DIABETES-RELATED COMPLICATIONS IN CANADA; PREVALENCE OF COMPLICATIONS, THEIR ASSOCIATION WITH DETERMINANTS AND FUTURE POTENTIAL COST-EFFECTIVENESS OF PHARMACY-BASED INTERVENTION

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ABSTRACT

In the 21st century, diabetes mellitus (DM) emerged as one of the most prevalent non-communicable diseases and poses a major problem for every health system in the world. Its global prevalence has more than doubled in the last three decades. As diabetes has become more prevalent, the health programming designed to target diabetes patients has remained inadequate and only heightened the burden. This heightened burden has manifested itself in the increased risk of complications common among patients with diabetes. These complications vary widely, and are typically categorized as either micro-vascular or macro-vascular depending upon the size of blood vessels that are compromised. Due to the havoc that can ensue by either type of complication, the increased risk of diabetes-related complications has been recognized as a serious threat to population health.

To gain insight into the threat posed and how it will likely present in the Canadian population, patient's data from the diabetes component of Survey on Living with Chronic Diseases in Canada (SLCDC-DM-2011) was analyzed. This analysis revealed that among Canadian diabetes patients, 80.26 percent reported having at least one type of diabetes-related complication. The most frequently reported complications were high blood pressure (54.65%), cataracts (29.52%), poor circulation (21.68%), and heart disease (19.4%). This analysis also revealed the predictive role of socio-economic factors associated with diabetes-related complications in Canada. Being married, having a higher income, and having a higher level of education were protective against most complications. In contrast, low levels of physical activity and high levels of HbA1C were important risk factors for many diabetes–related complications. Identifying common diabetes-related complications, protective factors and risk factors is useful for combating the threat posed by diabetes-related complications.

To combat this threat in practice, healthcare professionals will play a significant role in the control and management of diabetes and its complications. Diabetes is a chronic disease that needs long-term treatment, and thus multi-disciplinary teams will be required. Increasingly, pharmacists are being determined as having a prominent position on these teams due to their accessibility to the Canadian population, and their expanding scope of practice. This profession has contributed positively to the long-term prognosis of patients with diabetes, in part, by aiding in the control and management of the

disease. This aid oftentimes comes in the form of pharmacy-based interventions. Pharmacy-based interventions include a variety of services aimed at enabling patients with diabetes to have better control of their condition.

I conducted a systematic review and meta-analysis to evaluate the effects of pharmacy-based interventions on clinical and non-clinical outcomes associated with diabetes-related complications. Four main databases were searched. Based upon my meta-analysis, the standardized absolute mean difference in reduction of HbA1C (%) from baseline to the time of the last follow-up significantly favoured patients in the pharmacy-based intervention group compared to those receiving care as usual (0.96%; 95% CI 0.71: 1.22, P<0.001). In addition, the standardized absolute mean difference in reduction of BMI unit (kg/m2) was 0.61 (95% CI 0.20: 1.03, P<0.001) in favour of the pharmacy-based intervention group. Both of these results demonstrate the positive effect pharmacy-based interventions can have on clinical outcomes. However, there is a dearth of evidence about the effects of pharmacy-based interventions on non-clinical outcomes, including health care utilization and quality of life. Therefore, it was not possible to evaluate non-clinical outcomes associated with diabetes-related complications in the same way.

Each year healthcare expenses incurred from diabetes and its complications total more than US$827 billion. This health care cost is significant, and is only expected to grow alongside diabetes' increasing prevalence. In light of this, a debate over the comparative effectiveness of the different strategies used to manage diabetes and its complications has been sparked. The development of analytic models that can be used as tools in determining budget prioritization and cost-effectiveness of interventions is beginning to be prioritized. To conduct an economic evaluation of these interventions, simulation models are necessary. These models estimate health outcomes, such as life years saved or Quality Adjusted Life Years (QALYs) gained, and account for the costs and health consequences associated with diabetes, its complications and risk factors.

I developed a hybrid (agent-based/system dynamic) individual-level micro simulation model using 2,931 patient records from the SLCDC-2011. This model extrapolated the effects of pharmacy-based interventions on health outcomes, costs and health-related quality of life (HRQOL) over time through time-varying risk factors of diabetes-related complications. The treatment effects of pharmacy-based interventions were modeled as reductions in HbA1c levels, BMI, systolic blood pressure and LDL, all of which can affect the risk of progressing long-term complications. The annual costs of diabetes-related

complications, as well as, costs associated with pharmacy-based intervention from a societal prospective, were also considered. Using this data, the micro-simulation model was able to estimate the expected number of major health events (heart failure, stroke, amputation, and blindness), QALYs over a patient's lifetime, the patient's economic burden on the health care system, and the extent to which pharmacy-based intervention can modify these outcomes. Deterministic and probabilistic sensitivity analyses were conducted to evaluate the uncertainty around the results.

Based on the results from my micro-simulation model, a pharmacy–based intervention could avert a total of 155 deaths associated with complications, 19 heart failures, 159 strokes, 24 amputations and 29 blindness events in a population of 2,931 patients over the next 50 years. In addition, the intervention could add 1,246 additional life-years (0.42 per patients) and 953 additional quality-adjusted life-years (0.32 per patients). The intervention would also be cost-effective in comparison to usual care, as indicated by the incremental discounted cost per QALY gained ($3928). Overall, these results suggest that an integrated pharmacy-based intervention could be a cost-effective strategy to control and manage diabetes-related complications in Canada. This is promising and has important public health implications that should not be ignored.

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LIST OF ABBREVIATIONS

ABM	Agent based model
ADDQOL	Diabetes-Dependent Quality of Life
ATFIB	atrial fibrillation
BMI	Body Mass Index
CADTH	Canadian Agency for Drugs and Technologies in Health
CCHS	Canadian Community Health Survey
CDA	Canadian Diabetes Association
CFPNET	Canadian foundation for pharmacy
CGM	Continuous Glucose Monitoring
DALYs	Disability Adjusted life years
DM	Diabetes Mellitus
DMEP	drug management education programs
EMTREE	Excerpta Medica Tree
HbA1c	Glycosolated Hemoglobin
HDL	high density lipoprotein cholesterol
HRQOL	health-related quality of life
ICER	Incremental Cost-Effectiveness Ratio
LDL	Low-density lipoprotein
MESH	Medical Subject Headings
MICLAB	presences of micro- or macro-albuminuria
NMB	net monetary benefit
ODEM	Ontario Diabetes Economic Model
PICOS	Population, Intervention, comparison, outcome and study design
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis

PVD	PERIPHERAL VASCULAR DISEASE
QOL	QUALITY OF LIFE
QALYs	QUALITY ADJUSTED LIFE YEARS
RTCs	RANDOMIZE CONTROL TRIAL STUDIES
REB	RESEARCH ETHICS BOARD
SBP	SYSTOLIC BLOOD PRESSURE
SME	STANDARDIZED MEAN DIFFERENCE
SLCDC	SURVEY ON LIVING WITH CHRONIC DISEASES
T1D	TYPE 1 DIABETES
UKPDS	UNITED KINGDOM PROSPECTIVE DIABETES STUDY
US	UNITED STATES
WBC	WHITE BLOOD CELL COUNT
WHO	WORLD HEALTH ORGANIZATION

CHAPTER 1-INTRODUCTION

1.1. Overview and Rationale

1.1.1. Determinants of Diabetes Complications and its Burden

Diabetes mellitus (DM) is one of the most prevalent non-communicable diseases worldwide, and poses a major threat to the 21st century health care system (1, 2). Perhaps most threatening about DM is its unprecedented growth: In less than three decades, the number of adults diagnosed with diabetes has doubled (2). This translates to over 400 million people living with diabetes today, and an estimated 642 million who will live with diabetes by 2040(3). According to the Canadian Diabetes Association, 29 percent of Canadians are currently living with pre-diabetes or diabetes, and if current trends continue, this percentage will increase to 33 percent by 2025(4). In 2016 alone, the number of new cases of diabetes among Canadians was 347.8 per 100,000. These 348 Canadians will experience a total of 798.53 Disability Adjusted Life Years (DALYs) amongst themselves (5). This epidemiologic trend raises significant concern, especially when compared to the global incidence trend of diabetes (Figure 1).

Unsurprisingly, typical complications that develop alongside diabetes are more common among patients with diabetes than in the general population. Almost 89 percent or 9 out of 10 patients with diabetes report adverse health effects that are related to their condition (2). These complications vary widely, and are typically categorized as either micro-vascular or macro-vascular. Conditions that damage the body's smaller blood vessels, like retinopathy, neuropathy, and nephropathy, are categorized as micro-vascular (6-8). In contrast, conditions that result from damage to the body's larger blood vessels, like cardiovascular disease, are categorized as macro-vascular (6-8). Irrespective of the complications' categorization, patients with diabetes place a significant burden on the health care system. This burden is a result of both direct and indirect strains placed on healthcare services, family dynamics, and government (3).

In light of these strains and their effects on the Canadian health care system, a number of risk factors of diabetes-related complications have been recognized. For example, hemoglobin A1C (HbA1C) is universally accepted as a measurement of long-term blood glucose control. In clinical trials, lower levels of HbA1C reduced the likelihood of developing microvascular complications over the short-term, and

macrovascular complications over the long-term (9, 10). Importantly, some of these risk factors can be modified through lifestyle interventions. One such risk factor is obesity; an increased body mass index (BMI) is associated with the development of type 2 diabetes, diabetes-related complications or both (11, 12). Smoking has also been linked to the development of diabetes-related complications; Cigarette smoking increases the risk of some of the most serious complications, including cardiovascular disease, kidney disease, and neuropathy (13). Metabolic variables such as total cholesterol, triglycerides levels, and FPG have also been found to be positively associated with diabetes-related complications (15, 16). Similarly, age of onset and duration also share positive relationships with the development of diabetes-related complications (16-18). Identification of these risk factors means that prevention and management strategies can be developed to minimize their impact (14). Despite the ability to design prevention and management strategies that are specific to these factors, there is a dearth of literature examining the relationships between Canadian patient characteristics and diabetes-related complications.

1.1.2. Pharmacy Practice and Diabetes Care

When diabetes is diagnosed at an advanced stage, the burden that results is heightened. Unfortunately, diabetes management interventions are rarely promoted and there are limited interventions available that empower diabetes patients to effectively control and manage their condition. Again, this only heightens the resulting burden. However, if preventive strategies were introduced at the pre-diabetes or early diabetes change, this burden could be reduced (19). For example, half (50%) of type 2 diabetes cases could be delayed or prevented altogether if those patients followed a healthy eating plan and increased their physical activity (20). Further, when multi-factorial interventions are adopted, the number of diabetes-related complications and deaths resulting from diabetes are reduced by nearly 60 percent (20). In this vein, there are some community programs available. However, it is evident that more could be done to prevent or, at the very least, delay diabetes-related complications through the implementation of comprehensive prevention strategies.

Much of the literature to date suggests that comprehensive prevention strategies positively impact metabolic outcomes through the control and management of major risk factors, and, ultimately, reduce diabetes-related complications among various patient groups. Examples of these strategies include self-monitoring and self-management at the individual level, and pharmacy-based programming at the

community level. Self-monitoring and self-management have been shown to be associated with clinically important benefits in persons with diabetes (21-23), such as improved QOL, sustained weight loss, and increased cardiovascular fitness (23). Further, a random-effect modelling estimated the pooled mean difference in HbA1C between patients undertaking self-care management and patients in a control group to be 0.36% (0.20-0.50) (15). Thus, there is evidence pointing to the positive impact of comprehensive prevention strategies in the control and management of diabetes, and these strategies must be incorporated into practice.

Incorporation of comprehensive management strategies into practice will require cooperation and collaboration across multi-disciplinary health care teams. Diabetes is a chronic disease, and thus requires treatment over a long-time period. Consequently, an interdisciplinary team of healthcare professionals is required and each professional plays a pivotal role in contributing to patients' diabetes control and management (24). Increasingly, pharmacists are being recognized because of their accessibility to patients and expanding scope of practice. Only by ensuring that pharmacists can positively contribute to the long-term prognosis of diabetes patients will improvements in the control and management of diabetes is realized (25).

Pharmacy-based interventions include a wide range of services, all with the common aim of giving diabetes patients greater control and management over their disease. Common examples of pharmacy-based interventions include: consultations with pharmacists; patient education about self-monitoring and self-management techniques; preventive programming that emphasizes lifestyle modifications; reminders about annual physical examinations; assistance with adherence to medication; patient education about the correct use of insulin, anti-hyperglycemic medications and oral hypoglycemic agents; and, programming that increases patients' awareness about effective diabetes management (25-29). Recent reviews of pharmacy-based interventions have demonstrated that they have a positive impact on clinical outcomes (25-29). These findings are promising, especially because they suggest that pharmacy-based intervention may reduce diabetes-related complications, morbidity and mortality (25-29). However, before pharmacy-based interventions should be adopted as the best practice by health professionals, the clinical and non-clinical effectiveness of these interventions in the control and management of diabetes-related complications must be examined.

1.1.3. Economic Evaluation of Pharmacy-Based Interventions

Diabetes-related complications lead to premature death, reduce individuals' quality of life, and place a heavy economic burden on the whole of society to the tune of US$548 billion each year (3, 30-33). This cost is not limited to the health care system, but also includes indirect costs incurred by loss of productivity resulting from disability and/or premature death (34). Unfortunately, the prognosis in Canada is not much better. According to the Canadian Diabetes Cost Model, 2.7 million people have diabetes in 2010. This number is projected to increase by 1.5 million over this decade, and will reach 4.2 million by 2020 (2). In addition, the economic burden of diabetes in Canada was an estimated $12.2 billion in 2010, and is forecasted to increase to $16 billion by 2020 (3).

Comparing to the general population, diabetes patients are: twenty times more likely to be admitted to the hospital for an amputation of the lower limb; also twelve times and three times more likely to be admitted to the hospital for end-stage renal disease and cardiovascular disease respectively (14,35). This means that, of the Canadian healthcare dollars being expended on diabetes patients, eighty percent are incurred as a result of diabetes-related complications (36). The increased likelihood of requiring hospitalization may reflect these patients' inability to adhere to treatment plans as prescribed as a result of the high cost of medications, devices, and supplies that are frequently paid for out-of-pocket, for example (37).

Accommodating the increasing demand for accessible and reasonable health care services within budgetary constraints has forced Canada's decision-makers to find new ways to program, implement, and evaluate health services. In light of this, pharmacists are emerging as a potential avenue to improve health outcomes, as well as reducing the economic burden of health care. Although pharmacists' roles are expanding across the country, different approaches taken by provincial and territorial governments mean these roles are nuanced. Nevertheless, pharmacists are providing a larger complement of services targeting minor issues to complicated chronic conditions. This profession is undergoing a transformation, yet the literature describing pharmacists' changing role in the broader healthcare system is not well-articulated. Specifically, attention must be paid to economic analyses, especially because they oftentimes inform policymakers' decisions (38).

Rising health care costs, limitations on available health care resources, and debates over the comparative effectiveness of diabetes management strategies has led to an increased interest in

developing analytic models that can predict cost-effectiveness. These models complement clinical trials, which typically run over the short-term and provide data on intermediate outcomes like HbA1c, SBP, and LDL. This data populates analytic models, and provides a basis for predicting long-term health outcomes, like life-years saved or QALYs gained. The ability to account for costs and health consequences associated with risk factors add to the appeal of using these models to inform health practices and policies (38). Assessing the cost effectiveness of Pharmacy-based interventions will provide evidence for policy-maker about whether expanding these community-based interventions for diabetics' population across Canada is cost-effective or not.

1.2. Goals and objectives of the research

The purpose of this thesis is to examine diabetes-related complications in Canada. The study will address three principal research questions:

1) How prevalent are diabetes-related complications in Canada, and what determinants are associated with them?
2) What is the current state of evidence on the clinical effectiveness of pharmacy-based interventions in the control and management of diabetes?
3) What is the predicted effect of pharmacy-based interventions on reducing diabetes-related complications, especially in terms of their economic burden?

To answer each of these questions, this thesis has been organised into a series of three chapters.

Paper 1, presented in Chapter 2, used patients' data collected in the Survey on Living with Chronic Diseases in Canada (SLCDC) to provide a description of epidemiological trends and characteristics present among Canadian diabetes patients. We also examined the association between diabetes-related complications and select determinants.

Paper 2, presented in Chapter 3, describes the results of our systematic review and meta-analysis that evaluated the effects of pharmacy-based interventions on clinical outcomes associated with diabetes-related complications, and non-clinical outcomes among people with diabetes.

Paper 3, presented in Chapter 4, describe our individual patient micro-simulation model that we developed to estimate the incidence and mortality of four of the most common diabetes-related complications (heart failure, stroke, amputation, and blindness). We used risk equations based on the UK Prospective Diabetes Study (UKPDS). Based on the estimated effect of pharmacy-based interventions on reducing time-varying risk factors for diabetes-related complications, we extrapolated the potential effects of pharmacy-based interventions in relation to cost, health outcomes, and health-related quality of life (HRQoL) over time (Chapter 4).

The paper presented in Chapter 3 has been published in a peer-reviewed journal as "Yaghoubi M, Mansell K, Vatanparastc H, Steeves M, Zeng W, Farag M. Effects of pharmacy-based interventions on the control and management of diabetes in adults: a systematic review and meta-analysis. Can J Diabetes. 2017 Dec; 41(6):628-641. doi: 10.1016/j.jcjd.2017.09.014.". The permissions to include the reformatted paper in this thesis are included in Appendix A-1.

This thesis was deemed to be exempt from ethical review by the University of Saskatchewan Research Ethics Board (REB) based on Article 2.2 of Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans. More details are included in Appendix A-2

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CHAPTER 2-PREVALENCE OF DIABETES-RELATED COMPLICATIONS AND THEIR ASSOCIATION WITH DETERMINANTS IDENTIFIED IN CANADA'S SURVEY ON LIVING WITH CHRONIC DISEASES

This article has been submitted as: "Yaghoubi M, Mansell K, Vatanparast H, Steeves M, Zeng W, Farag M. Prevalence of diabetes-related complications and their association with determinants identified in Canada's Survey on Living with Chronic Diseases – Diabetes Component (SLCDC-DM-2011" for publication in a peer-reviewed journal. My contributions to this manuscript included conceiving and designing the study, running the all statistical analysis, interpreting the findings and manuscript preparation. Dr. Marwa Farag and Dr. Hassan Vatanparast helped in conception and design of the study. All authors helped in the interpretation of findings and in reviewing and editing the manuscript.

Analyzing the current epidemiological trends of diabetes-related complications is very important for public health policy makers in Canada hoping to reduce the burden of these complications. In this chapter, I describe the epidemiological trends and characteristics present among Canadians who have diabetes. I also use a multiple logistic regression to identify the most important risk factors associated with diabetes-related complications in Canada. The results of this chapter have been used to design the study and select input parameters for **chapter 3** and **chapter 4**.

2.1. Background

Globally, the prevalence of diabetes has more than doubled from 1980 to 2014 (from 4.7% to 8.5%) (1). This increased prevalence has also come with an increasingly high burden, which is partially due to inadequate health programming targeted specifically towards patients with diabetes, amongst other factors(2). Correspondingly, patients with diabetes are at an increased risk of experiencing complications related to their diagnosis, and this risk has been recognized as a serious threat to population health (3). These complications are typically categorized as either micro-vascular or macro-vascular complications (4-6).

The financial implications of diabetes-related complications are significant (1)(7). In light of this cost, the association between diabetes-related complications and various patient characteristics has been investigated extensively. Results from the multinational A1chieve study; observational study of 66,726 people with type 2 diabetes in 28 countries across Asia, Africa, Europe and South America; showed that the prevalence of micro-vascular diabetes-related complications was 27.2 percent in 2004, and the prevalence of macro-vascular complications was almost double at 53.3 percent(8). Patients' age, body mass index (BMI), and the duration of diabetes were all strongly positively associated with the development of both types of complications (8). However, patients were at a lower risk of developing micro vascular complications when they had a low level of A1C or glucose in their blood (8). Factors associated with diabetes-related complications in Canada have been examined for some specific complications including; visual impairment, erectile dysfunction, cardiovascular complications, and cognitive impairment (9-12). In addition; Hanley et al (13) evaluated risk factor associated with complications of type 2 diabetes among aboriginal Canadians in the Sandy Lake Diabetes Complications Study.

The aim of this study is to examine the association between diabetes-related complications and select determinants of Canadian patients, to provide a description of epidemiological trends and characteristics present among Canadian diabetes patients.

2.2. Data and methods

Data from the 2011 Survey on Living with Chronic Disease in Canada –Diabetes Component (SLCDC-DM-2011) was used. The SLCDC is a cross-sectional survey that collects the wide range of information about chronic disease in Canadian population. In this survey respondents answered questions about diagnosis of chronic condition, health care utilization and self-monitoring and self-management of their conditions. The SLCDC aimed to provide information on the impact of chronic disease condition on population, as well as how people with chronic disease control their health condition (14).

The inclusion criteria of participants specified that: individuals must be above the age of 20 years; must have self-reported having diabetes on the 2010 Canadian Community Health Survey (CCHS); and, consented to participate in the SLCDC-DM-2011(14).Members of the Canadian Armed Forces, institutionalized individuals, residents of First Nation reserves or Crown Land, and residents of Canada's three territories were excluded (14). To ensure the survey sample was representative of the Canadian population eligible for inclusion, the sample was weighted according to Statistics Canada's instructions (14). With weighting applied, 1,711,743 participants are represented based on 2,931 survey responses.

2.2.1.Dependent variables

In this analysis we have measured the association between diabetes-related complications as dependent variables and select determinants of Canadian patients including: socio-demographic factors, diabetes status, risk factors, and self-monitoring behaviour as independent variables. The SLCDC-DM-2011 asked participants, "Whether (they had) ever had 'specific complication' diagnosed by a health professional?" Sixteen different diabetes-related complications were specified in the above line of questioning. We categorized these sixteen complications into groups to create dependent variables in the three logistic regression models: (1) all diabetes-related complications; (2) micro-vascular complications; and (3) macro-vascular complications. Participants were considered to be a member of group 1 if they reported having had at least one of the sixteen diabetes-related complications specified on the SLCDC-DM-2011. Participants were considered to be a member of group 2 if they reported having had at least one of the following complications: neuropathy, retinopathy, cataracts, glaucoma, kidney failure, foot ulcer, poor circulation in the feet or legs, protein in urine, amputation, and/or blindness. Participants were considered to be a member of group 3 if they reported having had at least one of the following complications: heart disease or stroke.

2.2.2. Independent variables

Based on a thorough review of the literature, independent variables considered to be potential determinants of diabetes-related complications for Canadian patients were selected (8)(9)(10)(15)(16)(17). Each of the selected determinants were classified into one of four categories:(1) socio-demographic factors (sex, age, employment status, marital status, income level, and education); (2) diabetes status (type of diabetes, years with diabetes, injection of insulin);(3) risk factors (BMI, frequency of smoking, physical activity level, level of A1C);and (4) self-monitoring behaviour (frequency of checking blood glucose level).Justification and a detailed description of each independent variable is provided below.

2.2.2.1. Socio-demographic

Much of the literature highlights the importance of socio-demographic factors and their link with the appearance of diabetes-related complications among patients with diabetes. Factors that have been found to be associated with the diabetes-related complications include: an older age of onset (8)(10)(12)(15)(16); a patient's sex (8)(9); being unmarried (9)(15)(17); and a patient's socioeconomic status categorized by their level of education, income, and employment(18)(19). Based on this literature and within the confines of the SLCDC-DM-2011, the socio-demographic factors in this study were defined as follows: age (20-45 years, 45-70 years, and >70 years); sex (male or female); marital status (married, common-law, widowed, separated, divorced, and single); education (less than secondary school, secondary school, some post-secondary school, and post-secondary school); income (less than $50,000 per annum or more than $50,000 per annum); and, employment status (had a job, did not have a job, and unable to work).

2.2.2.2. Diabetes status

Three main sources that cause significant differences in patient health outcomes have been identified. These differences include: whether a patient has a diagnosis of type I or type II diabetes (20); the period of time that a patient has had diabetes,(21); and, the mode of treatments (22)(28).Therefore, in the present study diabetes status was defined in the following ways: diabetes status (type I or type II); years with diabetes (less than 10 years or more than 10 years); and, injection of insulin (yes or no).

2.2.2.3. Risk factors

Individuals are at increased risk of developing diabetes and experiencing diabetes-related complications if they are overweight or obese (15)(23)(24), smoke cigarettes ,engage in low levels of physical

activity,(24) and have a high level blood sugar(25). To quantify these risk factors in the present study, the following variables were used: BMI (range 18.5-25 kg/m2 as normal or and under 18.5 or over 25 kg/m2 as inappropriate); frequency of smoking (daily, occasional, former daily, former occasional, and never); physical activity level (active, moderate, and inactive); and, level of A1C (well, borderline, high, low).

2.2.2.4. Self-monitoring behaviour

When comparing disease-related morbidity and mortality between patients who self-monitor their blood glucose and those who do not, there are mixed results; thus, a self-monitoring variable was included in the present study as follows: frequency of checking blood glucose (per day, per week, per month, per year, and never).

2.2.3. Statistical analysis

Logistic regression models were used and fitted for each one of the three dependent variables. Additionally, sixteen logistic regression models were constructed individually for each diabetes-related complication included on the SLCDC-DM-2011.

Final logistic regression models were fitted by purposeful model selection. A standard contingency table was created for each categorical independent variable to determine if the cell frequency was equal to zero for any of the model outcomes. The association between diabetes-related complications and select determinants was then measured using odds ratios. In addition, the prevalence of each diabetes-related complication was calculated with a 95% confidence internal (Table 2.1).

All statistical analyses were performed using version 14 of STATA (StataCorp LLC, TX). First, bivariable analysis was conducted to test the association between each dependent variable and each independent variable. In this analysis, a significance value of 0.25 was used to: (1) adjust for the multiple comparisons being made and (2) rule out variables that would not contribute meaningfully to the multivariable analysis. Full results of the bivariable analysis are presented in Table 2.2 and Table 2.3.

Second, a multivariable regression analysis was conducted for each of the three grouped dependent variables: all diabetes-related complications, micro-vascular complications, and macro-vascular complications. The multicolinearity and interaction terms of each independent variable were tested and no multicolinearity or interaction terms were found. A p-value<0.05 was used to identify significant associations between the dependent and independent variables in these models. Additionally, the

goodness of fit was assessed using the Hosmer and Lemeshow tests from which it was determined that each model fit the data well. From these tests, the p-value of the all diabetes-related complications model was 0.86, the p-value of the micro-vascular complications model was 0.28, and the p-value for the macro-vascular complications model was 0.99. The Linktest was also used to examine model specifications, and yielded 0.98, 0.76, and 0.67 for each model respectively. These values indicate that there was no specification error in any of the study's models. Lastly, a multivariable regression model was constructed for each individual diabetes-related complication included on the SLCDC-DM-2011 as part of this study's sub-group analysis. All statistical tests mentioned previously were also performed in this sub-group analysis

2.3.Results

With weighting applied, there were a total of 1,711,743 Canadian participants who self-reported having diabetes on the SLCDC-DM-2011. Among them, 1,373,887 or 80.26 percent reported having at least one type of diabetes-related complication. The most commonly reported diabetes related complication was high blood pressure (54.65%, CI: 51.28-58.02). Other common diabetes-related complications included: cataracts (29.52%, CI: 26.71-32.32); poor circulation (21.68%, CI: 19.01-24.36); heart disease (19.40%, CI: 16.9-21.8); protein in the urine (14.65%, CI: 11.66-17.63), and erectile dysfunction (14.60%, CI: 12.42-16.92) (Table 2.1). More broadly, micro-vascular complications (50.93%, CI: 47.58-54.27) were twice as prevalent as macro-vascular complications (23.66%, CI: 20.86-26.47).

