Hypertension, • low physical activity, • current smokers, • duration of diabetes, • male sex
Soloman et al, 2000, United States [137]	Prospective cohort, 14 years	T2DM women, mean age 49 (n=39,092)	Cardiovascular complications	• Moderate alcohol consumption reduces cardiovascular risk
Tanasescu et al, 2001, United States [156]	Prospective cohort, 8 years	T2DM, male, mean age 60 (n=2,419)	Cardiovascular complications	• Moderate alcohol consumption reduces cardiovascular risk
Ajani et al, 2000, United States[139]	Prospective cohort, 5 years	T2DM, mean age 62 (n=2,790)	Cardiovascular complication	• Moderate alcohol consumption reduces cardiovascular risk
Blomster et al, 2014, United States [140]	Prospective cohort, 5 years	T2DM, mean age 65 (n= 11,140)	Cardiovascular complication, Eye complication, Renal complications	• Moderate alcohol consumption (wine) reduces cardiovascular risk and microvascular complications
Djousse et al, 2007, United States [141]	Prospective cohort, 6 years	T2DM, mean age 72 (n=4655)	Cardiovascular complication	• Light to moderate alcohol consumption reduces cardiovascular risk
Marques-Vidal et al, 2004, France, Ireland [142]	Prospective cohort, 5 years	T2DM men mean age 54 (n=9,750)	Cardiovascular complication	• High alcohol consumption reduces the cardiovascular risk
Makita S et al ,2012, Japan[143]	Prospective cohort, 5 years	T2DM men, mean age 64 (n=8041)	Cardiovascular complication	• Any alcohol consumption reduces cardiovascular risk
Aubert et al, 2014, Canada[144]	Cross sectional study	T2DM, mean age 65 (n=198)	Neuropathy	• sRAGE and carboxymethyllysine, • hyperglycemia, • waist circumference, • height, • peripheral arterial occlusive disease
Boru et al, 2004, Turkey [145]	Cross sectional study	T2DM, mean age 57 (n=866)	Neuropathy	• Duration of diabetes, • hyperglycemia, • hemoglobin A1C, • age
Kostev et al, 2014,	Prospective cohort, 4 years	T2DM, mean age 66	Neuropathy	• Age,

Germany, United Kingdom [151]		(n=730)		• peripheral artery disease, • insulin treatment, • male sex, • nephropathy, • hypertension
Liu et al, 2010, China[152]	Randomized prospective cohort, 1 year	T2DM, mean age 59 (n=1197)	Neuropathy	• Retinopathy, • hemoglobin A1C, hyperglycemia • diabetes duration, • age
Booya et al, 2005, Iran [146]	Case-control, cross sectional study	T2DM, mean age 55 (n=110)	Neuropathy	• Age, • male, • duration of diabetes
Dyck et al, 1999, United States[147]	Prospective cohort, 7 years	T2DM, mean age 62 (n=264)	Neuropathy	• Retinopathy, • duration of diabetes, • nephropathy, • hyperglycemia,
McClean et al, 2005, Ireland[148]	Cross sectional study	T2DM, mean age 63 (n=290)	Neuropathy, Eye complication	• Age, • duration of diabetes, • smoking
Basnal et al, 2014, India [149]	Cross sectional study	T2DM, mean age 57 (n=586)	Neuropathy	• Age, • duration of diabetes, • dyslipidemia, • microvascular complications, • macrovascular complications • No sex differences
Raman et al, 2012, India [150]	Cross sectional study	T2DM, mean age 55 (n=5999)	Eye complication, neuropathy, nephropathy	• Age, hypertension, • hemoglobin A1C, • hyperglycemia
Chyun et al, 2006, United States[175]	Cross sectional study	T2DM, mean age 60 (n=206)	Neuropathy	• female sex, • physical inactivity, • higher BMI, • the presence of depressive symptoms and anxiety
Adler et al, 1997, United	Prospective cohort	T2DM, mean age 64	Neuropathy	• age,

States [154]		(n=775)		• duration of diabetes, • glycohemoglobin level, • height, • history of lower-extremity ulceration, callus, and edema • Smoking inverse relationship
Baba et al, 2014 [158]	Prospective cohort, 15 years	T2DM, mean age 64 (n=1296)	Foot and leg complication	• Intermittent claudication, • peripheral sensory • neuropathy, • retinopathy, • cerebrovascular disease, • Hemoglobin A1C, • alcohol consumption, • renal impairment, • hypertension
Bortoletto et al 2014, Brazil[159]	Cross sectional study	T2DM, mean age 60 (n=337}	Foot and leg complication	• Duration of diabetes, • cardiovascular complication (previous stroke, myocardial infarction)
Dos Santos et al 2006, Brazil[160]	Cross sectional study	T2DM, mean age 60 (n=99)	Foot and leg complication	• Age, • lymphangitis, • cardiovascular complication, • duration of diabetes
Miyajima et al, 2006, Japan[161]	Prospective cohort, 2 years	T2DM, mean age 64 (n=210)	Foot and leg complication	• Multiple stenosis, • hemodialysis, • Hemoglobin A1C, • hyperglycemia, • retinopathy
Parisi et al, 2016, Brazil[162]	Cross sectional study	T2DM, mean age 57 (n=1455)	Foot and leg complication	• Duration of diabetes, • hyperglycemia, • male sex, • smoking, retinopathy, • hypertension • Ethnicity not a factor

Amin et al, 2014, Canada[190]	Population based cohort study, 5 years	T2DM, mean age 61 (n = 606 494)	Foot and leg complication	• Low socioeconomic status, • male sex
Abbott et al, 2005, United Kingdom[168]	Cross sectional study	T2DM, mean age 59 (n=15, 692)	Foot and leg complication	• Race (European), • male sex • Less risk for South-Asians (India, Pakistan, or Bangladesh), African, Caribbean
Ferguson et al, 2013, Jamaica[169]	Prospective study, 1 years	T2DM, mean age 56 (n=188)	Foot and leg complication	• High blood pressure, • neuropathy, • diabetes duration
Monami et al, 2009, Italy [170]	Prospective cohort, 4 years	T2DM, mean age 64 (n=1,945)	Foot and leg complication	• High blood pressure, • increased age
Margolis et al, 2008, United Kingdom[171]	Retrospective study, 2 years	T2DM, mean age 63 (n= 90,617)	Foot and leg complication	• Renal complication
Yusof et al, 2015, Malaysia[172]	Cross sectional study	T2DM, mean age 60 (n=218)	Foot and leg complication	• Duration of diabetes greater than 10 years • positive bacterial culture
Faglia et al, 2001, Italy [173]	Prospective cohort, 6 years	T2DM, mean age 63 (n=115)	Foot and leg complication	• Older age, • female sex
Iversen et al, 2008, Norway[174]	Cross sectional study	T2DM, mean age 66 (n =1,972)	Foot and leg complication	• Older age (>75 years), • height, • male sex, • insulin use, • macrovascular complications • Not high blood pressure
Litzelman et al, 1997, United States [175]	RCT, 1 year	T2DM, mean age 55 (n=352)	Foot and leg complication	• Neuropathy, • wounds, • low HDL
Boyko et al, 1999, United States[36]	Prospective cohort, 3 years	T2DM, mean age 63 (n=749)	Foot and leg complication	• Foot insensitivity, • past amputation, • insulin use, • hyperglycemia, • obesity,

				• eye complication, • high blood pressure
Sohn et al, 2011, United States [177]	Nested case control, 1 year and 5 years	T2DM, mean age 57 (n=135, 042)	Foot and leg complication	• Higher BMI, • Obesity, • normal weight • Less risk for overweight
Sohn et al, 2012, United States[178]	Retrospective study, 4 years	T2DM, mean age 56 (n= 115,226)	Foot and leg complication	• Low BMI • Less risk for high BMI, • overweight
Kastenbauer et al, 2001, Austria[179]	Prospective cohort, 3 years	T2DM, mean age 58 (n=177)	Foot and leg complication	• elevated vibration perception threshold, • increased plantar pressure, • daily alcohol intake
Bresater et al, 1996, Sweden [180]	Prospective cohort, 3 years	T2DM, elderly, mean age 70 (n=132)	Foot and leg complication	• Diabetes duration, • insulin treatment, • hyperglycemia, • hemoglobin A1C, • height, • alcohol intake
Attenburg et al, 2001, Germany [181]	Prospective cohort, 1 year	T2DM, mean age 64 (n= 94)	Foot and leg complication	• Alcohol consumption, • lower level of education, • low income
Kloos et al 2009, Germany [182]	Prospective study, 1 year	T2DM, mean age 65 (n= 59)	Foot and leg complication	• Cognitive function • alcohol not a risk factor
Hoban et al, 2015, Canada[183]	Prospective study, 2 years	T2DM, mean age 47 (n=97)	Foot and leg complication	• Depression, • anxiety • Alcohol not a risk factor
Lavery et al, 1998, United States[208]	Case control, 1 year	T2DM, mean age 52 (n=76)	Foot and leg complication	• Neuropathy, • foot deformity, • high plantar pressures, • history of amputation, • renal complication
de Sonnaville et al, 1997, The Netherlands[185]	Prospective cohort, 3 years	T2DM, mean age 64 (n=609)	Foot and leg complication	• diabetes duration, • cigarette smoking,

				• peripheral vascular disease, • sensory neuropathy
Guerrero-Romero et al, 1998, Mexico[186]	Cross sectional	T2DM, mean age 61 (n= 670)	Foot and leg complication	• diabetes duration, • cigarette smoking, • aging, • microalbuminuria
Monteiro-Soares et al, 2010, Portugal[188]	Retrospective cohort, 2 years	T2DM, mean age 65 (n=360)	Foot and leg complication	• type of footwear, • male sex • smoking habits not a risk factor
Suico et al, 1998, United States[189]	Prospective cohort, 1 year	T2DM, mean age 60 (n=295)	Foot and leg complication	• Self foot care habits • smoking habits not a risk factor
Armstrong et al, 2008, United States[190]	RCT, 1 year	T2DM, mean age 58 (n=225)	Foot and leg complication	• Age, • race (Hispanic)
Ferguson et al, 2010, United Kingdom[191]	Case-control, 6 years	T2DM, mean age NR (n=327)	Foot and leg complication	• Socioeconomic deprivation
Holman et al, 2012, England[192]	Prospective cohort, 3 years	T2DM, mean age NR (n= 16,693)	Foot and leg complication	• Negative correlation with race (Asians), • smoking, • social deprivation
Bergin et al, 2011, Australia[193]	Prospective cohort, 1 year	T2DM, mean age 53 (n= 798,007)	Foot and leg complication	• Male sex, • socioeconomic status
Leese et al, 2013, United Kingdom [194]	Prospective cohort, 3 years	T2DM, mean age, 64 (n=670)	Foot and leg complication	• Social deprivation
Altenburg et al, 2011, Germany [195]	Prospective cohort, case control, 2 years	T2DM, mean age, 64 (n=47)	Foot and leg complication	• Increased alcohol consumption, • lower level of education, • low income, • anxiety disorder
El-Asrar et al, 2001, Saudi Arabia[196]	Cross sectional study	T2DM, mean age 48 (n=648)	Nephropathy	• Retinopathy (eye complication), • neuropathy, • cerebrovascular disease

				(cardiovascular)
Mottl et al, 2014, United States [197]	RCT, 4 years	T2DM, mean age 60 (n= 3,369)	Renal complications, cardiovascular complications	• Retinopathy
Manaviat et al, 2004, Iran [198]	Cross sectional study	T2DM, mean age 54 (n=590)	Eye complication (retinopathy)	• BMI, • hemoglobin A1C, • microalbuminuria, • renal complications
Stack et al, 2001, United States [199]	Cross-sectional study	T2DM, mean age 58 (n=4,042)	Cardiovascular complication	• Renal complications, • measures of atherosclerosis and cardiac abnormalities, • serum albumin levels
Stack et al, 2001, United States[200]	Cross-sectional study	T2DM, mean age 59 (n=4,025)	Cardiovascular complication	• older age, • male sex, • smoking, • end stage renal failure
Foley et al, 1997, Canada[201]	Prospective study, 2 years	T2DM, mean age 53 (n=433)	Cardiovascular complication	• older age, • left ventricular hypertrophy, • smoking, • clinically diagnosed ischemic heart disease, cardiac failure, • hypoalbuminaemia, • renal complications
Chang et al, 2014, Taiwan [203]	Prospective cohort, 12 years	T2DM, mean age 59 (n= 648,851)	Cardiovascular complication	• Renal disease
Bansal et al, 2014, India[149]	Cross sectional study	T2DM, mean age 57 (n= 586)	Neuropathy	• Age, • duration of diabetes, • dyslipidemia, • glycated hemoglobin, • other microvascular complications, • cardiovascular complications, • alcohol consumption
Lai et al, 2015, Taiwan[204]	Prospective cohort, 10 years	T2DM, mean age 58 (n=1588)	Foot and leg complications	• Peripheral arterial occlusive disease,

