ASSESSING THE EFFECT OF CLINICAL INTERTIA ON DIABETES OUTCOMES: AN AGENT-BASED MODELING APPROACH

A Thesis

by

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ABSTRACT

Clinical inertia (CI) is the failure to intensify treatment in patients with evidence of poor glycemic control. It is a critical barrier in the effective management of type 2 diabetes and can have adverse effects, such as elevated risk of diabetes-related complications. The aims of this thesis are to study the long-term effects of CI and its interaction with population characteristics on the incidence of diabetes-related complications. An agent-based simulation has been constructed to study these effects. The base model was developed by researchers from The New York Academy of Medicine and the Icahn School of Medicine at Mount Sinai. It was then extended by adding an HbA1c update formula and treatment intensification processes, which offers a flexible avenue through which to compare diverse populations and parameters in a controlled and systematic approach.

To assess the accuracy of our model, we have conducted model validation using 5 published trials and compared the rates of complication incidence. We performed 12 validation exercises, comparing simulated outcomes with published outcomes. The R-square of the overall fit was 0.9065, indicating overall good agreement between the outcomes. Thus, we concluded that the model was reliable for modeling the progression of diabetes-related complications in a population.

Additionally, we performed a series of experiments to meet our aims. The results indicated that a 1-year, 3-year, and 7-year CI significantly increases the 25-year

cumulative incidence of most diabetes complications when compared to the non-CI group. It also indicates that CI has greater impact on specific race and age-group populations; for example, the 65-100 age-group experienced a significantly higher percent increase in the incidence of myocardial infarction, stroke, and retinopathy in comparison to the 45-64 age-group while experiencing a 3-year CI. Additionally, it indicates that the incidence of neuropathy and nephropathy due to a 3-year CI in a Native American population is significantly less than the non-Hispanic White, African American, Hispanic, and Asian populations undergoing a 3-year CI. Our model results provide insightful information for the development of effective diabetes treatment guidelines. Future research is needed to investigate the mechanism behind the differences among different population groups.

DEDICATION

To my family, my best friend, and fiancé, for all their unconditional love and support. I couldn’t have accomplished this without you all.

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Contributors

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All work for the thesis was completed by the student, under the advisement of Dr. Yan Li of the Center of Health Innovation at The New York Academy of Medicine and the committee members.

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CHAPTER I

INTRODUCTION

The first chapter of this thesis provides background information concerning diabetes, diabetes-related complications, and treatment. In the last two sections of this chapter, the motivation, goal, and methodology selected for this thesis are discussed.

I.1 Diabetes, Complications, and Treatment

I.1.1 Diabetes Mellitus (DM)

Diabetes mellitus is a complex, chronic disease where the body fails to produce or respond to the hormone insulin, which results in elevated blood glucose levels. Diabetes mellitus can be classified into the following three major categories: type 1 diabetes, type 2 diabetes, and gestational diabetes.

Type 1 diabetes, also known as insulin-dependent diabetes, develops when the body fails to create the hormone insulin to regulate blood glucose. Type 1 diabetes patients must receive insulin by injection or pump to regulate their glucose. Type 1 diabetes mellitus is most common among children and young adults; hence it is often referred to as juvenile diabetes. According to the Center of Disease Control (CDC), the risk factors for type 1 diabetes may be autoimmune, genetic or environmental, but it remains uncertain.[33]

Type 2 diabetes mellitus, also known as non-insulin-dependent diabetes mellitus (NIDDM), occurs when the body cannot create enough insulin to control blood glucose levels or when the body fails to respond appropriately to the insulin produced. This type of diabetes is associated with body weight, history of gestational diabetes, family history, age, sex, lifestyle, and race/ethnicity. Type 2 diabetes is common among adults above the age of 20, and makes up approximately 90% of all the diabetes cases. [33]

Unlike type 1 and type 2 diabetes, gestational diabetes mellitus (GDM) is usually a temporary illness. GDM is developed during pregnancy and is a result of pregnancy hormones. GDM is common among women with a family history of diabetes and obese women. The CDC reports that 5 - 10 % of women diagnosed with GDM will have diabetes after pregnancy, most commonly type 2 diabetes. [33]

In this thesis, we will focus on type 2 diabetes, due to its high prevalence worldwide. The objective of diabetes care and management is to reach and maintain a glycemic target assigned to each individual by their physician. For the typical non-pregnant individual with type 2 diabetes, the glycemic target is commonly set to a glycated hemoglobin (HbA1c) of less than 7% (53 mmol/mol).[46] The HbA1c is a measure of the mean blood glucose levels for the previous 2 to 3 months. People with type 2 diabetes use insulin, medications, and lifestyle modifications, such as improved diet and exercise, to meet their glycemic target. Failure to meet the glycemic goal can increase the person's risk of complications such as cardiovascular disease, retinopathy, neuropathy, nephropathy, and, in severe cases, death. It has been reported that an increase of 1% in HbA1c is associated with an increased risk of 18%, 12 -14%, and 37% in cardiovascular

events, death, retinopathy or renal failure, respectively.[17] Due to the elevated risk for complications, effective management of HbA1c levels is crucial.

Diabetes is a progressive epidemic throughout the world, especially within the United States. In 2012, 29.1 million Americans, or 9.3% of the United States population had diabetes and approximately 1.4 million more individuals are diagnosed with diabetes each year.[6] According to the American Diabetes Association (ADA), if present trends continue, by 2050 one in every three Americans will have diabetes. In the state of Texas, diabetes is the 6th leading cause of death with approximately 10.6% of the population impacted directly by the disease.[13, 14] For this reason, we are particularly interested in observing the progression of diabetes in the state of Texas, especially in Bexar County, which has a higher prevalence rate of diabetes than Texas at 14.2% and whose 4th leading cause of death is diabetes. [13, 14] Our experiments, later described in Chapter IV, will use data from different sources to simulate the Bexar County population.

I.1.2 Diabetic Complications

I.1.2.1 Neuropathy

Neuropathy is the medical term used to refer to general diseases of the nerves, which can be damaged from injury or sickness. Diabetes is the chronic disease most closely associated with neuropathy. There are three subdomains of neuropathy, the most common being peripheral neuropathy, which usually affects the feet and legs. Peripheral neuropathy in people with diabetes is commonly caused by poor glycemic control (HbA1c levels > 7%). It has been reported that up to 7.5% of type 2 diabetes patients had clinical

neuropathy at the time of diagnosis.[40] The symptoms of peripheral neuropathy include tingling, numbness, burning and pain. Due to the nerves being damaged, they cannot carry messages to the brain concerning cuts or sores on the feet. Consequently, it is important for people with diabetes to regularly check their feet for ulcers and cuts because unhealed cuts and ulcers can often lead to other complications including lower-extremity amputations (LEAs). LEAs are rare, but are extreme complications among people with diabetes. According to the World Health Organization (WHO), LEAs are 10 times more likely to occur in people with diabetes compared to people without diabetes.[24] According to the CDC, there are approximately 80,000 LEAs performed among people with diabetes every year.[7] In addition, there is a high mortality rate associated with this debilitating complication. The mortality rate for 1-year post amputation can be anywhere between 10% and 50%, and for 5-year post amputation between 30% and 80%.[24]

I.1.2.2 Retinopathy

Diabetic retinopathy (DR) is a disease of the retina caused by diabetes, in which the small blood vessels of the retina are damaged. DR is the leading cause of blindness in adults with diabetes. A person's risk for DR is associated with diabetes duration, poor glycemic control, race, smoking habits, blood pressure, and cholesterol levels. DR can be prevented by maintaining glycemic and cholesterol control, which is accomplished by receiving a comprehensive dilated exam at least once a year, and keeping a healthy lifestyle (exercise, no smoking, etc.). According to the Eye Disease Prevalence Research Group, in 2014 DR was estimated to have caused 195,000 cases of vision impairment and

blindness in the United States.[5] DR is responsible for approximately 20% of new blindness among people ages 45 to 74 with type 2 diabetes.[36]

I.1.2.3 Nephropathy

Nephropathy refers to kidney disease or damage. Diabetic nephropathy is a type of nephropathy caused by diabetes mellitus, and it is the leading cause of end-stage renal disease (ESRD).[19] It is estimated that approximately 40% of patients in the Unites States with ESRD have diabetes.[1] Diabetic nephropathy consists of 4 different phases: micro-albuminuria, macro-albuminuria, nephrotic syndrome, and chronic renal failure. There's an elevated risk of diabetic nephropathy among people with diabetes that have high blood pressure, elevated HbA1c levels, and those of races with higher risks for nephropathy, such as African Americans. It has been estimated that diabetes increases the risk of ESRD approximately 12-fold.[4] The projections from a UKPDS model reported that 34.3% of type 2 diabetes patients are likely to have persistent microalbuminuria or worse by 20 years of being diagnosed with diabetes and 38.3% by 25 years.[1] However, achieving glycemic control has been proven to be effective in preventing the development of microalbuminuria and delaying the progression into further stages of nephropathy.[20]

I.1.2.4 Cardiovascular Disease (CVD)

Cardiovascular disease (CVD), which leads to myocardial infarctions (MI) and strokes, is the leading cause of death in people with diabetes. According to the American Heart Association (AHA) at least 68% of individuals 65 years or older with diabetes die from some type of heart disease and 16% die of stroke.[42] In addition, the AHA also reports

that diabetic adults are 2 to 4 times more likely to die from heart disease than people without diabetes and people with diabetes also have a risk of mortality due to stroke that is almost 3-fold compared to non-diabetic people.[42] A Finnish population-based study, found that people with type 2 diabetes without previous MI have approximately the same risk of having a MI as a person without diabetes that has had a previous MI.[22] Other factors that increase the risk of CVD are age, hypertension, and obesity. One method for preventing cardiovascular events is maintaining controlled glucose levels.[44]

I.1.2.5 Mortality

According to WHO more than 3 million people worldwide die from diabetes and diabetes-related complications every year.[48] Due to the increased risk of developing diabetes-related complications, people with diabetes have a shorter life expectancy and higher all-cause mortality risk than non-diabetic individuals.[39]

I.1.3 Treatment

Type 2 diabetes is usually treated with combinations of medications and lifestyle modifications, all with the objective of reaching and maintaining glycemic control. Due to the increasing amount of anti-hyperglycemic drugs and the uncertainty on the best treatment algorithm, many of the national and international organizations founded to prevent diabetes have developed their own recommendations for the management and care of type 2 diabetes The treatment guideline developed by The American Diabetes Association (ADA) was published in their Standards of Medical Care in Diabetes.[46] We

used the ADA treatment algorithm when creating our model, adopting their algorithm for the modeling of the medical treatment process for simulated diabetic individuals.

The ADA suggests that most people newly diagnosed with type 2 diabetes should begin with lifestyle modifications, which may include daily exercise and a healthy diet. If the lifestyle intervention alone does not maintain the glucose levels within the glycemic goal, then the patient should initiate metformin monotherapy. If the patient is intolerant to metformin, ADA suggests starting with another anti-hyperglycemic drug. If the HbA1c target is not reached using metformin monotherapy within 3 months of therapy initiation, it is suggested that the patient shift to dual therapy. Dual therapy consists of maintaining metformin treatment and adding a second drug from the following options: sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin. The choice of the second-line drug is based on patient preferences with the goal of minimizing side effects, and reducing HbA1c levels. If the HbA1c goal is not met after 3 months of dual therapy, it is recommended that the patient starts triple therapy, which consists of the addition of another oral anti-diabetic drug. If the HbA1c target is not reached after 3 months of triple therapy, then treatment should advance to combination injectable therapy.

In the case of people newly diagnosed with diabetes with severely elevated glucose levels, the ADA recommends a different approach to the assignment of initial treatment. If the newly diagnosed diabetic has HbA1c levels greater than 9% and less than 10%, the ADA recommends dual therapy as the initial treatment. Similarly, if the diabetic has an HbA1c greater than 10% at diagnosis, the ADA recommends combination injectable

therapy as the initial treatment. A flowchart to the generally recommended ADA treatment algorithm is displayed in Figure 1.[46]

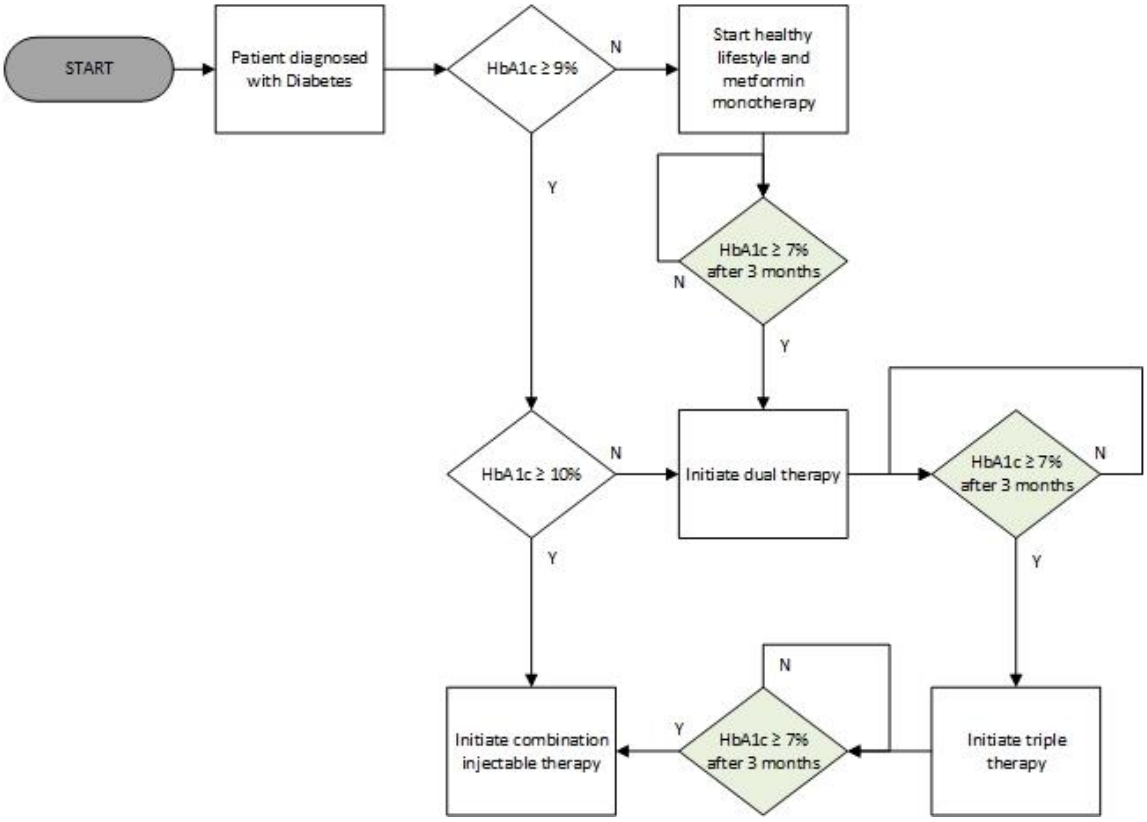

Figure 1. Flowchart of ADA's treatment algorithm for type 2 diabetes.

