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AN ANALYSIS OF THE LONG-TERM COST-EFFECTIVENESS OF INTENSIVE LIFESTYLE INTERVENTION FOR TYPE 2 DIABETES MELLITUS PREVENTION

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AN ANALYSIS OF THE LONG-TERM COST-EFFECTIVENESS OF INTENSIVE LIFESTYLE INTERVENTION FOR TYPE 2 DIABETES MELLITUS PREVENTION

by

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Dissertation

Presented to the Faculty of the Graduate School of

the University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas at Austin

May 2005

Dedication

This work is dedicated to the following people:

My beloved parents, George and Marcellyn Novak,
who always told me I could do anything I wanted to,
and provided me with every means to do so.

My beloved husband, William Nemeth, M.D.
Without his support, I would have been unable to complete this task.

My beloved daughter, Katherine Nemeth.
Thank you for being an example to me.

Acknowledgements

I would like to first acknowledge the members of my dissertation committee. Their support through this project, as well as throughout my entire tenure at the University of Texas is forever appreciated. In particular, I would like to thank Kenneth Lawson, my advisor. His guidance has made me both a better researcher and a better writer on every project we have embarked on together. I look forward to all of our future collaboration. I wish to thank James Wilson and Robert Salzman for allowing me to be a Teaching Assistant, and ultimately an Assistant Instructor for the Pharmacotherapy Laboratories. The experience I had there enhanced my clinical training, and allowed me to be able to feel comfortable enough to have the knowledge to write about metabolic disease.

I wish to thank all of my family: my parents, George and Marcellyn Novak; my husband, William Nemeth; my daughter, Katherine Nemeth; and my brother and sisters, Kelly Novak, Laurie Morian, and Jennifer Novak. They have provided incredible love and emotional support. In addition I would like to thank several of my friends that have walked every step of graduate school with me. They include Nina Beucler, Judy Haralson, Ann Hurt, Melissa Hahn, and Cindy Stone. I would not have been able to complete this adventure without them.

Thank you all from the bottom of my heart!

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Publication No. _____

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The University of Texas at Austin, 2005

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The purpose of this dissertation was to assess the long-term cost-effectiveness of type 2 diabetes mellitus prevention from a state of impaired glucose tolerance with the use of intensive lifestyle intervention. The analysis was primarily based on findings by the Diabetes Prevention Program (DPP). Additional goals of the analysis were: (1) to examine the effect of obesity on the results; and (2) to examine the effect of the study design of the DPP, in particular the healthcare exclusion criteria, on the analysis.

Two basic Markov models were designed for the dissertation. The first was designed to closely approximate the Diabetes Prevention Program study design and results, and the second was designed to attempt to approximate a more generalized U.S. population. These two basic models were then divided into two subcategories: a subcat-

egory that with adjustments intended to reflect the effects of obesity in the analysis; and a subcategory with no adjustments for obesity. This subdivision was then further divided by duration of effect of the three-year intervention: a three-year duration of effect and a lifetime duration.

The results showed, in all models examined, the lifestyle intervention arm of the analysis dominated the placebo arm. The incremental cost-effectiveness ratios derived for the models exhibited a wide range (-$551/LY to -$19,496/LY). The variables that appeared to most influence this wide range of ratios included the following: (1) overall direct medical costs; (2) effects of obesity on mortality rates; (3) effect of obesity on control cost of illness; and (4) duration of intervention. In addition, the maximum acceptable cost of intervention for any one of the models also depended on these variables.

Overall, diabetes prevention from the state of impaired glucose tolerance appears to dominate non-intervention. However, a large range of values were derived for both incremental cost-effectiveness ratios and maximum acceptable cost of intervention. These values appear to depend on cost inputs as well as obesity-adjustments to the models used for analysis. Researchers and policy makers should consider studying these possible influences in interpreting the study findings, conducting future research, or making decisions regarding implementation of interventions.

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LIST OF ABBREVIATIONS

ADA	American Diabetes Association
ANCOVA	Analysis of Covariance
AR	Attributable Risk
BLSA	Baltimore Longitudinal Study of Aging
BMI	Body-Mass Index
BRFSS	Behavioral Risk Factor Surveillance Survey
CBA	Cost-Benefit Analysis
CDC	Centers for Disease Control
CEA	Cost-Effectiveness Analysis
CUA	Cost-Utility Analysis
CI	Confidence Interval
Dl	Deciliter
DPP	Diabetes Prevention Program
DPPRG	Diabetes Prevention Program Research Group
DPS	Finnish Diabetes Prevention Program
EXP	Exponent
FPG	Fasting Plasma Glucose
HbA1c	Hemoglobin A1c (glycosylated hemoglobin)
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HMO	Health Maintenance Organization

HR	Hazard Ratio
HRQL	Health Related Quality of Life
ICD	International Classification of Disease
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IWQOL-Lite	Impact of Weight on Quality of Life-Lite
kg	Kilogram
kg/m2	Kilograms per Meter Squared
ln	Natural Logarithm
m2	Meter Squared
MCD	Multiple Cause of Death
MEPS	Medical Expenditure Panel Survey
MeSH	Medical Subject Headings
mg	Milligram
mg/dL	Milligrams per Deciliter
mmHg	Millimeters of Mercury
n	Sample Size
NDI	National Death Index
NGT	Normal Glucose Tolerance
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NIDDM	Non-Insulin Dependent Diabetes Mellitus

NIH	National Institute of Health
NMES	National Medical Expenditure Survey
OGTT	Oral Glucose Tolerance Test
PAR	Population Attribute Risk
QALY	Quality-Adjusted Life-Year
QOL	Quality of Life
QWB	Quality of Well Being
QWB-SA	Quality of Well Being—Self administered
RR	Relative Risk
SD	Standard Deviation
T2DM	Type 2 Diabetes Mellitus
UKPDS	United Kingdom Perspective Diabetes Study
U.S.	United States
VAS	Visual Analog Scales
WHO	World Health Organization

CHAPTER 1 - INTRODUCTION

1.1 Overview of theTopic

Type 2 diabetes mellitus (T2DM) is an epidemic in the United States (U.S.). In the year 2004, the Centers for Disease Control (CDC) estimates that at least 18 million American adults have diabetes (type 1 diabetes mellitus, T2DM, gestational diabetes, and all other categories), and lists this disease as the sixth leading cause of death.[1] The multiple complications of diabetes include microvascular complications such as retinopathy, renal disease, and peripheral neuropathy, as well as macrovascular complications of coronary heart disease, peripheral vascular disease, and stroke.[2] The 2002 cost of diabetes in the U.S. was estimated to be $132 billion, with direct medical cost accounting for $92 billion.[3] Diabetes is unfortunately a world-wide problem, with approximately 150 million people currently estimated to have this condition.[4] The current cost of treatment of diabetes and its complications is similar in most "westernized" countries, and is estimated at 7% to 14% of total healthcare costs.[5]

Obesity is considered to be one of the most preventable risk factors in the devel-

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1 Centers for Disease Control and Prevention. Diabetes: Disabling, Deadly, and on the Rise: At a Glance. *National Center for Chronic Disease Prevention and Health Promotion*. Available at: http://www.cdc.gov/nccdphp/aag/aag_ddt.htm. Accessed March 2004.

2 American Diabetes Association, National Institute of Diabetes and Digestive and Kidney Diseases. Prevention or delay of type 2 diabetes. *Diabetes Care*. 2004;27:S47-S54.

3 Centers for Disease Control and Prevention. Diabetes: Disabling, Deadly, and on the Rise: At a Glance. *National Center for Chronic Disease Prevention and Health Promotion*. Available at: http://www.cdc.gov/nccdphp/aag/aag_ddt.htm. Accessed March 2004.

4 Borch-Johnsen K, Lauritzen T, Glumer C, et al. Screening for type 2 diabetes- should it be now? *Diabetic Medicine*. 2003;20:175-181.

5 Ibid.

opment of T2DM.[6, 7] As with T2DM, the condition of obesity is also associated with morbidity and mortality, with overweight and obese persons possibly experiencing dyslipidemia, high blood pressure, and cardiovascular disease in addition to insulin resistance, hyperinsulinemia, and ultimately glucose intolerance.[8] Other disease conditions related to obesity include arthritis; cancers such as those of the breast, colon, and endometrium; gallbladder disease; and sleep disorders.[9] The condition of obesity is also characterized as an epidemic by the CDC. There was a 74% increase in the prevalence of obesity in U.S. from 1991 to 2000.[10] The American Obesity Association currently estimates that 127 million adults (64.5%) in the U.S. are overweight as defined by a body-mass index (BMI) ≥ 25 kg/m2, 60 million (30.5%) are obese (BMI ≥ 30 kg/m2), and 9 million (4.7%) are severely obese (BMI ≥ 40 kg/m2).[11]

Recent randomized controlled trials suggest that implementing lifestyle maintenance programs that emphasize weight loss and increased physical activity in patients with impaired glucose tolerance (IGT), a health state that is considered to be a

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6 Burke JP, Williams K, Narayan KMV, et al. A population perspective on diabetes prevention: whom should we target for preventing weight gain? *Diabetes Care*. 2003;26:1999-2004.

7 Leibson CL, Williamson DF, Melton III LJ, et al. Temporal trends in BMI among adults with diabetes. *Diabetes Care*. 2001;24:1584-1589.

8 Kannel WB, Wilson PWF, Nam B, et al. Risk Stratification of obesity as a coronary risk factor. *American Journal of Cardiology*. 2002;90:697-701.

9 American Obesity Association. AOA Fact Sheets. Available at: http://www.obesity.org/subs/fastfacts/obesity_US.shtml. Accessed March 2004.

10 Centers for Disease Control and Disease Prevention. Obesity Trends: 1991-2001 Prevalence of Obesity Among U.S. Adults, by Characteristics. *National Center for Chronic Disease Prevention and Health Promotion*. Available at: http://www.cdc.gov/nccdphp/dnpa/obesity/trend/prev_char.htm. Accessed March 2004.

11 American Obesity Association. AOA Fact Sheets. Available at: http://www.obesity.org/subs/fastfacts/obesity_US.shtml. Accessed March 2004.

pre-diabetic condition, may result in postponement or actual prevention of progression to T2DM. [12, 13] The Diabetes Prevention Program (DPP) is one such study which included 3,234 subjects with a diagnosis of IGT as defined by a two-hour post-load glucose ≥ 140 mg/dL and < 200 mg/dL, and a fasting plasma glucose of 95 mg/dL to 125 mg/dL. [14] The inclusion criteria also specified that the subjects had no other major disease state abnormalities, including cardiovascular disease. [15]

The starting cohort was randomized into one of three intervention groups. [16] The intervention groups included a cohort that received intensive lifestyle intervention, and two masked medication cohorts that received either metformin or a placebo. The latter two groups also received standard diet and exercise recommendations.

After an average follow-up of 2.8 years, there was a 58% relative reduction in progression from IGT to T2DM in the lifestyle intervention group, and a 31% relative reduction in the metformin group when compared to the placebo group. Weight loss in addition to increased physical activity were assumed to be the contributing factors for the success of the lifestyle intervention group. The goal of ≥ 7% weight reduction was achieved in 50% of this group.

Therefore, the DPP results are very encouraging for the possibility that lifestyle

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12 Tuomilehto J, Lindstrom J, Erikisson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New England Journal of Medicine*. 2001;344:1343-1350.

13 Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.

14 Diabetes Prevention Program Research Group. The Diabetes Prevention Program: design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care*. 1999;22:623-634.

15 Ibid.

16 American Diabetes Association, National Institute of Diabetes and Digestive and Kidney Diseases. Prevention or delay of type 2 diabetes. *Diabetes Care*. 2004;27:S47-S54.

interventions requiring only a modest amount of weight loss may be used to prevent progression from IGT to T2DM. It has been noted, however, that the weight loss achieved by these subjects required a very intensive delivery of treatment that might be difficult to reproduce in a setting other than a clinical trial. [17] Perhaps of even greater importance is that by using the criteria implemented in the DPP, approximately 17.1% of adults in the U.S. would currently qualify for diabetes prevention lifestyle interventions.. [18, 19] This translates to approximately 9.1 million adults, aged 45 years to 74 years.. [20] The potential costs of implementing lifestyle intervention programs for a group this large are staggering. An additional problem is that lifestyle counseling is not routinely reimbursed by the U.S. health care system. [21]

Current economic analyses of the results of the DPP have been limited to an analysis of costs associated with the program itself [22] and an analysis of within-trial cost-effectiveness comparing the metformin and lifestyle intervention arms of the study.[23] This latter study was limited to the three-year time horizon of the DPP, and did not

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17 Teutsch S. The cost of preventing diabetes: what do we know and what do we need to know? *Diabetes Care*. 2003;26:238-239.

18 Diabetes Prevention Program Research Group. The Diabetes Prevention Program: design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care*. 1999;22:623-634.

19 Saydah SH, Eberhardt MS, Loria CM, et al. Age and the burden of death attributable to diabetes in the United States. *American Journal of Epidemiology*. 2002;156:714-719.

20 Benjamin SM, Valdez R, Geiss LS, et al. Estimated number of adults with pre-diabetes in the US in 2000: opportunities for prevention. *Diabetes Care*. 2003;26:645-649.

21 American Diabetes Association, National Institute of Diabetes and Digestive and Kidney Diseases. Prevention or delay of type 2 diabetes. *Diabetes Care*. 2004;27:S47-S54.

22 Diabetes Prevention Program Research Group. Costs associated with the primary prevention of type 2 diabetes mellitus in the Diabetes Prevention Program. *Diabetes Care*. 2003;26:36-47.

23 Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518-2523.

incorporate the impact of long-term costs of diabetes morbidity and mortality. In addition, none of the effects of elevated BMI on healthcare costs, mortality, or utilities is included. These effects primarily would be related to disease abnormalities associated with obesity in addition to diabetes, such as coronary heart disease, hypertension, gallbladder disease, certain cancers, and osteoarthritis.

The American Diabetes Association (ADA) and the National Institute of Diabetes and Digestive and Kidney Diseases have both suggested that the cost-effectiveness of a DPP-like lifestyle intervention requires further research to determine if intervening in individuals at high risk of developing T2DM, such as those individuals with IGT, will "cost-effectively reduce the morbidity and mortality associated with diabetes."[24] They also suggest that the "additional health benefits" [25] of lifestyle intervention programs may directly influence the overall cost-effectiveness of the strategies. These additional health benefits may include all of those that occur secondary to weight loss, including improvements in the multitude of other disease conditions that are related to obesity.

1.2 Overview of the Dissertation

The dissertation attempts to address three major questions: (1) What is the long-term cost-effectiveness of the use of intensive lifestyle intervention to prevent T2DM from the state of IGT? (2) What is the effect of obesity on this evaluation? and (3) How does the evaluation change if an attempt is made to make the analysis more generalizable using a hypothetical population that may be more representative of that which is currently foundin the U.S. rather than the cohort studied by the DPP?

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24 American Diabetes Association, National Institute of Diabetes and Digestive and Kidney Diseases. Prevention or delay of type 2 diabetes. *Diabetes Care*. 2004;27:S47-S54.

25 Ibid.

While current research suggests that lifestyle intervention to prevent progression from IGT to T2DM is effective, it is not currently known whether this method of intervention is cost-effective over the lifetime of a subject. One option for the long-term analyses required for this project is to follow the DPP cohort over the duration of the subjects' lifetimes. While possible, this does not provide the information required to develop policy guidelines that are urgently needed today. Another more useful option is to use modeling techniques to incorporate the data derived by the DPP to project beyond the time horizon of the trial.

To use modeling to project beyond the DPP results, additional data will be required besides that found in the study. The literature review was therefore designed not only to address the above questions, but also to build a "database" to populate the parameters required for the Markov models that are discussed in the dissertation.

The information required for the dissertation is presented in the following manner. Chapter 2 begins with a discussion of the pathophysiology of abnormal glucose homeostasis, and introduces the reader to the basics of T2DM. Current published transition probabilities through the stages of normal glucose tolerance (NGT) to IGT to T2DM in studies other than the DPP are described. The role of obesity in the development of T2DM is then examined. The chapter ends with a discussion of studies leading to the DPP, and finally a discussion of the DPP itself.

Chapter 3 elaborates on the use of a cost-effectiveness analysis (CEA) for this dissertation. The underlying theory behind the methodology is discussed as a precursor to currently published studies on the long-term cost-effectiveness of lifestyle intervention for diabetes prevention. The DPP cost-analysis and three-year cost-effectiveness studies are then discussed.

Further data needed for the dissertation model is then explored. These data include

the cost of illness of the obese T2DM, IGT, and NGT subject. Current literature regarding the effect on mortality rates of abnormal glucose homeostasis, obesity, and their combined states is described. Additional literature on possible health-state utilities for these same populations is also given.

The generalizability of results found in the DPP study group is examined throughout the discussion of the above variables. One major factor that may influence lack of generalizability is the healthcare exclusion criteria found in the design of the DPP (subjects were excluded if they had cardiovascular disease, hypertension, renal disease, pulmonary disease, cancer or anemia).[26] The specific effects on direct healthcare costs and mortality resulting from these exclusions is emphasized. The conclusion of Chapter 3 lists the proposed hypotheses for the dissertation and their rationales.

Chapter 4 describes the methodology used for the dissertation. Markov modeling is introduced, as well as a discussion of the use of sensitivity analyses, and in particular, probabilistic sensitivity analyses. The discussion defines in detail the input parameters used in the models, and ranges required for one-way, two-way, and probabilistic sensitivity analyses.

Chapter 5 presents the results derived from the analysis. Base-case analyses for each model are given first, and the presentation of theses results is concluded with the application of the findings to the hypotheses tests presented in Chapter 3. Comparisons of the base-case results are then described in detail. An emphasis is placed on both the effect of cost inputs on the analyses as well as the effects of obesity adjustments. The chapter also includes an examination of the maximum acceptable cost of lifestyle inter-

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26 Diabetes Prevention Program Research Group. The Diabetes Prevention Program: design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care*. 1999;22:623-634.

vention for each model presented, and the factors that influence this value. Time free of diabetes and cost per glucose homeostasis state (NGT, IGT, and T2DM) are then presented. The chapter ends by describing results of sensitivity analyses conducted for the dissertation, including the following; (1) increasing the discount rate from 0% to 5%; (2) decreasing the treatment effect; (3) increasing the progression from IGT to NGT; and (4) inserting a possible reversion from T2DM to IGT.

Chapter 6 completes the dissertation with a discussion of the results and how they relate to the goals of the study. In addition, the possible impact of the results on policy making surrounding diabetes prevention using lifestyle intervention is presented. Future research required to adequately evaluate cost-effectiveness of diabetes prevention and limitations of the study conclude this chapter.

CHAPTER 2 – LITERATURE REVIEW: TYPE 2 DIABETES MELLITUS (T2DM)

There are two main purposes of this literature review. The first is to examine data that support the hypotheses that have been proposed for this model. As noted in the introduction, the general questions that will be examined include the possibility of long-term cost-effectiveness of T2DM prevention, the effect of obesity on this analysis, and finally, an attempt to extend the results of this analysis to a more generalizable cohort than that studied by the DPP. As these questions are addressed, a second goal, to accumulate data with which to populate the models of the dissertation, will also be accomplished.

As a first step, the underlying pathophysiology of the continuum from NGT to T2DM will be described. Important variables for the model such as the progression probabilities of NGT to IGT, IGT to T2DM, and the reversion probabilities of IGT to NGT will be examined. The risk factors that influence these transitions, including obesity will then be discussed. Finally, prevention studies that preceded the DPP will be examined as an introduction to a discussion of the study.

2.1 Natural History of T2DM

To understand diabetes prevention, one must first have a working knowledge of the underlying pathophysiology of T2DM. The following sections will outline the disease states that are currently thought to occur in the development from NGT to T2DM.

2.1.1 PATHOPHYSIOLOGY OF T2DM

Diabetes mellitus is a metabolic disorder of multiple etiologies. T2DM, a specific diagnostic classification of the general category of diabetes mellitus, is a chronic, pro-

gressive disease, which represents 80% to 90% of diabetes cases, with the other most common classification being type 1, or as previously known, insulin-dependent diabetes mellitus.[27]

T2DM is considered a heterogeneous multifactorial, polygenic disease.[28] The most common group of patients with this diagnosis, or approximately 70% to 85% of patients, have a poorly defined etiology for their condition. Of the remaining 15% to 30% of patients, 5% to 10% of patients are commonly classified as having maturity onset diabetes of youth, 5% to 10% are classified as having adult onset, autoimmune diabetes, and 5% to 10% are thought to have a rare genetic disorder as the etiology of their T2DM. [29]

Type 2 diabetes is a disease that appears to require a genetic basis as well as environmental or acquired factors to manifest itself. The environmental factors may be modifiable such as obesity or sedentary activity, or non-modifiable, such as aging. [30] In most individuals, the disease involves defects of both insulin resistance (also referred to as insulin sensitivity) and ß-cell insulin secretion. [31]

Genetic factors, which are still incompletely identified, are thought to predispose

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27 Gerich JE. The genetic basis of type 2 diabetes mellitus: impaired insulin secretion versus impaired insulin sensitivity. *Endocrine Review*. 1998;19:491-503.

28 Hayden MR. Islet amyloid, metabolic syndrome, and the natural progressive history of type 2 diabetes mellitus. *Journal of Pancreas*. 2002;3:126-138.

29 Gerich JE. The genetic basis of type 2 diabetes mellitus: impaired insulin secretion versus impaired insulin sensitivity. *Endocrine Review*. 1998;19:491-503.

30 Aitman T, Todd J. Molecular genetics of diabetes mellitus. *Baillieres Best Practice and Research: Clinical Endocrinology and Metabolism*. 1995;9:631-656.

31 Report of the WHO Consultation. *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications: Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva: World Health Organization; 1999.

an individual to T2DM.[32, 33] Early life events in genetically susceptible individuals, such as intrauterine nutrition, low birth weight, and formula feeding may be some of the first environmental factors that additionally influence the propensity to develop T2DM.[34]

The vast majority of patients with T2DM initially exhibit some degree of insulin resistance, although the disease can occur rarely in its absence. More importantly, insulin resistance may occur without the development of T2DM.[35] It is postulated that in patients who develop T2DM, insulin resistance has two components: an inherited component and a component that is environmentally acquired secondary to factors such as obesity and lack of physical activity. [36]

Multiple studies, conducted in a wide variety of ethnic populations, have reported that insulin resistance occurs in a pre-diabetic state which may last for many years before T2DM is diagnosed.[37] Insulin resistance ultimately leads to increased basal hepatic glucose production. Patients with insulin resistance are generally able to maintain normal plasma glucose concentrations because insulin secretion from the pancreatic ß-cells becomes augmented.[38] Many years of insulin resistance may ultimately ensue in the

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32 Aitman T, Todd J. Molecular genetics of diabetes mellitus. *Baillieres Best Practice and Research: Clinical Endocrinology and Metabolism.* 1995;9:631-656.

33 Gerich JE. Is reduced first-phase insulin release the earliest detectable abnormality in individuals destined to develop type 2 diabetes? *Diabetes*. 2002;51:S117-S121.

34 Ozanne SE, Hales CN. Pre- and early postnatal nongenetic determinants of type 2 diabetes. *Cambridge University Press*. Available at: http://www.expertreviews.org/02005240h.htm. Accessed March 2004.

35 Gerich JE. Contributions of insulin-resistance and insulin-secretory defects to the pathogenesis of type 2 diabetes mellitus. *Mayo Clinic Proceedings*. 2003;78:447-456.

36 Olefsky JM, Kruszynska YT. Insulin resistance. In: Porte D, Sherwin RS, Baron A, eds. *Ellenberg & Rifkin's Diabetes Mellitus*. 6 ed. New York: McGraw-Hill; 2003:367-400.

37 Ibid.

38 Inzucchi SE. Classification and Diagnosis of Diabetes Mellitus. In: Porte D, Sherwin RS, Baron A, eds. *Ellenberg & Rifkin's Diabetes Mellitus*. New York: McGraw-Hill; 2003:265-275.

patient who is destined to develop T2DM.[39] Ultimately, the final stage of pathogenesis occurs, ß-cell function deteriorates, and the patient is clinically diagnosed with T2DM.

2.1.2 THE CLINICAL STAGES OF T2DM

The following sections outline the currently hypothesized clinical development of T2DM.

2.1.2.1 Preclinical Phase

Type 2 diabetes mellitus appears to have a preclinical stage, characterized by insulin resistance, that is compensated for by increased secretion of insulin by ß-cells. This preclinical phase, which is thought to be silent in the patient, is not readily diagnosed, and is thought to occur for as long as nine to twelve years prior to an easily detectable pre-clinical phase such as IGT or impaired fasting glucose (IFG).[40, 41]

2.1.2.2 Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG)

The selection criteria for the DPP were defined as a two-hour post-load glucose ≥ 140 mg/dL and < 200 mg/dL, and a fasting plasma glucose (FPG) of 95 mg/dL to 125mg/dL.[42] The definitions and significance of these states will now be discussed.

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39 Gerich JE. Is reduced first-phase insulin release the earliest detectable abnormality in individuals destined to develop type 2 diabetes? *Diabetes*. 2002;51:S117-S121.

40 Harris MI, Klein R, Welborn TA, et al. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. *Diabetes Care*. 1992;15:815-819.

41 Harris R, Donahue K, Rathore SS, et al. Screening adults for type 2 diabetes: a review of the evidence for the U.S. preventive services task force. *Annals of Internal Medicine*. 2003;138:215-234.

42 Diabetes Prevention Program Research Group. The Diabetes Prevention Program: design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care*. 1999;22:623-634.

2.1.2.2.1 Definition and Prevalence

IGT is currently defined in the U.S. by the 1997 ADA criteria as a plasma glucose level of ≥ 140mg /dL to < 200 mg/dL at two hours after an oral glucose challenge.[43] IGT is considered to be a metabolic state that is intermediate between normal glucose homeostasis and diabetes, and it is considered to be a risk category for future T2DM.[44, 45] Patients with a diagnosis of IGT have an increased prevalence of cardiovascular disease risk factors.[46] These include dyslipidemia, hypertension, and microalbuminuria.

IGT should not be confused with a state referred to as impaired fasting glucose (IFG), which is currently diagnosed as a fasting plasma glucose of ≥ 100 mg/dL and < 126 mg/dL.[47] At the time of the DPP, IFG was diagnosed as a fasting plasma glucose of ≥ 110 mg/dL to < 126 mg/dL. Of note, all of the studies used in this dissertation, unless specified, were completed using the earlier diagnostic criteria with the higher cut point of 110 mg/dL. At the time of the DPP, IFG was diagnosed as a fasting plasma glucose of ≥ 110mg/dL to < 126 mg/dL.[48] Of note, all of the studies used in this dissertation, unless specified, were completed using the earlier diagnostic criteria with the higher cut point of

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43 National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes*. 1979;28:1039-1057.

44 Report of the WHO Consultation. *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications: Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva: World Health Organization; 1999.

45 Meigs JB, Muller DC, Nathan DM, et al. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of the Aging. *Diabetes*. 2003;52:1475-1484.

46 Benjamin SM, Valdez R, Geiss LS, et al. Estimated number of adults with pre-diabetes in the US in 2000: opportunities for prevention. *Diabetes Care*. 2003;26:645-649.

47 American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 2004;27:S5-S10.

48 The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 2000;23:S3-S4.

110 mg/dL.

The DPP may have anticipated this lowered threshold, which was officially announced in January 2004 by the ADA,[49] when they designed their study criteria with a lower FPG cut point of 95 mg/dL. The rationale for the ADA change is primarily based on the fact that the IFG and IGT categories are defined in order to characterize patients who may develop T2DM. The two tests now define similar proportions of individuals, whereas previously, IGT was a more sensitive test.[50]

A concern that remains is that researchers feel there may be two distinct phenotypic pathways to development of T2DM. This is based, in part, on the finding that regardless of the diagnostic threshold for IFG, patients may develop either isolated IGT or IFG.[51] Insulin resistance is found in both, but patients with the less frequently occurring "IFG" pathway appear to have more pronounced ß-cell abnormalities, and increased endogenous glucose production.[52]

In an analysis using NHANES III data of overweight people (BMI > 25 kg/m^2) with the previous IFG diagnostic threshold of 110 mg/dL, 11.9 million people (22.6%)had either IFG or IGT. [53]

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49 American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 2004;27:S5-S10.

50 Davidson MB, Landsman PB, Alexander CM. Lowering the criterion for impaired fasting glucose will not provide clinical benefit. *Diabetes Care*. 2003;26:3329-3330.

51 Meigs JB, Muller DC, Nathan DM, et al. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of the Aging. *Diabetes*. 2003;52:1475-1484.

52 Weyer C, Bogardus C, Pratley RE. Metabolic characteristics of individuals with impaired fasting glucose and/or impaired glucose tolerance. *Diabetes*. 1999;48:2197.

53 Benjamin SM, Valdez R, Geiss LS, et al. Estimated number of adults with pre-diabetes in the US in 2000: opportunities for prevention. *Diabetes Care*. 2003;26:645-649.

2.1.2.3 T2DM

2.1.2.3.1 Definition, Screening, and Prevalence

T2DM is defined as a fasting plasma glucose ≥ 126 mg/dl and/or a two-hour post glucose load of ≥ 200 mg/dl.[54] As noted in the introduction, the current estimated adult prevalence of T2DM in the U.S. is 18 million adults.[55] By the time that T2DM is clinically diagnosed, 20% to 30% of patients are found to have microvascular complications such as retinopathy, nephropathy, and neuropathy, and macrovascular complications such as cardiovascular, peripheral vascular and cerebrovascular disease.[56]

Approximately one-third of patients with T2DM are undiagnosed and untreated.[57] To put this number in perspective, it was estimated that the prevalence of undiagnosed diabetes in the U.S. population aged 20 years to 74 years was 3.2% from 1988 to 1994.[58] Undiagnosed diabetes is a major problem in that approximately one-third of these patients have microvascular complications that would respond to improved glycemic control.[59]

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54 Report of the WHO Consultation. *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications: Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva: World Health Organization; 1999.

55 Centers for Disease Control and Prevention. Diabetes: Disabling, Deadly, and on the Rise: At a Glance. *National Center for Chronic Disease Prevention and Health Promotion*. Available at: http://www.cdc.gov/nccdphp/aag/aag_ddt.htm. Accessed March 2004.

56 Segal L, Dalton A, Richardson J. Cost-effectiveness of the primary prevention of non-insulin dependent diabetes mellitus. *Health Promotion International*. 1998;13:197-209.

57 Harris MI, Eastman RC. Early detection of undiagnosed diabetes mellitus: a US perspective. *Diabetes/Metabolism Research and Reviews*. 2000;16:230-236.

58 Harris M, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. *Diabetes Care*. 1998;21(4):518-524.

59 Roman SH, Harris MI. Management of diabetes mellitus from a public health perspective. *Endocrinology and Metabolism Clinics of North America*. 1997;26:443-474.

In spite of the high rate of undiagnosed T2DM patients in the U.S., screening for T2DM remains controversial. In 2003, the U.S. Preventative Task Force concluded that "the evidence is insufficient to recommend for or against routinely screening asymptomatic adults for type 2 diabetes, impaired glucose tolerance, or impaired fasting glucose."[60] The ADA currently recommends routine screening of all adults beginning at age 45 years, with repeat tests every three years. If a patient has one or more of the risk factors listed in Table 2.1, screening is recommended at a "younger age" or "more frequently," though these values are not defined.[61]

Table 2.1 Risk Factors for Type 2 Diabetes Mellitus[a]

Age ≥ 45 years
Overweight (BMI ≥ 25 kg/m^2)
Family history of diabetes (first or second degree relative)
Habitual physical inactivity
High risk ethnicity (African American, Hispanic, Native American, Asian American, Pacific Islander)
Previously identified impaired fasting glucose or impaired glucose tolerance
History of gestational diabetes or delivery of a baby weighing > 9 lbs.
Hypertension (≥ 140/90 mmHg in adults)
Dyslipidemia (HDL cholesterol ≤ 35 mg/dL and/or triglyceride level ≥ 250 mg/dL)
Polycystic ovarian disease
History of vascular disease

[a] Source: American Diabetes Association. Screening for Type 2 Diabetes. *Diabetes Care*. 2003;26:S21-S24.
HDL, high-density lipoprotein; kg/m^2, kilograms per meter squared; mg/dL, milligrams per deciliter; mmHg, millimeters of Mercury

60 U.S. Preventative Services Task Force. Screening for type 2 diabetes mellitus in adults: recommendations and rationale. *Annals of Internal Medicine*. 2003;138:212-214.

61 American Diabetes Association. Screening for Type 2 Diabetes. *Diabetes Care*. 2003;26:S21-S24.

2.1.2.3.2 Possible Changes from the IGT State

Receiving the diagnosis of IGT does not automatically mean that the patient will progress to T2DM. In fact, while at an increased risk for T2DM when given this diagnosis, a patient with IGT may revert to NGT.[62, 63] In a review of five studies done by Yudkin et al., a repeat glucose tolerance test after a positive test at any time from less than 7 days to a mean of 8.5 months had a reversion to normal of 35% to 76%, and progression to T2DM of 4% to 9%.[64]

A possible explanation given for reversion to NGT by these authors is the phenomenon of "regression to the mean." An even more intriguing explanation for the variability found in patients tested with an OGTT for IGT is the possibility that the two-hour glucose tolerance test may reflect a "stress effect" when first performed, which may not occur on the repeat administration.[65] Interestingly, the DPP notes that "IGT may revert to NGT" in their article on the baseline characteristics of the randomized cohort.[66] This statement is not repeated in the published articles focused on the intervention.

The rate of progression from IGT to T2DM is also discussed by the DPP. The Diabetes Prevention Program Research Group suggests that rates of progression range from 2.3% per year to approximately 11%, with the higher values recorded in non-white ethnic groups.[67] These values were analyzed by Edelstein et al. in preparation for the

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62 Diabetes Prevention Program Research Group. The Diabetes Prevention Program: baseline characteristics of the randomized cohort. *Diabetes Care*. 2000;23:1619-1629.

63 Yudkin JS, Alberti KGMM, McLarty DG, et al. Impaired glucose tolerance: is it a risk factor for diabetes or diagnostic ragbag? *British Medical Journal*. 1990;301:397-402.

64 Ibid.

65 Ibid.

66 Diabetes Prevention Program Research Group. The Diabetes Prevention Program: baseline characteristics of the randomized cohort. *Diabetes Care*. 2000;23:1619-1629.

67 Ibid.

DPP, and are summarized in Table 2.2.[68] This work was done in part to establish the range of rates of progression to T2DM from IGT in order to predict the sample size and power needed for the study.

