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ANTICIPATING U.S. POPULATION-LEVEL HEALTH AND ECONOMIC IMPACTS USING DISCRETE-EVENT SIMULATION TO GUIDE HEALTH POLICY DECISIONS

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ANTICIPATING U.S. POPULATION-LEVEL HEALTH AND ECONOMIC IMPACTS USING DISCRETE-EVENT SIMULATION TO GUIDE HEALTH POLICY DECISIONS

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ABSTRACT

This dissertation presents two applications of discrete-event simulation (DES) to represent clinical processes: (1) a model to quantify the risk of the maternal obese and diabetic intrauterine environment influence on progression to adult obesity and diabetes, and (2) a model to evaluate health and economic outcomes of different smoking cessation strategies. The first application considers the public health impact of the diabetic and obese intrauterine environment's effect on the prevalence of diabetes and obesity across subsequent generations. We first develop a preliminary DES model to investigate and characterize the epidemiology of diabetes during pregnancy and birth outcomes related to maternal obesity and diabetes. Using data from the San Antonio Heart Study (SAHS), the 1980 Census and the NCHS we are able to verify a simplified initial version of our model. Our methodology allows us to quantify the impact of maternal disparities between different racial/ethnic groups on future health disparities at the generational level and to estimate the extent to which intrauterine exposure to diabetes and obesity could be driving these health disparities. The populace of interest in this model is women of child-bearing age.

The preliminary model is next modified to accommodate data and assumptions representing the United States population. We use a mixed-methods approach, incorporating both statistical methods and discrete event simulation, to examine trends in weight-gain over time among white and black women of child-bearing age in the US from 1980 to 2008 using United States Census projections and National Health and Nutrition Examination Survey (NHANES) data. We use BMI as a measure of weight

adjusted for height. We establish an underlying population representative of the population prior to the onset of the obesity epidemic. Assessing the rate of change in body mass index (BMI) of the population prior to the obesity epidemic allows us to make "unadjusted" projections, assuming that subsequent generations carry the same risk as the initial cohort. Unadjusted projections are compared to actual trends in the US population. This comparison allows us to quantify the trends in weight-gain over time. This model is interesting as a first step in understanding the trans-generational impact of obesity during pregnancy at the population level.

The aim of the second application is to understand the impact of different pharmacologic interventions for smoking cessation in achieving long-term abstinence from cigarette smoking is an important health and economic issue. We design and develop a clinically-based DES model to provide predictive estimates of health and economic outcomes associated with different smoking cessation interventions. Interventions assessed included nicotine replacement therapy, oral medications (bupropion and varenicline), and abstinence without pharmacologic assistance. We utilized data from multiple sources to simulate patients' actions and associated responses to different interventions along with co-morbidities associated with smoking. Outcomes of interest included estimates of sustained abstinence from smoking, quality adjusted life years, cost of treatment, and additional health-related costs due to long-term effects of smoking (lung cancer, chronic obstructive pulmonary disease, stroke, coronary heart disease). Understanding the comparative effectiveness and intrinsic value of alternative

smoking cessation strategies can improve clinical and patient decision-making and subsequent health and economic outcomes at the population level.

This dissertation contributes to the field of industrial engineering in healthcare. US population-level data structures are not always available in the desired format and there is not one method for managing the data. The key element is to be able to link the mathematical model with the available data. We illustrate various methods (i.e. bootstrap techniques, mixed-effects regression, application of probability distributions) for extracting information from different types of data (i.e. longitudinal data, cross-sectional data, incidence rates) to make population-level predictions. Methods used in cost-effectiveness evaluations (i.e. incremental cost-effectiveness ratio, bootstrap confidence intervals, cost-effectiveness plane) are applied to output measures obtained from the simulation to compare alternative smoking cessation strategies to deduce additional information. While the estimates resulting from the two models are topic-specific, many of the modules created for these studies are generic and can easily be transferred to other disease models. It is believed that these two models will aid decision makers in recognizing the impact that preventative-care initiatives will have, and to evaluate possible alternatives.

DEDICATION

This dissertation is dedicated to my two wonderful sons, Alex and Colin. I hope this work will motivate and encourage you to reach for your dreams.

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My parents, Melinda and George, have been extremely generous throughout many long years of education that led me to this point. I extend a very sincere thank you for always being supportive and willing to go out of your way to do anything you could to

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I am grateful for my grandparents, Alex and Vera, for the many lessons they have taught me over the course of my life. You have played a significant role in shaping the person that I am today. Thank you for always being a constant source of unconditional love and strength.

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Last but not least, I express thankfulness to my children Alex and Colin, who have inspired me in numerous ways. You both are an incredible source of happiness. Thank you for being the light at the end of the tunnel.

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CHAPTER ONE

INTRODUCTION

Disease prevention and control remains a crucial health issue and as costs associated with providing health care services spike, patient choices and care become more limited. In recent years mathematical modeling of disease dynamics has been used to answer health care questions. Integrating analytical techniques into public health research, policy, and practice can help lead clinicians and health policy decision makers to make recommendations and identify appropriate public health actions to help prevent disease, improve patient health, and manage rising health care costs. In this dissertation we provide two examples of predictive models for disease management: (1) a model to predict the impact of maternal obesity during pregnancy on the prevalence of obesity in subsequent generations at the population level across different racial and ethnic groups and to identify health disparities among these groups, and (2) a model to provide predictive estimates of health and economic outcomes associated with different smoking cessation interventions.

1.1 Background

Costs of health care have continued to increase for many years. “Expenditures in the United States on health care surpassed $2.3 trillion in 2008, more than three times the $714 billion spent in 1990, and over eight times the $253 billion spent in 1980.” [Kaiser] Health care costs associated with treating chronic diseases in the United States are an estimated 75 percent of national health expenditures. [CDC1] Approximately one in two adults in the US (133 million individuals) in 2005 had at least one chronic illness [Wu

and Green, 2000]. With an increase in the prevalence of chronic illness comes the increasing need for understanding of disease and persistent management and treatment of disease.

Mathematical models of disease provide both understanding and prediction of disease in a population. Modeling of disease dynamics has been used to choose the most effective interventions for preventing and treating disease, understand population robustness to disease threats, understand the clinical effectiveness and comparative value of different treatment strategies, screen an at-risk population for early signs of a disease, understand infectious disease transmission, understand the impact of individual behavior and decision making on population-level disease outcomes, predict the future population with a given disease, guide resource allocation decisions in health care (e.g., distributing funds, allocating organs for transplantation), and influence insurance coverage decisions (refer to Section 1.2). Information provided by analytical health care models contributes to informed decision-making of public policies impacting human life and health. Small increases in the efficiency of the health care system not only lead to improved patient outcomes but contribute to tremendous cost savings.

1.2 Research Aims

This dissertation presents two applications of discrete-event simulation (DES) to estimate long-term epidemiologic and economic consequences of disease processes. Thereby, this dissertation is compiled of work from two separate projects which are similar in their methodological approach.

For application one, we will first create a base simulation model to predict the risk of exposure to maternal obesity and diabetes during pregnancy on obesity and diabetes prevalence in future generations and to examine trends over time. The model will be verified using data for a single cohort. To enable the utilization of cross-sectional NHANES data (a nationally representative sample) we will apply bootstrap statistical methods and mixed-effects regression models. We then validate our method for modeling changes in attributes over time. We begin with an initial cohort and predict prevalence rates at baseline. Because we will use cross-sectional data to infer incidence rates, we will compare predicted values within an age group to actual values in that age group at baseline. That is, we will validate that individuals take on age appropriate characteristics according to the baseline cross-sectional values. We model the population prior to the onset of the obesity and diabetes epidemic. Using input data from different racial and ethnic groups we will quantify health disparities between groups at the population-level over time.

Regarding application two, we will describe the development and verification of a simulation to estimate US population-level health and economic outcomes of smoking cessation interventions. We will describe how we characterize smoking-related disease based on the available data. Analyses to understand the comparative effectiveness and intrinsic value of alternative smoking cessation strategies that can improve clinical and patient decision-making and subsequent health and economic outcomes at the population-level will be explained.

1.3 Literature Review

This section discusses health care modeling methodologies and applications regarding cost-effectiveness analysis, statistical procedures (logistic regression analysis and Bayesian analysis), decision trees, Markov structures (Markov cohort models and Markov decision processes), and discrete-event simulation (DES) techniques. Motivation behind the DES modeling approach selected for our models is discussed. Since the models presented in this dissertation are the first applications of DES to maternal obesity and smoking cessation treatment/smoking-related disease risks, DES models applied to other diseases are reviewed.

1.3.1 Cost-effectiveness analysis

Cost-effectiveness analysis combines information on monetary costs and health benefits (refer to Chapter 5.3) of medical interventions to provide a relative comparison of two or more treatment strategies. Health policy-makers use this information to make informed decisions about allocating resources. Different modeling methods can be applied to perform economic evaluations. Treatment strategies for a broad array of diseases including cervical cancer [Mandelblatt et al, 2002], colorectal cancer [McMahon et al., 2001], psoriatic arthritis [Bansback et al., 2006], depression [Pyne et al., 2010], morbid obesity [Campbell et al., 2010], mental illness [Dixon et al., 2002], prostate cancer [Hövels et al., 2009; Ito et al., 2010], HIV [Simpson et al., 2004], and sleep apnoea-hypopnea [Sadatsafavi et al., 2009], among many others, have been assessed using cost-effectiveness analysis. Chapter 4.1 provides a detailed review of modeling the cost-effectiveness of smoking cessation strategies.

1.3.2 Statistical procedures

Chhatwal et al. (2009) developed two logistic regression models to facilitate early breast cancer diagnosis where the probability of cancer is the outcome measure in each model. These logistic regression models used mammographic features to make breast cancer risk predictions which suggest that more accurate decisions may be made using the probability of cancer estimated in the two models. However, the results do not recommend when the decision should be made to biopsy a particular patient based on their risk of breast cancer, and do not consider how patient's risks and decisions change when individual patient attributes (e.g. age) are taken into account.

Many authors have been successful at creating prognostic models of disease using Bayesian structures to quantify the probability of a disease based on epidemiologic, demographic, and clinical information. Bayesian models of disease risk for breast cancer [Burnside et al., 2009; Velikova et al., 2009], prostate cancer [Smith et al., 2009], and end-stage renal disease [Dimitrov et al., 2003] have been proposed. A predictive model of patients with carcinoid was developed by van Gerven et al. (2008) using Bayesian inference. Models of survival prediction [Jayasurya et al., 2010] and prediction of local failure [Oh et al.; 2011] in lung cancer patients have adopted the Bayesian approach. Bayesian networks of gene interactions have been constructed by Armañanzas et al. (2008) and Chen et al. (2006).

Medical data is often hard to accumulate and Bayesian networks are efficient when information is lacking in comparison with other modeling methods. Nonetheless, to define probabilistic relationships between diseases and symptoms, Bayesian models

assume a simple representation of attributes where each problem instance revolves around predefined attributes. This is insufficient for medical applications in which patient attributes are uncertain, cannot be defined in advance, and change over time. Interdependencies among related entities cannot be specified in advance. Because of the complex nature of disease, clinical models often require a large state space. In Bayesian network modeling the size of the model space is large when few variables are included and increases exponentially when variables are added.

1.3.3 Markov structures

Previous models of disease most frequently used Markov structures. Sonnenberg and Beck (1993) provide an overview of Markov modeling to inform medical decisions. Markov models have been used to conceptualize Alzheimer's disease [Macdonald and Pritchard, 2000], depression [Le Lay et al, 2006], sepsis [Bauerle et al, 2000], human papillomavirus (HPV) infection and cervical carcinogenesis [Myers et al, 2000; Dasbach et al, 2006], HIV [Simpson et al, 2009], and Type 2 diabetes [The CDC Diabetes Cost-effectiveness Group, 2002].

A review of Markov models for coronary heart disease (CHD) interventions is discussed in detail in Cooper et al (2006). Decision tree analysis was typically used to model acute or short-term CHD interventions and Markov models represented chronic or long-term CHD interventions. While the majority of CHD studies evaluated the cost-effectiveness of treatment strategies, models were also developed to predict the prevalence of heart disease on the future population.

The Markov approach describes the transition of a homogeneous cohort of patients through health states over time. That is, portions of the cohort of patients move through the model from one event to another based on the likelihood of moving between states. Markov modeling does not represent and evaluate individuals progressing through the model. Markov models require mutually exclusive branches or rigidly defined health states which must signify every aspect of the disease and transition at fixed cycles. Since the individual can only be in one state at a given time, multiple distinct states are required to represent all combinations of patient characteristics. The following examples are adapted from Caro (2005). At least four states must be defined to represent the combination of obese (yes/no) and diabetic (yes/no) using Markov models. In some instances it is required that a continuous characteristic (e.g. weight-gain) be modeled as discrete (yes or no versus how much weight gained). A large number of states would be required to attempt to capture the continuous nature of the weight-gain attribute. Consider a change in weight of ±40 pounds which would require almost 20 states to reflect changes in weight in five pound increments. This problem is exacerbated if new states are generated over time. For example, week one after treatment represents one state, week two after treatment represents another state, and so forth. Similarly, the state space increases if the course of a disease is influenced by the individual's history (e.g. history of an event such as a stroke). Markov models may not be suitable in tracking a patient's disease history properly as they are too limited to consider multiple patient-specific demographic and health characteristics in a single model. Restrictions arise with high state-space complexity because as the size of the state space increases, the problem

becomes harder to solve and can lead intractable solutions. Additionally, Markov chains are not compatible when a decision needs to be made at multiple points in time.

Health care models involving medical treatment decisions have been formulated as Markov decision processes (MDPs) to help patients/clinicians design individualized treatment strategies which provide optimal clinical outcomes. Schaefer et al (2004) provides a good overview of MDP methodology and summarizes the MDP framework in terms of medical decision making. Schaefer et al (2004) also summarize several MDP applications to medical treatment decisions including the optimal control of an epidemic [Lefevre, 1981], a drug infusion plan for dispensing anesthesia [Hu et al., 1996], kidney transplantation [Ahn and Hornberger, 1996], mild hereditary spherocytosis treatment [Magni et al., 2000], ischemic heart disease (IHD) interventions [Hauskrecht and Fraser, 2000], breast cancer screening and treatment options [Chhatwal et al, 2010], and liver transplantation [Alagoz et al, 2002]. Pneumonia-related sepsis (Kreke et al., 2008), ventricular septum defect [Peek, 1999], HIV therapy [Shechter et al., 2008], type 2 diabetes treatment [Denton et al, 2009], and liver transplantation [Alagoz et al., 2004, 2007a, 2007b; Sandikci et al., 2008] are also among the studies in this area.

MDPs encompass similar limitations of standard Markov models but comprise additional challenges. Transition probabilities and rewards could vary based on each decision made therefore for every possible description of patient health and decision enough observations must exist to accurately estimate the transition probabilities. For example, the information contained in the state could be a state-action pair for which no clinical observations were taken. Therefore, MDPs are more data intensive than other

stochastic modeling techniques and the limitations regarding available data may make the state space larger and unfavorable.

1.3.4 Discrete-event simulation

In recent years, discrete-event simulation (DES) has emerged as the preferred method to characterize clinical processes [Caro 2005; Caro et al., 2010; Karnon and Brown, 1998]. Le Lay et al. (2006) reviewed Markov models of depression to identify methodological weaknesses. A DES of major depression was developed to illustrate the benefits of DES in representing disease progression. The performance of a published Markov model of HIV was compared to a new DES model of HIV in Simpson et al. (2009). The authors summarize the strengths and weaknesses of the Markov approach and DES approach in estimating the cost-effectiveness of two antiretroviral HIV treatments. Caro et al. (2010) discuss issues with the Markov cohort approach applied to treatment for heart disease. Furthermore, Ramwadhdoebe et al. (2009) explain when DES is the appropriate modeling technique and how to apply DES to health care modeling using pediatric ultrasound screening for hip dysplasia as an example. The authors discuss the DES model building process and explain the use of the model for informing health care policy makers.

DES modeling provides a comprehensive evaluation of patients progressing through the model, based upon individual-level demographic and health attributes (e.g. age, gender, body-mass index). Patients with differing attributes move from one event to another in sequential order while simultaneously taking into account important risk factors such as age, gender, disease history and a patient's attitude towards treatment,

together with any disease-related events (e.g. adverse/acute events such as a stroke or heart attack). Probabilities of transitioning between health states can be functions of the clinical and demographic measures and can therefore be dependent upon these background attributes. For example, gender and age could be assigned independently but the patient's body mass index (BMI) could depend on the gender and age attributes. Individual-based modeling allows different entities to experience different events, and the system behavior is a summary of each patient's unique clinical history, allowing for examination of health and economic outcomes at both the individual and population levels. Since DES modeling allows individual attributes to be included in the model, compound health states do not have to be defined thus improving the model precision [Le Lay et al., 2006; Cooper et al., 2006; Simpson et al., 2009].

Entities in a DES model can interact and compete with one another [Shechter et al., 2005]. Timing of interactions can be independent of fixed length Markov cycles or completely stochastic. Each interaction between individuals can generate a change in the state of the system. The path that each participant follows is not necessarily known a priori therefore it can be influenced by random local events or changes in the system caused by entities moving through the system. The chance for each of the different pathways can be assigned by stochastic distributions or fixed probabilities. Since DES draws random samples from distributions to variations around the mean, information regarding the effect of statistical uncertainty in model input(s) is provided. It is possible that a patient re-enters or follows the same pathway in the same run. DES is useful in

modeling recursive or random events and is a good approach if one has a very large state space to model.

DES models allow for the creation of lifetime scenarios even though data only exists for shorter durations. DES has better long-term predictive validity compared to Markov models as DES has the capability to predict more detailed outcomes, thereby representing the course of a disease more naturally with few limitations. DES allows evaluation of multifaceted stochastic systems and for consideration of probable changes in those systems due to different sources of variation. The user can easily perform probabilistic sensitivity analysis to study variation in the mean simulation output(s) of a model as one or more input parameters are varied. Thus, practitioners can identify the most important factors in a large discrete-event simulation. Additionally, the probabilistic element of DES allows one to plot the relationships between significant model outputs to gain an understanding of how different model predictions correlate.

DES has been applied to conceptualize HIV/AIDS progression. Bishai et al (2007) address allocation decisions for antiretroviral treatment (ART) in developing countries by comparing eight treatment strategies including pharmacologic treatment and laboratory monitoring. Costs and health outcomes for a cohort of 10,000 HIV-infected individuals were obtained. The model ran for 10 years (with the possibility of death) and was updated on a 6 month basis. Multiple data sources were used including the Multicenter AIDS Study (MACS) and the Women's Interagency HIV Study (WIHS), published literature, and parameters from clinical studies to characterize the progression of disease prior to ART initiation and after ART initiation. Quantification of the

incremental impact and cost-effectiveness of the interventions was presented. A DES model of HIV by Linas et al (2009) compared outcomes of two policies to determine AIDS Drug Assistance Programs (ADAPs) standards to minimize morbidity, mortality, and costs. The progression of HIV-infected patients on and off ART was conceptualized. Data from the Massachusetts ADAP in 2004 established a baseline cohort and five-year clinical outcomes and program utilization measures were compared. Rauner et al (2005) developed a DES describing mother-to-child transmission of HIV in sub-Saharan Africa. Two HIV/AIDS interventions were evaluated to identify potential benefits: (1) anti-retroviral treatment (ART), and/or (2) bottle-feeding strategies. The POST methodology was implemented. This model is unique in that mothers and babies were linked (by pointers in the entity structure) to one another (i.e. a mother could trace her own mother in addition to her offspring). To provide an example of why this is useful, if a mother advanced to AIDS while breastfeeding her child, the likelihood of the child developing HIV could be altered. A warm-up period of 12 years was required to establish the baseline population and model outcomes were evaluated after an additional 12 years. A cost-effectiveness analysis was performed to compare scenarios. Results were sensitive to assumptions regarding HIV prevalence and baseline infant mortality rate, both dependent on local conditions and the efficacy of ART.

DES models of coronary heart disease (CHD) have been developed for several purposes. Babad et al (2002) model prevention strategies for CHD where the baseline population consists of healthy individuals (i.e. individuals without CHD). Healthy individuals are simulated until they experience their first coronary event.

Demographic/clinical attributes included age, sex, systolic blood pressure, total cholesterol, and smoking. Adverse CHD events included the onset of stable angina, unstable angina, myocardial infarction (MI), and sudden cardiac death. Mortality from other cardiovascular disease, stroke, cancer, and all-cause reasons were modeled. Davies et al (1993) POST methodology was applied. Input measures were taken from three main sources: (1) The Health Survey for England (HSE), (2) The Framingham study, and (3) The British Regional Heart Study. This model is referred to in the literature and will be further identified as the Prevention model. Cooper et al (2002) model CHD progression, prevention, and intervention strategies for a baseline population of sick individuals (i.e. individuals with CHD). Individuals in this model experience who an acute coronary event (e.g. MI, unstable angina) are followed through treatment until reach stable symptomatic/asymptomatic states or death. Patient characteristics include age, sex, history of previous events, and the degree of coronary artery vessel disease. Risks in the model change following different treatment strategies. The POST modeling approach was used to construct the model. The model by Cooper et al (2002) is referred to in the literature and will be further identified as the Treatment model. Davies et al (2003) linked the models of Babad et al (2002) and Cooper et al (2002) to provide a complete structure of prevention and treatment within the population. The purpose of the model was to evaluate current and possible future treatment options for the population of England and Wales. Cooper et al (2008) extended the Treatment model [Cooper et al, 2002] to perform a cost-effectiveness analysis when drugs are given to patients with CHD to help prevent adverse coronary events (i.e. myocardial infarction, death).

Shechter et al (2005) modeled End-Stage Liver Disease (ESLD) using DES to evaluate the effects of possible changes in liver allocation policies in the US. Data from the United Network for Organ Sharing (UNOS) and quality-of-life estimates from the literature populated the model. Longitudinal data from patient data records of the University of Pittsburgh Medical Center was used to assign an individual's clinical attributes. DES was the chosen methodology to allow individual ESLD patients to compete for donor organs. Markov structures cannot generate queues or represent individual patients and patient interactions. Disease-specific Cox proportional hazards models provided estimates of post-transplant survival (survival estimates for the likelihood of death by the patient and organ rejection/loss). Outcomes obtained from the simulation were compared with actual UNOS measures to validate the model.

Davies et al (2004) developed two models of diabetic retinopathy (one for Type 1 diabetes and another for Type 2 diabetes) to evaluate the ideal setting, screening technique, and frequency of screening for early signs of diabetic retinopathy. The model was constructed using the POST modeling approach (Davies et al, 1993) and populated with data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy to represent the untreated progression of disease. Alternative screening and treatment policies of the United Kingdom were assessed using cost data from the National Health Service (NHS) in 2001. Outcomes indicated differences between policies only regarding the cost-effectiveness for screening.

A DES of gastric cancer using the POST modeling approach was developed and used to evaluate the benefits of screening for Helicobacter pylori infection (Davies et al, 2002). The target population consisted of individuals age 40 and older in the year 2000. Sources of input data to represent the general United Kingdom population were multiple including published databases and literature. Discounted and undiscounted output measures were obtained for costs, morbidity, deaths prevented, and years of life saved. Results favored a screening program for Helicobacter pylori infection. Roderick et al (2003) used DES modeling to perform a cost-effectiveness analysis in which population screening for Helicobacter pylori in preventing gastric cancer and peptic ulcer disease were compared with no screening. The population of England and Wales was represented and the POST modeling approach was applied. The authors concluded that Helicobacter pylori screening may be cost-effective over a time period greater than 25 years.

Gestel et al (2010) applied DES to conceptualize the progression of ocular hypertension in glaucoma patients and evaluated treatment decisions and effects. Health state utility values and costs associated with disease status were modeled. Health and economic outcomes were validated and three treatment strategies were compared using cost-effectiveness analyses.

1.4 Dissertation Organization

The remaining chapters of this dissertation are organized as follows. Material for the first application is presented in Chapters 2 and 3. In Chapter 2 we focus on the development and verification of the obesity and diabetes simulation model. Chapter 3 presents our approach for handling cross-sectional US population-level data structures

and modifies this simulation to accommodate this data. The material for topic two is presented in Chapters 4 and 5. The development and verification of the DES model to compare therapeutic options for smoking cessation is described in Chapter 4. In Chapter 5 the base case results of the smoking cessation simulation are discussed and sensitivity analysis results are presented. Each chapter provides background information and associated literature relevant to the chapter, in addition to discussing conclusions and future research opportunities. The dissertation is concluded with Chapter 6 in which we summarize the contributions of our research.

CHAPTER TWO

A DISCRETE-EVENT SIMULATION MODEL TO PREDICT LONG-TERM IMPACTS OF INTRAUTERINE EFFECTS ON DIABETES AND OBESITY PREVALENCE

This chapter introduces a discrete-event simulation (DES) model to investigate the impact of the maternal diabetic and obese intrauterine environment influence on the diabetes and obesity prevalence in subsequent generations. First, we discuss the methodology and present a description of the model. We next present and discuss the verification of the model and provide an example of the type of results that can be obtained from our model.

2.1 Model Introduction

The goal of this research is to provide quantification of the impact of maternal disparities between different racial/ethnic groups at the population level on health disparities affecting the populace in the future, where the populace of interest is women of child-bearing age. To this end we develop a DES model to predict the affects of exposure to maternal obesity and diabetes during fetal life on the prevalence of diabetes in subsequent generations to examine trends over long periods of time. The central hypothesis is that a mother's health influences the health of her offspring which in effect characterizes the health of the population, thereby influencing the health of future generations. Understanding the impact of fetal exposure to maternal diabetes and obesity on future generations will allow estimates to be made regarding the degree to which these exposures could be influencing health disparities.

The prevalence of obesity and diabetes continues to increase by epidemic proportions. A study conducted by the Centers for Disease Control and Prevention (CDC) between 1991 and 2001 observed an increase in the incidence of diabetes in the American population by 61% and an increase in the incidence of obesity by 74% [CDC2]. An analysis performed by the CDC from 2006 to 2008 revealed that the prevalence of obesity in African Americans was 51% higher when compared with Caucasians and the prevalence of obesity in Hispanics was 21% higher [CDC3].

As the incidence and prevalence of diabetes continues to escalate, women of reproductive age have an increased chance of becoming diabetic while pregnant. Diabetes is unique to women because the disease not only affects the mother's health but also impacts the health of the unborn child [Cowie et al., 2006]. Intrauterine exposure to maternal diabetes may contribute to the worldwide diabetes epidemic. Obesity during pregnancy predisposes a woman to develop diabetes. Offspring exposed to maternal diabetes during gestation may be at higher risk of obesity and diabetes than offspring not exposed to the intrauterine diabetic environment, which means this exposure may be driving the obesity and diabetes epidemics. Therefore, understanding the transgenerational epidemiology of diabetes due to intrauterine programming is important.