I.1.3.1 Clinical Inertia

Despite all the national and international evidence-based guidelines specifying the process of medication intensification, research suggests that only 33% of people with diabetes are achieving their glycemic target of an HbA1c less than 7% .[43] Additionally, a

UK study on 80,000 patients with type 2 diabetes reported to have an average time to intensification of 3 years among patients with HbA1c levels greater than 7% .[47] The delay in treatment intensification, despite the evidence of poor glycemic control, is called clinical inertia.

Clinical inertia can be a result of many different factors, including provider factors, patient factors, and the health care system.[35] In the provider-level, clinical inertia can occur due to a lack of knowledge and training, time constraints, or patient health concerns. For example, patients who are cared for by general practitioners were 2.95 times more likely to experience clinical inertia compared to patients treated by specialists. [35] The delay in treatment intensification can occur in the patient-level due to, for example, concerns about weight gain and/or hypoglycemia. Clinical inertia can also be an outcome of system-level factors such as poor access to health care services and expensive new medications.

Many studies have revealed evidence of high prevalence of clinical inertia in the management of type 2 diabetes, and identified the factors associated with it.[48, 35] Additional retrospective studies have identified some of the adverse short-term outcomes of clinical inertia, but there have been fewer studies regarding the long-term effects of clinical inertia on diabetes-related complications. The studies we found regarding the effects of clinical inertia on diabetes-related complications are described in detail in the literature review discussed in Chapter II.

I.2 Research Motivations and Goals

As discussed in previous sections, diabetes mellitus is a complex, chronic disease that can lead to other severe complications. According to WHO, diabetes is the 6th leading cause of death in the world, having claimed a total of 1.59 million deaths worldwide in 2015.[49] In the United States, it has been projected that the number of Americans with diagnosed diabetes will increase by 165%, from 11 million in 2000 to 29 million in 2050.[3] There is an evident need to control the prevalence of this chronic disease, which can be enabled by the effective and timely control of glycemic levels; however, clinical inertia remains a critical barrier to effective care. According to epidemiological data, clinical inertia is responsible for an excess of at least 200,000 avoidable diabetes-related complications per year.[48] Despite the various retrospective studies on clinical inertia, to our knowledge, no previous studies have examined the long-term effects clinical inertia has on diabetes-related complications.

Thus, the primary purpose of this study is to determine the long-term impacts of clinical inertia on diabetes-related complications across different populations using an agent-based model. The model was programmed in AnyLogic, a Java-based multi-method simulation suite. The aims of this study are to use the agent-based model to test the impact of clinical inertia on the incidence of diabetes-related complications, including retinopathy, neuropathy, nephropathy, and CVD. Another aim of the study is to use the model to test the impact of interactions between clinical inertia and population characteristics, such as age, on the aggregate onset of diabetes-related complications.

I.3 The Choice of an Agent-Based Modeling Approach for This Research

In the last few years, there has been an increase in the utilization of systems science methodologies such as system dynamics, discrete-event simulation, and agent-based modeling to solve problems in the public health domain, such as the management of chronic diseases.[30, 31]

To simulate the progression of diabetes and diabetes-related complications, we have selected agent-based modeling as our method. Although several simulation models of diabetes have been developed in other studies, many of them are Markov models, which do not consider population heterogeneity and past disease history. Moreover, Markov models have limitations in modeling adaptive behaviors, feedback loops, and contextual effects.[31] To the best of our knowledge, agent-based modeling has only been used to study the progression of diabetic retinopathy in a population. Agent-based modeling can model more complex properties and simulate agents who can represent heterogeneous individuals and behaviors and, thus, represents a more advanced approach for population health modeling.[32]

CHAPTER II

LITERATURE REVIEW

II.1 Research on the Use of Agent-Based Modeling in Chronic Disease Management

In 2013, Day et al. constructed an agent-based model of diabetic retinopathy (DR).[11] The model was developed based on medical records of patients from the VA St. Louis Healthcare System Eye Clinic. The authors considered many patient characteristics—such as gender, age, and HbA1c—and determined which of these factors were associated to the progression of DR using logistic regression models. Within the agent-based model, the progression of DR was modeled using a state chart, which consisted of non-proliferative DR, proliferative DR, and blindness states. The medical records were separated into a developing and testing dataset, which allowed for model validation. The simulated DR patients showed no significant deviation from the cohort of real-world patients with regards to their progression of DR, and other predictors. The authors state that agent-based modeling is an emerging platform with unexplored potential for the management and study of chronic diseases. Moreover, in a later publication in 2014, Day et al. used the same agent-based model to evaluate the effect of different screening intervals on the incidence of vision loss among a simulated cohort of patients.[12] The authors found that there was no significant difference between 1- and 2-year screening intervals and, thus, increasing the screening interval to 2 years was the most reasonable.

In 2014, Li et al. constructed an agent-based model of CVD to evaluate the effects of several lifestyle interventions—such as quitting smoking, improving diet, and weight loss—on the long-term prevalence and incidence of cardiovascular events across different populations.[29] Each of the simulated individuals in the population was assigned several behaviors, which were chosen according to the American Heart Association's (AHA) concept of ideal cardiovascular health. Data from the 2007 and 2012 Behavioral Risk Factor Surveillance System were used in the validation of the model. The authors showed that the effectiveness of an intervention varies from population to population and, thus, local health departments should consider population demographics when designing and implementing preventive interventions.

In 2015, Zhang et al constructed an agent-based model to study the impact of social influence on the incidence of adolescent overweight and obesity, in an effort to improve existing interventions.[52] The model was built using results from an R package, called SIENA (Simulation Investigation for Empirical Network Analysis), and the National Longitudinal Study of Adolescent Health. In order to ensure model accuracy, they performed model validation against empirical observations. Overall, they conducted five experiments in which characteristics of the high-BMI agents, agent interactions, strength of peer influence, BMI distribution, and dietary targets were varied. The results from the experiments suggested that an increased peer influence showed a substantial decrease in the prevalence of overweight; yet, the effect of peer influence varied by the distribution of BMI among the peers, where if the BMI was increased, strong peer include led to an increase in overweight prevalence.

II.2 Research on the Prevalence and Effects of Clinical Inertia

In 2016 Osataphan et al. conducted a retrospective cohort study at a university-based hospital in Thailand to assess the effects of clinical inertia, specifically the delay of insulin initiation, on the progression of DR within a non-insulin dependent diabetes mellitus (NIDDM) population.[35] Ninety-eight patients were included in the study, all of which were already using at least 2 oral anti-diabetic drugs (OADs) as treatment and had an HbA1c level >9%. Approximately 68.7% of study participants were classified into the clinical inertia group. Clinical inertia was defined as failing to intensify treatment with insulin after 3 months of poor glycemic control. After a mean follow-up time of 29.5 months, the median time of study enrollment to a new event of DR was significantly shorter within the clinical inertia group than the non-inertia group. The clinical inertia group had an incidence rate of 10 cases per 1000 person-months, while the non-inertia group had an incidence rate of 2.2 cases per 1000 person-months. The authors noted that a future study with a larger sample size and longer follow-up time would be beneficial to confirm the association between clinical inertia and diabetes related complications.

In 2015 Paul et al. conducted a retrospective cohort study to evaluate the effect of clinical inertia on the risk of macro-vascular events within the first 2 years post diagnosis for type 2 diabetes patients.[41] Based on a cohort of 105,477 patients, approximately 26% of the patients with poor glycemic control (HbA1c>7%) never received any treatment intensification during the 2 years post diagnosis. It was also found that all patients with poor glycemic control with a delay in intensification of 1 year had their risks of MI, stroke,

heart failure (HF), and composite macro-vascular events (CVE) increase by 67%, 51%, 64%, and 62%, respectively, compared to patients with HbA1c <7% who received treatment intensification before 1 year from diagnosis. The authors also considered the history of CVD and found that among patients with HbA1c >7% and no history of CVD, a 1-year delay in intensification significantly increased their risk of MI, HF, stroke, and CVE by 80%, 63%, 50%, and 64%, respectively. The authors found that clinical inertia was associated with 42% and 48% increased risk of CVE among patients with and without a history of CVD, respectively.

Based on the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model, Chen et al. constructed a discrete-event simulation model called Januvia Diabetes Economic (JADE) Model to study the impact of alternative HbA1c thresholds for treatment intensification.[8] The authors studied the effect of varying the threshold for intensifying therapy from OADS to insulin and the threshold for intensifying insulin to multiple-dose insulin (MDL) treatment. The JADE Model was developed using Microsoft Visual Basic 6.3 with Microsoft Excel 2003, and it consisted of five modules: initial conditions of population, treatment, risk factor/adverse events, diabetes-related events, and costs. The model was used to make projections on the number of diabetes-related complications based on patient data from the Real-Life Effectiveness and Care Patterns of Diabetes Managements study. The seven diabetes-related complications recorded by the model were ischemic heart disease, MI, congestive heart failure (CHF), stroke, amputation, renal failure, blindness, and death. The model showed that lower HbA1c thresholds for the intensification of treatment resulted in a decrease in the projected

number of patients experiencing diabetes-related complications. Based on model projections with intensification thresholds for basal insulin and MDL at 7.0%, the patients spent approximately 54% of their time with HbA1c>7.0%. In comparison, if the threshold was 9.0%, then the patients spent 95% of their time with HbA1c >7%. In addition, the model showed that clinical inertia could lead to a large increase in the incidence of MI; 644 patients more than the baseline were projected to experience at least 1 MI within the first 5 years post diagnosis if the threshold was 9.0% compared to 7.0%. The projected incidence of amputation also showed a large increase resulting from higher thresholds.

CHAPTER III

MODEL STRUCTURE AND PARAMETERS

This chapter describes the model structure and parameters used in our agent-based model. Our model simulates the progression of diabetes and 4 diabetes-related complications: retinopathy, neuropathy, nephropathy, and CVD. This model includes some of the structures and parameters from published papers and other models, such as the CDC RTI Model.[23]

III.1 Model User Interface

The agent-based model was constructed using AnyLogic University Researcher 7.3.6, which is a Java-based simulation suite.[16] This version of the software is accessible through the developer's website and available for free download. AnyLogic allows for user interface design, and the interface of our model is shown in Figure 2. Using the interface, the user can input the characteristics of the population they want to simulate, specify the run length of the simulation, and initiate the simulation by clicking the 'run' button.

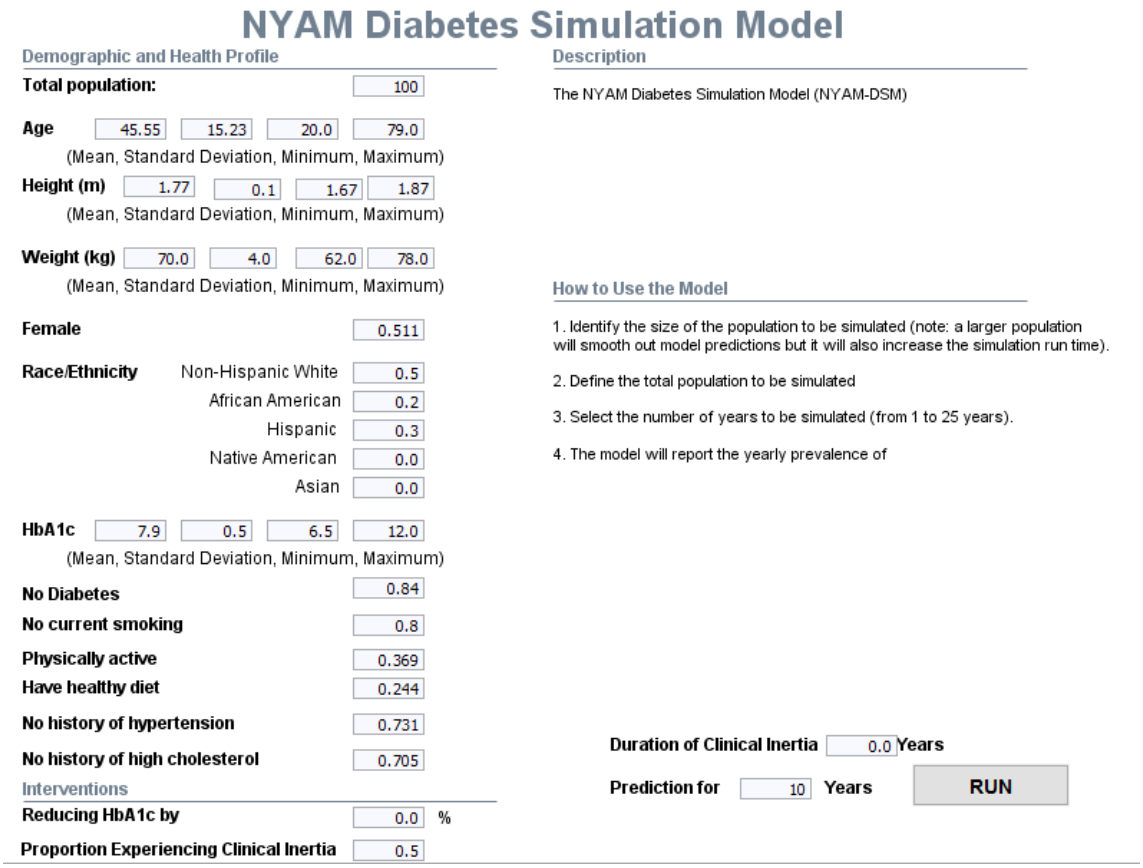

Figure 2. User interface of the agent-base model.