Table 2.1. Prevalence of diabetes-related complication in SLCDC-DM-2011

Complication	Type	Prevalence	
Low blood sugar (Hypoglycemia)		2.45% (1.30-3.61)	
Erectile Dysfunction		14.6% (12.42-16.92)	
Problem with Gum (periodontal Disease)		7.54% (5.88-9.20)	
High Blood Pressure		54.65% (51.28-58.02)	
Neuropathy	**Microvascular**	10.2% (8.20-12.29)	50.93% (47.58-54.27)
Diabetic eye disease (retinopathy)	**Microvascular**	6.88% (5.32-8.43)	
Cataract	**Microvascular**	29.52% (26.71-32.32)	
Glaucoma	**Microvascular**	7.13% (5.65-8.60)	
Kidney failure	**Microvascular**	5.09% (3.09-7.08)	
Foot ulcer	**Microvascular**	6.13% (4.22-8.04)	
Poor Circulation	**Microvascular**	21.68% (19.01-24.36)	
Protein in urine (Proteinuria)	**Microvascular**	14.65% (11.66-17.63)	
Amputation	**Microvascular**	0.48% (0.03-0.10)	
Blindness	**Microvascular**	1.83% (0.90-2.74)	
Stroke	**Macrovascular**	7.70% (5.64-9.76)	23.66% (20.86-26.47)
Heart disease	**Macrovascular**	19.4% (16.9-21.8)	

2.3.1.Bivariable analysis

Diabetes-related complications occurred most frequently among patients: aged 45-70 years (47.75%); who were males (46.11%); diagnosed with type II diabetes (64.40%); reporting inappropriately on the BMI index (73.38%), inactive on physical activity index (53.28%); and checking blood glucose levels daily (47.34%) (Table2.2).Bivariable analysis revealed significant associations between all determinants and diabetes-related complications with a few exceptions. In the all diabetes-related complication model,

type of diabetes and sex were not significantly associated with the outcome variable (Table 2.2). In the macro-vascular and micro-vascular complication model, BMI was not significantly associated with the outcome variable (Table 2.3). Results of the bivariable analysis are shown in Table 2.2 and Table 2.3. All predictor variables were included in the multivariable analysis.

Table 2.2. Bivariable analysis and characteristics of patients with diabetes-related complication

Characteristics (%)	No Complication n (%) N=337,856 19.74%	Complication n (%) N=1,373,887 80.26%	Odds Ratio	P-Value
Socioeconomic Factors				
Age				
20-45 Years (10.97)	76105(4.45)	111641(6.52)	1	
45-70 Years (60.27)	214189(12.51)	817431(47.75)	2.60(1.58-4.27)	0.000
70 or more (28.76)	47561(2.78)	444814(25.99)	0.96(0.67-1.39)	0.000
Sex				
Male (57.29)	191386(11.18)	789285(46.11)	1	
Female (42.71)	146470(8.56)	584602(34.15)	0.96(0.67-1.39)	0.86
Marital Status				
Married (62.70)	217567(12.71)	855694(62.7)	1	
Common Law (6)	39064(2.28)	102636(6)	0.41(0.17-0.99)	0.04
Widowed (11.69)	19045(1.11)	200067(11.6)	2.41(1.33-4.37)	0.004
Separated (2.46)	5266(0.31)	42152(2.46)	1.78(0.74-4.25)	0.19

Divorced (7.41)	23102(1.35)	126825(7.41)	1.14(0.68-1.89)	0.61
Single (9.73)	33809(1.98)	166597(9.73)	0.99 (0.61-1.61)	0.99
Employment				
Had a Job (36.8)	180583(10.5)	449265(26.2)	1	
Did not have a job (38.7)	117701(6.88)	545165(31.85)	1.86(1.23-2.79)	0.003
Unable to work (8.7)	13190(0.77)	130021(7.60)	3.96(1.79-8.74)	0.001
Income				
Less than $50,000(47.2)	130597(7.63)	678106(39.61)	1	
More than $50,000 (52.7)	207258(12.11)	659780(40.56)	0.64(0.45-0.9266)	0.01
Education				
Less than secondary (14.26)	28981(1.69)	215170(12.5)	1	
Secondary (11.50)	42627(2.49)	154281(9.01)	0.48(0.26-0.91)	0.25
Some-post (6.06)	24250(1.42)	870029(50.8)	0.44 (0.18-1.07)	0.07
Postgraduate (64.23)	229364(13.4)	55001(3.2)	0.51 (0.30-0.85)	0.01
Diabetes Status Factors				
Type of Diabetes				
Type 1 (8.22)	27253(1.59)	113520(6.63)	1	
Type 2 (79.75)	262170(15.3)	1102995(64.4)	1.01(0.58-1.37)	0.97
Duration of Diabetes				

Less than 10 Years (53.58)	239776(14.01)	677397(39.5)	1	
More than 10 Years (46.42)	98078(5.73)	696489(40.6)	2.51(1.80-3.50)	0.01
Insulin				
No (70.40)	267859(15.6)	937240(54.75)	1	
Yes (29.54)	69996(4.09)	435677(25.45)	1.77(1.18-2.67)	0.006
Risk Factors				
BMI Class				
Normal (21.62)	92301(5.47)	272847(16.16)	1	
Inappropriate (78.37)	238313(14.11)	1323596(73.38)	0.64(0.42-0.98)	0.04
Smoking				
Daily (13.02)	56325(3.29)	158872(9.2)	1	
Occasional (2.43)	9611(0.56)	31897(1.87)	1.17(0.31-4.45)	0.81
Former daily (38.93)	109308(6.39)	555960(32.48)	1.80 (1.08-2.98)	0.02
Former occasional (13.02)	34782(2.03)	187686(10.96)	1.91 (1.02-3.55)	0.04
Never (33.03)	127776(7.4)	436611(25.21)	1.21 (0.69-2.10)	0.49
Physical activity Index				
Active (15.58)	68785(4.02)	197937(11.56)	1	
Moderate (21.21)	101517(5.93)	261592(15.28)	0.89(0.53-1.49)	0.67

Inactive (63.07)	167553(9.79)	912010(53.28)	1.89 (1.17-3.03)	0.008
A1C				
Well (47.69)	112003(8.8)	447540(41.54)	1	
Borderline (26.80)	66349(5.52)	248118(18.67)	0.93(0.58-1.48)	0.77
High (24.61)	34487(3.28)	254262(20.8)	1.84 (1.11-3.05)	0.01
Low (0.90)	1020(0.10)	9506(1.14)	2.33 (0.34-15.74)	0.38
Self-monitoring Factors				
Checking Blood sugar				
Per day (55.55)	139937(8.18)	810917(47.34)	1	
Per week (25.47)	100858(5.89)	335065(19.57)	0.57(0.38-0.84)	0.006
Per month (5.84)	27373(1.60)	72608(4.24)	0.45 (0.15-1.31)	0.14
Per year or never (13.14)	69686(4.07)	155295(0.07)	0.38 (0.23-0.63)	0.000

Table 2.3 Bivariable logistic regression by Micro-vascular and Macro-vascular complications

Variables	Model (2) Microvascular (Yes vs. No)			Model (3) Macrovascular (Yes vs. No)		
	OR	**CI**	**P**	**OR**	**CI**	**P**
Age						
20-45 Years	1			1		
45-70 Years	2.15	(1.28-3.63)	0.004	4.22	(1.46-12.22)	0.008
70 or more	5.79	(3.37-9.29)	0.000	8.08	(2.80-23.29)	0.000
Sex						
Male	1			1		
Female	1.30	(0.99-1.70)	0.05	0.70	(0.53-0.94)	0.02
Marital Status						
Married	1			1		
Common Law	0.57	(0.29-1.11)	0.10	0.52	(0.24-1.11)	0.09

Widowed	3.26	(2.27-4.68)	0.00	1.60	(1.13-2.27)	0.008
Separated	1.24	(0.52-2.96)	0.61	2.34	(1.96-5.70)	0.06
Divorced	1.39	(0.93-2.07)	0.10	1.26	(0.79-1.99)	0.32
Single	0.98	(0. 65-1.48)	0.93	0.66	(0.38-1.16)	0.15
Employment						
Had a job	1			1		
Did not have a job	2.17	(1.53-3.05)	0.000	1.87	(1.17-2.97)	0.008
Unable to work	4.86	(2.79-8.45)	0.000	3.51	(1.90-6.47)	0.000
Income						
Less than $50,000	1			1		
More than $50,000	0.59	(0.45-0.77)	0.000	0.54	(0.37-0.72)	0.000
Education						
Less than secondary	1			1		
Secondary	0.44	(0.29-0.66)	0.000	0.55	(0.35-0.87)	0.01
Some-post	0.52	(0.30-0.90)	0.021	0.43	(0.24-0.78)	0.005
Post graduate	0.57	(0.41-0.79)	0.001	0.45	(0.32-0.64)	0.000

Type of Diabetes						
Type 1	1			1		
Type 2	0.66	(0.40-1.07)	0.09	1.18	(0.70-2.01)	0.25
Duration of Diabetes						
Less than 10 years	1			1		
More than 10 Years	2.87	(2.19-3.76)	0.000	2.00	(1.47-2.72)	0.000
Insulin						
No	1			1		
Yes	2.52	(1.86-3.40)	0.000	1.91	(1.37-2.67)	0.000
BMI Class						
Normal	1			1		
Inappropriate	0.78	(0.56-1.08)	0.14	1.03	(0.73-1.46)	0.83
Smoking						
Daily	1			1		
Occasional	0.43	(0.14-1.30)	0.13	0.39	(0.15-1.02)	0.05
Former daily	1.21	(0.83-1.77)	0.30	1.11	(0.73-1.67)	0.61
Former occasional	1.26	(0.76-2.09)	0.35	0.91	(0.51-1.61)	0.75

Never	0.93	(0.61-1.42)	0.76	0.70	(0.43-1.14)	0.16
Physical activity Index						
Active	1			1		
Moderate	1.27	(0.84-1.93)	0.25	1.34	(0.85-2.12)	0.20
Inactive	2.07	(1.42-3.02)	0.000	2.28	(1.51-3.44)	0.000
A1C						
Well	1			1		
Borderline	0.77	(0.52-1.13)	0.19	0.87	(0.55-1.37)	0.55
High	1.43	(0.98-2.10)	0.06	1.32	(0.86-2.05)	0.19
Low	2.18	(0.68-6.98)	0.18	0.32	(0.10-1.01)	0.05
Checking Blood sugar						
Per day	1	1		1		
Per week	0.58	(0.43-0.79)	0.000	0.78	(0.54-1.11)	0.17
Per month	0.55	(0.28-1.06)	0.07	0.71	(0.39-1.29)	0.27
Per year or never	0.49	(0.31-0.76)	0.002	0.75	(0.46-1.23)	0.26

2.3.2.Multivariable analysis by grouped diabetes-related complications

Result from multivariable analysis in three models in terms of three different dependent variable are shown in Table 2.4

Socio-Demographic Factors: The multivariable analysis reveals that people over the age of 70 years were 4.88 times more likely to report having a diabetes-related complication than people aged 20 to 45 years. This group was also 5.58 and 3.37 times more likely to report having a micro-vascular complication and a macro-vascular complication respectively than their younger counterparts. Female patients were 0.56 times less likely to report having a macro-vascular complication than male patients. Widowed patients were about twice as likely to report having a diabetes-related complication than married patients (OR=1.98), and were also roughly twice as likely to occurrence a micro-vascular complication (OR=2.02). Similarly, patients who did not have a job experienced an increased likelihood of having had both a micro-vascular (OR=1.70) and macro-vascular (OR=1.67) complication compared to their working counterparts. A complementary trend was revealed when analyzing income: that is, patients in the higher income category were less likely to report both micro-vascular (OR=0.67) and macro-vascular (OR=0.64) complications.

Diabetes Status; Patients with type II diabetes were less likely to have micro-vascular complications (OR=0.51) compared to patients with type I diabetes. There was no significant association between a patient's type of diabetes and the likelihood of developing a macro-vascular complication or any diabetes-related complication. The multivariable analysis also revealed that patients who had diabetes for more than 10 years were approximately double as likely to report having any diabetes-related complication (OR=2.20), a micro-vascular complication (OR=2.07), or a macro-vascular complication (OR=1.61) compared to those who had diabetes for less than 10 years. Patients who injected insulin were also at an increased risk of developing diabetes-related complications: that is, patients were 0.58 times more likely to report any diabetes-related complication and 1.05 times more likely to report a micro-vascular complication than patients who did not inject insulin.

Risk Factors; having an inappropriate BMI was found to be positively associated with having any diabetes-related complication in comparison to those with a normal BMI (OR=2.15). Compared to current daily smokers, patients who report currently smoke occasionally had a lower likelihood of having a micro-vascular complication (OR=0.23). Patients who were inactive were twice as likely to report

having macro-vascular complications compared to those who had active (OR=2.46). Patients who reported a having a high level of A1C were also more likely to report having a macro-vascular complication compared to patients with a well level of A1C (OR=1.88).

Self-Monitoring Behaviours; No significant associations were found between diabetes-related complications, micro-vascular complications, or macro-vascular complications and self-monitoring variables. Complete results for self-monitoring behaviour are presented in Table 2.4.

Table 2.4. Multivariable logistic regression of all diabetes-related complications, micro-vascular complications, and macro-vascular complications

Variables	Model 1 All Complication (Yes vs. No)			Model 2 Microvascular (Yes vs. No)			Model 3 Macrovascular (Yes vs. No)		
	OR	CI	P	OR	CI	P	OR	CI	P
Age									
20-45 Years	1			1			1		
45-70 Years	2.99	(1.66-5.39)	0.000	3.17	(1.50-6.67)	0.002	4.16	(1.46-11.87)	0.008
70 or more	5.88	(2.27-15.21)	0.000	6.58	(2.77-15.63)	0.000	4.37	(1.32-14.37)	0.01
Sex									
Male	1			1			1		
Female	0.83	(0.54-1.29)	0.42	1.21	(0.83-1.76)	0.30	0.44	(0.28-0.69)	0.000
Marital Status									
Married	1			1			1		

Common Law	0.78	(0.34-1.77)	0.56	0.61	(0.24-1.59)	0.32	0.29	(0.10-0.84)	0.02
Widowed	1.98	(0.96-4.08)	0.06	2.02	(1.12-3.63)	0.01	1.19	(0.53-2.66)	0.66
Separated	0.86	(0.25-2.95)	0.82	1.67	(0.57-4.85)	0.34	2.81	(1.05-7.48)	0.03
Divorced	0.82	(0.42-1.62)	0.58	1.01	(0.57-1.80)	0.94	1.07	(0.52-2.18)	0.84
Single	1.59	(0.78-3.24)	0.19	1.22	(0.65-2.28)	0.51	0.53	(0.23-1.24)	0.14
Employment									
Had a job	1			1			1		
Did not have a job	1.40	(0.83-2.36)	0.19	1.70	(1.13-2.57)	0.01	1.67	(1.02-2.72)	0.03
Unable to work	4.03	(1.20-13.43)	0.02	4.93	(2.38-10.20)	0.00	3.84	(1.72-8.56)	0.001
Income									
Less than $50,000	1			1			1		
More than $50,000	0.85	(0.53-1.37)	0.52	0.67	(0.42-1.00)	0.05	0.64	(0.39-1.06)	0.08
Education									
Less than secondary	1			1			1		
Secondary	0.88	(0.38-2.01)	0.38	1.14	(0.55-2.35)	0.70	0.75	(0.36-1.56)	0.44
Some-post	0.54	(0.20-1.45)	0.20	0.88	(0.38-1.99)	0.76	0.31	(0.12-0.83)	0.01

Post graduate	0.75	(0.38-1.47)	0.40	1.82	(1.01-3.30)	0.04	0.74	(0.41-1.32)	0.31
Type of Diabetes									
Type 1	NA	NA	NA	1			1		
Type 2				0.51	(0.24-1.08)	0.07	1.02	(0.42-2.43)	0.96
Duration of Diabetes									
Less than 10 years	1			1			1		
More than 10 Years	2.20	(1.36-3.56)	0.001	2.07	(1.40-3.04)	0.000	1.61	(1.02-2.52)	0.03
Insulin									
No	1			1			1		
Yes	1.58	(0.94-2.65)	0.08	2.05	(1.30-3.25)	0.002	1.51	(0.89-2.54)	0.12
BMI Class									
Normal	1			1			1		
Inappropriate	2.15	(1.26-3.68)	0.005	1.03	(0.63-1.69)	0.88	0.83	(0.46-1.49)	0.54
Smoking									
Daily	1			1			1		
Occasional	0.64	(0.16-2.47)	0.52	0.23	(0.06-0.86)	0.02	0.39	(0.10-1.52)	0.17
Former daily	1.47	(0.76-2.82)	0.24	0.96	(0.54-1.71)	0.90	0.64	(0.33-1.22)	0.18

Former occasional	2.18	(0.95-4.99)	0.06	1.21	(0.52-2.83)	0.65	0.92	(0.37-2.30)	0.87
Never	1.28	(0.67-2.45)	0.43	0.75	(0.41-1.35)	0.34	0.66	(0.32-1.33)	0.24
Physical activity Index									
Active	1			1			1		
Moderate	0.85	(0.45-1.61)	0.63	1.04	(0.61-1.77)	0.88	1.50	(0.74-3.01)	0.25
Inactive	1.27	(0.73-2.20)	0.39	1.33	(0.81-2.20)	0.25	2.46	(1.25-4.84)	0.009
A1C									
Well	1			1			1		
Borderline	0.94	(0.59-1.48)	0.79	0.77	(0.48-1.22)	0.27	1.29	(0.76-2.21)	0.33
High	2.01	(1.19-3.37)	0.008	1.40	(0.86-2.28)	0.16	1.88	(1.12-3.16)	0.01
Low	2.29	(0.47-11.08)	0.30	2.39	(0.63-9.03)	0.19	0.32	(0.05-1.77)	0.19
Checking Blood sugar									
Per day	1			1			1		
Per week	0.86	(0.52-1.42)	0.57	0.79	(0.51-1.21)	0.28	1.10	(0.66-1.83)	0.70
Per month	0.85	(0.41-1.73)	0.66	0.42	(0.20-0.84)	0.01	0.84	(0.35-1.97)	0.69

Per year or never	0.59	(0.29-1.21)	0.15	0.76	(0.38-1.53)	0.45	1.95	(0.90-4.19)	0.08

2.3.3.Multivariable analysis by individual diabetes-related complications

All significant associations between each diabetes-related complication reported in the SLCDC-DM-2011 and the study's independent variables are presented in Table 2.5. Select results will be presented and discussed here by diabetes-related complication. Also, detail results of multivariable analysis by each complication are shown in Appendix B.

Hypoglycemia; Both level of physical activity and A1C level were found to be important risk factors for hypoglycemia. Those who were inactive and who had a high A1Clevel were 6.75 times and 4.60 times more likely to report hypoglycemia compared to active patients and those with well A1C levels.

Periodontal Disease; Females were more likely to report having problems with their gums or periodontal disease compared with males (OR=1.67). Being unemployed (OR=2.52), injecting insulin (OR=2.52), and having a high level of A1C (OR=2.03) were also positively associated with this complication.

Erectile Dysfunction; Patients with an inappropriate BMI were more than twice (OR=2.08) as likely to report having erectile dysfunction as a result of their diabetes. Other factors positively associated with erectile dysfunction include high levels of A1C (OR=2.41), older age (OR=5.12), longer duration of diabetes (OR=1.56), and injecting insulin (OR=2.26). Patients who had never smoked were 0.51 less likely to report this complication compared to patients who smoked daily.

High Blood Pressure; Patients with an inappropriate BMI were twice as likely to have high blood pressure (OR=2.84). Females were also more likely to have high blood pressure compared with male patients (OR= 1.46). Other determinants found to be predictive of high blood pressure include: older age (OR=2.05), longer duration of diabetes (OR=1.44), and unemployment (OR=1.62).

Neuropathy; Patients who were separated from their partners were 4.60 times more likely to report having neuropathy compared to married patients. Being unemployed (OR=2.75) and injecting insulin (OR=2.60) were also found to be positively associated with having neuropathy as a result of one's diabetes. Females were 0.54 times less likely to have this complication compared to their male counterparts.

Retinopathy; A few determinants were strongly associated with retinopathy including: having diabetes for more than 10 years (OR=8.00); being over the age of 70 years (OR=3.30); and, injecting insulin

(OR=11.34). Former occasional smokers were 0.34 times less likely to report having retinopathy than daily smokers.

Cataracts; having cataracts was associated with: being female (OR=1.89); not having a job (OR=4.02); having diabetes for more than 10 years (OR=2.89); being moderately active (OR =1.86); and, injecting insulin (OR =1.70).

Glaucoma; Patients aged 45 to 70 years or older than 70 were 3.30 and 6.57 times more likely to have glaucoma respectively compared to patients aged 20 to 45 years. Having glaucoma was also positively associated with having diabetes for more than 10 years (OR= 1.69).

Kidney Failure; Kidney failure was strongly associated with the 'separated' marital status (OR=5.11). Also, female less likely to report this complication compared with males (OR=0.33). Patients who had more annual income also less likely to report kidney failure (OR=0.24)

Foot Ulcer; Patients who report being inactive or injecting insulin were roughly twice as likely to report having a foot ulcer as a result of their diabetes (OR=2.08 and OR=2.47).

Poor Circulation; Patients who report being inactive or injecting insulin were roughly twice as likely to having poor circulation as a result of their diabetes (OR=2.05 and OR=2.27).

Protein in Urine; Patients with high levels of A1C were more than twice as likely to have protein in their urine (OR=2.61).

Heart Disease; Heart disease was more likely among patients who have high levels of A1C (OR=1.65); are physical inactive (OR=2.23); have more than a 10-year duration of diabetes (OR=1.79); and, inject insulin (OR =1.53).

Stroke; A strong positive association was observed between stroke and both physical inactivity (OR= 2.52) and high levels of A1C (OR=2.24).

For each diabetes-related complication, every determinant that was found to be significantly associated with it is presented in Table 2.4. Because only 1.83 percent and 0.48 percent of SLCDC-DM-2011 participants reported experiencing blindness and amputation respectively, when logistic regression was performed on these complications it was determined that they did not fit the data well.

Table 2.5. Significant factors in multivariable logistic regression by each complication

Complications	OR	Value-P
Low blood sugar (Hypoglycemia)		
Physical activity (Inactive)	7.75 (1.85-32.42)	0.005
Checking Blood sugar (Per week)	0.24 (0.06-0.89)	0.03
A1C(High)	5.40 (1.64-17.73)	0.005
Erectile Dysfunction		
Age (45-70 Year)	5.12(1.65-15.83)	0.005
Duration (More than 10 Year)	1.56(0.94-2.58)	0.08
BMI Class (Inappropriate)	2.08(1.06-4.07)	0.03
Smoking (Never)	0.49(0.21-1.12)	0.08
Insulin (Yes)	2.26(1.22-4.18)	0.009
A1C(High)	2.41(1.29-4.51)	0.006
Problem with Gum (Periodontal Disease)		
Sex (Female)	1.67(0.92-3.01)	0.08
Employment (Unable to work)	2.52(0.94-6.76)	0.06
Insulin (Yes)	2.62(1.18-5.77)	0.01
A1C(High)	2.03(1.03-4.02)	0.04
High Blood Pressure		
Age (45-70 Year)	2.05(1.16-3.63)	0.01
Sex (Female)	1.46(1.03-2.08)	0.03
Employment (Did not have a job)	1.62(1.07-2.45)	0.02
Education (Post)	0.61(0.37-0.98)	0.04
Type of diabetes (Type 2)	0.29(0.12-0.68)	0.005

Duration (>10 Years)	1.44(0.97-1.13)	0.06
BMI Class (Inappropriate)	2.84(1.83-4.39)	0.000
Neuropathy		
Sex (Female)	0.54(0.30-0.97)	0.04
Marital Status (Separated)	4.60(1.10-19.11)	0.03
Employment (Did not have a job)	2.75(1.50-5.02)	0.001
Insulin (Yes)	2.60(1.37-4.91)	0.003
Checking Blood sugar (Per month)	0.23(0.6-0.75)	0.02
Retinopathy		
Age (70 or more)	3.30(0.96-11.34)	0.05
Marital Status (Divorced)	0.41(0.16-1.07)	0.01
Employment (Did not have a job)	0.43(0.21-0.87)	0.02
Income (More than 50K)	0.48(0.24-0.93)	0.03
Duration (>10 Years)	8.00(3.54-18.00)	0.000
Smoking (Former Occasion)	0.37(0.17-0.81)	0.01
Insulin (Yes)	11.34(5.58-23.00)	0.000
Cataract		
Age (70 or more)	8.15(3.09-21.5)	0.000
Sex (Female)	1.89(1.25-2.85)	0.002
Marital Status (Widowed)	2.60(1.36-4.96)	0.004
Employment (Did not have a job)	4.02(2.49-6.49)	0.06
Duration (>10 Years)	2.89(1.85-4.52)	0.000

Physical activity (Moderate)	1.86(0.98-3.54)	0.05
Insulin (Yes)	1.70(1.07-2.71)	0.02
Checking Blood sugar (Per week)	0.50(0.30-0.82)	0.006
Glaucoma		
Age		
45-70 Year	3.30(1.17-9.28)	0.02
70 or more Year	6.57(2.19-19.70)	0.001
Income (More than 50K)	0.48(0.24-0.97)	0.04
Duration (>10 Years)	1.69(0.97-2.94)	0.06
Kidney failure		
Sex (Female)	0.33(0.16-0.68)	0.003
Marital Status (Separated)	5.11(1.45-18.05)	0.01
Income (More than 50K)	0.24(0.11-0.55)	0.001
Checking Blood Sugar (Per week)	0.24(0.07-0.75)	0.01
Foot ulcer		
Employment (Unable to work)	2.84(1.14-1.03)	0.02
Income (More than 50K)	0.50(0.31-0.79)	0.004
Physical activity (Inactive)	2.08(1.11-3.87)	0.02
Insulin (Yes)	2.47(1.55-3.93)	0.000
Poor Circulation		

Employment (Unable to work)	2.18(1.14-4.16)	0.01
Physical activity (Inactive)	2.05(1.06-3.95)	0.03
Insulin (Yes)	2.27(1.42-3.62)	0.00
Proteinuria		
Age (45-70 Year)	0.50(0.25-0.97)	0.04
Employment (Did not have a job)	0.52(0.32-0.85)	0.009
Insulin (Yes)	2.31(1.34-3.99)	0.003
A1C(High)	2.61(1.46-4.67)	0.001
Stroke		
Employment (Did not have a job)	2.12(1.01-4.48)	0.04
Physical activity (Inactive)	2.52(1.06-5.97)	0.03
Checking Blood Sugar (Per Year or Never)	2.84(0.97-8.30)	0.05
A1C(High)	2.24(1.10-4.57)	0.02
Heart disease		
Age (45-70 Year)	6.25(1.89-20.64)	0.003
Sex (Female)	0.38(0.24-0.61)	0.00
Income (More than $50,000)	0.53(0.33-0.85)	0.009
Education (Some-post)	0.43(0.17-1.08)	0.07
Duration (>10 Years)	1.79(1.14-2.81)	0.01
Physical activity (Inactive)	2.23(1.15-4.30)	0.01
Insulin (Yes)	1.53(0.93-2.50)	0.08
A1C (High)	1.65(0.95-2.8)	0.06

2.4. Discussion

The present study aimed to estimate the prevalence of diabetes-related complications identified on the SLCDC-DM-2011 and identify associations between these complications and select determinants. Overall, our findings indicate that in Canada, the majority of diabetes patients experience complications, with high blood pressure, cataracts, poor circulation in the feet or legs, and heart disease being among the most common. Patients were more likely to have at least one complication when they were older, had diabetes for more than 10 years, were unemployed, had an inappropriate BMI, and had a high level of HbA1c. Other determinants, including sex, marital status, education, income, and physical activity, were also found to be significantly associated with micro-vascular and macro-vascular diabetes-related complications. The findings will be discussed in detail below by determinant category.