2.2 Model Description and Assumptions

This section describes the discrete-event simulation (DES) model to investigate the impact of intrauterine exposure to diabetes and obesity on the prevalence of diabetes and obesity in future generations. The underlying assumptions of the simulation are presented.

2.2.1 Structure of the simulation

The simulation model was developed using *Arena* 13.5 (a product of Rockwell Automation Technologies, Inc.) DES software, which allows for fast execution and incorporates special purpose features to enhance the modeling of dynamic processes. Four modules are included in the simulation: (1) creation of individuals, (2) disease progression, (3) population progression, and (4) statistics. Figure 2.1 provides a simplified depiction of how individuals flow through the model. The simulation starts with an underlying population and allows for the creation of new individuals each successive year. Demographic characteristics are initialized upon entry to the simulation. Once the individual has reached childbearing age, health measures [i.e. body mass index (BMI), diabetes status] are updated on an annual basis. Individuals meeting specified conditions are eligible to reproduce. The offspring appear in the simulation model upon reaching childbearing age to feed the birth rates and represent the change in population demographics over time. Once pre-determined standards have been realized, the individual is removed from the simulation. Output measures are calculated as the simulation progresses. Various run conditions and input parameters may be modified such as the number of replications, the run length, characteristics of individuals, and the number of times an individual can produce offspring. A detailed description of each module follows.

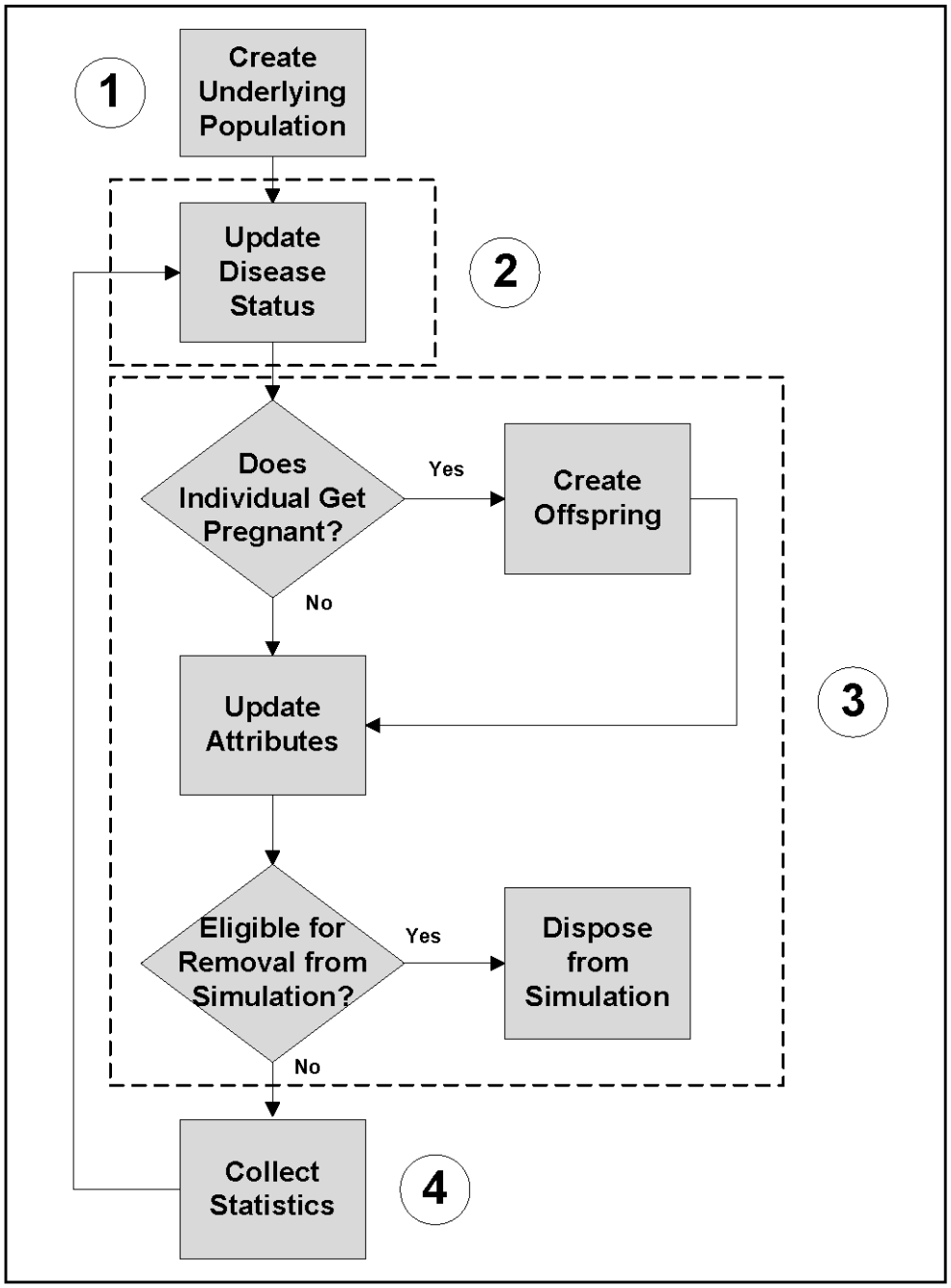


Figure 2.1: Top-level schematic of flow through the simulation.

2.2.2 Creation of individuals

The creation module initializes the underlying population and these individuals can take on attributes according to the characteristics of the population demographics. A

discrete number of individuals enter the simulation according to one arrival which represents a single cohort sampled from a chosen population. Upon entry into the simulation model, demographic characteristics (i.e. age) and pregnancy attributes (i.e. pregnancy status, number of pregnancies) are initialized. The age structure of the underlying population was constructed using 1980 US Census data. Since we only evaluate women of childbearing age, the age range of individuals in the simulation was restricted. All individuals entering the simulation at baseline are females who are not pregnant and who are considered to have no previous pregnancies. Baseline BMI is determined in the disease progression module.

Each individual is also assigned a subset of attributes taking on the characteristics of the mother. These attributes include clinical information routinely collected at delivery including maternal age, BMI, diabetic status, and obesity status. The maternal attributes for the underlying cohort represent the characteristics of a healthy individual. A healthy individual is characterized as neither diabetic nor obese. In other words, individuals in the starting population are assumed to not have been exposed to diabetes or obesity *in utero*.

Transition probabilities are dependent upon these background attributes. For example, age is assigned independently but the patient's BMI (used to determine obesity status) depends on age and ethnicity. Probabilities of developing diabetes are dependent on the mother's diabetic status, and the individual's obesity status and age.

2.2.3 Disease progression

Each year in the system, individuals travel through the disease progression module which consists of two sub-modules: diabetes disease and body mass index (BMI).

The diabetes disease sub-module updates a patient's diabetic status (diabetic/not diabetic). The diabetes disease sub-module can consider different types of diabetes (type I and type II diabetes mellitus) according to the available dataset. Once a patient becomes diabetic, we assume that the patient remains diabetic until leaving the system. Gestational diabetes mellitus (GDM) is taken into consideration in the population progression module as a diagnosis of GDM occurs during pregnancy and does not mean that an individual had diabetes before conception, or that the individual will have diabetes after giving birth.

The BMI sub-module assigns starting BMI values in addition to assigning cyclic changes in BMI. BMI values are updated annually by age group according to a specified distribution. The model can consider BMI with respect to specific population estimates for the patient's race/ethnic background and gender. A patient's BMI can either increase or decrease each year in the system. BMI values and annual changes in BMI may be restricted based on what is clinically feasible. BMI levels determine obesity status where a BMI of 30 kg/m^2 or greater classifies an individual as obese.

Fetal exposure to maternal diabetes was considered present if the mother was diagnosed as diabetic before delivery and absent if the mother was not diagnosed as diabetic. Transitions from healthy to diabetic are dependent on maternal attributes for exposed/not exposed to diabetes *in utero*, as well as the individual's obesity status and age. Offspring are not at risk to become sick (diabetic or obese) until they reach childbearing age. Upon reaching childbearing age, the offspring are assigned a starting BMI value based on the same data used to initialize BMI for the underlying cohort.

2.2.4 Population progression

The population progression module allows individuals to reproduce. Pregnancies were determined based upon probabilities drawn from NCHS natality files [CDC5]. The number of pregnancies per individual was restricted to a maximum of eight pregnancies. Two conditions define the eligibility to become pregnant. An individual must be of childbearing age and the maximum number of allowable pregnancies must not be attained. An individual who is not of childbearing age or who has exceeded her maximum number of pregnancies continues to cycle through the simulation with a chance of getting sick, but with no possibility of getting pregnant. Pregnancy status is adjusted with respect to demographic and clinical attributes. The likelihood of getting pregnant is evaluated with respect to age; however, pregnancy status can be determined according to the individual's race/ethnic group. Pregnant women acquire GDM based on age specific probabilities and are only considered diabetic for the duration of the pregnancy.

Table 2.1: Birth rates (births per 1,000 women in specified group), by age.

Age cohort	Birth rate
18 - 19	73.2
20 - 24	111.1
25 - 29	113.8
30 - 34	61.2
35 - 39	18.8
40 - 44	3.5

We assume that a pregnancy results in one live birth and the offspring is created (enters the simulation) the next iteration or simulated year through the system. The health of an infant is dependent on the mother's health. The offspring's clinical and demographic attributes are initialized and the offspring takes on the mother's race/ethnicity. A subset of attributes reflecting the mother's attributes is assigned when

the offspring enters the simulation. That is, the offspring carries intrauterine environment information into the future. Once the offspring is created the mother progresses through the model as usual and could become pregnant again in the future. We assume that forty-eight percent of offspring are female (based on US Census figures), and the male progeny are disposed from the system. Female offspring progress through the model and can procreate.

An accounting sub-module is embedded within the population progression module to update the age attribute. Since we are only interested in the prevalence of obesity and diabetes in women of childbearing age, the simulation updates the age of individuals within the childbearing age limits. When an individual reaches the upper limit of childbearing age, the individual is removed from the simulation. Upon leaving the simulation, attributes of the individual are output to a file and the individual's maternal family history can be viewed.

2.2.5 Statistics

The statistics module updates model outcomes. At any point in time, a cross sectional analysis can be made of individuals currently in the cohort to provide a prevalence-based measure of the effect of exposure to a disease. The model can accumulate population statistics including prevalence rates for obesity, type I and/or type II diabetes mellitus, and GDM. These prevalence rates can be viewed annually and cumulatively according to different patient attributes (e.g. age group). Additionally, the distribution for BMI of individuals in the system can be observed.

2.3 Model Verification

Several measures were taken to verify the model. To ensure conceptual verification of the model during the developmental stages, we collaborated with the Division of Biostatistics and Epidemiology in the Department of Medicine at the Medical University of South Carolina (MUSC). The model was verified by comparing simulated measures with data from the 1980 United States Census, the National Center for Health Statistics (NCHS), and results from the San Antonio Heart Study (SAHS) [Mitchell et al., 1991, Stern et al., 1984]. Because we desire an initial population that is representative of the population before the inception of the diabetes and obesity epidemic, numbers were obtained from the results of the San Antonio Heart Study (SAHS) to provide starting inputs for BMI values and type I diabetes mellitus status. Estimates of the prevalence of maternal diabetes during pregnancy were abstracted from population-based literature [Hunt and Schuller, 2007]. Estimates for the initial cohort represented women ages 18 to 44 years.

The SAHS was an 8-year longitudinal study of diabetes and cardiovascular disease. The SAHS cohort consists of 5158 men and non-pregnant women between the ages of 25 and 64 years. Households from three types of San Antonio neighborhoods were randomly sampled including low-income, inner city which is made up of approximately 100 percent Mexican Americans, middle-income, and high-income districts [Mitchell et al., 1991, Stern et al., 1984]. Data from the SAHS baseline and follow-up for females ages 25 to 44 was used as inputs to the model. Since we did not have data available for females between the ages of 18 to 24 years, this information was

deduced using data from participants ages 25 to 29 years. The sample size of females between the ages of 18 and 44 years was assumed to be 358. Data from the SAHS provided inputs for two important components of the simulation, the diabetes disease sub-module and the obesity disease sub-module.

SAHS data provided the diabetes incidence rates for the diabetes disease sub-module. Prevalence of diabetes in the SAHS cohort at baseline over all ages was 1.98 percent. At baseline, obese individuals are assumed to be 6.6 times more likely to develop diabetes than individuals who were not obese. We derive that at baseline 7.38 percent of obese individuals develop diabetes and 1.09 percent of non-obese individuals develop diabetes. Annual probabilities of developing diabetes consider obese individuals to be 10.7 times more likely to develop diabetes than individuals who are not obese. Using incidence of diabetes over the 7.5 year SAHS period, we derive the annual likelihood of diabetes based on obesity status using the cumulative geometric distribution (refer to Appendix A for computations).

Table 2.2: Probability of diabetes mellitus, by age and obesity status.

Age cohort	Not obese	Obese
< 30	0.0009	0.0094
30 – 34	0.0018	0.0211
35 – 39	0.0028	0.0329
40 – 44	0.0026	0.0314

**BMI of 30* kg/ m^2 *or more is considered obese*

SAHS statistics also provided data for the obesity sub-module. Because of the small sample size, all distributions for BMI were treated as a truncated normal distribution. A lower and upper bound of (μ-1.5σ) and (μ+5σ) respectively was established for baseline BMI. Lower and upper bounds for the change in BMI were -σ and +2σ, respectively. Numbers from the SAHS demonstrate that 13.7% of women ages

25 to 44 are obese at baseline. These numbers were used to initialize starting BMI values for the underlying population in the simulation. Yearly change in BMI was based on statistics for the change of BMI in the SAHS at baseline and at follow-up 7.5 years later.

Table 2.3: Input parameters for baseline BMI (kg/m^2) in the simulation.

Age cohort	Mean	St Dev
< 30	23.4683	5.0056
30 – 34	23.6806	4.4092
35 – 39	25.1876	6.6825
40 – 44	25.2332	5.7084

Table 2.4: Change in BMI (kg/ m^2) over 7.5 years.

Age cohort	Mean	St Dev
< 30	2.5956	2.8653
30 – 34	2.4881	3.3886
35 – 39	2.4119	2.6218
40 – 44	1.5767	2.1411

Table 2.5: Probability of developing GDM, by age.

Age cohort	Annual probability of GDM
< 30	0.01
30 – 34	0.03
35 – 39	0.05
40 – 44	0.08

2.4 Results

In this section we substantiate model performance computationally. We show by comparison of system measures and predicted measures that results obtained from the model closely represent those obtained from the system. Subsequently, we test different assumptions regarding the effects of the obese intrauterine environment on the prevalence of diabetes in the population over the long-term.

2.4.1 Verification results

A cohort of 10,000 individuals was simulated over an eight year horizon. The childbearing age range was 18 years to 44 years and the age structure was taken from the 1980 US Census. We measured average BMI, prevalence of obesity, and prevalence of

diabetes to verify accurate representation of disease progression. These output variables appeared to produce sufficiently small 95% confidence interval (CI) half-widths (HW) after 15 replications. The model was implemented using Rockwell's Arena Software version 13.5.

First, average BMI and obesity prevalence from the simulation were compared to SAHS data. Average BMI measured in the simulation at baseline and follow-up was 24.8 kg/m^2 and 26.9 kg/m^2 (95% CI HW of 0.03 and 0.03, respectively) and data from the SAHS gave a mean BMI of 24.5 kg/m^2 and 26.7 kg/m^2 at baseline and follow-up, respectively. Our model predicts obesity prevalence of 13.8% (95% CI HW of 0.23) at baseline compared to 13.7% obese at baseline in the SAHS. Prevalence of obesity in the simulation at follow-up measured 24.7% (95% CI HW of 0.27) and 24.3% of the SAHS population was obese at follow-up. Next we verified prevalence of diabetes in the simulation. Projected diabetes prevalence at baseline was 1.95% (95% CI HW of 0.06) compared to 1.98% in the SAHS at baseline. The simulation measured diabetes prevalence at 5.86% (95% CI HW of 0.13) and 5.79% of the SAHS population was diabetic at follow-up.

Table 2.6: Verification of performance measures.

Performance Measure	Baseline		Follow-up	
	Simulation	SAHS	Simulation	SAHS
Average BMI (kg/m^2)	24.8 (0.03)	24.5	26.9 (0.03)	26.7
Obesity prevalence (%)	13.8 (0.22)	13.7	24.2 (0.24)	24.3
Diabetes prevalence (%)	1.98 (0.08)	1.98	5.86 (0.13)	5.79
Note: Values in parentheses are 95% CI half-widths				

Since the CI half-widths of the simulated performance measures capture the SAHS numbers, we are 95% confident that the simulation projections and SAHS measures are statistically the same. Projected measures closely correspond to data from

the SAHS therefore we believe that our model accurately predicts the outcome of one cohort. The performance of the model is assumed to be both a verified implementation of the system in addition to a valid representation of the system. We believe that our model can realistically forecast other measurements of interest.

2.4.2 Prevalence of diabetes in future generations

Using SAHS data as simulation inputs we tested different assumptions regarding the effects of the intrauterine environment on the prevalence of diabetes over the long-term. A cohort of 10,000 individuals progressed through the simulation for 100 years. Output variables were assessed in 5-year intervals. The rate of change in BMI in the SAHS population was assumed to remain the same over time.

First, projections of diabetes prevalence were reported without maternal affects (base case). That is, we assume that future generations carry the same risk of disease as the underlying population. Next, we projected prevalence of diabetes accounting for maternal affects. Maternal affects is characterized as an increased risk of disease because of exposure to maternal disease *in-utero*. We assume an increased risk of diabetes to the child if exposed *in-utero* to maternal obesity to demonstrate the type of estimates that can be obtained from our model. Projections can also be made assuming an increased risk of diabetes due to intrauterine exposure to maternal diabetes or both maternal obesity and diabetes. We focus on the influence of exposure to maternal obesity during fetal life because obesity is considered a dominant trait driving America's diabetes epidemic [CDC4].

We considered different levels for risk of diabetes in individuals exposed to maternal disease. Risk factors for diabetes if exposed to maternal obesity during fetal life were 1.5-, 2.0-, 2.5-, and 3.0-fold. For example, a relative risk of 1.5 means that an individual who was exposed to an obese intrauterine environment has a 50 percent higher risk of diabetes than someone not exposed.

Regarding base case projections, after 13 years in the simulation individuals less than 30 years of age who entered the simulation have matured, and after 18 simulated years individuals who entered the simulation at age 34 or younger have aged. After 23 simulated years all individuals from the underlying population have aged such that remaining individuals from the initial cohort are between ages 40 and 44 years. Offspring of the underlying population have entered the model and are less than 30 years of age. After 30 simulated years none of the base population remains in the simulation, and the offspring from this base population are still less than age 30. After 35 simulated years the offspring have matured but do not exceed 34 years of age. After 40 simulated years the offspring and their offspring have matured but do not exceed 39 years of age. After 45 simulated years the offspring of the initial population and their offspring exist across all age groups and a steady flow of patients continues through the model.

Prevalence of obesity in the base model without maternal affects does not incorporate any additional risk to the offspring if the mother was diabetic while pregnant. As the underlying population ages, we can see a steady increase in the prevalence of diabetes. Diabetes prevalence steadily increases during the 18 year time period before any offspring enter the model. The prevalence of diabetes begins to decline at year 18 and

drops to 3.49 percent after 30 years as the young offspring enter the simulation. As the children begin to age the prevalence of diabetes climbs to a peak of 11.3 percent after 45 years. The prevalence of diabetes declines to 8.4 percent after 55 years and then slightly increases again to 9.3 percent after 65 years. Diabetes prevalence begins to stabilize after 65 years reaching a minimum of 8.45 percent and a maximum of 9.56 percent between years 65 and 100. We observe an increase in the prevalence of diabetes over time even without consideration of maternal affects.

Figure 2.2 illustrates sensitivity and the expected increase in diabetes prevalence for individuals age 18 to 44 years. Considering an increased risk of 1.5 for offspring exposed to maternal obesity *in-utero*, the prevalence of diabetes begins to stabilize after 65 years at 10.06%. Considering a risk factor of 2 for intrauterine exposure to obesity, the prevalence of diabetes begins to stabilize after 65 years at 10.51%. Considering an increased risk of 2.5 for offspring exposed to maternal obesity *in-utero*, the prevalence of diabetes begins to stabilize after 65 years at 10.85%. Considering a risk factor of 3 for intrauterine exposure to obesity, the diabetes prevalence begins to stabilize after 65 years at 12.19%. We observe that intrauterine exposure to maternal obesity leads to an intergenerational acceleration in the prevalence of diabetes in the pediatric population.

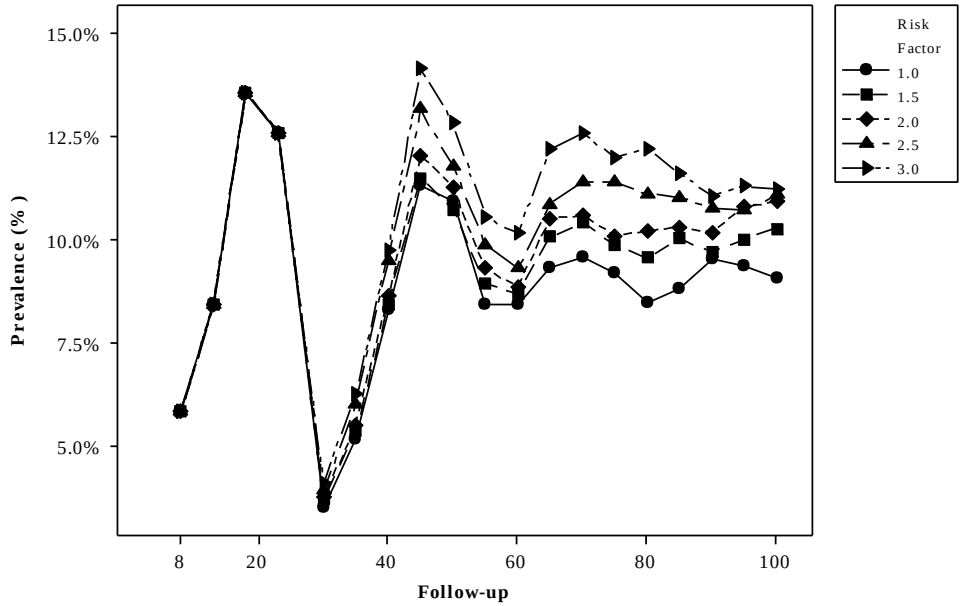


Figure 2.2: Diabetes prevalence (age 18 to 44 years) for increased risk of diabetes due to intrauterine exposure to maternal obesity.

In Figures 2.3, 2.4, 2.5, and 2.6 we show trends in the prevalence of diabetes by age cohort over time. Observing results across different age groups and across the risk factors tested, we notice a more considerable change from each age group at baseline in the prevalence of diabetes with respect to the risk factors tested. Among individuals less than 30 years of age, predictions were not substantially different from the baseline output. The prevalence of diabetes for individuals ages 30 and 34 actually experienced a decrease from the prevalence of diabetes at baseline. The prevalence for diabetes of individuals age 35 to 39 slightly increased when compared to the base model. We observe the largest increase in diabetes prevalence of individuals age 40 to 44. Observing prevalence of diabetes by age cohort, we notice a positive correlation between age and diabetes prevalence.

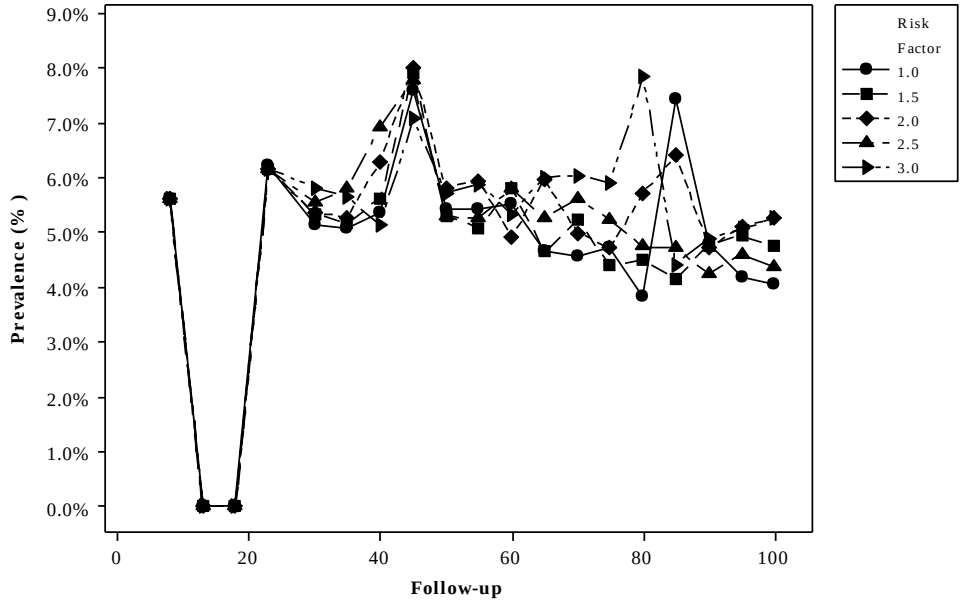


Figure 2.3: Diabetes prevalence (age 18 to 29 years) for increased risk of diabetes due to intrauterine exposure to maternal obesity.

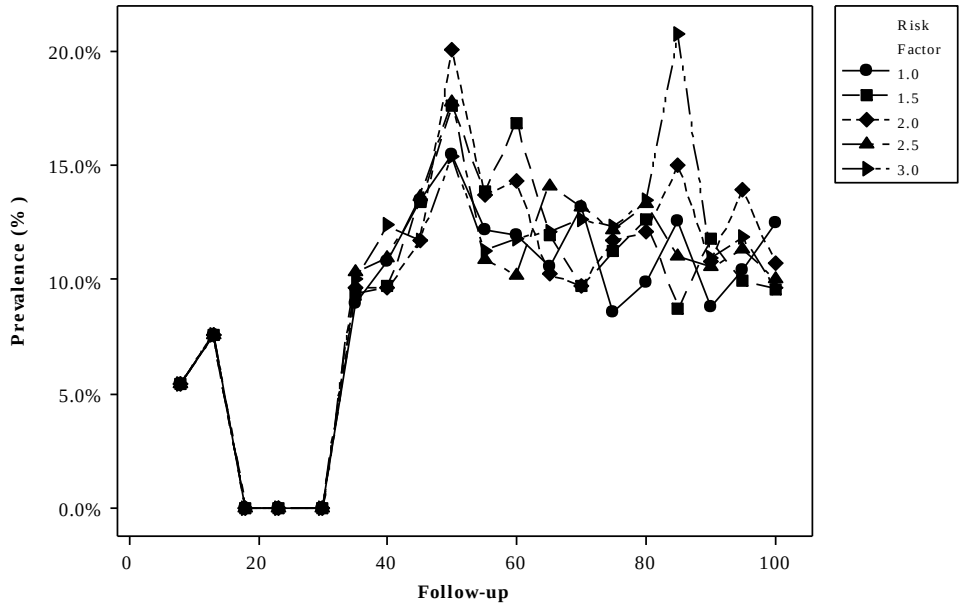


Figure 2.4: Diabetes prevalence (age 30 to 34 years) for increased risk of diabetes due to intrauterine exposure to maternal obesity.