				• neuropathy, • retinopathy, cardiovascular • complication (stroke), • male sex,
Verrone Quilici et al, 2016, Brazil [205]	Cross sectional study	T2DM, mean age 62 (n=100)	Foot and leg complications	• Neuropathy, • high blood pressure
Abolfotouh et al, 2011, Saudi Arabia [206]	Case-control study	T2DM, mean age 48 (n=100)	Foot and leg complications	• Duration of diabetes, • neuropathy
Hu et al, 2014, Saudi Arabia [207]	Prospective cohort, 1 year	T2DM, mean age NR (n=598)	Foot and leg complications	• Peripheral artery disease, • neuropathy
Aydin et al, 2010, Turkey[208]	Retrospective study	T2DM, mean age 62 (n=74)	Foot and leg complications	• Not Neuropathy
Peters et al, 2007, The Netherlands[209]	Prospective cohort, 2 years	T2DM, mean age 60 (n=91)	Foot leg complications	• Not Neuropathy
Scanlon et al, 2008, United Kingdom[85]	Cross-sectional study	T2DM, mean age 64 (n= 13,304)	Eye complication	• Socioeconomic status
Crawford et al, 2007 [176]	Systematic review, meta-analysis	T2DM, mean age NR (n=NR)	Foot and leg complication	• Neuropathy, • plantar pressure
Tang et al, 2014 [165]	Meta-analysis	T2DM, mean age NR (n=15,385)	Foot and leg complication	• Male sex
Monteiro-Soares et al, 2012[166]	Systematic review	T2DM, mean age NR (n= NR,71 included studies)	Foot and leg complication	• Male sex, • increasing age, • duration of diabetes, • neuropathy, • peripheral vascular disease, • smoking, • alcohol consumption, • higher BMI, • nephropathy, • retinopathy • No association with education, hypertension, cardiovascular complication
Clair C et al, 2015[156]	Systematic Review Meta-	T2DM, mean age 45	Neuropathy	• Smoking

	Analysis	(n= 5558)		
Qin et al, 2013 [132]	Meta-analysis	T2DM, mean age NR (n=130,000)	Cardiovascular complications	• Former smokers, • current smokers
Yau et al, 2012 [27]	Systematic review, pooled analysis	T2DM, mean age 50 (n=22,896)	Eye complications, retinopathy	• Duration of diabetes, glycemic control, • blood pressure

Table 2: Common risk factors associated with T2DM complications in the current literature

	Hyperglycemia	**Age**	**Diabetes Duration**	**Sex**	**Hypertension**	**Obesity**	**Ethnicity**	**Socioeconomic Status[a]**	**Lifestyle Factors[b]**
Eye Complications	↑	↑	↑	↑ / ↓	↑	↑	↑ / ↓	↑	↑
Renal Complications	↑	↑	↑		↑		↑ / ↓	↓	↑ / ↓
Cardiovascular Complications	↑	↑	↑	↑ / ↓	↑	↑	↑ / ↓	↑	↑ / ↓
Neuropathy Complications	↑	↑	↑	↑ / ↓		↑			↑
Foot/Leg Complications	↑	↑	↑	↑	↑ / ↓	↑ / ↓	↑ / ↓	↑ / ↓	↑ / ↓

[a]includes household income and/or education level of attainment; [b] includes smoking status and/or alcohol consumption

Table 3: Factors explored as being associated with diabetes related complications

Variable	Coding for Analyses
Modifiable risk factors	
Smoking status	• Never Smoked (reference) • Previous Smoker • Current Smoker
Alcohol consumption	• No alcohol (reference) • 1 – 3 times a month • 1 – 7 drinks per week
BMI	• Not obese (Underweight, normal weight, overweight) (reference) • Obese
Household income (all sources)	• ≤$29,999 • $30,000 - $59,999 • ≥ $60,000 (reference)
Level of education completed	• Less than Secondary School Education • Secondary School Graduation/ Some Post-Secondary Education • Post-Secondary Education (reference)
Medication to control high blood pressure	• Yes • No (reference)
Medication to control high cholesterol	• Yes • No (reference)
Non-modifiable risk factors	
Age	• < 65 years (reference) • ≥ 65 years
Years living with diabetes	• ≤ 5 years (reference) • 6 – 9 years • ≥ 10 years
Sex	• Male • Female (reference)
Racial Origin	• White (reference) • Non-white
Eye complication	• Yes • No (reference)
Renal complication	• Yes • No (reference)
Cardiovascular complication	• Yes • No (reference)
Foot or leg complication	• Yes • No (reference)
Neuropathy	• Yes • No (reference)

Table 4: Characteristics of respondents with T2DM in Canada (Sample n=2341, Canadian population n= 1 365 165)

Characteristics of T2DM Canadians	Respondents	Respondents % (95% CI)	Population Estimate	Population Estimate % (95% CI)
Sex				
Male	1183	49.5 (47.4 – 51.5)	789 527	57.8 (54.9 – 60.8)
Female	1158	42.2 (48.5 – 52.6)	575 638	42.2 (39.2 – 45.1)
Age				
< 65 years old	1312	56.0 (54.0 – 58.1)	757 739	54.8 (42.0 – 48.5)
≥ 65 years old	1029	44.0 (41.9 – 46.0)	617 426	45.2 (51.5 – 58)
Race				
White	2132	94.6 (93.7 – 95.6)	1 120 148	85 (81.5 – 88.5)
Non-white	122	5.4 (4.5 – 6.4)	197 674	15 (11.5 – 18.5)
Time since diagnosis of diabetes				
≤5 years	782	33.7 (31.8 – 35.6)	462 742	34.2 (30.7 – 37.6)
6 – 9 years	416	17.9 (16.4 – 19.5)	261 049	19.3 (15.5 – 22.0)
≥ 10 years	1124	48.4 (46.4 – 50.4)	631 037	46.6 (43.2 – 50)
Aboriginal status				
Aboriginal (First Nations, Inuit, and Métis) Citizen	79	3.4 (2.6 – 4.1)	43,019	3.2 (2.1 – 4.3)
Non-Aboriginal (non-Immigrant) Citizen	2256	96.6 (95.9 – 97.4)	1 319 191	96.8 (9.8 – 97.9)
Household income				
≤ $29,999	392	18.6 (16.9 – 20.3)	151 211	12.6 (10.4 – 14.7)
$30,000 - $59,999	819	38.9 (36.8 – 41.0)	441 619	36.7 (33.3 – 40.5)
≥ $60,000	893	42.4 (40.3 – 44.6)	612 104	50.8 (47.2 – 54.4)
Highest level of education				
Less than Secondary School Education	664	28.5 (26.7 – 30.3)	326 996	24.1 (21.3 – 26.9)

Secondary School Graduation and/or some Post-Secondary Education	557	23.9 (22.2 – 25.6)	343 548	25.3 (22.2 – 28.4)
Post-Secondary Education	1109	47.6 (45.6 – 49.6)	687 014	50.6 (47.2 – 54.1)
Smoking status				
Never smoked	669	28.1 (26.8 – 30.5)	446 445	32.7 (29.2 – 36.3)
Current smoker	292	12.5 (11.2 – 13.9)	156 015	11.4 (9.3 – 13.5)
Former smoker	1374	58.8 (56.9 – 60.8)	760 991	55.8 (52.3 – 59.23)
Alcohol consumption				
No alcohol	772	33.0 (31.1 – 34.9)	435 025	31.9 (28.6 – 35.2)
1 – 3 drinks a month	910	38.9 (37.0 – 40.9)	494 295	36.2 (32.7 – 39.7)
1 – 7 drinks per week	665	28.0 (26.2 – 29.9)	434 935	31.9 (28.5 – 35.2)
BMI				
Not obese	1255	53.6 (52.5 – 60.1)	757 695	56.3 (52.5 – 60.1)
Obese	1045	44.6 (40.0 – 47.5)	587 959	43.7 (39.0 – 47.4)
High Blood pressure medication				
Yes	1666	71.9 (70.0 – 73.7)	927 872	68.4 (65.0 – 71.8)
No	652	28.1 (26.3 – 30.0)	429 054	31.6 (28.2 – 35.1)
High Blood cholesterol medication				
Yes	1539	66.7 (64.8 – 68.6)	908 085	67.2 (63.8 – 70.6)
No	768	33.3 (31.4 – 35.2)	443 209	32.8 (29.4 – 36.2)
Medication Use to control diabetes				
Currently taking pills to control blood sugar	1847	78.9 (77.2 – 80.6)	1 117 688	85.8 (83.6 – 87.9)
Not taking pills to control blood sugar	399	17.0 (15.2 – 18.6)	185 317	14.2 (12.1 – 16.4)
Ever taken insulin injections	595	25.4 (23.7 – 27.2)	344 038	25.2 (22.2 – 28.2)
Never taken insulin injections	1745	74.5 (72.8 – 76.3)	1 020 952	74.8 (71.8 – 77.8)
Currently taking insulin injections	487	20.8 (19.2 – 22.5)	278 146	19.1 (13.6 – 24.7)

Not taking insulin injections	108	4.6 (3.7 – 5.5)	65 891	4.5 (3.6 – 5.6)
Note: Percentages in this table are weighted using Statistics Canada survey weights, which accounts for the probability of selection into the sample. To account for sampling design, bootstrap re-sampling method was used to estimate coefficients of variation and 95% CIs.				

Table 5: Frequency of each diabetes-related complications in Canada

Diabetes-related complication [a]	Respondents N	Respondents % (95% CI)	Population Estimate N	Population Estimate % (95% CI)
Eye complications	898	38.6 (36.6 – 40.1)	464 433	34.0 (31.0 – 37.0)
Diabetic eye disease	138	5.8 (4.9 – 6.9)	76 369	5.6 (4.1 – 7.1)
Partial or complete blindness	40	1.7 (1.2 – 2.2)	21 800	29.4 (14.2 – 44.7)
Cataracts	771	32.9 (31.0 – 34.8)	401 122	29.43 (26.6 – 32.3)
Glaucoma	199	8.5 (7.4 – 9.6)	93 846	6.9 (5.2 – 8.5)
Renal complications	327	14.5 (13.1 – 16.0)	214, 149	15.7 (13.0 – 18.4)
Protein in urine	255	10.9 (9.6 – 12.16)	175 620	13.3 (10.7 – 10.0)
Kidney failure	104	4.4 (3.6 – 5.3)	64 057	4.71 (3.2 – 6.2)
Neuropathy complication	218	10.8 (8.6 – 13.0)	147 783	10.8 (8.6 – 13.0)
Cardiovascular complications	615	22.1 (20.1 – 26.4)	308 312	22.6 (19.7 – 25.5)
Heart disease	420	22.3 (20.6 – 24.0)	261 445	19.3 (16.6 – 22.0)
Mini stroke	195	8.3 (7.2 – 9.5)	93 796	6.9 (5.2 – 8.6)
Foot or leg complications	584	24.9 (23.1 – 26.7)	332 606	24.4 (21.4 – 27.3)
Poor circulation in feet/legs	542	23.2 (21.4 – 24.9)	301 235	22.2 (19.5 – 25.0)
Foot or leg ulcers/infection	112	4.8 (3.9 – 5.6)	82 875	6.1 (4.0 – 8.1)
Gangrene/amputation	8	0.3 (0.10 – 0.6)	6452	7.8 (0 – 18.3)

Notes: A respondent could have answered, “yes” to one or more complication (i.e., if a respondent reported 2 different types of eye complications, the presence of an eye complication was captured once) Percentages in this table are weighted using Statistics Canada survey weights to reflect the Canadian population aged 20 years and older, living in private dwellings. To account for sampling design, bootstrap re-sampling method was used to estimate coefficients of variation and 95% CIs.