Six prospective studies were analyzed, and the conversion rate ranged from 35.8 (S.D. 2.6) per 1,000 person-years in the Baltimore Longitudinal Study of Aging (95% Caucasian, average age 59.4 years), to 87.3 per 1,000 person-years in the Pima IndianStudy (100% Pima Indians, average age 43.2 years).[69] For groups that included a mixture of Caucasians and Hispanics, age was an important factor in conversion rate. The San Antonio Heart Study, with an average age of 48.3, had a conversion rate of 43.5 per 1,000 person-years. On the other hand, the San Luis Valley Diabetes Study, with an average age of almost 60, had a conversion rate of 72.9 per 1,000 person-years. The average value of the six studies was 5.8% per year (58 cases per 1,000 person-years).

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68 Edelstein SI, Knowler WC, Bain RP, et al. Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. *Diabetes*. 1997;46:701-710.

69 Ibid.

Table 2.2 A Comparison of Studies of Progression of Impaired Glucose Tolerance to Type 2 Diabetes Mellitus[a]

Study	Mean Age in Years (Range)	Race/ethnicity	Sex	Conversion Rate per 1,000 Person-Years [b] (95% CI)
Baltimore Longitudinal Study of Aging	59.4 (23.2-92.5)	95% Caucasian, 4% African-American, 1% Other	73.8% Men 26.2% Women	35.8 ± 2.6 (30.7-40.8)
Rancho Bernardo Study	68.0 (52.0-82.0)	100% Caucasian	35.5% Men 64.5% Women	40 ± 5.7 (28.8-51.2)
San Antonio Heart Study	48.3 (25.0-65.0)	26.6% Non-Hispanic White, 73.4% Mexican-American	36.3% Men 63.7% Women	43.4 ± 4.2 (35.2-51.6)
Nauru Study	37.3 (12.0-75.0)	100% Micronesian	45.6% Men 54.4% Women	62.8 ± 5.3 (52.5-73.1)
San Luis Valley Diabetes Study	59.7 (31.2-75.0)	47.5% Non-Hispanic White, 52.2% Hispanic	39.6% Men 60.4% Women	72.9 ± 11.4 (50.6-95.2)
Pima Indian Study	43.2 (20.0-89.3)	100% Pima Indian	37.1% Men 62.9% Women	87.3 ± 4.2 (79.0-95.6)

[a] Source: Edelstein SI, Knowler WC, Bain RP, et al. Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. *Diabetes*. 1997;46:701-710.

[b] Conversion rate ± standard deviation
CI, confidence interval

The DPP ultimately chose a conversion factor of 65 per 1,000 person-years. This translates to a one-year probability of 0.0672 assuming a constant yearly transition probability. This was based on the entry criteria required by the DPP study of an abnormal IGT plus a FPG of 95 mg/dL to 125 mg/dL, and a diagnosis of diabetes being made using ADA diabetic criteria for a fasting or two-hour plasma glucose level.[70] As noted above,

70 Diabetes Prevention Program Research Group. The Diabetes Prevention Program: design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care*. 1999;22:623-634.

this lower fasting plasma glucose threshold value may approximate the prevalence of abnormal two-hour plasma glucose populations in the U.S. population.[71]

For the sake of clarification, one-year probabilities will be reported throughout the literature review. This is because probabilities will be required for the model, and the cycle length that will be used is a one-year period. In examining the literature evaluated for this project, two specific adjustments are often required to obtain these one-year values. The first is that findings are presented as probabilities, but in time frames other than that of one year. These probabilities must be converted to rates before they are adjusted to probabilities for one-year periods. In addition, many results are reported as rates, so they must be converted to probabilities.

The formula used to convert a probability to a rate is the following: [72]

$$\mu = -\ln[1-P(t)]/t$$

where μ equals the one-year rate, which is also called the annual hazard rate, t is the time period, and P(t) is the probability that an event occurs over this t time period. The following formula is then used to reconvert back to the needed probability value:

$$P(t) = 1 - \exp(-\mu).$$

2.1.2.3.3 Progression from Normal Glucose Tolerance(NGT) to IGT

In anticipation that the dissertation model will require a value for progression from NGT to IGT, a value not given by the DPP, the following two studies have been selected to calculate a preliminary value. Both studies are important for consistency because they

71 Meigs JB, Muller DC, Nathan DM, et al. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of the Aging. *Diabetes*. 2003;52:1475-1484.

72 Kuntz K, Weinstein M. Ch. 7 - Modeling in Economic Evaluation. In: Drummond M, McGuire A, eds. *Economic Evaluation in Health Care: Merging Theory with Practice*. New York: Oxford University Press; 2001:141-171.

include data for the progression from NGT to IGT that is derived from studies used by the DPP to calculate progression from IGT to T2DM, as seen in Table 2.2.

2.1.2.3.3.1 Values Calculated from the Baltimore Longitudinal Study of Aging

The Baltimore Longitudinal Study of Aging (BLSA)[73] is a prospective study that was begun in 1958 by the National Institute of Health (NIH), and is ongoing. The data studied for this analysis were derived from a population of subjects of mainly Caucasian race, and of middle and upper-middle socioeconomic class. The average age of the participants was 57 years. The mean BMI for this particular study was not given. The design is an open-cohort model, with dropouts replaced before every two-year exam period to maintain a study population of approximately 1,000. The study allows for calculation of transition probabilities from a state of NGT (as defined as a two-hour post challenge glucose level of < 140 mg/dL and a FPG < 110 mg/dL) to a state of IGT, as defined by abnormal two-hour post glucose levels. Therefore, the subject is not required to have an abnormal fasting plasma glucose to fall into this category. This is important, as this study design approximates the study criteria of the DPP.

The one-year transition probability that is calculated for this group of study subjects based on a ten-year follow up (assuming a constant annualized transition) is 0.0624. This is based on a ten-year cumulative incidence of 47.5%.[74] Using a five-year follow up (and again assuming a constant annualized transition), the one-year probability is calculated as 0.0718. This is based on a five-year cumulative incidence of 31.1%. [75]

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73 Meigs JB, Muller DC, Nathan DM, et al. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of the Aging. *Diabetes*. 2003;52:1475-1484.

74 Ibid.

75 Ibid.

2.1.2.3.3.2 The Pima Indian Study

The highest rate of progression from IGT to T2DM noted in Table 2.2 was in the Pima Indian Study[76] (87.3 per 1000-person years, or a 1-year probability of 0.0836). This study also calculated estimates of the rate of progression from NGT to IGT. They found that 79 of 254 subjects developed IGT from NGT over an approximate 3.9-year follow up (31.1%). The calculated 1-year probability is 0.0767.

2.1.2.3.4 Do You Have to Pass Through IGT to get to T2DM?

Is it possible to progress from NGT to T2DM without first being characterized as having either an abnormal FPG, IGT, or both? Meigs et al. addressed this question and felt this was an extremely rare occurrence. [77]

The authors found that of the 488 subjects who started the BLSA in a state of NGT using a FPG of < 110 mg/dL and a 2-h post glucose value of < 140 mg/dL, only 12 patients (2.46%) progressed to T2DM without first passing through some category of abnormal glucose homeostasis over the initial eleven-year study period.[78] The estimated one-year probability of this occurrence is 0.0023.

2.1.2.3.5 Reverting from T2DM to IGT or NGT

For completeness of the dissertation model, the possibility that a subject might revert from T2DM to IGT must be investigated. It is thought that the progressive ß-cell

76 Weyer C, Tataranni P, Bogardus C, et al. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of type 2 diabetes development. *Diabetes Care*. 2001;24(1):89-94.

77 Meigs JB, Muller DC, Nathan DM, et al. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of the Aging. *Diabetes*. 2003;52:1475-1484.

78 Ibid.

destruction found in T2DM subjects makes it unlikely that a patient will revert back to IGT without some sort of treatment intervention.[79] The goal becomes even more difficult in obese subjects.[80]

Weight loss has also been investigated as a treatment option for newly diagnosed patients with T2DM. Weight loss is thought to decrease fasting insulin levels in these patients, but has little effect on insulin secretion.[81] While a small but steady weight loss is suggested as the most "rewarding action" as an initial intervention for obese, type 2 diabetics, the mechanism of action may be more influenced by the state of negative caloric balance than the achievement of a lower, steady-state weight.[82, 83] It is generally thought that glycemic control improves very quickly with the energy restriction associated with low calorie diets, and this effect is independent of weight loss.[84] As energy restriction is relaxed, this improvement has been found to decrease, even in the presence of continued weight-loss maintenance.[85]

The UKPDS has evaluated the use of a low-fat, high-carbohydrate, high-fiber diet

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79 UKPDS Group. UK Prospective Diabetes Study 16: overview of six years' therapy of type 2 diabetes-a progressive disease. *Diabetes*. 1995;44:1249-1258.

80 Turner RC, Cull CA, Firghi V, et al. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus. *JAMA*. 1999;281:2005-2012.

81 Robbins D, Shair E. Current strategies for managing obesity in type 2 diabetes. *Medscape from WebMD*. Available at: http://www.medscape.com/viewprogram/341_pnt. Accessed Sept. 2004.

82 Ibid.

83 Kelley DE, Wing R, Buonocore C, et al. Relative effects of caloric restriction and weight loss in non-insulin-dependent diabetes mellitus. *Journal of Clinical Endocrinology and Metabolism*. 1993;77:1287-1293.

84 Hensrud DD. Dietary treatment and long-term weight loss and maintenance in type 2 diabetics. *Obesity Research*. 2001;9:348S-353S.

85 Ibid.

as a monotherapy to treat newly diagnosed type-2 diabetics.[86] Using an outcome of a hemoglobin A1c (HbA1c) < 7%, the currently ADA-recommended "normal" value, 23% of overweight subjects (defined as > 120% ideal body weight) maintained this "normal" level after three years on diet-therapy alone. The weight loss achieved was approximately 5 kg over the first three months. By six years, the percentage of subjects with a HbA1c < 7% had decreased to 12%, and by nine years the level had again decreased slightly to 11%. These results are difficult to translate to FPG and two-hour post challenge glucose values due to imperfect correlation of the tests.[87]

Few additional studies have evaluated the long-term effects of weight-loss maintenance in this population. Pascale et al. have studied the effect of calorie and calorie plus fat restriction in obese, T2DM subjects.[88] The authors found significant decreases in glucose levels after the sixteen-week intervention in both treatment intervention arms, but these values had returned to baseline after a one-year follow-up. The deterioration of glycemic improvement at the one-year follow-up was also found by Wing et al. in a study of 144 obese, type-2 diabetic subjects treated in a behavioral weight control program.[89]

Therefore, an apparent improvement in glycemic control with weight loss occurs in obese, type-2 diabetic subjects. This highest effect appears in the early stages of weight loss, and is apparently secondary to energy restriction as well as actual weight

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86 Turner RC, Cull CA, Firghi V, et al. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus. *JAMA*. 1999;281:2005-2012.

87 The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 2002;25:S5-S20.

88 Pascale RW, Wing RR, Butler BA, et al. Effects of a behavioral weight loss program stressing calorie restriction versus calorie plus fat restriction in obese individuals with NIDDM or a family history of diabetes. *Diabetes Care*. 1995;18:1241-1248.

89 Wing RR, Koeske R, Epstein LH, et al. Long-term effects of modest weight loss on type II diabetic patients. *Archives of Internal Medicine*. 1987;147:1749-1753.

loss. In addition, the effect seems to dissipate over long-term follow-up. Results are also difficult to interpret as most studies have used HbA1c values or FPG values that do not correlate with the IGT definitions used by the DPP.

In addition, current literature does not support reversion from T2DM to IGT as found in the case of reversion from IGT to NGT as described in section 2.1.2.3.2. It may be that there will be "fuzzy areas" in which a patient is found to cross back and forth from IGT to T2DM with the decrease in cut-off point for diagnosis for T2DM from 140 mg/dL to 126 mg/dL, but this research has not currently been undertaken.

2.1.2.3.6 The Risk Factors for IGT and T2DM

Multiple factors are associated with an increased risk of IGT. These include obesity, increased age, a family history of diabetes, ethnicity, and lipid abnormalities.[90] These factors are also associated with increased risk of T2DM, and have been examined in multiple studies with varying results as to their influence on progression from IGT to T2DM.[91]

In the analyses performed in preparation for the DPP, Edelstein et al. noted that there was remarkable consistency in the risk factors for progression from IGT to T2DM in the six studies that were examined.[92] The most significant risk factors for progression in all six studies were higher baseline fasting and two-hour postchallenge glucose concentrations, and obesity. Family history was inconsistently associated with increased rate of progression from IGT to T2DM. This is likely because subjects with IGT were

90 Edelstein SI, Knowler WC, Bain RP, et al. Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. *Diabetes*. 1997;46:701-710.

91 Ibid.

92 Ibid.

already an "enriched high risk group." Sex was not a predictor of progression of IGT to T2DM in any of the studies. Non-Caucasians were found to have a substantially higher risk of progression. Baseline age varied substantially in the six studies as a risk factor, and this factor is dependent on ethnicity as to rate of progression. Those populations with higher risk, such as Pima Indians or Hispanics, are more likely to progress from IGT to T2DM at an earlier age (before age 40 years to 50 years) than groups that were mainly Caucasian.[93]

As noted above, BMI was an independent predictor of progression from IGT to T2DM across the six combined studies. When the six studies were analyzed separately, BMI was an independent predictor of progression in the Baltimore Longitudinal Study, the Rancho Bernardo Study, and the San Antonio Heart Study. The three cohorts with T2DM across the six combined studies. When the six studies were analyzed separately, BMI was an independent predictor of progression in the Baltimore Longitudinal Study, the Rancho Bernardo Study, and the San Antonio Heart Study. The three cohorts with the highest T2DM incidence rates did not show BMI as a strong independent predictor of T2DM (the Naura Study, the San Luis Valley Diabetes Study, and the Pima Indian Study). This was thought to be in part because these populations, which were considered "very overweight," had reached a saturation point for obesity as a risk factor, at which point no additional risk for conversion to T2DM would be seen with additional weight.

2.2 The Role of Obesity In T2DM

Obesity is considered one of the most important, preventable risk factors in the development of T2DM.[94] One author noted that between 1970 and 1999, there were at least

93 Ibid.

94 Costacou T, Mayer-Davis E. Nutrition and prevention of type 2 diabetes. *Annual Review of Nutrition*. 2003;23:147-170.

least 28 prospective studies that confirmed the role of obesity as a strong predictor of T2DM.[95] It is estimated that 60% to 90% of the variance in T2DM status is related to obesity. [96,97]

2.2.1 MEASUREMENT AND CLASSIFICATION OF OBESITY

A common measure of obesity that will be used throughout this dissertation is BMI. This measure, which takes into account body weight and height, is calculated by dividing weight in kilograms by height in meters-squared.[98] There are five major categories of BMI using the World Health Organization (WHO) 2000 guidelines.[99] These are listed in Table 2.3.

Table 2.3 Body-Mass Index Weight Classification[a]

Classification	Body-Mass Index (BMI) in kg/m^2
Underweight	Less than 18.5
Normal Range	18.5 - 24.9
Overweight (Preobese)	25.0 - 29.9
Obese Class I	30.0 - 34.9
Obese Class II	35.0 - 39.9
Obese Class III (Severely Obese)	Greater than or equal 40

[a] Source: World Health Organization. *Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation on Obesity*. 2000. Geneva, World Health Organization.
kg/m^2, kilograms per meter squared

95 Brancati FL, Wang, N Y, Mead LA, et al. Body weight patterns from 20 to 49 years of age and subsequent risk for diabetes mellitus: the Johns Hopkins Precursors Study. *Archives of Internal Medicine*. 1999;159:957-963.

96 Colditz GA, Willett WC, Stampfer MJ, et al. Weight as a risk factor for clinical diabetes in women. *American Journal of Epidemiology*. 1990;132:501-513.

97 Anderson JW, Kendall CW, Jenkins DJ. Importance of weight management in type 2 diabetes: review with meta-analysis of clinical studies. *Journal of the American College of Nutrition*. 2003;22:331-339.

98 Kortt MA, Langley PC, Cox ER. A review of cost-of-illness studies on obesity. *Clinical Therapeutics*. 1998;20:772-779.

99 World Health Organization. *Obesity: Preventing and Managing the Global Epidemic. Report of the WHO Consultation on Obesity*. Geneva: World Health Organization; 2000.

The WHO has suggested that BMI may be used as a simple measure of obesity. The advantages of using BMI include that is easily assessed on physical exam, and can also be determined by self report.[100] The disadvantage of the measure is that it is not always an accurate indicator of obesity.[101] A high degree of adiposity is not always indicated by the calculated value because the etiology of increased weight is not distinguished, and may be a result of increased muscle mass or bone in addition to excess fat. There is much controversy over the most accurate measurement of adiposity in both clinical and research settings. The discussion of this controversial topic is beyond the scope of this dissertation report. BMI has been chosen as an obesity measurement as this is the value used by the DPP.

2.2.2 THE CORRELATION OF BODY-MASS INDEX (BMI) AND T2DM

There are few articles that have examined the correlation of BMI subcategories and the development of T2DM; however, there is general agreement that increased BMI is accompanied by an increased rate of diabetes. An examination of this topic is helpful to the dissertation model in two ways. First, an overview of this topic is required to help to explain why extensive lifestyle intervention emphasizing weight loss is successful. The second reason for examination is that as will be noted later, the DPP results suggest that lifestyle intervention to prevent T2DM may be less successful in subjects with a BMI ≥ 35 kg/m^2. A review of the correlates of BMI to development of T2DM may clarify the reasons for this difference in efficacy of treatment.

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100 Rogers RG, Hummer RA, Krueger PM. The effect of obesity on overall, circulatory disease, and diabetes-specific mortality. *Journal of Biosocial Science*. 2003;35:107-129.

101 James WP. What are the health risks? The medical consequences of obesity and its health risks. *Experimental and Clinical Endocrinology & Diabetes*. 1998;106:S1-S6.

The studies for this portion of the review were chosen in a MEDLINE search using the medical subject headings (MeSH) headings of BMI, Obesity and T2DM. Studies were selected to show the strikingly different results that have been presented on the correlation of BMI subcategories and T2DM. A brief explanation of the effect of study design and study population on the results will also be included.

2.2.2.1 Articles Suggesting That Increased BMI Increases Risk of Diabetes

Colditz et al. examined data collected in the Nurses' Health Study, a prospectively designed survey study of 121,700 female nurses aged 30 years to 55 years established in 1976.[102] At the beginning of the study, no participant was diagnosed with diabetes. At the end of the 14-year study period, the risk for developing T2DM in relation to attained weight over the period was evaluated. The age-adjusted relative risk (RR) reference was considered a BMI < 22 kg/m^2. The age-adjusted RRs determined for a BMI of 31 kg/m^2 to < 33 kg/m^2, 33 kg/m^2 to < 35 kg/m^2, and ≥ 35 kg/m^2 were 40.3, 54.0, and 93.2, respectively. After adjusting for age, BMI was the predominant risk factor for T2DM.

Table 2.4 has been constructed from the data presented in the study to estimate annual age-standardized incidence rates, and one-year probabilities of developing T2DM. The table has been constructed assuming that the transition rate to T2DM was constant over each year. This relationship held for both whites and African-Americans.

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102 Colditz GA, Willett WC, Rotnitzky A, et al. Weight gain as a risk factor for clinical diabetes mellitus in women. *Annals of Internal Medicine*. 1995;122:481-486.

Table 2.4 Incidence Rate per Fourteen-Year Period and One-Year Probability of Transition to T2DM in the Nurses' Health Study [a]

BMI (kg/m^2)	Age-Standardized Incidence Rate over the 14-Year Period per Person-Year	Probability per 1-Year Period
25 to 26.9	0.00104	0.00104
27 to 28.9	0.00204	0.00204
29.0 to 30.9	0.00354	0.00355
31.0 to 32.9	0.00521	0.00523
33.0 to 34.9	0.00704	0.00706
Greater than or equal 35	0.01191	0.01198

a Source: Colditz GA, Willett, WC, Rotnitzky A, et al. Weight gain as a risk factor for clinical diabetes mellitus in women. *Annals of Internal Medicine*. 1995;122: 481-486.
BMI, body-mass index; kg/m^2, kilograms per meter squared; T2DM, type 2 diabetes mellitus

The Nurses' Health Study findings were extended to 1996, and the authors again found that during the total 16 years of follow-up, "the most important risk factor for type 2 diabetes was body-mass index."[103] When defining overweight as a BMI of 25 kg/m2 or higher, 61% of cases of T2DM are attributed to this factor.

Chan et al. examined 51,529 male health professionals aged 40 years to 75 years over the period of 1987 to 1992 using a survey technique and observed similar relationships between BMI and T2DM.[104] When controlling for age, men with a BMI of ≥ 35 kg/m^2 had a multivariate RR of 42.1 compared to those men with a BMI < 23 kg/m^2.

2.3 Can Type 2 Diabetes Be Prevented?

Because of the epidemic increase in prevalence of T2DM, preventive activities merit serious investigation. One very compelling reason for prevention is suggested by data

103 Hu F, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *The New England Journal of Medicine*. 2001;345:790-797.

104 Chan JM, Rimm EB, Colditz GA, et al. Obesity, fat distribution, and weight gain as risk-factors for clinical diabetes in men. *Diabetes Care*. 1994;17:961-969.

generated by the United Kingdom Prospective Diabetes Study (UKPDS).[105] Intensive pharmacologic treatment of T2DM successfully lowered microvascular complications. It was also noted though that while blood glucose was lowered during the ten-year study period, fasting plasma glucose and HbA1C progressively increased. It has been suggested that "intervention prior to the onset of diabetes may be the only way of stopping people from getting onto this slippery slope." [106]

2.3.1 REQUIREMENTS FOR DISEASE PREVENTION

Four requirements are generally listed to justify a disease-prevention program.[107] These are listed in Table 2.5.

Table 2.5 The Four Requirements for Disease Prevention [a]

The disease is an important health problem.
The natural history of the disease is understood sufficiently to measure progression.
Screening for high risk individuals should not be burdensome and should be cost-effective.
A safe, effective, and reliable method of prevention exists.

[a] Source: U.S. Preventive Services Task Force. Guide to Clinical Preventive Services, 2nd Edition. Washington, DC. U.S. Department of Health and Human Services, Office of Disease Prevention and Promotion, 1996.

There is no question that the first two of these requirements are easily met when discussing T2DM. The third is not so easily established. As previously noted, while diagnostic criteria for both pre-diabetes and T2DM are well established, screening for

105 United Kingdom Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with suplhonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837-853.

106 Zimmet P, Shaw J, Alberti KGMM. Preventing type 2 diabetes and the dysmetabolic syndrome in the real world: a realistic view. *Diabetic Medicine*. 2003;20:693-702.

107 U.S. Preventive Services Task Force. *Guide to Clinical Preventive Services, 2nd Edition*. Washington, D.C.: U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion; 1996.

diabetes has not been effective, although it is currently recommended by the ADA. Most diabetes prevention studies have avoided the question of screening and have generally enrolled only subjects at high risk of progressing to T2DM, such as those in the category of IGT. The fourth requirement, the establishment of a safe and reliable method of T2DM prevention, has been described by the DPP.

A fifth requirement, while not listed, is discussed by the U.S. Preventive Services Task Force Guide.[108] This requirement is that the intervention should be cost-effective. The task force does not systematically incorporate cost-effectiveness analysis into their recommendations, but they do suggest that "cost-effectiveness analysis raises important questions about the opportunity costs of alternative choices that decision-makers should consider." The problem is that currently, the long-term cost-effectiveness of intensive lifestyle intervention to prevent T2DM remains unknown, and this is a central issue addressed in this dissertation.

2.3.2 DESCRIPTIONS OF DIABETES PREVENTION STUDIES OTHER THAN THE DIABETES PREVENTION PROGRAM

2.3.2.1 The Malmo Feasibility Study

The Malmo study was a non-randomized study that consisted of dietary treatment and increased physical activity to attempt to prevent progression from IGT to T2DM.[109] The average BMI was > 25 kg/m^2 for the 181 male study participants, and the age range was 47 years to 49 years. A body weight reduction of 2.3% to 3.7% in the intervention subjects over a six-year period resulted in normalized glucose tolerance in 50% of subjects with IGT.

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108 Ibid.

109 Eriksson KF, Lindgarde F. Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical activity. The 6-year Malmo Feasibility Study. *Diabetologia*. 1991;34:891-898.

2.3.2.2 The Da Qing Impaired Glucose Tolerance and Diabetes Study

The Da Qing study was published in 1997.[110] The study was methodologically limited because randomization was performed based on clinics rather than by individual patient. The study, which lasted over a six-year period, examined 577 subjects with IGT who were randomized to a diet group, exercise group, or a combined diet and exercise group. The mean age of the subjects was 45 years, and the mean BMI was 26 kg/m^2. There was a 13.3% incidence of progression to T2DM in the control group, 8.3% in the diet group, 5.1% in the exercise group, and 6.8% in the diet and exercise group. Using a proportional hazards analysis that adjusted for baseline BMI and fasting glucose, the diet, exercise, and combined groups were associated with a 33% ($p < 0.03$), 47% ($p < 0.0005$), and 38% ($p < 0.005$) respective reduction in incidence of conversion to T2DM when compared to the control group. The cumulative incidence of conversion to T2DM in the control group at six years was 67.7% (95% C.I,: 59.8% to 75.2%).

2.3.2.3 The Finnish Diabetes Prevention Study (DPS)

The results of the Finnish Diabetes Prevention Study (DPS) were published in 2001.[111] The study, which was conducted over a mean duration of 3.2 years, randomly assigned 522 subjects (172 men and 350 women) to a control group (brief diet and exercise counseling) or a lifestyle intervention group. The intervention group received individual counseling with a nutritionist for seven sessions during the first year of the study, and one session every three months thereafter.

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110 Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care*. 1997;20:537-544.

111 Tuomilehto J, Lindstrom J, Erikisson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New England Journal of Medicine*. 2001;344:1343-1350.

The mean BMI of the subjects enrolled was 31.2 kg/m^2, the mean age was 55 years, and the mean fasting plasma glucose was 110 mg/dL. The weight loss goal was 5% weight reduction, which was achieved by 43% of the intervention group and 13% of the control group. The exercise goal was > 150 minutes of exercise per week; this was achieved by 86% of the intervention group and 71% of the control group.

During the first year, the mean body weight decreased by 4.2 ± 5.1 kg in the intervention group versus 0.8 ± 3.7 kg in the control group. At two years, the intervention group maintained a significantly different mean weight loss than the control group at 3.5 kg ± 5.5 kg versus 0.8 ± 4.4 kg. At the end of a five-year period, the intervention group had maintained a mean weight loss of 2.1kg.

IGT progressed to T2DM at a rate of 3% per year in the intervention group, and 6% per year in the control group.[112] At four years, the cumulative incidence of T2DM was 11% (95% C.I.: 6% to 15%) in the intervention group, and 23% (95% C.I.: 17% to 29%) in the control group. The authors state that "according to the Cox regression analysis of all person-years accumulated, the cumulative incidence of diabetes was 58% lower in the intervention group than in the control group (hazard ratio, 0.4; 95% C.I.: 0.3 to 0.7; $p < 0.001$)."[113] The number needed to treat to prevent one case of T2DM was 22 for one year and 5 for five years.

2.3.3 THE DIABETES PREVENTION STUDY (DPP)

The DPP randomly assigned 3,234 subjects from 1996 to 1999 to one of three

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112 Zimmet P, Shaw J, Alberti KGMM. Preventing type 2 diabetes and the dysmetabolic syndrome in the real world: a realistic view. *Diabetic Medicine*. 2003;20:693-702.

113 Tuomilehto J, Lindstrom J, Erikisson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New England Journal of Medicine*. 2001;344:1343-1350.

interventions: placebo, metformin, or intensive lifestyle intervention.[114] The emphasis of the discussion of this study will be on the placebo and lifestyle intervention arms of the study, as these are the results that this model will evaluate.

Selection criteria included an age of at least 25 years and a BMI of > 24 kg/m^2 (> 22 kg/m^2 in Asians). As previously noted, the subjects' main entry criterion was a diagnosis of IGT based on the results of a single 75-g OGTT (two-hour post-load glucose ≥ 140 mg/dL and < 200 mg/dL), and a FPG of 95mg/dL to 125 mg/dL.[115]

Multiple exclusion criteria were incorporated into the DPP design.[116] These included any history of cardiovascular disease or uncontrolled hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 105 mmHg). Other exclusion criteria included the following: history of cancer within five years of the study; history of renal disease (creatinine ≥ 1.4 mg/dL for men or ≥ 1.3 mg/dL for women); anemia (hematocrit < 36% for men and < 33% for women); hepatitis; pulmonary disease; chronic infection such as human immunodeficiency virus (HIV) or active tuberculosis; or history of endocrine disease. The authors stated that "most exclusion criteria were chosen to reduce the risk of adverse effects related to the interventions."[117]

The average age of the subjects was 50.6 years, the average BMI was 34.0 kg/m^2 (obese class I), and there were 32.3% males and 67.7% females enrolled. Ethnic mixture included 54.7% whites, 19.9% African Americans, 15.7% Hispanics, 5.3% American Indians, and 4.4% Asians. A positive family history for T2DM was reported in 69.4% of

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114 Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.

115 Diabetes Prevention Program Research Group. The Diabetes Prevention Program: design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care*. 1999;22:623-634.

116 Ibid.

117 Ibid.

subjects. Fasting plasma glucose averaged 106.5 ± 8.3 mg/dL, and the two-hour post glucose level average was 164.6 ± 17.0 mg/dL. Average follow-up time was 2.8 years, with a range of 1.8 to 4.6 years. The blinded treatment phase was terminated in May 2001.

The lifestyle intervention consisted of individual counseling on nutrition and exercise for sixteen sessions over the first twenty-four weeks of the program. The subjects were then followed at a minimum of a monthly follow-up for the duration of the program.

The goal of the lifestyle intervention program was a 7% weight loss, which was achieved by 50% of the subjects in this arm of the study at the end of the twenty-four week curriculum. At the time of the most recent visit of the lifestyle subjects, 38% had a 7% weight loss. The lifestyle group lost approximately 5.45 kg (an average of 5% of body weight) at the end of two years, and 4.1 kg (an average of 3.5% body weight) at the end of three years.[118]

The primary outcome measurement of the study was a diagnosis of T2DM. Subjects were tested annually with an OGTT, and semiannually with a FPG test. Cut-off values for normal were ≥ 200 mg/dL for the OGTT, and ≥ 126 mg/dL for the FPG values. The subject was unmasked when these values were reached, but the subject was asked to remain on their assigned treatment regimen until their FPG exceeded 140 mg/dL.

The crude incidence of developing T2DM was 11.0 cases per 100 person-years in the placebo group, versus 4.8 cases per 100 person-years in the lifestyle intervention group. The incidence of T2DM was higher in the placebo group than expected and was thought to be secondary to the selection of patients at higher risk (abnormal IGT and higher IFG), or perhaps to the increased frequency of glucose testing. The estimated cumulative incidence of T2DM at three years was 28.9% in the placebo group and 14.4% in the lifestyle

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118 Teutsch S. The cost of preventing diabetes: what do we know and what do we need to know? *Diabetes Care*. 2003;26:238-239.

group. Cumulative incidence is very important because this value is used to calculate the one-year probability of transition from IGT to T2DM for the Markov Model. The one-year probability of developing T2DM is 0.1075 for the placebo group and 0.0505 for the lifestyle group.

Approximately 3% to 5% of the lifestyle cohort, and 6% to 11% of the control group developed diabetes on a yearly basis. Intensive lifestyle intervention reduced the risk of progression of IGT to T2DM by 58% (95% C.I.: 48% to 66%) when compared to the control group. The number needed to treat over a three-year period to prevent one case of T2DM is 6.9 (95% C.I., 5.4 to 9.5) for the lifestyle intervention group.

It is also important to note the percentage of subjects who had reverted to NGT in each group at the end of the three-year period. Using a definition of NGT as both a two-hour post-challenge glucose of < 140 mg/dL and a FPG of < 110 mg/dL, approximately 30% of patients in the lifestyle group and 19% of the placebo group reverted to normal. These values are given as estimations from graphical DPP presentations. The one-year probability of reversion to NGT then becomes approximately 0.1121 for the lifestyle group and 0.0678 for the placebo group.

The most common adverse effect in the lifestyle intervention group was a complaint of musculoskeletal symptoms, which had an occurrence of 24.1 events per 100 person-years, versus 21.1 events per 100 person-years in the placebo group. There were no statistically significant differences in the incidence of adverse events, hospitalizations or deaths between the two groups. [119]

There were three deaths in the lifestyle intervention group and five deaths in the

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119 Diabetes Prevention Program Research Group. Costs associated with the primary prevention of type 2 diabetes mellitus in the Diabetes Prevention Program. *Diabetes Care*. 2003;26:36-47.

placebo group over the first three years of the study (1.023 and 1.689 deaths per 1,000 person-years, respectively).[120] The one-year probability of death is 0.001 for the lifestyle group and 0.0017 for the placebo group using these figures. As a comparison, the probability of death for a subject of average age of 52 years is approximately 0.005 using data from life tables published in the National Vital Statistics Reports.[121]

It has been suggested by the authors of the DPP that the lifestyle group had a more successful effect in those subjects who had a BMI < 35 kg/m^2. Table 2.6 gives the incidence of T2DM according to baseline BMI. In addition, the estimated probability per one-year period is also calculated.

Table 2.6 Incidence of T2DM by Initial Body-Mass Index in the Diabetes Prevention Program[a]

	Incidence (In Cases per 100 Person-Years)		In Probability per 1-Year Period	
Body-Mass Index[b]	**Placebo**	**Lifestyle**	**Placebo**	**Lifestyle**
22 to less than 30	9.0	3.3	0.094	0.034
30 to less than 35	8.9	3.7	0.093	0.038
Greater than or equal 35	14.3	7.3	0.154	0.076

[a] Source: The Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine* 2003;346:393-403.
[b] Body-Mass Index reported in kg/m^2
CI, confidence interval; kg/m^2, kilograms per meter-squared; T2DM, type 2 diabetes mellitus

Compared to the placebo group, the lifestyle intervention group experienced a 65% (95% C.I.: 46% to 77%) reduction in incidence of T2DM in the BMI subcategory of

120 Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518-2523.

121 Arias E. *United States Life Tables*, 2000. Hyattsville, MD: National Center for Health Statistics; 2002. vol. 51;3.

22 kg/m^2 to < 30 kg/m^2, a 61% (95% C.I.: 40% to 75%) reduction in the BMI subcategory of 30 kg/m^2 to < 35 kg/m^2, and a 51% reduction (95% C.I.: 34% to 63%) in reduction in the BMI subcategory ≥ 35 kg/m^2.

2.3.4 CHAPTER SUMMARY

The basic pathophysiology of the development of T2DM has now been described as well as the role of obesity in this development. Given this background for the disease state of T2DM, the literature review will now turn to current studies on prevention of T2DM, and the possible cost-effectiveness of intensive life style intervention.