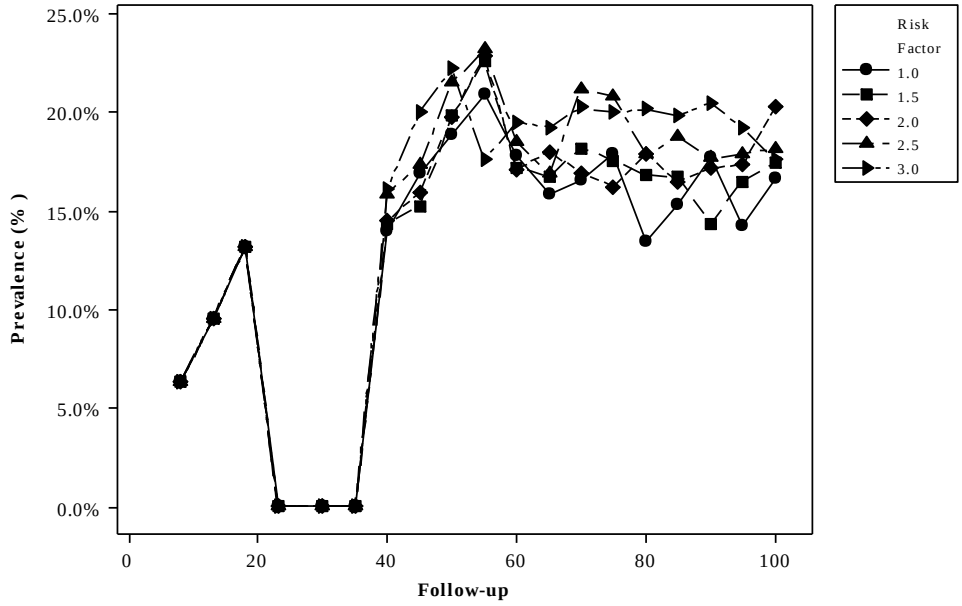


Figure 2.5: Diabetes prevalence (age 35 to 39 years) for increased risk of diabetes due to intrauterine exposure to maternal obesity.

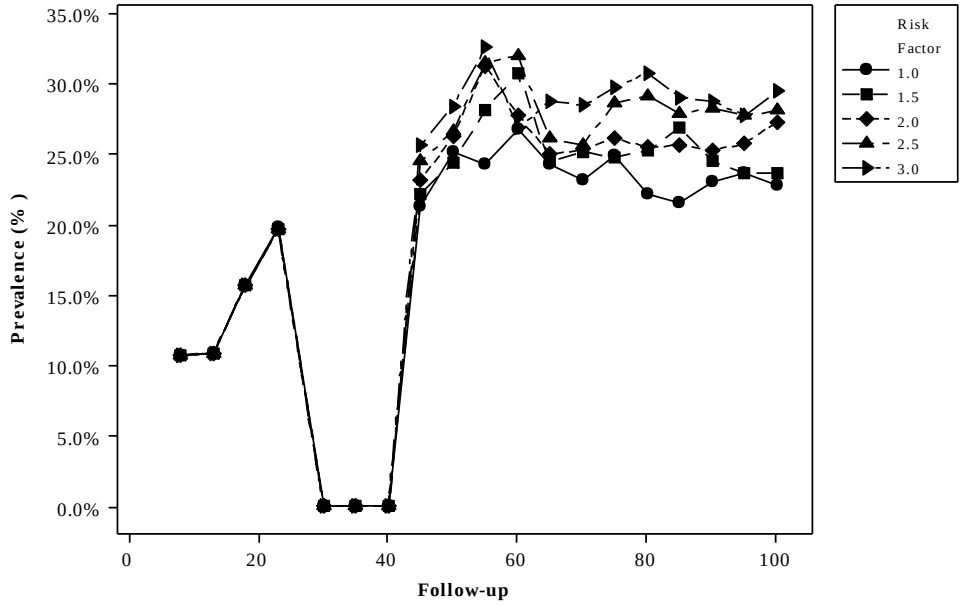


Figure 2.6: Diabetes prevalence (age 40 to 44 years) for increased risk of diabetes due to intrauterine exposure to maternal obesity.

2.5 Conclusions

In conclusion, we developed a simulation model to predict the impact of exposure to maternal obesity and diabetes during fetal life on the prevalence of obesity and diabetes in subsequent generations and to examine trends over long periods of time. We made projections of diabetes prevalence assuming an increased risk of diabetes in offspring exposed to maternal obesity *in-utero* to provide an example of the type of projections that can be obtained from our model. Projections could also be made assuming an increased risk of diabetes due to intrauterine exposure to maternal diabetes or both maternal obesity and diabetes. Studies have assessed the additive effect of fetal exposure to both obesity and diabetes but the degree to which adverse effects have on the developing fetus has not been quantified [Hunt and Schuller, 2007].

These three alternatives for taking into account *in-utero* exposures (increased risk of diabetes due to intrauterine exposure to obesity, diabetes, and both obesity and diabetes) are considered mutually exclusive cases. Since we are analyzing sensitivity with respect to the same risk factors and obesity prevalence is higher than diabetes prevalence at baseline, we would expect to notice the largest increase in the prevalence of diabetes with consideration to intrauterine exposure to maternal obesity. The underlying prevalence of diabetes is smaller at 1.98% diabetic. We would expect to notice less of an impact due to the influence of fetal exposure to maternal diabetes than exposure to obesity during gestation. Since we are assessing the same risk factors for each case and the percentage of the population that is both diabetic and obese is the smallest, we would expect to observe a nominal impact over the long-term as a result of exposure to both

diabetes and obesity *in-utero.* We speculate that the risk factors associated with maternal exposure to disease in reality are not the same across the three scenarios.

Verification efforts showed that our model accurately predicts the outcome of one cohort. However, extrapolation from the SAHS data is not ideal for three reasons. First, the sample size is small, consisting of a maximum and minimum of 575 and 250 samples respectively across age categories; second, the SAHS population is not representative of the national population and does not include African Americans; and third, obesity and diabetes incidence rates in San Antonio were already relatively high in the early eighties when the SAHS was initiated. Thus we would like to use baseline data which is large, accurate, and captures the population before the prevalence of obesity and diabetes increased.

In this chapter we only look at a specific cohort, however this simulation model can easily be modified to accommodate different data structures and assumptions. Future simulations representative of the US population will model subsequent generations among different racial and ethnic groups and will incorporate information on intrauterine exposure to obesity and diabetes in determining an individual's adult obesity and diabetes status. Chapter 3 aims to extend this simulation to quantify the impact of maternal disparities between different racial and ethnic groups at the US population-level on health disparities affecting the populace in the future.

CHAPTER THREE

TRENDS IN WEIGHT-GAIN AMONG WHITE AND BLACK WOMEN OF CHILDBEARING AGE IN THE UNITED STATES

3.1 Introduction

The prevalence of overweight and obesity among US adults have increased by epidemic proportions since 1980. Over the past 30 years the percentage of the US adult population that is obese has doubled with approximately 34 percent of adults age 20 years and over being obese (BMI $\geq$30 kg/m^2) and an additional 34 percent of adults age 20 years and over being overweight (30 kg/m^2>BMI $\geq$25 kg/m^2) in 2007-2008 [CDC7]. In contrast, the prevalence of obesity was relatively stable between 1960 and 1980; however, there is a noted shift in the early 1980s as can be observed by a striking increase in the prevalence of obesity between the second and third NHANES (i.e., from 1976-1980 to 1988-1994) [CDC9, Flegal et al., 1998]. Additional increases in the prevalence of obesity occurred in the 1990s [CDC9, Flegal et al., 2002]. The prevalence of obesity varies by racial and ethnic group with minority populations having a higher prevalence of obesity as well as more severe obesity [Flegal et al., 2010, Ogden et al., 2006].

The causes of the obesity epidemic are not completely understood. Early life exposures are emerging as potentially important risk factors for adult diseases including obesity and diabetes. The "fetal origin of disease" hypothesis proposes that gestational programming may critically influence adult health and disease [Barker, 1995]. As the prevalence of obesity increases, its impact on childbearing women and their infants also increases; therefore, the obese *in-utero* environment may be a cause as well as a result of

the obesity epidemic. Moreover, trans-generational effects, because of their long term implications, may also play a role in the perpetuation of the epidemic. Trans-generational effects include genetic information, shared environment and behaviors passed from one generation to the next as well as *in-utero* exposures which may impact gestational programming. Moreover, if intrauterine exposure to maternal obesity contributes to initiation or perpetuation of the obesity epidemic, then the prevalence of obesity will not only increase across all populations, but will disproportionately affect racial/ethnic groups with a higher initial prevalence of obesity. Hence, understanding the trans-generational impact of obesity may be one key to understanding health disparities.

Because it would take decades to conduct trans-generational studies at the population level, we instead use a mixed-methods approach, incorporating both statistical methods and discrete-event simulation (DES), to determine the trans-generational impact of maternal obesity across multiple racial and ethnic groups at the population level. Specifically, we examine trends in weight-gain over time among black and white (non-Hispanic) women of child-bearing age in the US between 1980 and 2008. This approach will enable us to model the trans-generational impact of maternal obesity during pregnancy. While substantial increases in the prevalence of overweight and obesity among women of reproductive age in the US have occurred over the past several decades, the mechanisms underlying the obesity epidemic and its contributing factors are not fully understood. In this chapter, we establish an underlying population representative of the population prior to the onset of the obesity epidemic and develop a simulation model to make projections assuming that subsequent generations carry the same risk as the initial

cohort. We compare the simulation projections to actual trends to estimate the increased risk in weight-gain over time. Our model uses data obtained from the US Census and the National Health and Nutrition Examination Survey (NHANES). We use body mass index (BMI in kg/m^2) as a measure of weight adjusted for height.

While the prevalence of overweight and obesity over the past two decades has been well documented among US adults [Flegal et al., 1998, Flegal et al., 2002, Flegal et al., 2010, Ogden et al., 2006], few studies specifically focus on women of childbearing age or on disparities between racial/ethnic groups. In one study, Chu et al. (2009) estimate the prevalence of prepregnancy obesity in 2004-2005 by analyzing Pregnancy Risk Assessment and Monotoring System (PRAMS) data. The work we present here goes beyond estimates of past and current trends; with a simulation model we forecast trends in weight gain. Several methods exist for conducting projections. Projections can be made using statistical models applied to population estimates. For example, Kelly et al. (2008) use prevalence data from 2005 and apply it to population projections to estimate overweight and obesity prevalence in adults worldwide in 2030. They make two estimates, one assumes that the prevalence of overweight and obesity remained constant; the other assumes an increased trend. Our methodology differs from this in that in addition to estimating actual trends in weight gain from past data and population estimates, we examine "unadjusted" weight-gain in the population over time assuming the rate of change in BMI with age of the US population had remained the same as in 1980. We do this by using a simulation model. Other methods used to make projections include Markov models, such as that used by Honeycutt et al. (2003) to forecast the

prevalence of diabetes in the US from 2000 to 2050. We choose to use simulation over a Markov model to model BMI trends for several reasons. First, if we wish to capture BMI directly (not just prevalence of obesity and overweight), which is dependent on age; the state space of such a model would be prohibitively large [BMI is a continuous variable while diabetes was modeled as binary variable in Honeycutt et al. (2003)]. It is important to be able to capture both BMI and risk by age because risk attributed to diseases of interest (e.g. diabetes) vary by BMI and the rate of change of BMI is different between age groups. Secondly, the simulation model allows the rate of change in BMI to vary over time, and can easily incorporate additional independent variables. This will be important in later work, where we attempt to explain the difference in the estimated values between actual trends and predicted trends by assigning risk to the children of women depending on the BMI level they experienced during pregnancy.

In this chapter we (1) develop a statistical model to assess the change in BMI as a function of age using data obtained through a cross-sectional study design and (2) develop and present validation methods for a DES model that examines trends in average BMI over generations at the population level. The structure of the chapter is organized as follows. In §3.2, we describe the statistical model and present the results of the data analysis. In §3.3 we model trends in population weight-gain over time based on the statistical analysis. We use a simulation model in §3.4 to model weight-gain trends and provide the validation of the simulation model. The chapter is concluded with a discussion in §3.5 where future research directions are also presented.

3.2 A Model of the Population Prior to the Onset of the Obesity Epidemic

In this section we describe a method to enable the utilization of cross-sectional data to make estimates of change in attributes of individuals over time. We apply our method to US population-level National Health and Nutrition Examination Survey (NHANES) BMI data. Our method allows us to characterize weight-gain in white and black women of childbearing age in the US population prior to 1980 (i.e. before the onset of the obesity epidemic). The rate of change in weight-gain prior to 1980 was less than the rate of change in weight-gain between 1980 and 2008. Using the rate of change in weight-gain before 1980 we model BMI in this population to estimate what the population would have looked like if the rate of change in weight-gain had not increased. This model will allow us to quantify the increase in weight-gain by comparing the simulated population to the actual population over time.

3.2.1 NHANES data

The NHANES program, part of the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention involves a sequence of cross-sectional health examination surveys beginning in 1960 which concentrate on different population groups and health issues. Each NHANES survey provides a nationally representative sample of the US non-institutionalized civilian population obtained using a complex, stratified, multistage probability cluster sampling design [CDC8]. Study periods include three NHANES surveys (NHANES I, 1971-1974; NHANES II, 1976-1980; and NHANES III, 1988-1994) and continuous NHANES which began in 1999. Beginning in 1999

NHANES became a continuous surveillance system releasing data in two-year periods (1999-2000, 2001-2002, 2003-2004, 2005-2006, and 2007-2008).

3.2.2 Method for utilization of cross-sectional data

We apply mixed-effects regression analysis and bootstrap techniques to make inferences about change in trends in BMI over time using cross-sectional data. Here we discuss the general steps required to enable the utilization of cross-sectional data to estimate change in some dependent variable of interest (in our case BMI) over time. Data is divided into cohorts (in our case defined by birth year) based on two key criterion: (1) number of available data points of the dependent variable for each possible value of the independent variable(s) within the cohort, and (2) fit of the regression model. Every cohort should contain enough data points to constitute a representative sample. Regression analysis is then performed separately for each cohort. Plots of the best fit regression line are created for each cohort and the graphs are superimposed. The form of the overlaid plot should approximate a straight line. If the slopes of the superimposed lines do not approximate a straight line, cohorts are re-grouped and the process repeats (regression analysis and evaluation of superimposed graphs).

Linear mixed-effects regression analysis is performed separately for each cohort to estimate the rate of change in the value of the dependent variable (e.g.. BMI) that results from changes in the independent variable(s) (e.g. age). A bootstrap resampling approach is applied to the data for each cohort separately. The size of the bootstrap sample is determined based on the total number of data points available for each cohort and the bootstrap sample size is the same across all cohorts. Bootstrapped data points are

collected over 100 iterations. Bootstrapping provides a sample representative of the original sample of uniform sample size across all cohorts. Linear mixed-effects regression models are fit to the bootstrapped sample drawn in each of the 100 replications thereby providing 100 regression equations. A random effect term accounts for error in the bootstrap samples which are not consistent across samples. Obtaining multiple equations allowed us to build a probability distribution around the expected value of the dependent variable (i.e. BMI) at the intercept, as well as around the rate of change of the dependent variable according to the independent variable (i.e. age).

3.2.3 Statistical analysis of BMI data

In this section, we apply our method to enable the utilization of cross-sectional NHANES data to estimate the rate of change in BMI of individuals over time. The NHANES I and II studies provide large data sets that capture the population before the prevalence of obesity increased [CDC9]. To obtain the BMI data, NHANES collected weight and height measurements that were taken through physical examination by trained health technicians and were conducted in a mobile examination center using standardized measuring techniques and equipment. Body mass index (BMI) was expressed as weight in kilograms divided by height in meters squared (kg/m^2) [CDC8].

We use linear mixed-effects regression models to estimate age and birth year cohort effects on BMI values of women ages 15 to 44 years in the US measured during NHANES I and NHANES II. We assess the relationship between BMI and age to gain insights into the change in BMI over time when the data is obtained through a cross-sectional study design. To avoid cohort effects, data from NHANES I and II surveys were

concatenated into one data set. The combined NHANES I and II data set was divided into groups of white women and black women based on birth year. Birth year cohorts were selected based on the number of available data points from the NHANES I and II surveys and based on the fit of various regression models evaluated. In our analysis, at least 30 BMI data points for each age represented in a birth year cohort were required to provide a representative sample. Data for white women was divided into five birth year cohorts: 1955 to 1959, 1950 to 1954, 1940 to 1949, 1935 to 1939, and 1930 to 1934. Data for black women was divided into two birth year cohorts: 1945 to 1959 and 1925 to 1944.

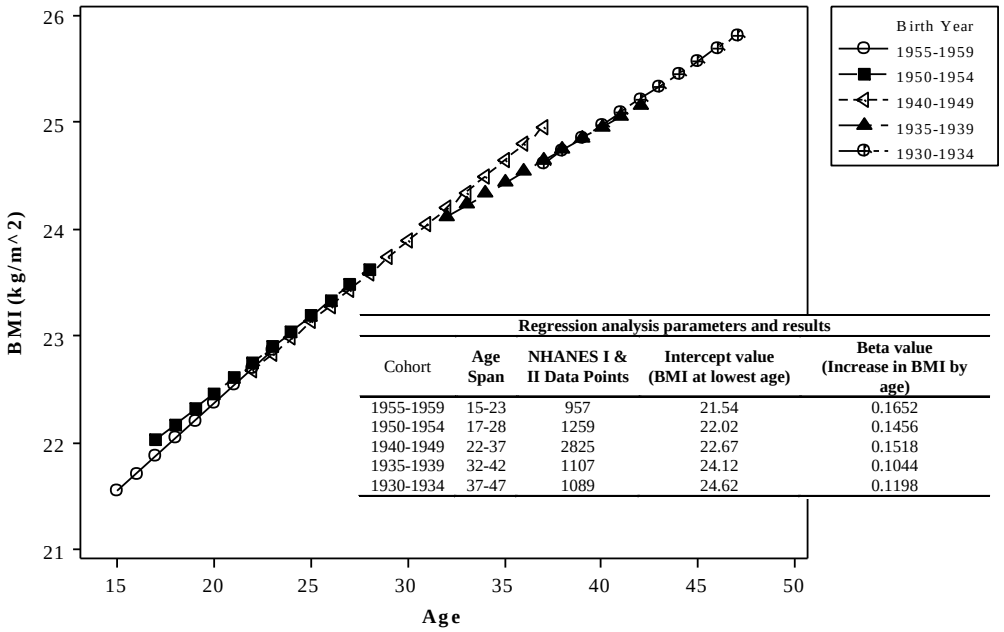
Regression analysis was performed separately for each birth year cohort to estimate the rate of change of BMI values stratified by age using SAS version 9.2 (sample SAS code for white women born between 1955 and 1959 is provided in Appendix C). Sampling weights were included in the regressions to control for unequal probabilities of selection in the sample design, lack of responsiveness, and areas under covered so that the numbers represented the US population. Analyses were conducted using the bootstrap approach to collect repeated random samples from the combined NHANES I and II dataset where the sampling was done with replacement. A sample of 500 BMI data points was collected from the combined NHANES I and II dataset over 100 iterations. The size of the bootstrap sample was determined based on the number of NHANES I and II data points available for each birth year cohort, see parameters in Figures 3.1 and 3.2. Regression analysis was used to fit a model to the bootstrapped BMI data points sampled in each of the 100 replications thereby providing 100 regression equations. Obtaining multiple equations allowed us to build a probability distribution

around the expected mean value of BMI at the intercept, as well as around the rate of change of BMI values according to age. The resulting distributions are shown in Tables B.1 and B.2 in the appendix.

3.2.4 Statistical analysis results

The table inserts shown in Figures 3.1 and 3.2 provide the age span for each birth year cohort, the number of available NHANES I and II data points, the size of the bootstrap sample, and the regression equations for white and black women, respectively. We note that the age span for different birth year cohorts overlaps in several cases. The plots shown in Figures 3.1 and 3.2 display the regression results of BMI versus age according to birth year cohort for white and black women, respectively. The regression results for all birth year cohorts are overlaid onto one graph. For white women (Figure 3.1) we see that the estimated BMI for a particular age does not vary significantly by birth year cohort. The exception occurs over the age span 32 to 37 years. For black women on the other hand (Figure 3.2), we see that there is a significant difference in the Beta values associated with the two birth year cohorts. How these differences are handled is discussed in Section 3.4.4.

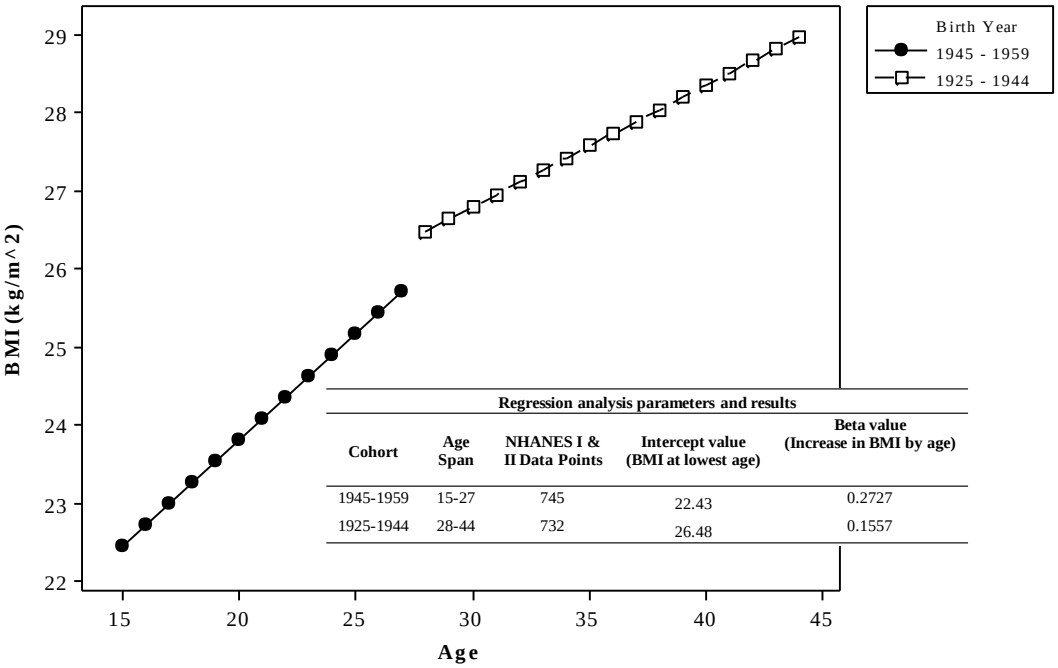
These results provide us with a characterization of weight-gain in the population prior to the onset of the obesity epidemic. The next section describes how the regression estimates are used to make projections about BMI trends of this population after 1980, if their risk for weight-gain had not changed over time.



Regression analysis parameters and results

Cohort	Age Span	NHANES I & II Data Points	Intercept value (BMI at lowest age)	Beta value (Increase in BMI by age)
1955-1959	15-23	957	21.54	0.1652
1950-1954	17-28	1259	22.02	0.1456
1940-1949	22-37	2825	22.67	0.1518
1935-1939	32-42	1107	24.12	0.1044
1930-1934	37-47	1089	24.62	0.1198

Figure 3.1: Plot of BMI (kg/m^2) vs. Age by birth year cohort for white women, regression parameters and results shown in table insert.



Regression analysis parameters and results

Cohort	Age Span	NHANES I & II Data Points	Intercept value (BMI at lowest age)	Beta value (Increase in BMI by age)
1945-1959	15-27	745	22.43	0.2727
1925-1944	28-44	732	26.48	0.1557

Figure 3.2: Plot of BMI (kg/m^2) vs. Age by birth year cohort for black women, regression parameters and results shown in table insert.

3.3 Unadjusted Population Weight-Gain Projections

In this section we recreate the population using the BMI estimates (stratified by age and race/ethnicity) obtained from the regression analysis in which risk of weight-gain is the risk in 1980. These "unadjusted" BMI projections reflect trends in this population if the rate of change in average BMI between 1980 and 2008 remained the same as it was in the 1980s (i.e. if the rate of change in BMI had not increased after 1980). We compare differences in BMI from 1980 to 2008 among white and black women of childbearing age in the US between NHANES BMI estimates (representing the actual population) and our unadjusted weight-gain projections. We expect the NHANES BMI trends for 1980 to be statistically the same as the unadjusted projections. We expect NHANES BMI trends

after 1980 to be higher than the unadjusted projections. The NHANES estimates (representative of the actual population in a given year) are higher because substantial increases in the prevalence of overweight and obesity among women of reproductive age in the US have occurred since 1980 and continue to occur [CDC7]. Comparison of unadjusted projections and actual trends in weight-gain in the US population allow us to quantify the increase in incidence rate over time which is not due to change in demographics over time.

3.3.1 Generation of the unadjusted BMI projections

To make unadjusted projections of this population over time we apply the regression estimates of BMI to the US Census age distributions according to race/ethnicity using Arena 13.5 software (a product of Rockwell Automation Technologies, Inc.). First, the age distribution is assigned using population characteristics for white and black women ages 15 to 44 years obtained from the US Census [1980, 1990, 2000, and 2008 (Census 2008 values are projected based on Census 2000 numbers)]. Next, age-specific BMI is assigned (independent of birth year cohort) according to the normal distribution. Age-specific estimates of BMI from the regression analysis provide the mean value of the distribution. The standard deviation is that of the actual concatenated NHANES I and II data set. Table B.1 in the appendix provides a detailed list of the BMI values (mean and standard deviation) by age and race. Arena was run in eight separate scenarios (for white women and black women in 1980, 1990, 2000, and 2008) and average BMI was computed for the population age range (15-44) and by age groups (15-19, 20-24, 25-29, 30-34, 35-39, and 40-44).

In Figure 3.1 we observe overlaps in the different age cohort regression lines for white women. When more than one point existed we used the average of the points to assign mean BMI. For example, in Figure 3.1 two data points exist for white women age 17 years, a point estimated from the regression equation for birth year cohort 1955 to 1959 and a point estimated from the regression equation for birth year cohort 1950 to 1954. BMI for women age 17 years are taken as the average of estimates for birth year cohorts 1955 to 1959 and 1950 to 1954 from the regression analysis.