Table 6: Results from Univariate and Multivariate Logistic Regressions Odds ratios (likelihood of complication) generated for individuals with T2DM according to the outlined set of variables – Eye complication

Covariates	Univariate Regression			Multivariate Regression		
	OR	**95 % CI**	**P-value**	**OR**	**95 % CI**	**P-value**
Sex						
Female (Reference group)						
Male	0.6	0.5 – 0.8	**0.0018***	0.6	0.4 – 0.9	**0.008***
Age						
< 65 years old (Reference group)						
≥ 65 years old	5.0	3.6 – 6.9	**<0.0001***	3.7	2.4 – 5.5	**<0.0001***
Racial origin						
White (Reference group)						
Non-white	0.7	0.4 – 1.1	0.1	0.8	0.4 – 1.7	0.6
Household income						
≥ $60,000 (Reference group)						
≤ $29,999	2.8	1.8 – 4.2	**<0.0001***	1.9	1.1 – 3.2	**0.01***
$30,000 - $59,999	1.7	1.2 – 2.5	0.8	0.8	0.7 – 1.7	0.3
Highest level of education						
Post-Secondary Education (Reference group)						
Less than Secondary School Education	1.8	1.3 – 2.6	**<0.0001***	1.0	0.6 – 1.4	0.6
Secondary School Graduation - some Post-Secondary	0.9	0.6– 1.3	**0.01***	0.8	0.5 – 1.2	0.2

Education						
Smoking status						
Never Smoked (Reference group)						
Current smoker	0.9	0.6 – 1.4	0.3	1.0	0.6 – 1.8	0.9
Former smoker	1.2	0.9 – 1.7	0.07	1.1	0.7 –1.5	0.8
Alcohol consumption						
No alcohol (Reference group)						
1 to 3 drinks a month	0.6	0.5 – 0.9	0.3	0.9	0.6 – 1.3	0.5
1 to 7 drinks per week	0.5	0.4 – 0.8	**0.018***	0.9	0.5 – 1.5	0.9
BMI						
Not obese (Reference group)						
Obese	0.7	0.6 – 1.0	0.08	0.8	0.6 – 1.2	0.2
High blood pressure medication						
No (Reference group)						
Yes	0.6	0.4 – 0.8	**0.011***	1.1	0.7 – 1.5	0.8
High blood cholesterol medication						
No (Reference group)						
Yes	0.6	0.5 – 0.9	**0.0047***	0.8	0.5 – 1.1	0.2
Time since diagnosis of diabetes						
≤5 years (Reference group)						

6 – 9 years	1.0	0.6 – 1.6	**0.0031***	1.3	0.8 – 2.2	0.5
≥ 10 years	3.4	2.4 – 4.8	**<0.0001***	2.3	1.6 – 3.5	**<0.0001***
Cardiovascular complication						
No (Reference group)						
Yes	2.4	1.7 – 3.3	**<0.0001***	1.8	1.1 – 2.9	**0.01***
Renal complication						
No (Reference group)						
Yes	1.3	0.8 – 1.9	0.3	1.1	0.7 – 1.9	0.6
Foot/Leg complication						
No (Reference group)						
Yes	2.2	1.6 – 3.1	**<0.0001***	1.4	0.9 – 2.2	0.1
Neuropathy complication						
No (Reference group)						
Yes	0.5	0.3 – 0.8	**0.005***	0.5	0.3 – 0.9	**0.03***

Note: Percentages in this table are weighted using Statistics Canada survey weights to reflect the Canadian population aged 20 years and older, living in private dwellings. Bold * indicates statistically significant at the $p<0.05$ level. To account for sampling design, bootstrap re-sampling method was used to estimate coefficients of variation and 95% CIs.

Table 7: Results from Univariate and Multivariate Logistic Regressions Odds ratios (likelihood of complication) generated for individuals with T2DM according to the outlined set of variables – Renal complication

Covariates	Univariate Regression			Multivariate Regression		
	OR	**95 % CI**	**P-value**	**OR**	**95 % CI**	**P-value**
Sex						
Female (Reference group)						
Male	0.9	0.6 – 1.4	0.7	0.8	0.4 – 1.5	0.5
Age						
< 65 (Reference group)						
≥65	0.9	0.6 – 1.4	0.6	0.9	0.5 – 1.4	0.6
Racial origin						
White (Reference group)						
Non-white	1.5	0.8 – 3.0	0.2	1.6	0.7 – 3.6	0.3
Household income						
≥ $60,000 (Reference group)						
≤ $29,999	1.1	0.6 – 1.9	0.7	0.9	0.5 – 1.8	0.9
$30,000 - $59,999	0.9	0.5 – 1.5	0.5	0.9	0.5 – 1.5	0.6
Highest level of education						
Post-Secondary Education (Reference group)						
Less than Secondary School Education	0.6	0.4 – 0.9	0.09	0.6	0.4 – 1.0	0.2
Secondary School Graduation - some Post-Secondary Education	0.8	0.5 – 1.4	0.9	0.8	0.4 – 1.4	0.9
Smoking status						
Never Smoked (Reference group)						
Current smoker	1.0	0.5 – 1.9	0.9	1.1	0.5 – 2.5	0.6
Former smoker	0.9	0.6 – 1.5	0.8	0.9	0.6 – 1.5	0.5
Alcohol consumption						

No alcohol (Reference group)						
1 to 3 drinks a month	0.7	0.4 – 1.0	0.5	0.5	0.3 – 0.9	0.2
1 to 7 drinks per week	0.6	0.3 – 1.1	0.3	0.6	0.3 – 1.2	0.6
BMI						
Not obese (Reference group)						
Obese	1.1	0.7 – 1.7	0.5	1.1	0.6 - 1.9	0.6
High blood pressure medication						
No (Reference group)						
Yes	1.1	0.7 – 1.9	0.6	1.1	0.6 – 2.0	0.7
High blood cholesterol medication						
No (Reference group)						
Yes	1.3	0.8 – 2.1	0.4	1.5	0.6 – 2.0	0.2
Time since diagnosis of diabetes						
≤ 5 years (Reference group)						
6 – 9 years	1.9	1.1 – 3.5	0.3	3.0	1.4 – 6.3	**0.02***
≥ 10 years	1.9	0.9 – 4.0	0.2	2.1	1.1 – 3.9	**0.04***
Cardiovascular complication						
No (Reference group)						
Yes	1.8	1.2 – 2.8	**0.006***	1.6	1.0 – 2.7	0.06
Eye complication						
No (Reference group)						
Yes	1.2	0.8 – 1.9	0.3	1.1	0.7 – 1.8	0.7
Foot/Leg complication						
No (Reference group)						
Yes	1.7	1.1– 2.6	**0.03***	1.3	0.8 – 2.3	0.3
Neuropathy complication						
No (Reference group)						
Yes	0.4	0.3– 0.9	**0.03***	0.5	0.3 – 1.1	0.08
Note: Percentages in this table are weighted using Statistics Canada survey weights to reflect the Canadian population aged 20 years and older, living in						

private dwellings. Bold * indicates statistically significant at the $p<0.05$ level. To account for sampling design, bootstrap re-sampling method was used to estimate coefficients of variation and 95% CIs.

Table 8: Results from Univariate Logistic Regressions Odds ratios (likelihood of complication) generated for individuals with T2DM according to the outlined set of variables – Cardiovascular complication

Covariates	Univariate Regressions			Multivariate Regressions		
	OR	**95 % CI**	**P-value**	**OR**	**95 % CI**	**P-value**
Sex						
Female (Reference group)						
Male	1.3	1.0– 1.8	0.06	1.9	1.3 – 2.7	**0.0006***
Age						
< 65 years (Reference group)						
≥ 65 years	1.9	1.3 – 2.7	**0.0003***	1.3	0.8 – 2.0	0.3
Racial origin						
White (Reference group)						
Non-white	0.6	0.3 – 1.3	0.2	0.8	0.3 – 2.1	0.6
Household income						
≥ $60,000 (Reference group)						
≤ $29,999	2.2	1.4 – 3.4	**0.01***	1.4	0.8 – 2.4	0.5
$30,000 - $59,999	1.8	1.3 – 2.7	0.15	1.5	0.9 – 2.3	0.3
Highest level of education						
Post-Secondary Education (Reference group)						
Less than Secondary School Education	1.5	1.0 – 2.1	**0.004***	1.0	0.7 – 1.6	0.8
Secondary School Graduation - some Post-Secondary Education	0.8	0.6 – 1.3	**0.04***	0.9	0.6 – 1.4	0.7
Smoking status						

Never Smoked (Reference group)						
Current smoker	1.3	0.7 – 2.2	0.9	1.3	0.7 – 2.5	0.6
Former smoker	1.6	1.1 – 2.2	0.07	1.3	0.8 – 2.0	0.7
Alcohol consumption						
No alcohol (Reference group)						
1 to 3 drinks a month	0.6	0.4 – 0.9	**0.008***	0.6	0.4 – 1.0	0.4
1 to 7 drinks per week	0.6	0.4 – 0.9	0.2	0.6	0.4 – 0.9	0.2
BMI						
Not obese (Reference group)						
Obese	1.3	0.9 – 1.8	0.14	1.3	0.8 – 2.0	0.3
High blood pressure medication						
No (Reference group)						
Yes	0.5	0.3 – 0.7	**0.0005***	0.7	0.5 – 1.1	0.1
High blood cholesterol medication						
No (Reference group)						
Yes	0.5	0.3 – 0.7	**0.0008***	0.6	0.3 – 0.9	**0.01***
Time since diagnosis of diabetes						
≤ 5 years (Reference group)						
6 – 9 years	0.6	0.4 – 1.1	**0.0008***	0.5	0.3 – 0.9	**0.005***
≥ 10 years	1.9	1.3 -2.8	**<0.0001***	1.1	0.7 – 1.8	0.05
Eye complication						

No (Reference group)						
Yes	2.4	1.7 – 3.3	**<0.0001***	1.9	1.2 – 3.0	**0.007***
Renal complication						
No (Reference group)						
Yes	1.8	1.2 – 2.8	**0.004***	1.4	0.9 – 2.4	0.2
Foot/Leg complication						
No (Reference group)						
Yes	2.4	1.7 – 3.5	**<0.0001***	2.0	1.3 – 3.0	**0.002***
Neuropathy complication						
No (Reference group)						
Yes	0.4	0.2 – 0.7	**0.001***	0.8	0.4 – 1.4	0.4

Note: Percentages in this table are weighted using Statistics Canada survey weights to reflect the Canadian population aged 20 years and older, living in private dwellings. Bold * indicates statistically significant at the $p<0.05$ level. To account for sampling design, bootstrap re-sampling method was used to estimate coefficients of variation and 95% CIs.