Socio-Demographic Factors

Analysis of Canadian diabetic patients' age yielded a strong positive trend across all models. That is, as age increased the odds of having any diabetes-related complications, micro-vascular complications, and macro-vascular complications increased. Increasing age was also strongly associated with most of the diabetes-related complications when analyzed individually. Findings from the present study support and extend the work of others who have found that an older age of onset is associated with diabetes-related complications (8)(16)(26). For example, diabetic patients in Australia over the age of 80 were 12.42 (CI: 1.26-121.85) times more likely to have retinopathy as a result of their diabetes (15). Similarly, diabetic patients in Canada over the age of 80 were 18.12 (CI: 6.63-49.51) times more likely to have visual impairments as a result of their diabetes (9). Although these likelihoods are stronger than what was found in the present study, differing age cut-offs may explain the differences in strength. Importantly, the overall trends implicating age as a predictive factor of numerous diabetes-related complications remains consistent. Age may be a predictive factor of diabetes-related complications because continuity of care among older adults is often poor, and older adults are more likely to have other medical conditions that complicate their health status (27).

Comparison of males and females reveals a number of sex differences in diabetes-related complications. Overall, females were less likely to have macro-vascular complications, and were also less likely to have neuropathy, kidney failure, and heart disease. However, females had a higher chance of having certain complications including retinopathy, cataracts, high blood pressure, and periodontal disease.

Differences in diabetes-related complications between the sexes have been found in previous examinations of Canadian diabetic patients and are consistent with the present study. When considering diabetes-related complications, the consistency with which sex differences have been documented indicates that genetic, lifestyle, environmental, or other socioeconomic factors that are known to affect the sexes differently may be at play (28).

Among Canadian patients with diabetes, marital status impacted the likelihood of experiencing a diabetes-related complication in diverse ways. Separated patients were more likely to report having a macro-vascular complication than their married counterparts. Separated patients were also more likely to have neuropathy and kidney failure compared to their married counterparts. Similarly, the literature suggests that those patients without partners are at an increased risk for developing neuropathy (OR=2.00, CI: 1.00-1.87) and visual impairments (OR=1.42, CI: 0.99-2.03) as a result of their diabetes compared to married patients (9) (15). It appears that being married is protective against diabetes-related complications, as it has been found to lower one's risk of premature death as a result of diabetes by 50 to 64 percent (17). Being married may provide diabetic patients with an immediate social support, and this may facilitate better adherence to prescribed treatment plans and self-care regimens (29). Others have proposed that not only being married but having a high level of marital satisfaction may be associated with a lower risk of developing metabolic syndromes (30). Further examination of the ways marital status and the real and perceived satisfaction it brings interacts with diabetes-related complication may be required to better understand this association.

The link between socioeconomic status and diabetes-related complications has warranted much attention, and the literature suggests that a low level of education and a low income can contribute negatively to an individual's lifestyle, which in turn has been shown to elevate their risk of developing diabetes and its related complications (28)(31). Further, higher levels of education have also been shown to reduce the likelihood that a diabetic patient will develop micro-vascular complications, end-stage renal disease, coronary artery disease, and retinopathy (18) (19). In the present study, this trend was also observed: that is, more highly educated patients had a lower likelihood of developing certain diabetes-related complications including: heart disease and high blood pressure. When considering income, a similar association was also found: patients with an annual income of more than $50,000 were less likely to report both micro-vascular and macro-vascular complications compared to those who earned less than $50,000 annually. This may be explained, in part, by the fact that high levels of

education and income are known to be associated with better adherence to prescribed medication regimens and an increased awareness of preventive health care programming (32)(33)(34). In sum, high levels of education and income are protective against diabetes-related complications suggesting the need to target health policies and programming at diabetes patients with lower levels of education and income.

Diabetes Status

Findings from the present study suggest that a patient's type of diabetes has little bearing on the diabetes-related complications they experience. With the exception of high blood pressure, no other significant associations were detected between diabetes-related complications and a patient's type of diabetes. In contrast, the literature commonly suggests that, in comparison to patients with type I diabetes, patients with type II diabetes are at an increased risk of neuropathy and macro-vascular complications as a result of their diabetes (20)(35). This trend may not be observed in the present study as a result of the difference in the number of patients reporting each type of diabetes: According to the SLCDC-DM-2011, 8.22 percent of patients reported having type I diabetes and 79.75 percent of patients reported having type II diabetes.

Unlike a patient's type of diabetes, the length of time that a patient has diabetes was strongly associated with both micro-vascular and macro-vascular complications in this study. This is unsurprising given that the duration of diabetes is a well-established predictive factor of diabetes-related complications in the literature (9)(15)(17). In fact, each 10-year increase in duration of diabetes has been shown to elevate patients' risk of experiencing diabetes-related complications, including coronary heart disease (OR=1.4), macro-vascular complications (OR=1.13), micro-vascular complications (OR=1.28), and premature death (1.15) (21) (36).

In both the present study and in the literature, injection of insulin has been shown to be strongly associated with micro-vascular complications (15)(22). However, the literature offers a more comprehensive picture, and suggests that only those patients with type II diabetes are put at risk when injecting insulin (22)(37).

Risk Factors

Analysis of risk factors reveals that high level of A1C, inappropriate BMI, and low physical activity are all positively associated with diabetes-related complications to varying degrees. Our findings suggest that high levels of A1C was the most important risk factor in predicting diabetes-related complications, and this predictive value has also been noted in the literature (25). In contrast, the risk of developing diabetes-related complications as a result of cigarette smoking appears to be more nuanced. In the present study, daily cigarette smoking was significantly associated with two individual diabetes-related complications: erectile dysfunction and retinopathy. There was no evidence to support an association between cigarette smoking and both micro-vascular and macro-vascular complications. This differs from the literature, where cigarette smoking has been shown to exacerbate serious diabetes-related complications, including cardiovascular disease, kidney disease and neuropathy (23). The lack of relationship in the present study may reflect the cross-sectional design of the SLCDC-DM-2011.

Another risk factor that was identified as a strong predictor of diabetes-related complications in this study was an inappropriate BMI score, and specifically being overweight or obese. More specifically, being overweight or obese was more predictive of: diabetes-related complications for type II diabetes patients; having erectile dysfunction; and, having high blood pressure. These findings complement the literature in which BMI has been shown to be associated with chronic diabetes-related complications, including an increased risk of cardiovascular complications (HR=1.34 to HR=2.45), cerebrovascular complications (HR=1.30 to HR=2.00), renal complications (HR=1.31 to HR=2.23), and lower extremity complications (HR=1.41 to HR=2.95) (19)(38)(39)(40). Being overweight or obese is oftentimes linked to physical inactivity, and the present study finds that being physically inactive is another risk factor for the development of diabetes-related complications, including micro-vascular complications, such as foot ulcers or poor circulation, as well as stroke and heart disease. Previous studies have implicated physical inactivity as a risk factor for the development of diabetes-related complications, including impaired renal function, retinopathy, cardiovascular disease, and hypertension (24)(41). Importantly, because physical inactivity has not only been linked to the development of diabetes-related complications among diabetes patients, but also the development of diabetes itself (42), there is a need to further the effectiveness of current health promotion strategies as they relate to exercise and diabetes prevention.

Self-Monitoring Behaviour

Our findings reveal that frequent self-monitoring behaviour was protective against some diabetes-related complications, including stroke. Similarly, the literature suggests that the total rate of all diabetes-related complications was lower among patients who self-monitor their blood glucose compared to those who do not (43). In order to gain this protective effect, patients may not be required to self-monitor daily: that is, self-monitoring less frequently than daily was still associated with a lower likelihood of reporting retinopathy, cataracts, and kidney failure in the present study. However, although there are a number of proven benefits of self-monitoring behaviour, this behaviour has not consistently been found to be independently associated with improved survival among diabetes patients (17). This inconsistency was also observed in the present study where differing frequencies of self-monitoring behaviour were protective against some diabetes-related complications, but not others. One caveat in the present study is that the temporal relationship between engaging in self-monitoring behaviour and subsequent experience of diabetes-related complications was not encountered for. Alternatively, associations observed in the present study may be due to incomplete adjustment of confounding covariates or chance.

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CHAPTER 3-EFFECTS OF PHARMACY-BASED INTERVENTIONS ON THE CONTROL AND MANAGEMENT OF DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS

Article reproduced with permission. Originally published as: "Yaghoubi M, Mansell K, Vatanparastc H, Steeves M, Zeng W, Farag M. Effects of pharmacy-based interventions on the control and management of diabetes in adults: a systematic review and meta-analysis. Can J Diabetes. 2017 Dec; 41(6):628-641. doi: 10.1016/j.jcjd.2017.09.014." My contributions to this study included conceiving and designing the systematic-review, conducting the meta-analysis, interpretation of the results, and preparation of the manuscript. Dr. Marwa Farag and Dr. Kerry Mansell helped in conception and design of the study. All authors helped in the interpretation of findings and in reviewing and editing the manuscript.

In this chapter, I aim to assess the current state of evidence on the effectiveness of pharmacy-based interventions in control and management of diabetes. Based on the findings in ***chapter 2***, high levels of A1C and inappropriate levels of BMI are considered main risk factors associated with most of diabetes-related complication in Canada. In this chapter I conduct a systematic review and meta-analysis to assess the effect of pharmacy-based interventions on reducing the main risk factors identified in ***chapter 2***. The findings from this chapter are used as main input parameters for building the micro-simulation model in ***chapter 4***.

3.1. Background

Promotion of community-based interventions, including early screening programs and education about how to effectively self-manage diabetes, can lead to a decrease in the burden of diabetes and related complications (1). Pharmacy-based interventions include a wide range of services, which aim to enable patients with diabetes to have greater control and management of their disease, such as pharmacist consultations, patient education about self-monitoring and self-management, preventive programming about lifestyle modifications, reminders about annual physical examinations, medication therapy adherence assistance, providing information about the correct use of insulin, antihyperglycemic medications, and other interventions to increase awareness about diabetes management. Recent reviews of the effectiveness of pharmacy interventions have demonstrated their positive impact on clinical outcomes. These positive impacts likely reduce the burden of diabetes-related complications, and, by doing so, subsequently lead to reductions in diabetes-related morbidity and mortality (2)(3)(4)(5) .

Although systematic reviews have evaluated the clinical and non-clinical effectiveness of pharmacy-based interventions among diabetes patients (2) (3) (4), no recent work has calculated the pooled effect of pharmacy-based interventions on mean reduction of A1C, except one meta-analysis that conducted in 2007(6). Therefore, previous reviews noted that there is a need to conduct a future and updated meta-analysis (3). The aim of this systematic review and meta-analysis was to evaluate the effects of pharmacy-based interventions on clinical outcomes associated with diabetes-related complications as well as non-clinical outcomes among people with diabetes. We followed PRISMA guidelines in conducting this systematic review and meta-analysis. The PICOs (Population, Intervention, comparison, outcome and study design) for this study were defined to focus the research question following PRISMA guidelines: we considered all patients with Diabetes (Level of HbA1c > 6.5%) as population; pharmacy-based interventions as an intervention; mean change of A1C level, BMI, health care utilization and quality of life as outcomes, usual care as a comparison and randomized control trial (RCTs) and non-randomized studies with comparator group as study designs. We performed the meta-analysis to assess the pooled effect of pharmacy-interventions on the mean reduction of A1C and BMI (kg/m2).

3.2.Material and methods

3.2.1.Search strategy

In February 2017, a search strategy was used to retrieve all relevant studies from the following databases: MEDLINE, EMBASE, CINAHL, and Cochrane Central Registered for Controlled Trials. The search strategy was developed with the assistance of a medical information specialist in MEDLINE via OVID. Keywords used in the search strategy were identified through experts' opinion and controlled vocabularies (Medical Subject Headings = MeSH and Excerpta Medica Tree = EMTREE). The keyword diabetes mellitus was used to identify literature discussing the health issue at hand. The keywords pharmacy, pharmacies, pharmacy service, community pharmacy service, pharmaceutical care, pharmaceutical service, and pharmacist were used in combination with diabetes mellitus to identify literature discussing the intervention at hand. This search strategy was adapted for EMBASE, CINAHL, and Cochrane databases. To ensure a highly sensitive search strategy, filters were not used to limit the retrieval of studies to those with a randomized controlled trial study design, those written in a particular language, or those from a certain time period. However, restrictions were placed on the study population in the initial retrieval of papers, and study populations had to include human participations and adults over the age of 18. Citation tracking of related papers was applied, and the references of all included studies were manually checked. Details of the search strategy are shown in appendix C.

3.2.2. Study selection

Two reviewers (MY-MF) independently screened all titles and abstracts retrieved during the initial search. Titles and abstracts were screened based on inclusion criteria, which included relevance to the research question. The full text was obtained for each study that met these criteria and screened against the inclusion criteria outlined below. Any disagreement concerning the eligibility of a study for this review was resolved through discussion with the third reviewer (HV). Duplicate publications of the same study were excluded unless subsequent publications provided additional information about an outcome of interest. The study selection process is presented in a Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow chart in (Figure 3.1) (7).

3.2.3. Inclusion and exclusion criteria

In this review we focused on AIC because this biomarker is considered a progressive risk factor for microvascular and macrovascular complications, hospitalization and death in patients with diabetes (8). We also focused on BMI (kg/m2) because obesity is considered one of the most important risk factors

for developing diabetes and its complications (9). We included mean difference of A1C and BMI across intervention and control group derived from randomized controlled trials in meta-analysis in order to ensure a high validity of reported findings. Additionally, non-clinical outcomes were considered in the systematic review but not in the meta-analysis. Since utilization of healthcare services is an important determinant of health outcomes (10) and quality of life is a significant measure of the value of health outcomes, we focused on health care utilization (inpatient admissions and emergency visits), and also quality of life in this review as non-clinical outcomes. Measures of these outcomes were derived from randomized controlled trials, non-randomized controlled trials, or retrospective studies with a comparator group. The inclusion of non-clinical outcomes creates a more comprehensive understanding of the effects of pharmacy-based interventions.

Studies were included in the systematic review if they met the following criteria: 1) the exposure of interest was a pharmacy-intervention which includes education about diabetes, self-management, self-monitoring of the condition, modification of pharmacotherapy, and/or patient counselling; 2) studies which reported at least one of the outcomes of interest including; the mean change in A1C level, BMI (kg/m2), health care utilization, and/or quality of life between intervention and control group; and, 3) it was a randomized controlled trial, non-randomized controlled trial, or retrospective study with a comparator group. In contrast, the meta-analysis included only those studies in which a randomized controlled trial study design was used. Studies were excluded if they met the following criteria: 1) selected outcomes were not reported; 2) other educational interventions outside of the pharmacists' scope of practice; and, 3) studies in which there was no control group.

3.2.4.Quality assessment

Quality assessment has been done by two reviewers independently. All of the included studies were assessed according to the Cochrane risk of bias tool, which includes consideration for the following criteria: 1) random sequence generation; 2) allocation concealment; 3) blinding of outcome assessment; 4) incomplete outcome data; 5) selective reporting; and 6) other sources of bias. Our application of this tool did not include blinding of study participants and personnel because this was inconsistent with the design of pharmacy- interventions. We checked all criteria for a judgment of "low risk ","high risk" and "unclear" as explained in detail in the Cochrane systematic review handbook and each study was rated as either "low risk", "high risk" or "unclear".

3.2.5. Data extraction

Data extraction has been done by two reviewers. Data were extracted and entered into a data extraction sheet, which included descriptive information about the study sample, the intervention and the results. The following data points were extracted from each study: last name of first author, year of publication, type of study design, target population, number of participants in the intervention group, number of participants in the control group, duration of follow-up period, outcome measures, and results. A summary of data extraction sheet is shown in Table 3.1.

3.2.6. Data synthesis and analysis

To calculate the mean difference of A1C levels and/or BMI between intervention and control groups, we subtracted the baseline (b) level or score from the follow-up (fu) level or score to find the change over time. Next, we subtracted the change in the control group from the corresponding change in the intervention group to quantify the net effect. The standard error (SE) was reported for each net effect calculated from the included studies. The SE reported was calculated either based on the confidence interval or p-value of the net effect, or based on the standard deviation (SD) of effects within parallel groups(20)(see Table 3.2). Meta-analysis was performed using Stata (version 14). The heterogeneity of studies in the meta-analysis was assessed using the Q test and we used I2 statistic to quantify heterogeneity. Additionally, potential publication bias among studies in the meta-analysis was assessed using the Egger's test and Begg's adjusted rank correlation test. Regarding sensitivity analysis, we used Influence Analysis based on Stata's matainf command to examine the effect of excluding each study on the pooled estimate of standardized mean difference (SMD) and explore the heterogeneity among studies. Also funnel plots were conducted to assess potential publication bias (Figure 3.3 and 3.4)

3.3. Results

Figure 3.1. Process of selection of studies for systematic review based on PRISMA flow diagram

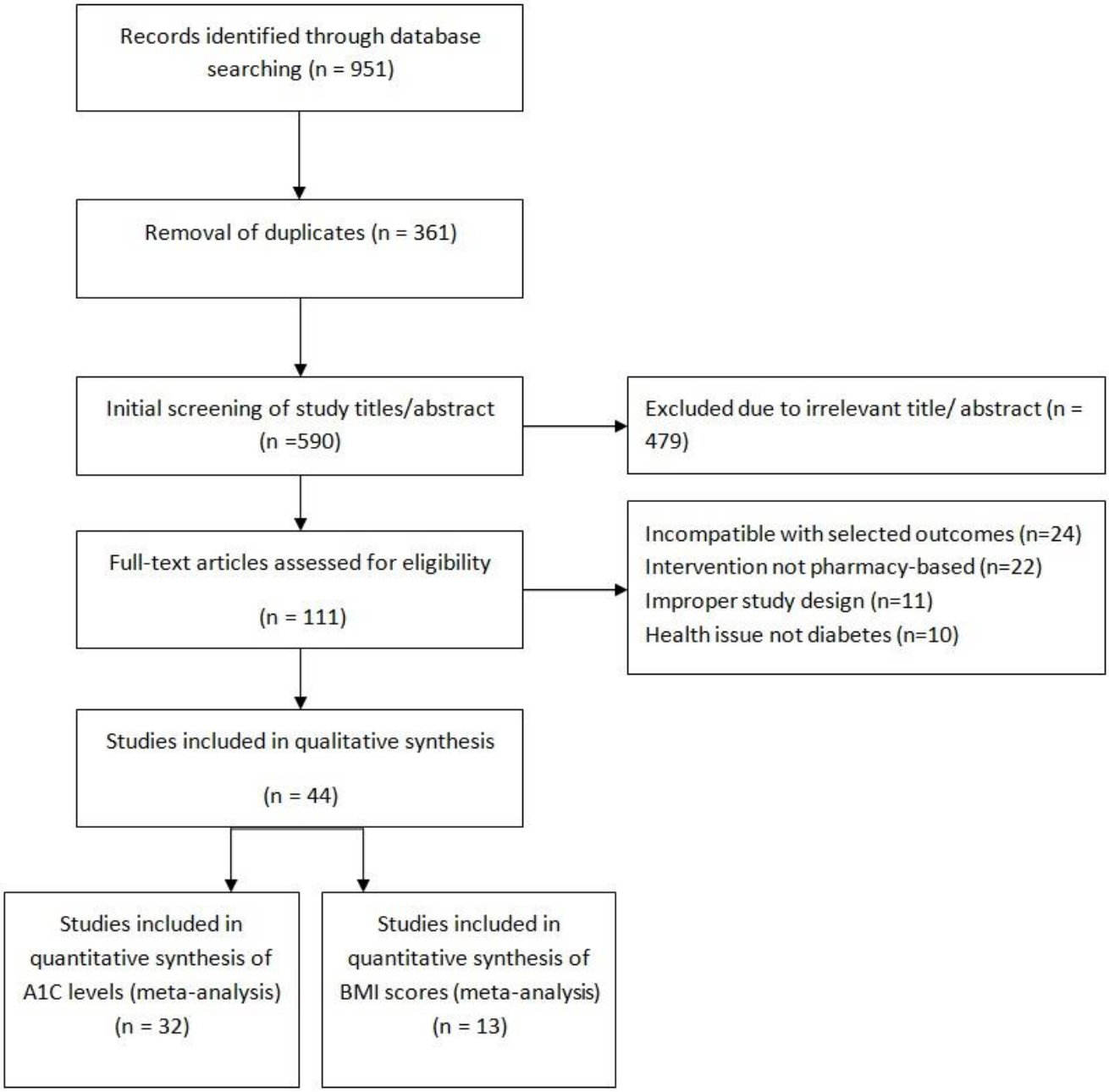


Table 3.1. Summary of 44 studies assessing pharmacy-based intervention for patient with type 2 diabetes

No	First Author (Year)	Type of Study	Participants	Intervention	Follow-up	Main Outcome(s)	Result
1	Adepu R (2007)(12)	Prospective, randomized controlled trial	35 intervention 35 control	Patient counseling on patients' perceptions	6-months	Fasting blood glucose, and quality of life	There was a decrease in the mean capillary blood glucose and improvement in the mean quality of life scores reported for the intervention group (P <0.05).
2	Adibe MO (2013)(13)	Randomized controlled trial	110 intervention 110 control	Pharmaceutical care including education and training	12-months	Health-related quality of life (HRQOL)	The overall HRQOL was significantly improved at 12 months in the pharmaceutical care intervention group when compared to the control group (P <0.0001).
3	Ali M (2012)(14)	Prospective, randomized	23 intervention	Pharmacist-led patient education	12-months	A1C, BMI, Blood pressure, Blood	Significant reductions were noted in A1C and all secondary outcomes improved

		controlled trial	23 control	and diabetes monitoring program		glucose, Lipid profile, and Quality of life	among members of the intervention group (P =0.001).
4	Al Mazroui NR (2009)(15)	Prospective, randomized controlled trial	117 intervention 117 control	Pharmaceutical care including education and self-monitoring	12-months	A1C, BMI, Blood pressure, CHD risk factors, and Quality of life	There were significant reductions in A1C and blood pressure, and improvements in quality of life scores among members of the intervention group. Theres were no significant changes in the control group.
5	Cani CG (2015)(16)	Randomized controlled trial	34 intervention 36 control	Pharmaceutical care plan and diabetes education	6-months	A1C, Quality of life, Knowledge of medication, and Adherence to medication regimen	A1C was significantly reduced for the intervention group. All secondary outcomes, including quality of life, improved among members of the intervention group.
6	Chung WW (2014)(17)	Prospective, randomized	120 intervention	Pharmaceutical care plan and	12-months	A1C, Fasting blood glucose, and	There were significant reductions in A1C and blood glucose among members of

		controlled trial	121 control	diabetes education		Medication adherence scale	the intervention group. A higher proportion of members in the intervention group reported medication adherence.
7	Chan CW (2012)(18)	Prospective, randomized controlled trial	51 intervention 54 control	Patient counseling sessions with pharmacists	9-months	A1C, BMI ,CHD risk factors, LDL, HDL, and dherence to medication regimen	A1C was significantly reduced in the intervention group ($P < 0.001$). Additionally, members of the intervention group had a statistically significant reduction in CHD risk ($P = 0.013$).
8	Chen JH (2016)(19)	Randomized controlled trial	50 intervention 50 control	Pharmaceutical care including education and medication	9-months	A1C, hospitalizations, and medical expenses	A1C significantly decreased for the intervention group ($P \leq 0.001$). Medical expenses and hospitalizations did not significantly differ across groups (P =

				consultation			0.767).
9	Clifford RM (2005)(20)	Randomized controlled trial	92 intervention 88 control	Pharmaceutical care including education and consultation	12-months	A1C, BMI, lood pressure, and CHD risk factors	Reductions were greater among members of the intervention group compared to the control group for A1C and blood pressure (P < or = 0.043). The risk of the first CHD event decreased among members of the intervention group (P = 0.002).
10	Cohen LB (2011)(21)	Randomized controlled trial	50 intervention 49 control	Pharmacist-led intensive behavioral and educational programming	6-months	A1C, CHD risk factors, lood pressure, LDL, and foot care	Significant improvements from baseline were found in the intervention group for exercise, foot care, and attainment of goal levels of A1C, LDL-C, and blood pressure.
11	Cohen HM (2005)(22)	Randomized controlled trial	36 intervention	Modification of pharmacotherapy	24-months	A1C, LDL, foot screening, and	There was a greater reduction in A1C among members of the intervention

			29 control	and provision of diabetes education by a clinical pharmacist		retinal examination	group (P = 0.03). LDL measurements, retinal examinations, and monofilament foot screening were more frequent in the intervention group.
12	Farsaei S(2011)(23)	Randomized controlled trial	87 intervention 87 control	Pharmacist-led patient education program	3-months	A1C, and fasting blood glucose	The mean fasting blood glucose and A1C of members of the intervention group decreased significantly (P < 0.001).
13	Fornos JA (2006)(24)	Randomized controlled trial	56 intervention 56 control	Pharmacotherapy follow-up (PF) program including detection and resolution of drug related problems and diabetes education	13-months	A1C, BMI, fasting blood glucose, lipid profile, blood pressure, drug-related problems, and drug knowledge	There were significant differences in the intervention group in: A1C, drug-related problems, and drug knowledge (P < 0.0001); fasting blood glucose (P = 0.0004); total cholesterol (P = 0.0054); and systolic blood pressure (P = 0.0006).

14	Jaber LA (1996) (25)	Randomized controlled trial	17 intervention 22 control	Pharmaceutical care including diabetes education and counseling	4-months	A1C, fasting plasma glucose, blood pressure LDL, HDL, and quality of life	There were statistically significant differences in A1C (P = 0.003) and fasting plasma glucose (P = 0.022). no significant changes in blood pressure, lipid profile, renal function, weight, and quality of life.
15	Jarab AS (2012)(26)	Randomized controlled trial	77 intervention 79 control	Pharmaceutical care including diabetes education and counseling	4-months	A1C, BMI, blood pressure, lipid profile, self-reported medication adherence, and self-care activities	There were significant reductions in A1C in the intervention group (P = 0.019). The intervention group had statistically significant improvements in other outcome measures.
16	Jameson JP (2010)(27)	Randomized controlled trial	52 intervention 51 control	Pharmaceutical care including medication management and	12-months	A1C	There were significant decreases in A1C in the intervention group (P = 0.06).

				education			
17	Jacobs M (2012)(28)	Prospective, randomized clinical practice	72 intervention 92 control	Pharmaceutical care including counseling, self-monitoring, and information about dietary guidelines	12-months	A1c, blood pressure, LDL, screening for retinopathy, and Screening for neuropathy	There were significant improvements for A1C , LDL and blood pressure in the intervention group ($P < 0.05$). Additionally, more intervention patients were screened for retinopathy and neuropathy ($P < 0.05$).
18	Kjeldsen LJ(2015)(29)	Randomized controlled trial	37 intervention 102 control	Medication adherence program	12-months	Quality of life, health care utilization, blood pressure, blood glucose levels, and Diabetes knowledge	A significant difference was not found for quality of life or health care utilization. Blood pressure improved in the EI group ($P = 0.020$) and the EI group increased their disease-related knowledge ($P = 0.006$), but the BI group did not ($P = 0.139$).