3.3.2 Comparison of average BMI

Comparison of unadjusted projections and actual trends in weight-gain among white and black women of childbearing age in the US population allow us to quantify the increase in BMI over time not due to age and race/ethnicity. We compare our unadjusted BMI projections to NHANES BMI data representative of the actual population in 1980, 1990, 2000, and 2008. NHANES estimates are not based on birth year; that is, NHANES estimates include all individuals between 15 and 44 years of age in the NHANES datasets. The NHANES dataset(s) most closely corresponding to the projected year was used as the comparison group. In some instances, more than two years of data were needed to have adequate sample sizes for analysis therefore NHANES datasets were combined to provide additional data points. Table 3.1 provides a summary of the specific NHANES datasets used to obtain BMI values representing the actual population in 1980, 1990, 2000 and 2008.

Table 3.1: Data sources used to obtain numbers representing the actual population.

Census Year	Comparison BMI
1980	NHANES I and II
1990	NHANES III
2000	NHANES 1999-2002
2008	NHANES 2005-2008

Tables 3.2 and 3.3 show the average unadjusted BMI projections and average BMI estimates obtained from the NHANES population by age cohort and year. Parentheses define 95 percent confidence interval half-widths. The projections for 1980 provide a verification of our statistical model. The 95 percent confidence intervals for the projected numbers and the actual NHANES numbers overlap (shown in Figure 3.6), therefore we conclude that our projections and actual NHANES numbers are statistically the same. In other words, the projected population in 1980 (developed from our regression model) adequately represents the 1980 population of the NHANES data; furthermore, each age cohort is adequately represented in terms of average BMI. Furthermore, we can see that beyond 1980, the projected BMI values are less than the NHANES values; this is true for all age cohorts and for both black and white women. Furthermore, for the overall population (women ages 15-44) the difference in average BMI is increasing with time for both black and white women.

Table 3.2: Average BMI (kg/m^2) of white women of childbearing age.

Age Cohorts	1980		1990	
	Unadjusted Projections	NHANES I & II	Unadjusted Projections	NHANES III
15 - 19	21.94 (0.08)	21.88 (0.22)	21.94 (0.08)	22.69 (0.56)
20 - 24	22.67 (0.07)	22.74 (0.22)	22.70 (0.06)	23.59 (0.71)
25 - 29	23.40 (0.07)	23.33 (0.25)	23.46 (0.07)	24.28 (0.63)
30 - 34	24.23 (0.08)	24.29 (0.29)	24.15 (0.11)	25.46 (0.72)
35 - 39	24.61 (0.10)	24.68 (0.31)	24.64 (0.09)	26.59 (0.81)
40 - 44	25.17 (0.11)	25.13 (0.33)	25.20 (0.12)	26.29 (0.77)
15 - 44	23.48 (0.03)	23.62 (0.11)	23.75 (0.03)	24.82 (0.28)
Age Cohorts	2000		2008	
	Unadjusted Projections	NHANES 1999-2002	Unadjusted Projections	NHANES 2005-2008
15 - 19	21.89 (0.08)	23.55 (0.56)	21.90 (0.09)	23.64 (0.60)
20 - 24	22.74 (0.07)	26.06 (1.09)	22.73 (0.05)	26.22 (1.23)
25 - 29	23.47 (0.08)	26.69 (1.03)	23.43 (0.08)	27.30 (1.23)
30 - 34	24.14 (0.10)	26.73 (1.07)	24.14 (0.13)	27.95 (1.06)
35 - 39	24.63 (0.08)	27.40 (1.18)	24.65 (0.08)	27.92 (1.10)
40 - 44	25.21 (0.12)	27.71 (1.11)	25.20 (0.12)	28.90 (1.03)
15 - 44	23.80 (0.04)	25.91 (0.40)	23.69 (0.04)	26.68 (0.42)

Note: Values in parentheses are 95% CI half-widths.

Table 3.3: Average BMI (kg/m^2) of black women of childbearing age.

Age Cohorts	1980		1990	
	Unadjusted Projections	NHANES I & II	Unadjusted Projections	NHANES III
15 - 19	22.96 (0.11)	22.81 (0.58)	23.01 (0.10)	24.71 (0.67)
20 - 24	24.36 (0.09)	24.20 (0.59)	24.38 (0.08)	26.19 (0.68)
25 - 29	25.87 (0.09)	25.70 (0.71)	25.84 (0.08)	27.24 (0.78)
30 - 34	27.03 (0.13)	27.13 (0.90)	27.10 (0.13)	29.05 (0.89)
35 - 39	27.78 (0.16)	28.35 (0.87)	27.77 (0.12)	29.44 (0.81)
40 - 44	28.69 (0.12)	28.37 (0.82)	28.65 (0.16)	30.61 (0.91)
15 - 44	25.59 (0.04)	25.80 (0.31)	26.02 (0.05)	27.78 (0.33)
Age Cohorts	2000		2008	
	Unadjusted Projections	NHANES 1999-2002	Unadjusted Projections	NHANES 2005-2008
15 - 19	23.00 (0.09)	25.67 (0.81)	22.98 (0.09)	26.69 (0.86)
20 - 24	24.36 (0.08)	29.05 (1.90)	24.38 (0.07)	29.96 (2.03)
25 - 29	25.88 (0.09)	30.11 (2.02)	25.84 (0.08)	30.66 (1.85)
30 - 34	27.06 (0.14)	31.29 (1.92)	27.09 (0.15)	31.42 (1.56)
35 - 39	27.81 (0.11)	30.10 (1.50)	27.78 (0.12)	32.08 (1.85)
40 - 44	28.65 (0.15)	32.73 (2.00)	28.68 (0.15)	30.75 (1.61)
15 - 44	26.15 (0.05)	28.44 (0.62)	26.01 (0.05)	29.26 (0.61)

Note: Values in parentheses are 95% CI half-widths.

3.3.1 Comparison of average BMI across age groups

We are interested in the difference between the average BMI of women based on NHANES (which represents the actual population and trends) and the unadjusted BMI estimates. Figures 3.4 and 3.5 provide these results by age cohort, for white and black women respectively. These figures show the differences in average BMI of the NHANES population and the projected population by age cohort in 1990, 2000, and 2008. For example, consider the difference in average BMI of white women 20 to 24 years of age in 1990 (0.88 kg/m^2). Average BMI computed from the NHANES III dataset represents the actual population 20 to 24 years of age in 1990 (23.59 kg/m^2). Projected average BMI of individuals age 20 to 24 years in 1990 is 22.70 kg/m^2) was obtained by applying our regression estimates to the Census 1990 age distribution. The difference between the actual NHANES value and the predicted value (i.e., average BMI of individuals age 20 to 24 computed from the NHANES I and II dataset minus unadjusted average BMI projections) for individuals age 20 to 24 years in 1990 is 0.88 kg/m^2.

Refer to Figure 3.4 for a discussion regarding the difference in average BMI for white women. The difference in average BMI in 1990 is fairly low (i.e., less than 1 kg/m^2) in half of the six groups. In 1990, the difference in average BMI for age cohorts 15 to 19, 20 to 24, and 25 to 29 was comparable ranging from 0.75 kg/m^2 to 0.88 kg/m^2. The age group with the largest discrepancy between the simulated and NHANES BMI values in 1990 were women in age cohort 35 to 39 (1.95 kg/m^2). In 2000, the difference in average BMI across all age cohorts escalated. The difference in average BMI of age cohort 15 to 19 was the smallest across all age cohorts (1.66 kg/m^2). Age cohorts 20 to 24

and 25 to 29 hold the largest difference in average BMI in 2000 (3.32 kg/m^2 and 3.22 kg/m^2, respectively). In 2008, we observe a difference in average BMI greater than 3 kg/m^2 across all age cohorts except age cohort 15 to 19 (1.73 kg/m^2). Difference in average BMI of age cohorts 15 to 19 and 20 to 24 began to level off between 2000 and 2008.

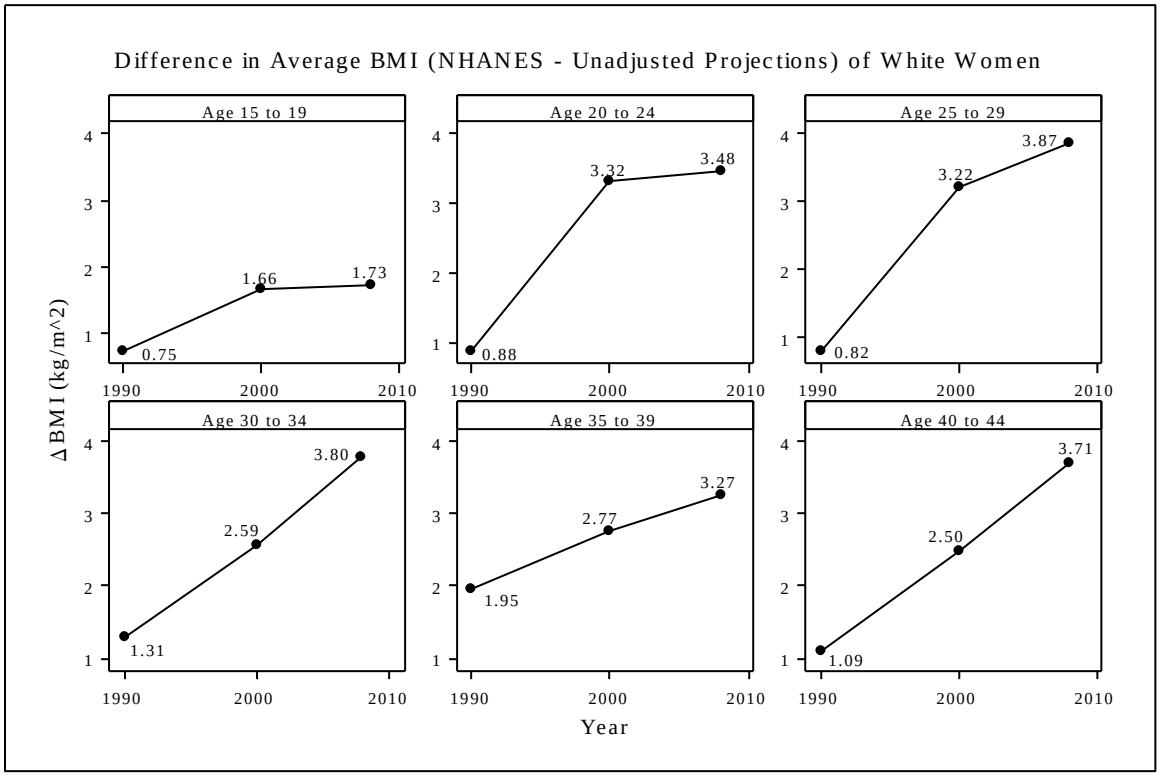


Figure 3.3: Difference in average BMI (NHANES-unadjusted projections) by year and age cohort of white women.

In contrast to white women, the difference in average BMI of black women across the various age cohorts in 1990 is high (Figure 3.5), ranging from 1.40 kg/m^2 to 1.96 kg/m^2 (compared to 0.75 kg/m^2 to 1.95 kg/m^2 for white women). Individuals age 40 to 44 have the largest difference in average BMI (1.96 kg/m^2) in 1990. Between 1990 and 2000 the difference in average BMI spikes, particularly among age cohorts 20 to 24 and 25 to

29, followed by age cohorts 30 to 34 and 40 to 44. In 2000, the difference in average BMI rises to more than 5 kg/m^2 in one age cohort (20 to 24). The difference in average BMI begins to level off between 2000 and 2008 among individuals age 30 to 34. Interestingly, between 2000 and 2008 the difference in BMI for black women age 40 to 44 actually decreases by almost 2 kg/m^2. This result differs greatly from white women age 40 to 44, where the difference in average BMI increased considerably between 2000 and 2008.

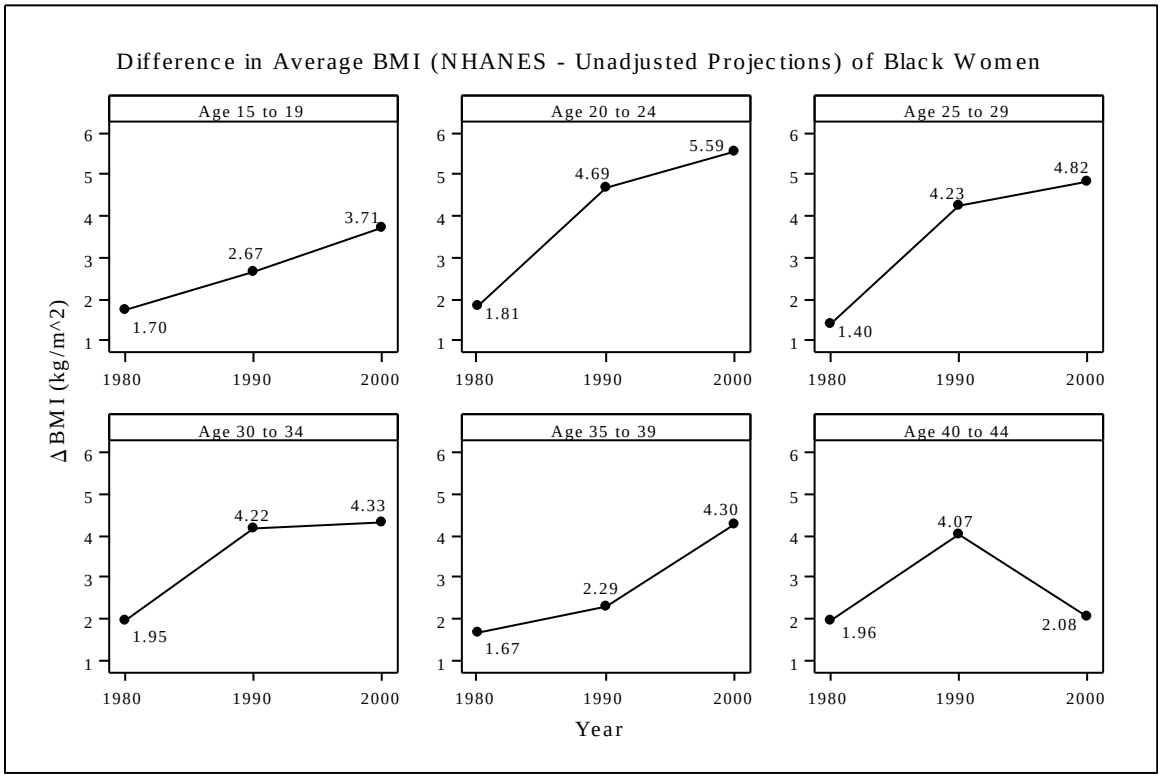


Figure 3.4: Difference in average BMI (NHANES-unadjusted projections) by year and age cohort of black women.

3.3.2 Comparison in trends over time for black and white women of all ages

Next we examine trends in BMI over all ages. In particular, Figure 3.6 compares average BMI of women of childbearing age (ages 15 to 44) computed from the NHANES

data sets to projected average BMI of women of childbearing age at baseline (1980) and for projections in years 1990, 2000, and 2008. NHANES values represent the actual population each year while the projections show average BMI of the population if the rate of change in BMI had remained stable (i.e. no additional risk since 1980). The 95 percent confidence intervals of average BMI for actual NHANES values and unadjusted projections are displayed. Average BMI of white and black women computed from the NHANES data sets and the projected values are displayed in one panel to show racial disparities in average BMI and the rate of change in BMI among white and black women of childbearing age.

The first important result is that the 95 percent confidence intervals about the projected numbers and actual NHANES numbers for white and black women age 15 to 44 years do not overlap in years 1990, 2000, and 2008; therefore the projected numbers and actual NHANES numbers are statistically different for years 1990, 2000, and 2008. This is true for both white and black women.

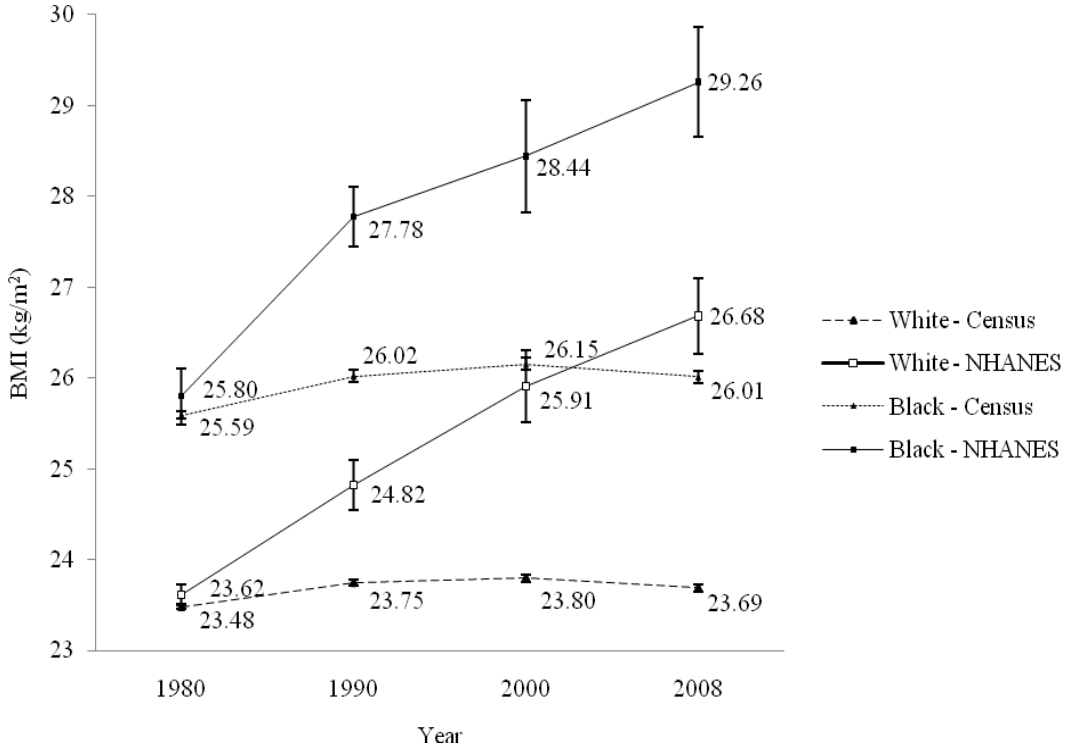


Figure 3.5: Unadjusted projections vs. NHANES for white and black women of childbearing age.

In 1980 black women of childbearing age had a higher baseline BMI level than white women of childbearing age, with actual average BMI of black women at 25.80 kg/m^2 compared to actual average BMI of white women at 23.62 kg/m^2, a difference of approximately 2 kg/m^2 (Figure 3.6). Not only did black women start out with a higher baseline BMI value, but the rate of change in average BMI increased faster in black women of childbearing age versus white women. Observing actual average BMI of individuals age 15 to 44 years (i.e. NHANES), we notice that both white and black women experience a steady increase in average BMI between 1980 and 2008. However, the rate of change in average BMI of black women increased more rapidly between 1980 and 1990 compared to the rate of change in average BMI of white women during this

time period. A change in average BMI of 1.98 kg/m^2 in black women compared to 1.2 kg/m^2 in white women. Between 1990 and 2000, the rate of change in average BMI of white women was higher than the rate of change in average BMI of black women. White women experience a change in average BMI of 1.09 kg/m^2 compared to 0.66 kg/m^2 in black women. The rate of change in average BMI of black women between 2000 and 2008 again accelerated faster when compared to white women, with a change in average of 0.82 kg/m^2 in black women and 0.77 kg/m^2 in white women. Overall, the actual change in average BMI between 1980 and 2008 was slightly greater among black women of childbearing age compared to white women (a change in average BMI of 3.46 kg/m^2 for black women and a change in average BMI of 3.06 kg/m^2 for white women).

3.4 Simulation Parameters and Results

In this section we use discrete-event simulation (DES) to examine weight-gain trends in the US population over time. The simulation model is important because it will allow us (in future research) to make projections of weight-gain in this population after 2008. The simulation model presented in Chapter 2 is modified to make projections regarding the rate of change in BMI in the US population if substantial weight-gain had not occurred in the 1980s. The reader should refer to Section 2.2 for a complete explanation of the simulation structure and assumptions. Our method for validating average BMI simulation projections from 1980 to 2008 is described.

3.4.1 Input data

Simulation projections were made to assess the ability of the model to forecast BMI. The bounds on childbearing age range adapted for the population-level model are

age 15 to 44 years. The starting population consisted of 10,000 women ages zero to 44 years, however, average BMI was only recorded for women of childbearing age (i.e. age 15 to 44 years). Incorporating these individuals into the simulation at baseline ensures that individuals will reach age 15 on an annual basis. NCHS natality files [CDC5] to estimate pregnancies and US life tables [CDC6] to estimate mortality allowed us to capture changes in age distribution of the US population over time. Model projections were made after zero years, 10 years, 20 years, and 28 years, with age structure representing the US population in 1980, 1990, 2000, and 2008, respectively. The regression analysis provided two key input measures for the BMI sub-module in the simulation: (1) age-specific baseline BMI values, and (2) age-specific change in BMI. Since there is an overlap in the slopes for certain ages, baseline BMI and updates to BMI for women were taken as the average of estimates from the regression analysis (refer to Section 3.2 for explanation). The individual's baseline BMI was assumed to be normally distributed (Table B.1 in the appendix). Table B.2 provides the BMI updates (annual change in BMI) used in the simulation model, by age and race; these are also assumed to be normally distributed.

3.4.2 Simulation projections

Projections for zero years represent our underlying population of 1980. Baseline BMI was used to make projections independent of the individual's birth year representing the population in 1980. Age-specific baseline BMI was assigned to individuals in the starting population and statistics were collected for average BMI with no time elapsing in the simulation. To further test the model, projections for average BMI were made over

time using age-specific baseline BMI and age-specific BMI updates independent of the individual's birth year. Average BMI was projected over time to provide estimates for the years 1990, 2000, and 2008. The results for all model projections were reported in terms of age cohort percentages average BMI according to age cohort (age 15 to 19 years, age 20 to 24 years, age 25 to 29 years, age 30 to 34 years, age 35 to 39 years, age 40 to 44 years, and age 15 to 44 years). We implemented common random numbers (CRN) for three parameters: (1) baseline age distribution, (2) baseline BMI, and (3) annual change in BMI.

The half-width of average BMI was assessed to determine a sufficient number of replications [Law, 2007]. The 95 percent confidence interval half-width was pre-specified to be no larger than 0.15 kg/m^2. Fifteen replications led to a sufficiently small half-width confidence interval for the output measure average BMI for all model scenarios. Increasing the number of replications did not produce smaller confidence intervals.

3.4.3 Simulation validation

We present two methods for validating our simulation model: (1) validation of population age distribution, and (2) validation of average BMI estimates. Method one compares the percentage age distribution of the US Census to our simulated age structure for 1980, 1990, 2000, and 2008. We consider age structure to be an important validation criterion because other performance measures (such as BMI) are influenced by the age attribute. Age structure results for white women are provided in Table 3.4.

Referencing Table 3.4, we validate our1980 and 1990 age percentage estimates across all age cohorts with 95% confidence interval half-widths in the range of 0.19% to

0.36%. In 2000, the difference in mean percentage of women ages 25 to 29 and 30 to 35 is very low (0.02% and 0.04%, respectively). This is substantial because women of these ages are more likely to get pregnant and will therefore have a greater influence on the population age structure in future generations. Women ages 15 to 19 and 40 to 44 maintain the lowest birth rates and will in turn have less affect on the overall population structure. Options for improving our simulation projections follow.

First, some input parameters did not assume standard errors, including the natality data and the mortality estimates. We could build a probability distribution around these input measures and conduct sensitivity analysis. Second, we could update mortality rates every year. Age-adjusted death rates in the US have experienced an overall downward trend [CRS, 2006] since 1980. Older individuals have higher risk of death and reducing the number of individuals age 40 to 44 will help iron out the distribution and shift the percentage towards age 15 to 19. Third, we do not assess variability in the Census estimates. Error and undercount of 44.2 million in the Census 2000 count was reported by the Accuracy and Coverage Evaluation (A.C.E.) [Census1]. The net undercount for non-Hispanic whites was 0.6%. An error of 0.51% and 0.10% for age cohorts 15 to 19 and 40 to 44 respectively in the Census age distribution would validate our simulation.

For 2008 Census age characteristics we note that the percentages are based on Census 2000 numbers. Population projections of the US for 2008 were based on assumptions of births, deaths, and immigration [Census2]. Therefore, we have more confidence in our projections because our numbers are based on actual natality data between 2000 and 2008.

Table 3.4: Comparison of the Census and simulation age distributions for white women.

Age	1980		1990	
Cohorts	Census (%)	Simulation (%)	Census (%)	Simulation (%)
15 - 19	19.38	19.39 (0.36)	14.17	14.12 (0.24)
20 - 24	20.04	20.00 (0.19)	15.56	15.57 (0.24)
25 - 29	18.53	18.43 (0.22)	18.00	18.22 (0.30)
30 - 34	16.96	17.15 (0.27)	18.87	18.77 (0.24)
35 - 39	13.65	13.65 (0.19)	17.51	17.29 (0.23)
40 - 44	11.44	11.38 (0.26)	15.88	16.03 (0.25)
Age	2000		2008	
Cohorts	Census (%)	Simulation (%)	Census (%)	Simulation (%)
15 - 19	15.50	14.70 (0.30)	16.82	16.65 (0.20)
20 - 24	14.40	14.57 (0.22)	16.57	15.86 (0.31)
25 - 29	15.00	15.01 (0.27)	16.66	16.26 (0.29)
30 - 34	16.51	16.55 (0.29)	15.42	15.25 (0.30)
35 - 39	19.13	19.35 (0.28)	16.83	17.19 (0.25)
40 - 44	19.46	19.82 (0.26)	17.69	18.79 (0.27)

Note: Values in parentheses are 95% CI half-widths.

In method two, model validation is achieved when the simulation reproduces actual average BMI for the starting cohort (1980 projections) and our hypothetical population over time (1990, 2000, and 2008 projections). For all years we consider our unadjusted average BMI projections to be the comparison group (representing actual population BMI). In Section 3.3 we statistically validated 1980 unadjusted BMI projections against average BMI estimates obtained from the NHANES I and II dataset. Simulation projections and unadjusted BMI projections (obtained using the regression estimates) are compared by age cohort. Average BMI results for white women are summarized in Table 3.5.

Refer to Table 3.5 for a comparison of average BMI unadjusted and simulation projections. In 1980 and 1990 we are 99% confident that we capture the true population average BMI. For 2000, simulation projections of average BMI validate for all age cohorts except 35 to 39. More importantly average BMI of the overall population (age 15 to 44 years) validates in comparison to unadjusted BMI projections. Average BMI of the

simulated population is driven by the projections of age structure in the simulation. We believe that although our 2000 estimates do not capture the actual estimate from the Census 2000 for age cohorts 15 to 19 and 40 to 44, if we model random variation in some of the input measures (e.g. birth rates, death rates) then our projections will capture the true value. In 2008, all age cohorts validate for the performance measure average BMI.