Table 9: Results from Univariate and Multivariate Logistic Regressions Odds ratios (likelihood of complication) generated for individuals with T2DM according to the outlined set of variables – Foot and leg complication

Covariates	Univariate Regression			Multivariate Regression		
	OR	95 % CI	P-value	OR	95 % CI	P-value
Sex						
Female (Reference group)						
Male	1.1	0.8 – 1.6	0.5	1.1	0.7 – 1.6	0.7
Age						
< 65 years (Reference group)						
≥ 65 years	1.3	0.9 – 1.8	0.2	0.9	0.5 – 1.4	0.5
Racial origin						
White (Reference group)						
Non-white	1.3	0.7 – 2.4	0.4	1.8	0.7 – 4.3	0.2
Household income						
≥ $60,000 (Reference group)						
≤ $29,999	1.8	1.1 – 2.8	0.09	1.3	0.7 – 2.2	0.5
$30,000 - $59,999	1.6	1.1 – 2.4	0.3	1.1	0.7 – 1.8	0.9
Highest level of education						
Post-Secondary Education (Reference group)						
Less than Secondary School Education	1.2	0.8 – 1.8	0.2	1.3	0.8 – 2.0	0.4
Secondary School Graduation - some Post-Secondary Education	0.9	0.7 – 1.5	0.6	1.1	0.6 – 2.0	0.9
Smoking status						

Never Smoked (Reference group)						
Current smoker	1.8	0.7 – 1.9	1.0	1.4	0.8 – 2.6	0.5
Former smoker	1.4	0.9 – 2.0	0.2	1.3	0.8 – 2.1	0.6
Alcohol consumption						
No alcohol (Reference group)						
1 to 3 drinks a month	1.3	0.9 – 1.7	0.3	1.0	0.7 – 1.6	0.5
1 to 7 drinks per week	0.9	0.7 – 1.1	**0.0003***	0.8	0.5 – 1.5	0.4
BMI						
Not obese (Reference group)						
Obese	1.30	1.0 – 1.9	0.09	1.2	0.8 – 1.8	0.3
High blood pressure medication						
No (Reference group)						
Yes	0.7	0.5 – 0.9	**0.03***	0.7	0.4 – 1.1	0.1
High blood cholesterol medication						
No (Reference group)						
Yes	1.0	0.71 – 1.4	0.9	1.3	0.9 – 2.0	0.2
Time since diagnosis of diabetes						
≤ 5 years (Reference group)						
6 – 9 years	0.9	0.6 – 1.6	**0.04***	1.2	0.7 – 2.2	0.9
≥ 10 years	2.3	1.6 – 3.4	**<0.0001***	1.6	0.9 – 2.7	0.1
Cardiovascular complication						

No (Reference group)						
Yes	2.4	1.7 – 3.5	**<0.0001***	2.0	1.4 – 3.1	**0.0006***
Renal complication						
No (Reference group)						
Yes	1.7	1.0 – 2.6	**0.03***	1.3	0.7– 2.2	0.4
Eye complication						
No (Reference group)						
Yes	2.2	1.6 – 3.1	**<0.0001***	1.5	1.0 – 2.2	0.07
Neuropathy						
No (Reference group)						
Yes	0.1	0.1 – 0.2	**<0.0001***	0.1	0.07 – 0.2	**<0.0001***
Percentages in this table are weighted using Statistics Canada survey weights to reflect the Canadian population aged 20 years and older, living in private dwellings. Bold * indicates statistically significant at the $p<0.05$ level. To account for sampling design, bootstrap re-sampling method was used to estimate coefficients of variation and 95% CIs.						

Table 10: Results from Univariate and Multivariate Logistic Regressions Odds ratios (likelihood of complication) generated for individuals with T2DM according to the outlined set of variables – Neuropathy complication

Covariates	Univariate Regression			Multivariate Regression		
	OR	95 % CI	P-value	OR	95 % CI	P-value
Sex						
Female (Reference group)						
Male	1.3	0.9 – 2.1	0.2	1.3	0.8 – 2.3	0.3
Age						
< 65 years (Reference group)						
≥ 65 years	0.9	0.5 – 1.4	0.6	0.6	0.3 – 1.2	0.7
Racial origin						
White (Reference group)						
Non-white	0.4	0.2 – 1.4	0.2	0.1	0.008 – 1.5	0.08
Household income						
≥ $60,000 (Reference group)						
≤ $29,999	2.0	1.0 – 4.0	0.4	1.6	0.7 – 3.6	0.9
$30,000 - $59,999	2.4	1.4 – 4.3	**0.04***	2.1	1.2 – 3.9	**0.03***
Highest level of education						
Post-Secondary Education (Reference group)						
Less than Secondary School Education	0.7	0.4 – 1.3	0.2	0.4	0.2 – 0.8	**0.01***
Secondary School Graduation - some Post-Secondary Education	1.1	0.6 – 1.9	0.4	0.9	0.5 – 1.8	0.9
Smoking status						

Never Smoked (Reference group)						
Current smoker	1.2	0.6 – 2.5	0.9	1.5	0.6 – 3.6	0.8
Former smoker	1.5	0.9 – 2.6	0.2	1.8	1.0 – 3.3	0.07
Alcohol consumption						
No alcohol (Reference group)						
1 to 3 drinks a month	0.6	0.3 – 1.0	0.7	0.9	0.5 – 1.8	0.3
1 to 7 drinks per week	0.4	0.2 – 0.7	**0.002***	0.6	0.3 – 1.2	0.4
BMI						
Not obese (Reference group)						
Obese	1.5	0.9 – 2.5	0.08	1.4	0.8 – 2.4	0.44
High blood pressure medication						
No (Reference group)						
Yes	0.8	0.5 – 1.4	0.5	1.4	0.8 – 2.5	0.52
High Blood cholesterol medication						
No (Reference group)						
Yes	0.8	0.4 – 1.4	0.5	1.2	0.7 – 2.3	0.5
Time since diagnosis of diabetes						
$\leq$ 5 years (Reference group)						
6 – 9 years	1.2	0.5 – 2.7	0.4	1.0	1.0 -3.8	0.5
$\geq$ 10 years	2.5	1.3 – 4.8	**0.001***	1.9	1.1 – 3.8	**0.01***
Cardiovascular complication						

No (Reference group)						
Yes	2.4	1.4 – 4.2	**0.001***	1.2	0.7 – 2.1	0.7
Renal complication						
No (Reference group)						
Yes	2.0	1.1 – 3.8	**0.03***	1.6	0.8 – 3.1	0.3
Foot/Leg complication						
No (Reference group)						
Yes	8.8	5.4 – 14.5	**<0.0001***	7.0	4.1 – 11.8	**<0.0001***
Eye complication						
No (Reference group)						
Yes	2.0	1.2 – 3.2	**0.005***	2.0	1.1 – 3.7	**0.006***

Percentages in this table are weighted using Statistics Canada survey weights to reflect the Canadian population aged 20 years and older, living in private dwellings. Bold * indicates statistically significant at the $p<0.05$ level. To account for sampling design, bootstrap re-sampling method was used to estimate coefficients of variation and 95% CIs.

REFERENCES

[1] Canadian Diabetes Association. Living with type 2 diabetes. Available at: https://www.diabetes.ca/diabetes-and-you/living-with-type-2-diabetes. Accessed January 7 2016.
[2] Canadian Diabetes Association. https://www.diabetes.ca/getmedia/5941b1c2-8b03-45bf-8db0-e18b969d9aa6/diabetes-charter-backgrounder-ontario-english.pdf.aspx Accessed: July 14 2016.
[3] Benjamin SM, Valdez R, Geiss LS, Rolka DB, Narayan KMV. Estimated number of adults with prediabetes in the U.S. in 2000: Opportunities for prevention.
Diabetes Care. 2003;26(3):645-649.
[4] Knowler WC, Barrett-Connor E, Fowler SE et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393-403.
[5] Tuomilehto J. Nonpharmacologic therapy and exercise in the prevention of type 2 diabetes. Diabetes Care. 2009;32(Suppl 2):S189-S193.
[6] Diabetes in Canada: Facts and figures from a public health perspective. Public Health Agency of Canada. 2011; 1-123.
[7] Canadian Diabetes Association. https://www.diabetes.ca/getmedia/5941b1c2-8b03-45bf-8db0-e18b969d9aa6/diabetes-charter-backgrounder-ontario-english.pdf.aspx Accessed: July 14 2016.
[8] Informetrica Limited. Economic Cost of Diabetes in Canada: An Overview. Toronto, ON: Canadian Diabetes Association; 2009.
[9] Diabète Québec. Diabetes: Canada at the Tipping Point, Charting a New Path. Toronto, ON: Canadian
[10] Brownlee, M. Biochemistry and molecular cell biology of diabetic complications. Nature. 414. 13 December 2001.
[11] World Health Organization. Diabetes facts. Available at: http://www.who.int/mediacentre/factsheets/fs312/en/ Accessed January 7 2016
[12] Idem. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. Am J Cardiol 1995;75:
894-903.
[13] UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703-13.
[14] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352:837-53.
[15] Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383-93.
[16] Garcia MJ, McNamara PM, Gordon T, Kannel WB. Morbidity and mortality in diabetics in the Framingham population. Sixteen year followup study. Diabetes 1974;23:105-11.
[17] Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in non diabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998;339(4):229-234.
[18] Public Health Agency of Canada. Unpublished analysis using 2008/09 data from the Canadian Chronic Disease Surveillance System (Public Health Agency of Canada); 2011.
[19] Simpson SH, Corabian P, Jacobs P, Johnson JA. The cost of major comorbidity in people with diabetes mellitus. CMAJ. 2003;168(13):1661-1667.
[20] Public Health Agency of Canada. Unpublished analysis using 2008/09 data from the Canadian Chronic Disease Surveillance System (Public Health Agency of Canada). 2011.
[21] Geiss LS, Herman WH, Smith PJ. Mortality in non-insulin-dependent diabetes. In: Harris MI, Cowie CC, Stern MP, et al, eds. Diabetes in America. 2nd ed. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995:233–257. NIH publication 95-1468.

[22] Harding S. Extracts from "concise clinical evidence". Diabetic retinopathy. BMJ. 2003 May 10;326(7397):1023-5.
[23] Watkins PJ. Retinopathy. BMJ. 2003 Apr 26;326(7395):924-6.
[24] Gregg EW, Albright AL. The public health response to diabetes – Two steps forward, one step back. JAMA. 2009;301(15):1596-1598.
[25] Morgan CL, Currie CJ, Stott NCH, Smithers M, Butler CC,Peters JR. The prevalence of multiple diabetes-related complications. Diabet Med 2000; 17: 146–51.
[26] Klein R, Klein BEK, Moss SE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: an update. Aust N Z J Ophthalmol 1990; 18: 19–22.
[27] Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, Chen SJ, Dekker JM, Fletcher A, Grauslund J, Haffner S, Hamman RF, Ikram MK, Kayama T, Klein BE, Klein R, Krishnaiah S, Mayurasakorn K, O'Hare JP, Orchard TJ, Porta M, Rema M, Roy MS, Sharma T, Shaw J, Taylor H, Tielsch JM, Varma R, Wang JJ, Wang N, West S, Xu L, Yasuda M, Zhang X, Mitchell P, Wong TY; Meta-Analysis for Eye Disease (META-EYE) Study Group.Diabetes Care. Global prevalence and major risk factors of diabetic retinopathy. 2012 Mar;35(3):556-64. doi: 10.2337/dc11-1909. Epub 2012 Feb 1.
[28] Buhrmann R, Hodge W, Beardmore J, Baker G et al. Foundations for a Canadian vision health strategy: Towards preventing avoidable blindness and promoting vision health. Toronto; ON: National Coalition for Vision Health; 2007. http://www.
visionhealth.ca/projects/documents/Foundations-For- A-Canadian-Vision-Health-Strategy.pdf. Accessed April 16 2016.
[29] Canadian Diabetes Association. Nerve damage. Available at: http://www.diabetes.ca/diabetes-and-you/complications/nerve-damage-diabetic-peripheral-neuropathy Accessed January 13 2016.
[30] Boyko EJ, Ahroni JH, Cohen V, Nelson KM, Heagerty PJ. Prediction of diabetic foot ulcer occurrence using commonly available clinical information: the Seattle Diabetic Foot Study. Diabetes Care. 2006 Jun;29(6):1202-7.
[31] Bartus CL, Margolis DJ. Reducing the incidence of foot ulceration and amputation in diabetes. Curr Diab Rep. 2004 Dec;4(6):413-8.
[32] Canilli SD, Davis KL, Kan HJ, Lucero MA, Rousculp MD. Prevalence and the associated burden of illness of symptoms of diabetic peripheral neuropathy and diabetic retinopathy. J Diabetes Complications. 2007 Sep-Oct;21(5):306-14.
[33] Gregg EW, Gu Q, Williams D, de Rekeneire N, Cheng YJ, Geiss L, Engelgau M. Prevalence of lower extremity diseases associated with normal glucose levels, impaired fasting glucose, and diabetes among U.S. adults aged 40 or older. Diabetes Res Clin Pract. 2007 Sep;77(3):485-8. Epub 2007 Feb 15.
[34] Maser RE, Steenkiste AR, Dorman JS, Nielsen VK, Bass EB, Manjoo Q, Diabetic retinopathyash AL, Becker DJ, Kuller LH, Greene DA, et al. Epidemiological correlates of diabetic neuropathy. Report from Pittsburgh Epidemiology of Diabetes Complications Study.
Diabetes. 1989 Nov;38(11):1456-61.
[35] The Diabetes Control and Complications Trial Research Group. Factors in development of diabetic neuropathy. Baseline analysis of neuropathy in feasibility phase of Diabetes Control and Complications Trial (DCCT). Diabetes 1988;
37: 476–81.
[36] Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Davignon DR, Smith DG. A prospective study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study. Diabetes Care. 1999 Jul;22(7):1036-42.
[37] Boulton AJM. The diabetic foot: from art to science. Diabetologia 2004; 47: 1343–1353.
[38] van Schie CH. A review of the biomechanics of the diabetic foot. Int J Low Extrem Wounds. 2005 Sep;4(3):160-70.
[39] van Houtum WH. Amputations and ulceration; pitfalls in assessing incidence. Diabetes Metab Res 2008; 24
[40] Margolis DJ, Malay DS, Hoffstad OJ, Leonard CE, MaCurdy T, López de Nava K, Tan Y, Molina T, Siegel KL. Prevalence of diabetes, diabetic foot ulcer, and lower extremity amputation among Medicare beneficiaries, 2006 to 2008: Data Points #1.
SourceData Points Publication Series [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011. 2011 Feb 17.
[41] Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA 2005; 293: 217–228.