19	Kraemer DF(2012)(30)	Randomized controlled trial	36 intervention 29 control	Patient counseling	12-months	A1C, BMI, blood pressure, LDL, HDL, health care utilization, Diabetes empowerment scale (DES)	There was a significant reduction in A1C (P = 0.0008) and cholesterol (P < 0.001) for the intervention group. The difference was not significant for BMI, blood pressure, health care utilization and DES across groups.
20	Krass I(2007)(31)	Randomized controlled trial	149 intervention 140 control	Community-level diabetes service including adherence support and self-management	6-months	A1C, blood glucose, BMI, blood pressure, cholesterol, triglycerides, and Quality of life	There was a significant reduction in A1C and mean blood glucose in the intervention group (P < 0.01). Improvements were also seen in blood pressure and quality of life among members of the intervention group.
21	Lim PC (2016)(32)	Open-labeled randomized study	39 intervention	Diabetes medication therapy adherence clinic	4-months	A1C, BMI, Fasting blood glucose, blood pressure,	There were significant reductions in A1C (P = 0.011) and fasting blood glucose (P = 0.002). Total cholesterol and LDL-C were

			37 control			LDL, HDL, and triglycerides	also significantly reduced in the intervention group (P = 0.001).
22	Mehuys E (2011)(33)	Randomized controlled trial	135 intervention 135 control	Predefined pharmacist intervention including medication adherence and promotion of a healthy lifestyle	6-months	A1C, fasting plasma glucose, adherence to medication, and knowledge score	There was a significantly reduction in A1C among members of the intervention group (P = 0.009), as well as improved self-management and better knowledge of diabetes.
23	Mansell , K (2016)(34)	Cluster randomized study	21 Intervention 9 Control	Education on self-monitoring blood glucose	6-months	A1C	Mean A1C change was -1.96 and -0.70 in the intervention and control group respectively (p= 0.37)
24	Mourão AO (2013)(35)	Randomized controlled trial	50 intervention	Pharmaceutical care including	6-months	A1C, BMI, fasting blood glucose,	significant reduction in A1C showed in intervention group (P = 0.001), as well as

			50 control	education and medication management		triglycerides, LDL, HDL, systolic blood pressure, and diastolic blood pressure	reductions in fasting plasma glucose, total cholesterol, LDL-C, triglycerides and systolic blood pressure.
25	Neto PR(2011)(36)	Randomized controlled trial	97 intervention 97 control	Pharmaceutical care including education and medication management	36-months	A1C, BMI, systolic blood pressure, diastolic blood pressure, LDL, HDL, triglycerides, CHD risk factors	There were significant reductions in A1C ($P < 0.00$), and all other clinical outcomes such as CHD risk factors ($P < 0.001$).
26	Obarcanin E (2015)(37)	Randomized controlled trial	39 intervention 26 control	Pharmaceutical care plan including medication management, self – management and	6-months	A1C, blood pressure, fasting lipids, and quality of life	Compared to baseline, A1C was significantly greater in the intervention group ($P = 0.0075$). The difference in the number of severe hypoglycemia events

				education			between the two groups was not significant (P = 0.1276). Well-being score improved significantly in the intervention group (P = 0.000).
27	Odegard PS(2005)(38)	Randomized controlled trial	43 intervention 34 control	Pharmacist intervention including medication-related management	12-months	A1C, appropriateness of medication, and Self-reported adherence to medication regimen	A1C did not differ between groups (P = 0.61). The appropriateness of medication did not improve (P = 0.65), and self-reported adherence did improve.
28	Planas LG(2012)(39)	Randomized controlled trial	30 intervention 22 control	Pharmacist-directed diabetes management including education, self-management , self-	9-months	A1C, systolic blood pressure, diastolic blood pressure, and LDL	A1C and systolic blood pressure were significantly reduced in the intervention group (P < 0.02). no significant change in diastolic blood pressure or LDL between groups.

				monitoring and medication adherence			
29	Ramanath KV(2011)(40)	Randomized controlled trial	52 intervention 48 control	Pharmaceutical care including medication adherence program	12-months	Quality of life, medication adherence, blood glucose level, and Diabetes knowledge	There was a significant increase in quality of life, diabetes knowledge scores, and adherence scores ($P < 0.05$) among members of the intervention group.
30	Rothman Rl (2005)(41)	Randomized controlled trial	99 intervention 95 control	Intensive management of patient care by clinical pharmacists including diabetes education and counseling	12-months	A1C, systolic blood pressure, diastolic blood pressure, Triglycerides, Diabetes Knowledge, satisfaction with care, health service	The intervention group showed significantly greater improvements than the control group for systolic blood pressure ($P = 0.007$), diastolic blood pressure ($P = 0.008$), and A1C ($P = 0.02$). Intervention patients had greater improvements in both diabetes

						utilizations	knowledge and satisfaction. Changes in total cholesterol levels and health service utilization were not significant.
31	Sarkadi A (2004)(42)	Randomized controlled trial	33 intervention 31 control	Experience-based group educational programming administered by pharmacists	24-months	A1C	At 24 months after baseline, A1C was significantly decreased (P = 0.04).
32	Scott DM(2006)(43)	Randomized controlled trial	64 intervention 67 control	Pharmacist-managed diabetes care program including diabetes education and counseling	9-months	A1C, BMI, quality of life, diastolic blood pressure, systolic blood pressure, LDL and HDL	There was a significant reduction in A1C (P = 0.003), systolic blood pressure (P = 0.02), and LDL (P = 0.01) in the intervention group. Quality of life was significantly higher in the intervention group (P = 0.002).
33	Sriram S	Randomized	60	Pharmaceutical	8-	A1C, BMI, quality of	A1C and fasting blood glucose were

	(2011)(44)	controlled trial	intervention 60 control	care including education and counseling	months	life, fasting blood glucose, and satisfaction score	significantly reduced (P < 0.01). an improvement in the quality of life score showed in intervention group(P < 0.01).
34	Suppapitiporn S (2005)(45)	Randomized controlled trial	180 intervention 180 control	Pharmaceutical care including drug counseling and education	6-months	A1C, and fasting blood glucose	Mean A1C and fasting blood glucose decreased among members of the intervention group compared to the control group (P < 0.013).
35	Taveira TH (2010)(46)	Randomized controlled trial	58 intervention 51 control	Pharmacist-led medical visit program including diabetes education and medication management	4-months	A1C, systolic blood pressure, LDL, HDL, lipid profile, and tobacco use	There was a significant reduction in A1C, systolic blood pressure, triglycerides, LDL, and HDL in the intervention group (P < 0.05). There was no significant change in lipid control or tobacco use between the groups.
36	Wishah RA (2015)(47)	Randomized controlled trial	52 intervention	Pharmaceutical care including	6-months	A1C, BMI, fasting blood sugar, LDL,	There was a significant reduction in A1C and fasting blood sugar (P < 0.05) among

			54 control	education. Counseling , medication adherence and self-management program		HDL, Diabetes knowledge, Medication adherence, and self-care activity	members of the intervention group. Knowledge, medication adherence, and self-care activities increased significantly for the intervention group compared to the control group (P < 0.05).
37	Brophy L (2014)(48)	Retrospective quasi-experimental	954 intervention 810 control	Drug therapy management (DTM) administered by a pharmacy	12-months	Inpatient admissions and rate of emergency visits	There was significant total cost savings (pharmacy + medical) compared with the corresponding control groups (P = 0.003).
38	Chung N (2014)(49)	Retrospective cohort study	225 intervention 557 control	Clinical pharmacy services including counseling and education	12-months	A1C, hospitalizations, and rate of emergency visits	The intervention group experienced significant reductions in A1C and a decreased rate of hospitalization. Compared to the control group, the

							intervention group also had a lower rate of emergency visits.
39	Correr CJ (2011)(50)	Quasi-experimental, non-randomized controlled trial	50 intervention 46 control	Pharmacotherapy follow-up (PF) program (assessment of medication outcome)	24-months	A1C, BMI, blood pressure, fasting capillary glycaemia, and medication regimen complexity index (MRCI)	There was a greater reduction in A1C (P < 0.001) and greater reduction in fasting capillary glycemia reduction (P = 0.022) in the intervention group. However, there were no significant differences in any other clinical measures between the groups. The MRCI decreased at the end of the follow-up period.
40	Johnson KA (2010)(51)	Retrospective, non-randomized clinical trial	222 intervention 262 control	Pharmacy care service including education and medication	24-months	A1c, BMI, blood pressure, and LDL	A1C was reduced significantly among intervention patients relative to the control group (P < 0.001). Similarly, there were significant improvements reported for blood pressure and LDL among

				management			intervention patients. No significant difference was found for BMI score.
41	McAdam-Marx(2015)(52)	Retrospective cohort analysis	303 intervention 394 control	Collaborative management of care for diabetes including education and medication management	12-months	A1C, health service cost, and health service utilization	The level of A1C was significantly reduced in the intervention group. The intervention group experienced a smaller average increase in health service costs.
42	Skinner JS (2015)(53)	Retrospective case –control	29 intervention 29 control	Medication therapy management (MTM) including educational, monitoring service and improve adherence	12-months	A1C, systolic blood pressure, diastolic blood pressure, LDL, HDL, and triglycerides	A1C was lower in the intervention group compared to the control ($P < 0.001$). Similarly, LDL was lower in the intervention group compared to the control ($P = 0.02$).

				medication			
43	Spence MM(2015)(54)	Retrospective cohort study	359 intervention 428 control	Outpatient pharmacy clinical service (OPCS) including diabetes education and medication adherence	12-months	A1C, LDL, health service utilization, and medication adherence	There was a greater, statistically significant reduction in A1C in the intervention group (P = 0.001). there was less likely to have an ED visit in intervention group (P = 0.040), but no significant difference in the hospital admission rates was shown.
44	Wertz D (2012)(55)	Quasi-experimental pre/post longitudinal study	214 intervention 180 control	Pharmacist-based educational services including education, medication management and self-monitoring	12-months	A1C, blood pressure, cost of Diabetes, and lipid Profile	There was a significant reduction in A1C, blood pressure, and lipid levels in the intervention group. The cost of diabetes increased for all groups over time.

3.3.1. Study selection

The initial search identified 951 studies, of which 361 were duplicates and thus excluded. During this screening, 479 studies were excluded because they were irrelevant to our research question. The remaining 111 studies underwent full-text assessment using the inclusion and exclusion criteria provided above. During this stage, a total of 68 studies were excluded: 24 studies were excluded because they were not compatible with this review's outcomes of interest; 22 studies were excluded because the interventions were not pharmacy-based; 11 studies were excluded because they did not follow a proper study design; and, 10 studies were excluded because they did not focus on diabetes. Thus, a total of 44 studies were included in the qualitative review. The process of selection of these studies is depicted in a PRISMA flow diagram (Figure 3.1) and a detailed description of the included studies is provided in Table 3.1. Of all included studies, 40 studies focused on pharmacy-based educational and behavioural consultation interventions addressing self-management, self-monitoring, medication adherence, and lifestyle modification and only 4 studies (38)(29)(50)(48) focused on medication-related interventions such as pharmacotherapy and follow-up programs . Of the 44 studies: 39 studies reported a mean reduction of A1C (%) as a clinical outcome; 16 studies reported a difference of BMI; 12 studies reported the effects of a pharmacy intervention on quality of life; and 9 studies reported the effects of a pharmacy intervention on health care utilization. Of the 44 studies, 42 studies examined people with type 2 diabetes and 2 studies (37) (49) considered people with type 1 diabetes as a target population. The Cochrane risk of bias tool was used to assess the risk of bias using six criteria. To assess random sequence generation, considerations were made for the type of study design. 36 studies made use of randomized controlled trials, two studies made use of non-randomized controlled trials, and six studies used a retrospective non-randomized design including three cohort studies, 1 case-control, one longitudinal and one quasi-experimental study. Studies that did not use a randomized controlled design were excluded from the meta-analysis. Among studies based on randomized controlled trials, consideration of allocation concealment and blinding of outcome assessment were difficult to assess because of the lack of information provided in most studies. Similarly, most studies also lacked adequate information about incomplete outcome data and selective reporting (Figure 3.2). Therefore, 32 studies were deemed of appropriate quality and were included in the meta-analysis calculating the pooled standardized mean difference (SMD) of A1C (%) and 13 studies were deemed of appropriate quality and were included in the meta-analysis calculating the pooled standardized mean difference (SMD) in BMI (kg/m2).

Table 3.2. mean difference of A1C and BMI from baseline to follow-up and net effect in intervention group versus control group

First Author	Mean difference	SD	Mean difference	SD	Difference in group	SE	P-value
A1C (%)							
Jaber LA	2.3	0.71	0.1	0.71	2.2	0.484	0.01
Sarkadi A	0.04	1.07	0.3	1.05	-0.26	0.251	0.01
Odegard PS	2	1.07	1.8	1.05	0.2	0.230	0.11
Rothman Rl	2.5	1.07	1.6	1.05	0.9	0.150	0.05
Suppapitiporn S	0.25	1.07	-0.79	1.05	1.04	0.112	0.05
Clifford RM	0.5	0.63	0	0.45	0.5	0.157	0.002
Cohen HM	2.1	1.95	0.9	2.92	1.2	0.253	0.03
Fornos JA	0.5	2.40	-0.7	2.69	1.2	0.192	0.08
Scott DM	1.72	1.07	0.7	1.05	1.02	0.185	0.003
Krass I	1	0.71	0.3	0.63	0.7	0.140	0.01
Al Mazroui NR	1.6	0.56	0.1	0.56	1.5	0.180	0.01
Taveira TH	0.9	1.07	0.1	1.05	0.8	0.199	0.05

Cohen LB	0.41	0.71	0.2	0.71	0.21	0.202	0.05
Farsaei S	1.8	2.25	-0.1	1.42	1.9	0.161	0.3
Sriram S	1.71	0.30	0.72	0.22	0.99	0.306	0.05
Mehuys E	0.6	1.55	0.1	1.30	0.5	0.123	0.1
Neto PR	0.7	0.61	0	0.73	0.7	0.153	0.8
Jacobs M	1.8	1.84	0.8	2.26	1	0.160	0.003
Chan CW	1.57	0.71	0.4	0.71	1.17	0.227	0.01
Kraemer DF	0.52	1.09	0.16	1.03	0.36	0.251	0.008
Planas LG	0.52	1.34	-0.11	1.23	0.63	0.285	0.02
Jarab AS	0.8	1.30	-0.1	1.05	0.9	0.166	0.01
Ali M	1.6	0.83	0.6	0.90	1	0.320	0.001
Mourão AO	0.6	1.04	-0.7	1.05	1.3	0.219	0.001
Chung WW	1.4	0.71	0.2	0.71	1.2	0.151	0.16
Obarcanin E	0.9	0.38	0.08	0.29	0.82	0.329	0.001
Cani CG	0.57	1.99	0.08	2.26	0.49	0.240	0.001
Wishah RA	1.7	1.07	0.3	1.05	1.4	0.215	0.05
Mansell K	1.69	1.03	0.7	1.30	0.99	0.416	0.37

Lim PC	0.9	0.39	0.08	0.22	0.82	0.312	0.001
Jameson JP	1.5	2.65	0.4	1.60	1.1	0.200	0.06
Chen JH	0.83	1.84	-0.43	2.12	1.26	0.205	0.002
BMI Level							
Clifford RM	0.6	0.84	-0.1	0.45	0.7	0.159	0.005
Fornos JA	0.9	0.84	0.3	7.42	0.6	0.189	0.01
Scott DM	0.4	4.98	0.2	6.11	0.2	0.175	0.1
Krass I	0.3	0.89	0.2	1.14	0.1	0.122	0.3
Al Mazroui NR	1.05	1.74	-0.01	2.02	1.06	0.133	0.004
Netro PR	0.1	0.30	0	0.10	0.1	0.145	0.001
Sriram S	1.85	0.21	-0.09	0.29	1.94	0.531	0.01
Ali M	3.86	5.87	1.09	7.97	2.77	0.298	0.05
Jarab AS	0.5	1.97	-0.4	1.61	0.9	0.163	0.1
Mourão AO	-0.1	0.45	0.3	0.63	-0.4	0.207	0.1
Wishah RA	0.5	4.95	-0.5	6.18	1	0.195	0.11
Lim PC	0.29	0.91	-0.09	0.60	0.38	0.233	0.14

3.3.2. A1C (%) outcome

Among 32 randomized controlled trials, 4,132 participants with type 2 diabetes mellitus, including 2,100 in an intervention group and 2,032 in a control group, were examined with an average of 9.96 months follow-up duration (3-36 months). Participants in the interventions group were exposed to some type of pharmacy-based intervention. A random effect model was used to estimate the pooled standardized mean difference in A1C (%) between the intervention and the control group. Results from the chi-square test for heterogeneity were significant (P < 0.001) and I-squared (93.1%) showed high heterogeneity between studies, therefore random effect models were used. The pooled estimate of the standardized net mean difference of HA1C (%) across groups was 0.96% (95% CI 0.71 to 1.22; P<0.001). The forest plot shows the standardized mean difference of A1C (%), and 95% CI for each study included in the meta-analysis (Figure 3.5). Importantly, there was no evidence of publication bias indicated by the Egger's test (P = 0.20) and Begg's adjusted rank correlation test (P=0.52) .Results of metan-based Influence Analysis to examine the effect of excluding each study on the pooled estimate of SMD determined that 8 studies including; Sriram S et al (44) Al Mazroui NR et al (15) Sarkadi A et al (42) Jaber LA et al(25) Lim PC et al(32) Obarcanin E et al(37) Chung WW et al(17)and Wishah RA et al (47)had the greatest impact on the pooled effect respectively; after excluding these 8 studies the pooled SMD was 0.65%(0.49% to 0.80%) and Heterogeneity decreased to I2=74.3%

3.3.3. BMI (kg/m2) outcome

Among studies under this review, 13 randomized controlled trials qualified for inclusion in the meta-analysis calculating the pooled mean difference in BMI. In total, 1,827 participants with type 2 diabetes mellitus, including 863 in an intervention group and 859 in a control group, were examined with average 10.66-month follow-up duration (4-36 month). Participants in the intervention group were exposed to some type of pharmacy-based intervention. A random effect model was used to estimate the pooled standardized mean difference in BMI between the intervention and the control group. Results from the chi-square test for heterogeneity were significant (P < 0.001) and I-squared (94.5%) showed high heterogeneity between studies, so random effect model was adopted. The pooled estimate of the standardized net mean difference in BMI across groups was 0.61(95% CI 0.20 to 1.03; P=0.000). The forest plot shows the standardized mean difference of BMI and 95% CI for each study included in the meta-analysis (Figure 3.6). Importantly, there was no evidence of publication bias indicated by the Egger's test (P = 0.08) and Begg's adjusted rank correlation test (P=0.83). Results of metan-based Influence Analysis to examine the effect of excluding each study on the pooled estimate of SMD

indicated that ,Sriram S et al(44) had the greatest impact on pooled effect; after excluding this study, the pooled SMD was 0.20(0.07 to 0.34) and Heterogeneity decreased to I2=48.8%.

Figure 3.2. Risk of bias assessment in included studies

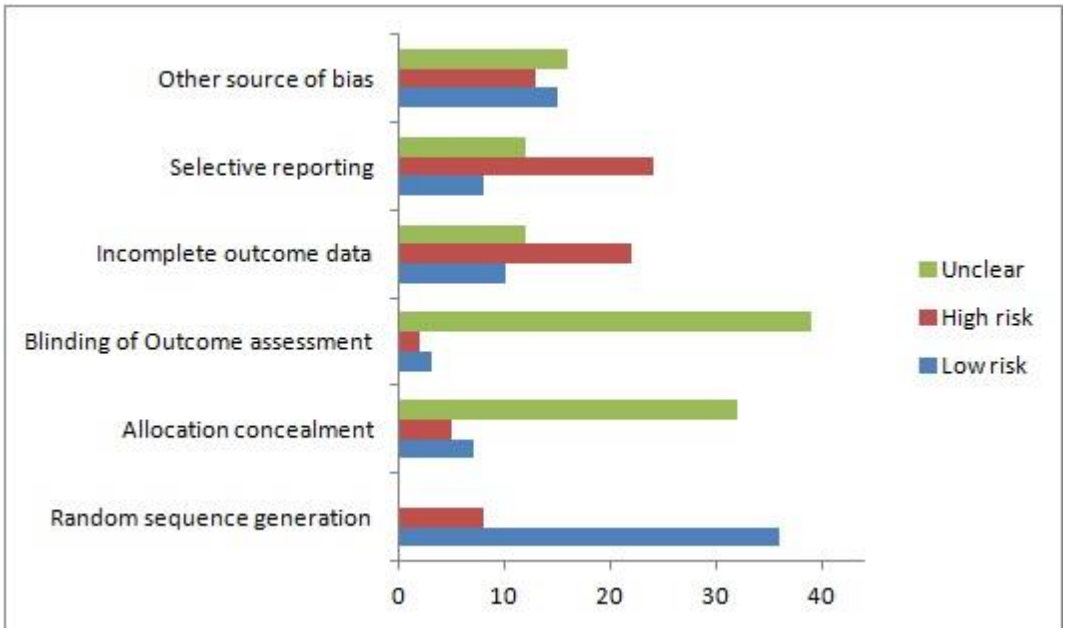


Figure 3.3. Funnel plot of standardize mean difference of HbA1c

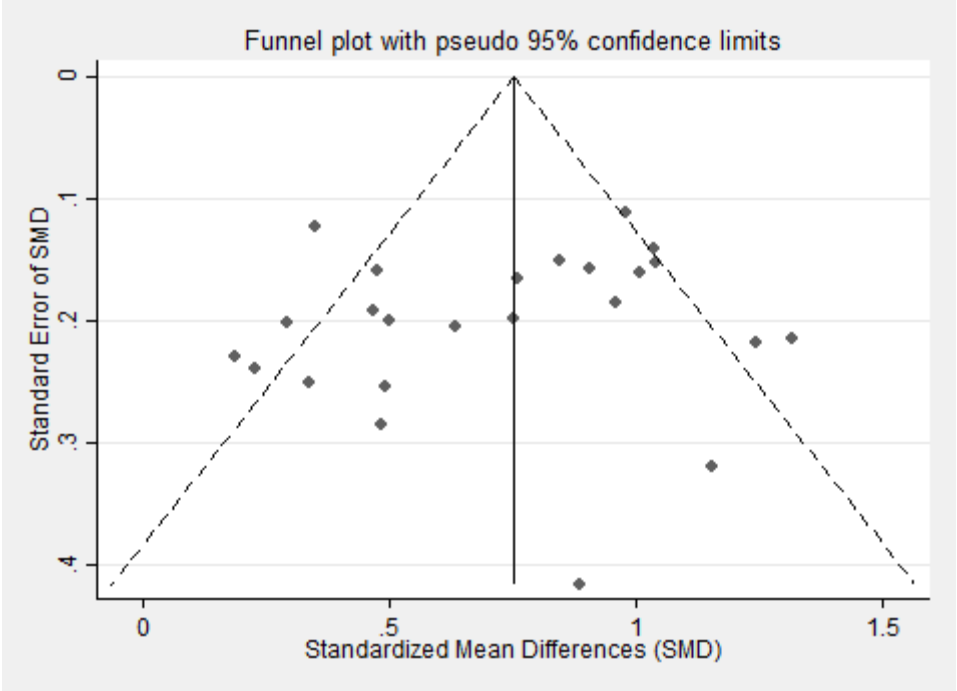


Figure 3.4. Funnel plot of standardize mean difference of BMI

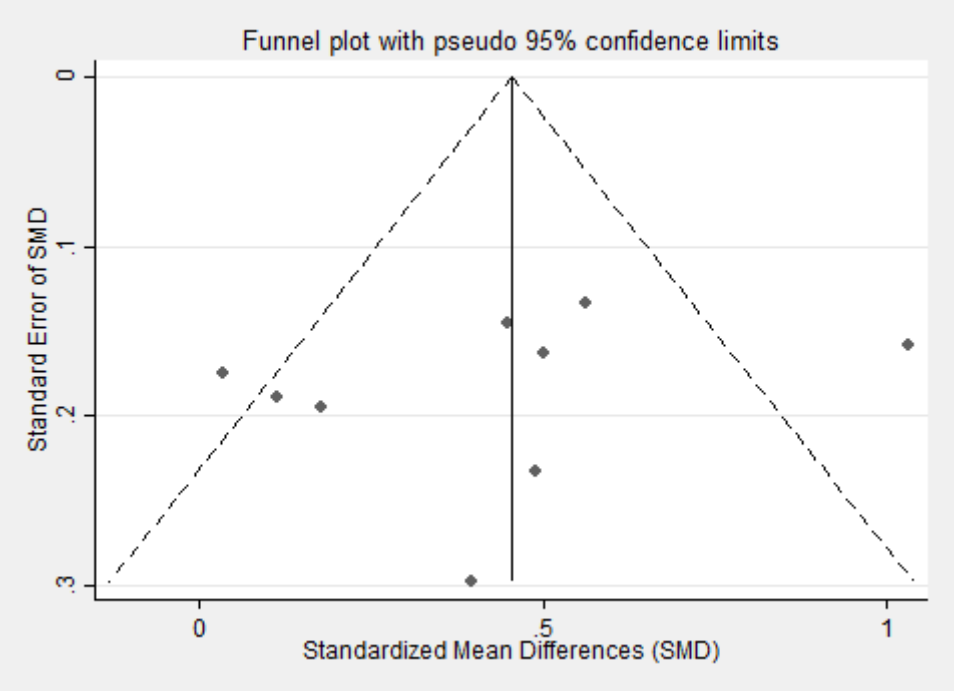


Figure 3.5. Forest plot of standardized net mean difference of A1C (baseline to the last follow-up) in intervention versus control group in 32 randomized controlled trials