CHAPTER 3 – LITERATURE REVIEW: COMPONENTS OF A COST-EFFECTIVENESS ANALYSIS OF PREVENTION OF T2DM

3.1 Chapter Overview – An Introduction to Cost-Effectiveness Analysis

How does a health care provider decide to allocate resources for health care, and in particular, preventive health care? Preventive care emphasizes a reduction in morbidity and mortality and involves a great deal of uncertainty. Diagnostic and treatment-oriented care interventions may be comparatively easier for the health care provider to analyze, and ultimately favor, because an "identifiable life" is part of the equation.[122] The dilemma where there are limited resources for health care is how to apply these resources: to allocate towards those in healthcare need, to allocate to prevent this need in the first place, or both. [123]

A cost-effectiveness analysis (CEA) is one method to aid in distribution of health care resources. Torrence et al. made the following statement about the value of a CEA when assessing the impact of introducing a new intervention: "Cost-effectiveness analysis describes and contrasts the costs and outcomes of a "treatment" course of events that would be expected to occur with the intervention and the costs and outcomes of a "comparator" course of events without the intervention."[124] A CEA "summarizes the expected benefits, harms, and costs of adopting and translating a clinical recommendation into

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122 Beauchamp TL, Childress JF. Ch. 6 - Justice. In: Beauchamp TL, Childress JF, eds. *Principles of Biomedical Ethics*. New York: Oxford University Press; 1994.

123 Ibid.

124 Torrance GW, Siegel JE, Luce BR. Ch. 3 - Framing and Designing the Cost-Effectiveness Analysis. In: Gold MR, Russell LB, Siegel JE, et al., eds. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press; 1996.

practice."[125] The analyst attempts to find the alternative that offers the maximal benefits for a given health expenditure. An alternative explanation might be that the analyst wishes to minimize the cost of achieving the health care benefit.[126]

The results of a cost-effectiveness analysis are commonly presented as a ratio with the net increase in health care cost in the numerator and the net increase in health care benefit in the denominator. Hunink et al. use the following formula to represent this ratio:[127]

$$\Delta C/\Delta E = (\Delta CProg + \Delta CInd + \Delta CMorb + \Delta CSE + \Delta CProg\Delta LE)/\Delta E$$

in which the numerator is represented by ΔCProg = the cost of the program; ΔCInd = the cost or savings created by implementing the intervention; ΔCMorb = the cost or savings secondary to averting mortality; ΔCSE = the cost of treatment of side effects; and ΔCProgΔLE = the cost of health care related to the disease addressed by the intervention in added years of life. The denominator, ΔE, represents the change in health benefit, which may be represented by values such as number of cases averted, number of life-years saved, or the combined measure of quality-of-life year, which allows for an interaction of quality of life with length of life.

For this dissertation analysis, it appears that the use of intensive lifestyle intervention is effective in preventing T2DM on a short-term basis at an acceptable cost (as will be described later in this chapter). Unfortunately, the decision to implement lifestyle intervention programs on a long-term basis for prevention of T2DM cannot wait until the current cohort under investigation lives out another 20 to 30 years (the anticipated range of

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125 Saha S, Hoerger TJ, Pignone MP, et al. The art and science of incorporating cost effectiveness into evidence-based recommendations for clinical preventive services. *American Journal of Preventive Medicine*. 2001;20:36-43.

126 Hunink MGM, Glasziou PP, Siegel JE, et al. Ch. 9 - Constrained Resources. In: Huninck MGM, Glasziou PP, Siegel JE, et al., eds. *Decision Making in Health and Medicine: Integrating Evidence and Values*. Cambridge: Cambridge University Press; 2001.

127 Ibid.

life expectancy for the cohort with an average age of 50.6 years) in order to use the actual data generated to produce a CEA.

Researchers who wish to evaluate cost-effectiveness in this sort of situation turn to what is described by Torrence et al. as a "what if" study, or a threshold analysis.[128] This type of analysis allows the researcher to explore the uncertainty of the problem using techniques such as sensitivity analyses to address issues including range of costs for the program, or acceptable efficacy rate of the intervention. This type of analysis may also be implemented for any of the other variables in the cost-effectiveness formula to help to generate information useful to policy makers when formulating recommendations to maximize health benefits within a defined health care budget. The Third U.S. Preventive Services Task Force also recommends using these types of sensitivity analyses to help delineate population subgroups that might benefit most from a healthcare service. [129]

The next section of this chapter will describe some of the theoretical bases behind CEAs. Current studies that have attempted to model and evaluate long-term cost-effectiveness of T2DM will be presented. The data that will be incorporated into the numerator and denominator of the cost-effectiveness model will then be discussed.

3.2 The Theory Underlying Cost-Effectiveness Analysis

There are two similar theoretical models upon which cost-effectiveness analysis is based. The first, welfare economics, is the basic underlying theoretical foundation for economic evaluation of health care. Garber et al. states that "welfare economics is

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128 Torrance GW, Siegel JE, Luce BR. Ch. 3 - Framing and Designing the Cost-Effectiveness Analysis. In: Gold MR, Russell LB, Siegel JE, et al., eds. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press; 1996.

129 Saha S, Hoerger TJ, Pignone MP, et al. The art and science of incorporating cost effectiveness into evidence-based recommendations for clinical preventive services. *American Journal of Preventive Medicine*. 2001;20:36-43.

concerned with the means by which we can assess the desirability – from the societal point of view – of alternative allocations of resources."[130] The main assumption of welfare economics is that individuals maximize a preference function.[131] This preference function, or "utility" is assumed to follow a logical consistency, and the overall welfare of society is a function of these individual preferences.[132] In a perfectly competitive market, the above, "rational" individuals will chose to maximize their utility, and therefore maximize social welfare. [133]

One basic concept of welfare economics is that each individual is the best judge of his or her welfare.[134] No new intervention is adopted if movement to an alternative creates a "worse" state for at least one individual. This leads to the concept of Pareto optimality. A situation is found to Pareto optimal if by re-allocation of resources, you cannot make someone better off without making someone worse off. [135]

An important concept in employing welfare economics as a theoretical framework for economic evaluation of healthcare is the use of a "social utility function," which is defined as the aggregate of individual utilities.[136] Problems arise not only in attempting to define this aggregate, but also in actually defining the person's utility itself. In addition, welfare

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130 Garber AM, Weinstein MC, Torrance GW, et al. Ch. 2 -Theoretical Foundations of Cost-Effectiveness Analysis. In: Gold MR, Russell LB, Siegel JE, et al., eds. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press; 1996.

131 Ibid.

132 Ibid.

133 Raftery J. Economic evaluation: an introduction. *British Medical Journal*. 1998;316:1013-1014.

134 Tsuchiya A, Williams A. Ch. 2 - Welfare economics and economic evaluation. In: Drummond M, McGuire A, eds. *Economic Evaluation in Health Care: Merging Theory with Practice*. Oxford: Oxford University Press; 2001.

135 McGuire A. Ch. 1 - Theoretical concepts in the economic evaluation of health care. In: Drummond M, McGuire A, eds. *Economic Evaluation in Health Care: Merging Theory with Practice*. Oxford: Oxford University Press; 2001.

136 Garber AM, Weinstein MC, Torrance GW, et al. Ch. 2 -Theoretical Foundations of Cost-Effectiveness Analysis. In: Gold MR, Russell LB, Siegel JE, et al., eds. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press; 1996.

economics does not allow for inclusion of any other aspect of utility other than that generated by the consumption of goods and services.[137]

As an alternative to welfare economics, the concept of "extra-welfarism" has been introduced. Utility, as measured by the extra-welfarists, is not only a value generated by consumption of goods and services, but also includes "extra" value from an individual's characteristics, such as that derived from an emotional or physical state.[138] An excellent explanation of these differences is given by Dhanani who states that welfare economics defines health care as "something that contributes to overall well being" while extra-welfarist economics defines health care as contributing to health itself.[139] The emphasis is on health in addition to utility. Extra-welfarists have been noted to stress the concept of need instead of the more traditional economic concept of demand. Culyer, in describing extra-welfarism, makes the statement that "need depends on the ability to benefit from healthcare; demand depends on preferences backed by the ability to pay.[140] Welfare economics, therefore, stresses concepts such as "willingness to pay" whereas extra-welfarists emphasize the concept of need when making assessments of the efficiency of health care systems.

One major problem which occurs when using either of these models is that they both assume the market is in perfect competition. The implications are that there is perfect information, free entry and exit from the market, the products are homogeneous, and the

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137 Dhanani K. The neo-classical and extra-welfarist approaches to health. Available at: http://www.econ.qmw.ac.uk/NHS_reforms.com/student_file/welfare4.1pdg. Accessed March 2004.

138 Ibid.

139 Ibid.

140 Culyer AJ, Newhouse JP. *Handbook of Health Economics*. New York: Elsevier; 2000.

buyers and sellers are unable to affect price.[141] This is obviously not the case when describing the health care market.

The differences between these two basic theoretical concepts allow for the different methodologies used for what has been broadly described here as "cost-effectiveness analysis." The methodologies include a cost-benefit analysis (CBA), a cost-effectiveness analysis (CEA), and a cost-utility analysis (CUA). All effects of an intervention are valued in monetary units in a CBA.[142] A CEA uses some non-monetary terms to measure some effects. This is particularly noted in valuation of life, which is measured in a non-monetary unit of health outcome. One difficulty described in using a CEA methodology is that one is unable to compare interventions using different outcomes, such as life-year saved, or cases of a disease prevented. A CUA is considered by many to be a form of CEA, in which effectiveness is measured as a preference-adjusted outcome, referred to as a utility. The most common utility measurement used is the quality-adjusted life-year (QALY), which allows for combining quantity and quality of life outcomes.[143] Using utility as an outcome, and therefore deriving a cost per quality-of-life ratio, helps to address the problem of comparisons across different outcomes that arises with the use of CEAs.

3.3 Current Evaluations of Long-Range Cost-Effectiveness of T2DM Prevention

The following studies attempt to assess the long-range cost-effectiveness of the use

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141 Dhanani K. The neo-classical and extra-welfarist approaches to health. Available at: http://www.econ.qmw.ac.uk/NHS_reforms.com/student_file/welfare4.1pdg. Accessed March 2004.

142 Chrischilles EA. Ch. 5- Cost-Effectiveness Analysis. In: Bootman JL, Townsend RJ, McGhan WF, eds. *Principles of Pharmacoeconomics*. Cincinnati: Harvey Whitney Books Company; 1996.

143 Coons SJ, Kaplan RM. Ch. 6- Cost-Utility Analysis. In: Bootman JL, Townsend RJ, McGhan WF, eds. *Principles of Pharmacoeconomics*. Cincinnati: Harvey Whitney Books Company; 1996.

of lifestyle intervention for prevention of T2DM. Before examining these studies, it is important to note the currently suggested limits for cost-effectiveness of a treatment used in the U.S. The U.S. Public Health Service has made no recommendation for a threshold value for cost effectiveness,[144] but a commonly cited value is $50,000 per QALY. [145, 146] Other guidelines suggest that a treatment is considered to be highly cost-effective at less than $20,000 per life-year saved or $20,000 per QALY, moderately cost-effective in the $20,000 to $40,000 range, and borderline cost-effectiveness in the $40,000 to $60,000 range. These same guidelines suggest that treatment is considered expensive at values of > $60,000 per life year saved or QALY.[147]

3.3.1 LONG-TERM PROJECTION IN THE U.S. USING DPP DATA

In an abstract presented at the 18th International Diabetes Federation Congress in 2003, Palmer et al. used a simulation model (a Markov model with Markov states of IGT, T2DM, and death, an unknown perspective, and unknown Markov cycle) to calculate costs per life-year gained over a patient's lifetime comparing the three treatment arms of the DPP: intensive lifestyle changes, metformin, or placebo.[148] Table 3.1 gives the results of the placebo and lifestyle comparisons. The lifestyle intervention was considered "highly cost-effective when judged by current international health economic standards." The

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144 Barnett PG. Introduction to cost-effectiveness analysis. *VA Health Service Research and Development Center*. Available at: http://www.herc.research.med.va.gov/CEM.htm. Accessed October 2004.

145 Ibid.

146 Owens DK. Interpretation of cost-effectiveness analyses. *Journal of General Internal Medicine*. 1998;13:716-717.

147 Gruninger U. Economic evaluation in health: a primer and/or a cheat sheet. Available at: http://ourworld.compuserve.com/Homepages/Ulrich_Grueninger/AVAL_1.html. Accessed July 2004.

148 Palmer AJ, Roze S, Cabrieres L, et al. Long-term projection of the costs of the Diabetes Prevention Program in the USA using the CORE diabetes prevention model: intensive lifestyle changes and metformin are both cost-effective. Paper presented at: 18th International Diabetes Federation Congress, 2003; Paris.

authors state in the abstract that the outcomes were most sensitive to the following variables: the efficacy of the lifestyle intervention to prevent development of T2DM; the probability of developing T2DM in the placebo arm; the duration of the effect of the interventions; the relative risk of mortality for the state of T2DM compared to IGT; and the costs of the intervention program.

Table 3.1 Results of the Long-Term Projection of the Costs of the Diabetes Prevention Program by Palmer et al.[a]

Treatment Arm	Life-Expectancy in Years	Total Lifetime Costs per Patient ($)	Cost per Life-Year Gained ($)
	Non-Discounted (Discounted)		
Placebo	23.8 (16.5)	80,045	Comparator
Lifestyle Intervention	24.6 (16.9)	84,652	11,518

[a] Palmer AJ, Roze S, Cabrieres L, et al. Long-term projection of the costs of the diabetes prevention program in the USA using the CORE diabetes prevention model: intensive lifestyle changes and metformin are both cost-effective. Paper presented at: 18th International Diabetes Federation Congress, 2003; Paris.

3.3.2 LONG-TERM PROJECTIONS USING INTERNATIONAL DATA

Palmer et al. have also addressed the cost-effectiveness of implementing DPP-like interventions in Australia, France, Germany, Switzerland, and the United Kingdom.[149] A three-state Markov model was again utilized (IGT, T2DM, and death), and direct-medical costs were included. Results showed an overall mean incremental improvement in life-expectancy of 0.90 years for the lifestyle intervention. The mean improvement in non-discounted life expectancy was 0.22. Cost savings were noted in all countries but the United Kingdom. Outcomes of this model were most sensitive to the same variables described in the Palmer et al. study presented in section 3.3.1: the efficacy of the lifestyle

149 Palmer AJ, Roze S, Valentine WJ, et al. Intensive lifestyle changes or metformin in patients with impaired glucose tolerance: modeling the long-term health economic implications of the Diabetes Prevention Program in Australia, France, Germany, Switzerland, and the United Kingdom. *Clinical Therapeutics*. 2004;26:304-321.

intervention to prevent development of T2DM; the probability of developing T2DM in the placebo arm; the duration of the effect of the interventions; the relative risk of mortality for the state of T2DM compared to IGT; and the costs of the intervention program.

3.3.3 EARLY COST-EFFECTIVENESS STUDIES OF DIABETES PREVENTION

Segal et al. evaluated the cost-effectiveness of multiple programs to prevent T2DM in a paper published in 1998.[150] Programs selected included intervention studies that were of both randomized control and observational study design. Table 3.2 describes the six major program types that were analyzed.

Table 3.2 Programs Analyzed by Segal et al.[a]

Program Type	Targeted Group
Intensive diet and behavioral modification	Seriously obese With and without IGT
Intensive diet and behavioral modification	Women with previous gestational diabetes IGT only
Surgery for severe obesity	Seriously obese With and without IGT
Group behavioral modification for men	Overweight and obese With and without IGT
General practitioner advice	Obese With and without IGT
Media campaign with community support	General population

[a] Segal L, Dalton A, Richardson J. Cost-effectiveness of the primary prevention of non-insulin dependent diabetes mellitus. *Health Promotion International*. 1998; 13:197-209.
IGT, impaired glucose tolerance

Outcomes used for the study were reduction in diabetes years and life-years saved. The authors stated they made no attempt to use QALYs as an outcome because the type-of evidence required was not available. This evidence would include utility scores for diabetes (preferably by disease stage), for obesity, and for successful and failed weight loss.

150 Segal L, Dalton A, Richardson J. Cost-effectiveness of the primary prevention of non-insulin dependent diabetes mellitus. *Health Promotion International*. 1998;13:197-209.

A five-year Markov-cycle model was developed for each program using the Markov states of T2DM, IGT and NGT. Transitions matrices were developed based on the results of the studies evaluated. Mortality vectors were derived for each program type, with one set of vectors developed for those subjects who maintained weight loss, and a second set for those who were either in the control group or were unsuccessful (both groups were assumed to have the same morbidity and mortality outcomes).

Potential downstream cost savings that were assumed to be generated secondary to prevention of T2DM were incorporated into the model. The cost of diabetes in Australia was estimated at A$1,800 per annum (A$ ~ US$1,340). A discount rate of 5% per annum was used for future benefits and costs.

Due to the variability in types of programs analyzed, there were great fluctuations in the life-years gained and reduction in diabetes years. Both of the first two programs described in Table 3.2 incorporated diet and behavioral modification, which are similar to the DPP lifestyle intervention. Costs of both of these programs are listed as A$2,500 (A$ ~ US$1,860) and are apparently a one-time charge in the first five-year Markov cycle. The intensive diet and behavioral modification program for the seriously obese (for the IGT group) resulted in a gross cost per life-year saved of US$4,300, and a net cost per life-year saved of US$1,900. This study had a reduction of incidence of T2DM from 70% to 30%.

Similar results were found for the intensive diet and behavioral program aimed at women with previous gestational diabetes. This program resulted in a gross cost per life-year saved of US$3,300 in the IGT only group, and net cost per life-year saved of US$1,700. There was 50% reduced incidence of T2DM in this group. At the time of this study, the authors stated that all of the programs "fell well within community expectations

of what constitutes reasonable cost to gain a year of life." [151]

There were numerous limitations to this study. The models were not particularly dynamic, as a single transition matrix was used to progress the cohorts in each model through the Markov states. The authors also felt the downstream cost-savings value was underestimated, in part due to the fact that "costs of managing other diseases, such as cardiovascular, for which weight and physical activity are also risk factors," were excluded.[152]

3.3.4 SUMMARY

The primary question addressed in this dissertation, "Is primary prevention of T2DM cost-effective on a long-term basis?" seems to be answered in the affirmative by the above studies. However, the studies also confirm the need for further research on the topic.

The Segal et al. study uses a very limited methodology.[153] The Palmer et al. studies do not incorporate NGT into the model. Neither set of authors incorporate the effect of obesity on costs, or mortality. In addition, neither study attempted to incorporate utilities into the evaluation. All of these limitations are addressed in this dissertation.

3.4 Current Economic Analyses of the DPP

The Diabetes Prevention Program Research Group (DPPRG) has published two economic analyses based on the results of the DPP. These studies include a cost-analysis of the program and a within-trial cost-effectiveness analysis comparing the lifestyle inter-

151 Ibid.

152 Ibid.

153 Ibid.

vention and metformin treatment arms to each other and to the placebo group.[154,155] A detailed description follows.

3.4.1 A COST-ANALYSIS OF THE DPP

In January 2003, a cost analysis of the DPP was published by the DPPRG.[156] The details of the intervention and results are discussed in Section 2.3.3. The costs include those for the intervention, direct medical costs, direct non-medical costs, and indirect costs, and are adjusted to year 2000 U.S. dollars using the Consumer Price Index and the Medical Consumer Price Index.[157] The research component of the study was omitted, which included the costs of recruitment, data collection, and surveillance. Direct medical costs included screening, the actual intervention, and care outside of the DPP. These costs were those "usually paid by health systems."[158] A description of these costs, which will be incorporated into the model used in this dissertation follows.

3.4.1.1 Screening

Screening was performed using an OGTT. The authors "estimated the direct medical cost of identifying one subject with IGT as the number of OGTTs performed to success-

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154 Diabetes Prevention Program Research Group. Costs associated with the primary prevention of type 2 diabetes mellitus in the Diabetes Prevention Program. *Diabetes Care*. 2003;26:36-47.

155 Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518-2523.

156 Diabetes Prevention Program Research Group. Costs associated with the primary prevention of type 2 diabetes mellitus in the Diabetes Prevention Program. *Diabetes Care*. 2003;26:36-47.

157 Labor Statistics Data. Consumer Price Index: Medical Care Services. *U.S. Bureau of Labor Statistics*. Accessed April 2004.

158 Diabetes Prevention Program Research Group. Costs associated with the primary prevention of type 2 diabetes mellitus in the Diabetes Prevention Program. *Diabetes Care*. 2003;26:36-47.

fully identify one randomized participant times the unit cost of the OGTT."[159] The direct medical cost of an OGTT was estimated at $17, and 8.1 OGTTs were required to identify a subject for successful randomization. The value used for the direct medical cost of OGTT per subject randomized was $139.

3.4.1.2 Cost of the Intervention

The lifestyle intervention, a sixteen-lesson curriculum including diet, exercise and behavioral modification, was given to each subject one-on-one over the first twenty-four weeks of the study. The subjects then continued to meet with counselors, either individually or in groups on a monthly basis. The intervention was most intensive in year one and was calculated to be $1,399 for this period. The cost of staffing for this year was $750 (54%). Year two cost was calculated to be $679, with staffing cost calculated to be $339 (50%). Year three cost was calculated to be $702, with staffing calculated at $337 (48%). The total cost of the intervention for three years was $2,780, which includes the cost of screening. The placebo group received what was described as standard lifestyle recommendations. The cost in year one for this arm was $43, and in year two and three was $18, for a total of $79. The cost rises to $218 for the three-year period when screening is included.

3.4.1.3 Cost of Care Outside of the DPP

The final component of direct medical costs was those costs that were "incurred or averted by the interventions that were captured by costs of medical care outside the DPP."[160] It is important to note that although the original report of the DPP states that

159 Ibid.

160 Ibid.

there was a significantly different rate of adverse musculoskeletal symptoms between the lifestyle group and the placebo group (see Section 2.3.3), the cost analysis of the report states that "there were no statistically significant differences in the incidence of serious adverse events or adverse events among the three intervention groups." [161]

The DPPRG used cost estimates for the following variables to calculate the direct costs of medical care outside of the DPP: hospital days; emergency room visits; urgent care visits; outpatient visits; calls to providers; and prescription medications (for medications outside of the DPP). The report does not indicate if these costs are secondary to adverse events related to the intervention, costs related directly to IGT or T2DM, or costs secondary to a health condition unrelated to either of the above. Interestingly, the authors state that costs of treatment for evaluations such as the exercise stress tests that were required in 19% of the lifestyle intervention subjects were "captured as adverse events." This was based on a pre-design requirement that participants who experienced new episodes of cardiovascular symptoms/events were eligible to continue DPP intervention except for those in the lifestyle arm. Cardiac risk in these subjects was designed to be evaluated by exercise testing in order to modify the exercise program if necessary.

The per capita direct medical costs over the three-year period were $5,011 ($1,670/year) for the placebo group and $4,579 ($1,526/year) for the lifestyle group (a 9.4% difference). Resource utilization was lower in five of the six categories evaluated for the lifestyle group (costs for emergency room visits were higher for the lifestyle group than for the placebo group).

3.4.1.4 Summary – How Useful is the DPP Data?

The authors state that "the per capita costs of the lifestyle intervention relative to

161 Ibid.

the placebo intervention were $2,269 over three years from the perspective of a large health system."[162] Conclusions drawn from the analyses suggested that most of this additional cost was secondary to "staff time used for counseling and adherence monitoring."[163] This information provides a very useful starting point for a value to include for the cost of an intensive lifestyle intervention in the dissertation model.

The calculated per capita direct medical costs of care outside of the DPP, while in an excellent format for a standard decision-tree model, are problematic for use in a Markov model format. The main difficulties in using these data are that a control group (non-IGT) value of health care is not given, and there is no differentiation between the costs of patients in each group who develop T2DM versus those who do not. These difficulties will be discussed in following sections that cover cost of illness of these states.

3.4.2 THE WITHIN-TRIAL COST-EFFECTIVENESS DPP ANALYSIS

3.4.2.1 Model Design

The cost-analyses provided by the above study allowed the DPPRG to perform a within-trial cost-effectiveness of the lifestyle intervention versus placebo for prevention of T2DM.[164] A decision-analysis model was utilized using the three-year study period. The analyses were run using two perspectives: the perspective of the health system and a societal perspective. Costs were adjusted to year 2000 U.S. dollars. The analyses were performed both undiscounted and using a discount rate of 3% for costs and benefits.

Outcomes used were cases of diabetes prevented and QALYs. Analyses using the health system perspective included only direct medical costs. Analyses from a societal

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162 Ibid.

163 Ibid.

164 Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518-2523.

perspective for cost per case of diabetes prevented included direct medical costs, direct nonmedical costs, and indirect costs. The societal perspective analyses of cost per QALY gained included direct medical and nonmedical costs.

3.4.2.2 Health Utilities

Health utilities were measured using the Self-Administered Quality of Well-Being Index. This quality of life instrument was administered annually. Table 3.3 gives the annual utility scores obtained for the lifestyle group and the placebo group.

Table 3.3 Utility Scores of the Diabetes Prevention Program[a]

	Utility Scores	
	Lifestyle	**Placebo**
Year		
1	0.703 ± 0.118	0.686 ± 0.121
2	0.695 ± 0.122	0.675 ± 0.122
3	0.692 ± 0.125	0.657 ± 0.125

[a] The Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or Metformin for the Primary Prevention of Type 2 Diabetes. *Diabetes Care*. 2003;26:2518-2523.

There were three deaths in the lifestyle group (1.023 deaths per 1,000 person-years) and five deaths in the placebo group (1.689 deaths per 1,000 person-years). Over the three-year period, the total QALYs gained in the lifestyle group versus the placebo group was 0.072.

3.4.2.3 Results

Results from the health system perspective will be emphasized, as that is the proposed perspective of the Markov model to be used in this dissertation.

Based on a number needed to treat of 6.9 participants to prevent one case of diabetes, the cost per case of diabetes prevented from the health system perspective versus placebo

was $15,655. The cost per QALY gained from the health system perspective was $31,512.

The following sensitivity analyses were performed: reducing personnel cost from 75% to 25%; reducing intervention effectiveness from 20% to 10%; translating the intervention from an individual counseling format to a group counseling format; and comparing discounting costs and outcomes at 3% versus no discounting. These results are given in Table 3.4, and will help as a guide for sensitivity analyses required for the dissertation.

Table 3.4 Baseline Results and Sensitivity Analyses of the Cost of the Diabetes Prevention Program per Case of Diabetes Prevented and Quality of Life Year (QALY) Gained from a Health System Perspective [a]

Variable	Cost per Case of Diabetes Prevented (U.S $)	Cost per QALY Gained (U.S. $)
Lifestyle vs. Placebo	15,655	31,512
Personnel Cost		
25% Reduction	11,755	23,662
50% Reduction	7,855	15,811
75% Reduction	3,956	7,963
Group Intervention	4,462	8,982
Intervention Effectiveness		
10% Reduction	17,243	35,013
20% Reduction	18,831	39,389
Discounting		
3% Discount Rate	15,804	32,029

[a] The Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or Metformin for the Primary Prevention of Type 2 Diabetes. Diabetes Care. 2003;26:2518-2523.

3.4.2.4 Summary

The DPPRG suggests that an intensive lifestyle intervention to delay or prevent T2DM is cost-effective from a health system perspective. Cost savings could potentially occur in each of the following direct medical cost categories: diabetes education; nutritional counseling; glucose monitoring; treatment; surveillance of complications; and treatment of

complications.[165] The authors then reiterate the need for estimating the long-term cost-effectiveness effects of intensive lifestyle intervention to prevent or delay T2DM using modeling beyond the time horizon of the DPP itself.

3.4.3 SUMMARY OF THE ECONOMIC ANALYSES OF THE DIABETES PREVENTION PROGRAM

A summary of the economic analyses developed by the DPPRG is valuable as a preparation for creating a Markov model to estimate the long-term effects of a lifestyle program to prevent T2DM. The modeler is able to identify data for variables that may be important to include in the dissertation model. A discussion of additional variables needed for a long-term Markov model follows.

3.5 The Numerator of a Diabetes Prevention Cost-Effectiveness Model: Cost-of-Illness (COI)

Collecting the information required to construct a Markov model can be thought of as "building a database." To model the numerator of a cost-effectiveness analysis beyond the time horizon of the DPP, numerous variables are required. These will first include analyzing the excess costs of IGT and T2DM. In addition, simply using these long-term excess costs of abnormal glucose homeostasis may not address the entire direct healthcare cost requirements of the models, as they may not include additional costs due to the obese nature of the cohort. Therefore, the long-term excess cost of obesity in relation to abnormal glucose homeostasis will also be addressed.

Subjects in the dissertation model also fall into the category of NGT. Costs involved with this population may be viewed in two possible ways. Traditionally, patients in this "normal" category are given no costs for health care outside of that for the intervention

165 Ibid.

because they are the control group to which the diabetic population is compared.

Another view, which will also be used in this model is to incorporate the fact that this NGT population is also a population with an average BMI of ≥ 30 kg/m^2. The average BMI of the DPP subject at the start of the study was 34 kg/m^2, a value that falls into the WHO category of obese class I (BMI values of 30 kg/m^2 to 34.9 kg/m^2). The 7% weight loss goal places this average patient in a BMI category of 31 kg/m^2, which still falls into this obesity category. Current literature supports the possibility that there may be an excess cost of medical care in these obese NGT patients; therefore, these excess costs should be incorporated into the model. The literature review will therefore also address the costs of obesity in subjects with NGT.

The perspective of this dissertation is that of the health care provider, so the values emphasized in the discussion will be direct medical costs and in particular, those used in the DPP. These include hospital days, emergency room visits, urgent care visits, outpatient visits, calls to providers, and prescription medications. All pertinent cost variables will be translated when possible into year 2000 dollars using the medical portion of the Consumer Price Index. [166]

This section of the dissertation will help to address the difficulty of using the cost of care that was presented in Section 3.4.1.4, the summary of the usefulness of the DPP data. As noted in Section 3.4.1.3 (Cost of Care Outside of the Diabetes Prevention Program), cost of care outside of the DPP is given for the placebo group and the intensive lifestyle intervention group. The values derived are a combined cost for all subjects in each cohort: those with NGT, those with IGT, and those with T2DM. For a Markov model approach, it may be more efficacious to determine these data separately for each category (NGT, IGT,

166 Labor Statistics Data. Consumer Price Index: Medical Care Services. *U.S. Bureau of Labor Statistics*. Accessed April 2004.

and T2DM) than in these combined states. In addition, figures for cost of medical care for a control group without abnormal glucose status will be examined.

3.5.1 HOW TO ASSESS COI OF A SPECIFIC DISEASE

Analyses that quantify the long-range economic impact of a disease are commonly called "cost-of-illness" (COI) studies. The primary component of COI of a disease is costs that are reported when the disease is listed as the primary diagnosis. Additional costs must be included such as those that are related to chronic complications from the disease and costs secondary to related comorbid conditions that have increased health care utilization.[167] The four basic methodologies to assess COI as described by Ettaro et al. will now be discussed as well as some of the methodological approaches to capturing the additional costs listed. [168]

3.5.1.1 COI Based on Aggregated Population Data

One common method of assessing COI is to study aggregated population data based on international classification of disease (ICD) codes related to the illness in question. Early in the use of this methodology, the only costs analyzed were those that were directly attributed to a disease. Therefore, the cost could not be included unless the disease in question was listed as the primary diagnosis. In the 1980s, the methodology began to change to incorporate disease events that were recorded with the disease being analyzed listed as a secondary or tertiary diagnosis. The addition of these costs was performed to address potential underestimation when calculating COI. One example of the type of

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167 Hodgson TA, Cohen AJ. Medical care expenditures for diabetes, its chronic complications, and its comorbidities. *Preventive Medicine*. 1999;29:173-186.

168 Ettaro L, Songer TJ, Zhang P, et al. Cost-of-illness studies in diabetes mellitus. *Pharmacoeconomics*. 2004;22:149-164.

problem that was frequently encountered when assessing COI of T2DM was the exclusion of costs of complications such as retinopathy or end-stage renal disease from an analysis because the diabetes diagnosis would be listed as a second or third diagnosis, or commonly, not at all.

Another method to address underestimation of costs using this methodology is to use the concept of attributable risk (AR) in the analysis. In the case of diabetes, AR seeks to identify "the relative contribution of diabetes to the overall risk of a disorder such as heart disease or renal failure."[169] AR can be considered from the perspective of the general population or from the diseased population. Using the general population perspective may underestimate risk, but disease-specific AR rates are often not readily available. One problem that occurs when using AR in a COI study is that confounders present in the analysis may lead to overstatement of the role of the disease.

3.5.1.2 The Survey Approach to COI

Self-reported surveys are another method to analyze COI. This methodology allows for an analysis on an individual level instead of an aggregate level, and is therefore, considered to be more precise. The downside of this precision is that it is more expensive, and is often based on limited sample sizes. Sampling variability due to small sample size may influence results.

3.5.1.3 Analyzing Excess Medical Costs of the Disease in Question

Ettaro et al. define excess medical costs as "the incremental difference in medical expenditures between a person with and a person without" the disease in question.[170]

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169 Ibid.

170 Ibid.

This methodology is quite helpful in an analysis of treatment interventions because the technique allows for an estimation of costs avoided. Most of the data that have been used for this methodology are derived from large administrative data sets or national medical expenditure surveys. There are two general approaches to assessing excess costs. The first method is to compute the difference without an attempt to match population characteristics. The second technique allows for case-control matching.

3.5.1.4 COI Analyses Based on Estimates of Previous Studies

Modeling techniques based on previous estimates of prevalence, healthcare use, and mortality are used in this methodology to estimate COI. The primary limitation of these analyses is that the changes in the cost of the disease in question may not depend, or only depend in part on the variables that are included in the model. Unlike changes in prevalence in a disease or secondary to inflation, the studies show that one variable that is not easily controlled for is a change in quantity or quality in health care practice related to the disease in question.

3.5.2 AN ANALYSIS OF DIABETES COI STUDIES

The following section includes a review of pertinent studies that will be used in the dissertation model to analyze the COI of diabetes.

3.5.2.1 COI Collected before 1998 [171]

In 2004, Ettaro et al. published a review article that analyzed the COI studies of diabetes that had been published with cost data collected prior to 1998.[172] The estimated COI

171 Ibid.

172 Ibid.

of diabetes (of all diagnostic categories) in the U.S. was $2.6 billion in 1969,[173] and rose to $98.2 billion by 1997.[174] Significant increases in costs were attributed to changes in diabetes prevalence and inflation. Another source of increased costs was the change in methodology of calculating COI to allow for inclusion of costs related to diabetes when the disease is listed as a secondary or tertiary diagnosis. An interesting way to evaluate the changes in COI of diabetes over the time period evaluated is to examine the ADA reports from 1987,[175] 1992[176] and 1997[177] on this topic.

3.5.2.1.1 A Comparison of the ADA COI Studies from 1987, 1992, and 1997

Ettaro et al. compared the ADA studies of the COI of diabetes from 1987 to 1997 in their review. These studies estimate COI of diabetes of all diagnostic categories, and not just T2DM. These studies all used aggregated data and attributable risk procedures. The COI direct medical cost reported values adjusted for inflation in 1997, and the values adjusted for inflation and diabetes prevalence in 1997 are reported in Table 3.5. The adjustment for inflation, as calculated by the authors of the study, used the change in gross domestic product deflator over time, and did not use the specific medical Consumer Price Index.