III.2 Agent's Characteristics

Each agent's characteristics, such as gender, race/ethnicity, height, weight, and age, are generated using the population characteristic, which can be input by users.

III.2.1 Gender

One of the user inputs is the proportion of females in the population. The proportion is utilized as the probability, p, in a Bernoulli distribution, which determines the gender of each agent. The gender will take the value 1 with probability p, which means

the agent is female; otherwise, the gender takes the value of 0 with probability 1-*p*, which means the agent is male.

III.2.2 Age

Each agent is assigned their age using the parameters inserted by the user. The parameters are used in a function programed into the model, which uses a normal distribution to return a value for each of the agents. The function ensures that the value falls within the minimum and maximum age values. This model was designed for the study of type 2 diabetes populations and, thus, it models only adult populations, which includes people 18 years and older. Additionally, a scheduled event within the model simulates the annual aging of each individual agent. When the event is triggered, a year is added to each of the agents' age, unless the agent has already died.

III.2.3 Race/Ethnicity

In real life, the risk of diabetes varies throughout ethnic groups; thus, the model was constructed to allow for the simulation of populations with various races/ethnicities. Race/ethnicity is assigned to each of the agents also using a function, which utilizes the user inputs as parameters. The races/ethnicities defined in our model include non-Hispanic White, African American, Asian, Hispanic, and Native American. Each of the races/ethnicities is represented by an integer for simplicity. The integers assigned are 1, 2, 3, 4, and 5 to White, African American, Asian, Hispanic, and Native American, respectively.

To simplify the model, we created a variable, RGL index that combines the gender and race of an agent to a single value. The RGL index is assigned whenever the simulation is initialized. The table describing the method of calculating each agent's RGL index is in Appendix A. The RGL index remains constant once it is assigned to an agent in the beginning of the simulation.

III.2.4 Height

The height of each agent is assigned using a function, which uses a normal distribution and the parameters (mean, standard deviation, minimum, and maximum) input by the user. An assumption of our model is that each of the agents has achieved their maximum height since they have reached adulthood; thus, the height for all agents remains a constant throughout the entirety of the simulation. Height in our model is specified in meters to simplify the calculation of the body mass index (BMI) of each agent. The method of calculating each agent's BMI is described in later sections.

III.2.5 Weight

The initial weight of each agent is determined using a function, which utilizes a normal distribution and the parameters (mean, standard deviation, minimum, and maximum) input by the user. Additionally, the weight in our model is assigned in kilograms (kg). Unlike the height parameter, the weight of an agent is continuously changing throughout the run of the simulation. Details on the process of an agent's weight change is presented in Section III.4.1.

III.3 Agent's Health Behaviors

Each agent has a set of state-charts that represent their health behaviors and health factors, which can develop simultaneously and interactively. During the run length of the simulation, agents may transition between states leading to status changes in their health. For our simulation, the transition between states happens at discrete-time intervals of 3 months. Every 3 months, the model determines what fraction of the agents that will transition from one state to another based on transition probabilities. The transition probability $p_{j,k}(t)$ is the probability that an agent in state j at time t will move at time t+1 to state k. The transition probabilities for all the state-charts are estimated from various published trials, and they can vary from agent to agent due to the transition probabilities being dependent on agent characteristics (gender, race, etc.) and the statuses of health behaviors and factors (smoking status, cholesterol, etc.). The health behaviors and factors state-charts are displayed in Figure 3.

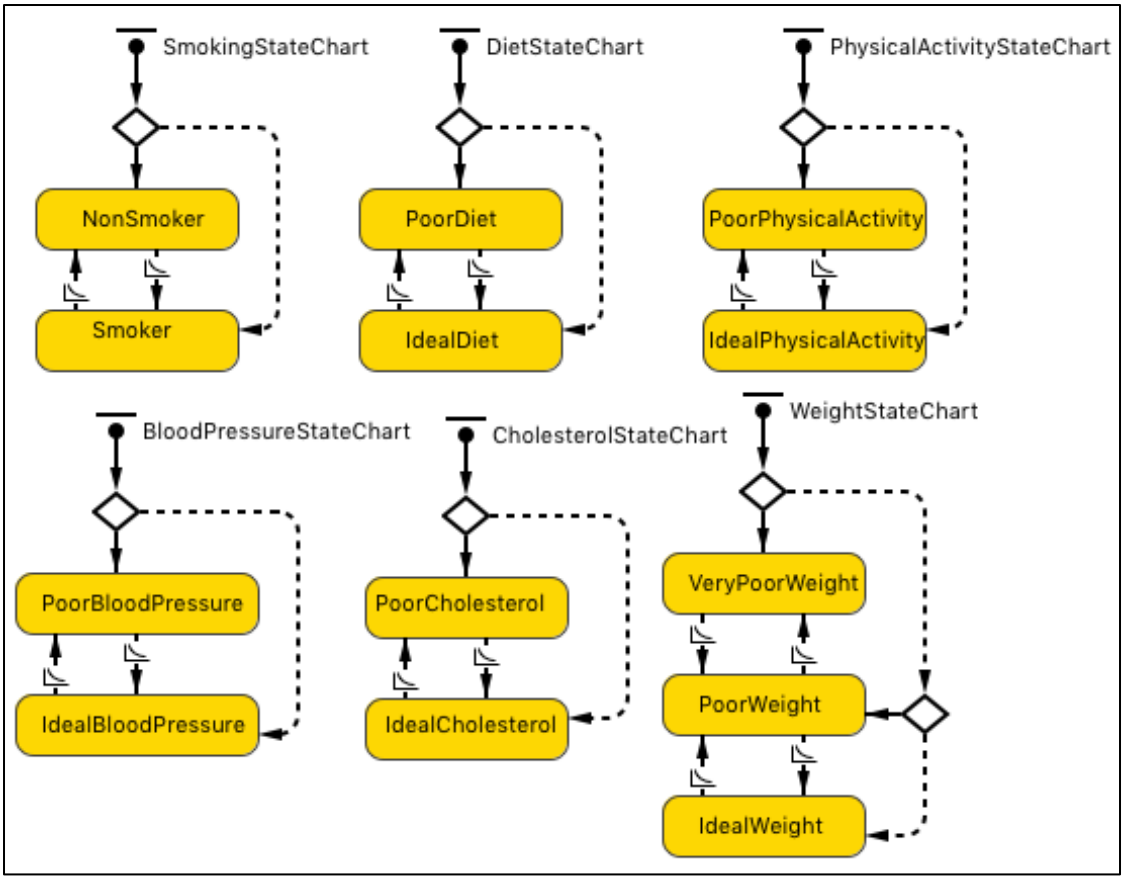

Figure 3. State-charts of the health behaviors and factors.

III.3.1 Smoking

The state-chart representing the current smoking status of the agent consists of two states, “Non Smoker” and “Smoker”. The proportion of currently non-smoking agents in the population is input by the user, which is then used by the model to determine the initial smoking status of each agent. The proportion is utilized as probability *p* in a Bernoulli distribution. The smoking status will take the value 1 with probability *p* to represent a smoker; otherwise, the status will be 0, which represents a non-smoker.

To determine the transition rates between the smoke states, the model uses the agent's age and probability tables, SmokeStartProbTable and SmokeStopProbTable. The tables contain the probability of an agent, given their age, to start or quit smoking. The probability tables are shown in detail in the Appendix B.

III.3.2 Physical Activity

The physical activity state-chart consists of two states, "Poor physical activity" and "Ideal Physical Activity". The initial physical activity status is determined using a Bernoulli distribution and the proportion of physically active people in the population, which is specified by the user, as probability *p*. The agents with ideal physical activity have a physical activity status of 1, and those who have poor physical activity status have a value of 0. The transition rates between the states are shown in Table 1.

	Poor to Ideal	**Ideal to Poor**	**Source**
Transition Rate	0.01225	0.01225	Dalziel et al.[9]

Table 1. Physical activity state-chart transition rates.

III.3.3 Diet

The diet state-chart consists of two states called "Poor Diet" and "Ideal Diet". The initial value of the dietary status is determined using a Bernoulli distribution and the user inputs. The dietary status takes a value of 1 to represent an agent with ideal diet, and 0 for a poor diet. The transition rates are shown in Table 2.

	Poor to Ideal	Ideal to Poor	Source
Transition Rate	0.00075	0.00075	Dalziel et al.[10]

Table 2. Diet state-chart transition rates.

III.4 Agent's Health Factors

In addition to the health behaviors, the simulated agents also have state-charts representing health factors. The health factors modeled for each agent are body weight, cholesterol, and blood pressure.

III.4.1 Body Weight

The body weight state-chart consists of three states, "Poor Weight", "Very Poor Weight", and "Ideal Weight". Initially, the model calculates the BMI for each agent by dividing their weight by their height squared. The calculated BMI is then used to assign each agent into their corresponding weight state. If the BMI is less than 25, then the agent's weight status is "Ideal Weight". If the BMI is greater than 25 but less than 30, then the agent's weight status is "Poor weight"; everything greater than 30 is considered "Very Poor Weight". Agents at the "Ideal Weight" state have a weight status value of 1; otherwise, the weight status is equal to 0. The transition rates between each state are displayed in Table 3.

Anytime in the simulation when an agent transitions into a new weight state, the agent is assigned a new BMI, which then is used to update their weight. The current weight

is updated by multiplying the height squared by the new BMI. The continuous change and update of weight is crucial to the HbA1c update formula described in section III.5.

Transition	Rate	Source
Poor to very poor	0.0025*0.76^DiestStatus*0.7^ActivityStatus	Ogden et al.[34], Kaukua et al.[28], and Paul et al.[41]
Poor to ideal	0.0025 * 2^DietStatus * 2^ActivityStatus	
Very poor to Poor	0.0025 * 2^DietStatus * 2^ActivityStatus	
Ideal to poor	0.0025*0.76^DiestStatus*0.7^ActivityStatus	

Table 3. Weight state-chart transitions.

The diet and activity status directly contribute to the transition rates between weight states; such that if an agent is currently in a poor weight state and has an ideal diet, where DietStatus is 1, and/or ideal activity status, where ActivityStatus is 1, the agent's transition rate into a healthier weight is greater.

III.4.2 Cholesterol

The cholesterol state-chart consists of two states, "Poor Cholesterol" and "Ideal Cholesterol". The parameters input by the user and a Bernoulli distribution determine the initial cholesterol status. The cholesterol status has value 1 whenever the agent has ideal cholesterol, and a value of 0 otherwise. The transition rates between the cholesterol states are determined using a probability table, HighCholesterolProbTable, which contains the probability of an agent having high cholesterol, and the agent's weight status. The

transition rates are displayed in Table 4, and the probability table is displayed in the Appendix B.

	Poor to Ideal	Ideal to Poor	Source
Transition Rate	0.00025	HighCholesterolProbTable(Age) * 1.24^(1-WeightStatus)	Panagiotakos et al.[40]

Table 4. Cholesterol state-chart transition rates.

III.4.3 Blood Pressure

The blood pressure state-chart consists of two states, "Poor Blood Pressure" and "Ideal Blood Pressure". The initial blood pressure status of an agent depends on the user inputs and a Bernoulli distribution, which returns a value of 1 for ideal blood pressure and 0 otherwise. The transition rates between blood pressure states are shown in Table 5. The transition from ideal blood pressure to poor ideal pressure is a constant rate; however, the transition from ideal to poor blood pressure is interrelated with the agent's weight status and their probability of hypertension. The probability table containing the probabilities of developing hypertension is displayed in Appendix B.

	Poor to Ideal	Ideal to Poor	Source
Transition Rate	0.00025	Main.HypertensionProbTable(Age)* 2.32^(1-WeightStatus)	Vasan et al.[50]

Table 5. Blood pressure state-chart transition rates.

III.4.4 Diabetes Status

Our model was constructed to allow for flexibility in assigning the agents' initial diabetes status. There are two methods to assigning the initial diabetes status. The first method utilizes the HbA1c statistics specified by the user. The model then uses them in a normal distribution to determine each of the agent's initial HbA1c. The initial HbA1c assignment method is designed so that it will not violate the minimum and maximum specifications. Once an agent is assigned an initial HbA1c, the model uses the HbA1c to determine the initial diabetes status of the agent. We assume in our model that the time from the onset of diabetes to diagnosis is set to 0 years. Thus, if the agent's HbA1c is greater than 6.5%, the agent is then "diagnosed" as diabetic and becomes active in the "Have Diabetes" state in the blood glucose state-chart. An agent in the "Have Diabetes" state is assigned a diabetes status equal to 1. Otherwise, the agent is considered non-diabetic and it is given a diabetes status of 0. The blood glucose state-chart is displayed in Figure 4.