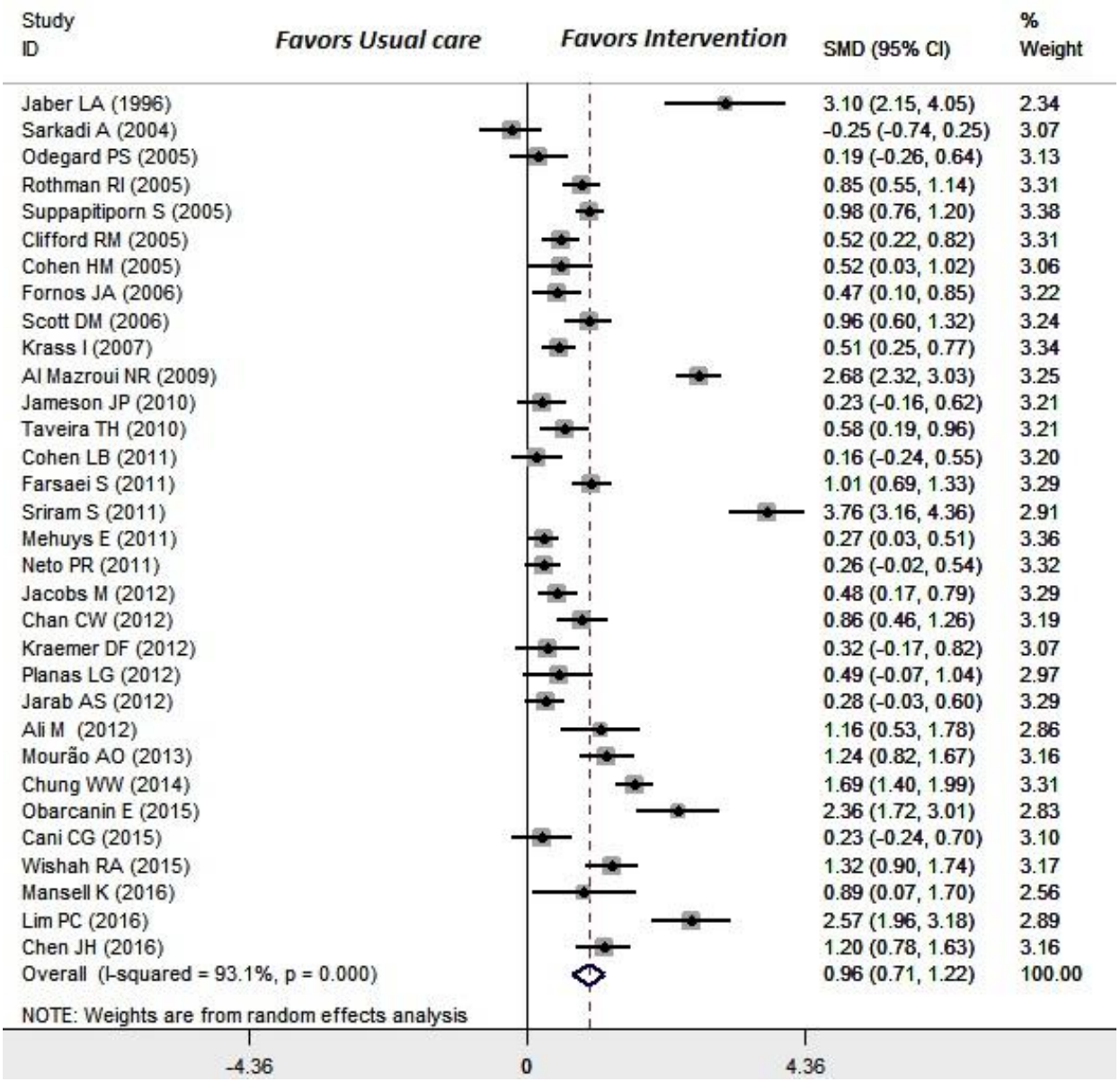
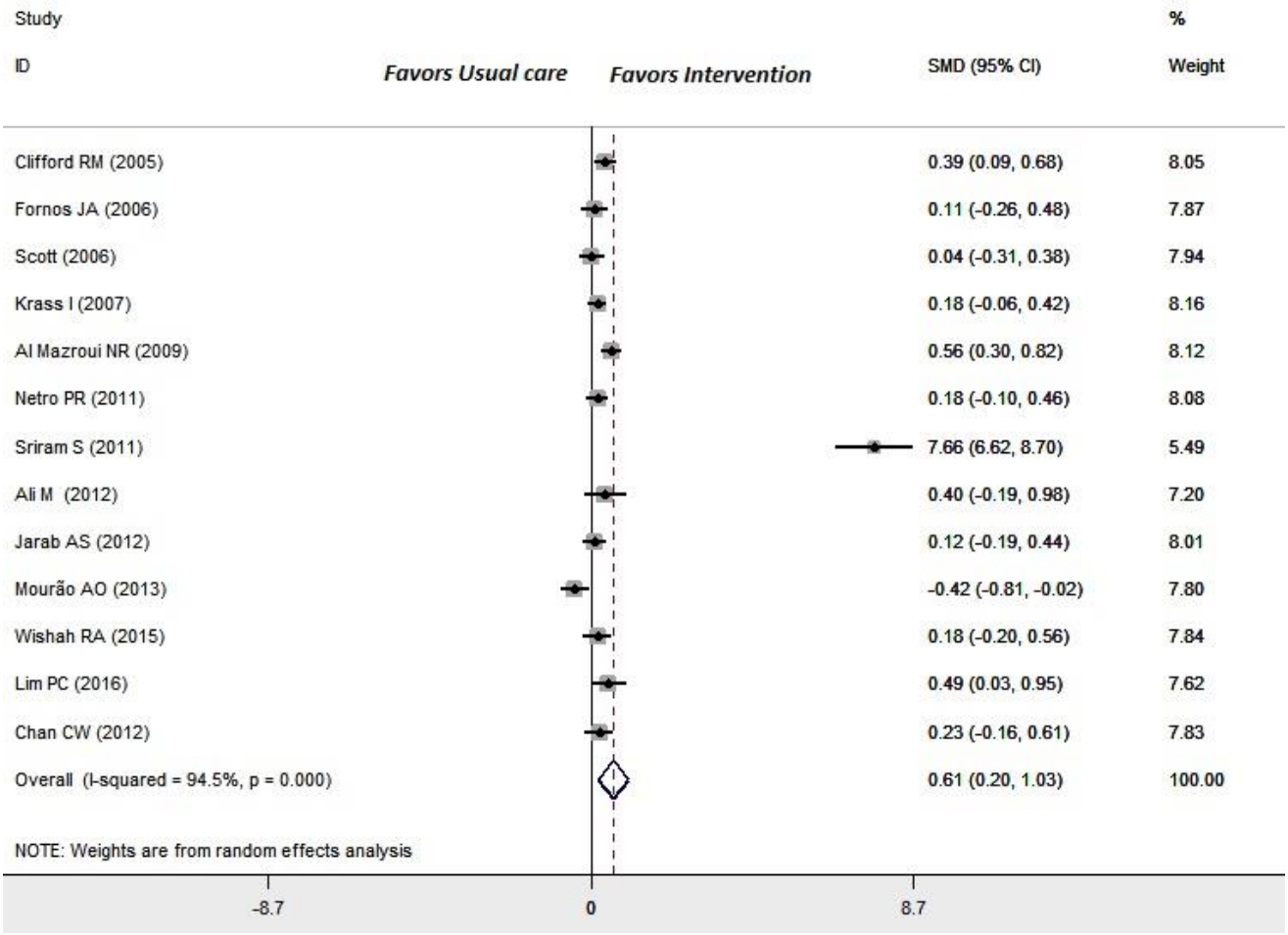


Figure 3.6. Forest plot of standardized net mean difference of BMI (kg/m2) (baseline to the last follow-up) in intervention versus control group in 13 randomized controlled trials



3.3.4. Quality of life outcome

Nine randomized controlled trials reported quality of life scores as one of the outcomes of a pharmacy-based intervention for patients with diabetes. In total, there were 1,564 participants, including 809 in an intervention group and 705 in a control group with average of 9.22 months follow-up duration (6-12 months). However, a meta-analysis was not conducted due to the variability of instruments used to assess the quality of life across included studies. Six included studies in this review demonstrated that pharmacy-based interventions are directly associated with improvements in quality of life among patients with diabetes in the intervention group compared to control group. (13)(14) (16) (31)(40) (44).Among four studies, which assessed the quality of life among diabetes patients using diabetes

specific questionnaires, just two studies reported significant improvement in the intervention versus control group after the follow-up duration (16)(44). Cani CG et al (16) used a validated Brazilian version of a diabetes quality of life measure and reported a net difference of 8.95 in the quality of life score improvement across the intervention and control group (P = 0.001). Sriram S et al(44) used the Audit of Diabetes-Dependent Quality of Life (ADDQOL) tool to assess the quality of life in their respective samples and reported that the net difference of quality of life score was 1.09 in the intervention compared to the control group (P = 0.01). Among six studies assessed the quality of life using generic questionnaires, four studies demonstrated a significant improvement in the intervention group versus control group (13) (14)(31)(40) . Adibe et al (13) reported that the net difference of overall HRQOL score was 0.22 between intervention and control groups (P = <0.0001). The study conducted by Ali et al(14) used the short form SF-36 to compare the quality of life scores between patients in the intervention and patients in the control group. This study reported a net difference of 16.99 in the quality of life score improvement across the intervention and control group (P = 0.001). Krass et al (31) used EQ-5D (health state scale score) and reported a net difference of 4.2 in quality of life between the intervention and control groups (P = 0.02). Lastly, Ramanath KV et al (40) used the World Health Organization-Brief Quality of Life questionnaire, and results showed a positive effect of pharmacy-based interventions on quality of life among diabetic patients. Specifically, the net difference in the quality of life score was 7.39 for the intervention group compared to the control group (P = 0.01). Figure 3.7 shows the net mean difference of improvement in quality of life in intervention versus control group for each study included in this review.

3.3.5. Health service utilization outcome

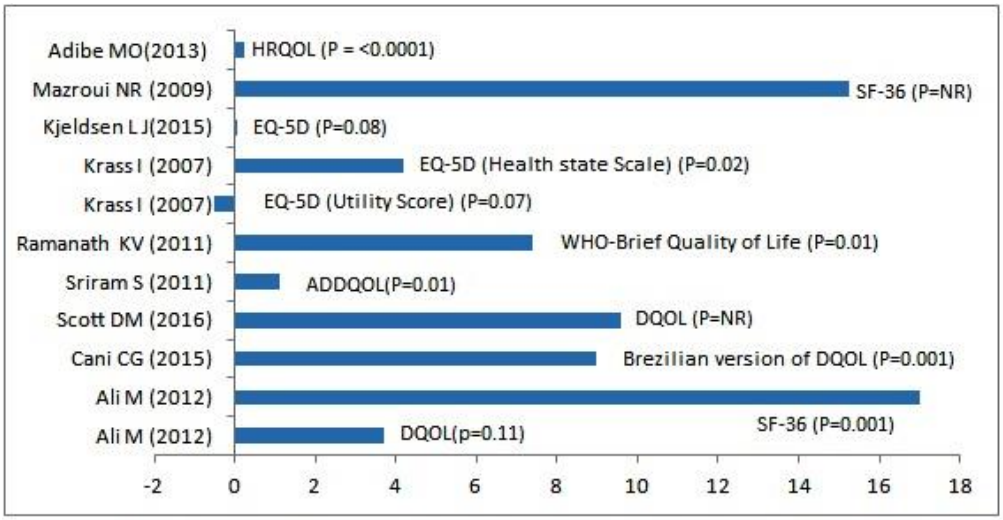
In total, six studies (three RTCs and three non-RTCs) estimated differences in heath service utilization related to diabetes, associated with patients receiving pharmacy-based intervention and those not receiving the pharmacy-based intervention; all of the studies considered a 12 month follow-up duration to assess the effect of intervention.

The three randomized controlled trials studies noted no significant differences in health care service utilization outcomes across intervention and control groups. Kjeldsen LJ et al noted no significant differences across groups in terms of the number of medications, general physician visits, and hospitalization rates (29). Additionally, differences in medication and supplies usage based on insurance claim data was not significantly different between those receiving pharmacy counseling and those not receiving this intervention (30). Lastly, Rothman et al (41) reported no statistically significant difference

in health care utilization rate between patients receiving pharmacist care and those not receiving such care.

Among non-RTCs studies, two studies (48) (49) noted a significant reduction in inpatient admissions and one study (54) showed a significant reduction in emergency visits in intervention group compared with the control group. Brophy et al (48) conducted a retrospective quasi-experimental study to assess health care service utilization among patients receiving collaborative pharmacy benefit manager health plans. They reported lower hospitalization rates in the intervention group compared with control group (P=0.002). A retrospective cohort study was performed by Chung N et al (49) to estimate the difference in the hospitalization rate of patients referred to a clinical pharmacist versus patients in a control group. They reported an average of eight more hospitalizations for patients in the control group (P = 0.06). A retrospective cohort study demonstrated that diabetic patients in the intervention group were less likely to visit the emergency room (1.67% vs. 4.21%, P = 0.04), but there was no difference in inpatient admission rate compared to controls (54). Figure 3.8 shows the net difference in reduction of inpatient admissions and emergency visits in the intervention versus control groups for each study included in this review.

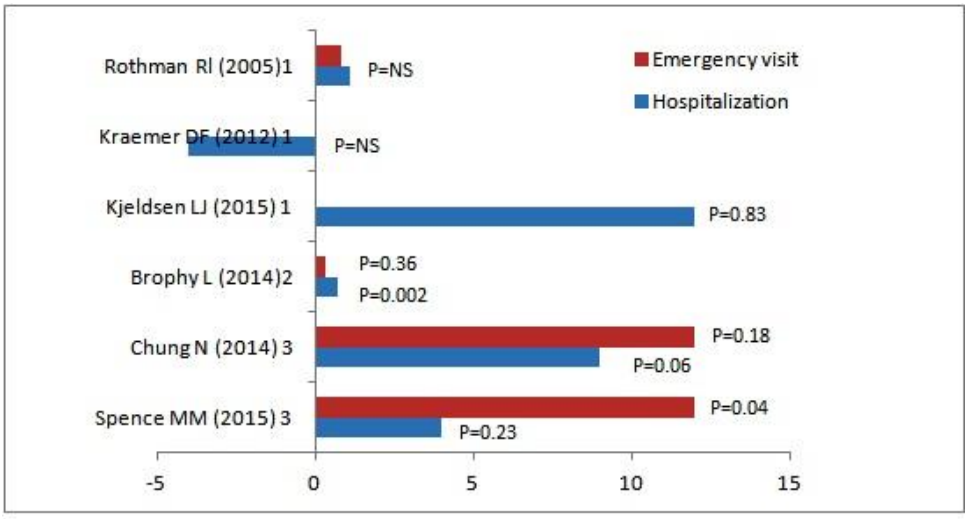
Figure 3.7. Net difference in improvement of quality of life score across intervention and control group among nine randomized controlled trials



Net difference in improvement of quality of life across intervention and control group

NS= Not Significant , NR= Not Reported

Figure 3.8.Net difference in reduction of inpatient admission and emergency visit across intervention and control group



Net difference in the reduction of inpatient admission and emergency visit across intervention and control group

1= RCT , 2= Retrospective quasi experimental 3= Retrospective cohort study

NS= Not significant

3.4. Discussion

This systematic review examined the effectiveness of pharmacy-based interventions among patients with diabetes. Although pharmacy-based interventions in this review included a wide range of interventions which have been implemented in different health care settings, there is some consistency regarding type of interventions among studies. Forty studies considered education-oriented programs for patients with type 2 diabetes; these educational programs covered areas such as self-management, self-monitoring, medication adherence, lifestyle modification and increased awareness about diabetes-complications. Only four studies have not included education –oriented interventions and focused on pharmacotherapy interventions to decrease risk of medication related problems. Three of these four studies were excluded from the meta-analysis because of study design (48) (50) and not reporting of A1C (29) and hence only one study of these four (38) was included in meta-analysis. Hence, although there is some inherent heterogeneity, the consistency of these studies lends some assurance to the results observed.

Our finding about the pooled standardized mean difference of AIC between the intervention groups versus the control groups supports the notion that pharmacy-based interventions have a significant effect on lowering A1C levels in patients with diabetes. There is consistency between results of all randomized controlled trial with non-RTCs studies in our review, therefore all seven non-RCTs ;which were excluded from meta-analysis ; determined significant reduction of A1C level in intervention group relative to control group(49)(50)(51)(52)(53)(54)(55).

According to the literature, there was one systematic review and meta-analysis which estimated the effect of pharmacist intervention on level of A1C in 2007(6). Machado M et al included 18 Randomized controlled trials and determined that pharmacist intervention decreased A1C level 0.62% in intervention group versus control group.

Other research also demonstrated the significant effect of different types of community-based interventions such as behavioural/educational interventions and self-care management programming on lowering A1C levels in patients with diabetes. Gary et al (56) conducted a meta-analysis to assess the effectiveness of behavioural/educational interventions in controlling diabetes. Among 18 randomized controlled trials, A1C was reduced by an average of 0.43% (56). Moreover, Ellis et al (57) assessed the effect of diabetes education on glycemic control through a meta-analysis and found changes in A1C

were 0.32% lower in the intervention group compared with the control group. Improvements in lowering A1C averaging 0.36% were also found for patients receiving self-care management programming according to a meta-analysis conducted by Minet et al (58). Our results show a net reduction of A1C of 0.96%, which is higher than estimates from previous studies, focused on behavioural/educational and self-care management interventions. The results of this meta-analysis confirm that pharmacy-based interventions are effective in reducing A1C levels. Since lowering A1C can help prevent diabetes–related complications, pharmacy-based interventions may help reduce some of this burden.

In terms of BMI, this review showed that, pharmacy–based interventions are associated with significant reduction in BMI in intervention group compared with control group (0.61: 95% CI 0.20 to 1.03 p=0.000). Comparatively, other studies have reported a net mean reduction in BMI among patients with diabetes of less than 0.61 as a result of community interventions. For example, Liang Chen et al (59) conducted a meta-analysis to assess the effectiveness of a lifestyle intervention on patients with type 2 diabetes. Results demonstrated that the standardized difference in means of change from baseline to the time of the last follow-up significantly favoured the intervention group compared to the control group in BMI (-0.29; 95% CI -0.52 to - 0.06, P = 0.014). Since overweight and obesity can increase an individual's risk of chronic complications of diabetes (60)(61) , lowering one's BMI through pharmacy-based interventions could also have a significant role in reducing diabetes complications.

Although result of meta-analysis among all randomized controlled trials show significant improvement in BMI, one retrospective, non-randomized clinical trial and one quasi-experimental study in our review; which were excluded from meta-analysis; demonstrated that, there is no significant relationship between improving BMI in intervention group compared with control group (50) (51), therefore type of study design might have great impact on result in this area.

Regarding the effect of pharmacy –based intervention on quality of life, a review of the included studies showed that the type of questionnaire used, and follow-up duration have an impact on results. Review of evidence included in our analysis indicated that more robust improvements in quality of life were detected using generic questionnaires. Average follow-up duration in studies, which report significant differences in quality of life between the intervention and control groups, is 10 months whereas; average follow-up for those studies reporting non-significant findings is about 6 months , this points to pharmacy –based interventions showing some improvement in quality of life in long term. Previous

reviews that assessed the effect of pharmacy-based interventions on quality of life determined that lack of sensitive questionnaires could be one of the reasons behind observing non-significant findings in some included studies (3). Patient reported quality of life and its measurement are becoming increasingly important and hence there is a need for conducting more research in this area especially as different health care payment models proliferate creating a need for understanding how the different models affect patients' quality of life. (62)(63).

When considering health service utilization, type and level of evidence have great impact on the result. Since significant difference between two group were reported only in retrospective studies (48)(49)(54) rather than RCTs, there is lack of reliability of finding in this area. Overlay, the results of the review provided a mixed picture of the effect of pharmacy-based interventions on health care utilization and pointed to the need for more research in health care resource use.

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CHAPTER 4-Patient-level micro-simulation model for evaluating the future potential cost–effectiveness of pharmacy-based interventions in the control and management of diabetes-related complications in Canada

My contributions to this manuscript included conceiving and designing the study, conducting micro-simulation model, extracting and estimating all input parameters, running the experiments, analyzing and interpreting the findings and manuscript preparation. Dr. Marwa Farag and Dr. Nathaniel Osgood helped in designing the micro-simulation model. All authors contributed in the interpretation of findings and in reviewing and revising the manuscript.

In this chapter, I use an agent-based model along with system dynamics to model the progression of four diabetes-related complications and evaluate the cost–effectiveness of pharmacy-based interventions in the control and management of diabetes-related complications in Canada over a life-time horizon. Findings of this study provide strong evidence for Canadian health policymakers to implement potential cost-effective pharmacy-based interventions for the control and management of diabetes-related complication in Canada.

4.1. Background

Diabetes is one of the growing non-communicable diseases worldwide (1-3) and is a leading cause of death in most developing countries (4) Diabetes is also associated with a number of micro-vascular and macro-vascular complications (5-8) which lead to premature death, reduce individuals' quality of life, and economic burden (3, 5-9). Due to high economic burden of diabetes in Canada (10-12), there is an opportunity to reduce this expenditure through the adoption of diabetes management interventions such as pharmacy-based ones. Pharmacy-based interventions include a wide range of services, all with the common aim of giving diabetes patients greater control and management over their disease (13-17). Rising health care costs, limitations on available health care resources, and debates over the comparative effectiveness of diabetes management strategies has led to an increased interest in developing analytic models that can evaluate the future potential cost-effectiveness of such intervention. These models compliment clinical trials, which typically provide data on intermediate outcomes like HbA1c, SBP, and LDL. Data from clinical trials can then be used to populate analytic models, and provides a basis for predicting long-term health outcomes, like life-years saved or QALYs gained.

This study aims to evaluate the future potential cost effectiveness of pharmacy-based interventions for diabetes management in Canada. In order to conduct this evaluation, we estimate life time outcome and quality-adjusted life expectancy among diabetes patients who experience diabetes-related complications (heart failure, stroke, amputation, and blindness) or diabetes-related death.

4.2. Methods

4.2.1. Model Overview

We evaluated the future potential cost-effectiveness of pharmacy-based interventions for patients with diabetes compared to usual care. Intermediate outcome of intervention was modeled as reduction of hemoglobin A1C (HbA1c) level, body mass Index (BMI), systolic blood pressure (SBP), and low-density lipoproteins (LDL) as most important risk factors of four common diabetes-related complications including heart failure, stroke, amputation and blindness. Cost was quantified as the annual cost of heart failure, stroke, amputation and/or blindness among diabetes patients; and, the cost associated

with pharmacy-based interventions borne by society. To fully capture the effect of the intervention, we extrapolated the potential effects of intervention in relation to cost, health outcomes, and health-related quality of life (HRQoL) over the next 50 years by calculating the incremental cost per QALY gained of pharmacy-based intervention versus usual care in base case scenario. This model considered both costs and health effects, which were adjusted by discount rate of 3% according to the Canadian Agency for Drugs and Technologies in Health (CADTH) guideline (18). Both deterministic and Monte Carlo probabilistic sensitivity analysis were used to estimate uncertainty around results. Detail of model overview are shown in Figure 4.1

4.2.2. Model Structure

Using Anylogic software package 8.2.3, a hybrid simulation model was developed, which included agent-based and system dynamics. Agent-based modeling (ABM) enables to simulate more complex interactions and processes associated with chronic disease. Thus, this technique is very suitable for incorporating individuals with different risk factors and health behavior characteristic and evaluating the impact of adjusting risk factors on the better control and management of diabetes (19).

We captured four major diabetes-related complications progresses among patients with heterogeneous characteristics through state-transition formalism as state charts in ABM model. Also, we used a system-dynamic approach to estimate accumulated costs and QALYs over time (Figure 4.2-4.3).

The simulation model mimicked a multistage study and was populated by data from the Survey on Living with Chronic Diseases in Canada (SLCDC). This data was used to build an individual-level micro-simulation model predictive of diabetes-related complications (heart failure, stroke, blindness, and amputation) and death, and the associated health care cost and QALYs in the presence and absence of pharmacist-based intervention. Within the model, a set of attributes known to be associated with diabetes-related complications was assigned to each person. The attributes were also subject to a set of rules (i.e. transition probabilities) and states reward (i.e. cost and utility). All parameters are shown in Table (4.1).