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173 Entamacher PS. *Report of economic impact of diabetes*. Washington, DC: US Government Printing Office; 1976. NIH Publication No. 76-1022.

174 American Diabetes Association. Economic consequences of diabetes mellitus in the US in 1997. *Diabetes Care*. 1998;21:296-309.

175 Pracon Inc. *Direct and indirect costs of diabetes in the United States in 1987*. Alexandria (VA): American Diabetes Association; 1988.

176 American Diabetes Association. *Direct and indirect costs of diabetes in the United States in 1992*. Alexandria (VA): American Diabetes Association; 1993.

177 American Diabetes Association. Economic consequences of diabetes mellitus in the US in 1997. *Diabetes Care*. 1998;21:296-309.

Table 3.5 A Comparison of American Diabetes Studies of the Direct Cost of Illness of Diabetes from 1987, 1992 and 1997 [a]

Original Year of Costing	As Reported ($ Billion)	Adjusted for Inflation ($ Billion; 1997 Values[b])	Adjusted for Inflation and Diabetes Prevalence ($ Billion; 1997 values[b])
1987	9.60	13.05	20.24
1992	45.22	50.98	70.80
1997	44.14	44.14	44.14

[a] Ettaro L, Songer TJ, Zhang P, et al. Cost-of-illness studies in diabetes mellitus. Pharmacoeconomics. 2004;22:149-64.
[b] Inflation adjustment using the gross domestic product deflator over time

3.5.2.1.1.1 Comparison of the 1987 ADA Study to the 1992 Study

At least part of the differences in direct costs which are noted when comparing the ADA studies of 1987 to 1992 is thought to be related to the large increase in costs calculated for hospital services during this period.[178] One factor contributing to the overall increase was the increase in the cost of a hospital day increased by approximately three times, from $572 to $1,706.[179] Another factor was the increase in the total number of hospital days related to diabetes during this period from 11.5 million to 20.2 million.[180] This large increase in hospital days may be secondary to increased diabetes prevalence or changes in practice patterns. Ettaro et al. suggested that the most important reasons for the increase was the inclusion of diabetes as a secondary diagnosis in the methodology used for cost collection. (See Section 3.5.1.1)

3.5.2.1.1.2 Comparison of the 1992 ADA Study to the 1997 ADA Study

Direct medical costs of diabetes declined from 1992 to 1997 using reported and

178 Ettaro L, Songer TJ, Zhang P, et al. Cost-of-illness studies in diabetes mellitus. *Pharmacoeconomics*. 2004;22:149-164.

179 Ibid.

180 Ibid.

adjusted data.[181] This decline was thought to be secondary to a decrease in inpatient hospital days from 20.2 million to 13 million. Ettaro et al. felt that at least part of this decline was due to the overall decrease in hospital admissions for all causes over this time period, as healthcare payers were seeking methods to contain costs by lowering inpatient hospital treatment. [182]

There was also a difference in methodology between these two studies. The 1992 study used disease-specific ARs, while the 1997 study used general population ARs (which is thought to underestimate risk). A second methodological change that occurred in 1997 was performed in an attempt to correct for the underestimation of secondary costs of diabetes due to the fact that the diagnosis of diabetes is often not reported in patient encounters that are related to complications of the disease. In the 1992 ADA study, costs from complications of diabetes were collected by using secondary diagnosis codes to identify healthcare utilization. In the 1997 study, primary diagnosis codes were combined with a population AR coefficient to reflect utilization assumed to be due to diabetes to in order to capture healthcare utilization secondary to diabetes complications.

3.5.2.1.2 Additional Studies of Interest using Data Collected Prior to 1998

The direct medical costs of diabetes changed dramatically over the 10-year period from 1987 to 1997. The ADA studies suggest that hospital use attributed to diabetes showed dramatic shifts in both positive and negative directions during the period. Any value calculated for COI using data from this period must take these changes in utilization into consideration. Other changes noted during the 10-year period include those secondary to the methodology used to calculate COI, as well as changes secondary to the

181 Ibid.

182 Ibid.

methodology used to calculate COI, as well as changes secondary to diabetes prevalence. In order to place the most accurate values for COI of T2DM in the dissertation model, all of these variables must be taken into account for both the initial cost periods, and all projected time periods.

The following section contains short summaries of pertinent articles published with data collected prior to 1998 that include COI data that may be helpful for the model. These studies are included because data were collected in a time period similar to that of the DPP, and similar direct medical costs were analyzed. Important cost variables will be translated to year 2000 U.S. dollars when possible by use of the medical portion of the Consumer Price Index.

Of note, the first two of the articles summarized are analyzed using data collected by the Kaiser Permanente health maintenance organization (HMO) system. Kaiser Permanente has been instrumental in collecting data on COI of diabetes, and also in improving the methodology for calculations of COI. The authors of the studies note that their results are probably underestimations of those in most other health care settings due to the probable lower cost of care provided in the Kaiser Permanente HMO setting.[183] They suggest using the ratio of total costs to control costs to compare their findings to those of other health care settings.

3.5.2.1.2.1 Excess Costs of Medical Care for Diabetes in the Kaiser Permanente System

A study by Selby et al. utilizes a case-controlled matching design of costs collected in 1994 to study excess costs of diabetes in the Kaiser Permanente system of Northern

183 Brown JB, Nichols GA, Glauber HS, et al. Type 2 diabetes: incremental medical care costs during the first 8 years after diagnosis. *Diabetes Care*. 1999;22:1116-1124.

California.[184] Acute and long-term complications of diabetes were identified, and an excess cost of $3,494 ($4,353 in 2000 dollar values) per age and sex-matched control was determined, which translates into a ratio of 2.4 for total costs to control costs for the diabetes group versus the control group. The largest proportion of excess costs was for hospitalizations (38%). This may reflect that these data were collected in the transition period prior to a decrease in use of inpatient hospital services.

3.5.2.1.2.2 Incremental Costs of T2DM in the First Eight Years after Diagnosis

A study by Brown et al. conducted at the Kaiser Permanente Northwest Division of Portland, Oregon analyzed the incremental cost change that occurred in patients from the time of diagnosis through the next eight-year period for patients with T2DM.[185] The period studied was 1988 to 1995. A matched-control design by sex and age was used. The average age at the year of diagnosis was 59.6 years. Values were adjusted to 1993 dollars using the U.S. medical price index, and a medical care insurer perspective was used. The direct costs utilized were for inpatient costs, outpatient costs, and pharmacy costs (including supplies).

These data were collected in the ten-year time period prior to the DPP, so it may not fully reflect an accurate value of excess COI. On the other hand, it serves as a check for the value that is finally determined for the model. It also allows for an analysis of the longitudinal trend in cost changes secondary to T2DM. In addition, the early years of T2DM may help in evaluation of COI of IGT.

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184 Selby JV, Ray GT, Zhang D, et al. Excess costs of medical care for patients with diabetes in a managed care population. *Diabetes Care*. 1997;20:1396-1402.

185 Brown JB, Nichols GA, Glauber HS, et al. Type 2 diabetes: incremental medical care costs during the first 8 years after diagnosis. *Diabetes Care*. 1999;22:1116-1124.

Table 3.6 has been constructed from data collected in this study to further aid in building COI variables for the dissertation model. Total mean direct costs, mean excess direct costs, and control costs, adjusted to year 2000 dollars, are given with the ratio of total costs to control costs for subdivided periods of years 1 to 3, years 4 to 6, and years 7 to 8. These periods were chosen to approximate the three-year time cycle used in the DPP economic analyses.

Table 3.6 Direct Medical Costs per Person and Type of Cost in Years 1 through 8 after T2DM Diagnosis [a]

	Total Costs ($)[b]	Excess Costs ($)[b]	Control Costs ($)[b]	Ratio of Total Costs to Control Costs
Years Since Diagnosis				
1 to 3	5,293	2,568	3,355	1.57
4 to 6	5,512	2,877	2,635	2.09
7 to 8	6,044	3,333	3,169	1.91
Average	5,563	2,875	2,688	2.07

[a] Brown JB, Nichols GA, Glauber HS, et al. Type 2 diabetes: incremental medical care costs during the first 8 years after diagnosis. Diabetes Care. 1999;22:1116-24.
[b] Adjusted to year 2000 dollars from 1993 dollars using the medical component of the Consumer Price Index
T2DM, type 2 diabetes mellitus

Total costs for subjects with diabetes were approximately double that of the matched control group. The largest contributors to direct costs were hospitalizations (46%). Pharmaceutical expenditures contributed 28% and outpatient costs contributed 26%.

3.5.2.1.3 Summary of Studies with Data Collected Prior to 1998

Summarizing the pertinent articles published with data collected prior to 1998 allows for preliminary estimates of COI of diabetes values and ranges to use in the sensitivity analyses. Most importantly, the articles help to calculate a multiplier to use in estimating

excess costs of T2DM for the dissertation model. With these preliminary data, more recent publications will now be examined and discussed.

3.5.2.2 Studies Published with Data Collected from 1998 to Present

A Pub Med literature search was performed using the Ettaro et al. study[186] as a reference. This article was chosen due to its 2004 publication date and the fact that the authors reviewed all articles that had data collected prior to 1998. The two major studies that analyze U.S. data on COI of diabetes after 1998 are now discussed.

3.5.2.2.1 The 2002 ADA COI Study

The ADA published a fourth COI of diabetes study using 2002 estimates in 2003.[187] The authors estimated that total costs of diabetes in 2002 were $132 billion, and total direct costs were $92 billion. The 1997 respective costs were $98.2 billion and $44.1 billion. The large increase in costs is thought to be due to both increased prevalence and increased costs of health care services.

The methodology used in the study is similar to that of the previous ADA studies. The authors use an estimate of 12.1 million people in the U.S. with diabetes in 2002 (versus 12 million in 2000). Prevalence rates by demographic group were projected onto the 2000 Census values. These CDC-derived prevalence rates for these 12.1 million people with diabetes by age group in 2000 were 18% for age 44 years and under, 43% for ages 45 to 64 years, 23% for ages 65 to 74 years, and 16% for ages 75 years and older.[188]

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186 Ettaro L, Songer TJ, Zhang P, et al. Cost-of-illness studies in diabetes mellitus. *Pharmacoeconomics*. 2004;22:149-164.

187 American Diabetes Association. Economic costs of diabetes in the U.S. in 2002. *Diabetes Care*. 2003;26:917-932.

188 Centers for Disease Control and Prevention. Prevalence of Diabetes and Impaired Fasting Glucose in Adults - United States, 1999-2000. *Morbidity and Mortality Weekly Report*. 2003;52:833-837.

Multiple sources of data were required to gather all of the information needed to derive the cost estimates. The authors combined the years of 1998 to 2000 for some data sources to increase the sample size. To calculate AR, odds ratios derived from Medical Expenditure Panel Survey (MEPS) data were combined with National Health Information Service (NHIS) prevalence data. Etiological fractions, adjusted for race, sex and age group were calculated for the following disease categories: neurological disease; peripheral vascular disease; cerebrovascular disease; renal disease; endocrine disease; ophthalmic disease; general medical conditions; and other medical conditions.

The authors defined health care expenditures attributable to diabetes as "those costs incurred by the population with diabetes above what would be expected if this population did not have diabetes."[189] Table 3.7 presents a summary of health care expenditures attributable to diabetes by age in 2002. The health care costs included are hospital inpatient days, office-based physician encounters, emergency department encounters, hospital outpatient and free-standing ambulatory surgical center encounters, outpatient medications, oral agents, and insulin delivery supplies. For the purpose of the dissertation model, these values are presented in year 2000 dollars.

Table 3.7 Excess Health Care Expenditures for Diabetes in the U.S. by Age in 2002 Adjusted to Year 2000 Dollars [a,b]

	Total Costs ($)[b]	Excess Costs ($)[b,c]	Ratio of Total Costs to Control Costs
Age			
Less than 45 Years	8,050	4,082	2.03
45 to 64 Years	8,379	4,411	2.11
Greater than or equal 65 years	11,212	7,244	2.83
Average	9,424	5,456	2.38

[a] American Diabetes Association. Economic costs of diabetes in the U.S. in 2002. *Diabetes Care*.2003;26:917-932.
[b] Adjusted to year 2000 dollars using medical component of the Consumer Price Index
[c] Using a control cost of $3,968

189 American Diabetes Association. Economic costs of diabetes in the U.S. in 2002. *Diabetes Care*. 2003;26:917-932.

The total per capita health care expenditure for people with diabetes in this study is $9,424 (year 2000 dollar adjustment) using the above health care cost inclusions. The value calculated for total annual per capita expenditure for health care for people without diabetes is $3,968 (year 2000 dollar adjustment), and is age-adjusted to control for demographic differences between the populations with and without diabetes. The ratio of total costs to control costs for patients aged < 65 years is consistent with that derived in the Brown et al. study in the eight years following diagnosis of T2DM with a range from 1.57 to 2.09 (Section 3.5.2.1.2.2)[190] The increased ratio of 2.83 at an age of ≥ 65 years may be helpful to include in the dissertation model to adjust for increased direct medical care costs due to T2DM with age.

3.5.2.2.2 A Final Check Value: Diabetes in a Large Employer Population

A final paper by Ramsey et al. is included in the summary of publications with data collected after 1998 as a check value.[191] The authors used a large claims database for the purpose of assessing the economic burden of diabetes from an employer's perspective. Claims were collected between 1996 and 1998. Subjects with and without diabetes were matched by age, sex, job, health plan, and location (by state) to determine excess health care costs of having the condition. The mean age of the diabetic population was 53 years, and the prevalence of diabetes was 3.5%. Forty-four percent of the subjects were female.

Diabetics in this study, as in all of the previously described, were more likely to use all types of services and to have more utilization of these services. As with the other services, cost increased with age. Table 3.8 gives the total direct costs for diabetics, non-

190 Brown JB, Nichols GA, Glauber HS, et al. Type 2 diabetes: incremental medical care costs during the first 8 years after diagnosis. *Diabetes Care*. 1999;22:1116-1124.

191 Ramsey S, Summers K, Leong SA, et al. Productivity and medical costs of diabetes in a large employer population. *Diabetes Care*. 2002;25:23-29.

diabetics, excess costs, and percent of excess in year 2000 adjusted values.

Table 3.8 Total Direct Medical Costs for Diabetics and Controls in a Large Employed Population [a]

	Mean Payment per Person ($)[b]			
	Diabetes Sample	**Control Sample**	**Excess Cost ($)[b]**	**Ratio of Total Costs to Control Costs**
Age Group				
46 to 55 Years (n=3,292)	6,426	2,446	3,980	2.63
56 to 64 Years (n=3,762)	8,071	3,432	4,639	2.35

[a] Ramsey S, Summers K, Leong SA, et al. Productivity and medical costs of diabetes in a large employer population. *Diabetes Care*. 2002;25:23-29.
[b] Adjusted to year 2000 dollars using the medical component of the Consumer Price Index
n, Sample size

3.5.2.2.3 Summary of COI of Diabetes

The articles summarized are helpful for the dissertation in many ways. It becomes apparent that total COI of T2DM can be addressed in the model as a multiplier of a control COI. This multiplier (the ratio of total costs to control costs) appears to be in a range from approximately 2.03 to 2.83 if the low value of 1.57 from the Brown et al. study[192] that is calculated using values from years one to three after the diagnosis of T2DM (Section 3.5.2.1.2.2) is eliminated. It may be that this low value is more consistent with excess COI values that will now be examined for IGT.

192 Brown JB, Nichols GA, Glauber HS, et al. Type 2 diabetes: incremental medical care costs during the first 8 years after diagnosis. *Diabetes Care*. 1999;22:1116-1124.

3.5.3 THE COST OF ILLNESS OF IGT

The "database" for use in the Markov model is slowly being constructed, but is far from complete. The next section of the dissertation takes us back to the fact that our population does not start in NGT or as a type 2 diabetic, but in the state of IGT. The additional problem that has been alluded to is that the cost data given for health care from the DPP were given for a combined subject group that has NGT, IGT and T2DM. These values cannot be "plugged" into the model without extracting the costs for the three groups separately. Finally, it is important to determine if the outside, direct health care costs given by the DPP (over and above that for the intervention) are similar to what was seen in the U.S. during the general time period of the study. This evaluation may be warranted because the intervention costs are thought to be more expensive than what would be seen in a clinical setting, and the same may be true for the care outside of the DPP. This section of the dissertation will begin to answer these questions by starting with an analysis of the COI of IGT.

3.5.3.1 Does IGT Have a COI, and if so, Why?

The DPP states that the per capita direct medical costs over the three-year period of the study were $5,011 for the placebo group and $4,579 for the lifestyle group. Do these values differ from those that would be found in a group of subjects with an average age of 50.9 years and an average BMI of 34 kg/m^2 who do not have IGT? In other words, do we need to calculate an excess cost of IGT to place into the Markov model?

Multiple studies have suggested that there is an increased risk of cardiovascular disease, stroke, and large-vessel occlusive disease in subjects with IGT. [193, 194, 195] While it

193 Haffner SM, Stern MP, Hazuda HP, et al. Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *Journal of the American Medical Association*. 1990;263:2893-2898.

194 Meigs JB, Nathan DM, D'Agostino RB, et al. Fasting and postchallenge glycemia and cardiovascular disease risk: the Framingham Offspring Study. *Diabetes Care*. 2002;25:1845-1850.

195 The DECODE Study Group. Glucose tolerance and cardiovascular mortality. *Archives of Internal Medicine*. 2001;161:397-404.

is out of the realm of this dissertation to discuss the pathophysiologic mechanisms for this increased risk, some proposed mechanisms of action include increased insulin resistance, or increases in other inflammatory substances such as fibrinogen or C-reactive protein.[196] In addition, patients with IGT are commonly found to be more obese, and have abnormalities of triglycerides, HDL cholesterol, and blood pressure, which may all lead to increased macrovascular risk.

Microvascular complications are also associated with IGT. These include retinopathy, neuropathy, and renal microproteinuria.[197] It has been suggested that the microvascular changes noted in patients with IGT may be more difficult to reverse with lifestyle intervention than the macrovascular reactive changes.[198]

Current literature suggests there is an excess health care risk associated with IGT, and therefore a subsequent excess cost. The next section of this chapter will discuss the calculation of this excess COI of IGT.

3.5.3.2 An Analysis of the Literature of COI of IGT

A MEDLINE search on the subject of COI of IGT gives no results for any economic analysis on this topic. The following paper by Nichols et al. gives some direction toward calculating a value of COI of IGT for the model. The information obtained from these studies will be examined in conjunction with the previous studies on COI of diabetes and the costs generated by the DPP to help derive a value for the COI of IGT.

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196 Haffner SM. Pre-diabetes, insulin resistance, inflammation, and CVD risk. *Diabetes Research and Clinical Practice*. 2003;61:S9-S18.

197 Singleton JR, Smith AG, Russell JW, et al. Microvascular complications of impaired glucose tolerance. *Diabetes*. 2003;52:2867-2873.

198 Ibid.

3.5.3.2.1 Incremental Medical Care Costs in the Eight Years Preceding T2DM Diagnosis

The Kaiser Permanente System Northwest Division expanded their COI of T2DM by evaluating the medical cost of patients who were ultimately to receive the diagnosis of T2DM in the eight years prior to diagnosis.[199] These data may be the closest approximation that can currently be made for a value for COI of IGT. Patients in this study were newly diagnosed in the years between 1995 and 1998. Excess costs were determined using a matched-control design. Patients were matched for year of birth, sex, and duration of health plan coverage. Values were adjusted to 1998 dollars using the medical component of the U.S. Consumer Price Index. The perspective was that of the medical insurer. The average age in the year prior to diagnosis was 60.1 years.

Table 3.9 gives the results of the data derived in this study in year 2000 dollars. These data have again been grouped to facilitate incorporation into the dissertation model. Years 8 to 6 prior to diagnosis correspond to an average age of 53 years to 55 years. Years 5 to 3 prior to diagnosis correspond to an average age of 56 years to 58 years. Years 2 and 1 prior to diagnosis correspond to an average age of 59 years and 60 years.

199 Nichols GA, Glauber HS, Brown JB. Type 2 diabetes: incremental medical care costs during the 8 years preceding diagnosis. *Diabetes Care*. 2000;23:1654-1659.

Table 3.9 Direct Medical Costs per Person and Type of Cost in Years 1 through 8 Prior to T2DM Diagnosis [a]

Years Prior to Diagnosis	Average Age of Period	Total Costs ($)[b]	Control Costs ($)[b]	Excess Costs ($)[b]	Ratio of Total Costs to Control Costs
- 8 to - 6	53 to 55	3,149	2,326	823	1.35
- 5 to - 3	56 to 58	3,906	2,841	1,065	1.37
- 2 to - 1	59 to 60	5,380	3,006	2,374	1.79
Average of Years -8 to -1		3,991	2,689	1,301	1.48

[a] Nichols GA, Glauber HS, Brown JB. Type 2 diabetes: incremental medical care costs during the 8 years preceding diagnosis. *Diabetes Care*. 2000;23:1654-1659.
[b] Adjusted to year 2000 dollars from 1993 dollars using the medical component of the Consumer Price Index
T2DM, type 2 diabetes mellitus

Medical costs for prediabetic patients exceeded those of the control group for all years, and these excess costs were substantial in the seven years prior to diagnosis. The average ratio of total costs to control costs was 1.48 and this ratio increased in the years immediately preceding the diagnosis of T2DM.

The largest difference in costs was noted in the two-year period prior to diagnosis of T2DM. The main driver of this cost increase was inpatient costs. The authors also state that "expenditures to prevent cardiovascular disease prominently contributed to health care costs in the years leading up to recognition of type 2 diabetes," which is consistent with the literature examined about morbidity secondary to IGT.

Of interest for this dissertation analysis, particularly the examination of COI of obesity that is to follow, is a statement the authors make as to other possible reasons for the high excess costs noted prior to diagnosis of T2DM. Nichols et al. state that an additional explanation for higher excess costs might be the fact that most of the patients who were

prediabetic were also obese.[200] They were unable to examine this more fully due to lack of data on obesity status of the patients analyzed.

3.5.4 THE COST OF ILLNESS OF OBESITY

How does obesity factor into this dissertation model? We have already noted that increased BMI increases the risk of developing T2DM. In addition, numerous studies suggest that medical costs increase with increased BMI.[201],[202] There may be an additional cost for obesity in the patient with T2DM. This could also occur in patients with IGT. The literature review will address the possibility that additional costs must be added to the derived COI of subjects with abnormal glucose homeostasis to adjust for obesity. Another more interesting possibility is that there is an excess COI for subjects with NGT secondary to obesity, and this possibility will also be examined.

3.5.4.1 Methodology of Determining the Cost of Obesity

Thompson et al. have pointed out that determining the cost of obesity is different than estimating a cost of illness for a disease like T2DM because obesity is better characterized as a risk factor for disease than as an actual disease itself.[203] When evaluating the COI of a disease such as T2DM, the researcher is able to derive actual cost figures attributable to treatment of the disease process. These same authors state that the cost of illness of obesity "is measured in terms of attributable expenditures on other diseases for which excess

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200 Ibid.

201 Wolf AM, Colditz GA. Social and economic effects of body weight in the United States. *American Journal of Clinical Nutrition*. 1996;63:466S-469S.

202 Thompson D, Brown JB, Nichols GA, et al. Body mass index and future healthcare costs: a retrospective cohort study. *Obesity Research*. 2001;9:210-218.

203 Thompson D, Wolf AM. The medical-care cost burden of obesity. *Obesity Reviews*. 2001;2:189-197.

body weight plays an etiological role."[204] One limitation of evaluating cost of obesity in this fashion is that there is no consensus as to which diseases are related to obesity, although the most commonly listed are coronary heart disease, T2DM, hypertension, gall-bladder disease, endometrial cancer, and osteoarthritis of the knee.[205] The cost of obesity will, in part, be determined by the selection of and number of diseases included in the economic evaluation.

A population-attributable risk (PAR) methodology is commonly used in database evaluations of cost of obesity. PAR evaluates the influence of a risk factor of the population under study. The resultant value is generally expressed as the proportion of disease risk that is attributable to the risk factor in question. PAR can also be described as an estimate of "the proportion of disease in a population that could have been prevented by eliminating obesity," or "the maximum proportion of disease in the population that was attributed to a specific exposure."[206] A common formula used to calculate PAR is the following where P represents prevalence of obesity, and RR represents relative risk of disease rate in exposed subjects versus that in subjects who are not exposed.

$$PAR = P(RR-1)/1 + P(RR-1)$$

Thompson et al. point out that a limitation of the PAR approach is the assumption that "each obese person has some quantifiable potential of developing all of the obesity-related diseases of interest." [207]

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204 Ibid.

205 Ibid.

206 Wolf AM, Colditz GA. Current estimates of the economic cost of obesity in the United States. *Obesity Research*. 1998;6:97-106.

207 Thompson D, Wolf AM. The medical-care cost burden of obesity. *Obesity Reviews*. 2001;2:189-197.

3.5.4.2 Is There an Excess Cost of Obesity in Patients with T2DM?

A MEDLINE search was completed using the MeSH headings of obesity, non-insulin dependent diabetes and cost of illness to evaluate the current literature to answer the question of the possibility that an excess cost of obesity should be added to the value for COI of T2DM in the dissertation model. The following articles suggest that there is little need to include any adjustment to COI of T2DM.

Heithoff et al. used the 1987 National Medical Expenditure Survey (NMES) database, a precursor of the MEPS database, to evaluate the association between body mass and health care expenditures.[208] While the presence of T2DM was highly collinear with body mass when predicting health care expenditures, the authors found that when incorporating T2DM in the regression model, no relationship was observed between BMI and health care expenditures. The authors stated that "the data offer no evidence that body mass has an independent influence on health care expenditures apart from the fact that increased body mass predisposes individuals to chronic and costly medical conditions."

Quesenberry et al. found similar results in an evaluation of the membership health survey completed by Kaiser Permanente subjects in 1993.[209] The goal of this study was to analyze the association of BMI and health care costs that could be explained by "diseases that could be caused or influenced by obesity." A strong association was noted between BMI and total health care costs. These authors also found that by controlling for diabetes, hypertension and coronary heart disease, "the age-sex adjusted association between BMI and total annual costs was to a large extent eliminated."

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208 Heithoff K, Cuffel B, Kennedy S, et al. The association between body mass and health care expenditures. *Clinical Therapeutics*. 1997;19:811-820.

209 Quesenberry CP, Caan B, Jacobson A. Obesity, health services use, and health care costs among members of a health maintenance organization. *Archives of Internal Medicine*. 1998;158:466-472.

A final study by Brandle et al. examined the possibility that there may be an additional COI secondary to obesity in subjects with abnormal glucose tolerance.[210] The authors studied a Michigan HMO population of 1,364 T2DM subjects with an average age of 66 years and a median duration of diabetes of > 8 years. More than 50% of the subjects had a BMI of < 30 kg/m^2.

The baseline, "control" median annual direct medical cost for a white male with diet-controlled T2DM, a BMI of 30 kg/m^2, and no diabetes-related complications was $1,684 (year 2000 dollars).

Table 3.10 gives multipliers derived from a linear regression model developed from the study data that examined variables that were positively associated with the direct cost of illness in subjects with a diagnosis of T2DM. Hispanic Americans were not analyzed in the study. African Americans had lower direct medical costs than whites, which was thought to be because this group received less health care. Increased BMI has a minimal effect on direct healthcare costs in this analysis.

Table 3.10 Baseline Direct Cost and Multipliers for Additional Demographic Characteristics from a Michigan HMO [a]

Baseline Cost	$1,684[b]
Disease Status	**Multiplier**
Female Sex	1.25
African American Race	0.82
Every Unit of BMI > 30 kg/m^2	1.01

[a] Brandle M, Zhou H, Smith BRK, et al. The direct medical cost of type 2 diabetes. *Diabetes Care*. 2003;26:2300-2304.

210 Brandle M, Zhou H, Smith BR, et al. The direct medical cost of type 2 diabetes. *Diabetes Care*. 2003;26:2300-2304.

3.5.4.3 Obesity Adjustments for NGT Subjects

The question also arises as to whether the model should incorporate an excess cost of obesity for subjects with NGT. In order to incorporate a value in the model, studies that have evaluated the cost of obesity in patients without T2DM must be examined. The one study that was found in the literature review was by Thompson et al. who examined data gathered in a 1990 health survey completed by patients in the Kaiser Permanente Northwest Division.[211] Utilization and costs of health care then were evaluated retrospectively from 1990 to 1998 for the 1,286 respondents. The age range of the subjects was 35 years to 64 years, and more than half (n=741) had a BMI of ≥ 25 kg/m^2.

For those patients who did not have T2DM, hypertension or hypercholesterolemia, the ratio of total annual health care expenditures for the BMI categories of 25 kg/m^2 to 29.9 kg/m^2 and ≥ 30 kg/m^2 were 0.99 (95% C.I. of 0.80 to 1.25) and 1.34 (95% C.I. of 1.02 to 1.74) respectively using a reference BMI category of 20 kg/m^2 to 24.9 kg/m^2.

This is the only study found that directly examines subjects without T2DM to allow for adjustment for COI due to obesity. The study suggests that, at a minimum, the dissertation models should allow for a sensitivity analysis that incorporates an excess COI for obesity in NGT subjects over control direct healthcare costs.

3.6 The Denominator of the Cost-Effectiveness Equation: Mortality

As mentioned in Section 3.1, the denominator of the cost-effectiveness equation requires a measurement of health benefit. These benefits may be measured as single measures such as number of life-years saved, or as combined measures such as a QALY

211 Thompson D, Brown JB, Nichols GA, et al. Body mass index and future healthcare costs: a retrospective cohort study. *Obesity Research*. 2001;9:210-218.

measurement.[212] The uses of each of these outcome measures have been explained by Hunink in the following way: "Differences in survival in CEA capture the life-saving and life-extending benefits of interventions, while in the QALY, the differences in weighted life years capture the duration of health effects."[213]

Mortality for the U.S. population is most commonly derived using the United States life tables published by the National Center for Health Statistics.[214] Adjustments to these numbers are often required to these numbers in a CEA to account for changes in mortality due to a disease condition, or the effects of a treatment intervention.

The following terms, which are referred to by Kuntz et al. as "relative reduction parameters," are commonly used in clinical literature when adjustments to mortality rates are made.[215] A hazard ratio (HR) is calculated by measuring the rate of an event with the intervention or in a particular disease state versus the rate of the event without the intervention or in a different disease state. Survival analysis techniques such as Kaplan-Meier methods or Cox proportional hazards models are used to estimate these ratios.

Hazard ratios are often referred to as relative risk (RR) ratios in the literature. The difference in the two terms is that RR depends on the time frame of the analysis, as one is evaluating the probability of the event over the time frame of the analysis. When one is comparing the RRs of a one-year and five-year period, the five-year ratio will be larger

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212 Hunink MGM, Glasziou PP, Siegel JE, et al. Ch. 9 - Constrained Resources. In: Huninck MGM, Glasziou PP, Siegel JE, et al., eds. *Decision Making in Health and Medicine: Integrating Evidence and Values*. Cambridge: Cambridge University Press; 2001.

213 Ibid.

214 Arias E. *United States Life Tables, 2000*. Hyattsville, MD: National Center for Health Statistics; 2002. vol. 51;3.

215 Kuntz K, Weinstein M. Ch. 7 - Modeling in Economic Evaluation. In: Drummond M, McGuire A, eds. *Economic Evaluation in Health Care: Merging Theory with Practice*. New York: Oxford University Press; 2001:141-171.

when underlying rates are constant. [216]

Several issues must be examined to adequately investigate the mortality variables required for the dissertation model. The effect of T2DM and IGT on mortality must be evaluated. In addition, the effect of obesity on mortality is also required. This will help to evaluate whether an adjustment must be made for obese patients who fall into all categories of glucose tolerance from NGT to T2DM.

A final issue that will be discussed will be the actual mortality figures that were derived from the DPP, and how these values compare to mortality figures from the U.S. life expectancy tables. The reasons for possible deviations will be discussed, as well as the relevance of these deviations to the dissertation model.

A MEDLINE search was performed using the following MeSH headings: obesity; diabetes mellitus, type II; impaired glucose tolerance; and mortality. The methods for study selection are described in each section. The following sections will describe the studies that are pertinent to calculate variables to input into the dissertation model.

3.6.1 THE EFFECT OF DIABETES ON MORTALITY

Multiple studies have suggested that premature mortality is a result of diabetes.[217, 218] The literature review will first start with an examination of studies that evaluated the effect of diabetes on mortality without incorporating the influence of obesity on hazard ratios.

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216 Ibid.

217 The DECODE study group on behalf of the European Diabetes Epidemiology Group. Glucose tolerance and mortality: comparison of WHO and American diagnostic criteria. *The Lancet*. 1999;354:617-621.

218 Saydah SH, Eberhardt MS, Loria CM, et al. Age and the burden of death attributable to diabetes in the United States. *American Journal of Epidemiology*. 2002;156:714-719.

3.6.1.1 The DECODE Study

The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study,[219] published in 1999, is important in that it examined a large sample size (18,048 men and 7,316 women) for a truncated follow-up of 10 years from 13 prospective European cohort studies that included a 2-hour post-challenge glucose measurement as part of the study design. The HR for death for subjects with a FPG ≥ 126 mg/dl and a 2-hour glucose level of ≥ 200 mg/dl was calculated as 2.27. When examining these data, it is important to note that the majority of European diabetes-related studies include subjects with lower BMIs than the DPP average (34 kg/m^2).

3.6.1.2 An Analysis Using NHANES II Data

Saydah et al. utilized NHANES II data from 1976 to 1980 linked to mortality status from 1976 to 1992 using the National Death Index (NDI) and the Social Security Administration's Death Master File.[220],[221] Subjects included in the study were aged 30 years to 75 years, with a follow-up of 12 years to 16 years. The sample size was 9,250. A smaller subgroup of the cohort (n=3,262) received a FPG test, and 225 subjects (6.9%) were considered to have undiagnosed diabetes. The criteria for undiagnosed diabetes were a FPG level of ≥ 126 mg/dL, or a 2-hour plasma glucose level ≥ 200 mg/dL.[222] The mean baseline BMI given in kg/m^2 for subjects with diabetes aged 50 years to 64 years was 28.2 versus 26.2 for those without. For subjects aged 65 years to 75 years the BMI

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219 The DECODE study group on behalf of the European Diabetes Epidemiology Group. Glucose tolerance and mortality: comparison of WHO and American diagnostic criteria. *The Lancet*. 1999;354:617-621.

220 Saydah SH, Eberhardt MS, Loria CM, et al. Age and the burden of death attributable to diabetes in the United States. *American Journal of Epidemiology*. 2002;156:714-719.

221 Saydah SH, Loria CM, Eberhardt MS, et al. Subclinical states of glucose intolerance and risk of death in the U.S. *Diabetes Care*. 2001;24:447-453.