[42] Public Health Agency of Canada August 2011; using 2008/09 data from the Canadian Chronic Disease Surveillance System (Public Health Agency of Canada)
[43] Collins AJ, Foley RN, Herzog C, et al. Excerpts from the US Renal Data System 2009 Annual Data Report. Am J Kidney Dis 2010;55:S1-S420.
[44] Bakris GL, Molitch M. Microalbuminuria as a risk predictor in diabetes: the continuing saga. Diabetes Care. 2014;37(3):867-75.
[45] National Kidney Foundation. KDOQI Clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis. 2012;60:850-886.
[46] Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T: Diabetic renal: diagnosis, prevention, and treatment. Diabetes Care 28:164–176, 2005
[47] Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR: Development and progression of renal in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int 63:225–232, 2003
[48] Canadian Institute for Health Information. Canadian organ replacement register annual report: Treatment of end-stage organ failure in Canada, 2000 to
2009. Ottawa, ON: Canadian Institute for Health Information; 2011.
[49] Public Health Agency of Canada (2011); adapted from Canadian Institute for Health Information. Canadian Organ Replacement Register Annual Report: Treatment of End-Stage Organ Failure in Canada, 2000 to 2009. 2011. Ottawa.
[50] Gregg EW, Li Y, Wang J, Burrows NR, Ali MK, Rolka D, Williams DE, Geiss L. Changes in diabetes-related complications in the United States, 1990-2010.
N Engl J Med. 2014 Apr 17;370(16):1514-23.
[51] Booth GL, Hux JE, Fang J, Chan BT. Time trends and geographic disparities in acute complications of diabetes in Ontario, Canada. Diabetes Care. 2005 May;28(5):1045-50.
[52] Kennon B, Leese GP, Cochrane L, Colhoun H, Wild S, Stang D, Sattar N, Pearson D, Lindsay RS, Morris AD, Livingstone S, Young M, McKnight J, Cunningham S. Reduced incidence of lower-extremity amputations in people with diabetes in Scotland: a nationwide study. Diabetes Care. 2012 Dec;35(12):2588-90. doi: 10.2337/dc12-0511. Epub 2012 Sep 25.
[53] Vamos EP, Bottle A, Edmonds ME, Valabhji J, Majeed A, Millett C., Changes in the incidence of lower extremity amputations in individuals with and without diabetes in England between 2004 and 2008. Diabetes Care. 2010 Dec;33(12):2592-7. doi: 10.2337/dc10-0989. Epub 2010 Sep 10.
[54] Gregg EW, Albright AL. The public health response to diabetes – Two steps forward, one step back. JAMA. 2009;301(15):1596-1598
[55] Shaw JE, Sicree RA & Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010;87:4–14.
[56] Brown K, Nevitte A, Szeto B, Nandi A1. Growing social inequality in the prevalence of type 2 diabetes in Canada, 2004-2012. Can J Public Health. 2015 Mar 12;106(3):e132-9. doi: 10.17269/cjph.106.4769.
[57] Baillot A, Pelletier C, Dunbar P, Geiss L, Johnson JA, Leiter LA, Langlois MF. Profile of adults with type 2 diabetes and uptake of clinical care best practices: results from the 2011 Survey on Living with Chronic Diseases in Canada - Diabetes component.
Diabetes Res Clin Pract. 2014 Jan;103(1):11-9. doi: 10.1016/j.diabres.2013.11.022. Epub 2013 Dec 4.
[58] Hwang J, Rudnisky C, Bowen S, Johnson JA. Socioeconomic factors associated with visual impairment and ophthalmic care utilization in patients with type II diabetes.Can J Ophthalmol. 2015 Apr;50(2):119-26. doi: 10.1016/j.jcjo.2014.11.014.
[59] Ng E, Vanderloo SE, Geiss L, Johnson JA. Concordance between self-report and a survey-based algorithm for classification of type 1 and type 2 diabetes using the 2011 population-based Survey on Living with Chronic Diseases in Canada (SLCDC)-Diabetes component. Can J Diabetes. 2013 Aug;37(4):249-53. doi: 10.1016/j.jcjd.2013.05.007. Epub 2013 Aug 2.
[60] Agborsangaya CB, Gee ME, Johnson ST, Dunbar P, Langlois MF, Leiter LA, Pelletier C, Johnson JA. Determinants of lifestyle behavior in type 2 diabetes: results of the 2011 cross-sectional survey on living with chronic diseases in Canada. BMC Public Health. 2013 May 7;13:451. doi: 10.1186/1471-2458-13-451.
[61] Bird Y, Lemstra M, Rogers M, Moraros J. The relationship between socioeconomic status/income and prevalence of diabetes and associated conditions: A cross-sectional population-based study in Saskatchewan, Canada.Int J Equity Health. 2015 Oct 12;14(1):93

[62] Wirta OR, Pasternack AI, Oksa HH, Mustonen JT, Koivula TA, Helin HJ, Lähde YE. Occurrence of late specific complications in type II (non-insulin-dependent) diabetes mellitus. J Diabetes Complications. 1995 Jul-Sep;9(3):177-85.
[63] Nittala MG, Keane PA, Zhang K, Sadda SR. Risk factors for proliferative diabetic retinopathy in a Latino American population. Retina. 2014 Aug;34(8):1594-9. doi: 10.1097/IAE.0000000000000117
[64] Olafsdottir E, Andersson DK, Dedorsson I, Stefánsson E. The prevalence of retinopathy in subjects with and without type 2 diabetes mellitus. Acta Ophthalmol. 2014 Mar;92(2):133-7. doi: 10.1111/aos.12095. Epub 2013 Mar 4.
[65] Okudaira M, Yokoyama H, Otani T, Uchigata Y, Iwamoto Y. Slightly elevated blood pressure as well as poor metabolic control are risk factors for the progression of retinopathy in early-onset Japanese Type 2 diabetes. J Diabetes Complications. 2000 Sep-Oct;14(5):281-7.
[66] Song SH, Gray TA. Early-onset type 2 diabetes: high risk for premature diabetic retinopathy. Diabetes Res Clin Pract. 2011 Nov;94(2):207-11. doi: 10.1016/j.diabres.2011.07.030. Epub 2011 Aug 19.
[67] Raman R, Vaitheeswaran K, Vinita K, Sharma T. Is prevalence of retinopathy related to the age of onset of diabetes? Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Report No. 5. Ophthalmic Res. 2011;45(1):36-41. doi: 10.1159/000314720. Epub 2010 Aug 11.
[68] Saif A, Karawya S, Abdelhamid A.Blood pressure is a risk factor for progression of diabetic retinopathy in normotensive patients with type 2 diabetes: correlation with carotid intima-media thickness. Endocr Regul. 2014 Oct;48(4):189-94.
[69] Teitelbaum BA, Roberts DK, Ecklund Winters J, Castells DD, Alexander CC. Blood pressure control in an African American sample with diabetes mellitus in an urban eye clinic. Optometry. 2005 Nov;76(11):653-6.
[70] Rahman S, Nawaz R, Khan GJ, Aamir AH. Frequency of diabetic retinopathy in hypertensive diabetic patients in a tertiary care hospital of Peshawar, Pakistan.
J Ayub Med Coll Abbottabad. 2011 Apr-Jun;23(2):133-5.
[71] Matthews DR, Stratton IM, Aldington SJ, Holman RR, Kohner EM; UK Prospective Diabetes Study Group. Risks of progression of retinopathy and vision loss related to tight blood pressure control in type 2 diabetes mellitus: UKPDS 69. Arch Ophthalmol. 2004 Nov;122(11):1631-40.
[72] Leske MC, Wu SY, Hennis A, Hyman L, Nemesure B, Yang L, Schachat AP; Barbados Eye Study Group. Hyperglycemia, blood pressure, and the 9-year incidence of diabetic retinopathy: the Barbados Eye Studies. Ophthalmology. 2005 May;112(5):799-805.
[73] Macky TA, Khater N, Al-Zamil MA, El Fishawy H, Soliman MM. Epidemiology of diabetic retinopathy in Egypt: a hospital-based study. Ophthalmic Res. 2011;45(2):73-8. doi: 10.1159/000314876. Epub 2010 Aug 12.
[74] Yoshida Y, Hagura R, Hara Y, Sugasawa G, Akanuma Y. Risk factors for the development of diabetic retinopathy in Japanese type 2 diabetic patients. Diabetes Res Clin Pract. 2001 Mar;51(3):195-203.
[75] Lim S, Kim KM, Kim MJ, Woo SJ, Choi SH, Park KS, Jang HC, Meigs JB, Wexler DJ. The association of maximum body weight on the development of type 2 diabetes and microvascular complications: MAXWEL study. PLoS One. 2013 Dec 4;8(12):e80525. doi: 10.1371/journal.pone.0080525. eCollection 2013.
[76] Kaštelan S, Tomić M, Gverović Antunica A, Ljubić S, Salopek Rabatić J, Karabatić M. Body mass index: a risk factor for retinopathy in type 2 diabetic patients. Mediators Inflamm. 2013;2013:436329
[77] Dirani M, Xie J, Fenwick E, Benarous R, Rees G, Wong TY, Lamoureux EL. Are obesity and anthropometry risk factors for diabetic retinopathy? The diabetes management project. Invest Ophthalmol Vis Sci. 2011 Jun 22;52(7):4416-21. doi: 10.1167/iovs.11-7208.
[78] Burgess PI, Allain TJ, García-Fiñana M, Beare NA, Msukwa G, Harding SP. High prevalence in Malawi of sight-threatening retinopathy and visual impairment caused by diabetes: identification of population-specific targets for intervention. Diabet Med. 2014 Dec;31(12):1643-50. doi: 10.1111/dme.12492. Epub 2014 Jun 7.
[79] Chiang PP, Lamoureux EL, Cheung CY, Sabanayagam C, Wong W, Tai ES, Lee J, Wong TY. Racial differences in the prevalence of diabetes but not diabetic retinopathy in a multi-ethnic Asian population. Invest Ophthalmol Vis Sci. 2011 Sep 29;52(10):7586-92. doi: 10.1167/iovs.11-7698.
[80] Ross SA, McKenna A, Mozejko S, Fick GH. Diabetic retinopathy in native and nonnative Canadians. Exp Diabetes Res. 2007;2007:76271. doi: 10.1155/2007/76271.