The second method of determining the initial diabetes status of the agents is using the proportion of people without diabetes specified by the user. The model uses the proportion as the probability for a Bernoulli distribution to assign the initial diabetes status of each agent. Once the agents enter their designated state, they are assigned an initial HbA1c that is associated with their diabetes status. For agents that are active in the "Diabetes" state, they are assigned an initial HbA1c using a uniform distribution with minimum of 6.5% and a maximum of 12%. For the agents that are in the "Non-diabetes"

state, they are assigned initial HbA1c values using a uniform distribution with minimum of 4.0% and maximum of 6.4%.

The transition rates between the diabetes states depend on the current weight status of the agent and their diabetes probability table shown in Appendix B. Once the agent enters the Diabetes state, the agent cannot return back to the non-diabetes state.

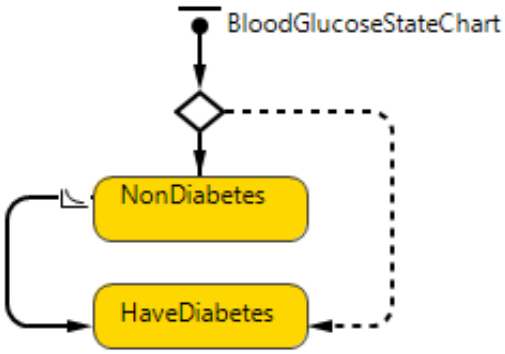

Figure 4. Blood glucose state-chart.

III.5 Complication State-charts

In the simulation, each complication is modeled using a state-chart. The state-charts are interrelated with the health behaviors and health factors state-charts. Initially, we assume that all agents have no history of any complication; thus, all agents begin the simulation at the normal state of each of the complication state-charts. Throughout the simulation run, the agent progresses simultaneously in the state-charts of these complications: cardiovascular disease, neuropathy, nephropathy, and retinopathy.

III.5.1 Cardiovascular Disease

The cardiovascular disease (CVD) state-chart, shown in Figure 5, consists of several states, which include MI, stroke, CVD-related death, and non-complication-related death. Each agent begins the simulation in the "No CVD" state, where we have programmed to determine each agent's 3-month probabilities of having a MI or Stroke. The probabilities depend on gender, age, blood pressure status, smoking status, cholesterol status, and diabetes status. Once the probabilities are calculated, they are used as the transition probabilities into the CVD states.

Due to the prevalence of fatal MI and stroke, the state-chart includes a decision point for each cardiovascular event, which determines whether the MI or stroke were fatal, based on a probability. The probability of a fatal stroke is determined using a condition which utilizes *RandomTrue* function, which generates *True* with a given probability *p.* The probability of a fatal MI is determined using the probability table *DeathFirstMI,* which contains the probability of an agent dying from their first MI. The probability table is shown in detail in Appendix B. If the MI or stroke were not fatal, the agents will transition into the MI or Stroke state, where they will remain until further transition. The transition rates between CVD states are shown in table 6.

In addition, this state-chart also includes the transition to a death state, which includes all other non-complication related deaths. The transition into the death state depends on a probability table shown in detail in Appendix B.

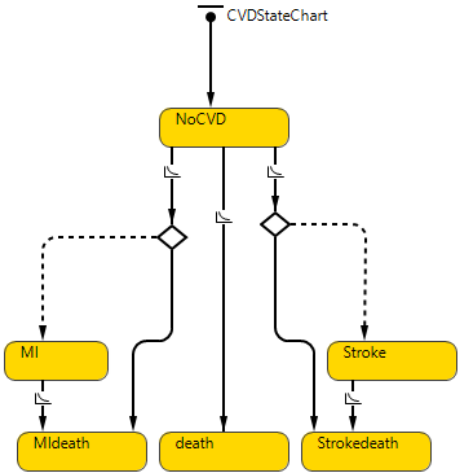

Figure 5. Cardiovascular Disease state-chart.

Transition	Rate	Source
No CVD to MI	ThreeMonthsProbMI * (pow(A1c/(7.0),3.07)) *pow(RGL,3.07) * 2	
No CVD to Stroke	ThreeMonthsProbStroke * (pow(A1c/(7.0),3.07)) * pow(RGL,3.07)*2	
No CVD to MI Death	randomTrue (Main.DeathFirstMI (Age))	Hunink et al.[25]
Stroke to Stroke Death	randomTrue (0.0376)	
MI to MI death	gender==0? Main.DeathMI1(Age):Main.DeathMI2(Age)	Weinstein et al.[51]
Stroke to Stroke Death	0.022875	
No CVD to Death	gender==0? Main.DeathOther1(Age):Main.DeathOther2(Age)	

Table 6. Cardiovascular disease state-chart transition rates.

III.5.2 Retinopathy

The retinopathy state-chart, shown in Figure 6, consists of three states, "RetiNormal", "Photo", and "Blindness". At the start of the simulation run each agent begins at the "RetiNormal" state, which means agents have no history of retinopathy. The transition rate from the normal state to the first stage of retinopathy, photocoagulation,

depends on the blood pressure status, HbA1c, and RGL index. The transition rates to subsequent states are shown in Table 7.

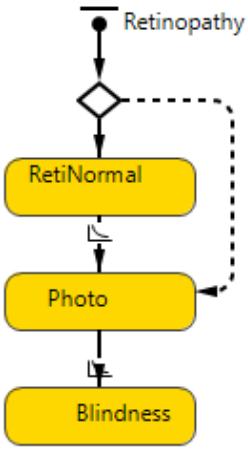

Figure 6. Retinopathy state-chart.

Transition	Rate	Source
RetiNormal to Photo	(BPStatus==0?0.00275:0.00145)* pow(A1c/(A1c+A1cChange),2.74)*pow(RGL,2.74)	Hoerger et al.[23]
Photo to Blindness	0.026625	Hoerger et al.[23]

Table 7. Retinopathy state-chart transition rates.

III.5.3 Neuropathy

The neuropathy state-chart, shown in Figure 7, consists of several states, which include normal state, peripheral neuropathy, lower-extremity amputations (LEA), subsequent LEA, and LEA-related deaths. All agents begin in the "NeuroNormal" state,

which indicates no history of neuropathy. The transition from the normal state to the first stage of neuropathy, "PeriNeuro", depends on the agent's HbA1c and RGL index. The transition rates from the neuropathy state-chart are shown in Table 8.

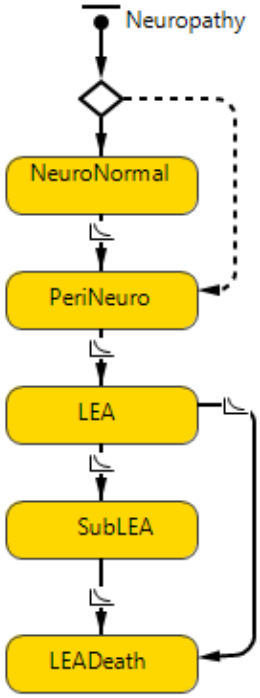

Figure 7. Neuropathy state-chart.

Transition	Rate	Source
NeuroNormal to PeriNeuro	0.005625*(pow(A1c/(7.0),3.07))*pow(RGL,3.07)	Hoerger et al.[23]
PeriNeuro to LEA	0.00168	
LEA to SubLEA	0.0275	
LEA to LEADeath	0.02625	
SubLEA to LEADeath	0.02625	

Table 8. Neuropathy state-chart transition rates.

III.5.4 Nephropathy

The nephropathy state-chart has several states, which include normal state, micro-albuminuria, clinical nephropathy (a.k.a. macro-albuminuria), ESRD, and ESRD-related deaths. The nephropathy state-chart is shown in Figure 8. Initially, all the agents are in the normal state, "NephNormal", and their transition rates into the first stage of nephropathy, micro-albuminuria, depend on the agent's HbA1c and RGL index. All the subsequent transition rates are displayed in Table 9. The transition rate between ESRD and ESRD death is different from the other rates. Once the agent enters the ESRD state, the model determines the agent's probability of death due to their new nephropathy status. The probability of death is determined using the agent's age, race and gender, and the probability is stored in the variable *ProbESRDDeath*.

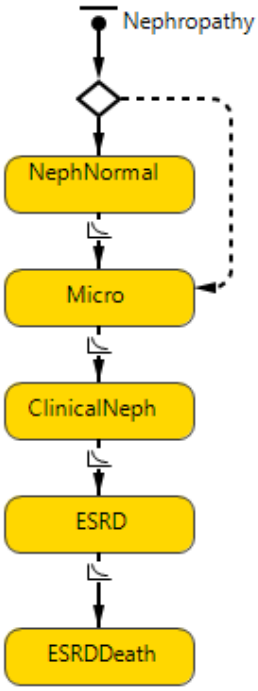

Figure 8. Nephropathy state-chart.

Transition	Rate	Source
NephNormal to Micro	0.00505*(pow(A1c/(7.0),4.28))*pow(RGL,4.28)	Adler et al.[1], UKPDS 38[21]
Micro to ClinicalNeph	0.0071	
ClinicalNeph to ESRD	0.0058175	
ESRD to ESRDDeath	ProbESRDDeath	Dong et al.[15]

Table 9. Nephropathy state-chart transition rates.

III.6 Glycemic Control and Treatment

Diabetes management is focused on the timely and effective management of glucose levels. Thus, it was crucial that our model effectively simulated the continuous changes in HbA1c levels and the progression of step-wise intensification of treatment for each agent with diabetes. According to ADA diabetes care guidelines, a diabetic individual

should have their HbA1c tested every 3 months, which then determines if the individual requires treatment intensification. To model this process, our model has an event that occurs every 3 months, which updates the HbA1c values and initiates the step-wise intensification, if necessary. The event updates the HbA1c of each of the agents using the following equation:

$$A1c_i = A1c_{i-1} + z + x - m$$

, where the variables *z*, *x*, and *m* represent the changes in HbA1c associated with the change in age, weight change, and medication intensification, respectively. The *z* variable represents the rate of change for HbA1c that is associated with aging, and it is calculated using the annual rate of change shown in Table 10. In order to use it in our model, we transformed the annual rate to a 3-month rate.

Annual Rate of Change for HbA1c	Source
0.2	Dong et al.[15]

Table 10. Annual rate of change for HbA1c.

The x variable represents the change in HbA1c associated with weight change, where the weight change is calculated each time the agent transitions between any of the weight states and the weight is updated. The change in weight used to determine the value of the *x* variable by multiplying the change in weight by a rate of change in HbA1c, which is shown in Table 11. In order for the HbA1c to only reflect the last 3 months, the x is set to 0 after every HbA1c update event.

	Rate of Change in HbA1c (per kg)	Source
Weight Gain	Normal (0.002, 0.2560)	Kamil et al.[27]
Weight Loss	Normal (0.03, 0.8534)	

Table 11. Rate of change for HbA1c associated with weight change. Normal (Mean, Standard Deviation)

Lastly, the *m* variable is associated with the change in HbA1c resulting from an intensification of treatment. During each HbA1c update event, a series of conditional statements are used to determine if an agent requires an intensification of treatment. Firstly, the agent must be alive to receive intensification of treatment. Secondly, the agent must have diabetes to receive any treatment. Thirdly, the agent must be in poor glycemic control. If the three conditions have been met, the agent can receive treatment intensification.

In order to track the agent's current treatment method, a variable *numTreatment* is given values from 1 to 4, each representing the medication stages recommended by the ADA, which are monotherapy, dual therapy, triple therapy, and combination injectable therapy. During each treatment intensification, the variable *numTreatment* is increased to the next treatment method and the *m* variable is assigned a value following the distribution shown in Table 12. After each HbA1c update, the *m* variable is set to 0 to avoid duplication. A flowchart of the process of assigning values to the variables is displayed in Figure 9.

One-Time Initial Treatment Effect on HbA1c	Source
Uniform (1, 1.25)	Sherifali et al.[45]

Table 12: One-time initial treatment effect on HbA1c.

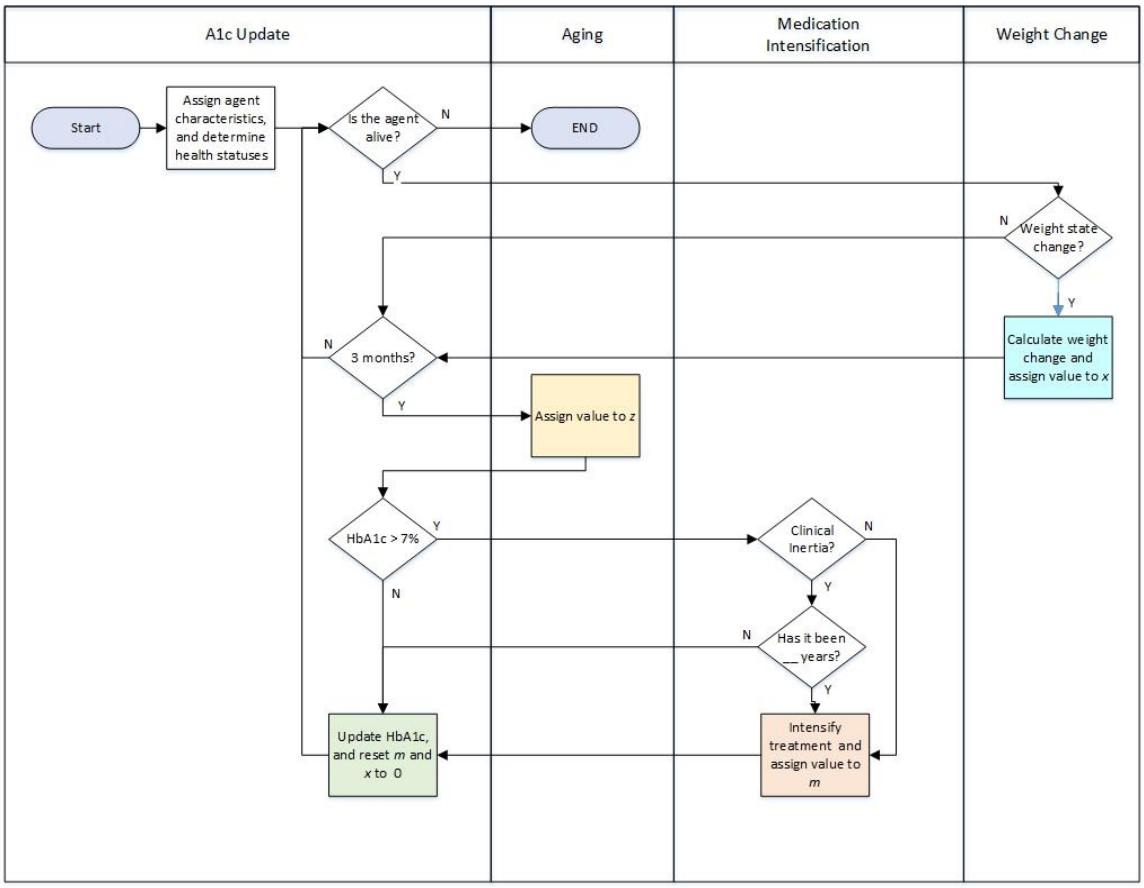

Figure 9. HbA1c update flowchart.