222 Ibid.

values were 27.6 and 26.0 for those subjects with and without diabetes, respectively.

Adjusting for age, sex, education, smoking, physical activity, total cholesterol level, BMI, and systolic blood pressure, the HR for all-cause mortality for subjects aged 50 years to 64 years was 1.9 (CI: 1.4, 2.5). For subjects aged 65 years to 74 years, this value dropped to 1.8 (CI: 1.5, 2.3).

3.6.1.3 The Interaction of T2DM, Obesity and Premature Mortality

One problem with the studies that have been examined addressing the effect of T2DM on mortality is that they calculate the HR of premature mortality due to diabetes without taking into account the BMI category of the subjects without diabetes, the comparison group. If obesity does have an independent effect on mortality, the HRs are, therefore, potentially inaccurate for subjects with diabetes because obesity will also increase mortality rates in the non-diabetic subjects.

Rogers et al. have recently published an observational study that evaluates the relationship of BMI and premature mortality for overall and diabetes-specific causes of death.[223] The authors used the NHIS data from 1987 to 1994 and linked it via the NDI to the Multiple Cause of Death (MCD) files from 1987 to 1997. The result of this linkage provided a sample size of 647,015 with 47,271 deaths, 1,209 from diabetes. This sample size allowed the authors to better analyze smaller subgroups, such as those with differing BMI obesity categories.

This is the only study found in the literature search of mortality that carefully delineates the effects of obesity on diabetes-related mortality. The HRs calculated by the authors are presented in Table 3.11. The derived figures were calculated using a model

223 Rogers RG, Hummer RA, Krueger PM. The effect of obesity on overall, circulatory disease, and diabetes-specific mortality. *Journal of Biosocial Science*. 2003;35:107-129.

that adjusted for age, sex, marital status, income, education, employment, and geographic local. The authors suggested that their results were consistent with the possibility that obesity significantly contributed to increased diabetes-specific mortality. The risk of death from diabetes increased from a HR of 1.63 for the BMI subcategory of 25.0 kg/m^2 to 30.0 kg/m^2 to 7.32 for those subjects with a BMI of ≥ 40 kg/m^2.

Table 3.11 The Hazard Ratios of Death by Underlying Cause of Diabetes in U.S. Adults, 1987-1997[a]

BMI	Hazard Ratio
18.5 to 25.0	Reference
25.0 to less than 30.0	1.63
30.0 to less than 35.0	2.64
35.0 to less than 40.0	4.15
Greater than or equal 40.0	7.32

[a] Source: Rogers RG, Hummer RA, Krueger PM. The effect of obesity on overall, circulatory disease, and diabetes-specific mortality. Journal of Biosocial Science. 2003;35:107-129.
BMI, body-mass index

3.6.1.4 Summary of the Literature of the Effect of Diabetes on Mortality

Current literature suggests that there is an apparent increased HR of mortality of approximately 2 in subjects with T2DM. Both the DECODE and Saydah et al. HRs for increased mortality for subjects with T2DM (2.27 and 1.9) are consistent with values calculated by Rogers et al. for subjects in a BMI range of 25 kg/m^2 to 35 kg/m^2 (a range of 1.63 to 2.64).

3.6.2 DOES THE DIAGNOSIS OF IGT ALSO IMPACT MORTALITY?

Current research strongly supports the possibility that diabetes increases the risk of premature mortality. The question then arises of whether the mortality rate for subjects with IGT in the dissertation model should also be increased due to the condition. The

following will address the literature evaluating this subject.

3.6.2.1 An Analysis of the Effect of IGT on Mortality Using NHANES II Data

Current researchers do suggest that IGT mortality is thought to be intermediate between the mortality rates for subjects with NGT and those with T2DM.[224] Saydah et al. have also analyzed the NHANES II data on this subject in a fashion similar to their studies on the effect of diabetes on premature mortality (Section 3.6.1.2).

Patients in this study with a FPG < 126 mg/dl and a 2-hour plasma glucose of > 140 mg/dl to ≤ 200 mg/dl were found to have a hazard ratio of 1.1 (95% CI: 0.8, 1.6) when adjusted for age, sex, race, education, smoking, physical activity, BMI, systolic blood pressure, and the ratio of total cholesterol to HDL cholesterol.

3.6.2.2 Other European Studies

The DECODE study group found that patients diagnosed with IGT using the same criteria as described in section 3.6.1.1 had an HR of increased mortality over control subjects of 1.38 (95% CI: 1.09, 1.74).[225] A similar value of 1.48 (95% CI: 0.88, 2.49) was calculated by de Vegt et al. using data from the Hoorn study.[226] The study, initiated in 1989, consisted of men and women aged 50 years to 75 years. Follow up extended until 1995. The sample size for this analysis was 2,363. The average BMI for the study was < 30 kg/m^2. Known diabetics were excluded.

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224 Saydah SH, Miret M, Sung J, et al. Postchallenge hyperglycemia and mortality in a national sample of U.S. adults. *Diabetes Care*. 2001;24:1397-1402.

225 The DECODE study group on behalf of the European Diabetes Epidemiology Group. Glucose tolerance and mortality: comparison of WHO and American diagnostic criteria. *The Lancet*. 1999;354:617-621.

226 de Vegt R, Dekker JM, Rhue HG, et al. Hyperglycemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. *Diabetologia*. 1999;42:926-931.

3.6.2.3 The Malmo Prevention Trial

One of the most interesting evaluations of the possible effect of IGT on mortality was performed using data from the Malmo Prevention Trial, a precursor of the DPP described in Section 2.3.2.1.[227] This follow up study included 423 subjects, and the goal was to ascertain if the program had a differential effect on involved subjects after 12 years of follow up. IGT subjects in the placebo/routine treatment arm of this study had a mortality rate of 14 subjects per 1,000 patient-years (95% CI: 8.7, 21.4) at the end of the 12-year follow up. This was in comparison to the mortality for the NGT group of 6.2 per 1,000 patient-years (95% CI: 5.7, 6.8).

The authors also found that overall mortality for the IGT intervention group was significantly lower than that found for patients who had IGT but were in the placebo/routine arm. This is consistent with the normalization of glucose values that was found initially at the six-year follow up, and continued to the twelve-year follow up. The subjects in the IGT intervention group at the time of the twelve-year follow up were found to have a total mortality of 6.5 (95% CI: 4.1, 9.9). The ratio of this value to the patients with NGT is 1.05.

The authors reported independent risk factors for death for the entire cohort of 1.02 (95% CI; 0.92, 1.09) for BMI, 1.19 (95% CI: 0.84, 1.70) for IGT, and 1.99 (95% CI: 1.05, 3.79) for diabetes. They also found that being in the IGT intervention group lowered the risk factor of death by 0.49 (95% CI: 0.27, 0.96).

3.6.3 THE INDEPENDENT EFFECT OF OBESITY ON MORTALITY

There appears to be an increased effect of mortality due to diabetes, and this effect

227 Eriksson K, Lindgarde F. No excess 12-year mortality in men with impaired glucose tolerance who participated in the Malmo Prevention Trial with diet and exercise. *Diabetologia.* 1998;41:1010-1016.

is exacerbated by obesity. The Rogers et al. study also suggests that obesity increases the risk of death over and above the risk associated with diabetes.[228] Establishing the effect of obesity on the risk of death for patients with NGT is also important for this dissertation model in that patients with this status may require an adjustment to their mortality rates due to increased BMI. The following studies will examine the effect of obesity on mortality, both positive and negative, and the factors that influence the results.

3.6.3.1 The Rogers et al. Study Results

Rogers et al. suggest that obesity has a significant impact on general health and resultant risk of death in all subjects, and not just those with diabetes.[229] Table 3.12 gives the calculated HRs of the effects of body mass on overall mortality for U.S. adults from 1987 to 1997 using NHIS data. The results show that while there is an increased risk of mortality due to obesity, this effect is most pronounced in BMI subgroups ≥ 35 kg/m^2.

Table 3.12 Hazard Ratios of the Effects of Body Mass on Overall Mortality for U.S. Adults from 1987-1997[a]

	Ages 45 to 64 Years	Ages 65 and Over
BMI		
18.5 to less than 25.0	Reference	Reference
25.0 to less than 30.0	0.85	0.86
30.0 to less than 35.0	1.02	0.94
35.0 to less than 40	1.23	1.13
Greater than or equal 40	1.61	1.21

[a] Source: Rogers RG, Hummer RA, Krueger PM. The effect of obesity on overall, circulatory disease, and diabetes-specific mortality. *Journal of Biosocial Science*. 2003;35;107-129.

128 Rogers RG, Hummer RA, Krueger PM. The effect of obesity on overall, circulatory disease, and diabetes-specific mortality. *Journal of Biosocial Science*. 2003;35:107-129.

129 Ibid.

The HR associated with obesity decreases with age. Of more importance, the overweight patients in this study aged 45 years and older (BMI 25 kg/m^2 to < 30 kg/m^2), and obese class I patients aged 65 years and older (BMI 30 kg/m^2 to < 35 kg/m^2) appear to have a decreased mortality risk compared to subjects in the normal BMI category (BMI 18.5 kg/m^2 to 25 kg/^{2}). The authors attribute this protective effect of being overweight to "unmeasured factors" such as lower rates of smoking. Other studies have also suggested that the lowest mortality rates are found in subjects with BMI of 24 kg/m^2 to 27 kg/m^2.[230]

3.6.3.2 The Düsseldorf Obesity-Mortality Study (DOMS)

Bender et al. examined data from the DOMS, a 33-year study with a median follow up of 14.8 years, and a sample size of 6,053.[231] The average BMI for the study population was 36.6 kg/m^2, and this value decreased with age. Mortality for all causes was evaluated for the 1,028 patients who died during the follow up period. The data were reported as standardized mortality ratios. The reference group was the population of North Rhine Westphalia. The standardized mortality rates by body-mass index and age are given in Table 3.13.

Age groups were divided into group I for ages 18 years to 29 years, group II for ages 30 years to 39 years, group III for ages 40 years to 49 years, and group IV for ages 50 years to 74 years. BMI subgroups (all values given in kg/m^2) were divided into group I, with BMI values of 25 to < 32, group II, with BMI values of 32 to < 36, group III, with BMI values of 36 to <40, and group IV, with BMI values of ≥ 40.

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230 Durazo-Arvizu RA, McGee DL, Cooper RS, et al. Mortality and optimal body mass in a sample of the U.S. population. *American Journal of Epidemiology*. 1998;147:739-749.

231 Bender R, Jockel K, Trautner C, et al. Effect of age on excess mortality of obesity. *JAMA*. 1999;281:1498-1504.

Table 3.13 Standardized Mortality Rates by Body-Mass Index and Age[a]

		Men		Women	
BMI (kg/m^2)	**Age**	**SMR**	**CI**	**SMR**	**CI**
25 to < 32	*40 to 49*	1.34	0.78 to 2.14	1.04	0.64 to 1.58
	50 to 74	1.01	0.70 to 1.42	0.91	0.69 to 1.19
32 to < 36	*40 to 49*	1.64	1.13 to 2.30	1.32	0.93 to 1.81
	50 to 74	1.14	0.87 to 1.47	1.12	0.91 to 1.35

[a] Source: Bender R, Jockel, K, Trautner, C, et al. Effect of age on excess mortality on obesity. *JAMA*. 1999;281:1498-1504.
BMI, body-mass index; CI, 95% confidence interval; kg/m^2, kilogram per meters-squared; SMR, standardized mortality rate

No excess mortality was associated with a BMI of at least 25 kg/m^2 but less than 32 kg/m^2 for either women or men aged 50 years to 74 years, which is similar to the result found for Rogers et al. The model did not analyze the effects of risk factors such as elevated blood pressure, cholesterol levels, impaired glucose tolerance, diabetes, or smoking, but the regression coefficients for age and BMI did not show significant changes when any one of these risk factors was added to the model.

3.6.3.3 The Nurses' Health Study

Manson et al. evaluated the association of BMI with overall mortality and that from specific causes using data from the 115,195 women enrolled in the Nurses' Health Study.[232] The original age of the cohort was 30 years to 55 years, and the follow up period was 16 years. Patients with cardiovascular disease at baseline were excluded from the study. There were 4,726 deaths at follow up.

232 Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women. *New England Journal of Medicine*. 1995;333:677-685.

The authors determined that 53% of deaths among women with a BMI of > 29 kg/m^2 could be attributed to obesity. After controlling for hypertension, diabetes and elevated cholesterol, mortality was lowest for women with BMI < 19 kg/m^2. Table 3.14 gives the corresponding multivariate risks of mortality for increasing BMI categories in the study. There was no modifying effect of age on mortality in this study.

Table 3.14 Relative Risks for Mortality with Increasing Body-Mass Index Using Nurses' Health Study Data [a]

	Body-Mass Index (Reported in kg/m^2)						
	Less than 19.0	19.0 to 21.9	22.0 to 24.9	25.0 to 26.9	27.0 to 28.9	29.0 to 31.9	Greater than or equal 32
Mean BMI	18.7	21.1	23.4	25.9	27.9	30.3	35.8
Multivariate Relative Risk[b]	1	1.2	1.2	1.2	1.5	1.8	1.7

[a] Source: Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women. *New England Journal of Medicine*. 1995;333:677-685.
[b] Adjusted for age, smoking, hypertension, diabetes and cholesterol level
BMI, body-mass index; kg/m^2, kilograms per meter squared

The relative risk values are higher in this analysis than in the previously cited studies. One major difference between these two study populations is that the Nurses' Health Study excluded subjects with cardiovascular disease at baseline, while the NHIS data and the DOMS data did not carry such exclusions.

3.6.3.4 An Analysis of the Effect of Obesity Using Framingham Data

Do the exclusion criteria of a study design have an impact on the calculated hazard ratios for mortality? The above studies seem to indicate that this may be a possibility. The following study produced an even higher ratio for premature mortality for obese subjects using Framingham Heart Study data, a study that also excluded subjects with cardiovas-

cular disease at baseline.

Peeters et al. examined data collected on 3,607 subjects aged 30 years to 49 years at baseline for a follow up period of 40 years.[233] The study examined mortality rates for two periods: period I extended from year 4 to year 28 of follow up, and period II extended from year 29 to year 40.

The derived HRs for the study are given in Table 3.15. For subjects with a BMI of 30 kg/m^2 or greater who were non-smokers, the HR for mortality was 2.05 for period I of follow up, and 2.27 for period II compared to subjects with a BMI of 18.5 kg/m^2 to 24.9 kg/m^2. For subjects with a BMI of 25 kg/m^2 to 29.9 kg/m^2 these values were 1.47 and 1.53, respectively. Adjustment for hypertension and diabetes lowered the HRs for mortality secondary to obesity.

Table 3.15 Mortality Hazard Ratios for Body-Mass Index Based on Framingham Heart Study Data[a]

	Period I (Year 4 to Year 28 of Follow Up)	**Period II (Year 29 to Year 40 of Follow Up)**
Body-Mass Index [b]		
18.5 to 24.9	Reference	Reference
25 to 29.9	1.47 (CI:1.06 to 2.04)	1.53 (CI:1.19 to 1.97)
Greater than or equal 30	2.05 (CI: 1.38 to 3.05)	2.27 (CI:1.67 to 3.1)

[a] Source: Peeters A, Barendregt JJ, Willekens F, et al. Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Annals of Internal Medicine*. 2003;138:24-32.
[b] Given in values of kg/m^2
kg/m^2, kilograms per meter squared; CI, 95% confidence interval

These values are again higher than previous values reported by Rogers et al. The results may be secondary to the fact that HR values are increased in calculations that are

233 Peeters A, Barendregt JJ, Willekens F, et al. Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Annals of Internal Medicine*. 2003;138:24-32.

based on data derived from an initial cohort that excludes subjects with cardiovascular disease at enrollment. One final study will be presented to address the issue of the effect of the exclusion of disease on enrollment on calculated hazard ratios secondary to obesity.

3.6.3.5 An Analysis Using Cancer Prevention Study II Data

Calle et al. analyzed the effect of obesity on mortality using data from the Cancer Prevention Study II, a prospective study of 1,184,657 subjects with an average age at enrollment of 57 years.[234] In 1982, a survey was completed that provided baseline information on demographics, family history, and "various aspects of behavior, environmental and occupational exposures, and diet." There were no exclusions due to health state for participants.

The authors analyzed the relative risk for death according to current or former smokers versus subjects who had never smoked. They further subdivided each of these categories into subjects who had a history of any of the following diseases: cancer, heart disease, stroke, respiratory disease, current illness of any type, or a weight loss of at least 4.5 kg in the previous year versus subjects with no history of disease at enrollment.

Table 3.16 gives the relative risk of death according to BMI category for non-smokers with no history of disease at enrollment. High BMI was associated with higher rates of death from all causes. Relative risk declined with age, but absolute risk increased substantially. Most importantly, these relative risk values for these subjects with no disease at baseline are larger than those given by Rogers et al. for similar BMI categories.

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234 Calle EE, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of U.S. adults. *New England Journal of Medicine*. 1999;341:1097-1105.

Table 3.16 The Relative Risk of Death by BMI Category in Non-Smokers With No History of Disease at Enrollment[a]

	BMI (kg/m^2)							
	23.5 to 24.9	25 to 26.4	26.5 to 27.9	28 to 29.9	30 to 31.9	32 to 34.9	35 to 39.9	Greater than or equal 40
White Men No History of Disease								
Multivariate RR[b]	1.00	1.04	1.09	1.28	1.32	1.66	2.17	2.58
95% CI		0.98 to 1.10	1.02 to 1.16	1.19 to 1.37	1.21 to 1.45	1.49 to 1.85	1.84 to 2.56	1.64 to 4.06
White Women No History of Disease								
Multivariate RR[b]	1.00	1.07	1.10	1.21	1.30	1.53	1.76	2.00
95% CI		1.01 to 1.13	1.04 to 1.17	1.14 to 1.28	1.22 to 1.39	1.42 to 1.65	1.6 to 1.94	1.69 to 2.36

[a] Source: Calle EE, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of U.S. adults. *New England Journal of Medicine*. 1999;341:1097-1105.
[b] Adjusted for age, level of education, physical activity, alcohol use, marital status, aspirin use, fat consumption, vegetable consumption, and use of estrogen replacement therapy (in women)
BMI, body-mass index; CI, confidence interval, kg/m^2, kilograms per meter squared; RR, relative risk

Table 3.17 gives the relative risk death values for non-smoking subjects with a history of disease at enrollment. These values were derived from graphical data from the Calle et al. article, so no confidence intervals are given. The relative risk of death values per BMI category for these patients with no exclusions are much closer in value to the Rogers et al. values, which most likely reflects the fact that the Rogers et al. study is based on subjects who have no exclusions due to health state on enrollment.

Table 3.17 The Relative Risk of Death by BMI Category in Non-Smokers With a History of Disease at Enrollment[a,b]

	BMI (kg/m^2)							
	23.5 to 24.9	25 to 26.4	26.5 to 27.9	28 to 29.9	30 to 31.9	32 to 34.9	35 to 39.9	Greater than or equal 40
White Men With A History of Disease								
Relative Risk	1.00	1.04	1.09	1.10	1.20	1.30	1.40	1.64
White Women With A History of Disease								
Relative Risk	1.00	1.05	1.05	1.10	1.10	1.18	1.30	1.50

Source: Calle EE, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of U.S. adults. *New England Journal of Medicine*. 1999;341:1097-1105.
[b] Derived from graphical data, No confidence intervals available
BMI, body-mass index; kg/m^2, kilograms per meter squared

3.6.3.6 A Summary of the Effect of Obesity on Mortality

The above studies help to determine whether an increased HR should be included for obese patients with NGT in the dissertation model. The studies suggest that there may or may not be an effect of obesity on mortality depending on the initial status of the subjects in the database that is being analyzed.

3.6.4 DOES WEIGHT LOSS ACTUALLY REVERSE THE EFFECT OF OBESITY ON MORTALITY?

The Malmo Prevention Study suggests that weight loss in patients with IGT decreased mortality rates. This suggests that increased mortality rates secondary to abnormal glucose homeostasis, obesity, or a combination of both conditions may approximate normal rates as patients lose weight, and their glucose values return to a NGT status.

Gregg et al. examined the effect of intentional weight loss in two recently published

studies.[235, 236] Using NHIS data collected in 1989 linked to NDI data with follow up until 1997, the authors found that 892 deaths were reported. Intentional weight loss was associated with a 24% lower mortality rate (HR 0.76; 95% CI: 0.6, 0.97). When adjusted for age, sex, race, smoking, education, and initial BMI, those who lost weight had a decreased mortality of 15% (HR 0.85; 95% CI 0.66, 1.11). These studies, along with the Malmo Prevention Study, seem to suggest that the increased mortality risk that accompanies obesity and abnormal glucose homeostasis can approach a more normal value with weight loss.

3.6.5 THE DPP MORTALITY DATA

How does the above mortality data apply to the results derived from the DPP? Over the three-year study period the mortality rate was 0.0010 for the lifestyle group and 0.0017 for the placebo group. The all-sex probability for mortality for a person aged 50 years in the year 2001 was 0.0044.[237] Why was there such a huge discrepancy in this cohort that included subjects with IGT and T2DM? The answer may lie in the design of the DPP study. Subjects were excluded from the study with significant ischemic heart disease, aortic stenosis, uncontrolled hypertension, renal insufficiency, and congestive heart disease.

3.6.6 SUMMARY

Mortality rates and their adjustments introduce substantial uncertainty into the dissertation model. The studies presented above suggest the following conclusions. There

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235 Gregg E, Gerzoff R, Thompson T, et al. Intentional weight loss and death in overweight and obese U.S. adults 35 years of age and older. *Annals of Internal Medicine*. 2003;138:383-389.

236 Gregg EW, Gerzoff RB, Thompson TJ, et al. Trying to lose weight, losing weight, and 9-year mortality in overweight U.S. adults with diabetes. *Diabetes Care*. 2004;27:657-662.

237 Arias E. *United States Life Tables, 2000*. Hyattsville, MD: National Center for Health Statistics; 2002. vol. 51;3.

appears to be an increased HR of mortality in subjects with diabetes, and there is further increase in HR secondary to increasing BMI. IGT also appears to increase HRs for mortality when compared to subjects with NGT at a level that is intermediate to that between subjects with T2DM and NGT.

There appears to be little effect of obesity on mortality in subjects with BMI < 35 kg/m^2 if the cohort being examined has no exclusions secondary to health state at enrollment. If there are exclusions secondary to health state, such as those secondary to cardiovascular disease, a HR as high as 2.27 may need to be incorporated into mortality figures for subjects with a BMI category of 30 kg/m^2 to < 35 kg/m^2. Finally, weight loss may allow for a decrease of the effect on mortality that is found in subjects with IGT and T2DM.

3.7 The Denominator of the Cost-Effectiveness Equation: Utilities

As noted in Section 3.6, mortality figures are necessary for single measures of outcomes such as life-years saved. These single measures are usually considered adequate in interventions that primarily extend life. Mortality estimates are also needed to measure combined effectiveness measures, the most common of which is the quality adjusted life year or QALY.

What is a QALY, and why do we need to use it for our effectiveness measure? A QALY is an integrated summary score that incorporates mortality with morbidity and patient preferences.[238, 239] The underlying theory for using QALYs assumes that the illness addressed may potentially affect life expectancy, and may also make quality of life less

238 Coons SJ, Kaplan RM. Ch. 6- Cost-Utility Analysis. In: Bootman JL, Townsend RJ, McGhan WF, eds. *Principles of Pharmacoeconomics*. Cincinnati: Harvey Whitney Books Company; 1996.

239 Ibid.

desirable prior to death.

Quality of life (QOL) may be important to measure in several situations. Gold et al. suggest that a measure of quality is important when: (1) the main effects of a single intervention may cause potential differences among groups; (2) the side effects of an intervention may be significant enough to have an effect on quality of life; and (3) the audience that is examining the analysis requires an evaluation of quality of life as well as duration of life.[240] However, the main reason suggested for using a measure of quality in the denominator of a cost-effectiveness analysis is when the intervention potentially has an effect on both mortality and morbidity.[241, 242]

There are several very important things to note about a cost-effectiveness analysis using quality of life. The health outcomes measured for the denominator involve preferences, which are generally referred to as utilities. A utility is the value that a subject places on a particular health status. Cost-effectiveness analyses that incorporate utilities are often referred to as cost-utility analyses (CUAs), and are suggested by some authors to be a subclass of CEAs.[243, 244]

3.7.1 COMMON MEASURES OF UTILITIES IN DIABETES STUDIES

As noted, a utility is a measure of a patient's preference for an outcome. There are multiple methods of assigning utilities. Common methods employed are the standard

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240 Gold MR, Patrick DL, Torrance GW, et al. Ch. 4 - Identifying and Valuing Outcomes. In: Gold MR, Russell LB, Siegel JE, et al., eds. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press; 1996.

241 Coons SJ, Kaplan RM. Ch. 6- Cost-Utility Analysis. In: Bootman JL, Townsend RJ, McGhan WF, eds. *Principles of Pharmacoeconomics*. Cincinnati: Harvey Whitney Books Company; 1996.

242 Ibid.

243 Ibid.

244 Sieber WJ, Groessl JJ, David KM, et al. *Quality of Well-Being Self-Administered (QWB-SA) Scale User's Manual*: Health Outcomes Assessment Program, University of California, San Diego; 2004.

gamble and time trade-off. Another common method involves a multi-attribute framework. This technique breaks health states into domains, assigns a value for each domain, and then collates these values into a single value.[245]

Visual analog scales (VASs) are also employed to measure utilities. VASs fall under the category of psychological scaling methods called rating scales. While used for CUAs, they are controversial because some authors feel they do not reflect preferences under uncertainty. [246]

Scores generated for rating scales are generally lower than those generated by other methods of measuring utilities. Hunink et al. make the statement that this is due to the fact that "there is no penalty associated with assigning a health state a rating scale value lower than that of perfect health."[247] The following have been suggested by these same authors as rating scale – utility transformation formulas.[248] Utility is represented by u and rating scale is represented by r in these formulas.

Torrance: $(1-u) = (1-r)1.6$

Weeks: $u = 1$ (for $r > 0.85$)

$u = 1.18 \times r$ (for $r < 0.85$)

The scales used for measurement of utilities in diabetes may be generic or disease specific, although most of the large prospective diabetic studies incorporate generic scales as will be described in the following sections.

One very common generic scale used in diabetes studies in the U.S. is the Quality of Well Being – Self Administered (QWB-SA) scale. This preference-based measure of util-

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245 Coons SJ, Kaplan RM. Ch. 6- Cost-Utility Analysis. In: Bootman JL, Townsend RJ, McGhan WF, eds. *Principles of Pharmacoeconomics*. Cincinnati: Harvey Whitney Books Company; 1996.

246 Hunink M, Glasziou PP, Siegel JE, et al. Ch. 4 - Valuing Outcomes. *Decision Making in Health and Medicine: Integrating Evidence and Values*. Cambridge: Cambridge University Press; 2001.

247 Ibid.

248 Ibid.

ity is the scale that was used in the cost-effectiveness analysis performed by the DPP comparing metformin, extensive lifestyle intervention, and placebo.[249]

The QWB-SA was derived from the Quality of Well Being (QWB) scale. The QWB instrument includes four dimensions: mobility, physical activity, social activity, and symptom/problem complexes.[250] It requires administration by a trained interviewer. The more newly designed self-administered scale (QWB-SA) includes several mental health items, and the symptom assessment follows a review of systems format which is thought to be more clinically useful to the researcher.[251] General equivalence has been found when the two scales are compared, although lower scores are found with the QWB-SA.[252]

The EuroQol EQ-5D is the most common generic scale used in diabetes studies in Europe.[253] Developed by the EuroQoL Group, it has two parts. First, the EQ-5D asks questions about the domains of the five dimensions of social relations, mobility, physical activity, and symptoms/impairment. The second part, the EuroQol VAS, has been described as a single measure that asks subjects to rate their health between the "worst imaginable state" which is rated as a value of 0, and the "best imaginable state" that is rated as a value of 1.

It important to note that neither of the two major sets of scales that will primarily be discussed, the QWB-SA or the EuroQoL EQ-5D and VAS, have been officially cross-val-

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249 Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518-2523.

250 Sieber WJ, Groessl JJ, David KM, et al. *Quality of Well-Being Self-Administered (QWB-SA) Scale User's Manual*: Health Outcomes Assessment Program, University of California, San Diego; 2004.

251 Ibid.

252 Sieber WJ, Ganiats T, Kaplan R. Validation of a self-administered quality of well-being (QWB) scale. *Medical Outcomes Trust Bulletin*. 1997;5:2-4.

253 Redekop WK, Koopmanschap MA, Stolk RP, et al. Health-related quality of life and treatment satisfaction in Dutch patients with type 2 diabetes. *Diabetes Care*. 2002;25:458-463.

idated with each other for diabetic U.S. subjects, although the research is currently underway. [254]

3.7.2 VALUES TO USE FOR THE DISSERTATION MODEL

Evaluation of the abstracts that have been presented dealing with long-term projections of cost-effectiveness of diabetes prevention in Sections 3.3.1 and 3.3.2 shows that current researchers have not included a utility measure in their cost-effectiveness analysis.[255, 256]

There are no standardized values for utility for obese subjects with T2DM or IGT, nor are there standardized values for obese subjects with NGT. One option to use for this analysis is also to simply leave out any cost utility evaluation. Another option is to attempt to incorporate patient preference values into the model using the data generated by the DPP. The utility values used in the DPP cost-effectiveness analysis comparing metformin, extensive lifestyle intervention and placebo are again listed in Table 3.18.

Table 3.18 Utility Scores of the Diabetes Prevention Program[a]

Utility Scores	
Lifestyle	**Placebo**
0.703 ± 0.118	0.686 ± 0.121
0.695 ± 0.122	0.675 ± 0.122
0.692 ± 0.125	0.657 ± 0.125

[a] The Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. Diabetes Care. 2003;26:2518-2523.

254 Coffey JT, Brandle M, Zhou H, et al. Valuing health-related quality of life in diabetes. *Diabetes Care*. 2002;25:2238-2243.

255 Palmer AJ, Roze S, Cabrieres L, et al. Long-term projection of the costs of the Diabetes Prevention Program in the USA using the CORE diabetes prevention model: intensive lifestyle changes and metformin are both cost-effective. Paper presented at: 18th International Diabetes Federation Congress, 2003; Paris.

256 Palmer AJ, Roze S, Valentine WJ, et al. Intensive lifestyle changes or metformin in patients with impaired glucose tolerance: modeling the long-term health economic implications of the Diabetes Prevention Program in Australia, France, Germany, Switzerland, and the United Kingdom. *Clinical Therapeutics*. 2004;26:304-321.

The utility scores given are the mean scores of the entire cohort that participated in either the lifestyle or placebo arms of the study collectively. There is no way to differentiate the utility score that was derived for subjects in each of the states of NGT, IGT or T2DM, nor is there a way to determine the effect that obesity had on the score.

In spite of this lack of information, can these values be used in our model, and for what groups? The following literature review will discuss the possibility that these values may be appropriate to incorporate into the model for all categories of impaired glucose homeostasis, at least as an initial value to use prior to performing sensitivity analyses. Articles selected for this literature review were found in a MEDLINE search using the following MeSH headings: quality of life; diabetes mellitus, type II; impaired glucose tolerance; and obesity.

3.7.2.1 Health Related Quality of Life in Diabetics using the QWB-SA

Coffey et al., in an effort to address the lack of standardized and consistent health utility scores for diabetics, set out to "describe the health utilities associated with diabetes and its treatments, complications, and comorbidities."[257] They used the QWB-SA in a group of T2DM subjects who were drawn from diabetic tertiary care clinics. The average age was 57.6 years (range of 49.9 years to 67.3 years) and the average BMI was 30.4 kg/m^2 (26.2 kg/m^2 to 36.0 kg/m^2). The average duration in years of diabetes was 10.4 years (range of 4.0 years to 17.2 years). The mean health utility score for diet controlled non-obese diabetic men without complications (microvascular, neuropathic, or cardiovascular) was 0.689 (S.E. 0.014). This score is very similar to the score of 0.686 obtained on the QWB-SA in year 1 of the placebo arm of the DPP.

257 Coffey JT, Brandle M, Zhou H, et al. Valuing health-related quality of life in diabetes. *Diabetes Care*. 2002;25:2238-2243.

Subjects with a BMI category classified as obese (not defined by the author, but assumed to be ≥ 30 kg/m^2) received a "penalty" of -0.021 (S.E. 0.007) derived using a multiple linear regression model. The actual value of 0.665 that is calculated for obese subjects is intermediate to the utility scores derived in years 2 and 3 of the DPP study. Subjects on oral antidiabetic agents received a penalty of -0.023 (S.E. 0.013), and those on insulin received a penalty of -0.034 (S.E. 0.013). More severe microvascular and macrovascular complications were accompanied by lower utility scores. Age, race, and duration of diabetes were not associated with significant reductions in scores.

3.7.2.2 Assessing Weight-Related Quality of Life in Obese Persons with T2DM

Another potentially useful study that specifically evaluates the effect of obesity on quality of life in persons both with and without diabetes was published by Kolotkin et al. in 2003.[258] The instrument used was the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) questionnaire. This instrument has five domains including physical function, self-esteem, sexual life, public distress, and work. The scores are given in a range from 0 to 100. Obese persons with (n=225) and without (n=972) diabetes were enrolled in a clinical trial comparing obesity medication to gastric bypass surgery. The average age of diabetics was 54.1 ± 10.1 years and for non-diabetics was 49.2 ± 10.6 years. The average BMI was 34.2 ± 4.6 kg/m^2 for diabetics, and 34.6 ± 4.8 kg/m^2 for non-diabetics.

While this study did not use a utility instrument, the results are very useful to the dissertation model. The authors first make the statement that they chose to evaluate the relationship between obesity and T2DM on quality of life due to the fact that approximately

258 Kolotkin RL, Crosby RD, Williams GR. Assessing weight-related quality of life in obese persons with type 2 diabetes. *Diabetes Research and Clinical Practice*. 2003;61:125-132.

80% of patients with T2DM are obese. They hypothesized that obesity might be a contributor to impairment in QOL scores in addition to the impairment found secondary to T2DM.

Using ANCOVA analysis, the authors found that when controlled for age, gender, and BMI, there were no differences between obese diabetic and non-diabetic subjects on any IWQOL-Lite scale. They also found that there was a greater impairment for both diabetics and non-diabetic subjects seeking treatment for obesity versus those obese subjects in each category who were not seeking treatment. They stressed the great importance of determining whether obese subjects in a study were seeking treatment for obesity when analyzing quality of life scores due to this increased impairment.

Therefore, in this population of obese subjects seeking treatment, diabetes status did not further influence impairment in QOL score, but obese subjects seeking treatment did have lower QOL than those subjects who were not seeking treatment.

3.7.2.3 Utility Scores in Diabetics using the EQ5D and the EuroQoL VAS

Redekop et al. examined health-related QOL in Dutch patients who were enrolled in the Cost of Diabetes in Europe – Type 2 (CODE-2) study using the EQ5D and the EuroQoL VAS.[259] The values derived in the study are given in Table 3.19.