Figure 4.1. Flow chart of simulation

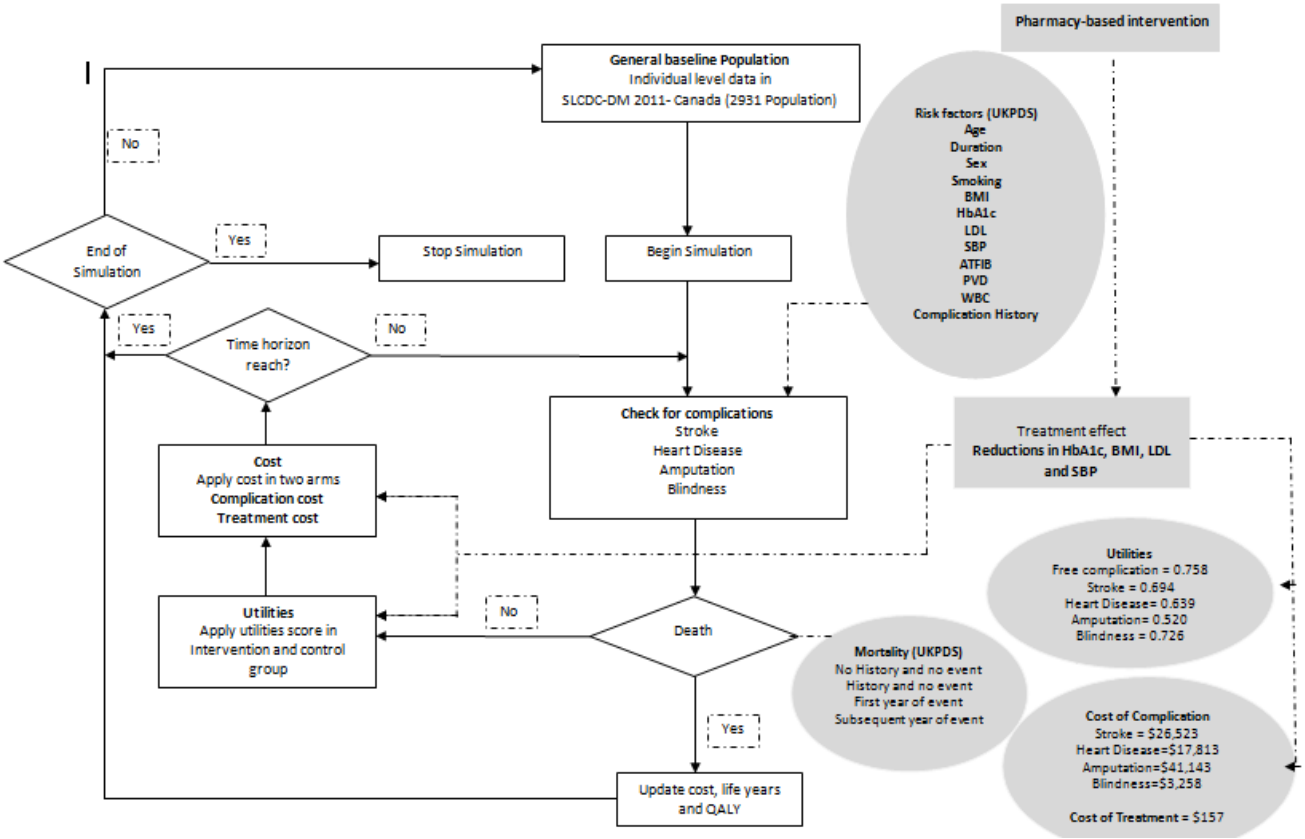


Figure 4.2: Agent-based model architectures in Anylogic

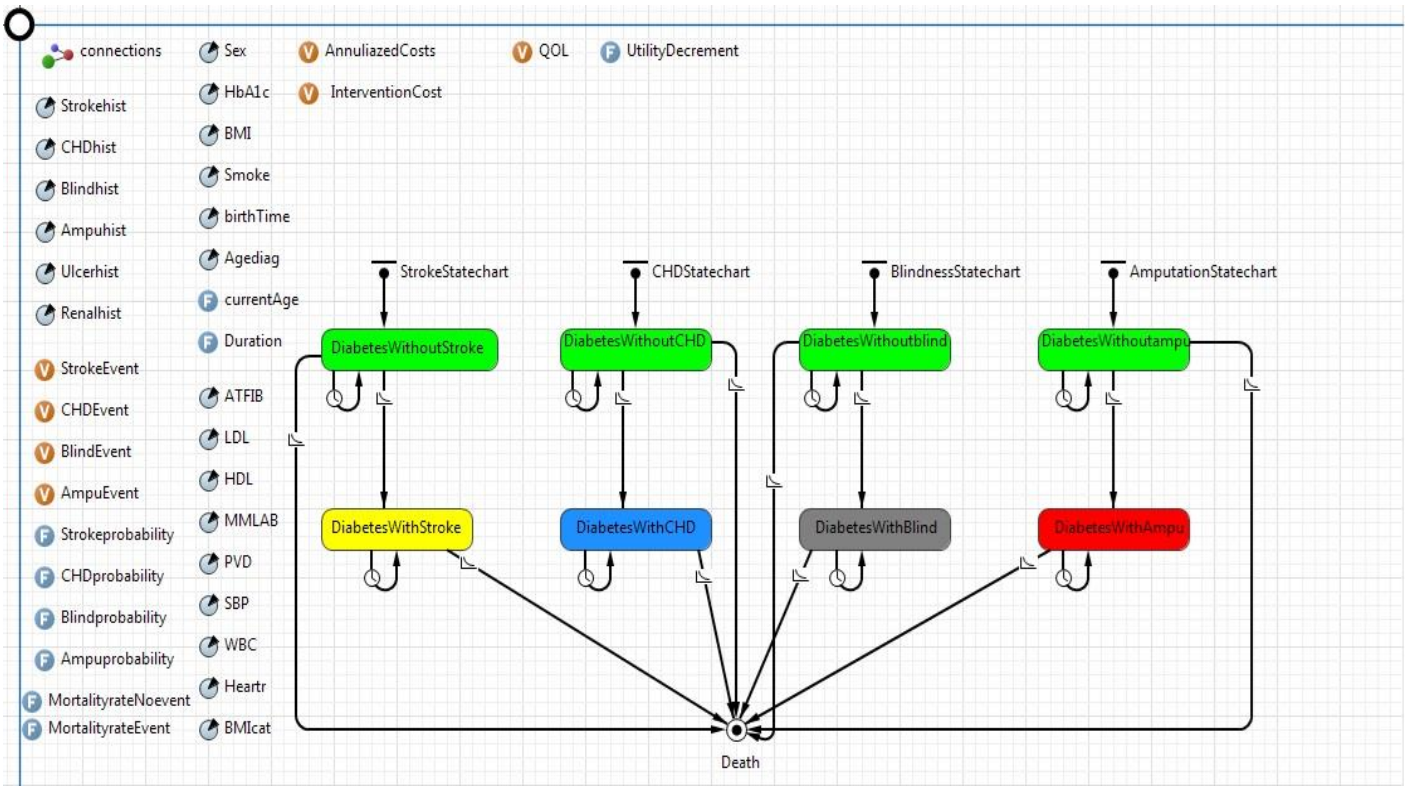
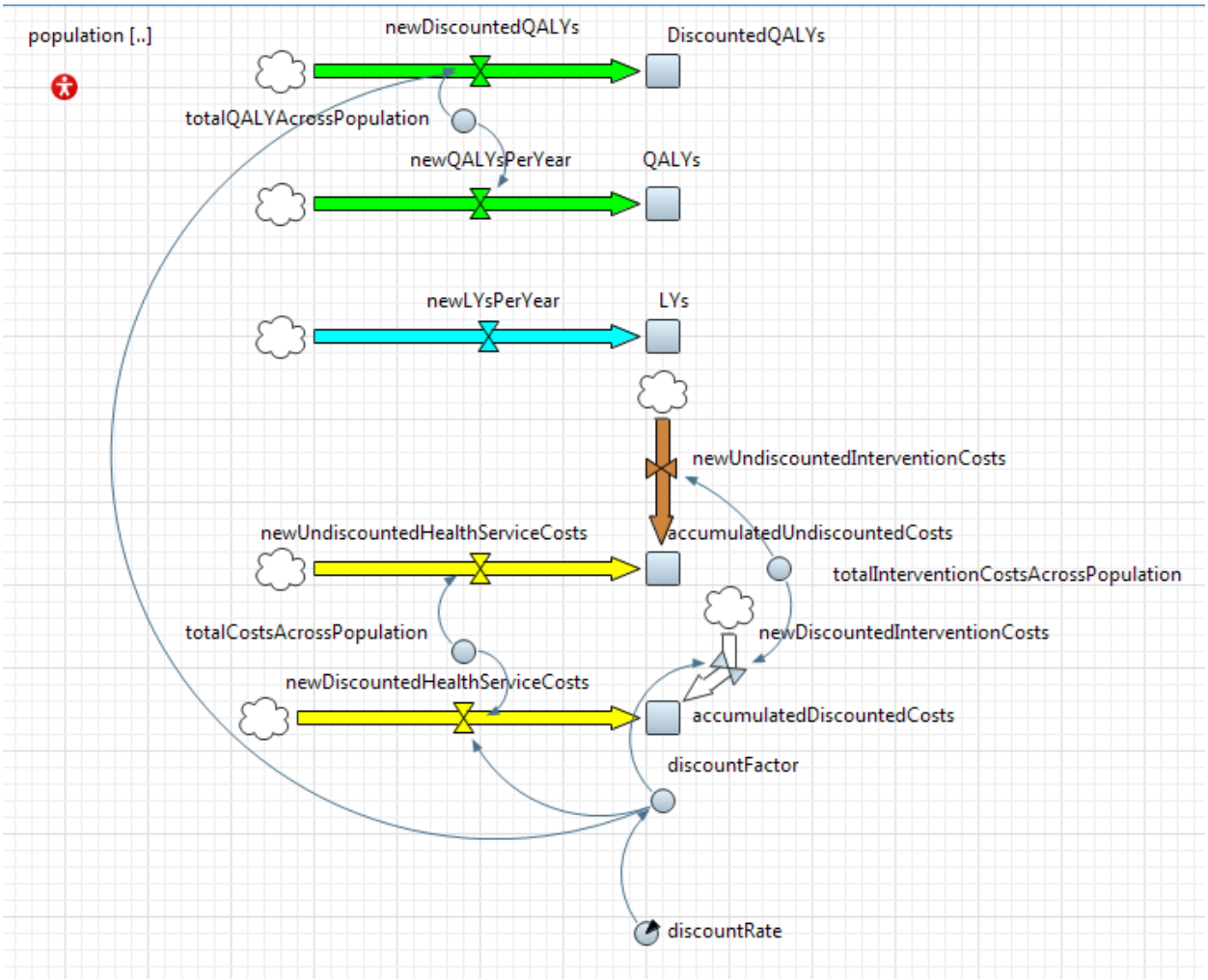


Figure 4.3. System dynamic model architectures in Anylogic



4.2.3. Data source

4.2.3.1. Diabetes Risk Factors

To estimate a diabetes patient's progression from complication free to a complication ridden state, we used the UK Prospective Diabetes Study (UKPDS) outcome model (20). This model was developed using data from 5,102 patients followed over a 20-year trial period, and 4,031 survivors followed over a 10-year post-trial monitoring period. The UKPDS model allowed us to estimate the main risk equations for developing the four diabetes–related complications of interest in our study: heart failure, stroke, amputation and blindness. It also allowed us to derive parametric proportional hazard models predictive of absolute risk factors of diabetes-related complications, including: age, sex, duration of diabetes,

smoking status, body mass index (BMI), HbA1c, SBP, LDL, high density lipoprotein cholesterol (HDL), heart rate, presences of micro- or macro-albuminuria (MICLAB), atrial fibrillation (ATFIB), peripheral vascular disease (PVD), white blood cell count (WBC), amputation history, heart failure history, stroke history, blindness history, renal disease history, and ulcer foot history. UKPDS model used a Weibull proportional hazards regression to calculate the occurrence of the composite outcome, which combined both fatal and non-fatal events (20).

We extracted baseline characteristics from the 2,931 diabetes patients included in the SLCDC survey 2011 (Table 4.1) and risk equations for each of the baseline variables were taken from the UKPDS. This allowed us to estimate transition probabilities of developing diabetes-related complications (See Appendix D). For some of the risk questions which the corresponding baseline variables were not available in the SLCDC survey, we estimated baseline variables based on age and sex specific.

4.2.3.2. Mortality

To estimate progression from a complication-free state to a state where at least one of the four major complications or death have occurred, our analysis considered four equations for calculating risk of mortality based on the UKPDS model. The first equation estimates the probability of death in the first year following an occurrence of heart failure, stroke, amputation or blindness, based on a logistic regression. Similarly, the second equation is based on logistic regression. It estimates the risk of diabetes-related mortality among patients with a history of any one of these complications in all subsequent years. The third equation is based on multivariate Gompertz proportional hazards survival models, and estimates death among diabetes patients without any history of diabetes-related complications. In this equation, death is the result of a cause unrelated to diabetes. The fourth equation is slightly more nuanced, and estimates death among diabetes patients without complication who had a history of co-morbidities (20). Transition probabilities of death were calculated from these equations based on logistic regression and Gompertz proportional hazards model (See Appendix E).

4.2.3.3. Treatment Effect

The impact that pharmacy-based interventions have on four major risk factors associated with diabetes-related complications was extracted from recent systematic reviews and meta-analyses. The four major risk factors include: HbA1c, BMI, SBP, and LDL.

Hemoglobin (HbA1c)

From baseline to the last follow-up 12 months later, the standardized absolute mean difference in the reduction of HbA1c was significantly more favorable in the pharmacy- based intervention group, then in the control group (0.96%; 95% CI 0.71:1.22, P<0.001) (13).

Body Mass Index (BMI)

From baseline to the last follow-up 12 months later, the standardized absolute mean difference in the reduction of BMI units was 0.61 (95% CI 0.20: 1.03, P=0.000) in favor of the pharmacy-based intervention group (13).

Systolic Blood Pressure (SBP)

In comparison to the control group, there were significant reductions in SBP among diabetes patients in the pharmacy-based intervention group after a 12-month period (-6.2 mmHg (95% CI -7.8 to -4.6)) (17).

Low Density Lipoprotein (LDL) Cholesterol

In comparison to the control group, there were significant reductions in LDL cholesterol among diabetes patients in the pharmacy-based intervention group after a 12-month period (-11.7 mg/dL (-15.8 to -7.6)) (17).

4.2.3.4. Health Utilities

We assumed that utility values derived from the American population are relevant to the Canadian population. We quantified HRQoL for a set of health states of interest based on American catalogue of EQ-5D utility values (21). Health states of interest include: following a stroke, following heart failure, after the age of 70 years. Following a stroke, the resulting utility was 0.694. Following heart failure, the resulting utility was 0.636. After the age of 70, a utility decrement of 0.00029 per year was applied to all years.

Under the assumption that utility values derived from the United Kingdom population are relevant to Canada, the UKPDS outcome model was used to estimate HRQoL for a set of health states of interest. Health states of interest include: following an amputation, and following blindness. Following amputation, a utility decrement of 0.520 was applied. Following blindness, a utility decrement of 0.726

was applied. A weight of zero was assigned to death. If applicable to incorporate the effect of concurrent complications, a multiplicative method approach was applied (21).

4.2.3.5. Cost of Treating Diabetes-Related Complications

Health care resource utilization and their costs associated with the management of diabetes-related complications were extracted from the Ontario Ministry of Health and Long-Term Care (22). Total costs of patients with diabetes and patients with complications were quantified in terms of hospitalizations, outpatient visits, emergency visits, home care and long-term management costs. Costs were inflated to the value of the 2016 Canadian dollar using the health component of the Canadian Consumer Price Index. On average, the annual cost for patients without diabetes-related complications was $2,075 (22). The estimated costs for each of the four diabetes-related complications in the first year they occur, and for all subsequent years are shown in Table (4.1).

4.2.3.6. Intervention Costs

To estimate the cost of pharmacy-based interventions, costs incurred by the implementation of the MedsCheck program served as a benchmark. This program is a pharmacy-based intervention targeted at diabetes patients in Canada (23). Based on the current fee schedule of the MedsCheck program in Alberta, the unit cost of the first annual consultation was determined to be $75 CAD, the unit cost of each subsequent consultation within that year was $25 CAD, and the unit cost of long-term follow-up was $75 CAD (23).

The indirect costs associated with wait-times and travelling related to pharmacy-based interventions were added to the model. Based on the MedsCheck program, the total time lost for pharmacy consultation was 2 minutes for waiting and 20 minutes for the duration of the consultation (24). Based on these estimates, we calculated an opportunity cost. The total time lost was multiplied by the number of pharmacy consultations in one year assuming that the entire study population would be the recipient of pharmacy-based interventions. This number was then multiplied by $24.96 CAD or the average wage per hour in Canada (25).

Based on data from Geographic Accessibility of Community Pharmacies, the cost of travelling to a pharmacy was estimated using the average travel time among patients who visited a pharmacist (26), and the mean fuel cost per kilometer (km) of $0.12/km CAD (27).

4.2.4. Incremental Cost-Effectiveness Analysis

An incremental analysis combined the joint estimates of costs and effects across the baseline scenario and the intervention scenario. The result of this analysis yielded the point estimate of the mean ICER. The ICER was calculated as the difference in costs between baseline and intervention divided by the difference in effects (i.e. QALYs) between baseline and intervention.

Measures of variance for the joint incremental costs and effects were obtained using Monte Carlo simulation and presented graphically using the cost-effectiveness plane. In order to convert health outcome (QALYs) to common metric as dollar, the net monetary benefit (NMB) was calculated. The NMB is equal to the QALYs multiplied by the ceiling ratio (CR) of willingness to pay (WTP) per QALY minus the strategy costs.

NMB = (QALYs * CR) – Costs

4.2.5. Sensitivity Analysis

Both probabilistic and deterministic sensitivity analyses were conducted to explore the model's uncertainty. The deterministic sensitivity analysis was conducted to investigate the impact of key assumptions and parameter values on the base-case analysis, including discount rate, time horizon, and treatment effect. The probabilistic sensitivity analyses were modeled through Monte Carlo simulation. Uncertainty in each of the underlying modeling parameters were characterized by assigning probability distribution to point estimates, and the model was run for 10,000 times for baseline estimate. Results were presented as plotted around point estimates of ICER on Incremental cost effectiveness plane.

Table 4.1. Microsimulation Model Parameters

Baseline Characteristic		
Mean Age	64	SLCDC-DM
Sex (Female)	42.71%	SLCDC-DM
Duration	20	SLCDC-DM
BMI	27.09	SLCDC-DM
HbA1c	7.6	SLCDC-DM
Smoke	15.8%	SLCDC-DM

Cost of Complication		
Heart Disease (First Year of Event)	$17,813	ODEM/CADTH
Heart Disease (Subsequent Years)	$4,994	ODEM/CADTH
Stroke (First Year of Event)	$26,523	ODEM/CADTH
Stroke (Subsequent Years)	$3,680	ODEM/CADTH
Blindness (First Year of Event)	$3,258	ODEM/CADTH
Blindness (Subsequent Years)	2,322	ODEM/CADTH
Amputation (First Year of Event)	$41,143	ODEM/CADTH
Amputation (Subsequent Years)	$5,683	ODEM/CADTH
Discount rate	0.03	CADTH
Cost of Intervention		
MedsCheck Program (First Year)	$157.18	CFPNET
MedsCheck Program (Subsequent Years)	$107.18	CFPNET
Utility Parameters		
Diabetes with no complication	0.758	Sullivan PW(2005)
Heart Disease	0.639	Sullivan PW(2005)
Stroke	0.694	Sullivan PW (2005)
Blindness	0.726	PM. Clarke et al
Amputation	0.520	PM. Clarke et al
Utility Decrement (After 70 Year)	0.00029	Sullivan PW (2005)
Treatment Effect		
HbA1c risk reduction by intervention	0.96%	M. Yaghoubi (2017)
BMI risk reduction by intervention	0.61	M. Yaghoubi (2017)
SBP risk reduction by intervention	6.2	Santschi V (2012)

LDL risk reduction by intervention	11.7	Santschi V (2012)

4.3. Results

The primary objective of the simulation model was to calculate the accumulated events of four diabetes-related complications over the lifetime of 2,931 patients with specific baseline characteristics and risk factors. As shown in Table 4.2, over the 50 years of usual care patients, there were 206 heart failures, 242 strokes, 29 amputations, and 51 cases of blindness. In comparison, over the lifetime horizon of pharmacy-based intervention patients, 159, strokes, 19 heart failures, 24 amputations and 29 cases of blindness events could be averted according to our model. The model also predicted 155 fewer death associated with complications among intervention groups compared to usual care over the lifetime horizon. The cumulative cost was discounted at 3% per year. Over 50 years, the cumulative discounted cost for usual care patients was $30,159,963 CAD total or $10,289 CAD per patient. In comparison, the cumulative discounted cost for pharmacy-based intervention patients was only slightly higher, at $33,904,268 CAD total or $11,567 CAD per patient.

The pharmacy-based intervention was associated with 0.42 additional life-years and 0.32 additional QALYs per patient in comparison to usual care. Cumulatively, the pharmacy-based intervention was associated with 15,207 QALYs or 5.18 per patient, whereas usual care was associated with 14,254 QALYs or 4.8 per patient (Table 4.2)

Improvements in HbA1c, BMI, SBP and LDL expected to result from the pharmacy-based interventions reduced the number of diabetes-related complications over the lifetime horizon. This reduction led to the addition of 0.32 QALYs, and an ICER of $3,929 CAD per QALY compared to usual care. Further, the NMB of the pharmacy-based intervention was calculated to be $247,433 CAD based on (5.18*50,000) – (11,567).

Despite changes to the ICERs across the one-way sensitivity analyses, the pharmacy-based intervention remained cost-effective. When the lifetime horizon was shortened to 20 years, the ICER changed to $2,831.9 CAD. When the lifetime horizon was shortened to 20 years and a 1.5% discount was applied to costs and effects, ICER changed to $4,923. When the anticipated effect of the intervention on HbA1c, BMI, LDL, and SBP was lowered, ICER changed to $4,580 (Table 4.2). Our probabilistic sensitivity

analyses involved varying all the parameters' uncertainties at the same time using Monte Carlo simulation. Then, 10,000 samples of cost and QALYs were used for both the usual care and intervention groups (Figure 4.4). As shown in the cost-effectiveness acceptability curve plot, 92% of iterations remained within a cost-effectiveness threshold of $50,000 per QALY (Figure 4.5).

Table 4.2. Result of Microsimulation Model

	Usual care	Pharmacist Intervention	Difference
Accumulated number of heart failure	206	187	19
Accumulated number of strokes	242	83	159
Accumulated number of amputations	29	5	24
Accumulated number of blindness	51	22	29
Accumulated number of deaths associated with events	401	246	155
Life years	18,853	20,099	1,246
Quality Adjusted Life Years (QALYs)	14,254	15,207	953
QALYs per patients	4.8	5.18	0.32
Discounted Costs	$30,159,973	$33,904,168	$3,744,195
Discounted Costs per patients	$10,289	$11,567	$1277
Undiscounted Costs	$40,846,595	$46,355,459	$5,508
ICER (Discounted)			$3928
ICER (Undiscounted)			$5779
NMB			$247,433
One-way sensitivity Analysis			
ICER (20 Years horizon)			$2831
ICER (Low discount rate)			$4923
ICER (Reduce treatment effect)			$4580

Figure 4.4. Incremental cost effectiveness plane

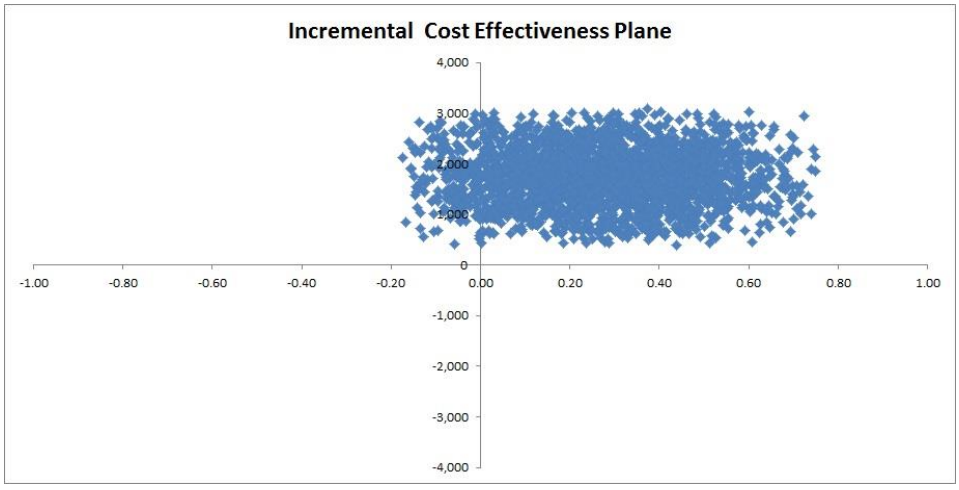
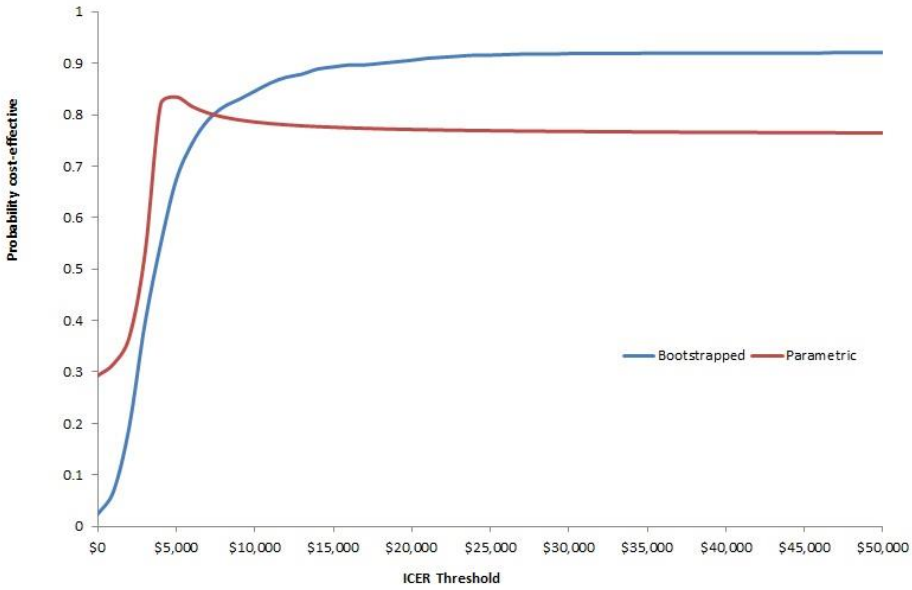


Figure 4.5. Cost effectiveness acceptability curve



4.4. Discussion

Using a patient-level micro-simulation model, the future potential cost-effectiveness of pharmacy-based intervention in the control and management of four diabetes-related complications was analyzed. Across a 50-year lifetime horizon, the intervention proved to be a cost-effective strategy when compared to the usual care (status quo) diabetes patients across Canada receive. The ICER remained below the cost-effectiveness threshold across both deterministic and probabilistic sensitivity analyses. This suggests that the implementation of pharmacy-based interventions could yield consistent results. This consistency is encouraging, especially in the context of the Canadian health care system where pharmacists' scope is impacted by the jurisdiction in which they practice (36-37).

The treatment effect of pharmacy-based interventions was assumed to be low in our analysis. The effect on HbA1c, BMI, SBP and LDL was set at 0.71, 0.20, 4.6, and 7.6 respectively. Based on these values, the

intervention resulted in the addition of 670 more QALYs compared to status quo. Our analysis included a wide range of services that made up an integrated pharmacy-based intervention. However, the results of a recent meta-analysis suggest that diabetes education delivered by pharmacists coupled with pharmaceutical care maximizes the effectiveness of such services (28). HbA1c was lowered by 0.86 and SBP was lowered by 4.94 when this scheme was followed (28). When our model was adjusted in accordance with this specific type of pharmacy-based intervention, the result did not change. Further research must be conducted to corroborate these findings, but this result suggests that pharmacy-based intervention could be effective in even the most resource limited settings.

Our results did change, however, when the discount rate and time horizon were reduced. In these scenarios, the pharmacy-based intervention group gained 1,031 and 1,112 QALYs respectively. These results highlight that this intervention will operate across jurisdictions and across patient lifespans.

Our findings add to the literature and support previous economic evaluations of simulated community care programs for diabetes patients in Canada and around the world. Another Canadian patient-level microsimulation mode, the Ontario Diabetes Economic Model (ODEM), suggested that the incremental cost-effectiveness per QALY of a multidisciplinary management program was $5,203 over 10 years (22). Pharmacy-based interventions have also proven to be cost-effective in reducing risk factors, like hypertension, associated with diabetes-related complications in Canadian patients (29). This mirrors the reductions in risk factors reported in the present study. Further, a Markov cost-effectiveness model evaluated pharmacy-based interventions in Kaiser Permanente Northern California and results demonstrated saving of $6,364 over the lifetime of a single diabetes patient; prevent cardiovascular disease among diabetes patients; and, is less expensive and more effective than usual care over a 10-year time span (30). Again, these positive results compliment the findings from present study. By adding to this literature, provincial governments and health professionals are given a source from which to draw when creating evidence-based practices for the treatment of diabetes patients.

Additionally, our findings compliment previous economic evaluations conducted in real time using emerging patient data. Over 36-months, a randomized controlled clinical trial estimated the ICER per QALY of pharmaceutical care used to manage diabetes and hypertension among elderly patients (31). This analysis demonstrated that pharmaceutical care did not significantly increase the cost of direct health care but did significantly improve health outcomes (31). More specifically, the ICER per QALY ($53.50) gained reflected favorably on its cost-effectiveness (31). In a North American context, the cost-

effectiveness of pharmacy-led drug management education programs (DMEP) has been evaluated. Results from these evaluations suggest that DMEPs are cost-effective relative to usual care, and avert $39 USD per day spends on glycemic symptoms among diabetes patients (32). The results from our simulated model are consistent with findings from clinical trials, and operational education programs. This consistency reinforces the idea that pharmacy-based interventions could be an effective means to manage diabetes and its related complications.

Lastly, our findings do not vary even when compared to the results yielded by different modeling techniques. When a discrete-event simulation model was used, alternative treatment strategies, like pharmacy-based interventions, were associated with enhanced long-term health outcomes among diabetes patients (33). Similarly, when a Markov cohort analysis was conducted to assess the cost-effectiveness of Continuous Glucose Monitoring (CGM) technology compared to self-monitoring, CGM led to an expected improvement of 0.52 QALYs and was cost-effective in 70% of the Monte Carlo simulations (34). When a decision tree model was used to estimate the cost-effectiveness of pharmacy-based ophthalmology screenings compared to in-person examinations, the ICER was $314 CAD per additional case detected, and $73 CAD per additional case correctly diagnosed (35).

Also, in another study authors used a modified Sheffield T1D policy model to simulate T1D complication and estimate cost effectiveness of continuous Glucose monitoring in diabetes trial consist of 158 patients. Result of this analysis demonstrated that, continuous glucose monitoring led to an ICER of $98,000 and not only improve HbA1c controlling but also is cost –effective intervention in threshold of $100,000 in USA. Lastly an economic model was developed by Houle SK and et al (37) to estimate the effect of a pharmacist- based hypertension management program on economic burden of health care system. Results of this study determined that, this intervention could save $115 per patient for a program lasting one year (37).

Overall, our finding suggests that pharmacy-based intervention could be a cost-effective intervention to control and manage diabetes-related complications in Canada

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CHAPTER 5- CONCLUSIONS AND POLICY IMPLICATIONS

5.1.Summary of findings

This thesis aimed to address three research questions: (1) the prevalence of diabetes-related complications and determinants associated with them; (2) the effectiveness of pharmacy-based interventions on the control and management of diabetes; and, (3) the cost-effectiveness of pharmacy-based interventions if implemented to manage health outcomes associated with diabetes-related complications.

Chapter 2 of this thesis estimated the prevalence of diabetes-related complications identified on the SLCDC-DM-2011, and identified associations between these complications and select determinants. Overall, our findings indicate that, in Canada, the majority of diabetes patients experience complications related to their condition. High blood pressure, cataracts, poor circulation, and heart disease are among the most common complications. Patients were more likely to have at least one complication when they were older, had diabetes for more than 10 years, were unemployed, had an unhealthy BMI, and had a high level of A1C. Other determinants, including sex, marital status, education, income, and physical activity, were also found to be significantly associated with specific diabetes-related complications. These findings support and extend the work of others who have found established associations between determinants and diabetes-related complications (1-8).

This chapter also highlighted that socio-economic determinants including marital status, education and income could be protective factors against some micro-vascular and macro-vascular complications. Our findings also confirm that low levels of physical activity and high levels of HbA1C were the most common risk factors for diabetes-related complications among Canadian patients. However, a prospective/longitudinal study design is needed to explore the effect of self-monitoring behaviour on the progression of diabetes–related complications. Since diabetes-related complications can be largely prevented or delayed through the mitigation of various risk factors, prevention strategies should target some of the risk factors identified.