Table 3.5: Average BMI unadjusted and simulation projections for white women.

Age Cohorts	1980		1990	
	Unadjusted Projections	Simulation Projections	Unadjusted Projections	Simulation Projections
15 - 19	21.94 (0.11)	21.96 (0.07)	21.94 (0.11)	21.84 (0.08)
20 - 24	22.67 (0.09)	22.70 (0.05)	22.70 (0.08)	22.63 (0.08)
25 - 29	23.40 (0.09)	23.45 (0.13)	23.46 (0.09)	23.49 (0.09)
30 - 34	24.23 (0.11)	24.17 (0.11)	24.15 (0.14)	24.19 (0.05)
35 - 39	24.61 (0.13)	24.70 (0.13)	24.64 (0.12)	24.87 (0.13)
40 - 44	25.17 (0.14)	25.17 (0.12)	25.20 (0.16)	25.44 (0.12)
15 - 44	23.48 (0.04)	23.50 (0.05)	23.75 (0.04)	23.81 (0.04)
Age Cohorts	2000		2008	
	Unadjusted Projections	Simulation Projections	Unadjusted Projections	Simulation Projections
15 - 19	21.89 (0.11)	21.85 (0.08)	21.90 (0.12)	21.87 (0.09)
20 - 24	22.74 (0.09)	22.63 (0.09)	22.73 (0.07)	22.61 (0.08)
25 - 29	23.47 (0.11)	23.38 (0.09)	23.43 (0.11)	23.42 (0.08)
30 - 34	24.14 (0.13)	24.14 (0.11)	24.14 (0.17)	24.14 (0.09)
35 - 39	24.63 (0.11)	24.87 (0.11)	24.65 (0.11)	24.76 (0.09)
40 - 44	25.21 (0.16)	25.42 (0.07)	25.20 (0.16)	25.40 (0.07)
15 - 44	23.80 (0.05)	23.86 (0.04)	23.69 (0.05)	23.74 (0.04)

Note: Values in parentheses are 99% CI half-widths.

3.4.4 Sensitivity analysis

We performed sensitivity analysis on the BMI updates for white individuals age 32 to 37 years due to the large difference in the slopes for this age range obtained from the regression analysis. Five different scenarios were tested for years 1980, 1990, 2000, and 2008. The base case scenario (scenario one), was the average of the slopes for birth year cohorts 1940 to 1949, 1935 to 1939, and 1930 to 1934. Scenario two involved averaging the points from birth year cohort 1935 to 1939 and 1930 to 1934. Scenario

three involved using the slope for birth year cohort 1940 to 1949. BMI updates for scenario four involved taking the average of scenarios one and two, and BMI updates for scenario five involved taking the average of scenarios one and three. The sensitivity analysis showed that average BMI was not sensitive to the BMI updates for individuals age 32 to 37 years. Tables A.3 and A.4 in the appendix show the input parameters (i.e. baseline BMI and BMI updates, respectively) used in the sensitivity analysis. Results of the sensitivity analysis are provided in Table B.5 in the appendix.

3.5 Discussion

The unadjusted projections provide an estimate of the population given that the rate of change in average BMI of white and black women of childbearing age in the 1980s had remained the same between 1980 and 2008. In the unadjusted projections we observe similar trends in average BMI for white and black women. In the unadjusted projections average BMI of both black and white women of childbearing age increases from 1980 to 1990 (a change in average BMI of 0.43 kg/m^2 for white women and 0.27 kg/m^2 for black women) and again slightly from 1990 to 2000 (white women experienced a change in BMI of 0.05 kg/m^2 and black women experienced a change in BMI of 0.13 kg/m^2). In the unadjusted projections the biggest change in average BMI occurs between 1980 and 1990 for both racial groups (0.43 kg/m^2 for white women and 0.27 kg/m^2 for black women). Average BMI slightly decreases between 2000 and 2008 among both white and black women of childbearing age (a change in average BMI of -0.11 kg/m^2 for white women and -0.14 kg/m^2 for black women).

The 95 percent confidence intervals in Figure 3.6 show a statistical difference in average BMI between the actual population and the projected population for years 1990, 2000, and 2008 for white and black women of childbearing age. The difference in average BMI each year is larger for black women compared to white women. For example, in 1990 actual average BMI of white women of childbearing age (i.e. obtained from the NHANES III data set) is 24.82 kg/m^2 and predicted average BMI is 23.75 kg/m^2, a difference of 1.07 kg/m^2. The difference in actual average BMI (27.78 kg/m^2) and predicted average BMI (26.02 kg/m^2) for black women of childbearing age in 1990 is 1.76 kg/m^2. The difference in actual average BMI versus projected BMI is greater among black women versus white women in 1990, 2000, and 2008.

In terms of health disparities, the results show two key findings. First, NHANES shows that black women not only started out with higher average BMI (25.80 kg/m^2) as compared to white women (23.62 kg/m^2) in 1980, before the onset of the obesity epidemic, but their weight gain between 1980 and 2008 was also higher. Resulting in an average BMI of 29.26 kg/m^2 (an increase of 3.46 kg/m^2 over 28 years) for black women as compared to 26.68 kg/m^2 (an increase of 3.06 kg/m^2 over 28 years) for white women over all ages (15-44). The disparity in average BMI between black and white women of childbearing increased by 0.4 kg/m^2 from 1980 to 2008. Secondly, the unadjusted projections show that this difference cannot be solely explained by the weight gain trends that were taking place in 1980; that is, the disparity has worsened. Our unadjusted projections predict that if weight gain trends from 1980 had prevailed the disparities between these groups would not have increased, rather the difference in BMI between

black and white women in 2008 would be 2.32 kg/m^2, which is not significantly different that the disparity seen in 1980.

The results we provide here are fundamentally different than what is currently available in the literature in that we base our unadjusted projections on the population previous to the onset of the obesity epidemic. Using cross-sectional data from NHANES I and II we determine the change in BMI due to age among white and black women of childbearing age. Based on the baseline population, our unadjusted projections show that the average BMI among women of childbearing age would be stable from 1980-2008. Instead, we find (as do many other studies) that the actual weight gain has increased over time. While the reasons for this could be many, understanding the difference between the baseline population and the current population is a first and key step to understanding the potential causes that could be behind the accelerated weight-gain seen over the past two decades, and that will drive longer term projections.

Lastly, we point out that other studies that make projections on the trends of diseases (most of these are done with respect to diabetes) begin with prevalence estimates in 2000 or later. At this point the obesity (and also diabetes) epidemics had already taken place; resulting in very high estimates. Wang et al. (2008) use NHANES 1976-1980 to 2003-2004 to calculate the average annual increase in the prevalence of obesity and overweight and apply this using a linear regression model to make projections through 2030, resulting in an estimated 87% of all adult women being overweight or obese. Other examples of projection studies which begin with data after the onset of the "diabesity" epidemic include: diabetes projections for the US population through 2031 [Mainous et

al., 2007] and through 2050 [Boyle et al., 2001], obesity projections for South Australia through 2013 [Dal Grande et al., 2005], and global diabetes projections through 2030 [King et al., 1998]. In this paper we considered the weight gain trends associated with NHANES I and II (1971-1974 and 1976-1980) and find that these trends would have resulted in stable average BMI levels compared to actual BMI trends over time.

As discussed in Section 3.4.3 (Tables 3.4 and 3.5), our simulation projections at baseline, 1990, and 2008 validate statistically for two measures (age structure and average BMI). In 2000, we validate average BMI across all age cohorts except 35 to 39. We believe that by incorporating random variation in birth and death estimates and accounting for Census errors, we can validate our 2000 estimates for age cohort 35 to 39. We are confident in our simulation projections for one generation of one cohort (white women of childbearing age). However, we acknowledge that our simulation has limitations.

In terms of limitations, first, a key limitation is that the Census 2000 data set contains an enormous amount of errors (many more than the Census 1990) [U.S. Census Monitoring Board, 2001]. This not only affects simulation projections (in terms of simulation validation), but also impacts the unadjusted BMI projections over time. Next, pregnancy probabilities are not subject to random variation. Registered births occurring in the US are not 100% accurate and may be influenced by non-sampling errors (i.e. the mother's age or race may be mistakenly documented) [CDC10]. Similarly, US life table errors (i.e. errors in death rates) such as mistakes in recording age on the death certificate may distort age-adjusted death counts. Under-registration of deaths is not assumed to be

significant for reasons including burial permit requests, acquirement of insurance benefits, and estate settlements. Last, reasons other than births or deaths shape the population (e.g. immigration) [Bell and Miller, 2005].

We are currently making attempts to address the limitations of our data sources. Sensitivity analysis will assess how robust the simulation is to these input measures. With the release of Census 2010 estimates our projections will be updated and age characteristics validated against actual Census estimates (rather than Census projections of 2008).

Future research will be conducted to test different models for attributing increased risk in weight-gain over time. Various epidemiologic models for increased risk will be evaluated to determine which model projections most closely resemble the actual data of the US population. The results will be used to predict effects due to the obese intrauterine environment. Once the risk factor is established, projections will be made regarding weight-gain and the prevalence of obesity over a longer time period (e.g. 100 years). These projections will demonstrate the extent to which these affects may be exacerbated over time. We seek to quantify the impact of intrauterine exposure to maternal obesity across multiple generations in different race/ethnicity groups at the population level thereby allowing estimations to be made regarding the extent to which intrauterine programming could be influencing health disparities. This research will aid decision makers in recognizing the impact of preventative-care initiatives as well as in the evaluation of possible alternatives.

CHAPTER FOUR

A DISCRETE-EVENT SIMULATION MODEL TO ESTIMATE HEALTH AND ECONOMIC OUTCOMES OF SMOKING CESSATION TREATMENTS

This chapter focuses on the development and verification of a DES model to estimate health and economic outcomes associated with smoking cessation interventions.

4.1 Model Introduction

According to the US Surgeon General, active cigarette smoking remains a major public health problem, despite numerous health warnings, FDA regulation, highly publicized litigation efforts against major tobacco companies, and a bevy of accumulated epidemiologic evidence chronicling the health risks of smoking [US Department of Health and Human Services, 2004]. Countless studies have demonstrated that "smoking is the single greatest cause of avoidable morbidity and mortality in the United States" [US Department of Health and Human Services, 2004]. However, smoking prevalence remains quite high, and despite the fact that 70% of smokers want to quit, long-term smokers have considerable difficulty breaking the habit and overcoming addiction to nicotine [CDC11].

Multiple smoking cessation therapies and interventions have been developed since the early 1960s to aid smokers who desire to quit; however, more than 46 million adults in the United States continue to smoke cigarettes and even with pharmacologic intervention, recidivism remains extremely high [CDC12]. Smokers who desire to quit often try numerous unsuccessful pharmacotherapies, which may be costly and generally ineffective, resulting in economic hardship and feelings of failure or guilt [Ranney et al.,

2006]. Considering the significant health and economic burden of smoking and the unavailability of a tried and true "magic bullet" for smoking cessation, comparative effectiveness studies are needed to compare different smoking cessation options and corresponding outcomes.

Although the effectiveness of smoking cessation therapies has been low, smoking cessation, when successful, has been shown to be highly cost-effective. Studies have compared placebo to different pharmacologic interventions for smoking cessation [Jackson et al., 2007; Neilson and Fiore, 2000]. Studies have compared the nicotine patch to smoking-cessation counseling [McGhan and Smith, 1996; Fiscella and Franks, 1996; Cromwell et al., 1997] and nicotine gum to smoking-cessation counseling [Cromwell et al., 1997]. Gilbert et al. (2004) included five pharmacological treatments including nicotine gum, patch, nasal spray, inhaler and bupropion in which the control group received smoking-cessation counseling and the treatment cohort was given counseling in addition to pharmacological treatment. Howard et al. (2008) compared varenicline, bupropion, nicotine replacement therapy, and unaided smoking cessation where the main objective of the study was to assess the cost-effectiveness of varenicline.

Cost-benefit studies of smoking cessation therapies that require decision making under uncertainty have employed decision tree analysis [Fiscella and Franks, 1996; McGhan and Smith, 1996; Nielsen and Fiore, 2000; Jackson et al., 2007] and Markov structures [Orme et al., 2001 (in Reifsnider, 2011); Gilbert et al., 2004; Gilbert et al., 2006 (in Reifsnider, 2011); Howard et al., 2008] to provide a simplified description of a complicated clinical problem which aids decision makers in understanding the risks and

benefits of various clinical options. To our knowledge, discrete-event simulation (DES) has not been employed to compare therapeutic options for smoking cessation and related health outcomes. Because individuals have varying levels of nicotine dependence and smoking intensity, and because of significant heterogeneity in treatment response, we believe the DES approach is a potentially more meaningful way to conceptualize the problem of smoking cessation.

The remaining chapter is organized as follows. In §5.2, a description of the data and assumptions of the simulation is provided. In §5.3, measures of health and economic evaluation are described and the simulation verification is described in §5.4. The chapter is concluded with §5.5, in which we discuss limitations of the model and future research directions.

4.2 Model Assumptions and Data

4.2.1 Simulation structure

We developed a DES model using Arena 13.5 software. The simulation consists of four main modules: creation of smokers, smoking cessation treatment, disease progression, and accounting (Figure 5.1). The accounting sub-module periodically updates patient attributes and population statistics. In terms of the progression of the model, first, individuals are created and all individuals are assumed to be smokers. Next, the smoker begins treatment and the model evaluates, according to trial-based efficacy evidence, whether or not the treatment was successful. If treatment is successfully completed, then the patient enters the non-smoker state; otherwise, the patient remains a smoker with no additional attempts at treatment. A periodic update of patient disease

progression, aggregate quality adjusted life-years (QALY), health utilities, costs, age, mortality, and statistical accumulation occurs annually regardless of the patient's smoking status. A detailed description of the operations of each sub-module follows.

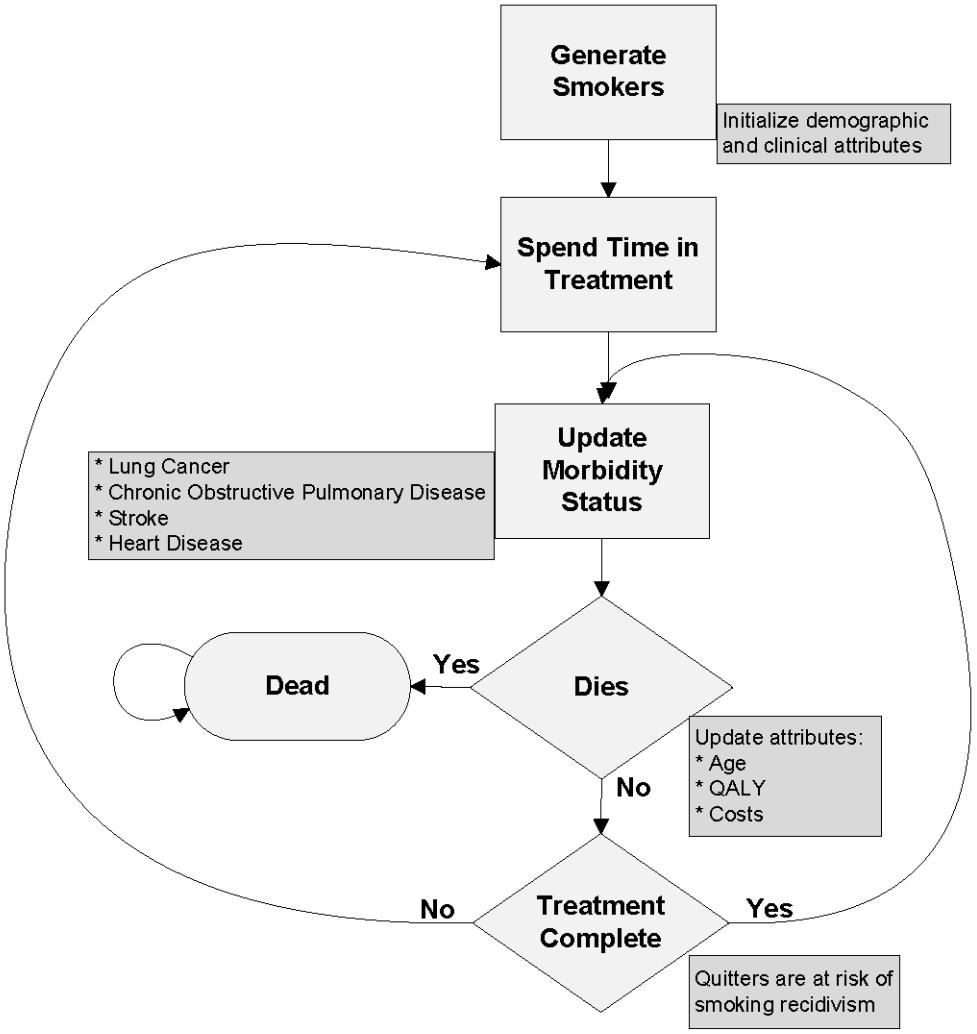


Figure 4.1: High-level schematic of simulation flow.

4.2.2 Creation of smokers

The creation module creates smokers and allows the administrator to input background demographic and clinical information of the underlying population. A discrete number of patients enter the system representing a single cohort sampled from a

chosen population. The initial cohort consists of 10,000 individuals made up of males and females ages 18 to 70 years, assigned according to 2008 US Census population tables [Census2] and US smoking prevalence estimates taken from the 2008 National Health Interview Survey (NHIS) [NCHS, Table 4.1]. Refer to Appendix table D.1 for the calculated distribution of smokers. No additional entities enter the simulation; however, individuals may exit the model due to death. Demographic and clinical attributes are assigned to each individual in the simulation at baseline including gender, age, and quality of life (refer to Section 4.3.1). Quality of life numbers were drawn from the literature [Fiscella and Franks, 1996; Stewart et al, 2009 (in Reifsnider, 2011)] and are assigned based on individual demographic attributes. For example, gender and age are assigned independently but utilities or quality of life associated with certain health states depend upon the gender and age attributes. Probabilities of transitioning between health states are also dependent upon these background attributes. All patients enter the model as smokers and are considered "healthy" at baseline. A healthy patient is characterized as a smoker with no serious smoking-related co-morbidities of interest [i.e., lung cancer, chronic obstructive pulmonary disease (COPD), stroke, coronary heart disease (CHD)].

Table 4.1: Smoking prevalence among adults in the US.

Age Group	Male	Female
18 - 44	0.254	0.203
45 - 64	0.246	0.205
65+	0.106	0.082

4.2.3 Smoking cessation treatment

Smoking cessation alternatives considered in this model include nicotine replacement treatment (NRT) interventions, bupropion, varenicline, and non-

pharmacologic-assisted cessation. The four NRT products considered in this model (patch, inhalator, gum, and nasal spray) are known to have different costs, adherence, and outcomes; hence, average statistics across the four NRT products are input into the simulation to represent the NRT treatment option. We run the simulation in five scenarios, one scenario for each of the four strategies (NRT, bupropion, varenicline, and non-pharmacologic-assisted) and one for no treatment.

Upon entry into the simulation, 100 percent of smokers make one attempt at treatment. Duration of active treatment is 12 weeks for all interventions of interest [AMA, 2000] and individuals are assumed to adhere to treatment for the full duration. Intervention-specific efficacy rates are applied at the end of year one at which time individuals either successfully quit smoking or remain smokers. Reported efficacy rates for smoking cessation are highly variable, therefore we performed a meta-analysis of the efficacy of smoking cessation strategies to obtain an estimate of the summary effect size across studies. A review of the medical literature identified 6 studies for NRT, 6 studies for bupropion, 5 studies for varenicline, and 4 studies for non-pharmacologic-assisted (Table 4.2). Results across studies per strategy were combined to provide a single pooled result quantifying how much each intervention is beneficial. The mid-point value was considered our baseline probability of treatment success.

Table 4.2: Efficacy rates (defined as treatment-specific, CO^2-verified, continuous abstinence rate over a one-year time period, i.e. during trial follow-up).

Cessation alternative	Proportion Abstinent	Reference*
NRT	0.13 (0.06-0.20)	Aubin et al, 2008; Bohadana et al, 2000; Jorenby et al, 1999; Nielson and Fiore, 2000; Silagy et al, 2002; Raw, McNeill, and West, 1998
Bupropion	0.225 (0.15-0.30)	Jorenby et al, 2006; Fossati et al, 2007; Jorenby et al, 1999; Nides et al, 2008; Silagy et al, 2002; Gonzales et al, 2006
Varenicline	0.215 (0.18-0.25)	Niaura et al, 2008; Garrison et al, 2008; Rigotti et al, 2010; Gonzales et al, 2006; Nides et al, 2008
Non-pharmacologic-assisted	0.05 (0.03-0.07)	Hughes et al, 2004; Raw, McNeill, and West, 1998; Foulds et al, 2004; Fiore, 2000

NRT = Nicotine Replacement Therapy
* Refer to Reifsnider (2011).

Successful quitters are referred to as former smokers and are at risk of relapse (refer to Section 4.2.5 for more explanation) as they move through the disease progression and accounting modules each year. Individuals who did not successfully quit smoking loop through the disease progression and accounting modules each year until death.

4.2.4 Disease progression

Although smoking is a risk factor for numerous non-communicable diseases, we chose to focus on lung cancer, chronic obstructive pulmonary disease (COPD), stroke, and coronary heart disease (CHD), for two reasons. First, these four diseases represent significant epidemiologic and economic burdens to American society [US DHHS, 2004] and second, good data exist on the probabilities and outcomes for these disease states in a smoking population. Diseases are either present/absent with the possibility of acute exacerbation or improvements in condition. Individuals may develop one or more smoking-related condition. Estimates of lung cancer, COPD, stroke, and CHD were determined by the literature and considered to be dependent upon demographic attributes

(age and gender) and the individual's smoking status - current smoker or former smoker. The disease progression module updates the individual's health state annually. The health state not only takes account of diagnoses of chronic conditions (and corresponding health utilities), but also considers incident complications associated with each co-morbidity, such as a COPD exacerbation.

An individual may develop different levels of COPD (mild, moderate, or severe). In the absence of good data about COPD transitions between mild, moderate, and severe disease, we assumed that people diagnosed with COPD were diagnosed with mild, moderate, and severe disease according to proportions in the literature and that they remained in those "states" until death. Baseline utility values are assigned to individuals who have COPD (Table 4.9 of Section 4.3.1). Individuals living with COPD are at risk of COPD exacerbations (minor or major). Refer to Table 5.3 for estimates of COPD.

Annual incidence of COPD exacerbation is modeled for each COPD level by applying the binomial probability distribution. For example, the exacerbation rate per annum for mild disease of 0.79 is converted to an annual probability of 0.5462 [$1\text{-}e^{(0.79)}$]. We assume a maximum of 4 possible COPD exacerbations annually. Since the expected value, $E(x)$, of a binomial distributed random variable is the product of the number of trials [(n); 4] and the proportion of success [(p), COPD exacerbation] we compute the likelihood of independent COPD exacerbations to be 0.1366. The probability table is given in Table D.2 of the Appendix. Next, we determine how many major exacerbations occurred using the binomial distribution formula and given the annual number of COPD exacerbations and the percentage of minor exacerbations (refer to Appendix Table D.3

for computed probabilities). COPD utility values are weighted based on the number and type of COPD exacerbations. COPD exacerbations lower the baseline COPD utility values for a period of 3 months.

Table 4.3: Lifetime probability of developing COPD, by gender and smoking status.

Risk of developing COPD[a]	Cumulative/lifetime probability of COPD**
Current smoker	
Male	0.32
Female	0.32
Former smoker/non-smoker*	
Male	0.13 (0.12-0.14)
Female	0.13 (0.12-0.14)
Severity of COPD[b]	Proportion in each severity category
Mild disease	70.34% (68-73%)
Moderate disease	19.33% (19-20%)
Severe disease	10.33% (8-13%)
COPD exacerbation[c]	Exacerbation frequency (per annum)
Mild disease	0.79
Moderate disease	1.22
Severe disease	1.47
Minor exacerbation[c]	
Mild disease	94%
Moderate disease	93%
Severe disease	90%

COPD = chronic obstructive pulmonary disease
**We assume a former smoker carries the same risk as a non-smoker*
*** Lifetime probability calculated by converting lifetime rate to annual probability using sex-specific life expectancy tables for smokers at 50 years; former smokers group denominator calculated using the average LE between current smokers and general population*
(a) Reference is Pelkonen et al. (2008), (b) Reference is Wilson, Devine, and So (2000), (c) Reference is Spencer et al. (2005) [(refer to Reifsnider (2011)]

Individuals are at risk of multiple stroke exacerbations over their lifetime. Estimates of stroke are provided in Table 4.4. Stroke utility values are weighted to reflect the two month period following the first stroke event. Subsequent strokes result in a permanent decrement in the stroke utility value. Utility values for stroke are shown in Table 4.9.

Table 4.4: Age-standardized rate of stroke per 100,000 person-years, by gender and smoking status.

	Current smoker	Former smoker*
Male	656.6	496.4
Female	565.6	506.7

** We assume a former smoker carries the same risk as a non-smoker*

Table 4.5: Risk of lung cancer, by smoking status.*

Current smoker**	Incidence rate
Age < 55 years***	0.0000
Age 55-64 years	6.0000
Age 65-74 years	7.5000
Age 75-84 years	8.1667
Age > 84 years	8.1667

** Incidence rate of lung cancer among nonsmokers, in person years (100,000)*
***Current smoker = averaged 1pack/day and 2 packs/day for 25 years, 40 years, and 50 years*
****We assume that individuals less than 55 years of age do not develop lung cancer*
Former smoker: relative risk = 10
Reference: in Reifsnider (2011)

Table 4.6: Age-specific, ten-year rate of CHD, by gender, age, and smoking status.