259 Redekop WK, Koopmanschap MA, Stolk RP, et al. Health-related quality of life and treatment satisfaction in Dutch patients with type 2 diabetes. *Diabetes Care*. 2002;25:458-463.

Table 3.19 Quality of Life Reported by Dutch Type 2 Diabetic Patients Enrolled in the CODE-2 Study[a]

	EQ5D Utility Score[b]	Euroqol VAS Score[b]
	(n=1,136)	*(n=1,124)*
Overall	0.74 (0.27)	0.68 (0.18)
Age (in Years)		
Less than 50	0.79 (0.26)	0.69 (0.18)
50 to 59	0.75 (0.26)	0.69 (0.18)
60 to 69	0.78 (0.25)	0.70 (0.18)
Greater than or equal 70	0.70 (0.28)	0.67 (0.18)
Obesity	0.70 (0.28)	0.66 (0.19)
No Obesity	0.77 (0.26)	069 (0.1)
Duration of Diabetes (in Years)		
Less than 5	0.77 (0.25)	0.70 (0.17)
5 to 10	0.73 (0.29)	0.67 (0.19)
Greater than or equal 10	0.70 (0.28)	0.66 (0.18)

a: Source: Redekop WK, Koopmanschap MA, Stolk RP, et al. Health-related quality of life and treatment satisfaction in Dutch patients with type 2 diabetes. *Diabetes Care*. 2002.;25:458-463.
b: Utility scores given in means and standard deviations
CODE-2, Cost of Diabetes in Europe-Type 2; EQ5D, EuroQoL 5D; VAS, visual analog score; n, sample size

Diabetics reported an EQ5D mean score of 0.74 (SD 0.27), which was only slightly lower than the utility score reported by the general population (United Kingdom population aged 60 years to 69 years: women = 0.81 and men = 0.78). Obesity, defined in this population as a BMI of > 30 kg/m^2, was associated with a penalty of -0.007 units.

The VAS score was strikingly similar to the score generated using the QWB-SA by the DPP placebo group. As noted above, these two scales have not been cross-validated.

Koopmanschap also used the EQ5D to perform a more generalized study on 4,189 T2DM subjects from five European countries.[260] The average utility score in these subjects with an average age of 66 years was 0.69 (compared to a score of 0.74 for the over-

260 Koopmanschap MA. Coping with type II diabetes: the patient's perspective. *Diabetologia*. 2002;45:S18-S22.

all score in the Redekop study). Diabetic patients without complications had a utility score of 0.76. There was also no variation in score according to treatment with oral antidiabetic drugs versus treatment with diet and exercise (0.71 for both groups). In this model, independent predictors of poor quality of life included age, sex (female) and BMI. The poor quality of life associated with BMI occurred at a cut point of 27 kg/m^2. The VAS scale was not evaluated in this study.

3.7.2.4 How to Explain the Differences between the Lifestyle and Placebo Arm

Rubin et al. reviewed the published literature on quality of life in diabetics in 1999.[261] Their literature review helps to answer the question of whether there is a legitimate reason for a difference between the utility values of the two arms of the DPP.

The first hypothesis that might come to mind is that the difference may be secondary to improved glycemic control. This relationship is equivocal in the literature that was presented up to the point of the publication, but the authors felt that overall "the benefits of good glycemic control more than offset the increased burden it may involve, at least for the majority of patients." In addition, it was suggested that medical interventions including counseling and educational interventions improved QOL, but the basis for this improvement is unknown. The options might include factors such as better glycemic control, increased activity, or increased weight loss.

It may be possible that the combination of diet and exercise used in the intensive lifestyle intervention arm of the study has an influence on the improved utility scores found in these subjects. In general, obese subjects in general who use diet and exercise to attempt weight loss have been found to experience better health related quality of life

261 Rubin RR, Peyrot M. Quality of life and diabetes. *Diabetes/Metabolism Research and Reviews.* 1999;15:205-218.

(HRQL) than those using diet alone, or those subjects not attempting to lose weight.[262] This study used CDC and Prevention's Behavioral Risk Factor Surveillance Survey (BRFSS) data. Exercise was defined as participating in physical activity for 30 minutes or more, five times a week, and dieting was defined as any attempt at eating less. The authors of this study pointed out that the improved HRQL might be an antecedent event, as subjects with higher HRQL scores at baseline might be more able to exercise than those with lower scores.

3.7.2.5 The Effect of Obesity on Health Utilities

If the decision is made to use the DPP utility data for all obese subjects, regardless of glucose homeostasis, the literature must be investigated to confirm that obesity is thought to have a negative effect of health utility in subjects with NGT. The one study that specifically addresses the topic of the effect of obesity using a generic utility measurement was performed by Groessl et al. on 1,326 adults from the Rancho Bernardo longitudinal study using the QWB scale.[263] The characteristics of the BMI groups are given in Table 3.20.

Table 3.20 Underlying Characteristics and Utility Scores of the Rancho Bernardo Longitudinal Study[a]

	BMI (in kg/m^2)			
Variable	**20 to 24.9 (n = 618)**	**25 to 29.9 (n = 491)**	**Grater than or equal 30 (n = 148)**	**p value**
% Female	67.6	50.1	57.4	$p < 0.001$
% Exercise	74.6	75.4	58.9	$p < 0.001$
% With Diabetes	5	5.3	11.6	$p = 0.019$
Age	72.8	71.6	69.1	$p < 0.001$
Adjusted QWB Score[b]	0.709	0.695	0.663	$p < 0.001$

[a] Groessl EJ, Kaplan RM, Barrett-Connor E, et al. Body mass index and quality of well-being in a community of older adults. *American Journal of Preventive Medicine*. 2004;26:126-129.
[b] Adjusted for gender, age, smoking, and exerciseBMI, body-mass index; kg/m^2, kilograms per meter squared; n, sample size; QWB, quality of well being

262 Hassan MK, Joshi AV, Madhavan SS, et al. Obesity and health-related quality of life: a cross-sectional analysis of the US population. *International Journal of Obesity and Related Metabolic Disorders.* 2003;27:1227-1232.

263 Groesl EJ, Kaplan RM, Barrett-Connor E, et al. Body mass index and quality of well-being in a community of older adults. American Journal of Preventive Medicine. 2004;26:126-129.

Obese subjects, with a mean age of 69.1 years in this study had significantly lower adjusted QWB scores than those subjects who had normal or overweight BMI scores. The percentage of diabetes in this subgroup was almost twice that of those subjects with normal or overweight BMI subcategories.

Significant decreases in quality of life with increasing levels of obesity were also found using the Health Utility Index Mark III in a study involving 38,151 Canadian subjects, aged 20 years to 64 years (52.4% male).[264] Significant decreases were found in each of the eight attributes measured in the instrument (vision, hearing, speech, mobility, dexterity, cognition, emotion, and pain), with the most significant changes noted in the domains of mobility, cognition, and pain.

Similar findings were also found using CDC and Prevention's 2000 BRFSS data on 182,372 subjects.[265] Significant decreases in limitations were noted for each of the three domains measured (physical, mental and activity).

3.7.2.6 Summary

The review of the literature suggests several important points. There are little standardized data on health utilities for obese subjects regardless of glucose status. It is suggested that increasing levels of obesity have a negative effect on health utilities. The diagnosis of diabetes may have little effect on the already diminished QOL status of an obese subject. Finally, lifestyle interventions such as exercise may improve QOL status. With these points in mind, it may be appropriate to use the DPP utility data as a starting point for a sensitivity analysis to use in the dissertation model.

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264 Trakas K, Oh PI, Singh S, et al. The health status of obese individuals in Canada. *International Journal of Obesity*. 2001;25:662-668.

265 Hassan MK, Joshi AV, Madhavan SS, et al. Obesity and health-related quality of life: a cross-sectional analysis of the US population. *International Journal of Obesity and Related Metabolic Disorders*. 2003;27:1227-1232.

3.8 Weight Loss Maintenance

A final variable to examine for the dissertation model is the rate of weight loss maintenance that can be expected by subjects who participate in intensive lifestyle interventions to prevent progression from IGT to T2DM. This is important if we assume that diabetes prevention is caused, at least in part, by the modest reductions in body weight that have been found in the studies described in Section 2.3.

As a summary, the goal of the lifestyle intervention in the DPP was a 7% weight loss, which was achieved by 50% of the subjects in this arm of the study at the end of the twenty-four week curriculum.[266] At the time of the most recent visit, 38% had a 7% weight loss. The lifestyle group lost an average of 5% of their body weight at the end of two years (an average of 5.45 kg), and an average of 3.5% of their body weight at the end of three years (an average of 4.1 kg).[267]

Studies examining weight loss maintenance in diabetics support the weight loss findings of the DPP.[268] Hensrud et al. found that diabetic subjects enrolled in comprehensive weight loss programs of ten weeks to twenty weeks duration generally lost an average of 2 kg to 10 kg. By the end of one year, most patients were found to regain one-third to one-half of the original weight that was lost, regardless of the weight loss approach. They found that weight loss from baseline rarely exceeded 5 kg.

The DPP may actually have a higher rate of weight loss maintenance than is seen in the general U.S. population. Wing et al., who define weight loss maintenance as a sustained maintenance of at least 10% of initial body weight for at least one year, have found

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266 Teutsch S. The cost of preventing diabetes: what do we know and what do we need to know? *Diabetes Care*. 2003;26:238-239.

267 Ibid.

268 Hensrud DD. Dietary treatment and long-term weight loss and maintenance in type 2 diabetics. *Obesity Research*. 2001;9:348S-353S.

that approximately 20% of overweight/obese subjects are able to achieve this goal. If a criterion of 5 kg or greater weight loss for at least one year is used, a range of successful maintenance from 13%[269] to 22%[270] has been reported.

In a meta-analysis of long-term weight loss maintenance observational studies in subjects who completed structured weight-loss programs, it was found that at the end of five years the average obese individual maintained an approximate 3 kg weight loss. This represented an average of approximately 3.2% below initial body weight.[271]

Weight loss maintenance seems to stabilize at two years to five years, as it has been found that maintaining weight for this period seems to decrease subsequent weight regain by approximately 50%.[272] This stabilization is more likely to occur in subjects who have participated in very low-energy diets than in those who participate in hypoenergetic balanced diets.[273] Stabilization also appears to improve with age.[274]

3.9 Proposed Hypotheses

The literature review suggests that while there is evidence that intensive lifestyle intervention appears to help prevent the progression of IGT to T2DM, there is little research into the long-term cost-effectiveness of such treatment. Obesity appears to play

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269 Wadden TA, Sternberg JA, Letizia KA, et al. Treatment of obesity by very low calorie diet, behavior therapy, and their combination: a five-year perspective. *International Journal of Obesity*. 1989;13:39-46.

270 Stalonas PM, Kirschenbaum DS. Behavioral treatment for obesity: eating habits revisited. *Behavior Research and Therapy*. 1985;16:1-14.

271 Anderson JW, Konz EC, Frederich RC, et al. Long-term weight-loss maintenance: a meta-analysis of US studies. *American Journal of Clinical Nutrition*. 2001;74:579-584.

272 McGuire MT, Wing RR, Klem ML, et al. What predicts weight regain among a group of successful weight losers? *Journal of Consulting and Clinical Psychology*. 1999;67:177-185.

273 Anderson JW, Konz EC, Frederich RC, et al. Long-term weight-loss maintenance: a meta-analysis of US studies. *American Journal of Clinical Nutrition*. 2001;74:579-584.

274 Ibid.

a major role in any evaluation that is used to determine this cost-effectiveness. Therefore, the following hypotheses are proposed for this dissertation.

H1: In a population similar to that studied by the DPP that is diagnosed with IGT and no other disease-state abnormalities, long-term intensive lifestyle intervention to prevent progression to T2DM is cost-effective.

Rationale:

Current short-term cost-effectiveness analysis of the DPP results[275] *and projected long-term cost-effectiveness evaluations of T2DM prevention*[276], [277] *suggest that intensive lifestyle intervention is cost-effective. The DPP study group had a BMI range of approximately 27 kg/m^2 to 41 kg/m^2, with an average of 34 kg/m^2.*[278]

H2: In a population that is diagnosed with IGT and no other disease-state abnormalities that fall into a specific BMI classification of 30 kg/m^2 to < 35 kg/m^2, long-term intensive lifestyle intervention to prevent progression to T2DM is cost-effective.

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275 Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518-2523.

276 Palmer AJ, Roze S, Cabrieres L, et al. Long-term projection of the costs of the Diabetes Prevention Program in the USA using the CORE diabetes prevention model: intensive lifestyle changes and metformin are both cost-effective. Paper presented at: 18th International Diabetes Federation Congress, 2003; Paris.

277 Palmer AJ, Roze S, Valentine WJ, et al. Intensive lifestyle changes or metformin in patients with impaired glucose tolerance: modeling the long-term health economic implications of the Diabetes Prevention Program in Australia, France, Germany, Switzerland, and the United Kingdom. *Clinical Therapeutics*. 2004;26:304-321.

278 Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.

H3: In a population that is diagnosed with IGT and no other disease-state abnormalities that falls into a BMI classification of > 35 kg/m^2, long-term intensive lifestyle intervention to prevent progression to T2DM is cost-effective.

Rationale:

The DPP results suggest that the use of intensive lifestyle intervention to prevent T2DM may be more efficacious in subjects with a BMI < 35 kg/m^2 (see Table 2.6).[279] *These hypotheses allow for a division into BMI subgroups to examine the effect of increasing levels of obesity on the cost-effectiveness of the intervention.*

H4: If adjustments to mortality hazard rates and direct healthcare costs that are suggested by current literature are made for the exclusion of baseline disease-state abnormalities as well as obesity in an evaluation of a population similar to that studied by the DPP (average BMI classification of obese class I, and diagnosis of IGT), long-term intensive lifestyle intervention to prevent progression to T2DM is cost-effective.

Rationale:

This hypothesis includes the following modifications to H1 that are discussed in the literature review:

(1) the need for an increased mortality hazard rate for obese subjects with NGT reflecting this finding in studies of mortality in cohorts that have baseline exclusions of disease abnormalities, and in particular, cardiovascular disease,in their design (Section 3.6.3),[280, 281]

279 Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518-2523.

280 Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women. *New England Journal of Medicine*. 1995;333:677-685.

281 Peeters A, Barendregt JJ, Willekens F, et al. Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Annals of Internal Medicine*. 2003;138:24-32.

(2) the need for an increased mortality hazard rate for obese subjects with T2DM with increasing BMI (Section 3.6.1.3) ,[282]

(3) the need for the possible inclusion of an increased cost of illness for obese subjects with NGT (Section 3.5.4.3). [283]

H5: In a population with IGT and an average BMI category of obese class I that is drawn from a hypothetical cohort that has no disease-state exclusions in the base line study design criteria, and in which no adjustments are made for obesity, long-term intensive lifestyle intervention to prevent progression to T2DM is cost-effective.

Rationale:

The rationale for this hypothesis again follows that outlined in H1, except that it allows for a more generalizable population, i.e. one with multiple beginning disease state abnormalities in addition to IGT. This beginning health status appears to be more representative of an obese population. [284]

H6: In a population with IGT and an average BMI category of obese class I that is drawn from a hypothetical cohort that has no disease-state exclusions in the base line study design criteria, and in which adjustments are made for obesity, long-term intensive lifestyle intervention to prevent progression to T2DM is cost-effective.

Rationale:

This hypothesis (in similar fashion to H4) includes the following modifications to H5 that were discussed in the literature review:

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282 Rogers RG, Hummer RA, Krueger PM. The effect of obesity on overall, circulatory disease, and diabetes-specific mortality. *Journal of Biosocial Science*. 2003;35:107-129.

283 Thompson D, Brown JB, Nichols GA, et al. Body mass index and future healthcare costs: a retrospective cohort study. *Obesity Research*. 2001;9:210-218.

284 Wolf AM, Colditz GA. Current estimates of the economic cost of obesity in the United States. *Obesity Research*. 1998;6:97-106.

(1) the need for an increased mortality hazard rate for obese subjects with T2DM with increasing BMI (Section 3.6.1.3), [285]

(2) the need for the possible inclusion of an increased cost of illness for obese subjects with NGT (Section 3.5.4.3). [286]

On the other hand, unlike H4, where mortality hazard rates for obese subjects with NGT were adjusted due to exclusion of disease-state abnormalities at baseline, there is no need to make these adjustments due to the inclusion of all possible health states in the analysis.

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285 Rogers RG, Hummer RA, Krueger PM. The effect of obesity on overall, circulatory disease, and diabetes-specific mortality. *Journal of Biosocial Science*. 2003;35:107-129.

286 Thompson D, Brown JB, Nichols GA, et al. Body mass index and future healthcare costs: a retrospective cohort study. *Obesity Research*. 2001;9:210-218.

CHAPTER 4 – METHODOLOGY

The major problem identified in this dissertation is that while current research suggests that lifestyle intervention to prevent progression from IGT to T2DM is effective over a three-year period, it is not currently known whether this method of intervention is cost-effective over the lifetime of a subject. Modeling techniques, therefore, were required to extrapolate the DPP three-year data over the long-term.

A healthcare model has been described as "any mathematical structure that represents the health and economic outcomes of patients, or populations under a variety of scenarios."[287] Kuntz and Weinstein have suggested that in some cases, the only approach that may be available to address a research problem may be constructing a model that is based entirely on data acquired from literature sources and existing databases.[288] Using available data to construct a model allows for simulation of a clinical trial that can attempt to answer questions not answered directly by current data, such as those required for this dissertation.

Another advantage of modeling, described by Kuntz and Weinstein, is that treatment effects derived from clinical studies based on cohorts that are not particularly representative of the general population can be extrapolated to attempt to make the results more generalizable.[289] As noted, the DPP subjects started in a state of IGT. At least some of these subjects started the study with both clinically defined IFG and IGT, which is not as common in the general population as either of these abnormalities alone (see Section

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287 Kuntz K, Weinstein M. Ch. 7 - Modeling in Economic Evaluation. In: Drummond M, McGuire A, eds. *Economic Evaluation in Health Care: Merging Theory with Practice*. New York: Oxford University Press; 2001:141-171.

288 Ibid.

289 Ibid.

2.1.2.2.1). In addition, the health care exclusions that are part of the study criteria are not reflective of most obese subjects, in general, or of obese subjects with abnormal glucose homeostasis, in particular (see Section 2.3.3 for exclusion criteria).

Along with the possible improvement in generalizability afforded by modeling, these mathematical techniques allow us to incorporate differing scenarios into the baseline analyses. The major scenario that modeling allows us to examine is the effect of obesity on costs, mortality, and healthcare utility in subjects at various stages of glucose homeostasis. Modeling also allows for incorporation of sensitivity analyses to test the major effects of all variables and transition probabilities, and the possible interactions of these various factors.

Modeling, therefore, allows us to extrapolate the data from the literature review and the DPP study to a time horizon beyond the trial, attempting to answer the question of long-term cost effectiveness of lifestyle intervention to prevent T2DM. Modeling also allows us to attempt to make the DPP data more generalizable. In addition, modeling allows for incorporation of the effects of factors such as obesity and weight loss on generalized health states, costs, mortality, and healthcare utilities.

Finally, the results of the modeling analyses used in this dissertation and other evaluations of extensive lifestyle intervention to prevent T2DM may aid in the design of future research.[290] In the most general way, this particular set of dissertation models allows the researcher to ask the question, "Should this intervention even be undertaken?" If the answer is affirmative, the investigator can progress to more specific research questions. Examples in this case would be determining subgroups to most effectively target for treatment, or establishing cost ranges for the intervention.

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290 Briggs A, Goeree MA, Blackhouse G, et al. Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. *Medical Decision Making*. 2002;22:290-308.

4.1 Markov Modeling

Frequently cited articles describing the use of Markov modeling for healthcare research are those by Beck and Pauker, published in 1983,[291] and Sonnenberg and Beck, published in 1993.[292] The later article describes Markov models as "analytical structures that represent key elements of a disease and are commonly used in economic evaluations."[293] The models have found particular use when evaluating the progression of chronic diseases such as T2DM, where input data, such as transition probabilities, costs or utilities, change over time because they are based on "transitions between defined health states."[294, 295]

To construct a Markov model, several steps are required.[296, 297, 298] The disease states required for the model must first be specified. Kuntz and Weinstein emphasize the importance that each of these states must reflect "the relevant states of health associated with the disease and treatment over time."[299] Other authors have stated that the states must

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291 Beck JR, Pauker SG. The Markov process in medical prognosis. *Medical Decision Making*. 1983;3:419-458.

292 Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Medical Decision Making*. 1993;13:322-338.

293 Ibid.

294 Kuntz K, Weinstein M. Ch. 7 - Modeling in Economic Evaluation. In: Drummond M, McGuire A, eds. *Economic Evaluation in Health Care: Merging Theory with Practice*. New York: Oxford University Press; 2001:141-171.

295 Kahn J. *Lecture 6 - Portraying disease progression: Markov modeling*. San Francisco: UCSF Department of Epidemiology and Biostatistics; 2003.

296 Glick H. Introduction to Markov Models. Available at: www.uphs.upenn.edu/dgimhsr/MARK0303.pdf. Accessed July 2004.

297 Briggs A, Sculpher M. An introduction to Markov modelling for economic evaluation. *Pharmacoeconomics*. 1998;13:397-409.

298 Kuntz K, Weinstein M. Ch. 7 - Modeling in Economic Evaluation. In: Drummond M, McGuire A, eds. *Economic Evaluation in Health Care: Merging Theory with Practice*. New York: Oxford University Press; 2001:141-171.

299 Ibid.

represent "clinically and economically important events in the disease process to be modeled."[300] Each state must be mutually exclusive, and the subject cannot be in more than one state at a time.

Markov cycle lengths are then assigned. These are chosen to best approximate the stages of the disease or treatment in question.

The next step is to assign transition probabilities to the model. Markov models are differentiated into two distinct types by the transition probabilities that are incorporated into the analysis.[301] Markov chain models use constant transition probabilities over time, while time-dependent Markov processes allow transition probabilities to vary over time.

The model is then populated with estimates of transition probabilities that have been derived from current literature or trial data. The initial distribution in the Markov states is then assigned. All subjects may start in one state, or the cohort may be divided among the states. Generally, the assumption is made that subjects all start in a "well" state, or in this case the "IGT" state. Estimates of health costs and utilities (which are referred to in the model as "variables") are then inserted into the model.

There are two major methods of evaluating Markov models.[302] Cohort simulation is a method that takes each "hypothetical cohort" through the model simultaneously. The results of this type of evaluation give "average" results for the hypothetical cohort. The alternative method of evaluation is a first-order Monte Carlo simulation, which allows for the random selection of subjects to each go through the model individually. Briggs suggests that using this technique is similar to adjusting for population variability in a cohort,

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300 Briggs A, Sculpher M. An introduction to Markov modelling for economic evaluation. *Pharmacoeconomics*. 1998;13:397-409.

301 Ibid.

302 Glick H. Introduction to Markov Models. Available at: www.uphs.upenn.edu/dgimhsr/MARK0303.pdf. Accessed July 2004.

or stated in another way, adjusting for alternative pathways through the model.[303] It is important to note that variability is due to differences in the patient's progress through the disease state, and is not due to variation in parameter values in this evaluation method. In other words, each subject is allowed to have his or her own "history" throughout the model. The major advantage of this method is that past information can be tracked through the model, allowing for increased complexity of the health state descriptions. The major outputs that are generally reported after a Markov analysis are lifetime costs, life expectancy, percentage of subjects in each Markov stage, and incremental cost effectiveness in terms of costs per life-year gained and costs per QALY.

4.2 Sensitivity Analyses

One of the most important uses of modeling is to manage uncertainty.[304] This is especially pertinent in early stages of research about the applicability of a treatment such as lifestyle intervention to prevent T2DM, as there is a substantial amount of uncertainty associated with almost all of the transition probabilities and cost and utility variables used. It has been suggested that analysts using Markov modeling should include "assessment of the implications of uncertainty for their result" for any analyses performed.[305]

In a study with substantial uncertainty, sensitivity analyses are important for two major reasons.[306] Sensitivity analyses suggest that the modeler knows the potential effect of variation of the input data. In addition, sensitivity analyses allow for an evaluation of

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303 Briggs A. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics*. 2000;17:479-500.

304 Sculpher M. The Role and Potential of Probabilistic Modeling. Paper presented at: Society for Medical Decision Making, 2003; Chicago.

305 Briggs A. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics*. 2000;17:479-500.

306 Marseille E. *Lecture 5: Cost-effectiveness analysis: sensitivity analysis*. San Francisco: UCSF Department of Epidemiology and Biostatistics; 2003.

the effect of variation of input data on the final results of the study. The most important result of the later, as previously noted, is to aid in design of further research studies.

Briggs identified several major divisions of parameter uncertainty that are found in healthcare modeling.[307] Uncertainty surrounding analytic methods may include the actual method of modeling, the methods involved in evaluating costs or utilities, or how to include discount rates in the model. In addition, as previously discussed, first-order uncertainty is that which is associated with "variability in the underlying population from which the model is drawn."[308]

The input data used in the model are an additional source of uncertainty. This is commonly referred to as second-order uncertainty.[309] The common method of evaluating this second-order uncertainty is referred to as deterministic sensitivity analyses, or more commonly seen in the literature as one-way, two-way, or multi-way sensitivity analyses. A more recently introduced method of evaluating parameter uncertainty is referred to as probabilistic sensitivity analysis.

4.2.1 DETERMINISTIC SENSITIVITY ANALYSES

Deterministic sensitivity analyses are a standard in healthcare economic analyses. In a one-way sensitivity analysis, all other input is held constant as one variable at a time is altered over a predetermined range by the modeler. This allows for an evaluation of the dependence of the results on that particular input.[310] Another important use of one-way sensitivity analyses is to "identify errors in the formulas that link inputs to outcomes,"

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307 Briggs A. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics*. 2000;17:479-500.

308 Ibid.

309 Ibid.

310 Marseille E. *Lecture 5: Cost-effectiveness analysis: sensitivity analysis*. San Francisco: UCSF Department of Epidemiology and Biostatistics; 2003.

which is more commonly known as debugging.[311] A final important use of one-way sensitivity analyses is to substantiate results. This step can ultimately allow for identification of further research needs.

The problem with one-way sensitivity analyses is that uncertainty may be underestimated, as it is unlikely that there will be no variation of other input parameters in the model.[312] It has also been suggested that bias is introduced when using deterministic sensitivity analysis. There are two major reasons for this bias: interpretation of the sensitivity analysis may be arbitrary depending on the modeler; and interaction between parameters may be ignored.[313, 314]

4.2.2 PROBABLISTIC SENSITIVITY ANALYSIS

Probabilistic sensitivity analysis is a method that has been introduced to address the problem of failing to recognize the interaction between variables in a model. As originally introduced by Critchfield et al., the first step for a probabilistic sensitivity analysis is to choose a probability density function for each variable that is to be evaluated using this technique.[315] These distribution functions relate to the nature of each variable.[316]

The following are current common recommendations for distributions of major classes

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311 Ibid.

312 Briggs A, Goeree MA, Blackhouse G, et al. Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. *Medical Decision Making*. 2002;22:290-308.

313 O'Brien BJ, Drummond MF, Labelle RJ, et al. In search of power and significance: issues in the design and analysis of stochastic and cost-effectiveness studies in health care. *Medical Care*. 1994;1994:150-163.

314 Briggs A. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics*. 2000;17:479-500.

315 Critchfield GC, Willard KE, Connelly DP. Probabilistic sensitivity analysis methods for general decision models. *Computers and Biomedical Research*. 1986;19:254-265.

316 Briggs A. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics*. 2000;17:479-500.

of parameters used in Markov models. Cost data may be normally distributed, but if data are skewed, a gamma distribution may be more appropriate.[318] A gamma distribution is constrained to be positive and is fully continuous.[319]

The beta distribution is a continuous distribution which is conjugate to the binomial distribution.[320] Transition probabilities are bounded by 0-1 intervals and are commonly given a beta distribution.[321] When the original data are not available, it is suggested that the method of moment's estimation be utilized to determine the beta input parameters. Utilities may also be represented by beta distributions if they are far from zero.[322] On the other hand, it is suggested that relative risks be represented by log-normal distributions.

The above distributions assume that the modeler has actual statistical data or meta-analysis results to work with. When these data options are not available, and a theoretical foundation is not available for the distribution in question, two distributions are available to insert into the probabilistic sensitivity analysis. The first is the triangular distribution, which allows input of the data using a lower limit value, a most likely value (the mode), and an upper limit value.[323] A second distribution method to use in this situation is the uniform distribution, or rectangular distribution.[324] In this distribution, the probability

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318 Briggs A. Probabilistic cost-effectiveness modeling: practical aspects of modeling: fitting distributions and drawing simulations. Paper presented at: Society of Medical Decision Making, 2003; Chicago.

319 Briggs A, Goeree MA, Blackhouse G, et al. Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. *Medical Decision Making*. 2002;22:290-308.

320 Ibid.

321 Briggs A. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics*. 2000;17:479-500.

322 Briggs A. Probabilistic cost-effectiveness modeling: practical aspects of modeling: fitting distributions and drawing simulations. Paper presented at: Society of Medical Decision Making, 2003; Chicago.

323 Triangular Distribution. Vanguard Software Corporation. Available at: http://www.vanguardsw.com/dphelp4/dph00121.htm. Accessed July 2004.

324 Uniform Distribution. Available at: davidmlane.com/hyperstat/A12237.html. Accessed July 2004.

of occurrence is the same for all values of X.

4.3 Models Required for this Dissertation

Figure 4.1 shows the prototype for all models used to extrapolate long-term cost-effectiveness of intensive lifestyle intervention to prevent T2DM. The models used were designed using DATA 4.0 software (TreeAge Software, Inc., Williamstown, Massachusetts).[325]

The following are the basic models that were used to test the study hypotheses. Appendix 1 contains an overview table of the models and the hypotheses. Appendix 2 includes complete tables of input data for Models 1A and 1B, and Appendix 3 includes the same for Models 2A and 2B. Appendix 4 includes a list of assumptions used in this methodology section.

Model 1A: A population similar to that studied by the DPP is assumed. This population has no major disease-state abnormalities except for IGT at baseline. The population has an average BMI that falls into the category of obese class I. No adjustments were made to cost or mortality variables secondary to obesity or the healthcare exclusions. This model was used to address H1, H2, and H3 by adjusting transition probabilities between the Markov states to reflect the efficacy of the DPP intervention at different BMI classifications.

Model 1B: A population similar to that studied by the DPP is assumed. This population has no major disease-state abnormalities except for IGT at baseline. The population has an average BMI that falls into the category of obese class I. Adjustments were made to cost and mortality variables secondary to obesity and healthcare exclusions. This model addresses H4.

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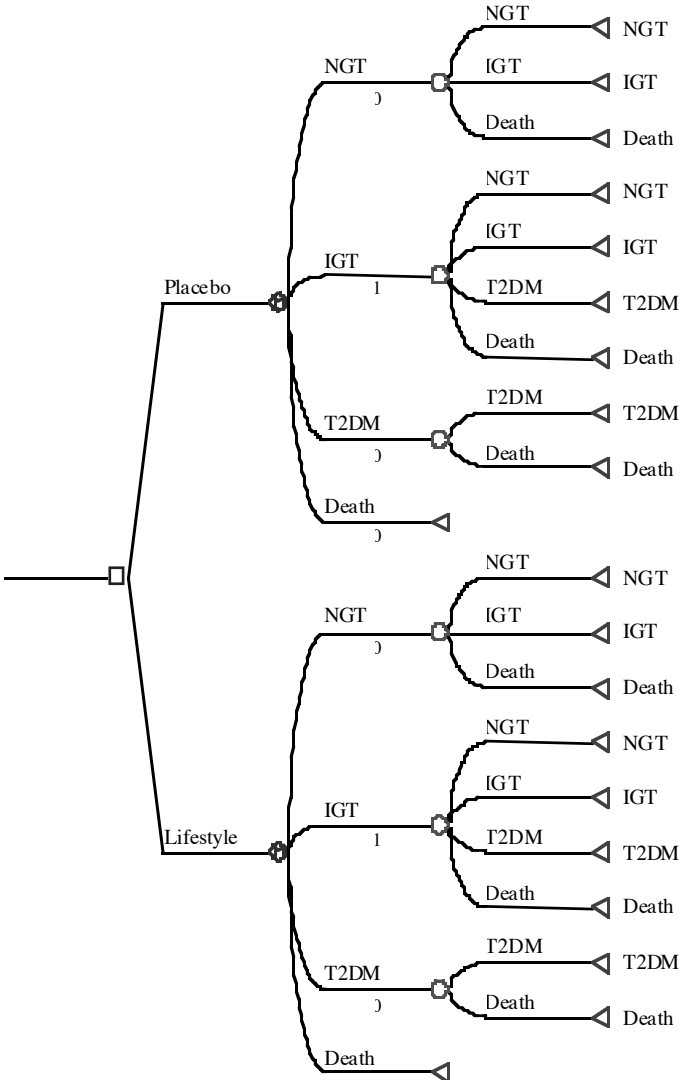
325 TreeAge Software, Inc. Available at: http://www.treeage.com/.

Model 2A: An IGT population that has no disease state exclusions at baseline with average BMI category of obese class I is assumed in order to make the analysis more generalizable. No additional adjustments were made for obesity. This model addresses H5.

Model 2B: An IGT population that has no disease state exclusions at baseline with an average BMI category of obese class I is assumed in order to make the analysis more generalizable. Adjustments for obesity were made to mortality and cost variables. This model addresses H6.

Figure 4.1 Prototype Model for Dissertation Models



IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T2DM, type 2 diabetes mellitus

The two arms from the first choice node are those corresponding to the placebo and intensive lifestyle intervention arms of the study. The four Markov states included are NGT, IGT, T2DM and Death. All subjects start in the IGT state; they may remain in the IGT state or move to any of the other three states. From the state of NGT a subject may remain in the state of NGT, or progress to the states of IGT or Death. The assumption was made that progression from NGT to T2DM without progressing through the state of IGT is sufficiently unlikely to not include this as an option in the model. The assumption was also made that a subject will not spontaneously revert back to IGT from T2DM. A sensitivity analysis based on the possibility that a newly diagnosed T2DM subject may revert back to the IGT state (see section 2.1.2.3.5) was conducted for Models 2A and 2B.

The Markov cycle length is one year. The term "stage" is used synonymously with the term "cycle" throughout the following discussions. All subjects in the model started at a baseline age of 50 years. The model is designed to run until subjects reach the age of 85 years. All patients started at a BMI of 34 kg/m^2 (except for the subgroups of Model 1A). Probabilities for progression from IGT to T2DM, and reversion from IGT to NGT, as well as utility values were taken from the DPP results.[326]

The probability variables that were used in the placebo arm of all models for progression through the states of glucose homeostasis are listed in Table 4.1. The one-year probabilities of progression from IGT to T2DM and reversion to NGT from the state of IGT were taken from DPP results.[327]

A one-year probability for progression from NGT to IGT of 0.0767 was chosen for the placebo arm of the study. This value, derived from the Pima Indian Study discussed in

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326 Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.