III.7 Agent's Life Cycle

In order to best describe the model, the following section describes two scenarios, non-clinical inertia and clinical inertia, which were used for the experiments specified in Chapter IV.

In the case of a typical agent, the agent is initially assigned all of their characteristics (age, weight, height, etc.), and statuses of their health factors (cholesterol, blood pressure, etc.) and health behavior state-charts (smoking, physical activity, etc.) according to the user inputs. The agent is also initially given the status of its complication status, which starts in the "normal state". Figure 10 shows the flowchart for a typical agent in the non-clinical inertia scenario. Meanwhile, Figure 11 displays the flowchart for a typical agent in a 3-year clinical inertia scenario.

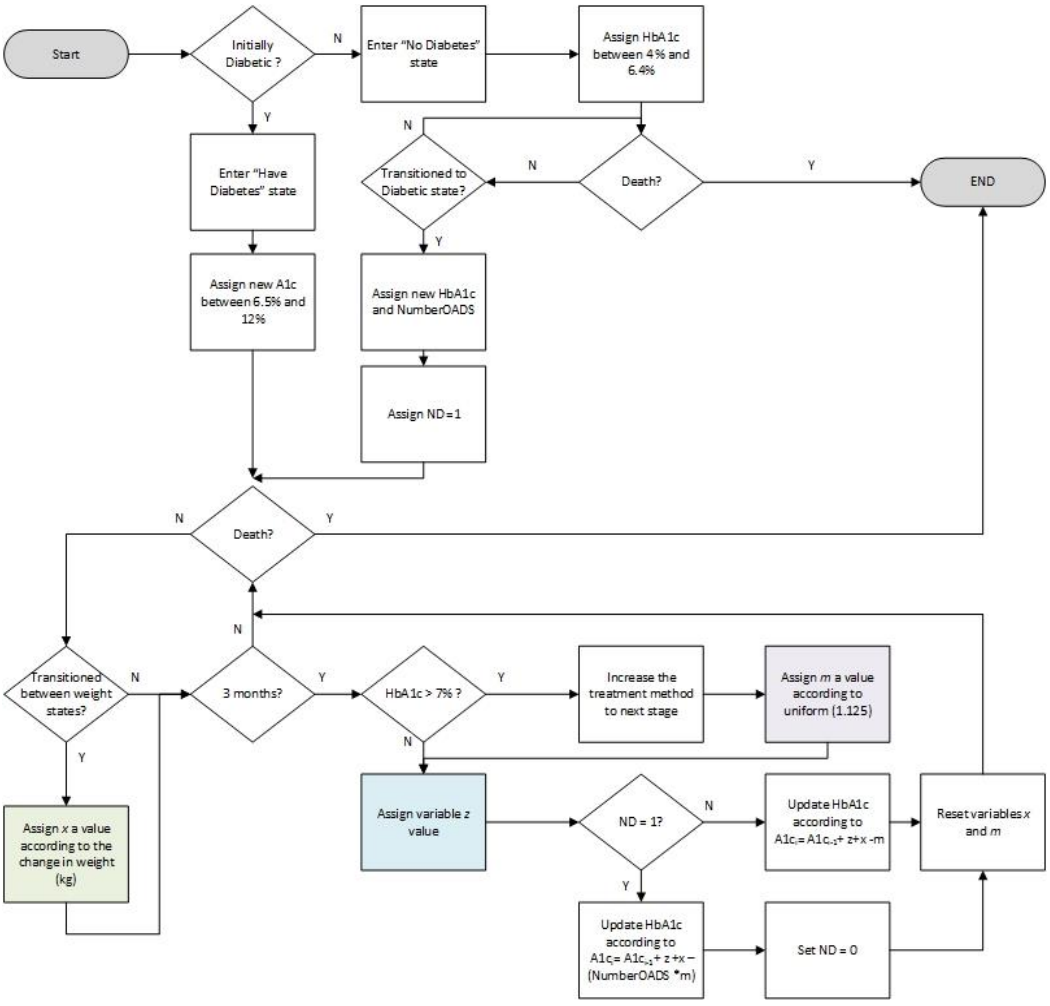

Figure 10. Non-clinical inertia flowchart.

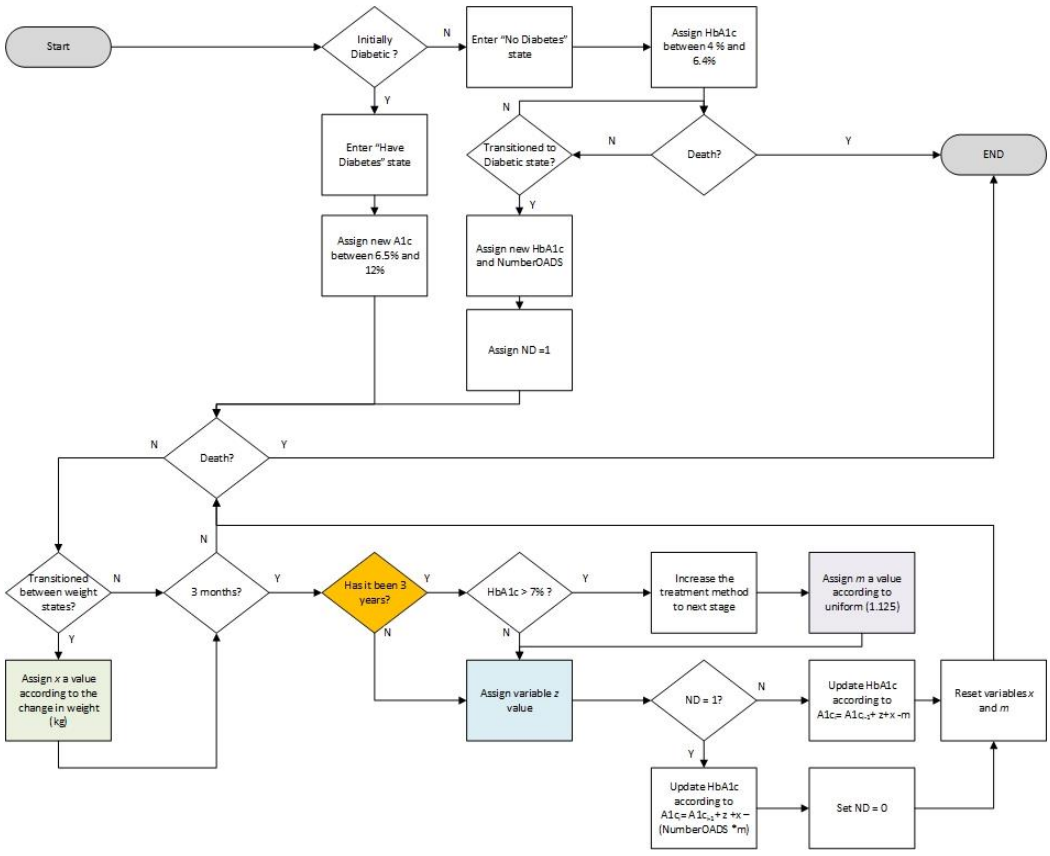

Figure 11. Clinical inertia flowchart.

CHAPTER IV

VALIDATION

IV.1. Model Validation

To assess the accuracy of our agent-based model, we conducted model validation using several published clinical trials and compared the rates of complication incidence between simulation results and trial outcomes. We performed 14 validation exercises comparing the simulated outcomes with the outcomes from 6 published trials. To simulate the outcomes of each of the clinical trials, we generated a population cohort with similar baseline characteristics, which were provided in each of the trials, and then modeled the development of diabetes-related complications for the same follow-up durations as in the trial.

Based on the structure of our model, we created the simulated population using the following variables: age, sex, ethnicity/race, BMI, HbA1c, smoking status, blood pressure, total cholesterol, physical activity, and diet. For each of the complication, we utilized published trials that had outcomes only for type 2 diabetes patients. The outcomes that were measured were regarding the following complications: retinopathy, cardiovascular disease, neuropathy, nephropathy, and mortality. We assessed the goodness-of-fit for the model by plotting the model results against the published trial results and then calculating

the R-squared value, which measures how much of the actual variance our model can explain.

The details in each study and the comparison between outcomes are shown in Table 13. The results show that for most of the complications, the simulated results closely match published results.

Trial	Treatment Group	Duration	Outcome	Study Result	Model Result
UKPDS 33[26]	Newly diagnosed NIDDM people	10yrs.	Absolute risk of retinopathy events per 1,000 pt-yrs	11	5.95
			Absolute risk of MI events per 1,000 pt-yrs	17.4	7.20
			Absolute risk of stroke events per 1,000 pt-yrs	5.00	3.14
ACCORD[17]	Newly diagnosed NIDDM people ages 40 – 75 in UK or Ireland	4yrs.	Cumulative incidence of CVD death	1.8%	1.1%
			Cumulative incidence of non-fatal MI	4.6%	4.30%
			Cumulative incidence of non-fatal stroke	1.20%	2.50%
Partanen et. Al[40]	Finnish newly diagnosed NIDDM people	10yrs.	Cumulative Incidence of neuropathy	20.90%	16.50%

Table 13. Summary comparison of published study results with results from the model.

Study	Treatment Group	Duration	Outcome	Study Result	Model Result
UKPDS 64[1]	Newly diagnosed Type 2 diabetics	15 yrs.	Cumulative incidence of micro-albuminuria or worse nephropathy	28.0%	25.9%
			Cumulative incidence of macro-albuminuria or worse nephropathy	7.1%	7.5%
			Cumulative incidence of ESRD or worse nephropathy	2.3%	2.1%
Li et. Al[29].	Control group of Chinese people w/ IGT	6yrs	All-cause mortality cumulative incidence	3.7%	4.7%
		20yrs		29.3%	24.2%

Table 13 (continued).

To further evaluate the model's accuracy, we compared the aggregate fit across complications by plotting the model results against clinical study results and estimating the correlation. The plot for the validation results is shown in Figure 12. The regression line slope of 0.7951 is close to 1.00, and the value of R-squared is 0.9065, which indicates that our model explains approximately 91% of the variance in the actual data. The model fits the data well because the results fall closely to the 45-degree line, which denotes perfect correlation between model and study results.

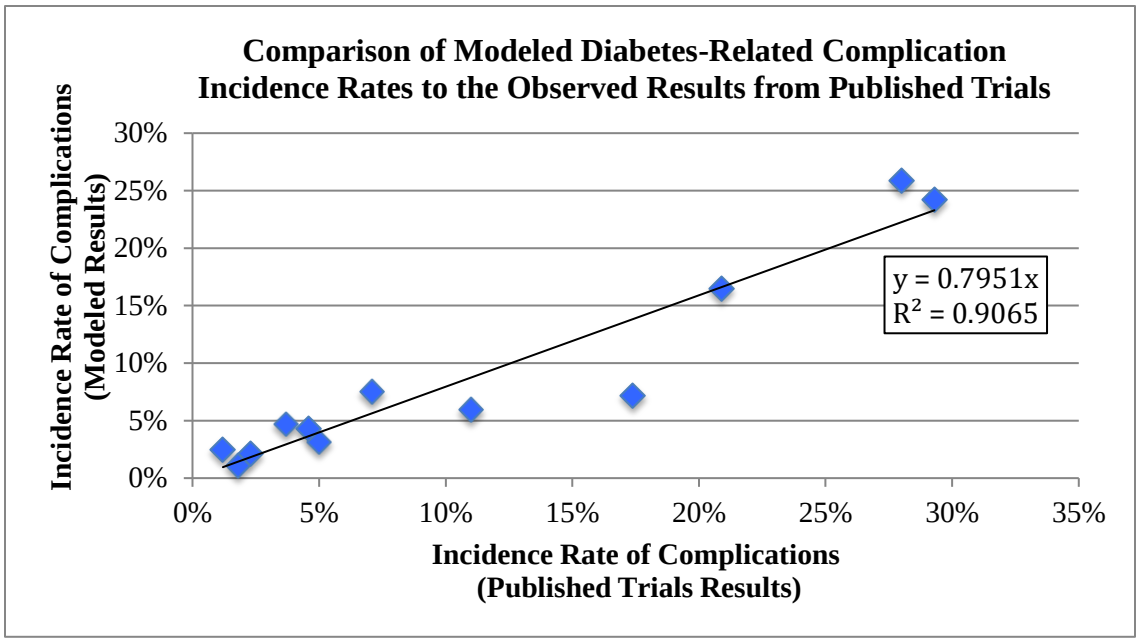

Figure 12. Comparison of the modeled diabetes-related complication incidence rates to the observed results from published trials.