Chapter 3 of this thesis calculated the pooled effect of pharmacy–based interventions on the control and management of diabetes after conducting a systematic review and meta-analysis. Interventions in the reviewed studies included patient education and counselling interventions focused on self-management, self-monitoring, lifestyle and diet modification, medication adherence and awareness of the risk of developing diabetes-related complications. Results from the meta-analysis suggested that pharmacy-based interventions have a significant effect on decreasing HbA1C and lowering BMI; however, the effect on quality of life and health care utilization is still not clear. Timing, duration of pharmacy-based interventions, and duration of follow-up are likely to affect the assessed results of interventions in the reviewed studies. Population characteristics, like severity of illness, age and gender, could have also affected the assessed effectiveness of interventions in the studies. We used a random-effect model to account for heterogeneity across studies. After excluding some heterogeneous studies, the results of influence analysis support the positive impact of pharmacy-based interventions on minimizing the effects of two major risk factors associated with diabetes-related complications. There is consistency between findings of this chapter with evidence in the literature (9-14). However, further investigation of the effects of pharmacy-based interventions on health care utilization and quality adjusted life years is warranted.

Chapter 4 of this thesis presents novel findings about diabetes-related complications in Canada calculated by an individual level micro-simulation model. Using this model, the future potential cost-effectiveness of a pharmacy-based intervention in the control and management of four diabetes-related complications was analyzed. Across a 50-year lifetime horizon, the intervention proved to be a cost-effective strategy when compared to the usual care (status quo) diabetes patients across Canada receive. The ICER remained below the cost-effectiveness threshold across both deterministic and probabilistic sensitivity analyses. This suggests that the implementation of pharmacy-based interventions could yield consistent results. This consistency is encouraging, especially in the context of the Canadian health care system where pharmacists' scope is impacted by the jurisdiction in which they practice (15, 16).

5.2. Conclusion

Canadian health policymakers should afford consideration to pharmacy-based interventions in the management of diabetes and its related complications. Through the expansion of education-based services by community pharmacies, there is the potential to reduce the incidence of diabetes-related

complications, and death resulting from diabetes. This is an important avenue that should not be overlooked, especially because it offers a solution to the growing and complex problems caused by diabetes.

5.3. Thesis limitations

This thesis has a number of limitations. In **chapter 2**, the cross-sectional design of the SLCDC-DM-2011 used means that causal relationships between patient characteristics and diabetes-related complications may not be accurately depicted. Further, patients were asked to self-report their survey response, and thus there is an increased of risk of recall bias. Lastly, our ability to access data on other types of diabetes-related complications not reported on the SLCDC-DM-2011 was restricted. Despite, these limitations, the findings are relevant because they provide a comprehensive quantitative analysis of diabetes-related complications that were included on Canada's SLCDC-DM-2011.

In **chapter 3,** it was not possible to conduct a meta-analysis on quality of life and/or health care utilization. This is because of the different instruments and methodologies used across studies. In the quantitative meta-analysis that we did conduct, we were only able to considered two clinical outcomes; FBG, blood pressure, and cholesterol levels were not included because they were not consistently reported in the reviewed studies. Moreover, it was necessary to use BMI to predict one of the clinical outcomes, obesity. However, this proxy may not be the most accurate, as waist circumference has been deemed the better indicator. Despite this, waist circumference was not consistently reported across the reviewed studies, and so we were unable to predict the effect of pharmacy-based interventions on obesity using this measure.

I would also like to acknowledge the limitations in the micro-simulation model presented in **chapter 4.** First, individual-level data was required for all included parameters, and some of the input variables had to be assumed based on the literature. Second, there is dearth of evidence describing the treatment effect of pharmacy-based interventions over the long-term. Consequently, we assumed that treatment effects were constant over time.

5.4.Future work

As health care systems evolve with the changing health demands of the Canadian population, evidence will be required to inform best practices. Diabetes and its related complications are an example of one such demand that has emerged in the Canadian health landscape and will continue to grow. Importantly, this thesis highlights potential areas for future research that will fill the gaps and allow for a more seamless adoption of effective solutions. In **chapter 2** of this thesis, the need for prospective and longitudinal studies was identified. Prospective and longitudinal studies will allow for the causal relationship between diabetes-related complications and select determinants to be explored. In **chapter 3**, we identified a lack of high-quality evidence that assesses the effect of pharmacy-based interventions on quality of life and health care utilization. To fill this gap, more clinical trials should be that include these outcome variables. The results presented in **chapter 4** provide valuable information for policymakers trying to implement pharmacy–based interventions that are effective in the control and management of debates. This information must be supplemented by future research that uses different types of simulation models. Discrete event simulation modelling, for example, could be used to predict the time that corresponds to the emergence of risk factors and the emergence of a major diabetes–related complication (17)

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APPENDICES

Appendix A.1. permissions to reproduce article (Chapter 3)

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Yaghoubi Kalaterahman, Mohsen
Wed 10/10/2018 14:36
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To: erin.bankes@diabetes.ca <Erin.Bankes@diabetes.ca>;

Dear Editor,

Last year, we published in Canadian Journal of Diabetes the article entitled" Effects of pharmacy-based interventions on the control and management of diabetes: a systematic review and meta-analysis "(please see the complete reference of the paper at end of this email).

I would like to kindly request the permission to produce this article for including in in mu doctoral thesis.

I am looking forward to hearing from you.

Regards,

Mohse Yaghoubi

Yaghoubi M, Mansell K, Vatanparastc H, Steeves M, Zeng W, Farag M. Effects of pharmacy-based interventions on the control and management of diabetes in adults: a systematic review and meta-analysis. Canadian journal of diabetes. 2017 Dec 31;41(6):628-41.

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I was able to speak with my manager and have confirmed that you may go forward with reproducing your article in your thesis. Please include a statement in your thesis citing the published article.

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Appendix A.2. Ethic

Regarding the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans *"Research that relies exclusively on information that is publicly available, or made accessible through legislation or regulation, does not require REB review"*

I had permission to access to data from the 2011 Survey on Living with Chronic Diseases in Canada – Diabetes Component (SLCDC-DM-2011) through legislation / regulation under an agreement with Saskatchewan Research Data Center (Contract number: Proj-16-SSH-SKY-4673).

Ethical Approval

REPLY REPLY ALL FORWARD

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Saskatchewan Research Data Centre
Wed 17/10/2018 09:34

To: Yaghoubi Kalaterahman, Mohsen;

Hi Mohsen,

There has been similar question in the past regarding use of Statistics Canada data as it relates to ethics.
The following policy is on the ethics site here at UofS.

"Research that relies exclusively on information that is publicly available, or made accessible through legislation or regulation, does not require REB review. Exemption from REB review for research involving information that is legally accessible to the public is based on the presence of a legally designated custodian/steward who protects its privacy and proprietary interests (e.g., an access to information and privacy coordinator or a guardian of Canadian census data)."

Article 2.2 of the Tri-Council Policy Statement on Ethics has been helpful in this regard as justification.
http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/
This is from the Government of Canada and what the UofS policy is based on.
Stats Canada data is accessible by legislation/regulation.

Hope this helps.

Thanks,
Ruben

Ruben Mercado, PhD
Analyst, Microdata Access Division
Saskatchewan Research Data Centre (SKY RDC)
Research Data Centres Program, Statistics Canada

Research Exempt from REB Review

Some research is exempt from REB review where protections are available by other means. This Policy allows the following exemptions from the requirement for REB review, as outlined below.

Article 2.2 Research that relies exclusively on publicly available information does not require REB review when:

(a) the information is legally accessible to the public and appropriately protected by law; or

(b) the information is publicly accessible and there is no reasonable expectation of privacy.

Appendix B. Multivariable regression result of each specific complication

B-1 Stroke

stroke	Odds Ratio	Linearized Std. Err.	t	P>|t|	[95% Conf.	Interval]
agecat						
2	2.383798	1.802279	1.15	0.251	.5410459	10.50279
3	2.17416	1.686721	1.00	0.317	.474715	9.957498
employment						
2	2.128858	.8076917	1.99	0.047	1.011482	4.48059
3	7.196824	3.665775	3.87	0.000	2.650017	19.54489
2.income	.5290378	.2115766	-1.59	0.112	.2414424	1.159204
education						
2	.4769703	.2688045	-1.31	0.189	.1579153	1.440651
3	.2961599	.2512792	-1.43	0.152	.0560761	1.564138
4	.9385057	.4124862	-0.14	0.885	.3963167	2.222447
2.durationofd	.780457	.2688567	-0.72	0.472	.3971024	1.533894
faindex						
2	1.972112	.9717408	1.38	0.168	.7502326	5.184027
3	2.522228	1.108385	2.11	0.035	1.065239	5.972025
2.insulin	1.291674	.4922932	0.67	0.502	.6116366	2.727798
checkingbs						
2	1.277686	.4504568	0.70	0.487	.6398863	2.551205
3	.760281	.4243995	-0.49	0.624	.2543702	2.272386
4	2.843621	1.553326	1.91	0.056	.9739932	8.302093
checkingbp						
2	.2567846	.1667788	-2.09	0.036	.0718306	.91797
3	.2698428	.1782128	-1.98	0.047	.0738805	.9855796
4	.3243938	.1818133	-2.01	0.045	.1080543	.9738744
a1c						
2	.8049554	.3489874	-0.50	0.617	.3439208	1.884018
3	2.243798	.8140447	2.23	0.026	1.101385	4.571183
4	1.194963	.9366151	0.23	0.820	.256851	5.559393
_cons	.0210345	.0189868	-4.28	0.000	.0035811	.12355

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B.2 Heart Disease

heart	Odds Ratio	Linearized Std. Err.	t	P>|t|	[95% Conf.	Interval]
agecat						
2	6.254813	3.807976	3.01	0.003	1.894975	20.64549
3	6.973637	4.528897	2.99	0.003	1.950937	24.92731
2.dhhxx_sex	.3897629	.0912629	-4.02	0.000	.2462298	.6169648
dhh_mari						
2	.482835	.257615	-1.36	0.173	.1695503	1.374988
3	1.295317	.4682546	0.72	0.474	.6374338	2.63219
4	1.431255	.7613424	0.67	0.500	.5041793	4.06302
5	.9751693	.3471448	-0.07	0.944	.4851052	1.960307
6	.584252	.243587	-1.29	0.198	.2578975	1.323589
employment						
2	1.427671	.3463411	1.47	0.142	.8871094	2.297625
3	1.802089	.6347407	1.67	0.095	.9030966	3.595986
2.income	.5332061	.128739	-2.60	0.009	.3320645	.8561853
education						
2	.947312	.3374327	-0.15	0.879	.4710477	1.905115
3	.4331268	.2024168	-1.79	0.074	.1731865	1.083218
4	.8846513	.2456491	-0.44	0.659	.5131355	1.525149
2.durationofd	1.798487	.4117312	2.56	0.010	1.147868	2.817879
2.bmiclass	.7324904	.2110057	-1.08	0.280	.4163069	1.288814
typeofsmk						
2	.4162366	.2612533	-1.40	0.163	.1215272	1.425631
3	.6654454	.2166299	-1.25	0.211	.3513994	1.260155
4	.8166909	.364404	-0.45	0.650	.3403825	1.959513
5	.6215486	.2250601	-1.31	0.189	.3055096	1.264519
faindex						
2	1.598382	.5456725	1.37	0.170	.8182163	3.122433
3	2.232991	.746552	2.40	0.016	1.159018	4.30213
2.insulin	1.533165	.3840609	1.71	0.088	.937993	2.505984
checkingbs						
2	1.054274	.2738915	0.20	0.839	.63336	1.754915
3	1.182648	.4958849	0.40	0.689	.5196079	2.691755
4	1.474431	.5540345	1.03	0.302	.7055588	3.081172
checkingbp						
2	.3870029	.1724204	-2.13	0.033	.1615076	.9273324
3	.631729	.3188761	-0.91	0.363	.234718	1.70026
4	.4078491	.1663699	-2.20	0.028	.1832373	.9077898
a1c						
2	1.435761	.3739832	1.39	0.165	.8613806	2.393145
3	1.654164	.4460172	1.87	0.062	.974748	2.807143
4	.6398045	.4864495	-0.59	0.557	.1440057	2.842594
_cons	.0705359	.0655938	-2.85	0.004	.0113828	.4370921

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B.3 Low Blood Sugar

bloods	Odds Ratio	Linearized Std. Err.	t	P>|t|	[95% Conf.	Interval]
agecat						
2	2.19613	1.790279	0.97	0.335	.4438698	10.86577
3	2.728036	2.754324	0.99	0.320	.376548	19.76422
employment						
2	1.529652	.9229869	0.70	0.481	.468389	4.995497
3	2.07219	2.049696	0.74	0.461	.2977525	14.42128
2.income	.7338279	.4632238	-0.49	0.624	.212759	2.531049
2.durationofd	.3787134	.239754	-1.53	0.125	.1094068	1.310923
typeofsmk						
2	3.029305	3.490407	0.96	0.336	.316128	29.0284
3	1.107974	.981067	0.12	0.908	.1951084	6.291923
4	.2348671	.3160448	-1.08	0.282	.016772	3.288974
5	.7842825	.8284669	-0.23	0.818	.0987784	6.22706
faindex						
2	2.937472	2.318115	1.37	0.172	.624822	13.80992
3	7.751129	5.655912	2.81	0.005	1.85268	32.42869
2.insulin	1.178506	.6684971	0.29	0.772	.3873857	3.585253
checkingbs						
2	.2462401	.1613772	-2.14	0.033	.0680934	.8904566
3	.5249936	.4363798	-0.78	0.438	.1028281	2.680378
4	1.958923	1.597458	0.82	0.410	.3957093	9.697468
checkingbp						
2	.0554038	.0496742	-3.23	0.001	.0095458	.3215652
3	.0934909	.087449	-2.53	0.011	.0149278	.5855193
4	.1704492	.1072632	-2.81	0.005	.0496074	.5856572
a1c						
2	1.853125	1.462362	0.78	0.434	.3941889	8.711739
3	5.409362	3.274726	2.79	0.005	1.649946	17.73464
4	1.538192	2.13933	0.31	0.757	.1005288	23.53587
_cons	.0062792	.0089992	-3.54	0.000	.0003777	.1044023

B.4 Foot ulcer

footul	Odds Ratio	Linearized Std. Err.	t	P>|t|	[95% Conf.	Interval]
agecat						
2	1.270189	.5891569	0.52	0.606	.5114856	3.154303
3	.554501	.331508	-0.99	0.324	.1716842	1.790913
2.dhhxx_sex	.6040612	.198801	-1.53	0.126	.3168028	1.151789
dhh_mari						
2	.0851084	.0654939	-3.20	0.001	.0188183	.3849154
3	.6596821	.464653	-0.59	0.555	.1657491	2.625538
4	1.275401	.8131359	0.38	0.703	.3653084	4.452805
5	.4365606	.250395	-1.45	0.149	.1417609	1.344413
6	1.20419	.4827896	0.46	0.643	.548578	2.643333
employment						
2	1.509817	.681657	0.91	0.362	.6228854	3.659657
3	2.840862	1.313701	2.26	0.024	1.147124	7.035416
2.income	.7856904	.295536	-0.64	0.521	.3757476	1.642883
education						
2	.9406791	.5979282	-0.10	0.923	.270451	3.271858
3	1.68781	1.094193	0.81	0.420	.4733593	6.018052
4	2.868373	1.506772	2.01	0.045	1.023876	8.035706
2.durationofd	2.040417	.9596319	1.52	0.130	.8112733	5.131812
2.bmiclass	.8173267	.3056022	-0.54	0.590	.3926009	1.701532
typeofsmk						
2	.6608218	.4618987	-0.59	0.553	.1677974	2.602457
3	1.041012	.4565475	0.09	0.927	.4404987	2.460178
4	1.307075	.8148049	0.43	0.668	.3849325	4.438301
5	.943291	.4811171	-0.11	0.909	.3469425	2.564684
faindex						
2	1.33046	.8427421	0.45	0.652	.3841791	4.607549
3	3.745799	2.361827	2.09	0.036	1.087781	12.89874
2.insulin	2.942547	1.023974	3.10	0.002	1.487135	5.822322
checkingbs						
2	.5430401	.2324655	-1.43	0.154	.2345559	1.257238
3	.9795668	.6526233	-0.03	0.975	.2652273	3.617845
4	1.476241	1.008537	0.57	0.569	.3866445	5.636408
checkingbp						
2	.321872	.2883969	-1.27	0.206	.0555374	1.865439
3	.6907901	.5734619	-0.45	0.656	.1356209	3.518565
4	.5269642	.3931964	-0.86	0.391	.1219837	2.276462
_cons	.0107163	.0155736	-3.12	0.002	.0006199	.1852455

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B.5 Erectile Dysfunction

erect	Odds Ratio	Linearized Std. Err.	t	P>|t|	[95% Conf.	Interval]
agecat						
2	5.121672	2.945228	2.84	0.005	1.65666	15.83398
3	12.74941	8.722726	3.72	0.000	3.328904	48.8291
dhh_mari						
2	.671297	.3935027	-0.68	0.497	.212446	2.121196
3	.4752015	.3504112	-1.01	0.313	.111768	2.020404
4	3.089096	2.727093	1.28	0.202	.546155	17.47217
5	1.146092	.4514684	0.35	0.729	.5289799	2.48313
6	.6635678	.2884176	-0.94	0.346	.2827414	1.557332
employment						
2	1.091899	.3369329	0.28	0.776	.5958695	2.000848
3	1.592786	.6325074	1.17	0.241	.7305672	3.472599
2.income	.6623789	.1904066	-1.43	0.152	.3767686	1.164497
2.duration~d	1.563561	.4018977	1.74	0.082	.944087	2.589509
2.bmiclass	2.084941	.712767	2.15	0.032	1.065826	4.078508
typeofsmk						
2	1.085851	.9541717	0.09	0.925	.1935236	6.09266
3	1.0011	.3670271	0.00	0.998	.487489	2.055844
4	.991505	.4881033	-0.02	0.986	.3772834	2.605687
5	.4904653	.2063547	-1.69	0.091	.2147697	1.120066
faindex						
2	.9341652	.3614634	-0.18	0.860	.4371149	1.996419
3	.8923078	.3282085	-0.31	0.757	.4334935	1.836736
2.insulin	2.263865	.7091838	2.61	0.009	1.224118	4.186755
checkingbs						
2	.9346287	.286793	-0.22	0.826	.5117714	1.706877
3	1.637246	.7755113	1.04	0.298	.6461835	4.148317
4	.7099511	.3620005	-0.67	0.502	.2609699	1.931374
checkingbp						
2	.8283525	.4244039	-0.37	0.713	.303031	2.264348
3	1.213566	.6720606	0.35	0.727	.4092695	3.598468
4	.4851566	.2354007	-1.49	0.136	.1871929	1.257403
a1c						
2	1.542258	.4734416	1.41	0.159	.8442779	2.81727
3	2.414281	.7694865	2.77	0.006	1.291535	4.513042
4	21.04865	20.59978	3.11	0.002	3.083156	143.6988
_cons	.0403943	.0395193	-3.28	0.001	.0059207	.2755899

B.6 High Blood pressure

bloodp	Odds Ratio	Linearized Std. Err.	t	P>|t|	[95% Conf.	Interval]
agecat						
2	2.05488	.5984969	2.47	0.014	1.160593	3.638251
3	1.375795	.4989032	0.88	0.379	.6755362	2.801939
2.dhhxx_sex	1.468354	.2635673	2.14	0.032	1.032584	2.088028
dhh_mari						
2	1.053816	.4114717	0.13	0.893	.4899514	2.266608
3	.5852854	.2025991	-1.55	0.122	.2968224	1.154088
4	1.378009	.8699544	0.51	0.612	.3994563	4.753731
5	1.045438	.2796003	0.17	0.868	.6186905	1.76654
6	1.069639	.2965877	0.24	0.808	.6209233	1.842622
employment						
2	1.628294	.3409271	2.33	0.020	1.07988	2.455219
3	1.846057	.6361851	1.78	0.075	.9390364	3.629173
2.income	1.068634	.2145505	0.33	0.741	.7207796	1.584365
education						
2	.8819395	.2797385	-0.40	0.692	.473418	1.642982
3	.5360111	.1980524	-1.69	0.092	.2596699	1.106435
4	.6105541	.1502664	-2.00	0.045	.3767659	.9894109
2.durationofd	1.445482	.2883419	1.85	0.065	.9774341	2.137655
2.bmiclass	2.843595	.6323794	4.70	0.000	1.838347	4.398535
typeofsmk						
2	1.493868	1.001023	0.60	0.549	.4013276	5.560651
3	1.272161	.3328897	0.92	0.358	.7614421	2.125433
4	1.714059	.5736641	1.61	0.108	.8890535	3.304637
5	1.314753	.3664172	0.98	0.326	.7610916	2.271179
faindex						
2	1.394248	.4084652	1.13	0.257	.7848358	2.47686
3	1.298407	.3422031	0.99	0.322	.7742851	2.177312
2.insulin	1.021217	.2320627	0.09	0.926	.6539474	1.594752
checkingbs						
2	1.257681	.2655555	1.09	0.278	.8311998	1.902987
3	1.23736	.4548764	0.58	0.562	.6016459	2.544786
4	1.3292	.4537855	0.83	0.405	.6804115	2.596625
checkingbp						
2	.7709241	.3397883	-0.59	0.555	.3247548	1.83007
3	.3091675	.1391557	-2.61	0.009	.1278729	.7474964
4	.148194	.059541	-4.75	0.000	.0673872	.3258997
a1c						
2	.9990177	.2131272	-0.00	0.996	.6574195	1.518112
3	1.206754	.2613413	0.87	0.386	.7891104	1.845439
4	1.959433	1.530788	0.86	0.389	.4232844	9.070449
_cons	.5226087	.3556053	-0.95	0.340	.137576	1.985229

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B.7 Cataract

catara	Odds Ratio	Linearized Std. Err.	t	P>|t|	[95% Conf.	Interval]
agecat						
2	2.758459	1.253743	2.23	0.026	1.131084	6.727256
3	8.153526	4.030672	4.24	0.000	3.091986	21.50074
2.dhhxx_sex	1.892331	.397075	3.04	0.002	1.253865	2.855902
dhh_mari						
2	.5889595	.3311217	-0.94	0.347	.195508	1.774215
3	2.604169	.8563659	2.91	0.004	1.366295	4.963569
4	2.085998	1.282468	1.20	0.232	.6245975	6.966709
5	1.445928	.4507991	1.18	0.237	.7844497	2.66519
6	.8956939	.2817457	-0.35	0.726	.4832883	1.660019
employment						
2	4.028596	.9815069	5.72	0.000	2.498125	6.496709
3	5.37386	2.010076	4.50	0.000	2.580214	11.19224
2.income	1.101063	.2452265	0.43	0.666	.7113618	1.704252
education						
2	.5792116	.2227153	-1.42	0.156	.2724518	1.231359
3	1.201003	.5248086	0.42	0.675	.5096923	2.829958
4	1.63405	.4392409	1.83	0.068	.9644609	2.76851
2.durationofd	2.896641	.6598797	4.67	0.000	1.852835	4.528482
2.bmiclass	.74989	.1773513	-1.22	0.224	.4715559	1.19251
typeofsmk						
2	.5207565	.4167997	-0.82	0.415	.1083525	2.502824
3	.888334	.2775437	-0.38	0.705	.4813183	1.639533
4	.8364823	.3044963	-0.49	0.624	.4096071	1.708229
5	.8546479	.2746428	-0.49	0.625	.4550348	1.605203
faindex						
2	1.865166	.6100611	1.91	0.057	.9819612	3.542752
3	1.722669	.5061788	1.85	0.064	.9680557	3.065515
2.insulin	1.708156	.4041993	2.26	0.024	1.07388	2.71706
checkingbs						
2	.5008152	.1265201	-2.74	0.006	.3051243	.8220119
3	.4913377	.1997461	-1.75	0.081	.2213474	1.090651
4	1.153348	.3900976	0.42	0.673	.5940729	2.239139
checkingbp						
2	.9247067	.3281907	-0.22	0.825	.4609696	1.854965
3	.454667	.2115093	-1.69	0.090	.1825651	1.13232
4	.6775741	.2219836	-1.19	0.235	.3563517	1.288353
a1c						
2	.6823413	.1744058	-1.50	0.135	.4133047	1.126505
3	.7189532	.1715721	-1.38	0.167	.4502095	1.148118
4	.7898612	.5816735	-0.32	0.749	.1863072	3.348667
_cons	.0152376	.011348	-5.62	0.000	.003536	.0656626

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B.8 Gloucoma

glauco	Odds Ratio	Linearized Std. Err.	t	P>|t|	[95% Conf.	Interval]
agecat						
2	3.307979	1.740311	2.27	0.023	1.178964	9.281644
3	6.571164	3.679327	3.36	0.001	2.191655	19.7021
2.dhhxx_sex	.9946382	.2731257	-0.02	0.984	.5804927	1.704251
dhh_mari						
2	1.951021	1.044436	1.25	0.212	.6828675	5.574262
3	1.280514	.4330812	0.73	0.465	.6596902	2.485584
4	.3493595	.2444013	-1.50	0.133	.0886067	1.377459
5	1.130521	.4918122	0.28	0.778	.4816958	2.653286
6	1.240306	.4468883	0.60	0.550	.6118798	2.514152
employment						
2	1.221146	.3791839	0.64	0.520	.6642166	2.245046
3	1.252593	.5474056	0.52	0.606	.5316335	2.951259
2.income	.4879206	.1710555	-2.05	0.041	.24534	.9703534
education						
2	.5970239	.2386057	-1.29	0.197	.2726543	1.307287
3	.3782233	.2527654	-1.45	0.146	.1019944	1.402556
4	1.262927	.3847215	0.77	0.444	.6949206	2.295205
2.durationofd	1.694392	.4774933	1.87	0.061	.9750006	2.944576
2.bmiclass	.9805824	.3498432	-0.05	0.956	.4871147	1.973954
typeofsmk						
2	.5918808	.3913831	-0.79	0.428	.1618308	2.164748
3	1.060293	.3626409	0.17	0.864	.542171	2.073554
4	1.354784	.6933544	0.59	0.553	.4965897	3.696088
5	.9641649	.3579	-0.10	0.922	.4655943	1.996618
faindex						
2	.9973625	.4311615	-0.01	0.995	.4272405	2.328272
3	1.095197	.4497366	0.22	0.825	.4895047	2.450349
2.insulin	1.360267	.4237525	0.99	0.323	.7384294	2.505759
checkingbs						
2	.7888641	.2641654	-0.71	0.479	.4090754	1.521251
3	.5551698	.3177659	-1.03	0.304	.1806955	1.705707
4	1.009976	.4183492	0.02	0.981	.4482632	2.275566
checkingbp						
2	1.056441	.5285082	0.11	0.913	.3960737	2.81783
3	.653125	.3314053	-0.84	0.401	.2414591	1.766644
4	1.270966	.5449804	0.56	0.576	.548204	2.946631
_cons	.012865	.010782	-5.19	0.000	.0024868	.0665564