327 Ibid.

Section 2.1.2.3.3.2, was chosen using the following reasoning.[328] The DPP subjects' rate of one-year transition probability from IGT to T2DM in the placebo group of 0.1075 was much higher than the value of 0.0676 that was expected (Sections 2.1.2.3.2 and 2.3.3).[329, 330] This higher value was attributed to the "selection of patients at higher risk" (i.e. with a combined state of IFG and IGT), or more frequent glucose testing.[331]

The Pima Indians had the highest rate of progression from IGT to T2DM of all studies evaluated by Edelstein et al. (one-year transition probability of 0.0836).[332] Therefore, the assumption was made for this study that the transition probability from NGT to IGT for this cohort would also reflect this high progression rate, and the value might be realistic for the DPP model.

The literature review also noted a high transition probability of progression from NGT to IGT in the Miegs et al. study discussed in Section 2.1.2.3.3.1 (a one-year transition probability of 0.0624 based on a ten-year follow-up, which is 18.6% less than the Pima Indian Study value).[333] These higher values might be a reflection of the use of an abnormal OGTT to define IGT, as this test is considered more sensitive for the diagnosis. A sensitivity analysis was conducted for this transition probability (using the Pima Indian value of 0.0767) using values 20% greater.

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328 Weyer C, Tataranni P, Bogardus C, et al. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of type 2 diabetes development. *Diabetes Care*. 2001;24(1):89-94.

329 Diabetes Prevention Program Research Group. The Diabetes Prevention Program: design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care*. 1999;22:623-634.

330 Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.

331 Ibid.

332 Edelstein SI, Knowler WC, Bain RP, et al. Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. *Diabetes*. 1997;46:701-710.

333 Meigs JB, Muller DC, Nathan DM, et al. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of the Aging. *Diabetes*. 2003;52:1475-1484.

Table 4.1 Transition Probabilities Used in the Placebo Arm of All Models

Variable	One-Year Probability	Source
Progression from IGT to T2DM	0.1075	a
Reversion from IGT to NGT	0.0678	a
Progression from NGT to IGT	0.0767	b

Sources:
a: Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.
b: Weyer C, Tataranni PA, Bogardus C, et al. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening glucose tolerance during each stage of type 2 diabetes development. *Diabetes Care*. 2001;24:89-94.

The transition probabilities used in the intensive lifestyle arm of all models are listed in Table 4.2. Once again, the one-year probabilities of change from IGT to NGT or T2DM were taken directly from the DPP study. The probability of progression from NGT to IGT was calculated using the Pima Indian Study value of 0.0767 and lowering it by the same rate of decrease as that found from IGT to T2DM between the placebo and lifestyle arms of the DPP study (53% using probability rates), resulting in a value of 0.0406.[334] A sensitivity analysis was also conducted for this variable, using a 20% greater value (0.0487).

Table 4.2 Transition Probabilities Used in the Intensive Lifestyle Arm of All Models

Variable	One-Year Probability	Source
Progression from IGT to T2DM	0.0505	a
Reversion from IGT to NGT	0.1121	a
Progression from NGT to IGT	0.0406	b

Sources:
a: Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.
b: Weyer C, Tataranni PA, Bogardus C, et al. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening glucose tolerance during each stage of type 2 diabetes development. *Diabetes Care*. 2001;24:89-94.

334 Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.

The transition probabilities used for progression to the Death stage in each model will be described in detail below, but the baseline mortality rates were derived from U.S. Life Table statistics for the year 2000.[335] The year 2000 was used because costs in this model were adjusted to the year 2000 using the Medical Consumer Price Index.[336]

No specific values are given in the models for the probability of staying in a specific Markov state from cycle to cycle (i.e. starting in the NGT state and ending in the NGT state in the next cycle). TreeAge DATA 4.0 software includes a built-in complementary probability expression that "automatically calculates 1.0 minus the sum of probabilities at the other branches." [337]

Table 4.3 lists cost variables for screening and intervention that were used in all models in the dissertation. These cost values were derived from the cost analysis performed by the DPP for the study as discussed in 3.4.1.[338] All costs are in year 2000 dollars.

Table 4.3 Costs of Screening and Intervention in Years One through Three of the Diabetes Prevention Program[a]

	Placebo Arm	Intensive Lifestyle Arm
Variable		
Screening (1st Year)	$139	$139
Intervention		
Year 1	$43	$1,399
Year 2	$18	$679
Year 3	$18	$702

[a] Source: The Diabetes Prevention Program Research Group. Costs associated with the primary prevention of type 2 diabetes mellitus in the Diabetes Prevention Program. *Diabetes Care*. 2003;26:36-47.

335 Arias E. *United States Life Tables, 2000*. Hyattsville, MD: National Center for Health Statistics; 2002. vol. 51;3.

336 Labor Statistics Data. Consumer Price Index: Medical Care Services. *U.S. Bureau of Labor Statistics*. Accessed April 2004.

337 *DATA Healthcare User's Manual*. Williamstown, MA: TreeAge Software, Inc.; 2002.

338 Diabetes Prevention Program Research Group. Costs associated with the primary prevention of type 2 diabetes mellitus in the Diabetes Prevention Program. *Diabetes Care*. 2003;26:36-47.

Utility values also do not vary between the models. As discussed in Section 3.7, the values given in Table 3.18 were used for all three groups of NGT, IGT and T2DM for the first three years. The value of 0.692 was used for the NGT, IGT and T2DM groups of the lifestyle group for years four and higher of the model, and the value of 0.657 was used for the NGT, IGT and T2DM for the placebo arm.[339]

The treatment intervention was modeled to occur over the first three Markov cycles to mimic the three-year duration of the program. Two scenarios will be reported for duration of treatment effect. The first scenario made the assumption that the treatment effect will last for a subject's lifetime. This scenario was based on the assumption that the efficacy of the program is due, at least in part, to weight loss maintenance, and that weight loss is maintained in the lifestyle intervention program at the rate that was attained at the end of the third year of the study, or 38%.[340] While this value is higher than the 20% value of sustained weight loss maintenance reported by Wing et al.,[341] it reflects the stabilization at two years to five years of weight loss maintenance reported by McGuire et al.[342] The models were also analyzed assuming that duration of efficacy of the lifestyle duration only occurs for the initial three years of the program, and at the fourth year, lifestyle intervention probabilities will revert back to the placebo values.

All base-case models were first run without using discount rates, and then discount rates of 3% and 5% were incorporated for both costs and health consequences. This is in accordance to current frequently cited recommendations in Gold's *Cost-Effectiveness in Health and Medicine*.[343]

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339 Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518-2523.

340 Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.

341 Wing RR, Hill JO. Successful Weight Loss Maintenance. *Annual Review of Nutrition*. 2001;21:323-341.

342 McGuire MT, Wing RR, Klem ML, et al. What predicts weight regain among a group of successful weight losers? *Journal of Consulting and Clinical Psychology*. 1999;67:177-185.

343 Lipscomb J, Weinstein MC, Torrance GW. Ch. 7- Time Preference. In: Gold MR, Russell LB, Siegel JE, et al., eds. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press; 1996.

The following sections will describe in greater detail each of these models. The variables included for each model will be given, with the rationale behind their choice. Sensitivity analyses will also be described.

4.3.1 MODEL 1A: A MODEL BASED ON THE DPP COHORT

Model 1A was designed to most closely approximate the cohort that was studied by the DPP. As previously noted, the DPP study criteria excluded patients who had healthcare abnormalities other than IGT. As discussed in the literature review, the major areas affected by the exclusion criteria are costs and mortality. The following will include a description of all input parameters not included in Tables 4.1, 4.2, and 4.3 necessary to populate Model 1A. The discussion will also include assumptions required to select this data. Any possible effect that the exclusion of healthcare states in design criteria of studies has on input data will also be emphasized to reflect the healthcare exclusions used in the design criteria of the DPP. As noted, a complete table of input data for the model is contained in Appendix 2.

4.3.1.1 Model 1A: Cost of Direct Medical Care Outside of the Intervention

The average yearly direct medical costs for each of the first three years of all subjects in the placebo arm of the DPP study was $1,670 and in the lifestyle arm was $1,526 (Section 3.4.1.3).[344] The major problem with using these values is there is no breakdown for costs for each specific group of NGT, IGT or T2DM subjects, and this type of cost adjustment is required for all of the models used in this dissertation.

344 Diabetes Prevention Program Research Group. Costs associated with the primary prevention of type 2 diabetes mellitus in the Diabetes Prevention Program. *Diabetes Care*. 2003;26:36-47.

In addition, direct medical cost values for the DPP are even lower than control values found for patients with NGT in all studies examined in Section 3.5. One hypothesis for these low costs is that they reflect the exclusion of healthcare abnormalities other than IGT as a selection criterion for the DPP. Therefore, the following steps have been taken to incorporate direct healthcare costs for the states into the dissertation model.

4.3.1.1.1 Control Cost of Illness for NGT Subjects

Due to the extreme difference between the DPP direct healthcare cost values and those reported in the reviewed literature, the decision was made to use two different control figures for subjects with NGT in this model (the basic "control" cost). For the first three years of the study, the approximate control direct cost of healthcare found in the DPP was used. For the subsequent years after year three, a second, higher and possibly more representative, direct healthcare cost was used. The derivation of both of these values will now be discussed.

The literature review suggests that a subject with IGT has an increase in outside costs of healthcare of approximately 1.5 times control costs (Section 3.5.3.2.1).[345] The approximate increased cost of care for a subject with diabetes is 2 times the control cost (Section 3.5.2).[346,347] Using the three-year, per capita direct medical costs for the placebo group derived from the cost-analysis of the DPP ($5,011),[348] these increased cost of care ratios noted above, the approximate three-year cumulative incidences of progressing through

345 Nichols GA, Glauber HS, Brown JB. Type 2 diabetes: incremental medical care costs during the 8 years preceding diagnosis. *Diabetes Care*. 2000;23:1654-1659.

346 Brown JB, Nichols GA, Glauber HS, et al. Type 2 diabetes: incremental medical care costs during the first 8 years after diagnosis. *Diabetes Care*. 1999;22:1116-1124.

347 American Diabetes Association. Economic costs of diabetes in the U.S. in 2002. *Diabetes Care*. 2003;26:917-932.

348 Diabetes Prevention Program Research Group. Costs associated with the primary prevention of type 2 diabetes mellitus in the Diabetes Prevention Program. *Diabetes Care*. 2003;26:36-47.

the states of glucose homeostasis given in Section 2.3.3 (NGT = 19%, IGT = 52%, and T2DM = 29%),[349] and basic algebraic manipulation gives an approximate per capita control cost of NGT patients for the first three years of the study. The algebraic formula for this calculation is given below:

> The average three-year direct cost per patient for the entire placebo group (all groups of glucose homeostasis) =
>
> The cumulative incidence of NGT status at the end of three years X (Control Cost)
>
> +
>
> The cumulative incidence of IGT status at the end of three years X 1.5 X (Control Cost)
>
> +
>
> The cumulative incidence of T2DM status at the end of three years X 2.0 X (Control Cost)
>
> OR
>
> $5,011 = 0.19 (Control Cost) + 0.52(1.5) (Control Cost) + 0.29(2.0) (Control Cost)

Solving for Control Cost for three years gives a value of $3,233. Therefore, the one-year per capita direct control cost is approximately $1,078.

For the control cost value used for the subsequent years after year three, the assumption was made that medical costs should more closely approximate those which were found in the literature review. A control cost for subjects with NGT of $2,688 was chosen

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349 Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.

to use for years four to the completion of the model (subject age of 85 years). This figure was taken from the Kaiser Permanente control cost figures[350, 351] because these figures were thought to be lower than average direct healthcare costs that were generated at the time by non-managed care systems. The reasoning behind increasing healthcare costs and using this specific value is that in spite of dramatically lower direct healthcare costs seen in the first three years of the DPP, which is assumed to be, in part, secondary to design criteria of healthcare exclusions, healthcare costs will ultimately increase in this cohort. The assumption is made, however, that this increase will not be as high as those reported in Section 3.5.

4.3.1.1.2 Cost of Abnormal Glucose Homeostasis

The decision was made to multiply control costs of illness by the ratio of total health-care costs to control costs for T2DM and IGT to derive values for cost of illness for each of these subgroups.

T2DM multipliers can be approached in several different ways for the model. Using the studies reported in Section 3.5 of the literature review, it is noted that the ratio of total health care costs to control for T2DM ranges from approximately 2.03 to 2.83, with an average approximate value of 2.27.[352, 353, 354] The low value of 1.57 for years one through three after diagnosis of T2DM by Brown et al. was eliminated as an outlier, with the

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350 Brown JB, Nichols GA, Glauber HS, et al. Type 2 diabetes: incremental medical care costs during the first 8 years after diagnosis. *Diabetes Care*. 1999;22:1116-1124.

351 Nichols GA, Glauber HS, Brown JB. Type 2 diabetes: incremental medical care costs during the 8 years preceding diagnosis. *Diabetes Care*. 2000;23:1654-1659.

352 Brown JB, Nichols GA, Glauber HS, et al. Type 2 diabetes: incremental medical care costs during the first 8 years after diagnosis. *Diabetes Care*. 1999;22:1116-1124.

353 Ramsey S, Summers K, Leong SA, et al. Productivity and medical costs of diabetes in a large employer population. *Diabetes Care*. 2002;25:23-29.

354 American Diabetes Association. Economic costs of diabetes in the U.S. in 2002. *Diabetes Care*. 2003;26:917-932.

assumption that this value might be more indicative of the excess cost values found for subjects with IGT (section 3.5.3.2.1). A triangular distribution was used, with the most likely value being 2.27, and upper and lower ranges of 2.03 and 2.83.

A multiplier for IGT excess cost was based on the Nichols et al. study (Section 3.5.3.2.1).[356] A triangular distribution was applied using the values of 1.35, 1.48, and 1.79, with 1.48 being the most likely value.

Subjects with NGT were given the control cost for each cycle of the model for direct medical care outside of the healthcare system. These cost multipliers are summarized in Table 4.4.

Table 4.4 Cost Multipliers for Markov States of Glucose Homeostasis for Model 1A

Markov State	Planned Ajustments to Control Cost	Source
NGT	None	
IGT	Use a Multiplier with Triangular Distribution of 1.35, 1.48, 1.79	a
T2DM	Use a Multiplier with Triangular Distribution of 2.03, 2.27, 2.83	b,c,d

Sources:
a: Nichols GA, Glauber HS, Brown JB. Type 2 diabetes: incremental medical care costs during the 8 years preceding diagnosis. *Diabetes Care*. 2000;23:1654-1659.
b: Brown JB, Nichols GA, Glauber HS, et al. Type 2 diabetes: incremental medical care costs during the first eight years after diagnosis. *Diabetes Care*. 1999;22:1116-1124.
c: American Diabetes Association. Economic costs of diabetes in the US. in 2002. *Diabetes Care*. 2003;26:917-932.
d: Ramsey S, Summers K, Leong SA, et al. Productivity and medical costs of diabetes in a large employer population. *Diabetes Care*. 2002;25:23-29.

4.3.1.2 Mortality Rates for the Model

Mortality rates in the DPP study may reflect the exclusion of healthcare abnormalities other than IGT as part of the study design. The one-year mortality rate of 0.0017 found in the placebo group and 0.0010 for the lifestyle group for the first three years of the

356 Nichols GA, Glauber HS, Brown JB. Type 2 diabetes: incremental medical care costs during the 8 years preceding diagnosis. *Diabetes Care*. 2000;23:1654-1659.

study is much lower than the value of 0.0044 found in the U.S. Life Tables for a subject aged 50 years (Section 3.6.5).[357, 358] The decision was again made to use the DPP values as listed above for the first three years of the study.

For subsequent years, the standard life table mortality figures were incorporated using the data from the year 2001, which was the year of the termination of the study.[359] NHANES II data suggest that diabetes increases the mortality rate by a multiplier of approximately 1.9.[360, 361] A hazard ratio multiplier using a triangular distribution of 1.4, 1.9, and 2.5 was used to increase the standard mortality rate for diabetics in this model (Section 3.6.1).

There also appears to be a possible increase in mortality rate due to IGT as noted in the literature review. A triangular distribution was used for this multiplier, with the values of 0.8, 1.1, and 1.6 being used as derived from NHANES II data (Section 3.6.2).[362]

No adjustment to mortality rates was given to subjects who pass into the Death stage from the NGT stage. A summary of the hazard ratios used for Model 1A for the years subsequent to cycle year three are given in Table 4.5.

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357 Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518-2523.

358 Arias E. *United States Life Tables, 2000*. Hyattsville, MD: National Center for Health Statistics; 2002. vol. 51;3.

359 Ibid.

360 Saydah SH, Loria CM, Eberhardt MS, et al. Subclinical states of glucose intolerance and risk of death in the U.S. *Diabetes Care*. 2001;24:447-453.

361 Saydah SH, Eberhardt MS, Loria CM, et al. Age and the burden of death attributable to diabetes in the United States. *American Journal of Epidemiology*. 2002;156:714-719.

362 Saydah SH, Miret M, Sung J, et al. Postchallenge hyperglycemia and mortality in a national sample of U.S. adults. *Diabetes Care*. 2001;24:1397-1402.

Table 4.5 Hazard Ratio Multipliers for Mortality in Model 1A

Markov State	Adjustments to Mortality Rates After Cycle Year 3	Source
NGT	None	
IGT	Use a Hazard Ratio Multiplier of 0.8, 1.1, and 1.6	a
T2DM	Use a Hazard Ratio Multiplier of 1.4, 1.9, and 2.5	b,c

a: Saydah SH, Miret M, Sung J, et al. Postchallenge hyperglycemia and mortality in a national sample of U.S. adults. *Diabetes Care*. 2001;24:1397-1402.
b: Saydah SH, Loria CM, Eberhardt MS, et al. Subclinical states of glucose intolerance and risk of death in the U.S. *Diabetes Care*. 2001;24:447-453.
c: Saydah SH, Eberhardt MS, Loria CM, et al. Age and the burdens of death attributable to diabetes in the United States. *American Journal of Epidemiology*. 2002;156:714-719.

4.3.1.3 Model 1A Specifications

Figure 4.2 shows the Markov model required for Model 1A. The first information shown in a TreeAge generated Markov model (when examining from left to right) is a "variable box" that is found under the first choice node (the node from which the placebo and lifestyle arms emanate). The variable box contains variable input that is used as default through the tree. There are no specific rules for nomenclature for the variables used in a model, and therefore variable names are subject to the preference of the modeler. Figure 4.3 shows the variable box information for Model 1A. The names and definitions of variables are given in Table 4.6 (as well as Appendix 2), and will be described in detail through the next sections.

Figure 4.2 Model 1A

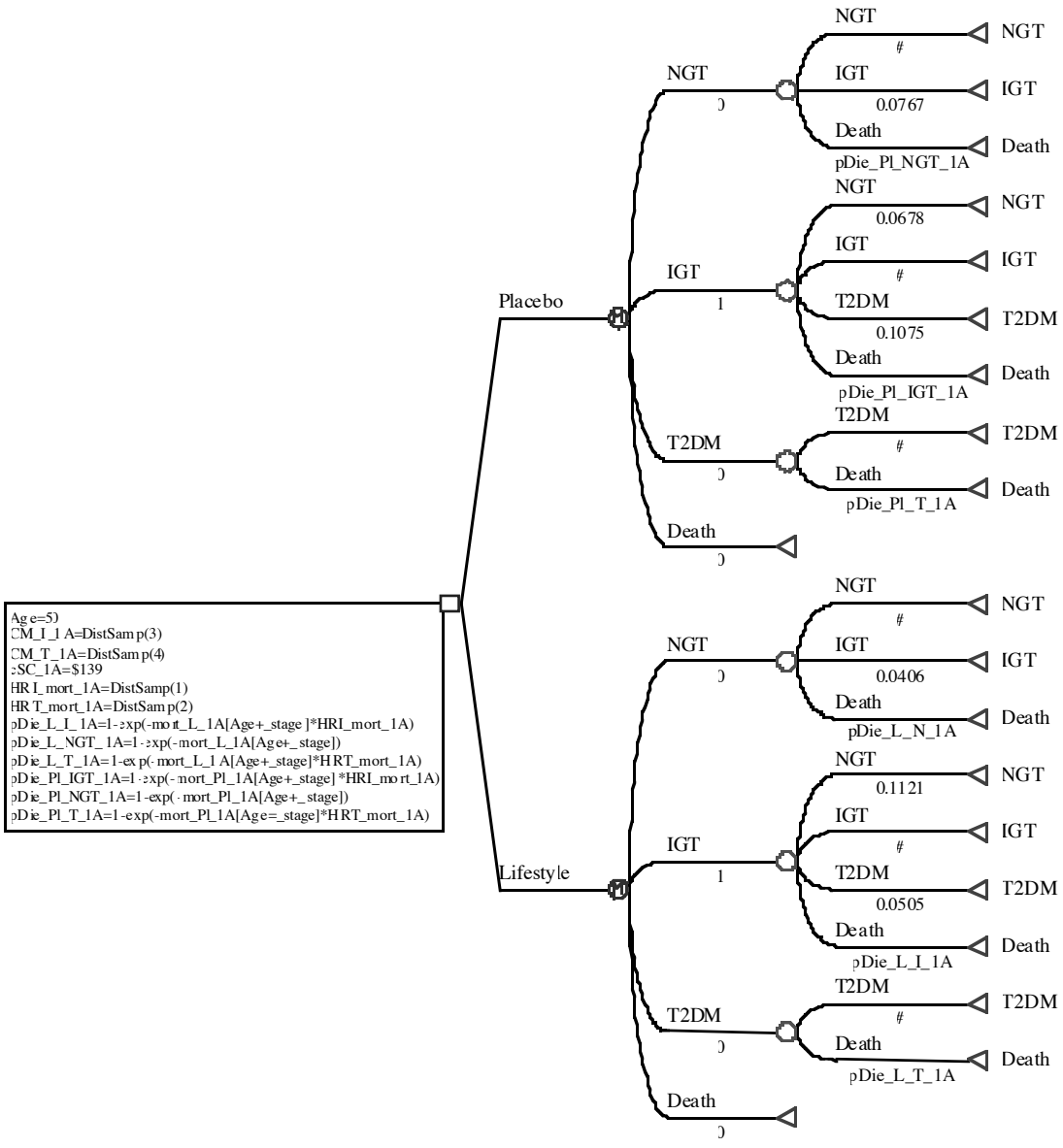


Figure 4.3 Variable Information for Model 1A

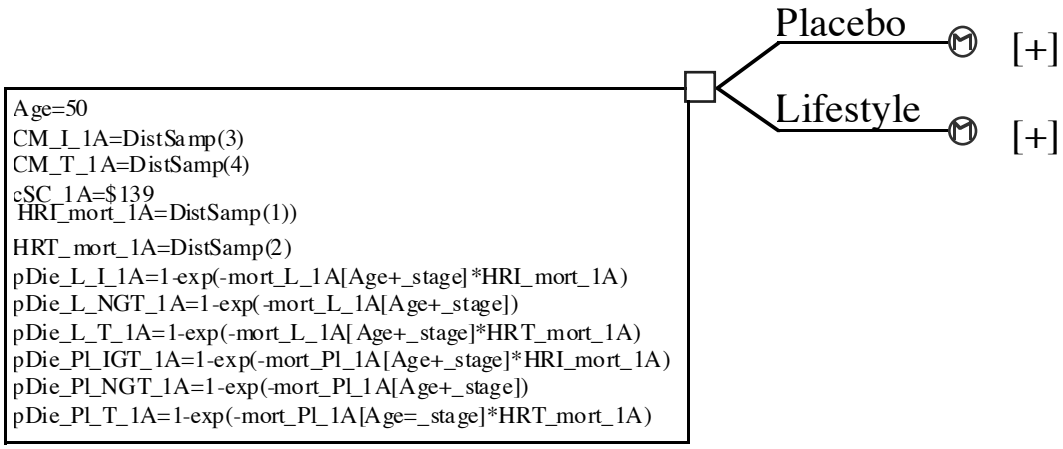


Table 4.6 Variable Information for Model 1A

Variable	Definition	Formula or Distribution
Age	50 years	
CM_I_1A	Cost multiplier of IGT in 1A	Triangular distribution of 1.35, 1.48, and 1.79 (DistSamp3)
CM_T_1A	Cost multiplier of T2DM in 1A	Triangular distribution of 2.03, 2.27, and 2.83 (DistSamp4)
cSC_1A	Cost of screening in 1A	$139
HRI_mort_1A	Hazard ratio of mortality for IGT in 1A	Triangular distribution of 0.8, 1.1, and 1.6 (DistSamp1)
HRT_mort_1A	Hazard ratio of mortality for T2DM in 1A	Triangular distribution of 1.4, 1.9, and 2.5 (DistSamp2)
pDie_Pl_NGT_1A	Probability of death for a NGT subject in the placebo arm	1-exp(-mort_Pl_1A[Age+_stage])
pDie_Pl_IGT_1A	Probability of death for an IGT subject in the placebo arm	1-exp(-mort_Pl_1A[Age+_stage] *HR_I_mort_1A)
pDie_Pl_T_1A	Probability of death for a T2DM subject in the placebo arm	1-exp(-mort_Pl_1A[Age+_stage] *HR_T_mort_1A)
pDie_L_NGT_1A	Probability of death for a NGT subject in the lifestyle arm	1-exp(-mort_L_1A[Age+_stage])
pDie_L_I_1A	Probability of death for an IGT subject in the placebo arm	1-exp(-mort_L_1A[Age+_stage] *HR_I_mort_1A)
pDie_L_T_1A	Probability of death for a T2DM subject in the lifestyle arm	1-exp(-mort_L_1A[Age+_stage] *HR_T_mort_1A

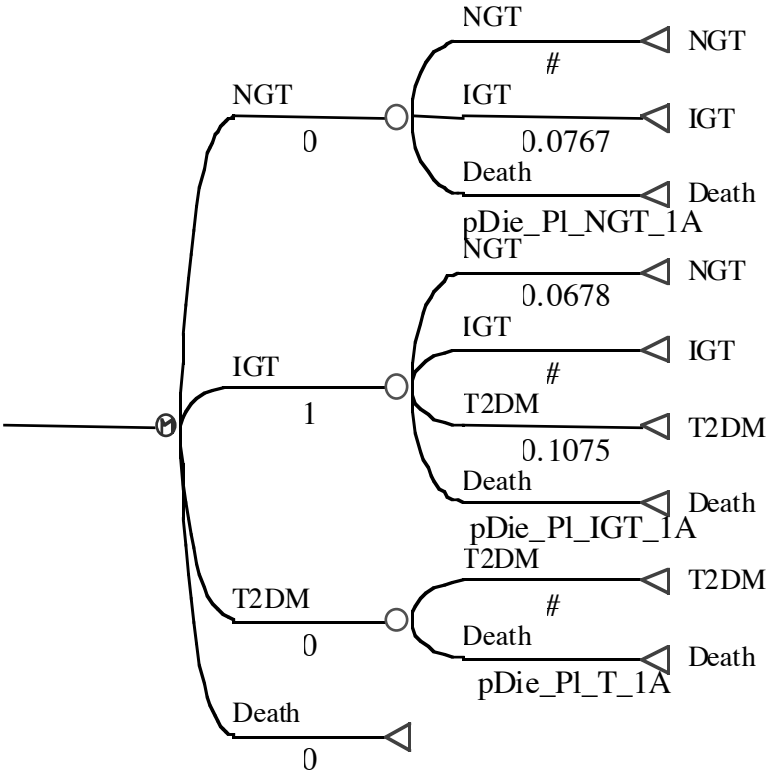
(mort_Pl_1A) refers to the mortality table for the placebo arm of 1A
(mort_L_1A) refers to the mortality table for the lifestyle arm of 1A
[Age+_stage] refers to the number of the cycle under evaluation in an imported table
DistSamp, distribution sample; exp, exponential

4.3.1.3.1 Transition Probabilities for Model 1A: Lifetime Duration of Effect

The following section describes the required transition probabilities for the subset of Model 1A that assumes lifetime duration of the effect of the intensive lifestyle intervention. Figure 4.4 illustrates the specific transition probabilities for the placebo arm of Model 1A. All subjects started in the IGT state, so the number 1 was placed under IGT as an initial state probability, while all other initial state probabilities were given a 0 value.

Specific values for progression from IGT to T2DM, reversion from IGT to NGT, and progression from NGT to IGT as noted in Table 4.1 (and Appendix 2) were inserted into appropriate transition probabilities for the model. The # symbol represents the built-in complimentary probability expression.

Figure 4.4 Placebo Arm of Model 1A



Variable Definitions:
pDie_Pl_NGT_1A: The probability of a NGT subject in the placebo arm dying in Model 1A
pDie_Pl_IGT_1A: The probability of an IGT subject in the placebo arm dying in Model 1A
pDie_Pl_T_1A: The probability of a T2DM subject in the placebo arm dying in Model 1A

IGT, impaired glucose tolerance; NGT, normal glucose tolerance; p, probability; Pl, placebo; T2DM, type 2 diabetes mellitus

The mortality transition probabilities require the input of data that varies in the first three-years to reflect the DPP mortality rates as described in section 4.3.1.2. The mortality rates were then changed to those found in the year 2000 U.S. Life Table values, and

therefore increase with age.[363] The baseline table required for Model 1A, which is also the mortality per age for a NGT placebo subject is given in table 4.7. These data will be referred to in the model equations as "mort_Pl_1A."

Table 4.7 Mortality Rates for Placebo Arm of Model 1A (mort_Pl_1A)[a,b]

Age	Mortality Rate	Age	Mortality Rate	Age	Mortality Rate
50	*0.0017*	62	0.0125	74	0.0346
51	*0.0017*	63	0.0136	75	0.0377
52	*0.0017*	64	0.0148	76	0.0409
53	0.0056	65	0.0161	77	0.0444
54	0.0061	66	0.0174	78	0.0485
55	0.0067	67	0.0189	79	0.0533
56	0.0073	68	0.0207	80	0.0588
57	0.0080	69	0.0227	81	0.0651
58	0.0088	70	0.0247	82	0.0721
59	0.0096	71	0.0267	83	0.0797
60	0.0104	72	0.0290	84	0.0882
61	0.0114	73	0.0317	85	0.0968

Sources:
a: Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518-2523.
b: Arias E. *United States Life Tables, 2000*. Hyattsville, MD: National Center for Health Statistics; 2002. vol. 51;3.
Italicized values reflect DPP mortality figures.

The model also requires adjustments for increased HRs for mortality for the IGT and T2DM subjects as outlined in Table 4.5 (and Appendix 2). It is apparent that no single number can reflect all of the transitions required for a model that varies transition probabilities according to cycle, so the mortality transition probabilities equations must reflect both the changes in mortality rates as well as adjustments for HRs.

Using the methodology described by Kuntz et al., the following basic formula was

363 Arias E. *United States Life Tables, 2000*. Hyattsville, MD: National Center for Health Statistics; 2002. vol. 51;3.

developed for the required mortality transition probabilities.[364] The example given is for a subject with NGT from the placebo arm. The label in the model, pDie_Pl_NGT_1A represents the following formula used in the model: 1-exp(-mort_Pl_1A[Age +_stage]). The equation, pDie_Pl_NGT_1A converts annual rates to annual probabilities as required by the TreeAge software. This mathematic conversion is described in Section 2.1.2.3.2 and requires the following basic formula: probability = 1-exp(-rate).

As can be seen, the values found in Table 4.7 have been inserted into the equation for the NGT subject as reflected by the insertion of the "mort_Pl_1A" value. The multiplication variable "[Age+_stage]" is required in the software to insert the appropriate value for mortality per age of subject in each Markov stage (or cycle, remembering that these terms may be used interchangeably). Age is defined as 50 years for this model.

The following formulas are those which were inserted into the model to define the mortality transition probabilities:

pDie_Pl_NGT_1A = 1-exp(-mort_Pl_1A[Age +_stage])

pDie_Pl_IGT_1A = 1-exp(-mort_Pl_1A[Age +_stage]*HRI_mort_1A)

pDie_Pl_T_1A= 1-exp(-mort_Pl_1A[Age +_stage]*HRT_mort_1A).

The latter two formulas reflect the increased HRs of mortality described in Table 4.5. These hazard ratio formulas are defined as the following:

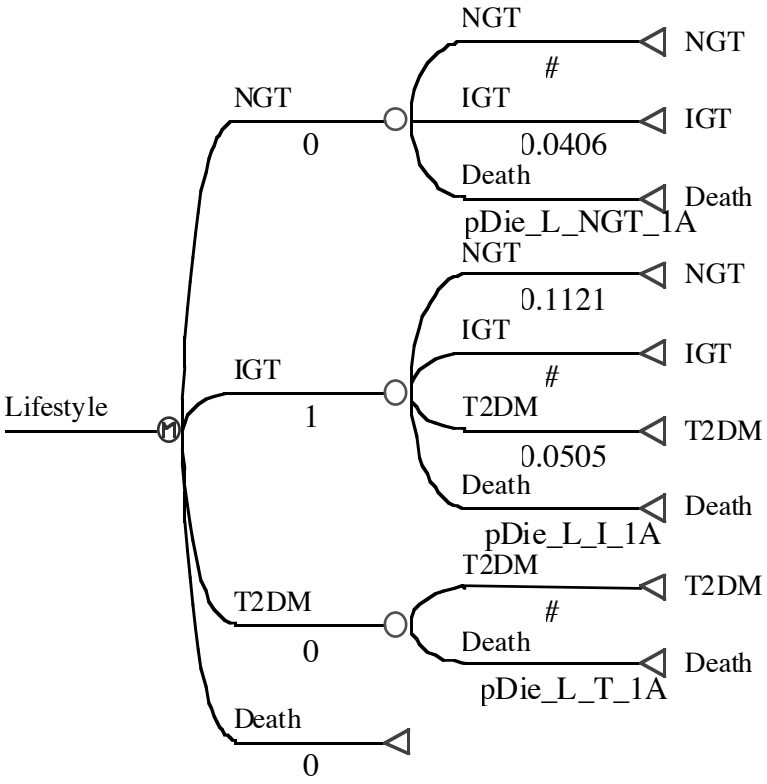
HRI_mort_1A = hazard ratio of mortality for IGT subjects = a triangular distribution of 0.8, 1.1, and 1.6

364 Kuntz KM, Kim JJ, Heijenbrok-Ka. M, et al. Methods for Decision Analysis in Public Health and Medicine. Boston: Harvard University; 2003.

HRT_mort_1A = hazard ration of mortality for T2DM subjects = a triangular distribution of 1.4, 1.9, and 2.5.

The same procedure, as illustrated in Figure 4.5, was followed for the lifestyle arm of Model 1A. Transition probabilities for NGT to IGT, IGT to T2DM, and IGT to T2DM were directly inserted from Table 4.2 (and seen in Appendix 2).