[81] Gao X, Gauderman WJ, Marjoram P, Torres M, Chen YD, Taylor KD, Rotter JI, Varma R. Native American ancestry is associated with severe diabetic retinopathy in Latinos. Invest Ophthalmol Vis Sci. 2014 Aug 21;55(9):6041-5. doi: 10.1167/iovs.14-15044.
[82] Kajiwara on IM, Kohner EM, Aldington SJ, Turner RC, Holman RR, Manley SE, Matthews DR. UKPDS 50: risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis. Diabetologia. 2001 Feb;44(2):156-63.
[83] Brown AF, Ettner SL, Piette J, et al. Socioeconomic position and health among persons with diabetes mellitus :aconceptual frame- work and review of the literature. Epidemiol Rev. 2004;26:63-77.
[84] Moss SE, Klein R, Klein BE. Factors associated with having eye examinations in persons with diabetes. Arch FamMed. 1995;4: 529-534.
[85] Scanlon PH, Carter SC, Foy C, Husband RF, Abbas J, Bachmann MO. Diabetic retinopathy and socioeconomic deprivation in Gloucestershire. J Med Screen. 2008;15(3):118-21.
[86] Perruccio AV, Badley EM, Trope GE. A Canadian population-based study of vision problems: assessing the significance of socioeconomic status. Can J Ophthalmol. 2010 Oct;45(5):477-83
[87] Wise LA, Rosenberg L, Radin RG, Mattox C, Yang EB, Palmer JR, Seddon JM. A prospective study of diabetes, lifestyle factors, and glaucoma among African-American women. Ann Epidemiol. 2011 Jun;21(6):430-9. doi: 10.1016/j.annepidem.2011.03.006.
[88] Rossing K, Christensen PK, Hovind P, Tarnow L, Rossing P, Parving HH. Progression of renal in type 2 diabetic patients. Kidney Int. 2004 Oct;66(4):1596-605.
[89] Pang C, Jia L, Jiang S, Liu W, Hou X, Zuo Y, Gu H, Bao Y, Wu Q, Xiang K, Gao X, Jia W. Determination of diabetic retinopathy prevalence and associated risk factors in Chinese diabetic and pre-diabetic subjects: Shanghai diabetic complications study. Diabetes Metab Res Rev. 2012 Mar;28(3):276-83. doi: 10.1002/dmrr.1307.
[90] Parving HH, Lewis JB, Ravid M, Remuzzi G, Hunsicker LG; DEMAND investigators. Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: a global perspective. Kidney Int. 2006 Jun;69(11):2057-63.
[91] Araki S, Nishio Y, Araki A, Umegaki H, Sakurai T, Iimuro S, Ohashi Y, Uzu T, Maegawa H, Kashiwagi A, Ito H; Japanese Elderly Intervention Trial Research Group. Factors associated with progression of diabetic renal in Japanese elderly patients with type 2 diabetes: sub-analysis of the Japanese Elderly Diabetes Intervention Trial. Geriatr Gerontol Int. 2012 Apr;12 Suppl 1:127-33.
[92] Hypertension in Diabetes Study (HDS): I. Prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardiovascular and diabetic complications. J Hypertens. 1993 Mar;11(3):309-17.
[93] Okada H, Fukui M, Tanaka M, Inada S, Mineoka Y, Nakanishi N, Senmaru T, Sakabe K, Ushigome E, Asano M, Yamazaki M, Hasegawa G, Nakamura N. Visit-to-visit variability in systolic blood pressure is correlated with diabetic renal and atherosclerosis in patients with type 2 diabetes. Atherosclerosis. 2012 Jan;220(1):155-9.
[94] Lewis EJ, Hunsicker LG, Bain RP, Rohde RD, The Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med 1993;329:1456–1462.
[95] Brenner BM, Cooper ME, de Zeeuw D, et al., RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861–869.
[96] Lewis EJ, Hunsicker LG, Clarke WR, et al., Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851–860.
[97] Yang CW, Park JT, Kim YS, Kim YL, Lee YS, Oh YS, Kang SW. Prevalence of diabetic nephropathy in primary care type 2 diabetic patients with hypertension: data from the Korean Epidemiology Study on Hypertension III (KEY III study). Nephrol Dial Transplant. 2011 Oct;26(10):3249-55. Epub 2011 Mar 3.
[98] Young BA, Maynard C, Boyko EJ: Racial differences in diabetic renal, cardiovascular disease, and mortality in a national population of veterans. Diabetes Care 26: 2392–2399, 2003.
[99] Karter AJ, Ferrara A, Liu JY, Moffet HH, Ackerson LM, Selby JV: Ethnic disparities in diabetic complications in an insured population. JAMA 287: 2519–2527, 2002
[100] Pugh JA, Medina RA, Cornell JC, Basu S: NIDDM is the major cause of diabetic end-stage renal disease. More evidence from a tri-ethnic community. Diabetes 44: 1375–1380, 1995

[101] Young BA, Pugh JA, Maynard C, Reiber G. Diabetes and renal disease in veterans. Diabetes Care 27[Suppl 2]: B45–B49, 2004
[102] Kohler KA, McClellan WM, Ziemer DC, Kleinbaum DG, Boring JR. Risk factors for microalbuminuria in black americans with newly diagnosed type 2 diabetes. Am J Kidney Dis. 2000 Nov;36(5):903-13.
[103] Young BA, Katon WJ, Von Korff M, Simon GE, Lin EH, Ciechanowski PS, Bush T, Oliver M, Ludman EJ, Boyko EJ. Racial and ethnic differences in microalbuminuria prevalence in a diabetes population: the pathways study. J Am Soc Nephrol. 2005 Jan;16(1):219-28. Epub 2004 Nov 24.
[104] Chaturvedi N, Stephenson JM, Fuller JH. The relationship between smoking and microvascular complications in the EURODIAB IDDM Complications Study.
Diabetes Care. 1995 Jun;18(6):785-92.
[105] Gambaro G, Bax G, Fusaro M, Normanno M, Manani SM, Zanella M, Dangelo A, Fedele D, Favaro S. Cigarette smoking is a risk factor for nephropathy and its progression in type 2 diabetes mellitus. Diabetes Nutr Metab. 2001 Dec;14(6):337-42.
[106] Ikeda Y, Suehiro T, Takamatsu K, Yamashita H, Tamura T, Hashimoto K. Effect of smoking on the prevalence of albuminuria in Japanese men with non-insulin-dependent diabetes mellitus. Diabetes Res Clin Pract. 1997 Apr;36(1):57-61.
[107] Dunkler D, Kohl M, Heinze G, Teo KK, Rosengren A, Pogue J, Gao P, Gerstein H, Yusuf S, Oberbauer R, Mann JF; ONTARGET Investigators. Modifiable lifestyle and social factors affect chronic kidney disease in high-risk individuals with type 2 diabetes mellitus. Kidney Int. 2015 Apr;87(4):784-91.)
[108] Sazlina SG, Mastura I, Ahmad Z, Cheong AT, Adam BM, Jamaiyah H, Lee PY, Syed-Alwi SA, Chew BH, Sriwahyu T. Control of glycemia and other cardiovascular disease risk factors in older adults with type 2 diabetes mellitus: data from the Adult Diabetes Control and Management. Geriatr Gerontol Int. 2014 Jan;14(1):130-7. doi: 10.1111/ggi.12070. Epub 2013 Apr 15.
[109] Schulze MB, Shai I, Manson JE, Li T, Rifai N, Jiang R, Hu FB. Joint role of non-HDL cholesterol and glycated haemoglobin in predicting future coronary heart disease events among women with type 2 diabetes. Diabetologia. 2004 Dec;47(12):2129-36. Epub 2004 Dec 15.
[110] Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. HOT Study Group. Lancet 1998;351:1755-62
[111] Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation. 1983;67:968–977.
[112] Cho E, Manson JE, Stampfer MJ, Solomon CG, Colditz GA, Speizer FE, Willett WC, Hu FB. A prospective study of obesity and risk of coronary heart disease among diabetic women. Diabetes Care. 2002 Jul;25(7):1142-8.
[113] Rabkin SW, Mathewson FA, Hsu PH. Relation of body weight to development of ischemic heart disease in a cohort of young North American men after a 26 year observation period: the Manitoba Study. Am J Cardiol. 1977;39:452–458.
[114] Sowers JR. Diabetes mellitus and cardiovascular disease in women. Arch Intern Med. 1998;158:617–621.
[115] Garcia MJ, McNamara PM, Gordon T, Kannel WB. Morbidity and mortality in diabetes in the Framingham population: sixteen-year follow-up study. Diabetes. 1974;23:105–111.
[116] McFarlane SI, Castro J, Kaur J, Shin JJ, Kelling D Jr, Farag A, Simon N, El-Atat F, Sacerdote A, Basta E, Flack J, Bakris G, Sowers JR. Control of blood pressure and other cardiovascular risk factors at different practice settings: outcomes of care provided to diabetic women compared to men. J Clin Hypertens (Greenwich). 2005 Feb;7(2):73-80.
[117] Strom Williams JL, Lynch CP, Winchester R, Thomas L, Keith B, Egede LE. Gender differences in composite control of cardiovascular risk factors among patients with type 2 diabetes. Diabetes Technol Ther. 2014 Jul;16(7):421-7. doi: 10.1089/dia.2013.0329. Epub 2014 Apr 15.
[118] Homko CJ., Zamora L., Santamore WP., Kashem A., McConnell T., Bove AA.: Gender differences in cardiovascular risk factors and risk perception among individuals with diabetes. Diabetes Educ2010;36:483–488
[119] Sekerija M., Poljicanin T., Erjavec K., Liberati-Cizmek A., Prasek M., Metelko Z.: Gender differences in the control of cardiovascular risk factors in patients with type 2 diabetes—a cross sectional study. Intern Med 2012;51:161–166

[120] Vimalananda VG, Biggs ML, Rosenzweig JL, Carnethon MR, Meigs JB, Thacker EL, Siscovick DS, Mukamal KJ. The influence of sex on cardiovascular outcomes associated with diabetes among older black and white adults. J Diabetes Complications. 2014 May-Jun;28(3):316-22. doi: 10.1016/j.jdiacomp.2013.12.004. Epub 2013 Dec 26.
[121] Ma JM, Xu JQ, Anderson RN, Jemal A. Widening Educational Disparities in Premature Death Rates in Twenty Six States in the United States, 1993–2007. PLoS One. 2012;7:e41560.
[122] Saydah SH, Imperatore G, Beckles GL. Socioeconomic Status and Mortality: The Contribution of Health Care Access and Psychological Distress Among United States Adults With Diagnosed Diabetes. Diabetes Care. 2012
[123] McEwen LN, Kim C, Karter AJ, Haan MN, Ghosh D, Lantz PM, et al. Risk factors for mortality among patients with diabetes: the Translating Research Into Action for Diabetes (TRIAD) Study. Diabetes Care. 2007;30:1736–1741.
[124] Wang Y, Katzmarzyk PT, Horswell R, Zhao W, Li W, Johnson J, Ryan DH, Hu G. Racial disparities in cardiovascular risk factor control in an underinsured population with Type 2 diabetes. Diabet Med. 2014 Oct;31(10):1230-6.
[125] Larrañaga I, Arteagoitia JM, Rodiabetic retinopathyiguez JL, Gonzalez F, Esnaola S, Piniés JA; Sentinel Practice Network of the Basque Country. Socio-economic inequalities in the prevalence of Type 2 diabetes, cardiovascular risk factors and chronic diabetic complications in the Basque Country, Spain. Diabet Med. 2005 Aug;22(8):1047-53.
[126] Ford ES, DeStefano F. Risk factors for mortality from all causes and from coronary heart disease among persons with diabetes. Findings from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. Am J Epidemiol. 1991;133(12):1220–1230.
[127] Morrish NJ, Stevens LK, Fuller JH, Jarrett RJ, Keen H. Risk factors for macrovascular disease in diabetes mellitus: the London follow-up to the WHO Multinational Study of Vascular Disease in Diabetics. Diabetologia. 1991;34(8):590–594.
[128] Wan EY, Fong DY, Fung CS, Lam CL. Incidence and predictors for cardiovascular disease in Chinese patients with type 2 diabetes mellitus - a population-based retrospective cohort study. J Diabetes Complications. 2016 Apr;30(3):444-50.
[129] Nilsson PM, Cederholm J, Eeg-Olofsson K, et al. Smoking as an independent risk factor for myocardial infarction or stroke in type 2 diabetes: a report from the Swedish National Diabetes Register. Eur J Cardiovasc Prev Rehabil. 2009;16(4):506–512.
[130] Al-Delaimy WK, Manson JE, Solomon CG, et al. Smoking and risk of coronary heart disease among women with type 2 diabetes mellitus. Arch Intern Med. 2002;162(3):273–279.
[131] Turner RC, Millns H, Neil HA, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). BMJ. 1998;316(7134):823–828.
[132] Qin R, Chen T, Lou Q, Yu D. Excess risk of mortality and cardiovascular events associated with smoking among patients with diabetes: meta-analysis of observational prospective studies. Int J Cardiol. 2013;167(2):342–350.
[133] Karim R, Buchanan TA, Hodis HN, Li Y, Mack WJ. The association of smoking and subclinical atherosclerosis in Type 2 diabetes: modification by duration of diabetes. Diabet Med. 2005 Jan;22(1):81-7.
[134] Khuwaja AK, Rafique G, White F, Azam SI. Macrovascular complications and their associated factors among persons with type 2 diabetes in Karachi, Pakistan--a multi-center study. J Pak Med Assoc. 2004 Feb;54(2):60-6.
[135] O'Keefe JH, Bybee KA, Lavie CJ. Alcohol and cardiovascular health: the razor-sharp double-edged sword. J Am Coll Cardiol 2007;50:1009–1014
[136] van de Wiel A. Diabetes mellitus and alcohol. Diabetes Metab Res Rev 2004;20:263–267
[137] Solomon CG, Hu FB, Stampfer MJ, et al. Moderate alcohol consumption and risk of coronary heart disease among women with type 2 diabetes mellitus. Circulation 2000;102:494–499
[138] Tanasescu M, Hu FB, Willett WC, Stampfer MJ, Rimm EB. Alcohol consumption and risk of coronary heart disease among men with type 2 diabetes mellitus. J Am Coll Cardiol 2001;38:1836
[139] Ajani UA, Gaziano JM, Lotufo PA, et al. Alcohol consumption and risk of coronary heart disease by diabetes status. Circulation 2000;102:500–505