CHAPTER V

EXPERIMENTS AND OUTPUTS

This chapter provides information on the designed experiments and the statistics collected on the model populations in effort to meet the aims specified in Chapter I.

V.1 Description of Experiments and Model Outputs

To meet the aims of this thesis, we designed an experiment for each of the aims. The aims of this thesis are:

Aim 1: Use the agent-based model to study the impact of clinical inertia on the incidence of diabetes-related complications.

Aim 2a: Use the agent-based model to study the impact of interactions between clinical inertia and age on the aggregate onset of diabetes-related complications.

Aim 2b: Use the agent-based model to study the impact of interactions between clinical inertia and race on the aggregate onset of diabetes-related complications.

Aim 2c: Use the agent-based model to study the impact of interactions between clinical inertia and gender on the aggregate onset of diabetes-related complications.

For all of the experiments described in the following paragraphs, the simulations had a run length of 25 years and were replicated 15 times each. Each of the replications consisted of a population of 10,000 simulated agents with diabetes, which were modeled

according to the population characteristics of Bexar County, Texas. The population characteristics are described in detail in Appendix C.

V.1.1 Experiment 1: Impact of the Clinical Inertia on the Incidence of Complications

For the first aim of this project, we designed an experiment which used the incidence of complications as the response variables and the duration of clinical inertia as the factor. We created 4 simulations where each modeled different durations of clinical inertia, which were 3 months, 1 year, 3 years, and 7 years. The duration of clinical inertia represented the time that an agent remained in poor glycemic control before their first treatment intensification. The simulation with the 3-month clinical inertia was the non-clinical inertia scenario based on the ADA guidelines which require patients to wait a 3-month period after each treatment initiation and before the physicians can suggest treatment intensification. The non-clinical inertia scenario was used as the baseline group, which was used to compare to the other scenarios with longer clinical inertia durations. The purpose of this experiment was to make the comparisons and calculate the percent increase in the incidence of complications between the non-clinical inertia and clinical inertia groups. Additionally, the controls of this experiments were the population demographics and the remaining user inputs. The results from this experiment are displayed in Table 14.

Additionally, we utilized Minitab Software to perform two-sample t-tests to compare the different scenarios. The two-sample t-test is designed to compare the means

of two populations while assuming the response variables were normally distributed and the data from both populations have equal variances. In the case of not normally distributed data, we used Mann-Whitney statistical tests, which uses the median to make the comparisons instead of the mean. For each of the clinical inertia groups, we compared their cumulative incidences to the ones from the baseline group. The two-sample t-tests showed that there was a statistically significant difference between the baseline and all clinical inertia groups, in which the clinical inertia scenarios had a higher cumulative incidence for all complications, except for fatal MI. The results from the Mann-Whitney tests are displayed in Appendix D. It was also observed that as the clinical inertia duration increases so does the percent increase in incidence of complications.

	No Clinical Inertia	1 – YR Clinical Inertia vs. No Clinical Inertia	3 – YR Clinical Inertia vs. No Clinical Inertia	7 – YR Clinical Inertia vs. No Clinical Inertia
25-year Cumulative Incidences				
MI	435.8 (16.1)	8% (4,13)**	35% (30,39) **	80% (76,84) **
Stroke	272.6 (18.1)	8% (3,15) **	30% (24,35) **	76% (70, 83) **
Fatal MI	13.90 (3.60)	2% (-34, 30)	12% (-16, 39)	35% (10,61) **
Death	1434 (23.8)	4% (2,5) **	7% (6,8) **	14% (12,15) **
CVD Death	247.7 (17.8)	15% (8,23) **	45% (40,51) **	98% (91,104) **
Neuropathy	2371 (39.5)	8% (6,10) **	28% (27,30) **	65% (64,67) **
Retinopathy	874.5 (32.4)	7% (4,10) **	Not Normally Distributed++	71% (67,75) **
Nephropathy	2185.2 (32.9)	16% (14,17) **	54% (52,56) **	104% (103,106) **

Table 14. 2-Sample t-test Results of Experiment 1Mean Cumulative Incidence (Standard Deviation) from 15 Replications. Incidence increase from non-clinical inertia group to clinical inertia group (95% Confidence Intervals). ** P- value < 0.05, statistically significant. ++ Mann-Whitney results displayed in the Appendix.

V.1.2 Experiment 2: Impact of the Interaction between Clinical Inertia and Population Characteristics on the Incidence of Complications

For the second aim, we constructed three individual experiments to study the impact of the interaction between clinical inertia and several population characteristics, which were age, gender, and ethnicity/race, on the incidence of diabetes-related complications. In each of the three experiments, the response variables were the incidence of complications, and the controls were the population demographics and the remaining user inputs. Each experiment had different factors: age, gender, and ethnicity, where each factor had subcategories. In each experiment, two populations were simulated for each subcategory. The first modeled the baseline non-clinical inertia group, which received treatment intensification as necessary and as recommended by the ADA. The second modeled the clinical inertia group which experienced a 3-year delay in treatment intensification. All of the populations were modeled to be 100 % diabetic, because we are only interested in the effect of clinical inertia on the health of people with diabetes.

V.1.2.1 Experiment 2a: Impact of the Interaction between Clinical Inertia and Age on the Incidence of Complications

For this experiment, we utilized the National Health and Nutrition Examination Survey as a guide to determine an appropriate way to divide agents into age-groups. The age-groups were determined as 20 to 44, 45 to 64, and 65 to 100.

In an effort to understand the implications of the model results, we performed a series of statistical tests, which consisted of 2-sample t-tests and one-way ANOVA tests.

Similarly to experiment 1, we used Minitab software to run these tests. Initially, to confirm that the clinical inertia group resulted in higher incidence of complication, we used 2-sample t-tests to compare the mean incidences between the baseline and the clinical inertia scenario of each age group. The results in Table 15 show that the clinical inertia scenario did have significantly higher incidences on all complications than the non-clinical inertia group.

Secondly, we used one-way ANOVA tests to compare each of the clinical inertia group's mean percent increase in complication incidence in effort to study the different effect of clinical inertia between age-groups. For each of the complications, we compared three percent increases of incidences, where each corresponded to an age-group. Several ANOVA results suggested one of the means was different, and thus, we also performed 2 sample t-tests between all means, trying all combinations, to understand which means were significantly different. The results are shown in Table 16.

The model seems to suggest that the 65-100 age group is affected by clinical inertia significantly more than the 45-64 age group in the incidences of MI, stroke, and retinopathy by 21.6%, 21.8%, and 27.8%, respectively. The 65-100 age group also is affected by clinical inertia significantly more than the 20-44 age group in the incidences of retinopathy, nephropathy, and complication-related deaths by 21.8%, 27.1%, 6.1%, and 16.4%, respectively. According to the model results, it might be of interest for public health officials to investigate the effects of clinical inertia on elderly populations in the future to validate the results from our models.

	Ages 20 -44		Ages 45- 64		Ages 65 -100	
	No Clinical Inertia	3-Year Clinical Inertia vs. No Clinical Inertia	No Clinical Inertia	3-Year Clinical Inertia vs. No Clinical Inertia	No Clinical Inertia	3-Year Clinical Inertia vs. No Clinical Inertia
25-year Cumulative Incidences						
MI	218.4 (18.6)	Not Normally Distributed++	1343.3 (43.3)	22% (20,24)**	941.6 (26)	44% (42,46)**
Stroke	143.2 (15.0)	19% (13,26)**	696.9 (16.6)	22% (20,25)**	991.8 (32.8)	44% (41,46)**
Fatal MI	1.4 (1.2)	Not Normally Distributed++	46.9 (8.9)	49% (36, 63)**	79.4 (7..6)	Not Normally Distributed++
Fatal Stroke	4.6 (1.7)	Not Normally Distributed++	24.87 (5.62)	28% (13,44)**	35 (6.92)	41% (27,54)**
Complication-Related Death	398.2 (17.5)	49% (45,52)**	1382.7 (45.5)	32% (29,35)**	1798.1 (30.9)	Not Normally Distributed++
Cardiovascular Disease Death	118.1 (10.1)	32% (25,39)**	1148.5 (39)	28% (25,31)**	1738.9 (26.4)	45% (44,46)**
Neuropathy	3721.9 (39.3)	Not Normally Distributed++	3161.1 (27.5)	21% (20, 22)**	1323.5 (36)	47% (45,49)**
Retinopathy	1419.2 (29.1)	19% (17,21)**	1321.7 (26.6)	18% (17, 20)**	500.7 (16.3)	Not Normally Distributed++
Nephropathy	3430 (47.8)	31% (30,32)**	2928.5 (37)	37% (36, 38)**	1285.0 (36.7)	Not Normally Distributed++

Table 15. 2-Sample t-test Results of Experiment 2a. Mean Cumulative Incidence (Standard Deviation) from 15 Replications. Incidence increase from non-clinical inertia group to clinical inertia group (95% Confidence Intervals). ** P- value < 0.05, statistically different. ++ Mann-Whitney results displayed in the Appendix

	ANOVA	2 Sample T-test
MI **	At least one mean is different	• The percent increase in the incidence of MI due to a 3-year clinical inertia in the 65-100 population is significantly greater than the 45-64 population by 21.6%
Stroke**	At least one mean is different	• The percent increase in the incidence of stroke due to a 3-year clinical inertia in the 65-100 population is significantly greater than the 45-64 population by 21.8%
Retinopathy	At least one mean is different	• The percent increase in the incidence of retinopathy due to a 3-year clinical inertia in the 65-100 population is significantly greater than the 20 – 44, and 45-64 population by 27.1% and 27.8%, respectively
Nephropathy++	At least one mean is different	• The percent increase in the incidence of nephropathy due to a 3-year clinical inertia in the 45-64 population is significantly greater than the 20-44 population by 6.1%
Complication-Related Deaths++	At least one mean is different	• The percent increase in the incidence of complication related deaths due to a 3-year clinical inertia in the 45-64 population is significantly greater than the 20-44 population by 16.4%

Table 16. ANOVA and 2-Sample t-test Results from Comparing the Different Effect of Clinical Inertia Between Age Groups.

V.1.2.2 Experiment 2b: Impact of the Interaction between Clinical Inertia and Ethnicity/Race on the Incidence of Complications

In this experiment, we studied the following ethnicities/races: Non-Hispanic White, African American, Hispanic, Native American, and Asian. We performed two-sample t-tests to understand the effect of clinical inertia compared to non-clinical inertia group, and then performed the ANOVA test to understand the differences in the effect of clinical inertia between ethnicities/races.

The results for the two-sample t-tests are shown in Table 17. The results from the ANOVA tests are shown in Table 18. According to our model, the non-Hispanic White group is affected by clinical inertia significantly more than the African American population in the incidence of neuropathy, and nephropathy by 2.7% and 3.0%, respectively. The model also shows that the Native American group is affected by clinical inertia significantly less than the non-Hispanic White, African Americans, Hispanic and Asian population groups in the incidence of neuropathy by 5.4%, 2.7%, 3.8%, and 4.2%, respectively; similarly, it is significantly less in the incidence of nephropathy by 11.0%, 8.0%, 7.9%, and 13.9%, respectively. The Asian group was impacted by the 3-year clinical inertia significantly more than the African American, Hispanic, non-Hispanic White, and Native American groups in the incidence of nephropathy by 5.9%, 5.9%, 2.9%, and 13.9%. The non-Hispanic White was affected by the clinical inertia significantly more than the Hispanic, and Native American population in the incidence of complication-related deaths by 6.5%, and 5.8%, respectively.