Current smoker	Incidence rate	Former smoker*	Incidence rate
Male		Male	
Age < 30 years**	0.0000	Age < 30 years**	0.0000
Age 30-34 years	0.0336	Age 30-34 years	0.0200
Age 35-39 years	0.0504	Age 35-39 years	0.0300
Age 40-44 years	0.0672	Age 40-44 years	0.0400
Age 45-49 years	0.0672	Age 45-49 years	0.0400
Age 50-54 years	0.1008	Age 50-54 years	0.0600
Age 55-59 years	0.1176	Age 55-59 years	0.0700
Age 60-64 years	0.1512	Age 60-64 years	0.0900
Age 65-69 years	0.1848	Age 65-69 years	0.1100
Age 70-74 years	0.2352	Age 70 years	0.1400
Age > 74 years**	0.2352	Age > 74 years**	0.1400
Female		Female	
Age < 30 years**	0.0000	Age < 30 years**	0.0000
Age 30-34 years	0.0074	Age 30-34 years	0.0050
Age 35-39 years	0.0147	Age 35-39 years	0.0100
Age 40-44 years	0.0294	Age 40-44 years	0.0200
Age 45-49 years	0.0441	Age 45-49 years	0.0300
Age 50-54 years	0.0735	Age 50-54 years	0.0500
Age 55-59 years	0.1029	Age 55-59 years	0.0700
Age 60-64 years	0.1176	Age 60-64 years	0.0800
Age 65-69 years	0.1176	Age 65-69 years	0.0800
Age 70-74 years	0.1176	Age 70-74 years	0.0800
Age > 74 years**	0.1176	Age > 74 years**	0.0800

CHD = coronary heart disease
** We assume a former smoker carries the same risk as a non-smoker*
***We assume that individuals less than 30 years of age do not develop CHD*
****We assume the risk for CHD in the oldest age group is equal to the next closest age group*
Reference: in Reifsnider (2011)

Improvements in condition are taken into account by allowing the health state utility to be modified for post-exacerbation improvements over time, which is relevant for acute events such as stroke and COPD exacerbations. For example, patients who have suffered a stroke are considered to have a history of stroke, which is an improvement over the actual stroke event itself, and patients who have suffered more than one stroke are considered to have a history of multiple strokes. An individual who experiences a stroke has a corresponding utility of 0.425 for the event itself (in this case, we assume quality of life is seriously affected for two months) [Wolf et al., 1992 (in Reifsnider, 2011)]. After two months, the individual's condition improves but still has an average

utility considerably worse than perfect health, 0.725, reflecting stroke-related disability [Howard et al., 2008]. If the same person has an additional stroke, the utility drops substantially because we assume that multiple strokes lead to significant disability/morbidity.

Individuals are at risk for disease-specific mortality per annum. We model two causes of death - disease-specific mortality and all-cause mortality - which allows both deaths from smoking-related diseases of interest and death from natural causes to be taken into account. Deaths due to lung cancer, COPD, stroke, and CHD complications are accrued within the disease progression module. Mortality from all causes is determined in the accounting module.

Case fatality rates are used to estimate disease-specific risk of mortality (Table 4.7). Case fatality rates are specific to those people who have already been diagnosed with a disease; that is the proportion of individuals with a disease who die from the disease during a given time period. Information is not available for smoking status-adjusted case fatality rates. Since the incidence rates for disease have been adjusted by smoking status, there is no reason to think that once diagnosed with the disease of interest, smokers should have differential risk of death than non-smokers. So, once individuals have the disease of interest, we assume their prognosis is similar.

Table 4.7: Case fatality rates over the time period of interest.

Co-morbidity	Case fatality rate	Reference
CHD		
At 1 year	44.5%	MacIntyre et al, 2000
At 5 years	76.5%	
At 10 years	87.6%	
Stroke (exacerbation)		
1 year overall	35% (32-38%)	Nieuwkamp et al, 2009; Feigin et al, 2003
Lung Cancer		
At 5 years	85%	Parkin et al, 2002
COPD		
After at 1+ major exacerbation	15.6%	Hoogendoorn et al, 2010

CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease

We assume the case fatality rate of CHD and lung cancer to increase linearly over time. COPD-related death is possible if at least one major exacerbation occurred, regardless of the level of disease (mild, moderate, or severe). A case fatality rate of 35 percent is assumed if an individual experiences at least one stroke annually.

4.2.5 Accounting module

The accounting module serves several purposes. First, patient attributes including age and health utilities and QALYs (refer to Section 4.3.1) are periodically updated. Next, non-disease-specific all-cause mortality is determined in the accounting module and recidivism after successful treatment. Outcomes are measured to draw insights into the long-term health and economic effects of smoking cessation.

We used life tables from the Centers for Disease Control and Prevention (CDC)/National Center for Health Statistics (NCHS) on age-specific, gender-specific, all-cause mortality in the American population [Rogers and Powell-Griner, 1991 (in Reifsnider, 2011)] to determine non-disease-specific death. The CDC/NCHS data on all-cause mortality in the American population includes deaths from diseases we are interested in tracking in the model (i.e. lung cancer, COPD, stroke, CHD) but will include

"healthy" nonsmokers as a potential balance. We expect the incidence of death due to lung cancer, COPD, stroke, and heart disease to be lower in the healthy, nonsmoking population, which may help counter some of the possible/theoretical double counting of deaths in the model. It is unclear how to fully separate these risks at this time since we do not have a measure for "all-cause mortality, excluding deaths from lung cancer, COPD, stroke, and heart disease".

Using the published literature, we estimated the probability of recidivism after successful treatment (Table 4.8). Former, successfully treated, smokers can be assumed to relapse according to annual probability, which is based upon the total time abstinent; that is to say, the longer a former smoker has remained abstinent from smoking, the more likely he/she is to continue to refrain. There is no time period after which a former smoker has no risk of relapse. Gilpin, Pierce, and Farkas (1997; in Reifsnider, 2011) established in their cohort study of 1449 former smokers that even after 10 years of abstinence from smoking, there was no time period after which former smokers had no risk of relapse. Therefore, although the risk of relapse diminishes significantly over time, no former smoker is ever completely immune to the potential for relapse. Recidivism rates depend on the number of years abstinent and are not treatment specific.

Table 4.8: Probability of recidivism after 12 months continuous abstinence (defined as non-treatment-specific, prolonged abstinence beyond 12 months).

Time period	Proportion relapsed (among those who were continuously abstinent at 12 mos)	Reference*
Years 1-2	0.165 (0.09-0.24)	Hughes et al, 2008; Gilpin, Pierce and Farkas, 1997; Wetter et al, 2004
Years 2-5	0.097 (0.024-0.17)	Wetter et al, 2004; Hughes et al, 2008; Krall et al, 2002
Years 5-10	0.0425 (0.005-0.08)	Wetter et al, 2004; Krall et al, 2002; Hughes et al, 2008
Years 10+	0.0055 (0.001-0.01)	Cromwell et al, 1997; Krall et al, 2002

* Refer to Reifsnider (2011)

In addition to updating patient characteristics, the model generates statistics on smoking prevalence, incidence of relapse, average QALYs gained due to an intervention (i.e. effectiveness), death from smoking-related conditions, smoking cessation treatment costs, and costs associated with managing a smoking-related chronic disease or exacerbation (refer to Section 4.3.2 for cost information). Epidemiologic and economic outcomes can be viewed annually or cumulatively.

4.3 Health and economic measures

4.3.1 Quality of life

Quality-adjusted life year (QALY) is a measure of disease burden on both quality and quantity of life and can account for morbidity and mortality on quality of life. A QALY can be thought of as a year of life quantified by the quality of life or value of living in a particular state of health. The quality of life element is measured in terms of health utilities. The basic concept behind a QALY is that the amount of time spent in a particular health state is weighted by a health state utility score which attempts to reduce multi-dimensional health outcomes to a single representation or measure of health. Health state utility scores represent the severity of a disease relative to perfect health and are scaled between 0 (indicating death) and 1 (indicating perfect health). QALYs provide a

common measurement to compare treatment options in terms of health related quality of life by quantifying how much someone's life could be extended or improved by an intervention.

Health state utilities, as a measure of quality of life associated with particular conditions, were drawn from the peer-reviewed literature (Table 4.9). We incorporated gender- and age-specific utility values, where possible. We assumed that smokers in good health had a slightly lower utility than former smokers in good health and that quality of life decreased with age, in accordance with the literature (Table 4.10).

Table 4.9: Health state utility values for smoking-related co-morbidity.

Co-morbidity	Utility	Reference*
CHD	0.645 (0.50-0.79)	Gold et al, 1998; Sullivan and Ghushchyan, 2006; Barton et al, 2008
Stroke		
Months 0-2 after first stroke event	0.425 (0.33-0.52)	Wolf et al, 1992; Hoerger et al, 2004; Sturm et al, 2002; Tengs and Lin, 2003
Months 2+ after first stroke event (improvement after rehabilitation)	0.725 (0.55-0.90)	Tengs et al, 2001, 2003; Duncan et al, 2000; Howard et al, 2008; Barton et al, 2008; Mittmann et al, 1999; Tengs and Lin, 2003
After subsequent/second stroke (lasting disability)	0.24 (0.15-0.33)	Howard et al, 2008; Tengs and Lin, 2003
Lung Cancer	0.50 (0.39-0.61)	Gold et al, 1998; Trippoli et al, 2001
COPD		
Baseline mild disease	0.82 (0.81-0.83)	Spencer et al, 2005; Rutten-van Molken et al, 2006
Baseline moderate disease	0.775 (0.72-0.83)	Spencer et al, 2005; Rutten-van Molken et al, 2006
Baseline severe disease	0.70 (0.67-0.73)	Spencer et al, 2005; Rutten-van Molken et al, 2006
Minor exacerbation (3 mos) mild disease	0.72	Spencer et al, 2005
Minor exacerbation (3 mos) moderate disease	0.658	Spencer et al, 2005
Minor exacerbation (3 mos) severe disease	0.475	Spencer et al, 2005
Major exacerbation (3 mos) mild disease	0.52	Spencer et al, 2005
Major exacerbation (3 mos) moderate disease	0.45	Spencer et al, 2005
Major exacerbation (3 mos) severe disease	0.41	Spencer et al, 2005

CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease
* Refer to Reifsnider (2011)

Table 4.10: Health state utility values for current and former smokers.

Current smokers	Female utility value	Male utility value
Age 24 and younger*	0.91	0.93
Age 25 - 29	0.89	0.91
Age 30 - 34	0.87	0.88
Age 35 - 39	0.84	0.86
Age 40 - 44	0.82	0.83
Age 45 - 49	0.80	0.81
Age 50 - 54	0.78	0.78
Age 55 - 59	0.76	0.76
Age 60 - 64	0.74	0.74
Age 65 - 69	0.72	0.71
Age 70 and older*	0.70	0.69
Former smokers	Female utility value	Male utility value
Age 24 and younger*	0.94	0.95
Age 25 - 29	0.92	0.93
Age 30 - 34	0.9	0.93
Age 35 - 39	0.89	0.92
Age 40 - 44	0.87	0.9
Age 45 - 49	0.86	0.89
Age 50 - 54	0.84	0.87
Age 55 - 59	0.82	0.85
Age 60 - 64	0.79	0.83
Age 65 - 69	0.77	0.8
Age 70 and older*	0.75	0.78

** Assumption; Note: quality of life expressed as mean, where 1.0 is equal to optimum health and 0.0 is equal to death*
Refer to Reifsnider (2011)

Incorporating concepts from financial analyses and the health state utilities leads to the development of the QALY equation. A common practice in economic evaluations is to discount both future costs and benefits. Discounting in the context of economic evaluations deals with time preference and implies that costs and benefits occurring at different points in time are valued differently. That is, individuals prefer to enjoy benefits in the present while postponing any negative effects. For example, taking into account the opportunity cost of investing now rather than in the future would mean that future costs must be discounted. Discounts are applied on an annual basis. Expenses sustained during the first year would not be discounted. Let us assume that a standard annual discount rate of 3.0 percent is applied for all economic outcomes. Expenses sustained during the

second year would then be discounted by 3.0 percent which means that these expenses would be divided by 1.03. Expenses acquired during the third year would be divided by 1.03^2 and each consecutive year would be discounted by an additional 3.0 percent. Therefore the discount factor is given by equation (2) where *r* is the annual discount rate and *t* is time in years.

$$\text{Discount factor} = \frac{1}{(1+r)^{(t-1)}} \tag{4.1}$$

Similarly, this economic concept of discounting is utilized in health care management. Annual discount rates are applied to health outcomes to account for the fact that health is worth more now than later.

Equation (1) was used to calculate the aggregate quality of life-years over the patient's lifetime and is the sum of all QALYs associated with different health states over the natural lifetime of the patient (i.e. for each year of life in each health state, the relative/weighted value (utility) of that year in that health state). We define *t* as the time in years in which the patient is cycling through the simulation model. The health state utility during year *t* is defined by U_t and represents an annual assessment of quality of life. U_t can be thought of as the "expense" to the patient of living in a certain health state during year *t*. We define *T* as the total number of years the patient cycles through the simulation model until death, and *r* is the annual discount rate applied for all economic and health outcomes. A standard annual discount rate of 3.0 percent was applied for all economic and health outcomes [Gold et al., 1996]. For example, person A is healthy in year 1 (utility value = 1), has a stroke in year 2 (utility value = 0.5), goes through rehabilitation and attains some functional recover in year 3 (utility value = 0.75), and dies

at the beginning of year 4 (utility value = 0). This person's QALY over the 4 year period of time is 1 + 0.485437 + 0.706947 + 0 = 2.19238.

$$QALY_T = \sum_{t=1}^{T} \frac{U_t}{(1+r)^{(t-1)}} \quad (4.2)$$

4.3.2 Costs

We use 2010 costs of co-morbidities and smoking cessation products. Treatment is paid for upfront; if a patient dies during year one then the total cost of treatment has been incurred. Costs of pharmacological interventions are summarized in Table 4.11. Zero cost is associated with the non-pharmacologic-assisted option. Cost for each co-morbidity and event costs (2010 values, $US) were derived from multiple sources and are shown in Table 4.12.

Table 4.11: Costs (2010 values, $US) of pharmacological treatment.

Treatment	Annual cost in 2010 US$	Reference
NRT	$485.29	Howard et al, 2008
Bupropion	$348.69	Red Book: Pharmacy's Fundamental Reference 2010
Varenicline	$430.53	Red Book: Pharmacy's Fundamental Reference 2010
Non-pharmacologic-assisted	$0.00	

NRT = Nicotine Replacement Therapy

Table 4.12: Cost (2010 values, $US) of treating co-morbidity and event costs.

Co-morbidity/Event	Annual cost in 2010 $US	Reference*
Cost of treating CHD		
First year after diagnosis	$8,930	Tsevat et al, 2001; Howard et al, 2008
Subsequent years after diagnosis	$4,239	Tsevat et al, 2001; Howard et al, 2008
Cost of treating stroke		
First year after diagnosis	$41,391	Taylor et al, 1996
Subsequent years after diagnosis	$17,688	Taylor et al, 1996
Phase-specific cost of treating lung cancer		
Initial treatment phase (5.7 mos)	$13,759	Kuticova et al, 2005
Secondary treatment phase (7.4 mos)	$4,468	Kuticova et al, 2005
Terminal treatment phase (5.6 mos)	$11,249	Kuticova et al, 2005
% receiving terminal treatment only (no initial treatment)	9%	Kuticova et al, 2005
% receiving secondary treatment after failing initial treatment	29%	Kuticova et al, 2005
% receiving terminal treatment immediately after failing initial treatment	27%	Kuticova et al, 2005
Annual cost of treating COPD	$5,369	Halpern et al, 2003

CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease
* Refer to Reifsnider (2011)

We seek to assess the gains in health relative to the costs of different health interventions, therefore annual discounting was also applied to total costs (i.e. treatment cost, costs of co-morbidity, co-morbidity event costs). Discounting of costs assumes that a dollar in the present is worth more than a dollar in the future. Let C_t represent the total cost incurred during year *t*. Equation (2) was used to calculate the sum of all costs over the lifetime of the patient.

$$Cost_T = \sum_{t=1}^{T} \frac{C_t}{(1+r)^{(t-1)}} \quad (4.3)$$

4.4 Model Accreditation

Integrated practices were employed during the model development process to ensure the credibility of the model. First, the assumptions underlying the conceptual model were established based upon consultations that took place with clinicians during

the formative stages of the simulation model. Additionally, discussions with clinicians established that the model structure and causal relationships reasonably represent the actual system. During the implementation stages of the model, testing verified that the logic and mathematical correlations behind the simulation model operate according to model specifications. In addition to the interactions of the aggregate model, each sub-module was evaluated to determine the appropriate level of detail. Next, input data and performance of output measures were assessed during the modeling building process to substantiate model accuracy in accordance with the models intended purpose. Clinicians performed both qualitative and quantitative analysis of output behaviors to confirm that the predicted values were of reasonable magnitude.

4.5 Conclusions

We developed a discrete event simulation model to explore comparative effectiveness of various smoking cessation options available to smokers in a US population. Recognizing that smoking has significant health impacts in terms of morbidity and mortality from smoking-related diseases, this model expands upon the current literature by (1) simultaneously comparing multiple pharmacologic and non-pharmacologic options for smoking cessation, which many clinical trials have failed to do, and (2) using an innovative modeling approach, discrete event simulation, which allows for individual-level variation in smoking intensity, risk, treatment adherence, and relapse to be taken into account in assessing the effectiveness of various smoking cessation strategies.

In terms of limitations and ongoing research needs, we identified a need for better smoking-related disease risk data by pack-years. Much of the available data on health risks from smoking is reported according to general categories of "never smoked", "former smoker", "light current smoker" and "heavy current smoker", the latter two of which are not well defined and not well validated. Additionally, recognizing that smoking status and disease risk are both heavily dependent on socioeconomic and socio-demographic characteristics, it would be useful in future models to incorporate additional information about race/ethnicity, education, income/wealth, and occupation, provided good data are available. These individual-level factors have been shown in the literature to be important confounders or mediators affecting the causal relationship between smoking and disease incidence. Another limitation of this work is that we did not consider geographic or environmental factors related to smoking and disease risk; future work could compare risk of recidivism based on location (e.g., different states, urban versus rural) or environment (e.g., occupational environment, including other environmental exposures such as asbestos or atmospheric pollution).

CHAPTER FIVE

ESTIMATING COST-EFFECTIVENESS OF ALTERNATVE SMOKING CESSATION STRATEGIES

The purpose of this chapter is to evaluate and analyze the results of the simulation model presented in Chapter 4. We introduce our key statistic for assessing cost-effectiveness. A detailed comparative and sensitivity analysis of smoking cessation alternatives is presented and we discuss potential health policy impacts associated with the predictions of the model.

5.1 Incremental cost-effectiveness ratio

In this section we introduce analytical methods for comparing alternative treatment strategies. The incremental cost-effectiveness ratio (ICER) is a standard measure used to compare the cost-effectiveness of two treatment options. ICERs provide a common unit of measurement to estimate the additional cost and health outcome (measured in QALYs, refer to Chapter 5.3.1) obtained through an intervention. The ICER is computed by dividing the incremental cost (difference in average cost associated with two interventions) by the incremental health benefits (difference in average QALY of two interventions). Comparing different treatments in this manner answers questions about whether an intervention is efficient and comparatively efficient. Mathematically, the ICER is represented as follows:

$$ICER = \frac{\mu_{C_2} - \mu_{C_1}}{\mu_{E_2} - \mu_{E_1}} = \frac{\Delta_C}{\Delta_E} \tag{5.1}$$

We let μ_{C_T} and μ_{C_C} signify the expected cost of the investigated treatment (T_2) and the expected cost of the control treatment (T_1), respectively. Similarly, the expected health effectiveness of T_2 and the expected health effectiveness of T_1 are denoted by μ_{E_T} and μ_{E_C}, respectively.

In this dissertation, the parameters for the ICER are estimated from the simulation model (presented in Chapter 4) and therefore the true population cost and effectiveness is unknown with certainty. We can easily obtain confidence intervals (CIs) around the sample costs and effects, however in cost-effectiveness analysis we care about the uncertainty surrounding the ICER. This is not straightforward because when Δ_C and Δ_E are two normal random variables (each variable is associated with a mean and variance) then the ratio has a standard Cauchy distribution. A Cauchy distributed variable does not have a theoretical mean and variance however it is characterized by its mode and median values. Therefore methods have been introduced to calculate CIs of Cauchy distributed ICERs including nonparametric bootstrapping [Hunink et al, 1993; Briggs, 1997; Campbell and Torgerson, 1999], Fieller's method [Chaudhary and Stearns, 1996], and the delta method [O'Brien et al., 1994]. We focus on the use of nonparametric bootstrapping for significance testing of the ICER.

Black (1990) first introduced the incremental cost-effectiveness plane (Figure 5.1) to explain the comparative cost-effectiveness of bootstrap ICER estimates. The horizontal axis measures the incremental effectiveness of T_2 and the incremental cost of T_2 is measured by the vertical axis. Each of the four quadrants implies a different level of cost-effectiveness. Points that imply an intervention is more effective while saving money

(dominant) fall in the south east (SE) quadrant. The north east (NE) quadrant indicates cost-effectiveness where health effect is positive at higher cost. If points lay in the north west (NW) quadrant, higher cost is associated with lower effectiveness and the intervention is excluded. When both cost and effect are low, points sit in the south west (SW) quadrant, and it is questionable whether a treatment is cost-effective compared to the control treatment.

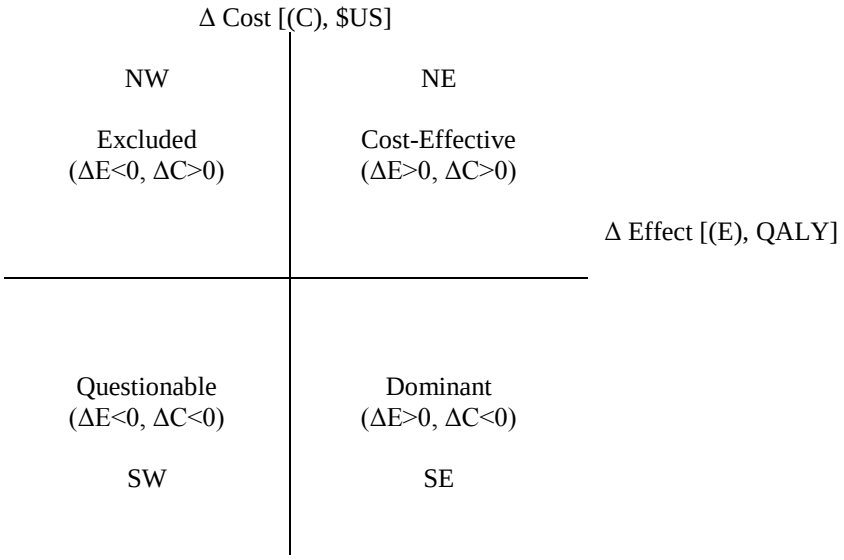


Figure 5.1: Incremental cost-effectiveness plane (NE = northeast quadrant; NW = northwest quadrant; SE = southeast quadrant; SW = southwest quadrant; QALY = quality adjusted life year).

The cost-effectiveness plane helps answer questions about sampling uncertainty (e.g. what is the probability T_2 is cost-effective relative to T_1). Estimates of treatment cost-effectiveness are important to health decision-makers who make determinations such as whether or not a treatment should be reimbursed. General rules for deciding which treatment (T_2 or T_1) to choose are given in Table 5.1 [Cohen and Reynolds, 2008].

Table 5.1: Implications of the cost-effectiveness plane.

Quadrant	Implication
NE (+)	T_2 (investigated treatment) is cost-effective – cost-increasing tradeoff
SE (-)	T_2 (investigated treatment) is dominant – choose T_2
SW (-)	T_2 (investigated treatment) is questionable – cost-reducing tradeoff
NW (+)	T_1 (control treatment) is dominant – choose T_1

We acknowledge that there are limitations with using the ICER statistic. When significant uncertainty exists about the sign of the ICER it is difficult to interpret CIs around the ICER. ICERs located in the NE and SW quadrants (both yielding positive values) are hard to distinguish, as are ICERs falling in the NW and SE quadrants (both having negative values). Different quadrants indicate very different conclusions about the cost-effectiveness of the investigated treatment (T_2). For example, ICERs located in the SE quadrant indicate that T_1 is dominated by T_2 and ICERS sitting in the NW quadrant indicate opposite results, that T_1 is dominant. Therefore, reasonable caution should be taken when interpreting cost-effectiveness studies.

5.2 Base-case analyses

This section presents the base case results of the simulation model to estimate health and economic outcomes of alternative smoking cessation strategies. Results of a cost-effectiveness analysis on base-case estimates are provided.

5.2.1 Simulation parameters

A cohort of 10,000 individuals was followed annually over a horizon of 1 year, 10 years, 30 years, and lifetime with output measures observed over five scenarios, one simulation run for each intervention of interest and one simulation run with no treatment attempt. Cost of treatment options and smoking-related disease and health utility values

are summarized in Chapter 4.3. All costs and QALYs were discounted at an annual rate of 3%.

To obtain tighter 95% confidence intervals around our performance values, 75 replications were carried out leading to sufficiently small half-widths for most output variables. Common random numbers (CRNs) were applied to reduce stochastic variation between runs. CRNs are particularly important in disease modeling when comparing different treatment arms [Stout and Goldie, 2008].

5.2.2 Base-case results

The reader should refer to Table 5.2 for results of smoking prevalence over time. Among smokers attempting to quit smoking, 2 year recidivism rates among those alive at follow-up were the following: nicotine replacement treatment, 89.13%; bupropion, 81.14%; varenicline, 81.98%, and non-pharmacologic-assisted, 95.84%. Nicotine replacement treatment, bupropion, varenicline, and non-pharmacologic-assisted had a recidivism rate of 93.67%, 89.07%, 89.55%, 97.58% among those alive at 30 years, respectively.

Table 5.2: Smoking prevalence among those alive at follow-up.

	2 years	10 years	30 years	Lifetime
NRT	89.13	93.42	93.67	N/A
Bupropion	81.14	88.60	89.07	N/A
Varenicline	81.98	89.10	89.55	N/A
Non-pharmacologic-assisted	95.84	97.49	97.58	N/A
No Treatment	100.00	100.00	100.00	N/A

NRT = Nicotine Replacement Therapy; N/A = not applicable

Table 5.3: Prevalence of smoking-related disease.

	2 years	10 years	30 years	Lifetime
NRT				
CHD	1.04	5.95	20.07	31.78
At least one stroke	1.17	5.55	13.38	17.44
One stroke	1.17	5.45	12.72	16.13
Multiple strokes	0.00	0.10	0.66	1.32
Lung Cancer	0.04	0.23	0.96	1.73
COPD	0.81	3.81	9.18	12.07
At least one co-morbidity	3.03	15.03	39.81	54.65
Bupropion				
CHD	1.00	5.78	19.71	31.31
At least one stroke	1.16	5.58	13.34	17.43
One stroke	1.16	5.48	12.69	16.13
Multiple strokes	0.00	0.09	0.65	1.31
Lung Cancer	0.03	0.22	0.92	1.69
COPD	0.79	3.66	8.92	11.72
At least one co-morbidity	2.96	14.74	39.22	53.96
Varenicline				
CHD	1.02	5.83	19.76	31.32
At least one stroke	1.17	5.59	13.41	17.50
One stroke	1.17	5.49	12.74	16.19
Multiple strokes	0.00	0.10	0.67	1.31
Lung Cancer	0.03	0.23	0.92	1.68
COPD	0.78	3.67	8.94	11.79
At least one co-morbidity	2.98	14.83	39.35	54.10
Non-pharmacologic-assisted				
CHD	1.05	6.03	20.31	32.09
At least one stroke	1.19	5.62	13.55	17.64
One stroke	1.18	5.53	12.87	16.30
Multiple strokes	0.00	0.09	0.68	1.34
Lung Cancer	0.04	0.26	1.01	1.83
COPD	0.82	3.90	9.37	12.31
At least one co-morbidity	3.07	15.28	40.34	55.25
No Treatment				
CHD	1.06	6.11	20.48	32.27
At least one stroke	1.21	5.66	13.55	17.62
One stroke	1.20	5.56	12.87	16.29
Multiple strokes	0.00	0.10	0.68	1.33
Lung Cancer	0.04	0.27	1.05	1.88
COPD	0.83	3.99	9.56	12.48
At least one co-morbidity	3.12	15.48	40.67	55.56

NRT = Nicotine Replacement Therapy; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease

Table 5.4: Prevalence of mortality.