[140] Blomster JI, Zoungas S, Chalmers J, Li Q, Chow CK, Woodward M, Mancia G, Poulter N, Williams B, Harrap S, Neal B, Patel A, Hillis GS. The relationship between alcohol consumption and vascular complications and mortality in individuals with type 2 diabetes. Diabetes Care. 2014;37(5):1353-9.
[141] Djoussé L, Biggs ML, Mukamal KJ, Siscovick DS. Alcohol consumption and type 2 diabetes among older adults: the Cardiovascular Health Study. Obesity (Silver Spring). 2007 Jul;15(7):1758-65.
[142] Marques-Vidal P, Montaye M, Arveiler D, et al. Alcohol consumption and cardiovascular disease: differential effects in France and Northern Ireland. The PRIME study. Eur J Cardiovasc Prev Rehabil. 2004;11:336–343..
[143] Makita S, Onoda T, Ohsawa M, et al. Influence of mild-to-moderate alcohol consumption on cardiovascular diseases in men from the general population. Atherosclerosis. 2012;224:222–227
[144] Aubert CE, Michel PL, Gillery P, Jaisson S, Fonfrede M, Morel F, Hartemann A, Bourron O. Association of peripheral neuropathy with circulating advanced glycation end products, soluble receptor for advanced glycation end products and other risk factors in patients with type 2 diabetes. Diabetes Metab Res Rev. 2014 Nov;30(8):679-85. doi: 10.1002/dmrr.2529.
[145] Börü UT, Alp R, Sargin H, Koçer A, Sargin M, Lüleci A, Yayla A. Prevalence of peripheral neuropathy in type 2 diabetic patients attending a diabetes center in Turkey. Endocr J. 2004 Dec;51(6):563-7.
[146] Booya F, Bandarian F, Larijani B, Pajouhi M, Nooraei M, Lotfi J. Potential risk factors for diabetic neuropathy: a case control study. BMC Neurol. 2005 Dec 10;5:24.
[147] Dyck PJ, Davies JL, Wilson DM, Service FJ, Melton LJ 3rd, O'Brien PC. Risk factors for severity of diabetic polyneuropathy: intensive longitudinal assessment of the Rochester Diabetic Neuropathy Study cohort. Diabetes Care. 1999 Sep;22(9):1479-86.
[148] McClean MT, Andiabetic retinopathyews WJ, McElnay JC. Characteristics associated with neuropathy and/or retinopathy in a hospital outpatient diabetic clinic. Pharm World Sci. 2005 Jun;27(3):154-8.
[149] Bansal D, Gudala K, Muthyala H, Esam HP, Nayakallu R, Bhansali A. Prevalence and risk factors of development of peripheral diabetic neuropathy in type 2 diabetes mellitus in a tertiary care setting. J Diabetes Investig. 2014 Nov;5(6):714-21. doi: 10.1111/jdi.12223. Epub 2014 Apr 2
[150] Raman R, Gupta A, Krishna S, Kulothungan V, Sharma T. Prevalence and risk factors for diabetic microvascular complications in newly diagnosed type II diabetes mellitus. Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study (SN-DR, report 27). J Diabetes Complications. 2012 Mar-Apr;26(2):123-8.
[151] Kostev K, Jockwig A, Hallwachs A, Rathmann W. Prevalence and risk factors of neuropathy in newly diagnosed type 2 diabetes in primary care practices: a retrospective database analysis in Germany and U.K. Prim Care Diabetes. 2014 Oct;8(3):250-5. doi: 10.1016/j.pcd.2014.01.011. Epub 2014 Feb 14.
[152] Liu F, Bao Y, Hu R, Zhang X, Li H, Zhu D, Li Y, Yan L, Li Y, Lu J, Li Q, Zhao Z, Ji Q, Jia W. Screening and prevalence of peripheral neuropathy in type 2 diabetic outpatients: a randomized multicentre survey in 12 city hospitals of China. Diabetes Metab Res Rev. 2010 Sep;26(6):481-9. doi: 10.1002/dmrr.1107.
[153] Chyun DA, Melkus GD, Katten DM, Price WJ, Davey JA, Grey N, Heller G, Wackers FJ. The association of psychological factors, physical activity, neuropathy, and quality of life in type 2 diabetes. Biol Res Nurs. 2006 Apr;7(4):279-88.
[154] Adler AI, Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Smith DG. Risk factors for diabetic peripheral sensory neuropathy. Results of the Seattle Prospective Diabetic Foot Study. Diabetes Care. 1997 Jul;20(7):1162-7.
[155] Kles KA, Vinik AI. Pathophysiology and treatment of diabetic peripheral neuropathy: the case for diabetic neurovascular function as an essential component. Curr Diabetes Rev. 2006 May;2(2):131-45.
[156] Clair C, Cohen MJ, Eichler F, Selby KJ, Rigotti NA. The Effect of Cigarette Smoking on Diabetic Peripheral Neuropathy: A Systematic Review and Meta-Analysis. J Gen Intern Med. 2015 Aug;30(8):1193-203. doi: 10.1007/s11606-015-3354-y. Epub 2015 May 7.
[157] Swade TF, Emanuele NV. Alcohol & diabetes. Compr Ther. 1997 Feb;23(2):135-40.
[158] Baba M, Davis WA, Davis TM. A longitudinal study of foot ulceration and its risk factors in community-based patients with type 2 diabetes: the Fremantle Diabetes Study. Diabetes Res Clin Pract. 2014 Oct;106(1):42-9. doi: 10.1016/j.diabres.2014.07.021. Epub 2014 Jul 26.
[159] Bortoletto MS, de Andiabetic retinopathyade SM, Matsuo T, Haddad Mdo C, González AD, Silva AM. Risk factors for foot ulcers--a cross sectional survey from a primary care setting in Brazil. Prim Care Diabetes. 2014 Apr;8(1):71-6. doi: 10.1016/j.pcd.2013.04.003. Epub 2013 Apr 30.

[160] Dos Santos VP, da Silveira DR, Caffaro RA. Risk factors for primary major amputation in diabetic patients. Sao Paulo Med J. 2006 Mar 2;124(2):66-70.
[161] Miyajima S, Shirai A, Yamamoto S, Okada N, Matsushita T. Risk factors for major limb amputations in diabetic foot gangrene patients. Diabetes Res Clin Pract. 2006 Mar;71(3):272-9. Epub 2005 Aug 31.
[162] Parisi MC, Moura Neto A, Menezes FH, Gomes MB et al. Baseline characteristics and risk factors for ulcer, amputation and severe neuropathy in diabetic foot at risk: the BRAZUPA study. Diabetol Metab Syndiabetic retinopathy. 2016 Mar 17;8:25. doi: 10.1186/s13098-016-0126-8. eCollection 2016.
[163] Zubair M, Malik A, Ahmad J.Incidence, risk factors for amputation among patients with diabetic foot ulcer in a North Indian tertiary care hospital. Foot (Edinb). 2012 Mar;22(1):24-30. doi: 10.1016/j.foot.2011.09.003. Epub 2011 Nov 12.
[164] Lai YJ, Hu HY, Lin CH, Lee ST, Kuo SC, Chou P. Incidence and risk factors of lower extremity amputations in people with type 2 diabetes in Taiwan, 2001-2010.
[165] Tang ZQ, Chen HL, Zhao FF. Gender differences of lower extremity amputation risk in patients with diabetic foot: a meta-analysis. Int J Low Extrem Wounds. 2014 Sep;13(3):197-204. doi: 10.1177/1534734614545872. Epub 2014 Aug 8.
[166] Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Predictive factors for diabetic foot ulceration: a systematic review. Diabetes Metab Res Rev. 2012 Oct;28(7):574-600. doi: 10.1002/dmrr.2319.
[167] Amin L, Shah BR, Bierman AS, Lipscombe LL, Wu CF, Feig DS, Booth GL. Gender differences in the impact of poverty on health: disparities in risk of diabetes-related amputation. Diabet Med. 2014 Nov;31(11):1410-7. doi: 10.1111/dme.12507. Epub 2014 Jun 7.
[168] Abbott CA, Garrow AP, Carrington AL, et al. Foot ulcer risk is lower in South-Asian and African-Caribbean compared with European diabetic patients in the UK. Diabetes Care 2005; 28: 1869–1875.
[169] Ferguson TS, Tulloch-Reid MK, Younger NO, Wright-Pascoe RA, Boyne MS, McFarlane SR, Francis DK, Wilks RJ. Diabetic foot complications among patients attending a specialist diabetes clinic in Jamaica: prevalence and associated factors. West Indian Med J. 2013 Mar;62(3):216-23.
[170] Monami M, Vivarelli M, Desideri CM, et al. Pulse pressure and prediction of incident foot ulcers in type 2 diabetes. Diabetes Care 2009; 32: 897–899.
[171] Margolis DJ, Hofstad O, Feldman HI. Association between renal failure and foot ulcer or lower extremity amputation in patients with diabetes. Diabetes Care 2008; 31(7): 1331–1336.
[172] Yusof NM, Rahman JA, Zulkifly AH, Che-Ahmad A, Khalid KA, Sulong AF, Vijayasingham N. Predictors of major lower limb amputation among type II diabetic patients admitted for diabetic foot problems. Singapore Med J. 2015 Nov;56(11):626-31. doi: 10.11622/smedj.2015172
[173] Faglia E, Favales F, Morabito A. New ulceration, new major amputation, and survival rates in diabetic subjects hospitalized for foot ulceration from 1990 to 1993. Diabetes Care 2001; 24: 78–83.
[174] Iversen MM, Mifdtjell K, Ostbye T, et al. History of and factors associated with diabetic foot ulcers in Norway: the Nord-Trondelag Health Study. Scand J Public Health 2008; 36(1): 62–68
[175] Litzelman DK, Marriott DJ, Vinicor F. Independent physiological predictors of foot lesions in patients with NIDDM. Diabetes Care 1997b; 20(8): 1273–1278.
[176] Crawford F, Inkster M, Kleijnen J, Fahey T. Predicting foot ulcers in patients with diabetes: a systematic review and meta-analysis. QJM. 2007 Feb;100(2):65-86.
[177] Sohn MW, Budiman-Mak E, Lee TA, Oh E, Stuck RM. Significant J-shaped association between body mass index (BMI) and diabetic foot ulcers. Diabetes Metab Res Rev. 2011; 27:402–409.
[178] Sohn MW, Budiman-Mak E, Oh EH, Park MS, Stuck RM, Stone NJ, Pearce WB. Obesity paradox in amputation risk among nonelderly diabetic men. Obesity (Silver Spring). 2012 Feb;20(2):460-2. doi: 10.1038/oby.2011.301. Epub 2011 Oct 13.
[179] Kästenbauer T, Sauseng S, Sokol G, Auinger M, Irsigler K. A prospective study of predictors for foot ulceration in type 2 diabetes. J Am Podiatr Med Assoc. 2001 Jul-Aug;91(7):343-50.
[180] Bresäter LE, Welin L, Romanus B. Foot pathology and risk factors for diabetic foot disease in elderly men. Diabetes Res Clin Pract. 1996 Apr;32(1-2):103-9.
[181] Altenburg N, Joraschky P, Barthel A, Bittner A, Pöhlmann K, Rietzsch H, Fischer S, Mennicken G, Koehler C, Bornstein SR. Alcohol consumption and other psycho-social conditions as important factors in the development of diabetic foot ulcers. Diabet Med. 2011 Feb;28(2):168-74.
[182] Kloos C, Hagen F, Lindloh C, Braun A, et al. Cognitive function is not associated with recurrent foot ulcers in patients with diabetes and neuropathy. Diabetes Care 2010; 32: 894–896.