	White		African American		Hispanic	
	No Clinical Inertia	3-Year Clinical Inertia vs. No Clinical Inertia	No Clinical Inertia	3-Year Clinical Inertia vs. No Clinical Inertia	No Clinical Inertia	3-Year Clinical Inertia vs. No Clinical Inertia
25-year Cumulative Incidences						
MI	538.9 (23.6)	26% (23, 30) **	625.9 (25.7)	Not Normally Distributed++	633.9 (15.6)	25% (22, 28) **
Stroke	307.5 (22.6)	Not Normally Distributed++	377.5 (22.3)	24% (18, 29) **	377.5 (17.9)	24% (20, 29) **
Fatal MI	18.9 (3.6)	4% (-12, 19)	20.6 (3.9)	14% (-3, 31) **	20.3 (4.3)	20% (3, 38) **
Fatal Stroke	13.8 (3.1)	10% (-11, 31)	13.9 (3.4)	Not Normally Distributed++	13.9 (3.4)	Not Normally Distributed++
Comp. Death	665.9 (31.3)	44% (40, 47) **	786.7 (28.5)	38% (35, 41) **	806.8 (26.3)	37% (34, 40) **
Death	2793 (115)	Not Normally Distributed++	2868 (113)	5% (3, 8) **	2857.1 (89.4)	5% (3, 8) **
CVD Death	444.1 (29.8)	35% (30, 40) **	526.6 (29.3)	29% (25, 34) **	536.8 (19.7)	30% (25, 34) **
Neuropathy	3092.3 (63.4)	21% (19, 22) **	526.8 (21.4)	Not Normally Distributed++	3587.8 (56.0)	19% (18, 20) **
Retinopathy	1198.3 (39.8)	19% (16, 22) **	1415.9 (32.9)	18% (16, 20) **	1381.3 (33.4)	16% (18, 22) **
Nephropathy	2735.6 (45.3)	36% (35, 37) **	3371.7 (34.1)	33% (32, 34) **	3387.0 (57.9)	33% (32, 34) **

Table 17. The 2-Sample t-test Results of Experiment 2b. Mean Cumulative Incidence (Standard Deviation) from 15 Replications. Incidence increase from non-clinical inertia group to clinical inertia group (95% Confidence Intervals). ** P- value < 0.05,t statistically different. ++ Mann-Whitney results displayed in the Appendix

	Native American		Asian	
	No Clinical Inertia	**3-Year Clinical Inertia vs. No Clinical Inertia**	**No Clinical Inertia**	**3-Year Clinical Inertia vs. No Clinical Inertia**
25-year Cumulative Incidences				
MI	841.7 (18.6)	23% (21, 25) **	464.9 (21.5)	27% (23, 31) **
Stroke	503.4 (24.4)	23% (19, 28) **	273.5 (14.2)	30% (25, 35) **
Fatal MI	24.7 (4.4)	21% (7, 35) **	15.5 (4.4)	13% (-9, 35)
Fatal Stroke	17.6 (4.7)	44% (26, 62) **	10.1 (3.5)	24% (-5, 52)
Comp. Death	1047.5 (31.1)	38% (35, 41) **	583.6 (21.0)	42% (39, 45) **
Death	2971.3 (90.3)	7% (5, 10) **	2751.0 (103)	Not Normally Distributed++
CVD Death	698.1 (27.4)	31% (27, 36) **	392.8 (17.9)	34% (30, 38) **
Neuropathy	4620.3 (60.0)	15% (14, 16) **	2744.4 (40.5)	20% (18, 21) **
Retinopathy	1824.9 (39.3)	18% (16, 20) **	1057.6 (23.2)	Not Normally Distributed++
Nephropathy	4751.8 (57.3)	25% (24, 26) **	2297.0 (49.9)	39% (37, 40) **

Table 17 (continued). The 2-Sample t-test Results of Experiment 2b

	ANOVA	2 Sample T-test
MI	All means are equal	All means are equal
Stroke	All means are equal [P-value: 0.113]	The percent increase in the Incidence of stroke in the non-Hispanic White population is significantly greater the Native American population by 7.6%.
CVD Death	All means are equal	All means are equal
Neuropathy	At least 1 mean is different	• The percent increase in the incidence of neuropathy due to a 3-year clinical inertia in non-Hispanic White population is significantly greater than the African American population by 2.7% • The percent increase in the incidence of neuropathy due to a 3-year clinical inertia in a Native American population is significantly less than the non-Hispanic White, African American, Hispanic, and Asian population by 5.4%, 2.7%, 3.8%, and 4.2%, respectively
Nephropathy	At least 1 mean is different	• The percent increase in the incidence of nephropathy due to a 3-year clinical inertia in the non-Hispanic White population is significantly greater than the African American, Hispanic, and Native American population by 3.0%, 3.1%, and 11.0%, respectively • The percent increase in the incidence of nephropathy due to a 3-year clinical inertia in Asian population is significantly greater than the African American, Hispanic, White, and Native American population by 5.9%, 5.9%, 2.9%, and 13.9%, respectively • The percent increase in the incidence of nephropathy due to a 3-year clinical inertia in Native American population is significantly less than the African American, Hispanic, Asian, non-Hispanic White population by 8.0%, 7.9%, 13.9%, and 11.0%, respectively
Retinopathy	All means are equal	All means are equal
Complication-Related Deaths	At least one mean is different	• The percent increase in the incidence of complication-related deaths due to a 3-year clinical inertia in the non-Hispanic White population is significantly greater than the Hispanic, and Native American population by 6.5%, and 5.8%, respectively

Table 18. ANOVA and 2-Sample t-test Results from Comparing the Different Effect of Clinical Inertia Between Ethnicities/Races.

V.1.2.3 Experiment 2c: Impact of the Interaction between Clinical Inertia and Gender on the Incidence of Complications

In this experiment, the two subcategories were female and male. Similar to the previous experiments, we performed 2 sample t-tests to understand the effect of clinical inertia compared to non-clinical inertia group, and then performed ANOVA test to understand the differences in the effect of clinical inertia between males and females. The results for the comparison of the non-clinical inertia group and the clinical inertia group are shown in Table 19.

The results show that clinical inertia does result in higher incidence rates for all complications in both gender populations. The results from the ANOVA tests are shown in Table 20. The model results suggest that clinical inertia does not affect females and males differently.

	Female		Male	
	No Clinical Inertia	3-Year Clinical Inertia vs. No Clinical Inertia	No Clinical Inertia	3-Year Clinical Inertia vs. No Clinical Inertia
25-year Cumulative Incidences				
MI	491.3 (24.8)	24% (20, 28) **	718.8 (24.2)	26% (23, 28) **
Stroke	384.5 (25.5)	22% (17, 27) **	331.5 (20.9)	28% (23, 33) **
Fatal MI	17.5 (4.3)	1% (-20, 19)	22.4 (4.5)	14% (-3, 31)
Fatal Stroke	15.1 (5.0)	10% (-13, 32)	12.2 (4.0)	27% (3, 51) **
Comp. Death	705.1 (32.2)	40% (36, 43) **	818.3 (25.3)	40% (37, 43) **
Death	2442.8 (96.7)	Not Normally Distributed++	3201.8 (94.8)	6% (3, 8) **
CVD Death	456.2 (29.9)	31% (26, 35) **	558.5 (32.6)	31% (26, 36) **
Neuropathy	3417.0 (58.5)	19% (18, 20) **	3461.3 (59.2)	20% (19, 21) **
Retinopathy	1322.0 (33.3)	20% (18, 22) **	1340.5 (40.6)	21% (19, 23) **
Nephropathy	3115.8 (46.1)	Not Normally Distributed++	3245.4 (62.5)	34% (33, 35) **

Table 19. The 2-Sample t-test Results of Experiment 2c. Mean Cumulative Incidence (Standard Deviation) from 15 Replications. Incidence increase from non-clinical inertia group to clinical inertia group (95% Confidence Intervals). ** P- value < 0.05 statistically different. ++ Mann-Whitney results displayed in the Appendix

	ANOVA	Conclusion
MI	All means are equal	Clinical inertia does not affect the gender populations' incidence of complications differently.
Stroke	All means are equal	
CVD Death	All means are equal	
Neuropathy	All means are equal	
Retinopathy	All means are equal	
Nephropathy	All means are equal	
Complication-related Deaths	All means are equal	

Table 20. ANOVA and 2-Sample t-test Results from Comparing the Different Effect of Clinical Inertia Between Genders.

CHAPTER VI

DISCUSSION AND CONCLUSION

This chapter provides a summary of the development of our agent-based model, and the results obtained from the experiments. Lastly, potential areas of future work are presented.

VI.1 Discussion

Clinical inertia is a critical barrier to the effective treatment of diabetes mellitus. Despite its prevalence, there have been few studies on its effects. A clear understanding of the effects clinical inertia has on diabetes and diabetes-related complications is critical. Computer modeling is increasingly being recognized as a practical approach to study different chronic diseases, such as diabetes, and various treatment methods.[30, 31] This study sets out to assess the impact of clinical inertia using a flexible, agent-based simulation model. In our study, we found that clinical inertia increases the incidence of diabetes-related complications among type 2 diabetes agents. These results are broadly consistent with the existing literature, such as the reported outcomes by Osataphan et al. and Paul et al., which state that clinical inertia increases the risk of diabetes complications.[31, 37]

Additionally, the study demonstrated that clinical inertia increases the incidence of diabetes-related complications significantly more on certain age and ethnicity groups. This is the first study, to our knowledge, that examines the effect of the interaction between

clinical inertia and population characteristics on the incidence of diabetes-related complications.

Our study has some limitations. First, our model only predicts the first event of diabetes complications, similar to the CDC RTI model, on which our model is partially based on. Consequently, we are only able to track the cumulative incidence of only the first event of diabetes complications. Secondly, our model's treatment intensification algorithm is based solely on the agent's glycemic levels, whereas in reality a treatment intensification may be based on other risk factors, such as agent age or overall health. Third, the treatment intensification algorithm does not include the discontinuation of medication, which in reality can happen due to medication side effects. Fourth, our model assumes that the patients are fully adhered to their medication instructions. Fifth, the agents in our model are not in additional treatments or interventions, whereas in reality, they might be in multiple treatments and/or interventions for other health conditions. Sixth, our model assumes that the time from the onset of diabetes to diagnosis is set to 0 years, whereas in reality the patient may go undiagnosed for a few weeks or months. Finally, the modeling of clinical inertia assumes that it is a one-time occurrence, where the patient resumes timely treatment intensification after their first episode of clinical inertia. This assumption was made due to lack of literature on the frequency of clinical inertia.

Although it has several limitations, our model was validated using previously published clinical trials. Additionally, even though the experiments were conducted on Bexar County population, the validation of our model supports the accuracy of the agent-

based model for other populations. Our study's findings can contribute considerably to the development and evaluation of treatment guidelines for type 2 diabetes patients. More research in this area is necessary, particularly with real patient data.

VI.2 Summary of Thesis Research

In conclusion, this thesis provides a simulation tool to evaluate the effects of clinical inertia on long-term outcomes of type 2 diabetes patients. The results of this study broaden the knowledge on clinical inertia on long-term outcomes. Our study suggests that clinical inertia leads to higher incidence rates of diabetes-related complications, and that clinical inertia does not affect genders differently, but it does increase the incidence rate of complication for particular age and ethnic groups. These findings may help health providers and policymakers better understand the potential adverse impact of clinical inertia on diabetes outcomes across different populations.

VI.3 Contribution

The thesis research made two important contributions to the knowledge of clinical inertia research and chronic disease modeling.

Previous research has sought to understand the prevalence and causes of clinical inertia on the treatment of type 2 diabetes. Our thesis offers a deeper understanding of clinical inertia by studying its long-term effects and the effects of its interaction with different population characteristics on the incidence of diabetes-related complications. Our study reported that clinical inertia increases the incidence of complications in the long-term, and that it affects some ethnic and age groups on a higher scale than others. To

the best of our knowledge, there are no other studies on the effects of clinical inertia on age-groups, ethnic groups, nor gender. Thus, the implications of our model results provide valuable and insightful information for the development of effective diabetes treatment guidelines, in particular, for the population groups that are suggested to be most affected by the delay of treatment intensification.

Our thesis research also made contributions through the development of the agent-base model, which was specifically modified to study clinical inertia. To the best of our knowledge, agent-based modeling has only been used to study the progression of diabetic retinopathy in a population. Our model can offer more flexibility, by providing projections of the incidence of 5 different diabetes-related complications and the prevalence of diabetes in a broader range of simulated populations. A large portion of the previous modeling work on diabetes has been through Markov models, which offer less intuitive user interfaces. Our model is built with Anylogic, which allows for intuitive animated presentations for users to understand the system in a more effortless way.

Most importantly, the current model has the capacity for straightforward integration of other diabetes interventions. While the integration of other diabetes interventions is out of the scope of this thesis, it is among one of the avenues for future work discussed in the next section.

VI.4 Future Work

A few areas with potential for improvement have been identified, but fall outside the scope of this thesis due to time limitations and other considerations. First, additional

investigation using the agent-based model should be performed. For example, an investigation on the impact of clinical inertia on the time to onset of diabetes-related complications and death. Secondly, further research should be conducted with regards to the interaction of clinical inertia and population characteristics, particularly age and ethnicity/race. Lastly, further improvements should be made to the agent-based model to include additional interventions (diet, physical activity, medication, etc.), all in an effort to help evaluate or create treatment algorithms for type 2 diabetes patients.

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APPENDIX A

Calculating RGL Index

```
if (Race==1 && gender==0)
{RGL=1;}
else if (Race==1 && gender==1)
{RGL=1;}
else if (Race==2 && gender==0)
{RGL=1.04;}
else if (Race==2 && gender==1)
{RGL=1.09;}
else if (Race==3 && gender==0)
{RGL=1.09;}
else if (Race==3 && gender==1)
{RGL=1.04;}
else if (Race==4 && gender==0)
{RGL=1.19;}
else if (Race==4 && gender==1)
{RGL=1.19;}
else if (Race==5 && gender==0)
{RGL=0.95;}
else
{RGL=0.95;}
```

Figure A-1. Series of if statements to determine RGL index for each agent, where 1 is female and 0 is male, and 1,2,3,4,5 correspond to non-Hispanic White, African American, Hispanic, Native American, and Asian, respectively.

APPENDIX B

Smoking Initiation and Cessation Probability Tables.

Table B-1 and Table B-2 contain the age-specific smoke initiation and cessation probabilities, respectively.[18]

Age	Probability of Starting to Smoke
9.0	0.001255503
11.0	0.002522152
13.0	0.005089752
15.0	0.010368573
17.0	0.018676257
19.0	0.018676257
21.0	0.009030316
23.0	0.005089752
25.0	0.002522152
27.0	0.002522152
29.0	0.001887421
31.0	0.001255503
33.0	6.26372E-4

Table B-1. The age-specific probabilities of smoking initiation.

Age	Probability of Quitting Smoking
21.0	0.01378232
22.0	0.01378232
23.0	0.01378232
24.0	0.01378232
25.0	0.01378232
26.0	0.01378232
27.0	0.01378232
28.0	0.01378232
29.0	0.01378232
30.0	0.01378232
31.0	0.01378232
32.0	0.01378232
33.0	0.01378232
34.0	0.01378232
35.0	0.002522025
36.0	0.002522025
37.0	0.002522025
38.0	0.002522025
39.0	0.002522025
40.0	0.002522025
41.0	0.002522025
42.0	0.002522025
43.0	0.002522025
44.0	0.002522025
45.0	0.002522025
46.0	0.002522025
47.0	0.002522025
48.0	0.002522025
49.0	0.002522025
50.0	0.002522025

Table B-2. The age-specific probabilities of smoking cessation.