	2 years	10 years	30 years	Lifetime
NRT				
CHD	0.58	5.09	18.80	30.47
Stroke	0.41	1.96	4.93	6.59
After one stroke	0.41	1.93	4.69	6.10
After multiple strokes	0.00	0.03	0.24	0.49
Lung Cancer	0.01	0.14	0.70	1.33
COPD	0.01	0.12	0.75	1.46
All-causes	0.78	4.96	24.46	60.15
Total	1.78	12.28	49.64	100.00
Bupropion				
CHD	0.56	4.95	18.46	30.01
Stroke	0.41	1.99	4.92	6.60
After one stroke	0.40	1.96	4.67	6.11
After multiple strokes	0.00	0.03	0.25	0.49
Lung Cancer	0.01	0.13	0.67	1.29
COPD	0.01	0.12	0.74	1.43
All-causes	0.78	4.96	24.61	60.67
Total	1.76	12.15	49.41	100.00
Varenicline				
CHD	0.57	4.98	18.51	30.05
Stroke	0.41	1.98	4.93	6.61
After one stroke	0.41	1.94	4.69	6.12
After multiple strokes	0.00	0.03	0.25	0.49
Lung Cancer	0.01	0.14	0.68	1.29
COPD	0.01	0.13	0.74	1.43
All-causes	0.78	4.92	24.62	60.62
Total	1.77	12.13	49.48	100.00
Non-pharmacologic-assisted				
CHD	0.60	5.14	19.03	30.81
Stroke	0.42	2.01	4.98	6.66
After one stroke	0.42	1.98	4.73	6.15
After multiple strokes	0.00	0.04	0.25	0.50
Lung Cancer	0.01	0.16	0.74	1.38
COPD	0.01	0.13	0.77	1.50
All-causes	0.78	4.91	24.28	59.65
Total	1.81	12.35	49.80	100.00
No Treatment				
CHD	0.59	5.22	19.18	30.95
Stroke	0.41	2.01	5.00	6.68
After one stroke	0.41	1.98	4.76	6.19
After multiple strokes	0.00	0.04	0.24	0.50
Lung Cancer	0.01	0.16	0.77	1.44
COPD	0.01	0.13	0.78	1.51
All-causes	0.78	4.94	24.36	59.41
Total	1.80	12.46	50.09	100.00

NRT = Nicotine Replacement Therapy; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease

Results of the base-case analysis found that on average bupropion was most effective at reducing prevalence of lung cancer, COPD, stroke, and CHD. Without intervention on average 55.56% of smokers will develop at least one smoking-related condition over the lifetime of the simulation. Bupropion was also found on average to reduce mortality prevalence the most. Compared with the non-pharmacologic-assisted cessation option, all pharmacologic treatments (varenicline, NRT, and bupropion) prevent smoking-related disease and death.

Base-case estimates of average cost and effect are summarized in Figure 5.2. The average discounted QALYs a cohort of 10,000 former smokers could accumulate over a lifetime is 15.14 (95% CI half-width of 0.01). Average QALYs attained over a lifetime when smokers make no attempt at quitting is 14.48 (95% CI, 14.47-14.49) at an average cost of $28626 (95% CI, $28464-$28788). The high cost associated with the no treatment option is attributable to costs incurred from smoking-related disease.

No statistically significant differences were found in the average lifetime costs or effects (QALYs) of bupropion (average cost between $28004-$28391, average effect between 14.70-14.72) and varenicline (average cost between $28240-$28573, average effect between 14.69-14.71). Bupropion was more effective and less costly than NRT. No statistical differences were found in cost of bupropion and non-pharmacologic-assisted cessation, however effectiveness increases with bupropion by 0.16 QALYs. Average cost of varenicline was not statistically different from the other four treatment arms, however it was statistically more effective than NRT, non-pharmacologic-assisted, and no treatment. The population could increase their average effect over a lifetime by 0.14

QALYs with NRT and 0.07 QALYs with non-pharmacologic-assisted cessation with no statistical difference in average cost. All options to assist smoking cessation improved health outcomes compared with no treatment, however only bupropion did so at lower average cost.

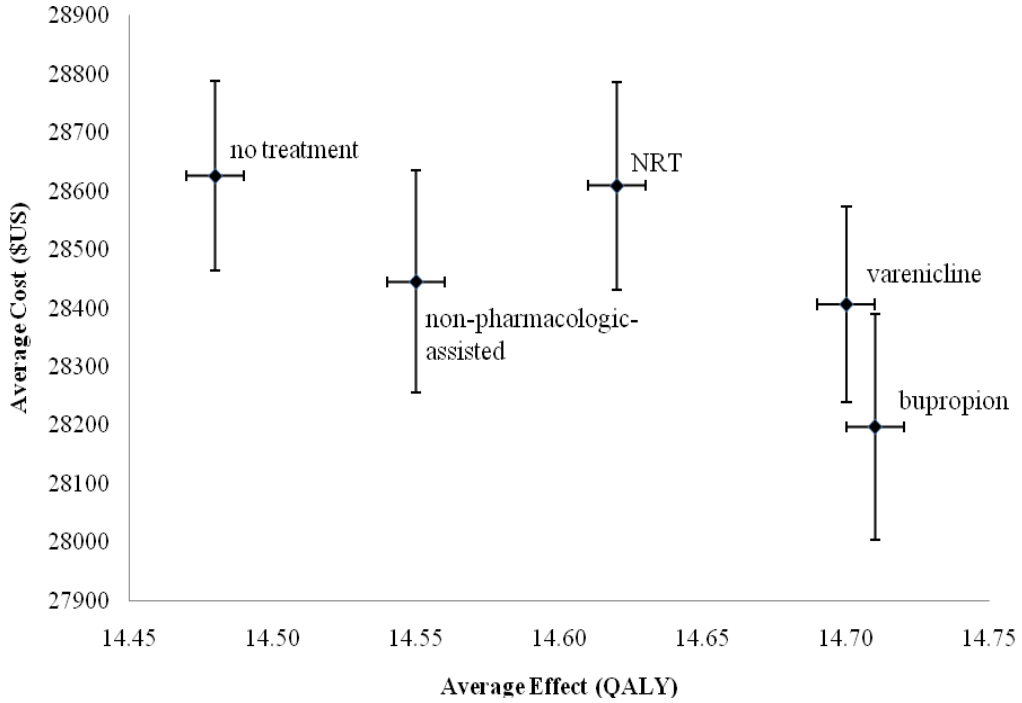


Figure 5.2: Average discounted cost and effect of the five treatment arms (with 95% CIs).

Cost-effectiveness analyses were performed after 2 years, 10 years, 30 years, and lifetime and were measured using the ICER statistic (refer to Section 5.1). We first calculate ICERs by comparing each treatment option (NRT, bupropion, and varenicline, non-pharmacologic-assisted) to no intervention. ICERs The results of the analysis are presented in Table 5.5.

Regarding NRT, bupropion, and varenicline in reference to no treatment we observe that cost-effectiveness improves over time. Costs in year 2, primarily attributable

to treatment expense, are high and the health benefits are small. However, over a lifetime smoking-related disease and mortality are less, and in turn costs are reduced because cost of prevented disease is not accumulated and QALYs are higher. The ICER for bupropion versus no treatment is the smallest (-$1857.71) followed by varenicline (-$1005.64). Although the incremental cost of NRT is very low compared to bupropion and varenicline, it is also less effective by 0.09 and 0.10 QALYs, respectively.

We have to take caution in assessing the non-pharmacologic-assisted option compared to no treatment. This is a case where the negative ICER value is misleading. Consider year 10 for example in which the incremental cost is negative (-$102.11), however the incremental health effect is zero. Money is saved because incidences of smoking-related conditions are reduced however, QALYs are not substantially impacted.

Table 5.5: Smoking cessation strategies compared to no treatment.

Treatment	2 years	10 years	30 years	lifetime
NRT				
Incremental cost	$459.98	$316.34	$40.15	-$16.82
Incremental effect	0.01	0.04	0.10	0.13
ICER	$76,663.33	$7,869.15	$389.05	-$124.68
Bupropion				
Incremental cost	$316.56	$114.36	-$317.76	-$428.76
Incremental effect	0.01	0.07	0.18	0.23
ICER	$30,733.98	$1,636.05	-$1,773.21	-$1,857.71
Varenicline				
Incremental cost	$399.77	$247.51	-$105.78	-$219.33
Incremental effect	0.01	0.07	0.17	0.22
ICER	$40,792.86	$3,688.67	-$621.50	-$1,005.64
Non-pharmacologic-assisted				
Incremental cost	-$15.52	-$102.11	-$198.29	-$180.78
Incremental effect	0.00	0.02	0.05	0.07
ICER	N/A	-$6,462.66	-$4,157.02	-$2,760.00

We next analyzed ICERs over a lifetime horizon by comparing the four smoking cessation strategies to each other (NRT, bupropion, varenicline, non-pharmacologic-assisted) in a successive stepwise manner based on costs incurred and effects (measured

in QALYs) achieved. The four competing smoking cessation interventions were ranked in order of increasing effectiveness and we compared cost-effectiveness of each strategy to the strategy with the next highest QALY [Hallinen et al., 2010]. We want to determine how available interventions compare to one another by obtaining maximum effect before taking account of cost. Tables 5.6-5.8 show the results of the incremental analysis.

In Table 5.6 the negative ICER for varenicline means that by adopting varenicline instead of NRT effect is increased and cost is reduced. NRT is dominated by varenicline because it is more expensive and less effective and is therefore excluded. The ICERs are recalculated (Table 5.7) for the three remaining treatment options. We observe from Table 5.7 that non-pharmacologic-assisted is dominated by varenicline and is the next alternative excluded. Table 5.8 compares bupropion versus varenicline to show that bupropion is the dominant option.

Table 5.6: Stepwise comparison of smoking cessation interventions – step one.

Treatment	Mean Cost (C)	Mean Effect* (E)	Incremental Cost (ΔC)	Incremental Effect (ΔE)	ICER (ΔC/ΔE)
Non-pharmacologic-assisted	$28,445.29	14.55	$28,445.29	14.55	$1955.37
NRT	**$28,609.25**	**14.62**	**$163.95**	**0.07**	**$2359.63**
Varenicline	$28,406.74	14.70	-$202.50	0.08	-$2436.19
Bupropion	$28,197.31	14.71	-$209.44	0.01	-$16452.10
* Effect is measured in QALYs					

Table 5.7: Stepwise comparison of smoking cessation interventions – step two.

Treatment	Mean Cost (C)	Mean Effect* (E)	Incremental Cost (ΔC)	Incremental Effect (ΔE)	ICER (ΔC/ΔE)
Non-pharmacologic-assisted	**$28,445.29**	**14.55**	**$28,445.29**	**14.55**	**$1955.37**
Varenicline	$28,406.74	14.70	-$38.55	0.15	-$252.62
Bupropion	$28,197.31	14.71	-$209.44	0.01	-$16452.10
* Effect is measured in QALYs					

Table 5.8: Stepwise comparison of smoking cessation interventions – step three.

Treatment	Mean Cost (C)	Mean Effect* (E)	Incremental Cost (ΔC)	Incremental Effect (ΔE)	ICER (ΔC/ΔE)
Varenicline	**$28,406.74**	**14.70**	**$28,406.74**	**14.70**	**$1932.45**
Bupropion	$28,197.31	14.71	-$209.44	0.01	-$16452.10
* Effect is measured in QALYs					

5.3 Uncertainty Analyses

To allow for uncertainty in the economic evaluation, we first perform a probabilistic sensitivity analysis on certain base-case estimates. Next, key parameters are varied in univariate and multivariate sensitivity analyses to estimate the influence of different parameters on the results. Various factors influence the choices of health policy decision-makers, therefore we assess the sensitivity, acceptability, and efficiency of the results obtained from the simulation.

5.3.1 Stochastic uncertainty in comparing costs and effects

Probabilistic sensitivity analysis was performed to confirm the validity of the base-case incremental cost-effectiveness ratios (ICERs) for bupropion compared to varenicline. In Section 5.2.2 we explained the uncertainty for the average cost and effect and observed no statistical difference between bupropion and varenicline. Comparison of bupropion to varenicline (Table 5.8) showed varenicline is dominated by bupropion. In this section we assess the uncertainty for the incremental cost and effect ratio of bupropion in reference to varenicline.

We applied the nonparametric bootstrap method using the cost and effect estimates of the two treatment strategies obtained from the simulation to estimate a confidence interval (95%) for the ICER. Four steps were required to produce a bootstrap distribution for the ICER. First, paired cost and effect estimates from the simulation for bupropion were sampled with replacement. The sample size was that of the original sample [the number of replications in the DES model (i.e. 75)]. We obtain a new estimate for average cost and effect with bupropion. Second, cost and effect pairs for the control

treatment (i.e. varenicline) were sampled with replacement 75 times and a new estimate for average cost and effect with the control treatment was attained. Next, the ICER of the bootstrapped re-samples was computed. Sampling and calculation of the ICER was performed 1000 times [Briggs et al., 1997; Campbell and Torgerson, 1999]. Construction of the 95% confidence interval (CI) for the bootstrapped ICERs was achieved using the percentile method [Briggs et al., 1997; Campbell and Torgerson, 1999]. ICER estimates were ranked from smallest to largest and the lower and upper bounds of the CI were represented by the 25^{th} and 976^{th} observations, respectively. The results of bootstrapping to compare bupropion to varenicline are provided in Table 5.9.

Table 5.9: Incremental costs and effects (QALY) of 1,000 bootstrapped comparisons of Bupropion vs NRT.

Bupropion versus varenicline	Mean (CI)	Median ICER [(ΔC/ ΔE), bootstrap CI]
Incremental Cost (ΔC)	-208.86	-13738.83
Incremental Effect (ΔE)	0.01	(-208723.42, 14518.98)

The 1000 ICER estimates were plotted on the cost-effectiveness plane (Figure 5.3) allowing us to evaluate uncertainty of our bootstrapped ICERs. In the base-case analysis bupropion was found to dominate varenicline (indicated by the square in Figure 5.3). Although the estimates cover all four quadrants, indicating some uncertainty about whether bupropion is dominant or cost-effective, the scatter plot shows bupropion to be the dominant (more effective and less costly) treatment strategy with a high probability of 0.849. This supports the results of our base-case analysis. All four quadrant probabilities are summarized in Table 5.10.

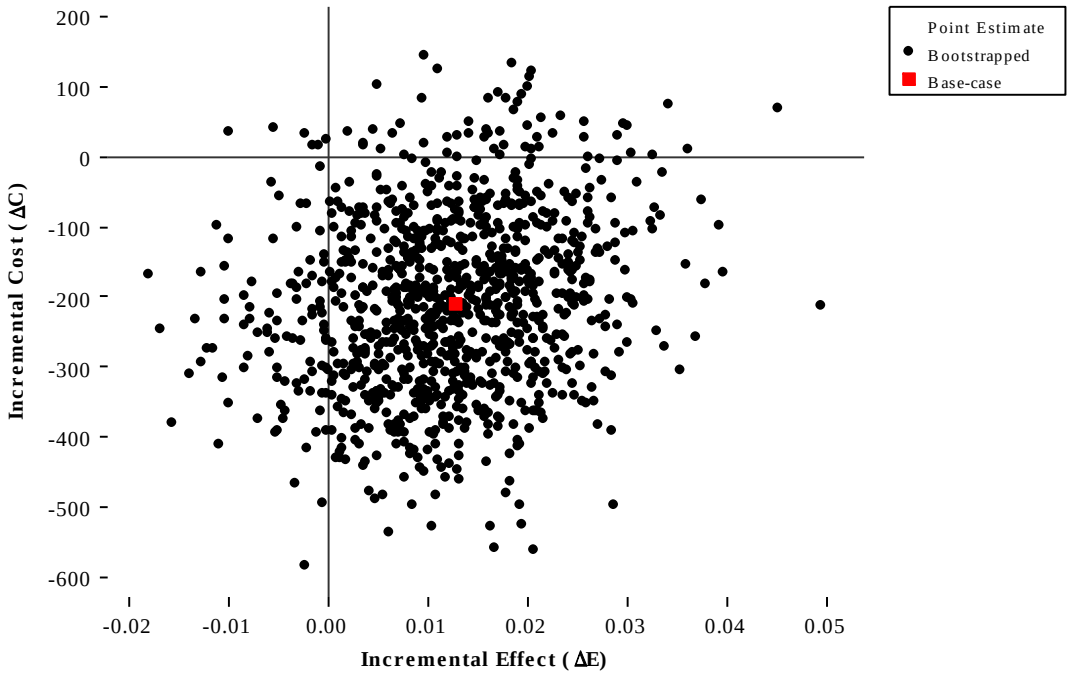


Figure 5.3: Scatter plot of the 1,000 bootstrap pairs presented on the cost-effectiveness plane of bupropion vs. varenicline.

Table 5.10: Quadrant probabilities of bupropion vs. varenicline.

Quadrant	Probability
NE (bupropion is cost-effective)	0.055
NW (varenicline dominates)	0.006
SW (bupropion is questionable)	0.090
SE (bupropion dominates)	0.849

5.3.2 Sensitivity analysis

Multiple one-way sensitivity analyses were performed on the lifetime ICER to assess the robustness of the simulation when key input parameters are varied. These parameters include all health state utility values of the smoking-related diseases, discount rate on costs and QALYs, abstinence rates, and treatment costs. Holding other variables constant, we varied the group of recidivism rates at a low and high value (refer to table 4.8) in a multi-way sensitivity analysis. Finally, sensitivity analysis is restricted to subsets of the base-case population (e.g. assessing a group of all females).

First, health state utilities were altered one at a time at the low value and high value presented in Table 4.9. The discount rate (on both costs and QALYs) was adjusted to 1% and 5% [Weinstein et al., 1996]. Results show that our model is strong in that none of the incremental costs and incremental effects resulting from multiple univariate sensitivity analyses on health state utilities differed from our base-case estimate. Base-case ICER for bupropion versus varenicline (-$16452.10 per QALY saved) was sensitive to the discount rate at 1% and 5% with a percent change to the base-case ICER of 29% and -30%, respectively.

Next, we evaluated the efficacy rates (percent who stop smoking after the first year) for bupropion and varenicline over the range obtained from our meta-analysis (Table 4.2; Bupropion: 15%-30%, Varenicline: 18%-25%) using a step size of 1%. Figure 5.5 shows the impact of the abstinence rate on cost per QALY for two treatments, bupropion and varenicline. Then, we examined implications of treatment cost of bupropion and varenicline when the price of treatment is $0 to $800 with step size $100. Figure 5.6 shows the impact of varying the cost of bupropion and varenilcline. We observe in Figure 5.5 that if the treatment efficacy of bupropion and varenicline are equal, the cost per effect ($/QALY) is less for bupropion. Figure 5.6 shows that if cost treatment for bupopion and varenicline are the same, cost per effect ($/QALY) is always less for bupropion. Treatment efficacy is higher for bupropion in reference to varenicline, therefore the QALY value (denominator) is always higher for bupriopion and the cost per effect ratio is smaller. Therefore, bupropion is not only less expensive, but also more effective.

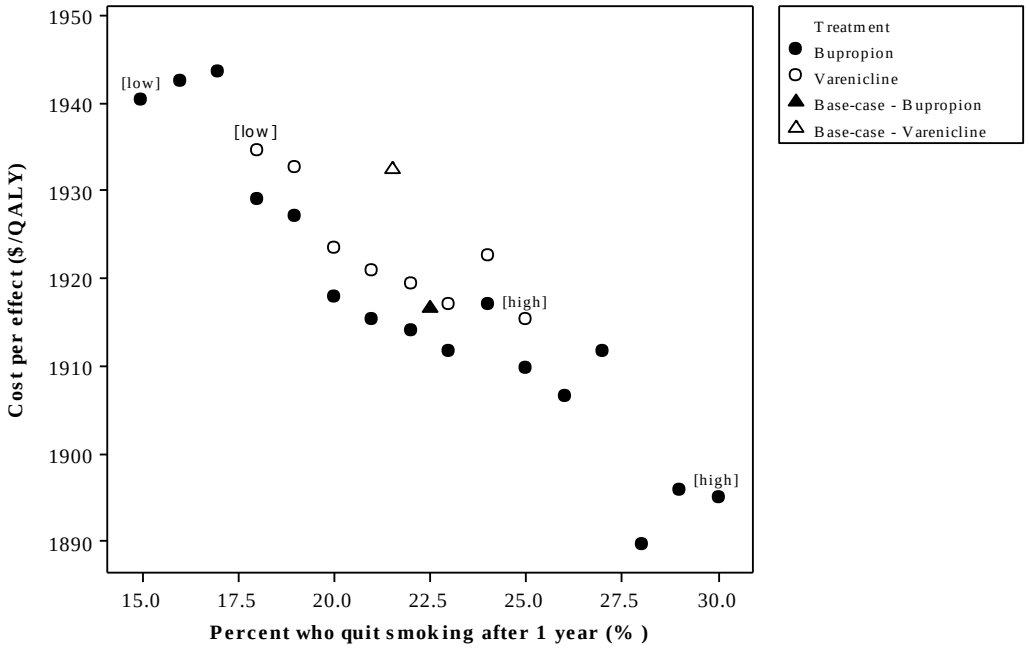


Figure 5.4: One-way sensitivity analysis of treatment efficacy of bupropion and varenicline.

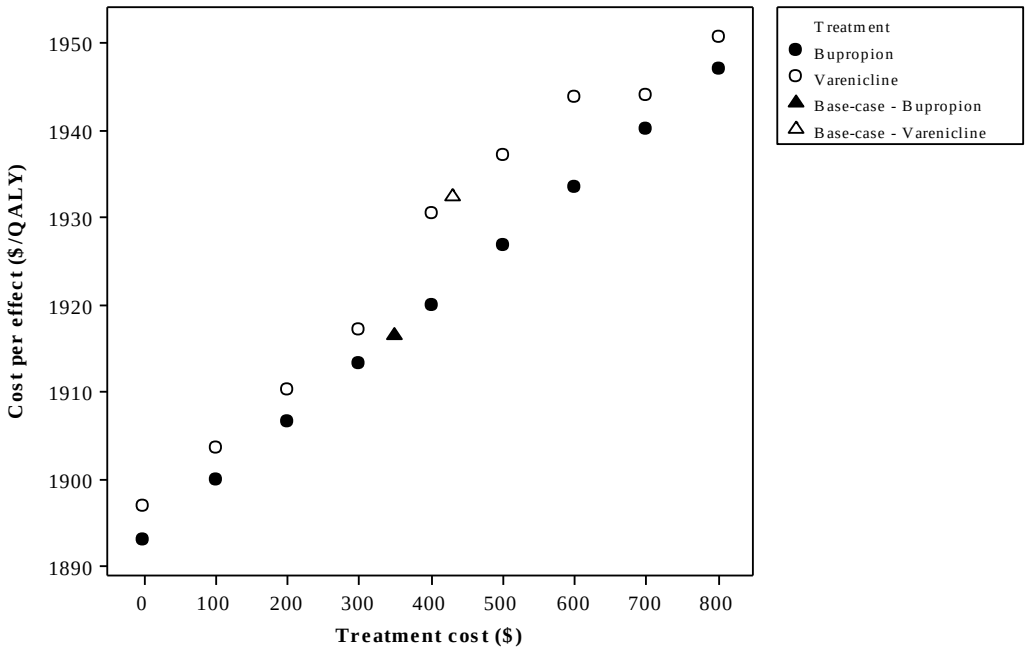


Figure 5.5: One-way sensitivity of treatment cost of bupropion and varenicline.

Multi-way sensitivity analysis of recidivism rates was performed at low and high values (Table 4.8). Refer to Table 5.11 for a summary of these results. Results of the multi-way sensitivity analysis at low recidivism rates place the ICER in the NE (cost-effective) quadrant. When recidivism is high, we find that the incremental cost of bupropion compared to varenicline is -$317.86 compared to -$209.44 in the base-case. Incremental effect is much smaller (0.0007 QALYs) than the base-case estimate (0.01 QALYs).

Table 5.11: Multi-way sensitivity analysis of recidivism rates.

Recidivism rate	Incremental Cost (ΔC)	Incremental Effect (ΔE)	ICER (ΔC/ΔE)
Low value	$31.45	0.0228	$1,379.43
High value	-$317.86	0.0007	-$454,083.14

ICERs of bupropion in reference to varenicline of an all female and all male population are evaluated. Very different results are estimated for an all female cohort versus an all male cohort (Table 5.12). For an all female population, bupropion is less costly (-$68.33) and slightly more effective (0.0203 QALYs) with an ICER of -$3371. When the same simulation is run for an all male population, money is saved (-$92.77), however health benefits are also lost (-0.0026). The ICER for an all male cohort is $35,914 and a cost-reducing tradeoff must be made in choosing bupropion.

Last, costs and effects of a young cohort of all 18-year olds and individuals all 50 years of age at baseline (older age group) are estimated. Among both age groups cost is saved while health benefits are gained (Table 5.12). Bupropion is dominant in comparison to varenicline in both cases with ICERs of -$49,158 and -14,852 for individuals 18 years of age and 50 years of age, respectively.

Table 5.12: Sensitivity analysis by subset of the base-case population.

Parameter	Incremental Cost (ΔC)	Incremental Effect (ΔE)	ICER (ΔC/ΔE)
Sex			
Female	-$68.33	0.0203	-$3,371.00
Male	-$92.77	-0.0026	$35,914.44
Age			
18 years of age	-$169.20	0.0034	-$49,158.22
50 years of age	-$207.01	0.0139	-$14,852.23

5.4 Discussion

In this study, we used estimates of cost and QALY from the simulation presented in Chapter 4 of smokers attempting pharmacologic smoking cessation treatment (NRT, bupropion, and varenicline), non-pharmacologic-assisted cessation, and no treatment. Cost effectiveness was estimated using the incremental cost-effectiveness ratio (ICER) statistic. We first assessed the cost-effectiveness of the alternative treatment strategies by comparing all treatment options to no treatment. Next a stepwise comparison of the treatments was performed where decisions must be made between choosing bupropion and varenicline. We found burpropion to be the dominant treatment for smoking cessation.

Probabilistic sensitivity analysis confirmed the base-case findings for bupropion versus varenicline and nonparametric bootstrapping showed that bupropion was dominant with probability 84.9%. Our simulation was robust to changes in health state utility values in our one-way sensitivity analysis. For all female versus all male populations cost-effectiveness results differed greatly. In fact, the only case where bupropion was cost-reducing resulted when the simulation was run for an all male population. This implies that limited health care dollars are better off helping females versus males.