[183] Hoban C, Sareen J, Henriksen CA, Kuzyk L, Embil JM, Trepman E. Mental health issues associated with foot complications of diabetes mellitus. Foot Ankle Surg. 2015 Mar;21(1):49-55. Epub 2014 Sep 22.
[184] Lavery LA, Armsrong DG, Vela SA, Quebedeaux TL, Fleischli JG. Practical criteria for screening patients at high risk for diabetic foot ulceration. Arch Intern Med 1998; 158: 157–162.
[185] de Sonnaville JJ, Colly LP, Wijkel D, Heine RJ. The prevalence and determinants of foot ulceration in type II diabetic patients in a primary health care setting. Diabetes Res Clin Pract. 1997 Mar;35(2-3):149-56.
[186] Guerrero-Romero F, Rodiabetic retinopathyíguez-Morán M. Relationship of microalbuminuria with the diabetic foot ulcers in type II diabetes. J Diabetes Complications. 1998 Jul-Aug;12(4):193-6.
[187] Boyko EJ, Ahroni JH, Cohen V, et al.Prediction of diabetic foot ulcer occurrence
using commonly available clinical information: the Seattle Diabetic Foot Study. Diabetes Care 2006; 29(6):1202–1207.
[188] Monteiro-Soares M, Dinis-Ribeiro M. External validation and optimisation of a model predicting foot ulcers in patients with diabetes. Diabetologia 2010; 53: 1525–1533.
[189] Suico JG, Marriott DJ, Vinicor F, Litzelman DK. Behaviors predicting foot lesions in patients with non-insulin dependent diabetes mellitus. J Gen Int Med 1998; 13(7): 482–484
[190] Armstrong DG, Holtz-Neiderer K, Wendel C, Mohler MJ, Kimbriel HR, Lavery LA. Skin temperature monitoring reduces the risk for diabetic foot ulceration in high-risk patients. Am J Med 2007; 120: 1042–1046.
[191] Ferguson HJ, Nightingale P, Pathak R, Jayatunga AP. The influence of socio-economic deprivation on rates of major lower limb amputation secondary to peripheral arterial disease. Eur J Vasc Endovasc Surg. 2010 Jul;40(1):76-80. doi: 10.1016/j.ejvs.2010.03.008. Epub 2010 Apr 1.
[192] Holman N, Young RJ, Jeffcoate WJ. Variation in the recorded incidence of amputation of the lower limb in England. Diabetologia. 2012 Jul;55(7):1919-25. doi: 10.1007/s00125-012-2468-6. Epub 2012 Mar 8.
[193] Bergin SM, Brand CA, Colman PG, Campbell DA. The impact of socio-economic disadvantage on rates of hospital separations for diabetes-related foot disease in Victoria, Australia. J Foot Ankle Res. 2011 Jun 20;4:17. doi: 10.1186/1757-1146-4-17.
[194] Leese GP, Feng Z, Leese RM, Dibben C, Emslie-Smith A. Impact of health-care accessibility and social deprivation on diabetes related foot disease. Diabet Med. 2013 Apr;30(4):484-90. doi: 10.1111/dme.12108.
[195] Altenburg N, Joraschky P, Barthel A, Bittner A, Pöhlmann K, Rietzsch H, Fischer S, Mennicken G, Koehler C, Bornstein SR. Alcohol consumption and other psycho-social conditions as important factors in the development of diabetic foot ulcers. Diabet Med. 2011 Feb;28(2):168-74.
[196] El-Asrar AM, Al-Rubeaan KA, Al-Amro SA, Moharram OA, Kangave D.
Retinopathy as a predictor of other diabetic complications. Int Ophthalmol. 2001;24(1):1-11.
[197] Mottl AK, Pajewski N, Fonseca V, Ismail-Beigi F, Chew E, Ambrosius WT, Greven C, Schubart U, Buse J. The degree of retinopathy is equally predictive for renal and macrovascular outcomes in the ACCORD Trial. J Diabetes Complications. 2014 Nov-Dec;28(6):874-9. doi: 10.1016/j.jdiacomp.2014.07.001. Epub 2014 Jul 12.
[198] Manaviat MR, Afkhami M, Shoja MR. Retinopathy and microalbuminuria in type II diabetic patients. BMC Ophthalmol. 2004 Jul 1;4:9.
[199] Stack AG, Bloembergen WE. A cross-sectional study of the prevalence and clinical correlates of congestive heart failure among incident US dialysis patients. Am J Kidney Dis. 2001; 38: 992–1000.
[200] Stack AG, Bloembergen WE. Prevalence and clinical correlates of coronary artery disease among new dialysis patients in the United States: A cross-sectional study. J Am Soc Nephrol. 2001; 12: 1516–23.
[201] Foley RN, Culleton BF, Parfrey PS et al. Cardiac disease in diabetic end-stage renal disease. Diabetologia. 1997; 40: 1307–12.
[202] Wang AY. Cardiovascular risk in diabetic end-stage renal disease patients.
J Diabetes. 2011 Jun;3(2):119-31.
[203] Chang YT, Wu JL, Hsu CC, Wang JD, Sung JM. Diabetes and end-stage renal disease synergistically contribute to increased incidence of cardiovascular events: a nationwide follow-up study during 1998-2009. Diabetes Care. 2014;37(1):277-85.
[204] Lai YJ, Hu HY, Lin CH, Lee ST, Kuo SC, Chou P. Incidence and risk factors of lower extremity amputations in people with type 2 diabetes in Taiwan, 2001-2010.

[205] Verrone Quilici MT, Del Fiol Fde S, Franzin Vieira AE, Toledo MI. Risk Factors for Foot Amputation in Patients Hospitalized for Diabetic Foot Infection. J Diabetes Res. 2016;2016:8931508. doi: 10.1155/2016/8931508. Epub 2016 Feb 22.
[206] Abolfotouh MA, Alfaifi SA, Al-Gannas AS. Risk factors of diabetic foot in central Saudi Arabia. Saudi Med J. 2011 Jul;32(7):708-13.
[207] Hu Y, Bakhotmah BA, Alzahrani OH, Wang D, Hu FB, Alzahrani HA. Predictors of diabetes foot complications among patients with diabetes in Saudi Arabia. Diabetes Res Clin Pract. 2014 Nov;106(2):286-94. doi: 10.1016/j.diabres.2014.07.016. Epub 2014 Aug 7.
[208] Aydin K, Isildak M, Karakaya J, Gürlek A. Change in amputation predictors in diabetic foot disease: effect of multidisciplinary approach. Endocrine. 2010 Aug;38(1):87-92. doi: 10.1007/s12020-010-9355-z. Epub 2010 Jun 20.
[209] Peters EJ, Armstrong DG, Lavery LA. Risk factors for recurrent diabetic foot ulcers. Diabetes Care 2007; 30(8): 2077–2079.
[210] Survey on Living with Chronic Diseases in Canada - User Guide – 2011. Ottawa, ON: Statistics Canada; 2011. http://www23.statcan.gc.ca/imdb-bmdi/document/5160_D4_T1_V2-eng.htm
[211] Canadian Community Health Survey. User Guide for the Public use Microdata File 2010. Ottawa, ON: Statistics Canada; 2010. and Statistics Canada Website Canadian Community Health Survey - Annual Component (CCHS) http://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&Id=164081 Accessed on January 17 2016.
[212] Statistics Act. 1970-71-72, c. 15, s. 1. Government of Canada http://laws-lois.justice.gc.ca/eng/acts/S-19/
[213] Rust KF, Rao JN. Stat Methods Med Res. 1996 Sep;5(3):283-310. Variance estimation for complex surveys using replication techniques.
[214] Sterne Jonathan AC, White Ian R, Carlin John B, Spratt Michael, Royston Patrick, Kenward Michael G et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls BMJ 2009; 338 :b2393
[215] Canadian Community Health Survey (CCHS) Annual Component, 2009-2010 Common Content Derived Variable (DV) Specifications. http://www23.statcan.gc.ca/imdb-bmdi/pub/document/3226_D71_T9_V1-eng.pdf Accessed: May 14 2016
[216] Allison, P. D. Logistic Regression Using the SAS System: Theory and Application, Cary, NC: SAS Institute Inc. 1999
[217] Liberman A. How much more likely? The implication of odds ratios for probabilities. American Journal of Evaluation Vol 26, No. 2, 253-266 June 2005.
[218] Introduction to SAS. UCLA: Statistical Consulting Group. From http://www.ats.ucla.edu/stat/sas/notes2/ Accessed: July 14 2016.

[219] Hosmer DW, Lemeshow S. Applied Logistic Regression. New York: Wiley; 2000.
[220] Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. Source Code for Biology and Medicine. 2008;3:17. doi:10.1186/1751-0473-3-17.
[221] Furnival, G. M. and Wilson, R. W. (1974), Regression by Leaps and Bounds Technometrics, 16, 499–511.
[222] SAS/STAT(R) 9.2 User's Guide, Second Edition, www.support.sas.com Accessed: June 17 2016.
[223] Allison P. Measures of Fit for Logistic Regression. Statistical Horizons LCC and University of Pennsylvania. https://support.sas.com/resources/papers/proceedings14/1485-2014.pdf Accessed July 27 2017.
[224] Canadian Diabetes Association Web site. The Prevalence of Diabetes. http://www.diabetes.ca/about-diabetes/types-of-diabetes Accessed June 19 2016.
[225] Jurado J, Ybarra J, Solanas P, Caula J, Gich I, Pou JM, Romeo JH. Prevalence of cardiovascular disease and risk factors in a type 2 diabetic population of the North Catalonia diabetes study.J Am Acad Nurse Pract. 2009 Mar;21(3):140-8.
[226] Sprafka JM, Burke Gl, Folsom AR, McGovern PG, Hahn LP.Trends in prevalence of diabetes mellitus in patients with myocardial infarction and effect of diabetes on survival: the Minnesota Heart Survey. Diabetes Care. 1991;14537- 543

[227] Shah AD, Langenberg C, Rapsomaniki E, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1·9 million people. The Lancet Diabetes & Endocrinology. 2015;3(2):105-113.
[228] Statistics Canada Web site. Summary of changes over time – Canadian Community Health Survey - Annual Component (CCHS). http://www.statcan.gc.ca/eng/concepts/index . Accessed June 17 2016.
[229]Donaldson, S.I. & Grant-Vallone, E.J. Journal of Business and Psychology (2002) 17: 204.
[230] Herbert J, Clemow L, Pbert L, et al. Social Desirability Bias in Dietary Self-Report May Compromise the Validity of Dietary Intake Measures. Int J Epidemiol 1995; 24 (2): 389-398.
[231] Shields, M, Connor, Gorber, S Janssen I, Tremblay, M. Bias in self-reported estimates of obesity in Canadian health surveys: An update on correction equations for adults. Health reports / Statistics Canada, Canadian Centre for Health Information = Rapports sur la santé / Statistique Canada, Centre canadien d'information sur la santé. 22. 35-45. 10.1016/S1499-2671(11)52226-9.
[232] Ording AG, Sørensen HT. Concepts of comorbidities, multiple morbidities, complications, and their clinical epidemiologic analogs. Clinical Epidemiology. 2013;5:199-203. doi:10.2147/CLEP.S45305.
[233] Hosmer, Jr., D. W., Lemeshow, S. and Sturdivant, R. X. (2013)Applied Logistic Regression, Third Edition, John Wiley & Sons, Inc., Hoboken, NJ, USA. doi: 10.1002/9781118548387.ch10