High Cholesterol Probability Table

Table B-3 shows the age-specific probabilities of an agent having high cholesterol.[37]

Age	Probability of High Cholesterol	
25.0	0.0	
26.0	0.002761417	
27.0	0.002761417	
28.0	0.002761417	
29.0	0.002761417	
30.0	0.002761417	
31.0	0.002761417	
32.0	0.002761417	
33.0	0.002761417	
34.0	0.002761417	
35.0	0.00580027	
36.0	0.00580027	
37.0	0.00580027	
38.0	0.00580027	
39.0	0.00580027	
40.0	0.00580027	
41.0	0.00580027	
42.0	0.00580027	
43.0	0.00580027	
44.0	0.00580027	
45.0	0.015873991	
46.0	0.015873991	
47.0	0.015873991	
48.0	0.015873991	
49.0	0.015873991	
50.0	0.015873991	
51.0	0.015873991	
52.0	0.015873991	
53.0	0.015873991	
54.0	0.015873991	
55.0	0.032555574	
56.0	0.032555574	
57.0	0.032555574	
58.0	0.032555574	
59.0	0.032555574	
60.0	0.032555574	
61.0	0.032555574	
62.0	0.032555574	
63.0	0.032555574	
64.0	0.032555574	
65.0	0.034494073	
66.0	0.034494073	
67.0	0.034494073	
68.0	0.034494073	
69.0	0.034494073	
70.0	0.034494073	

Table B-3. The age-specific probabilities of having high cholesterol.

Blood Pressure Probability Table

Table B-4 shows the age-specific probabilities of an agent having hypertension.[50]

Age	Probability of Hypertension
50.0	0.0
55.0	0.002156969
65.0	0.003695434

Table B-4. The age-specific probabilities of having hypertension.

Diabetes Probability Table

Table B-5 shows the age-specific probabilities of an agent having diabetes.

Age	Probability of Diabetes
17.0	0.0
18.0	7.2579E-4
19.0	7.2579E-4
20.0	7.2579E-4
21.0	7.2579E-4
22.0	7.2579E-4
23.0	7.2579E-4
24.0	7.2579E-4
25.0	7.2579E-4
26.0	7.2579E-4
27.0	7.2579E-4
28.0	7.2579E-4
29.0	7.2579E-4
30.0	7.2579E-4
31.0	7.2579E-4
32.0	7.2579E-4
33.0	7.2579E-4
34.0	7.2579E-4
35.0	7.2579E-4
36.0	7.2579E-4
37.0	7.2579E-4
37.0	7.2579E-4
38.0	7.2579E-4
39.0	8.51086E-4
40.0	8.51086E-4
41.0	8.51086E-4
42.0	8.51086E-4
43.0	8.51086E-4
44.0	8.51086E-4
45.0	8.51086E-4
46.0	8.51086E-4
47.0	8.51086E-4
48.0	8.51086E-4
49.0	0.002282805
50.0	0.002282805
51.0	0.002282805
52.0	0.002282805
53.0	0.002282805
54.0	0.002282805
55.0	0.002282805
56.0	0.002282805
57.0	0.002282805
58.0	0.002282805
59.0	0.002988369
60.0	0.002988369
61.0	0.002988369
62.0	0.002988369
63.0	0.002988369
64.0	0.002988369
65.0	0.002988369
66.0	0.002988369
67.0	0.002988369
68.0	0.002988369
69.0	0.002383508
70.0	0.002383508
71.0	0.002383508
72.0	0.002383508
73.0	0.002383508
74.0	0.002383508
75.0	0.002383508
76.0	0.002383508
77.0	0.002383508
78.0	0.002383508
79.0	0.002383508

Table B-5. The age-specific probabilities of having diabetes.

Death from First MI Probability Table

Table B-6 shows the age-specific probabilities of having a fatal MI.

Age	Probability of Death from First MI
0.0	0.0
15.0	0.003872436
44.0	0.003872436
45.0	0.008507964
54.0	0.008507964
55.0	0.018771998
64.0	0.018771998
65.0	0.042281841
74.0	0.042281841
75.0	0.083777257
99.0	0.083777257
100.0	1.0

Table B-6. The probability of death from first MI, specified by age.

Death after First MI

Table B-7 and Table B-8 shows the age-specific probabilities of dying after first MI for females and males, respectively.

Age	Probability of Death After First MI
0.0	0.0
15.0	0.001151989
44.0	0.001151989
45.0	0.002685801
54.0	0.002685801
55.0	0.004632085
64.0	0.004632085
65.0	0.008277202
74.0	0.008277202
75.0	0.027596477
99.0	0.027596477
100.0	1.0

Table B-7. The age-specific probabilities of dying after first MI for females.

Age	Probability of Death After First MI
0.0	0.0
15.0	6.25587E-4
44.0	6.25587E-4
45.0	0.001553617
54.0	0.001553617
55.0	0.002988369
64.0	0.002988369
65.0	0.006334943
74.0	0.006334943
75.0	0.025023707
99.0	0.025023707
100.0	1.0

Table B-8. The age-specific probabilities of dying after first MI for males.

All-cause Mortality Probability Table

Table B-9 and Table B-10 shows the age-specific probabilities of all-cause mortality for females and males, respectively.

Age	Probability of Death
18.0	2.75114E-4
19.0	2.75114E-4
20.0	3.50184E-4
21.0	3.50184E-4
22.0	3.50184E-4
23.0	3.50184E-4
24.0	3.50184E-4
25.0	3.75211E-4
26.0	3.75211E-4
27.0	3.75211E-4
28.0	3.75211E-4
29.0	3.75211E-4
30.0	5.00375E-4
31.0	5.00375E-4
32.0	5.00375E-4
33.0	5.00375E-4
34.0	5.00375E-4
35.0	6.25587E-4
36.0	6.25587E-4
37.0	6.25587E-4
38.0	6.25587E-4
39.0	6.25587E-4
40.0	7.75903E-4
41.0	7.75903E-4
42.0	7.75903E-4
43.0	7.75903E-4
44.0	7.75903E-4
45.0	0.001076738
46.0	0.001076738
47.0	0.001076738
48.0	0.001076738
49.0	0.001076738
50.0	0.0016541
51.0	0.0016541
52.0	0.0016541
53.0	0.0016541
54.0	0.0016541
55.0	0.002685801
56.0	0.002685801
57.0	0.002685801
58.0	0.002685801
59.0	0.002685801
60.0	0.004353345
61.0	0.004353345
62.0	0.004353345
63.0	0.004353345
64.0	0.004353345
65.0	0.006793923
66.0	0.006793923
67.0	0.006793923
68.0	0.006793923
69.0	0.006793923
70.0	0.010179377
71.0	0.010179377
72.0	0.010179377
73.0	0.010179377
74.0	0.010179377
75.0	0.015742871
76.0	0.015742871
77.0	0.015742871
78.0	0.015742871
79.0	0.015742871
80.0	0.025185596
81.0	0.025185596
82.0	0.025185596
83.0	0.025185596
84.0	0.025185596
85.0	0.048286099
86.0	0.048286099
87.0	0.048286099
88.0	0.048286099
89.0	0.048286099
99.0	0.048286099
100.0	1.0

Table B-9. The age-specific probability of all-cause mortality for females.

Age	Probability of Death
18.0	1.00015E-4
19.0	1.00015E-4
20.0	1.00015E-4
21.0	1.00015E-4
22.0	1.00015E-4
23.0	1.00015E-4
24.0	1.00015E-4
25.0	1.25023E-4
26.0	1.25023E-4
27.0	1.25023E-4
28.0	1.25023E-4
29.0	1.25023E-4
30.0	1.75046E-4
31.0	1.75046E-4
32.0	1.75046E-4
33.0	1.75046E-4
34.0	1.75046E-4
35.0	2.50094E-4
36.0	2.50094E-4
37.0	2.50094E-4
38.0	2.50094E-4
39.0	2.50094E-4
40.0	3.50184E-4
41.0	3.50184E-4
42.0	3.50184E-4
43.0	3.50184E-4
44.0	3.50184E-4
45.0	5.75497E-4
46.0	5.75497E-4
47.0	5.75497E-4
48.0	5.75497E-4
49.0	5.75497E-4
50.0	9.51357E-4
51.0	9.51357E-4
52.0	9.51357E-4
53.0	9.51357E-4
54.0	9.51357E-4
55.0	0.001528501
56.0	0.001528501
57.0	0.001528501
58.0	0.001528501
59.0	0.001528501
60.0	0.00250943
61.0	0.00250943
62.0	0.00250943
63.0	0.00250943
64.0	0.00250943
65.0	0.00377128
66.0	0.00377128
67.0	0.00377128
68.0	0.00377128
69.0	0.00377128
70.0	0.005952946
71.0	0.005952946
72.0	0.005952946
73.0	0.005952946
74.0	0.005952946
75.0	0.009304044
76.0	0.009304044
77.0	0.009304044
78.0	0.009304044
79.0	0.009304044
80.0	0.015742871
81.0	0.015742871
82.0	0.015742871
83.0	0.015742871
84.0	0.015742871
85.0	0.037003713
86.0	0.037003713
87.0	0.037003713
88.0	0.037003713
89.0	0.037003713
99.0	0.037003713
100.0	1.0

Table B-10. The age-specific probability of all-cause mortality for males.

APPENDIX C

Bexar County Population Data

Total Population	10,000			
Age	34.98 (mean)	22.17 (standard deviation)	20 (Min.)	100 (Max.)
Height	1.52 (mean)	0.50 (standard deviation)	1.67 (Min.)	1.87 (Max.)
Weight	80 (mean)	14 (standard deviation)	62 (Min.)	140 (Max.)
Female	50.4%			
Race	White	30%		
	African American	7%		
	Hispanic	58.9%		
	Native American	1.5%		
	Asian	2.6%		
HbA1c	7.02 (mean)	1.72 (standard deviation)	3.3 (Min.)	19.9 (Max.)
No Diabetes	91%			
No Smoking	84%			
Physically Active	78%			
Diet	22%			
No History of Hypertension				
No History of High Cholesterol				

Table C-1. The Bexar County 2013 data used to run experiments. This data was obtained through County Health Rankings and the Texas Demographic Center. The weight and height parameters were estimated using BMI data, and diet percent was estimated using access to healthy food in Bexar County. No data was available for the history of hypertension or high cholesterol.

APPENDIX D

Mann-Whitney Test Results

	No Clinical Inertia	1 – YR Clinical Inertia vs. No Clinical Inertia	3 – YR Clinical Inertia vs. No Clinical Inertia	7 – YR Clinical Inertia vs. No Clinical Inertia
25-year Cumulative Incidences				
Fatal Stroke	11.5	9% (-3,17)	26% (9,52) **	61% (52, 78) **
Comp. Death	319.50	18% (12, 23) **	51% (48, 56) **	100% (95, 105) **
Retinopathy	861.5		30% (24, 33) **	

Table D-1. The Mann-Whitney results to experiment 1. Median Cumulative Incidence. Incidence increase from non-clinical inertia group to clinical inertia group (95% Confidence Intervals). ** P- value < 0.05, statistically different.

	Ages 20 -44		Ages 45- 64		Ages 65 -100	
	No Clinical Inertia	3-Year Clinical Inertia vs. No Clinical Inertia	No Clinical Inertia	3-Year Clinical Inertia vs. No Clinical Inertia	No Clinical Inertia	3-Year Clinical Inertia vs. No Clinical Inertia
25-year Cumulative Incidences						
MI	223.0	25% (19, 30)				
Fatal MI					78.0	46% (37, 54)
Fatal Stroke	4.0	75% (50, 125)				
Comp. Death					1797.0	46% (45, 47)
Neuropathy	3727.0	18% (17, 19)	3168.0	21% (20, 22)		
Retinopathy					493.0	46% (44, 49)
Nephropathy					1273.0	77% (74, 80)

Table D2. The Mann-Whitney results to experiment 2a.

	White		African American		Hispanic	
	No Clinical Inertia	3-Year Clinical Inertia vs. No Clinical Inertia	No Clinical Inertia	3-Year Clinical Inertia vs. No Clinical Inertia	No Clinical Inertia	3-Year Clinical Inertia vs. No Clinical Inertia
25-year Cumulative Incidences						
MI			621.0	25% (23, 29)		
Stroke	305.0	32% (26, 37)				
Fatal Stroke			14.0	36% (14,64)	14.0	21% (7,43)
Death	2824.0	6% (3,8)				
Neuropathy			3583.0	19% (17, 20)		

Table D-3. The Mann-Whitney results to experiment 2b. Median Cumulative Incidence. Incidence increase from non-clinical inertia group to clinical inertia group (95% Confidence Intervals). ** P- value < 0.05, statistically different.

	Native American		Asian	
	No Clinical Inertia	3-Year Clinical Inertia vs. No Clinical Inertia	No Clinical Inertia	3-Year Clinical Inertia vs. No Clinical Inertia
25-year Cumulative Incidences				
Death			2777.0	5% (2,8) **
Retinopathy			1052.0	18% (16, 20) **

Table D-3. The Mann-Whitney results to experiment 2b (continued)

	Female		Male	
	No Clinical Inertia	3-Year Clinical Inertia vs. No Clinical Inertia	No Clinical Inertia	3-Year Clinical Inertia vs. No Clinical Inertia
25-year Cumulative Incidences				
Death	2442.8 (96.7)	8% (5, 11)		
Nephropathy	3115.8 (46.1)	34% (32, 35)		

Table D-4. The Mann-Whitney results to experiment 2c. Median Cumulative Incidence. Incidence increase from non-clinical inertia group to clinical inertia group (95% Confidence Intervals). ** P- value < 0.05, statistically different.