Our results differ from previous cost-effectiveness studies of smoking cessation therapies where varenicline was found to dominant in comparison to bupropion [Howard et al., 2008]. One major difference between these studies and our research is that there efficacy rates rely on a single clinical efficacy study. We obtain measures through a meta-analysis of studies that investigate the efficacy of smoking cessation strategies. The midpoint of the range is used as our base-case estimate of treatment efficacy. We perform sensitivity analysis over the range of efficacy rates for bupropion and varenicline. In future research, we will examine how the results change when the sample-size-weighted-average for each treatment efficacy rate is applied.

In conclusion, we have shown that using discrete-event simulation is a powerful tool with which we can examine comparative effectiveness of smoking cessation strategies in a diverse patient population. We have further demonstrated that the long-term benefits of smoking cessation at a younger age significantly accrue over a patient's lifetime. As such, it is critical for policymakers and insurers to encourage and consider providing incentives for smoking cessation as early as possible and for clinicians and patients to engage in shared decision making about which treatment strategy would be best for the patient in terms of long-term abstinence, overall resources invested, and cumulative health risks avoided over time.

CHAPTER SIX

CONTRIBUTIONS

Chapter 2 introduced a discrete-event simulation (DES) model to quantify the public health impact of the maternal obese and diabetic intrauterine environment on obesity and diabetes prevalence in subsequent generations. The model was verified using longitudinal data and we provided examples of the types of predictions our model can generate. This dissertation is the first to apply discrete-event simulation to estimate the impact of maternal obesity and diabetes on obesity and diabetes prevalence.

In Chapter 3 we used a mixed-methods approach, incorporating both statistical methods and discrete-event simulation, to examine trends in weight-gain over time among white and black women of child-bearing age in the US from 1980 to 2008 using United States Census projections and National Health and Nutrition Examination Survey (NHANES) data. We addressed the question of how to update changes in clinical characteristics over time using data obtained through a cross-sectional study design. We responded by developing a method to gain insights into the processes of change of attributes using bootstrapping principles and mixed-effects regression models. This was used to determine the change in BMI due to age in the simulation model allowing us to examine trends in average BMI over generations at the population-level. Our results are different than what is currently available in the literature in that our simulation projections are based on the population prior to the onset of the obesity epidemic.

In Chapter 4 we constructed the first DES model to estimate the cost-effectiveness of different smoking cessation strategies available to smokers in the US population.

While previous models for comparing therapeutic smoking cessation options use efficacy of treatment derived from a single study, we contribute to the literature by combining results of different studies to model treatment efficacy. We described the data and model assumptions and verification.

Chapter 5 provided results of the base-case model to evaluate smoking cessation treatments. A sensitivity analysis was performed to understand the comparative effectiveness and intrinsic value of four alternative smoking cessation strategies that can improve clinical and patient decision-making and subsequent health and economic outcomes at the population level. We provided examples of different analyses that can be done using results of our model.

This dissertation contributes to the area of industrial engineering in healthcare by providing two US population-level DES models to inform health policy decisions. US population-level data structures require special handling and assumptions due to the availability of medical data and the nature of the study design. The key element is to be able to link mathematical models with the available data. Input measures are important because the models are only as strong as the data and assumptions upon which they are built. Data taken from multiple sources (United States Census, National Health and Nutrition Examination Survey (NHANES), Centers for Disease Control and Prevention (CDC)/National Center for Health Statistics (NCHS), and the literature) is not obtainable in the desired format, and there is not one method for managing the data. Preparing a valid representation of the data is crucial. We illustrate various methods for extracting information from the data to make population-level predictions. Specifically,

In Chapter 2, data from a longitudinal study was utilized to update attributes (i.e. BMI level, diabetes status) of individuals in the simulation. Extracting necessary information from this data involved different types of methods.

- Using the mean and variance of the difference in average BMI (kg/m^2) at baseline and follow-up of the longitudinal study, annual changes to BMI were computed. Updates to BMI values per year were approximated by a normal distribution.
- Baseline estimates of diabetes prevalence taken from the longitudinal study and information on increased likelihood of diabetes in obese versus not obese individuals were used to derive baseline estimates of diabetes adjusted by obesity status.
- Annual probabilities of developing diabetes over time based on obesity status were deduced using (a) baseline prevalence of obesity and (b) diabetes incidence rates follow-up from the longitudinal study, and (c) the increased risk of diabetes known to obese versus non-obese individuals. This was accomplished by applying the cumulative geometric distribution.
- Validating BMI and diabetes characteristics over a short time period (i.e. 8 years) allowed us to make projections of diabetes prevalence accounting for obese individuals having a different/higher risk of diabetes than non-obese individuals.
- Furthermore, incorporating births into our model and keeping record of an individual's mother's BMI and diabetes characteristics, allowed us to make projections of diabetes prevalence over time when children of obese and/or

diabetic women had an increased risk of diabetes from children not exposed to obesity and/or diabetes during pregnancy.

In Chapter 3, cross-sectional data of the National Health and Nutrition Examination Survey (NHANES) provided US population-level information on BMI.

- We developed a method for extracting information from the cross-sectional data set which allowed us to make US population-level estimates of change in attributes (i.e. BMI) over time. This technique combined bootstrap statistical methods and mixed-effects regression models. We described how we handled cases of missing or insufficient data. This method allowed us to characterize the change in weight-gain of white and black women of childbearing age in the US prior to the onset of the obesity epidemic.
- A method for validating our baseline (i.e. 1980) unadjusted average BMI projections was presented.
- Unadjusted projections of average BMI over a 28-year time period were made. These projections of average BMI between 1980-2008 are fundamentally different from what is currently available in the literature in that we make projections of the population before the obesity epidemic took place. Previous studies formulate projections on trends of diseases based on population data in 2000, at which time the obesity (and also diabetes) epidemics had already initiated.
- Estimates of baseline BMI and change in BMI over time from the statistical analysis provided population-level estimates for the simulation model (presented

in Chapter 2). We proposed two methods for validating that individuals in the simulation take on age appropriate characteristics (according to baseline cross-sectional values): (1) validation of the Census age distribution, and (2) validation of average BMI. We demonstrated these methods for projections of white women of childbearing age.

In Chapter 4, information was extracted from data of multiple sources, presenting in many different formats. Various statistical methods were applied to represent the data.

- Disease incidence (for lung cancer, stroke, and CHD) required conversions from rates of disease per annum to annual probabilities. For example, given the case rate of stroke over a time period, we computed the probability of an individual having a stroke in any given year. The cumulative exponential distribution function was used in this computation.
- In other cases (number of COPD exacerbations) where more than one occurrence was possible in a year the binomial probability distribution was used to estimate annual incidence.
- Similarly, the number of exacerbations (out of the total annual COPD exacerbation) that were major exacerbations was determined using the binomial distribution formula.

In Chapter 5, we apply statistical methods to deduce information from the output measures of the simulation (presented in Chapter 4).

- We introduced the incremental cost-effective ratio (ICER) as a statistic for quantifying cost-effectiveness of one treatment relative to another.

- Two different methods for comparing costs and health effects (QALYs) of the alternative smoking cessation strategies using the ICER were provided. First, we made separate comparisons of each treatment option (NRT, bupropion, varenicline, and non-pharmacologic-assisted) to the no treatment control group to quantify incremental cost per incremental health effect (QALY). Next, the four treatment strategies were compared to each other in a successive stepwise manner to gain information about how treatments perform in comparison to each other.
- Like any statistical measure the ICER point estimate is associated with some degree of uncertainty. Non-parametric bootstrap procedures allowed us to estimate an uncertainty range for the ICER of two treatment options (bupropion versus varenicline). We computed the 95% confidence interval for the bootstrapped ICERs using the percentile method. Information about the uncertainty of cost-effectiveness of a treatment option (bupropion) from the base-case estimations was provided.
- Bootstrap estimates were analyzed using the cost-effectiveness plane method which allowed us to address questions about the probability of cost-effectiveness when comparing two treatment options (bupropion in reference to varenicline). While the estimates resulting from the two models are topic-specific, many of the modules created for these studies are generic and can easily be transferred to other disease models. It is believed that these two models will aid decision makers in recognizing the impact that preventative-care initiatives will have, and to evaluate possible alternatives.

APPENDICES

Appendix A

Conditional Probability of Diabetes

Diabetes incidence rates taken from the SAHS study are provided in Table A.1.

Table A.1: Incident diabetes rates over the 7.5 year period.

Age cohort	Incidence
< 30	1.59
30 – 34	3.41
35 – 39	5.10
40 – 44	4.90

Prevalence of obesity in the SAHS population at baseline was 13.7 percent. Obese individuals are assumed to be 10.723 times more likely to develop diabetes than individuals who were not obese. The calculations are the following:

$$P(\text{diabetes}) = P(\text{diabetes}|\text{obese})P(\text{obese}) + P(\text{diabetes}|\text{not obese})P(\text{not obese})$$

$$P(\text{diabetes}) = P(\text{diabetes}|\text{obese})P(\text{obese}) + P(\text{diabetes}|\text{not obese})(1-P(\text{obese}))$$

We know that: $P(\text{diabetes}|\text{obese}) = (10.723)[P(\text{diabetes}|\text{not obese})]$

$$P(\text{diabetes}) = (10.723)(P(\text{diabetes}|\text{not obese}))P(\text{obese}) + P(\text{diabetes}|\text{not obese})(1-P(\text{obese}))$$

For example, the derivation for the probability of diabetes for individuals less than 30 years of age given obesity status is provided.

$$0.0159 = (10.723)(P(\text{diabetes}|\text{not obese}))(0.137) + P(\text{diabetes}|\text{not obese})(1-0.137)$$

Rearrange the terms:

$$0.0159 = P(\text{diabetes}|\text{not obese})((10.723)(0.137) + (1-0.137))$$

$$P(\text{diabetes}|\text{not obese}) = 0.0068$$

$$P(\text{diabetes}|\text{obese}) = (10.723)(0.0068) = 0.0729$$

This is the conditional probability of diabetes over 7.5 (round to 8) years. We want the annual probability of developing diabetes given obesity status. We use the cumulative distribution function (CDF) of a geometric random variable to determine the probability of developing diabetes given obesity status in one year.

The CDF of a geometric random variable X is:

$F(x) = P(X \leq x) = 1 - (1\text{-}p)^k \qquad k = 1, 2, \ldots$

where p is the probability of succeeding on one try.

If we make independent attempts over and over, the geometric random variable counts the number of attempts needed to obtain the first success. The CDF can be interpreted as the probability of succeeding within k attempts.

Referring to the example, the probability of diabetes mellitus given obesity status for individuals less than 30 years of age is the following:

$P(\text{diabetes}|\text{non-obese}) = 1 - (1 - 0.0068)^{(1/7+1)} = 0.0009$

$P(\text{diabetes}|\text{obese}) = 1 - (1 - 0.0731)^{(1/7+1)} = 0.0094$

Note that a potential drawback of using the geometric distribution is that it satisfies the *memoryless property*.

Appendix B

DES Distribution Input Parameters and Sensitivity Analysis Results

Table B.1: Distribution parameters for unadjusted BMI (kg/m^2) projections and baseline BMI in the simulation model.

	White Women		Black Women	
Age	Mean	SD	Mean	SD
15	21.5433	3.4282	22.4345	4.7431
16	21.7085	3.8278	22.7072	4.8048
17	21.9470	4.4140	22.9800	5.5909
18	22.1024	3.6399	23.2527	3.9708
19	22.2578	3.9704	23.5254	6.4735
20	22.4132	4.1106	23.7982	4.8807
21	22.5686	3.7814	24.0709	5.6945
22	22.7081	4.0617	24.3437	7.6422
23	22.8623	4.8443	24.6164	4.6313
24	23.0097	5.4161	24.8891	4.8132
25	23.1584	4.6566	25.1619	5.8713
26	23.3071	3.9366	25.4346	5.1306
27	23.4558	5.1977	25.7074	6.6887
28	23.6045	5.5674	26.4814	4.9856
29	23.7392	5.3541	26.6371	7.2702
30	23.8911	5.3520	26.7927	7.8335
31	24.0429	5.4873	26.9484	7.2204
32	24.1591	6.2145	27.1041	6.4911
33	24.2872	5.6085	27.2598	6.3269
34	24.4154	4.8513	27.4154	7.1926
35	24.5435	5.7674	27.5711	6.0806
36	24.6716	4.7902	27.7268	7.4565
37	24.7398	5.3306	27.8825	6.9395
38	24.7448	5.6666	28.0382	6.4886
39	24.8569	5.5871	28.1938	7.2594
40	24.9690	5.7611	28.3495	5.2604
41	25.0811	5.0280	28.5052	7.9332
42	25.1932	6.0894	28.6609	5.9704
43	25.3384	5.7728	28.8165	6.5386
44	25.4582	5.8072	28.9722	5.9604

Table B.2: Distribution parameters for BMI (kg/m^2) updates (annual change in BMI) in the simulation model.

	White Women		Black Women	
Age	Mean	SD	Mean	SD
15	0.1652	0.6857	0.2727	0.7316
16	0.1652	0.6857	0.2727	0.7316
17	0.1554	0.4935	0.2727	0.7316
18	0.1554	0.4935	0.2727	0.7316
19	0.1554	0.4935	0.2727	0.7316
20	0.1554	0.4935	0.2727	0.7316
21	0.1554	0.4935	0.2727	0.7316
22	0.1542	0.3998	0.2727	0.7316
23	0.1542	0.3998	0.2727	0.7316
24	0.1487	0.4921	0.2727	0.7316
25	0.1487	0.4921	0.2727	0.7316
26	0.1487	0.4921	0.2727	0.7316
27	0.1487	0.4921	0.2727	0.7316
28	0.1487	0.4921	0.1557	0.6049
29	0.1518	0.6816	0.1557	0.6049
30	0.1518	0.6816	0.1557	0.6049
31	0.1518	0.6816	0.1557	0.6049
32	0.1281	0.5886	0.1557	0.6049
33	0.1281	0.5886	0.1557	0.6049
34	0.1281	0.5886	0.1557	0.6049
35	0.1281	0.5886	0.1557	0.6049
36	0.1281	0.5886	0.1557	0.6049
37	0.1253	0.5283	0.1557	0.6049
38	0.1121	0.7154	0.1557	0.6049
39	0.1121	0.7154	0.1557	0.6049
40	0.1121	0.7154	0.1557	0.6049
41	0.1121	0.7154	0.1557	0.6049
42	0.1121	0.7154	0.1557	0.6049
43	0.1198	1.0612	0.1557	0.6049
44	0.1198	1.0612	0.1557	0.6049

Table B.3: Sensitivity analysis baseline BMI (kg/m^2) for age 32 to 37 years.

	Scenario 1		Scenario 2		Scenario 3	
Age	Mean	SD	Mean	SD	Mean	SD
32	24.1591	0.3381	24.1235	0.3836	24.1947	0.5568
33	24.2872	0.3381	24.2279	0.3836	24.3466	0.5568
34	24.4154	0.3381	24.3323	0.3836	24.4984	0.5568
35	24.5435	0.3381	24.4368	0.3836	24.6502	0.5568
36	24.6716	0.3381	24.5412	0.3836	24.8021	0.5568
37	24.7398	0.2573	24.6327	0.2674	24.9539	0.5568

	Scenario 4		Scenario 5	
Age	Mean	SD	Mean	SD
32	24.1413	0.2556	24.1769	0.3257
33	24.2576	0.2556	24.3169	0.3257
34	24.3739	0.2556	24.4569	0.3257
35	24.4901	0.2556	24.5969	0.3257
36	24.6064	0.2556	24.7369	0.3257
37	24.6862	0.1856	24.8468	0.3067

Table B.4: Sensitivity analysis updates to BMI (kg/m^2) for age 32 to 37 years.

	Scenario 1		Scenario 2		Scenario 3	
Age	Mean	SD	Mean	SD	Mean	SD
32	0.1281	0.5886	0.1044	0.9597	0.1518	0.6816
33	0.1281	0.5886	0.1044	0.9597	0.1518	0.6816
34	0.1281	0.5886	0.1044	0.9597	0.1518	0.6816
35	0.1281	0.5886	0.1044	0.9597	0.1518	0.6816
36	0.1281	0.5886	0.1044	0.9597	0.1518	0.6816
37	0.1253	0.5283	0.1121	0.7154	0.1518	0.6816

	Scenario 4		Scenario 5	
Age	Mean	SD	Mean	SD
32	0.1163	0.5629	0.1400	0.4503
33	0.1163	0.5629	0.1400	0.4503
34	0.1163	0.5629	0.1400	0.4503
35	0.1163	0.5629	0.1400	0.4503
36	0.1163	0.5629	0.1400	0.4503
37	0.1187	0.4447	0.1386	0.4312

Table B.5: Sensitivity analysis results for average BMI (kg/m^2) by age cohort and year.

Year	Age Cohort	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
	15 - 19	21.93	21.93	21.93	21.93	21.93
	20 - 24	22.71	22.71	22.71	22.71	22.71
	25 - 29	23.44	23.44	23.44	23.44	23.44
1980	30 - 34	24.15	24.11	24.18	24.13	24.16
	35 - 39	24.70	24.63	24.80	24.67	24.75
	40 - 44	25.21	25.21	25.21	25.21	25.21
	15 - 44	23.50	23.48	23.52	23.49	23.51
	15 - 19	22.42	22.42	22.42	22.42	22.42
	20 - 24	23.20	23.20	23.20	23.20	23.20
	25 - 29	23.47	23.47	23.47	23.47	23.47
1990	30 - 34	24.21	24.19	24.22	24.20	24.21
	35 - 39	24.84	24.74	24.96	24.79	24.90
	40 - 44	25.38	25.23	25.55	25.31	25.47
	15 - 44	23.97	23.92	24.02	23.94	23.99
	15 - 19	22.40	22.40	22.40	22.40	22.40
	20 - 24	23.17	23.17	23.17	23.17	23.17
	25 - 29	23.97	23.97	23.97	23.97	23.97
2000	30 - 34	24.69	24.68	24.71	24.69	24.70
	35 - 39	24.83	24.71	24.94	24.77	24.89
	40 - 44	25.43	25.30	25.58	25.37	25.51
	15 - 44	24.20	24.15	24.25	24.18	24.23
	15 - 19	22.41	22.41	22.41	22.41	22.41
	20 - 24	23.16	23.16	23.16	23.16	23.16
	25 - 29	23.93	23.93	23.93	23.93	23.93
2008	30 - 34	24.66	24.65	24.68	24.65	24.67
	35 - 39	25.37	25.27	25.49	25.31	25.42
	40 - 44	25.72	25.59	25.87	25.65	25.79
	15 - 44	24.28	24.24	24.33	24.26	24.30

Appendix C

Sample SAS Code

```
Libname nh1 "M\BMI by Birth Year";
data allw;
  set nh1.nh0123;
  where race='W';
  newid=left(trim(id))||left(trim(seqn));
  run;

/*numbers in dataset name correspond to birth years*/
/*age is centered to that the intercept is the lowest age
of the category*/
data w5559;
  set allw;
  where yob>='1955' and yob<'1959' and age>=15 and age<=23;
  agec=age-15;
  run;
*******************************************************
*regression example 5559 birth year -- 1955 and 1959*
*******************************************************
;
%let itnum=100;
%let sampsize=500;
*SRS means Simple Random Sampling;
proc surveyselect data=w5559 method=SRS n=&sampsize
reps=&itnum seed=40070 out=r5559;
run;
proc sort data=r5559; by replicate; run;
*** Full: With Random and method=REML ***  ;
**NOTE: this includes the main effect of agecat ;
ods graphics on;
proc mixed data=r5559 method=REML noclprint=2 empirical;
  class newid;
  model bmi=agec/cl solution covb ddfm=res
outpm=output5559;
  by replicate ;
  random intercept/ subject=newid;
  ods output SolutionF=betaparms;
run;
ods select fitstatistics;
proc reg data=output5559;
```

```
     model bmi=pred;
*    by replicate;
run;
quit;
ods graphics off;
proc contents data=betaparms; run;
*NOTE: First open the output data file betaparms_mix and
see if the effect columns correspond to what I have used
below;
* summary of parameter estimates*********;
data nh1.betaparms5559 (keep=replicate inter vinter tvinter
dfinter pvinter b1 vb1 tvb1 dfb1 pvb1);
retain inter tvinter dfinter b1 vb1 tvb1 dfb1 pvb1;
set betaparms;
by replicate;
if effect eq 'agec' then do;
     b1 = estimate; vb1=StdErr; tvb1=tvalue; pvb1=Probt;
dfb1=df;  end;
if effect eq 'Intercept' then do;
    inter=estimate; vinter=StdErr; tvinter=tvalue;
pvinter=probt; dfinter=df; end;
 if last.replicate then do;
    output;
  end;
  else delete;
run;
proc means data=nh1.betaparms5559;
  var b1 inter;
  run;
```

Appendix D

Computations for the Smoking Cessation DES Inputs

Table D.1: Age distribution of smokers.

Age	Male			Female		
	Number in the US	Number of Smokers	P(age|smoke)	Number in the US	Number of Smokers	P(age|smoke)
18	2,282,042	579,639	0.024	2,162,940	439,077	0.022
19	2,224,534	565,032	0.023	2,112,751	428,888	0.021
20	2,188,236	555,812	0.023	2,086,884	423,637	0.021
21	2,155,654	547,536	0.022	2,062,647	418,717	0.021
22	2,162,386	549,246	0.022	2,068,296	419,864	0.021
23	2,154,443	547,229	0.022	2,060,702	418,323	0.021
24	2,134,690	542,211	0.022	2,039,250	413,968	0.021
25	2,159,241	548,447	0.022	2,058,541	417,884	0.021
26	2,157,349	547,967	0.022	2,083,273	422,904	0.021
27	2,174,226	552,253	0.023	2,125,979	431,574	0.021
28	2,155,475	547,491	0.022	2,106,378	427,595	0.021
29	2,070,323	525,862	0.021	2,019,348	409,928	0.020
30	2,016,724	512,248	0.021	1,968,179	399,540	0.020
31	1,974,327	501,479	0.020	1,930,843	391,961	0.019
32	1,945,812	494,236	0.020	1,910,458	387,823	0.019
33	1,974,872	501,617	0.020	1,939,809	393,781	0.020
34	1,926,499	489,331	0.020	1,905,546	386,826	0.019
35	1,962,294	498,423	0.020	1,949,570	395,763	0.020
36	2,046,138	519,719	0.021	2,037,513	413,615	0.021
37	2,154,037	547,125	0.022	2,154,393	437,342	0.022
38	2,205,790	560,271	0.023	2,186,689	443,898	0.022
39	2,091,135	531,148	0.022	2,088,056	423,875	0.021
40	2,039,111	517,934	0.021	2,046,859	415,512	0.021
41	2,037,007	517,400	0.021	2,056,617	417,493	0.021
42	2,094,378	531,972	0.022	2,114,992	429,343	0.021
43	2,229,898	566,394	0.023	2,249,584	456,666	0.023
44	2,251,737	571,941	0.023	2,294,963	465,877	0.023
45	2,243,116	551,807	0.023	2,294,799	470,434	0.023
46	2,250,985	553,742	0.023	2,303,860	472,291	0.023
47	2,263,325	556,778	0.023	2,329,012	477,447	0.024
48	2,309,119	568,043	0.023	2,359,664	483,731	0.024
49	2,215,240	544,949	0.022	2,284,705	468,365	0.023

50	2,206,404	542,775	0.022	2,280,669	467,537	0.023
51	2,151,695	529,317	0.022	2,237,945	458,779	0.023
52	2,088,599	513,795	0.021	2,180,369	446,976	0.022
53	2,085,043	512,921	0.021	2,169,687	444,786	0.022
54	1,979,014	486,837	0.020	2,082,836	426,981	0.021
55	1,912,892	470,571	0.019	2,024,202	414,961	0.021
56	1,847,781	454,554	0.019	1,959,188	401,634	0.020
57	1,774,943	436,636	0.018	1,892,368	387,935	0.019
58	1,769,416	435,276	0.018	1,886,571	386,747	0.019
59	1,693,399	416,576	0.017	1,820,005	373,101	0.019
60	1,692,209	416,283	0.017	1,823,349	373,787	0.019
61	1,665,640	409,747	0.017	1,800,563	369,115	0.018
62	1,356,184	333,621	0.014	1,481,887	303,787	0.015
63	1,271,328	312,747	0.013	1,399,272	286,851	0.014
64	1,254,678	308,651	0.013	1,394,030	285,776	0.014
65	1,244,631	131,931	0.005	1,396,116	114,482	0.006
66	1,123,417	119,082	0.005	1,274,736	104,528	0.005
67	1,021,173	108,244	0.004	1,172,433	96,140	0.005
68	971,772	103,008	0.004	1,124,069	92,174	0.005
69	919,903	97,510	0.004	1,073,613	88,036	0.004
70	877,737	93,040	0.004	1,036,312	84,978	0.004

Table D.2: Probability tables for COPD exacerbations

COPD Level	x	f(x,p,n)
Mild[a]		
	0	0.5558
	1	0.3516
	2	0.0834
	3	0.0088
	4	0.0003
Moderate[b]		
	0	0.4606
	1	0.3940
	2	0.1264
	3	0.0180
	4	0.0010
Severe[c]		
	0	0.4251
	1	0.4054
	2	0.1450
	3	0.0230
	4	0.0014

a. Exacerbation frequency (per annum) = 0.79
b. Exacerbation frequency (per annum) = 1.22
c. Exacerbation frequency (per annum) = 1.47

Table D.3: Probability tables for minor COPD exacerbation

Mild COPD[a]			Moderate COPD[b]			Severe COPD[c]		
n	x	f(x,p,n)	n	x	f(x,p,n)	n	x	f(x,p,n)
4			4			4		
	0	0.0000		0	0.0000		0	0.0001
	1	0.0008		1	0.0013		1	0.0036
	2	0.0191		2	0.0254		2	0.0486
	3	0.1993		3	0.2252		3	0.2916
	4	0.7807		4	0.7481		4	0.6561
3			3			3		
	0	0.0002		0	0.0003		0	0.0010
	1	0.0102		1	0.0137		1	0.0270
	2	0.1590		2	0.1816		2	0.2430
	3	0.8306		3	0.8044		3	0.7290
2			2			2		
	0	0.0036		0	0.0049		0	0.0100
	1	0.1128		1	0.1302		1	0.1800
	2	0.8836		2	0.8649		2	0.8100
1			1			1		
	0	0.0600		0	0.0700		0	0.1000
	1	0.9400		1	0.9300		1	0.9000

a. P(minor exacerbation | COPD exacerbation event) = 0.94
b. P(minor exacerbation | COPD exacerbation event) = 0.93
c. P(minor exacerbation | COPD exacerbation event) = 0.90

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