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B.9 Problem with Gum (periodontal Disease)

gums	Odds Ratio	Linearized Std. Err.	t	P>|t|	[95% Conf.	Interval]
agecat						
2	.6437618	.3370718	-0.84	0.400	.23052	1.797802
3	.356797	.2445986	-1.50	0.133	.0929943	1.368944
2.dhhxx_sex	1.674816	.5029592	1.72	0.086	.9293001	3.01841
dhh_mari						
2	.8054587	.5108395	-0.34	0.733	.232163	2.794432
3	1.694137	.8543253	1.05	0.296	.6300629	4.55526
4	.2106749	.1941279	-1.69	0.091	.034569	1.283924
5	.6579824	.2620068	-1.05	0.293	.3013126	1.43685
6	.7376813	.4084491	-0.55	0.583	.2490091	2.185356
employment						
2	1.235314	.5096178	0.51	0.609	.5499985	2.774552
3	2.527197	1.267918	1.85	0.065	.9446422	6.761001
2.income	.7224512	.2574428	-0.91	0.362	.359138	1.453301
2.durationofd	.7232148	.2362359	-0.99	0.321	.3810825	1.37251
2.bmiclass	1.223062	.5238509	0.47	0.638	.5279579	2.833331
typeofsmk						
2	.8490783	.6949308	-0.20	0.842	.1705153	4.227972
3	.8839385	.3695522	-0.30	0.768	.3893077	2.007018
4	1.558827	.7709038	0.90	0.369	.5909249	4.1121
5	1.691216	.7501905	1.18	0.236	.7085051	4.036966
2.insulin	2.621129	1.056319	2.39	0.017	1.189047	5.778005
checkingbs						
2	2.070697	.8886277	1.70	0.090	.8923965	4.804799
3	1.436152	1.279131	0.41	0.685	.2503248	8.239432
4	2.41156	1.348187	1.57	0.116	.8055271	7.219648
a1c						
2	.9511401	.4007167	-0.12	0.905	.4162618	2.173314
3	2.034747	.7076591	2.04	0.041	1.028618	4.025007
4	3.805814	3.549962	1.43	0.152	.6107754	23.71448
_cons	.0293548	.0200831	-5.16	0.000	.0076718	.1123207

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B.10) Retinopathy

retino	Odds Ratio	Linearized Std. Err.	t	P>|t|	[95% Conf.	Interval]
agecat						
2	1.777648	.8331606	1.23	0.220	.7089165	4.457555
3	3.309996	2.078915	1.91	0.057	.9656165	11.34619
2.dhhxx_sex	.7525321	.2755883	-0.78	0.438	.3669148	1.543422
dhh_mari						
2	.4815595	.3510824	-1.00	0.316	.1152409	2.012303
3	1.140794	.5750441	0.26	0.794	.4244361	3.066211
4	.1033784	.1435502	-1.63	0.102	.0067852	1.575067
5	.4195624	.2010872	-1.81	0.070	.163879	1.074162
6	1.223042	.466256	0.53	0.597	.5790205	2.583385
employment						
2	.4329357	.1556322	-2.33	0.020	.2138945	.8762885
3	.3955702	.2344598	-1.56	0.118	.1236861	1.265104
2.income	.4822504	.1615773	-2.18	0.030	.2499549	.9304297
education						
2	.4060376	.2604527	-1.41	0.160	.1153845	1.428844
3	1.003287	.7097001	0.00	0.996	.2505235	4.017929
4	1.747188	.8558925	1.14	0.255	.668414	4.567031
2.durationofd	8.006247	3.328732	5.00	0.000	3.542079	18.09672
2.bmiclass	.5037263	.2032009	-1.70	0.089	.2283297	1.111289
typeofsmk						
2	.9781541	.836863	-0.03	0.979	.1826437	5.238537
3	1.824413	.9668756	1.13	0.257	.6451672	5.159099
4	5.870324	3.622452	2.87	0.004	1.749862	19.69339
5	2.688311	1.526284	1.74	0.082	.8827616	8.186825
faindex						
2	.869904	.4185066	-0.29	0.772	.3385717	2.235075
3	.9167003	.4129726	-0.19	0.847	.3788524	2.218119
2.insulin	11.34252	4.096813	6.72	0.000	5.585083	23.03508
checkingbs						
2	1.002723	.3544913	0.01	0.994	.5012196	2.006016
3	.1828883	.1882773	-1.65	0.099	.0242793	1.377642
4	2.22188	1.788257	0.99	0.321	.4582668	10.77266
checkingbp						
2	1.548699	.9715468	0.70	0.486	.4524548	5.30101
3	1.629689	1.06422	0.75	0.455	.45272	5.866509
4	1.93037	1.015613	1.25	0.211	.6878007	5.417745
a1c						
2	1.092979	.4359926	0.22	0.824	.499812	2.390106
3	.8866676	.2956122	-0.36	0.718	.4610594	1.705159
4	.7855181	.8330323	-0.23	0.820	.0981251	6.288286
_cons	.0021487	.0025115	-5.26	0.000	.000217	.0212743

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B.11) Protein in urine (Proteinuria)

proteinu	Odds Ratio	Linearized Std. Err.	t	P>|t|	[95% Conf.	Interval]
agecat						
2	.5023271	.1694479	-2.04	0.041	.2591974	.9735151
3	.7809696	.3740723	-0.52	0.606	.3052137	1.998316
2.dhhxx_sex	.8040344	.1923707	-0.91	0.362	.502875	1.285551
dhh_mari						
2	1.782917	.8413225	1.23	0.221	.7065672	4.498928
3	1.374185	.6372237	0.69	0.493	.5533839	3.41243
4	.52745	.2975313	-1.13	0.257	.1744413	1.594826
5	.777659	.336162	-0.58	0.561	.333081	1.815635
6	1.34747	.4809101	0.84	0.404	.6690982	2.713617
employment						
2	.5255493	.1301751	-2.60	0.009	.3233048	.8543088
3	.4584809	.1916043	-1.87	0.062	.2019841	1.040699
2.income	.68715	.178159	-1.45	0.148	.4132249	1.142659
education						
2	.5178696	.2586661	-1.32	0.188	.1944151	1.379466
3	1.33807	.7699685	0.51	0.613	.4328011	4.136846
4	1.243823	.4837037	0.56	0.575	.5800712	2.667079
2.durationofd	1.207283	.3123399	0.73	0.467	.7268095	2.005385
2.bmiclass	.9161754	.2543497	-0.32	0.753	.531475	1.579335
typeofsmk						
2	2.215961	1.8874	0.93	0.350	.4168725	11.77934
3	.8844054	.3039052	-0.36	0.721	.4507419	1.735301
4	.7369259	.3317407	-0.68	0.498	.3047483	1.781995
5	1.075677	.4002615	0.20	0.845	.5184435	2.231837
faindex						
2	.8397576	.3078992	-0.48	0.634	.4090868	1.723822
3	1.224422	.392708	0.63	0.528	.6526996	2.296938
2.insulin	2.316624	.6428838	3.03	0.003	1.344174	3.992599
checkingbs						
2	.6381917	.1995475	-1.44	0.151	.3456153	1.178445
3	.6302865	.3418861	-0.85	0.395	.217501	1.82648
4	1.321705	.570874	0.65	0.519	.5664932	3.083714
checkingbp						
2	.417405	.2236806	-1.63	0.103	.1459005	1.194148
3	.3541603	.1868458	-1.97	0.049	.1258282	.9968317
4	.3181038	.1532588	-2.38	0.018	.1236375	.8184415
a1c						
2	1.336133	.4082189	0.95	0.343	.7338134	2.432841
3	2.614374	.7737057	3.25	0.001	1.463067	4.67166
4	5.173627	5.311115	1.60	0.110	.6907039	38.75237
_cons	.6047881	.4440107	-0.68	0.493	.1432844	2.552747

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B.12)Poor Circulation

poorcircu	Odds Ratio	Linearized Std. Err.	t	P>|t|	[95% Conf.	Interval]
agecat						
2	1.296216	.4595643	0.73	0.464	.6466366	2.598333
3	1.274559	.546276	0.57	0.571	.5498664	2.954355
2.dhhxx_sex	.9513082	.1970627	-0.24	0.810	.6336674	1.428174
dhh_mari						
2	.6187853	.2468344	-1.20	0.229	.2829671	1.353144
3	1.248248	.4160338	0.67	0.506	.6492086	2.400034
4	.8725009	.4701441	-0.25	0.800	.3032143	2.510626
5	.8972163	.3069856	-0.32	0.751	.4585999	1.755336
6	1.005447	.3355138	0.02	0.987	.5225167	1.93472
employment						
2	1.164316	.2829643	0.63	0.531	.7228455	1.87541
3	2.182393	.7197562	2.37	0.018	1.142857	4.167486
2.income	.5027611	.118854	-2.91	0.004	.3162148	.7993577
education						
2	1.142699	.3964463	0.38	0.701	.5786186	2.256687
3	.8491447	.3472816	-0.40	0.689	.3807096	1.893954
4	1.335132	.3796436	1.02	0.310	.7643665	2.332098
2.durationofd	1.093695	.2558717	0.38	0.702	.6912015	1.730565
2.bmiclass	1.129223	.3159753	0.43	0.664	.6522565	1.954976
typeofsmk						
2	.3789829	.2443592	-1.50	0.133	.1069959	1.34237
3	.9289236	.2700183	-0.25	0.800	.5252493	1.642837
4	.665556	.3557486	-0.76	0.446	.2332704	1.898933
5	.6023312	.1891178	-1.61	0.107	.3253679	1.115054
faindex						
2	1.425667	.4772929	1.06	0.290	.7393172	2.749192
3	2.080994	.6602297	2.31	0.021	1.116883	3.877343
2.insulin	2.474475	.5867089	3.82	0.000	1.554196	3.939675
checkingbs						
2	.9712389	.2565135	-0.11	0.912	.5785548	1.630451
3	.7317763	.3323347	-0.69	0.492	.3002705	1.783381
4	1.038201	.4122406	0.09	0.925	.47647	2.26218
checkingbp						
2	.7019195	.3241182	-0.77	0.443	.283751	1.73635
3	.5413133	.2639047	-1.26	0.208	.2080411	1.408472
4	.748854	.322938	-0.67	0.503	.321398	1.744822
a1c						
2	.60028	.1760766	-1.74	0.082	.3376648	1.067141
3	1.370716	.3668594	1.18	0.239	.8108822	2.317059
4	2.798363	2.30986	1.25	0.213	.554319	14.12695
_cons	.1528465	.109009	-2.63	0.009	.0377331	.6191395

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B.13)Nephropathy

neurop	Odds Ratio	Linearized Std. Err.	t	P>|t|	[95% Conf.	Interval]
agecat						
2	.7170818	.2951371	-0.81	0.419	.3198629	1.607583
3	.4541736	.2262524	-1.58	0.113	.1709474	1.20665
2.dhhxx_sex	.5472388	.1625191	-2.03	0.043	.305629	.9798491
dhh_mari						
2	.8774091	.5195951	-0.22	0.825	.2746271	2.803243
3	.8003652	.3830821	-0.47	0.642	.3130142	2.046503
4	4.602436	3.341256	2.10	0.036	1.108067	19.11655
5	.7960927	.3493735	-0.52	0.603	.3366052	1.88281
6	.6543146	.2492446	-1.11	0.266	.3099533	1.381265
employment						
2	2.751617	.8438227	3.30	0.001	1.507843	5.021341
3	3.882094	1.571943	3.35	0.001	1.754422	8.590097
2.income	.8187825	.2409846	-0.68	0.497	.4596759	1.458429
education						
2	1.631754	.8339625	0.96	0.338	.5988093	4.446525
3	1.443297	.8952202	0.59	0.554	.4275505	4.872189
4	1.808178	.8064498	1.33	0.184	.7539029	4.336777
2.durationofd	1.333586	.4065554	0.94	0.345	.7333768	2.425017
2.bmiclass	1.623092	.5623302	1.40	0.162	.8226492	3.20237
typeofsmk						
2	.7452733	.4838594	-0.45	0.651	.2085754	2.662981
3	1.236178	.4521513	0.58	0.562	.6032595	2.533134
4	1.027005	.5745027	0.05	0.962	.3428085	3.076761
5	.7256838	.2917631	-0.80	0.425	.3298065	1.596745
faindex						
2	1.1672	.5200071	0.35	0.729	.4871161	2.79678
3	1.956199	.8099271	1.62	0.105	.8684024	4.406614
2.insulin	2.602075	.8432073	2.95	0.003	1.378086	4.913185
checkingbs						
2	.6413193	.2033034	-1.40	0.161	.3443746	1.194311
3	.2332809	.1549646	-2.19	0.029	.0633884	.8585159
4	.6196259	.3184769	-0.93	0.352	.2260966	1.698107
checkingbp						
2	.4930191	.2917325	-1.20	0.232	.154455	1.573713
3	.7478069	.5080685	-0.43	0.669	.1972575	2.834951
4	.6303423	.3446499	-0.84	0.399	.215682	1.842209
a1c						
2	1.303842	.45205	0.77	0.444	.6605162	2.573749
3	1.28134	.4548146	0.70	0.485	.6387026	2.570575
4	2.597557	1.91264	1.30	0.195	.6128148	11.01035
_cons	.0308495	.0355531	-3.02	0.003	.0032175	.2957862

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B.14) Kidney failure

kidney	Odds Ratio	Linearized Std. Err.	t	P>|t|	[95% Conf.	Interval]
agecat						
2	2.883788	2.640548	1.16	0.248	.4785937	17.3764
3	1.397442	1.468501	0.32	0.750	.1778976	10.97734
2.dhhxx_sex	.3352624	.1212646	-3.02	0.003	.1649191	.6815514
dhh_mari						
2	2.362052	1.517624	1.34	0.181	.6698466	8.329206
3	2.225799	1.3516	1.32	0.188	.6764061	7.324268
4	5.118323	3.288763	2.54	0.011	1.451362	18.0501
5	.3068582	.1934137	-1.87	0.061	.0891283	1.056477
6	.5954479	.3246262	-0.95	0.342	.2043778	1.734818
employment						
2	1.628372	.7963417	1.00	0.319	.6239717	4.249546
3	2.421464	1.298548	1.65	0.099	.845788	6.932577
2.income	.2499758	.1022561	-3.39	0.001	.1120566	.5576456
education						
2	1.969326	1.253726	1.06	0.287	.5649479	6.864784
3	.014207	.0174825	-3.46	0.001	.0012713	.1587617
4	1.10762	.5291752	0.21	0.831	.4339237	2.827278
2.durationofd	1.344275	.6221396	0.64	0.523	.5423096	3.332184
2.bmiclass	.6274438	.2653353	-1.10	0.271	.273743	1.438158
typeofsmk						
2	1.114118	1.204238	0.10	0.920	.1337144	9.282908
3	.7099001	.3981687	-0.61	0.541	.2362724	2.132954
4	.4305309	.360264	-1.01	0.314	.083404	2.222398
5	.4358199	.3614544	-1.00	0.317	.0856669	2.217179
faindex						
2	1.337542	1.224071	0.32	0.751	.2221913	8.05171
3	1.921582	1.576213	0.80	0.426	.3845167	9.602903
2.insulin	1.086128	.6108676	0.15	0.883	.3603951	3.273279
checkingbs						
2	.2431944	.1398917	-2.46	0.014	.0786953	.7515509
3	.6099016	.7084248	-0.43	0.670	.0624892	5.952705
4	.6981447	.3802524	-0.66	0.510	.2398706	2.031954
checkingbp						
2	.2732251	.1773443	-2.00	0.046	.0764901	.9759686
3	.0613215	.054127	-3.16	0.002	.010857	.3463517
4	.1670852	.0907511	-3.29	0.001	.0575789	.4848558
a1c						
2	.3552239	.1891772	-1.94	0.052	.1249811	1.009625
3	1.066801	.4295797	0.16	0.872	.4842406	2.350204
4	2.497042	2.516633	0.91	0.364	.3458554	18.02839
_cons	.1896787	.2321886	-1.36	0.175	.0171893	2.093044

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Appendix C. Search Strategy

- **MEDLINE**

1. Diabetes mellitus / or exp diabetes mellitus, type 2/
2. (diabet# or DM) adj2 (“type 2” or “type ii”)).mp.
3. (diabet# adj2 (“type 1” or “type I”)).mp.
4. T2DM.ti,ab
5. NIDDM.ti,ab
6. 1 or 2 or 3 or 4 or 5
7. Exp pharmaceutical service/
8. Exp Clinical pharmacy/
9. Exp Community pharmacy/
10. Exp Pharmacy based intervention/
11. Exp Pharmacist/
12. 7 or 8 or 9 or 10 or 11
13. 6 AND 12

- **EMBASE**

Same MESH, keywords and limits will be used as per MEDLINE search, with appropriate syntax used

- **COCHRANE**

Same MESH, keywords and limits will be used as per MEDLINE search, syntax adjusted for Cochrane library database

- **CINHAL**

Same keyword used peer MEDLINE search

Table C.1. Summary of search results

Databases	N of Results
Ovid MEDLINE<1946 to Present>	326
EBM Reviews - Cochrane Central Register of Controlled Trials < February 2017>	274
CINAHL	205
Embase <1974 to 2017 February >	146
Total Results (Including Duplicate Records)	**951**
Total Results (Excluding 361 Duplicate Records Found by EndNote X4)	**590**

Appendix D. Estimating the progression from diabetes with no complication to diabetes-related complication state

Table D.1. ***Risk equation for developing four diabetes-related complications based on UKPDS study***

Risk equation for developing complications	Mean	Se	Functional form	Source
Stroke *				
λ	-13.053	1.41	Weibull	Hayes AJ (2013)
P	1.466	0.15	Weibull	Hayes AJ (2013)
Age of Diagnoses	0.666	0.01	Weibull	Hayes AJ (2013)
Sex	-0.42	0.19	Weibull	Hayes AJ (2013)
HbA1c	0.092	0.05	Weibull	Hayes AJ (2013)
Smoke	0.331	0.21	Weibull	Hayes AJ (2013)
Heart Failure history	0.481	0.27	Weibull	Hayes AJ (2013)
Amputation history	1.09	0.47	Weibull	Hayes AJ (2013)
LDL	0.016	0.007	Weibull	Hayes AJ (2013)
ATFIB	1.467	0.39	Weibull	Hayes AJ (2013)
MMALB	0.42	0.19	Weibull	Hayes AJ (2013)
SBP	0.17	0.04	Weibull	Hayes AJ (2013)
WBC	0.04	0.01	Weibull	Hayes AJ (2013)
Heart Failure *				
λ	-12.332	1.6	Weibull	Hayes AJ (2013)
P	1.514	0.17	Weibull	Hayes AJ (2013)
Age of Diagnoses	0.068	0.01	Weibull	Hayes AJ (2013)
BMI	0.072	0.01	Weibull	Hayes AJ (2013)
Amputation History	0.0658	0.64	Weibull	Hayes AJ (2013)
Ulcer foot History	0.654	0.57	Weibull	Hayes AJ (2013)
ATFIB	1.562	0.48	Weibull	Hayes AJ (2013)
LDL	0.012	0.009	Weibull	Hayes AJ (2013)
MMALB	0.771	0.22	Weibull	Hayes AJ (2013)
PVD	0.479	0.26	Weibull	Hayes AJ (2013)
Amputation*				
λ	-14.844	2.36	Weibull	Hayes AJ (2013)
P	2.067	0.37	Weibull	Hayes AJ (2013)
Age of Diagnoses	0.023	0.02	Weibull	Hayes AJ (2013)
Sex	-0.445	0.37	Weibull	Hayes AJ (2013)
HbA1c	0.248	0.08	Weibull	Hayes AJ (2013)
Stroke History	1.299	0.47	Weibull	Hayes AJ (2013)
ATFIB	1.088	0.78	Weibull	Hayes AJ (2013)
HDL	-0.059	0.06	Weibull	Hayes AJ (2013)
MMALB	0.602	0.35	Weibull	Hayes AJ (2013)
PVD	1.01	0.37	Weibull	Hayes AJ (2013)

SBP	0.086	0.07	Weibull	Hayes AJ (2013)
WBC	0.04	0.01	Weibull	Hayes AJ (2013)
Heart rate	0.098	0.09	Weibull	Hayes AJ (2013)
Blindness				
λ	-11.607	1.48	Exponential	Hayes AJ (2013)
Age of Diagnoses	0.047	0.01	Exponential	Hayes AJ (2013)
HbA1c	0.171	0..06	Exponential	Hayes AJ (2013)
Heart Failure History	0.841	0.54	Exponential	Hayes AJ (2013)
Stroke History	0.61	0.39	Exponential	Hayes AJ (2013)
SBP	0.068	0.06	Exponential	Hayes AJ (2013)
WBC	0.052	0.03	Exponential	Hayes AJ (2013)
Heart rate	0.08	0.05	Exponential	Hayes AJ (2013)

Following descriptions derived from the supplementary material of United Kingdom Prospective Diabetes model (UKPDS2) (1)

The Weibull model of UKPDS for heart failure in table D.1 assumes a baseline hazard given by:

$$H0\ (t) = Pt^{p-1}\ \exp(\lambda)$$

And in the proportional hazards model;

$$h(t|xj) = h0(t)\exp\ (\beta jxj) = Pt^{p-1}\ \exp(\lambda + \beta jxj)$$

The parameters requiring calculation are λ, βj and p, which are given in Table D.1; time at risk (t) in the model is duration of diabetes. The unconditional probability of heart failure occurring between time t and t+1 can be estimated using the integrated hazard. The integrated hazard at time t is:

$$h(t|xj) = \exp(\lambda + \beta jxj)\ t^{p}$$

And the unconditional probability of heart failure in the interval t to t+1 is:

$$1 - \exp\ \{(\mathrm{H}(\mathrm{t}|xj) - H(t+1|xj)\}$$

For example the calculation of the probability of heart failure in the current year for a one patient record in SLCDC with following characteristic (male, 70 years of age, with 8 years of diabetes, LDL 3.0 mmol/l, BMI of 32, eGFR 50, with microalbuminuria and a history of amputation) estimated as below:

t_1= 8 years diabetes

H (t1|xj) = exp (-12.332 + 0.068*62 + 3*10*0.012 + 0.072* 32 + (50/10)*-0.22 + 0.771 +0.658) * 8 1.514

= 0.1388

t_2= 9 years diabetes

H (t2|xj) = exp (-12.332 + 0.068*62 + 3*10*0.012 + 0.072* 32 + (50/10)*-0.22 + 0.771 +0.658) * 9 1.514

= 0.1659

Probability of heart failure in current year= 1- exp (0.1388-0.1659) = 0.027

Appendix E. Estimating the Probability of death in the 1st year of complication/s and no history of events

Table E.1.Death equations based on UKPDS study

Death equation (No History / No event)	Mean	Se	Functional form	Source
λ	-10.908	0.58	Gompertz	Hayes AJ (2013)
ϕ	0.098	0.007	Gompertz	Hayes AJ (2013)
Sex	-0.229	0.15	Gompertz	Hayes AJ (2013)
Smoke	0.379	0.17	Gompertz	Hayes AJ (2013)
Death equation (History/No event)				
λ	-9.207	1.08	Gompertz	Hayes AJ (2013)
ϕ	0.073	0.01	Gompertz	Hayes AJ (2013)
Smoke	0.374	0.26	Gompertz	Hayes AJ (2013)
Heart Failure History	0.632	0.25	Gompertz	Hayes AJ (2013)
Stroke History	0.473	0.23	Gompertz	Hayes AJ (2013)
Amputation history	0.539	0.38	Gompertz	Hayes AJ (2013)
BMI	-0.293	0.23	Gompertz	Hayes AJ (2013)
MMALB	0.348	0.20	Gompertz	Hayes AJ (2013)
WBC	0.048	0.02	Gompertz	Hayes AJ (2013)
Renal History	1.15	0.38	Gompertz	Hayes AJ (2013)
Death equation (First Year of Event)				
λ	-6.916	1.15	Logistic	Hayes AJ (2013)
Age	0.058	0.01	Logistic	Hayes AJ (2013)
Duration	0.042	0.01	Logistic	Hayes AJ (2013)
Smoke	0.444	0.22	Logistic	Hayes AJ (2013)
Heart Failure Event	1.309	0.30	Logistic	Hayes AJ (2013)
Stroke Event	0.547	0.34	Logistic	Hayes AJ (2013)
Amputation Event	-0.734	0.62	Logistic	Hayes AJ (2013)
Heart rate	0.124	0.06	Logistic	Hayes AJ (2013)
PVD	0.367	0.25	Logistic	Hayes AJ (2013)
Death equation (Subsequent Year of Event)				
λ	-4.868	1.62	Logistic	Hayes AJ (2013)
Age	0.05	0.01	Logistic	Hayes AJ (2013)
Heart Failure History	-0.507	0.37	Logistic	Hayes AJ (2013)
Heart Failure Event	0.583	0.47	Logistic	Hayes AJ (2013)
Stroke History	0.44	0.35	Logistic	Hayes AJ (2013)
Stroke Event	-0.619	0.47	Logistic	Hayes AJ (2013)
Amputation History	0.753	0.58	Logistic	Hayes AJ (2013)
Amputation Event	-1.267	0.66	Logistic	Hayes AJ (2013)
Renal disease History	0.089	0.07	Logistic	Hayes AJ (2013)
WBC	0.584	0.58	Logistic	Hayes AJ (2013)
PVD	0.352	0.34	Logistic	Hayes AJ (2013)
ATFIB	1.081	0.76	Logistic	Hayes AJ (2013)
HDL	0.068	0.05	Logistic	Hayes AJ (2013)

Following descriptions derived from the supplementary material of United Kingdom Prospective Diabetes model (UKPDS2) (1)

Probability of death in the 1st year of complication/s and no history of events:

Logistic regression was used to model mortality in the year of an event. The probability of survival is given by;

$$\mathrm{S} = \frac{e^{-z}}{1 + e^{-z}}$$

Where

$$\mathrm{z} = \lambda + \beta 1x1 + \beta 2x2 + \beta 3x3 + \cdots \beta nxn$$

Current year MI

As an example, using the coefficients in Table E.1, for a one patient record in SLCDC with following characteristic (70 year-old male smoker with 12 years of diabetes, heart rate 80 bpm, has an MI but has no history of other events)

z= (-6.916 +0.058*70 + 0.042*12 +0.124*80/10 +0.444 + 1.309) = 0.393

Probability of survival = $\exp$ (-0.393)/ (1+ $\exp$ (-0.393)) =0.403

Probability of death in current year = 0.597

Current year heart failure

Similarly, the same person with heart failure

z= (-6.916 +0.058*70 + 0.042*12 +0.124*80/10 +0.444) = -0.916

Probability of survival = $\exp$ (0.916)/(1+ $\exp$ (0.916)) =0.714

Probability of death in current year = 0.286

Also Gompertz regression model was used, in which the hazard of death increases exponentially with age. The Gompertz model assumes a baseline hazard given by:

$$H0\ (t) = \exp(\phi t)\exp(\lambda)$$

and in the proportional hazards model

$$h(t|xj) = h0(t)\exp\ (\beta jxj) = \exp(\phi t)\exp(\lambda + \beta jxj)$$

The parameters required are λ, βj and ϕ, which are given in table E.1; time at risk (t) in the model is current age. The probability of death occurring between time t and t+1 can be estimated using the integrated hazard. The integrated hazard at time t is:

$$h(t|xj) = \phi^{-1} \exp(\lambda + \beta jxj)\{\exp(\phi^{t}) - 1\}$$

And the unconditional probability of death in the interval t to t+1 is:

$$1 - \exp\{(\mathrm{H}(\mathrm{t}|xj) - H(t+1|xj)\}$$

As an example, using the coefficients in Table E, for a patient record in SLCDC with following characteristics (a 70 year-old male smoker with 12 years of diabetes, who is overweight, has a white blood cell count of 6x106/ml and a history of heart failure but no events in the current year)

t_1=70 years; t_2=71 years

H ($t_1|x_j$) = 0.073^{-1} exp (-9.207-0.293 +0.374 +0.048*6 + 0.632) { exp (0.073*70)-1}
= 0.6201
H ($t_2|x_j$) = 0.073^{-1} exp (-9.207-0.293 +0.374 +0.048*6 + 0.632) { exp (0.073*71)-1}
= 0.6674

Probability of death between age 70 and 71 years = 1- exp (0.6201-0.6674) =0.046

References

(1) Hayes AJ, Leal J, Gray AM, Holman RR, Clarke PM. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia. 2013 Sep 1;56(9):1925-33.