Figure 4.5 Intensive Lifestyle Arm of Model 1A



Variable Definitions:
pDie_L_NGT_1A: The probability of a NGT subject in the lifestyle arm dying in 1A
pDie_L_IGT_1A: The probability of an IGT subject in the lifestyle arm dying in 1A
pDie_L_T_1A: The probability of a T2DM subject in the lifestyle arm dying in 1A

IGT, impaired glucose tolerance; L, lifestyle

Once again, mortality transition probabilities require input of data that vary to reflect the DPP mortality rates for the first-three Markov cycles, as well as the increases in

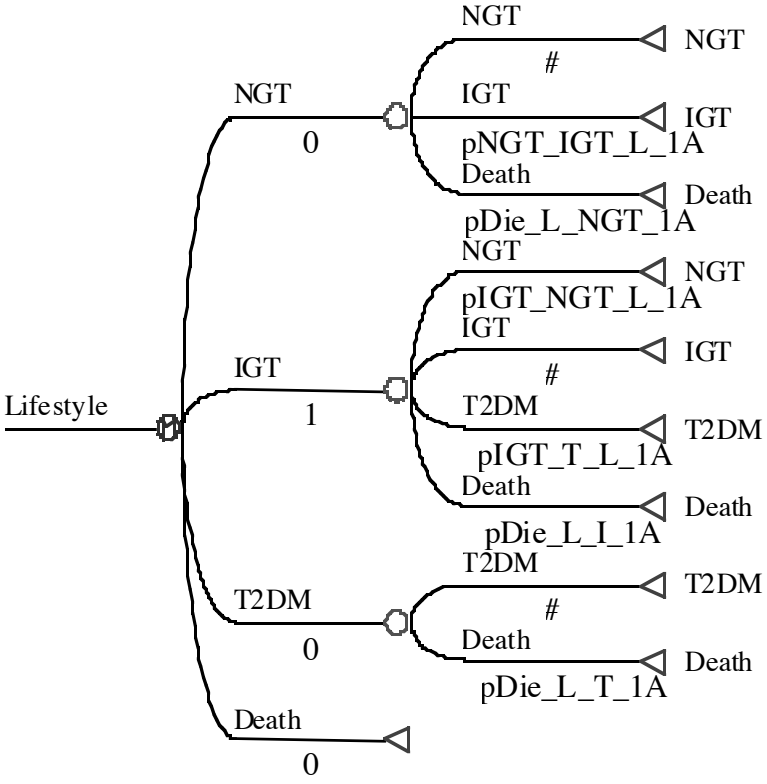
mortality found with age in the U.S. Life Tables. The mortality table required for the lifestyle arm is labeled "mort_L_1A." This table is essentially the same as Table 4.7 ("mort_Pl_1A") but the values for the first three Markov cycles (Ages 50 years, 51 years, and 52 years) are 0.0010, the mortality rate for the intensive lifestyle arm found by the DPP.

The probability formulas for death found in the lifestyle arm use the same hazard ratios for mortality for the IGT and T2DM state (HRI_mort_1A and HRT_mort_1A respectively). Therefore, the only difference for the death transition probabilities for this arm is the mortality table information.

4.3.1.3.2 Transition Probabilities for Model 1A: Three-Year Duration of Effect

Model 1A requires the following modifications (as illustrated in Figure 4.6) to adjust for an outcome measurement that assumes a three-year duration of the intensive lifestyle intervention effect. The transition probabilities of progression from NGT to IGT and IGT to T2DM, as well as the reversion from IGT to NGT in the lifestyle arm were assumed to revert back to the placebo values in the fourth stage of the model. This change required the substitution of the following formulas for the previously fixed transition probabilities. In addition, these formulas required the values outlined in Table 4.8 to allow for the changes of the transition probabilities with each cycle.

Figure 4.6 Lifestyle Arm of Model 1A Adjusted for Three-Year Duration of Treatment Effect



Variable Definitions:
pDie_L_NGT_1A: The probability of a NGT subject in the lifestyle arm dying in 1A
pDie_L_IGT_1A: The probability of an IGT subject in the lifestyle arm dying in 1A
pDie_L_T_1A: The probability of a T2DM subject in the lifestyle arm dying in 1A
pNGT_IGT_L_1A: The probability of progressing from NGT to IGT in 1A (three-year duration of effect)
pIGT_NGT_L_1A: The probability of reverting from IGT to NGT in 1A (three-year duration of effect)
pIGT_T_L_1A: The probability of progressing from IGT to T2DM in 1A (three-year duration of effect)

The new formulas required for this model are the following:

pNGT_IGT_L_1A = pNGT_I_Life_1A[Age+_stage]

pIGT_NGT_L_1A = pIGT_N_Life_1A[Age+_stage]

pIGT_T_L_1A = pIGT_T_Life_1A[Age+_stage}

The three tables required for these formulas are found in Table 4.8. These tables give the values for the first ten stages. It is again important to note that the reader can determine that these equations require the insertion of tables by the inclusion in the equation of the function [Age+_stage]. By referring to Figure 4.6, the reader can see that the first three

cycle values are those that were used in the intensive lifestyle arm of Model 1A with a lifetime treatment duration effect. At cycle 4, the transition probabilities revert back to the placebo rates.

Table 4.8 Transition Probability Tables Required for Model 1A: Three-Year Duration of Treatment Effect

Age	pNGT_IGT_L_1A	pIGT_N_Life_1A	pIGT_T_Life_1A
50	*0.0406*	*0.11221*	*0.0505*
51	*0.0406*	*0.11221*	*0.0505*
52	*0.0406*	*0.11221*	*0.0505*
53	0.0767	0.0678	0.1075
54	0.0767	0.0678	0.1075
55	0.0767	0.0678	0.1075
56	0.0767	0.0678	0.1075
57	0.0767	0.0678	0.1075
58	0.0767	0.0678	0.1075
59	0.0767	0.0678	0.1075

Italicized values represent original values from the DPP
pNGT_IGT_Life_1A: the table required to represent transition probabilities from NGT to IGT for the lifestyle arm of 1A (treatment effect duration of three years)
pIGT_N_Life_1A: the table required to represent transition probabilities from IGT to NGT for the lifestyle arm of 1A (treatment effect duration of three years)
pIGT_T_Life_1A: the table required to represent transition probabilities from IGT to T2DM for the lifestyle arm of 1A (treatment effect duration of three years)

4.3.1.3.3 Markov State Rewards for Model 1A

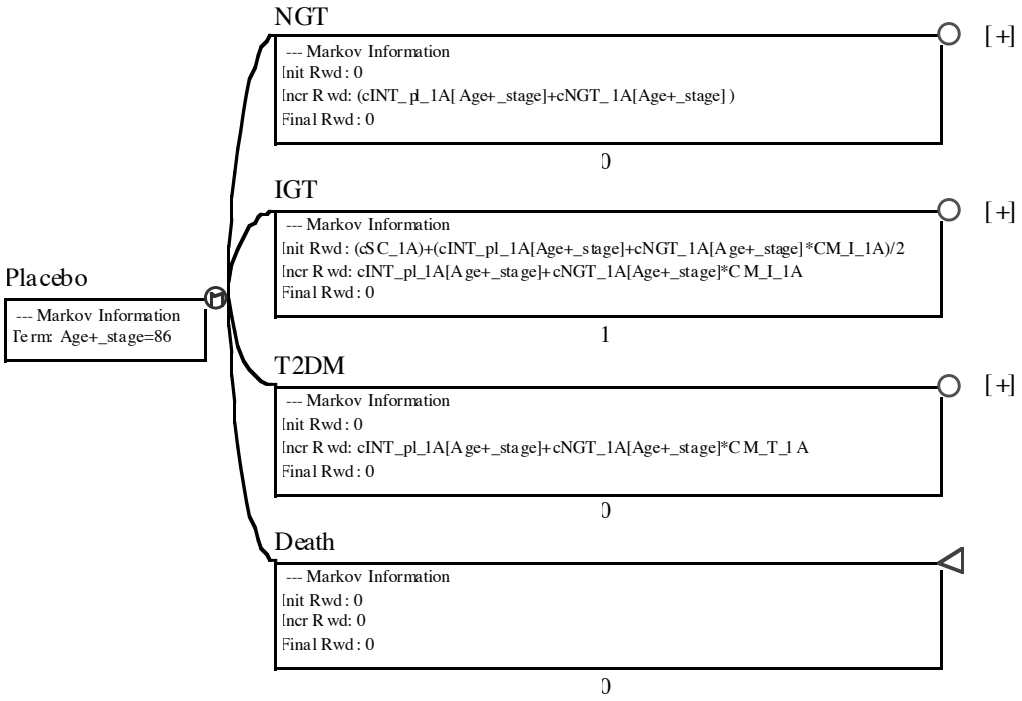
Using the TreeAge Data program, additional assignment of the values of costs, utilities, and life expectancy are all termed state rewards. These specific values will now be illustrated.

4.3.1.3.3.1 Markov State Rewards for Costs

Figure 4.7 illustrates the Markov state rewards for costs for Model 1A. The follow-

ing variables have been described in Table 4.6 (and Appendix 2): CM_I_1A (the cost multiplier of IGT for IA); CM_T_1A (the cost multiplier for T2DM for 1A); and cSC_1A (the cost of screening for 1A).

Figure 4.7 Markov State Rewards for Costs for the Placebo Arm of Model 1A



Two additional variables are required for the cost input, and these values were inserted as tables. As a reminder, tables in the model include the function [Age+_stage] to allow for matching the stage (or cycle) to the age for each Markov cycle. The additional variables are cINT_pl_1A, which represents the cost of the intervention for the placebo for model 1A, and cNGT_1A, which represents the cost of a NGT subject (for both the placebo and lifestyle arm). The cNGT_1A values may also be considered the direct medical control costs for this model. The first ten values for each of these tables are found in Table 4.9.

Table 4.9 Cost Tables for Placebo Arm of Model 1A for the First-Ten Stages

Age	cINT_pl_1A	cNGT_1A
50	$43	$1,100
51	18	1,100
52	18	1,100
53	0	2,688
54	0	2,688
55	0	2,688
56	0	2,688
57	0	2,688
58	0	2,688
59	0	2,688

cINT_pl_1A: cost of intervention for the placebo arm for model 1A
cNGT_pl_1A: direct medical costs for a normal glucose tolerance subject in the placebo arm

The cost of the intervention directly reflects the costs from the DPP for the placebo arm. The direct medical costs for NGT are those derived in section 4.3.1.1.1 for the first three-years of the study. The costs then increase to reflect the more probable increase in direct medical costs for the cohort as described in the same section.

The specific formulas used for the Markov state rewards for the placebo arm of the model involve knowledge of the initial state probabilities of the cohort and of the concept behind the half-cycle correction. As the entire cohort starts in the IGT stage, this cost information will be described first.

The Markov reward box for the IGT arm as seen in Figure 4.7 contains the following equation:

InitRwd: (cSc_1A) + (cINT_pl_1A[Age+_stage] + cNGT_1A[Age+_stage] * CM_I_1A)/2.

InitRwd is the abbreviation for the initial reward, which occurs during the first stage, which is referred to as stage zero. The cost event that occurs during the first stage only occurs for subjects in the IGT Markov state, as this is the state in which the cohort starts.

The equation starts with the following formula: (cSc_1A) + (cINT_pl_1A[Age+_stage]. From Table 4.6 (and Appendix 2) the reader is aware that the variable cSc_1A represents the cost of screening for the IGT cohort, a cost applied to all subjects in this arm. Table 4.9 gives the first ten values for cINT_pl_1A, the cost of intervention for the placebo arm. For all cycles not given, the cost of the intervention is zero. The intervention value is also given to all subjects for the first-three years, but this entry only inserts the first stage value of $43.

The final part of the equation, cNGT_1A[Age+_stage] * CM_I_1A/2, allows for the insertion of the direct medical control costs of the IGT subject. The function, cNGT_1A[Age+_stage], as given in Table 4.8 is multiplied by the cost multiplier for an IGT subject, CM_I_1A. The equation is divided by 1/2 to account for the half-cycle correction (HCC). This correction allows for the direct medical costs of an IGT subject to occur at the middle of the Markov cycle. It has been found that if all rewards (costs, utilities, and life expectancy) accrue at the beginning of the cycle, they are overestimated. If rewards occur at the end of the cycle, they are underestimated.[365] Therefore this type of HCC was inserted for utilities and life expectancy in a similar fashion.

The IGT Markov reward box in Figure 4.7 then lists the next equation:

IncrRwd: cINT_pl_1A[Age+_stage] + (cNGT_1A[Age+_stage]) * CMI_1A.

IncrRwd is the abbreviation for incremental reward, or that which occurs for the stages that occur after stage zero. This formula does not include the cost of screening, but does include the cost of the intervention and the direct medical costs for an IGT subject (direct medical costs for a NGT subject multiplied by the cost multiplier for IGT).

FinalRwd is the abbreviation for final reward. As this model is an absorbing process defined as a Markov model in which almost the entire cohort is dead at the termination of the model, no final entry is required.[366]

365 *DATA Healthcare User's Manual*. Williamstown, MA: TreeAge Software, Inc.; 2002.

366 Ibid.

No initial or final rewards are required for the NGT or T2DM states (because all subjects start in the IGT state), and therefore, no HCC are required. The incremental reward for the NGT subjects is the following:

cINT_pl_1A[Age+_stage] + cNGT_1A[Age+_stage].

The subject receives the costs of the intervention as well as direct medical costs as listed in Table 4.8.

The incremental cost for the T2DM subject is the following:

cINT_pl_1A[Age+_stage] + cNGT_1A[Age+_stage] * CM_T_1A.

This equation again allows for intervention cost inclusion as well as direct medical costs for the subject with T2DM.

Figure 4.8 illustrates the Markov state rewards for costs for the lifestyle arm of model 1A, and Table 4.10 gives the required cost tables for the model.

Figure 4.8 Markov State Rewards for Costs for the Lifestyle Arm of Model 1A

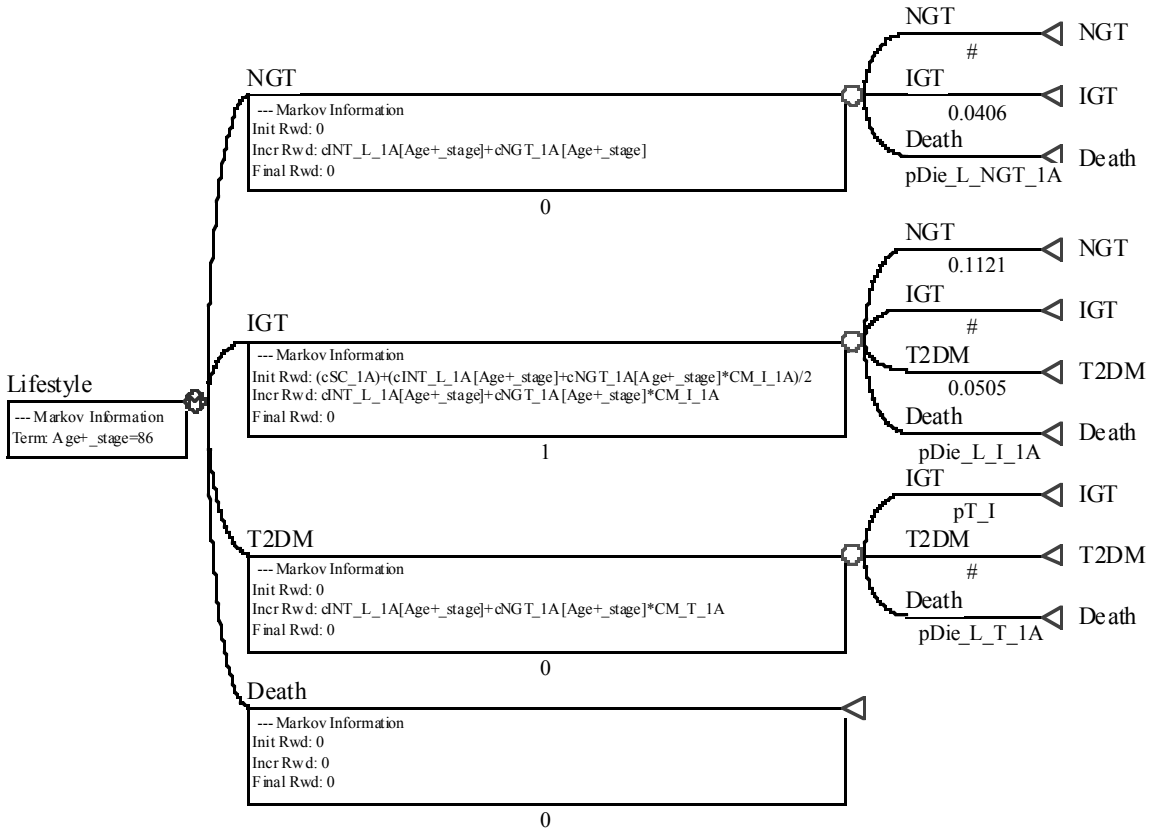


Table 4.10 Cost Tables for Lifestyle Arm of Model 1A for the First-Ten Stages

Age	cINT_L_1A
50	$1,399
51	679
52	702
53	0
54	0
55	0
56	0
57	0
58	0
59	0

cInt_L_1A: cost of intervention for the lifestyle arm for model 1A

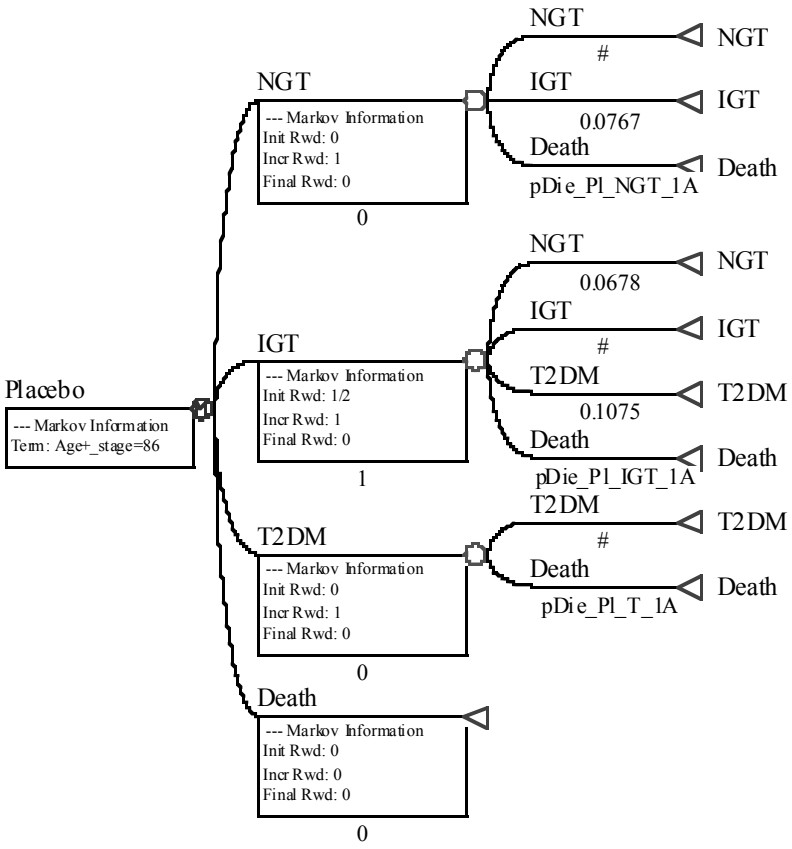
The cost reward formulas for the lifestyle arm of Model 1A follow the same format as that described for the placebo arm, except that the cost of the lifestyle intervention is inserted (cINT_L_1A).

4.3.1.3.3.2 Markov State Rewards for Life Expectancy

Figure 4.9 illustrates the state rewards for life expectancy for the placebo arm of Model 1A. These state rewards are identical for both the placebo and lifestyle arms. An HCC was used for the IGT node of the model. These cost rewards were used for the cost-effectiveness calculations for the model. When an actual life expectancy value is calculated, the HCC is removed according to the protocol outlined in the TreeAge training course.[367]

367 *TreeAge Software 2-Day Training Course*. Williamstown, Mass.: TreeAge Software, Inc; 2004.

Figure 4.9 Markov State Rewards for Life in the Placebo Arm of Model 1A



4.3.1.3.3.3 Markov State Rewards for Utilities

Figure 4.10 illustrates the Markov state rewards for utilities for the placebo arm for Model 1A. The lifestyle arm contains similar formulas, except the variable, uPl_1A[Age+_stage] is replaced with uLife_1A[Age+_stage]. These values are those derived from the DPP as described in section 3.7. The first ten cycles of the tables for these variables are given in Table 4.11.

Figure 4.10 Markov State Rewards for Utilities for the Placebo Arm of Model 1A

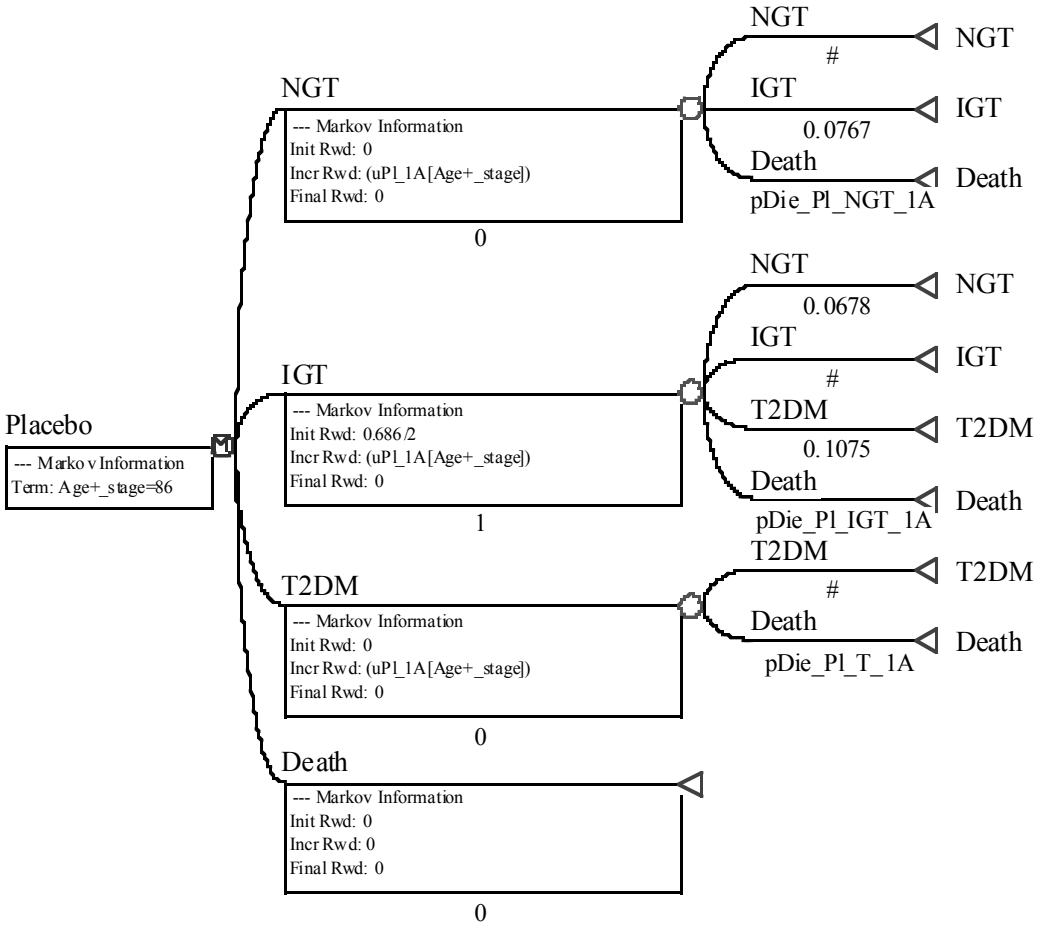


Table 4.11 Utility Values for the First-Ten Cycles of Model 1A

Age	uPl_1A	uLife_1A
50	*0.686*	*0.703*
51	*0.675*	*0.695*
52	*0.657*	*0.692*
53	0.657	0.692
54	0.657	0.692
55	0.657	0.692
56	0.657	0.692
57	0.657	0.692
58	0.657	0.692
59	0.657	0.692

uPl_1A: utility of the placebo arm of model 1A
uLife_1A: utility of the lifestyle arm of model 1A

The initial reward (IntRwd) arm of the IGT arm of the placebo in Figure 4.10 contains the first utility cycle reward, 0.686/2, which is the initial reward corrected by the HCC. The cycle-specific rewards were then inserted for the incremental rewards (IncRwd) for all-three nodes (NGT, IGT, and T2DM) of the placebo arm. The same format was used for the lifestyle arm, except that the uLife-1A values were inserted.

4.3.1.4 Model 1A Submodels Based on Baseline BMI

A sensitivity analysis was conducted for Model 1A based on the differences of efficacy of intensive lifestyle intervention to prevent T2DM by baseline BMI category in the DPP as outlined in Table 2.6. A complete table of input data for the submodels is included in Appendix 2. These submodels were based on the finding that subjects in both the intervention arm and the placebo arm with a BMI ≥ 35 kg/m^2 were more likely to progress to T2DM from the IGT state than subjects with a BMI less than this value.[368]

4.3.1.4.1 Submodel of 1A: BMI of 30 kg/m^2 to < 35 kg/m^2

For the submodel that evaluates long-term cost-effectiveness for the subgroup with a BMI of 30 kg/m^2 to < 35 kg/m^2, the following input parameters changed to reflect the DPP results. As noted in Table 2.6, the placebo group in this BMI category had a one-year transition probability form IGT to T2DM of 0.0851 (based on a progression of 8.9 cases per 100 person-years).[369] This transition probability is a 26% improvement over that found for the overall DPP cohort (11 cases per 100 person-years, or a one-year transition probability of 0.1075). The assumption was made that this same improvement will be found for reversion to IGT to NGT. The overall DPP cohort had a one-year transition probabil-

368 Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.

369 Ibid.

ity of 0.0702 for this progression, and the assumption was made that the DPP subcategory of BMI from 30 kg/m^2 to < 35 kg/m^2 will improve their reversion rate by the same 26% to 0.0885. The lower rate of transition from NGT to IGT of 0.0602 found in the Meigs et al. data was used for the model. These values are shown in Table 4.12.

Table 4.12 Probability Variables Used in the Placebo Arm of the DPP Submodel Based on a BMI Category of 30 kg/m^2 to < 35 kg/m^2

Variable	One-Year Probability	Source
Progression from IGT to T2DM	0.0851	a
Reversion from IGT to NGT	0.0885	a
Progression from NGT to IGT	0.0602	b

Sources:
a: Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.
b: Meigs JB, Muller DC, Nathan DM, et al. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of the Aging. *Diabetes*. 2003;52:1475-1484.

The one-year transition probability from IGT to T2DM for the lifestyle arm of the BMI subcategory of 30 kg/m^2 to < 35 kg/m^2 is 0.0363. This is a 39% improvement over the overall cohort transition probability of 0.0505. Once again, using the above methodology, the one-year transition probability for reversion from IGT to NGT becomes 0.1653 (reflecting a 39% improvement over the 0.1189 value found in the overall group). This 39% improvement is also reflected in the assumption of a decreased transition from NGT to IGT, calculated from the Meigs et al. value of 0.0602 to a value of 0.0433. These values are given in Table 4.13. All other values for variables remained as in Model 1A.

Table 4.13 Probability Variables Used in the Intensive Lifestyle Arm of the DPP Submodel Based on a BMI Category of 30 kg/m^2 to < 35 kg/m^2

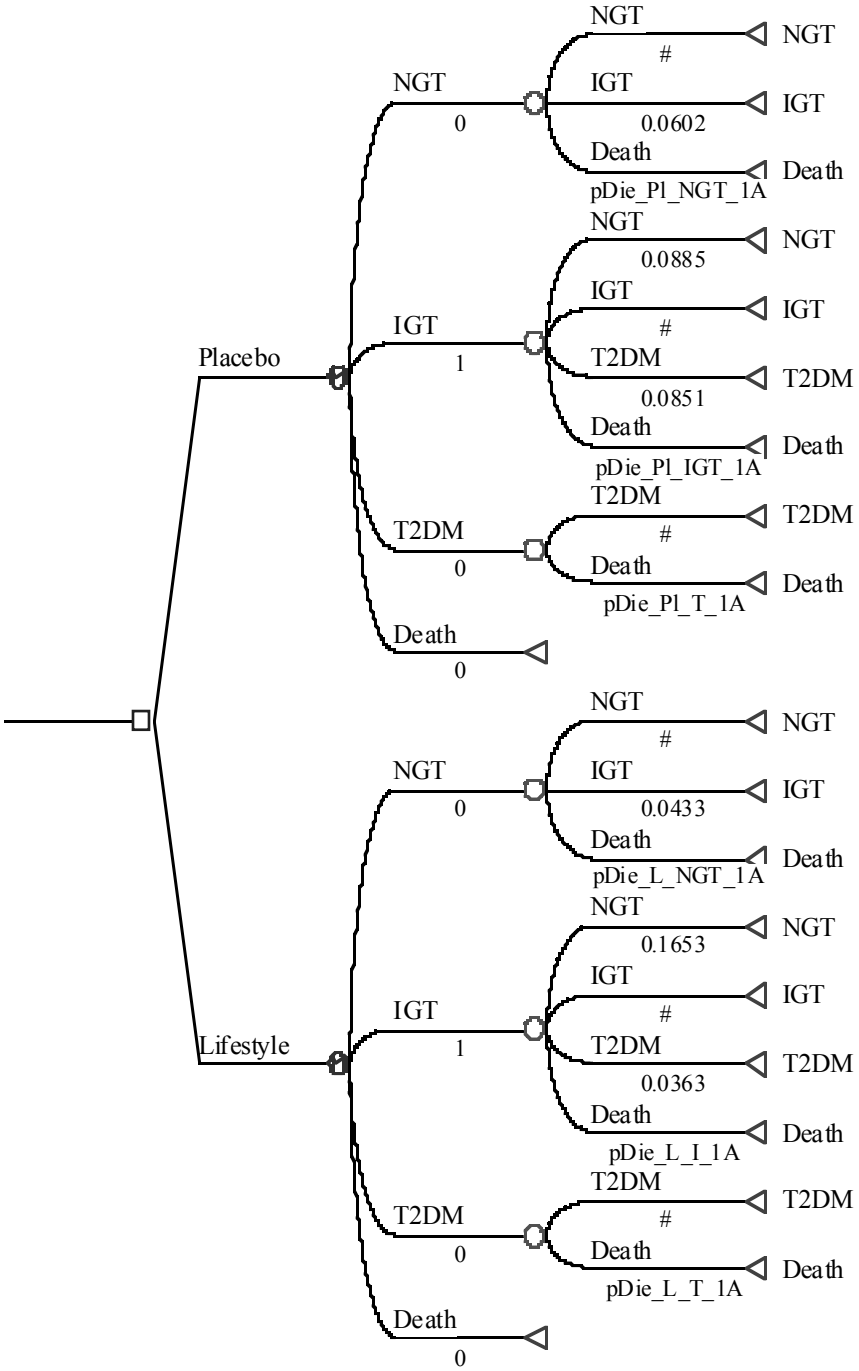
Variable	One-Year Probability	Source
Progression from IGT to T2DM	0.0363	a
Reversion from IGT to NGT	0.1653	a
Progression from NGT to IGT	0.0433	b

Sources:
a: Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.
b: Meigs JB, Muller DC, Nathan DM, et al. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of the Aging. .*Diabetes*. 2003;52:1475-1484.

4.3.1.4.1.1 Model Specifications

Figure 4.11 illustrates the changes required for transition probabilities as outlined in Tables 4.11 and 4.12. Appendix 2 contains a table with all input data for this model. The submodel of BMI of 30 kg/m^2 to < 35 kg/m^2 that evaluates a three-year effect of the intervention required the transition probability changes for cycles 1 through 3 for NGT to IGT, IGT to NGT, and IGT to T2DM, and then the lifestyle arm transition probabilities reverted back to those of the placebo. The methodology required for this analysis is outlined in section 4.3.1.3.2.

Figure 4.11 Submodel of 1A for BMI Subcategory of 30 kg/m^2 to < 35 kg/m^2



Variable Definitions:
pDie_Pl_NGT_1A: The probability of a NGT subject in the placebo arm dying in Model 1A
pDie_Pl_IGT_1A: The probability of an IGT subject in the placebo arm dying in Model 1A
pDie_Pl_T_1A: The probability of a T2DM subject in the placebo arm dying in Model 1A
pDie_L_NGT_1A: The probability of a NGT subject in the lifestyle arm dying in 1A
pDie_L_IGT_1A: The probability of an IGT subject in the lifestyle arm dying in 1A
pDie_L_T_1A: The probability of a T2DM subject in the lifestyle arm dying in 1A

IGT, impaired glucose tolerance; NGT, normal glucose tolerance; p, probability; Pl, placebo; T2DM, type 2 diabetes mellitus

4.3.1.4.2 Submodel of 1A: BMI ≥ 35 kg/m^2

As a comparator, the model was again evaluated using the progression rates from IGT to T2DM found in the DPP results for subjects with a BMI ≥ 35 kg/m^2. Table 4.14 gives the values that were used for the placebo arm of the subgroup.

Table 4.14 Probability Variables Used in the Placebo Arm of the DPP Submodel Based on a BMI Category of ≥ 35 kg/m^2

Variable	One-Year Probability	Source
Progression from IGT to T2DM	0.1332	a
Reversion from IGT to NGT	0.0567	a
Progression from NGT to IGT	0.0767	b

Sources:
a: Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.
b: Weyer C, Tataranni PA, Bogardus C, et al. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening glucose tolerance during each stage of type 2 diabetes development. *Diabetes Care*. 2001:24:89-94.

The placebo arm had an increase in progression from IGT to T2DM over the overall placebo arm of the cohort of 23.9% (a one-year transition probability of 0.1332 versus 0.1075, respectively). The assumption was made that reversion from IGT to NGT is reduced by this same amount. The one-year transition probability from the Pima Indian Study for progression from NGT to IGT was used for the submodel, as this group has the highest rate of progression from both NGT to IGT, and IGT to T2DM.[370]

Table 4.15 lists the values used for the intensive lifestyle arm of the submodel of the subgroup of BMI ≥ 35 kg/m^2. This subgroup had a 39.4% increase in progression to T2DM from IGT when compared to the overall lifestyle arm of the cohort (a one-year transition probability of 0.0704 and 0.0505, respectively).

370 Weyer C, Tataranni P, Bogardus C, et al. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of type 2 diabetes development. *Diabetes Care*. 2001;24(1):89-94.

Table 4.15 Probability Variables Used in the Intensive Lifestyle Arm of the DPP Submodel Based on a BMI Category of ≥ 35 kg/m^2

Variable	One-Year Probability	Source
Progression from IGT to T2DM	0.0704	a
Reversion from IGT to NGT	0.0853	a
Progression from NGT to IGT	0.0465	b

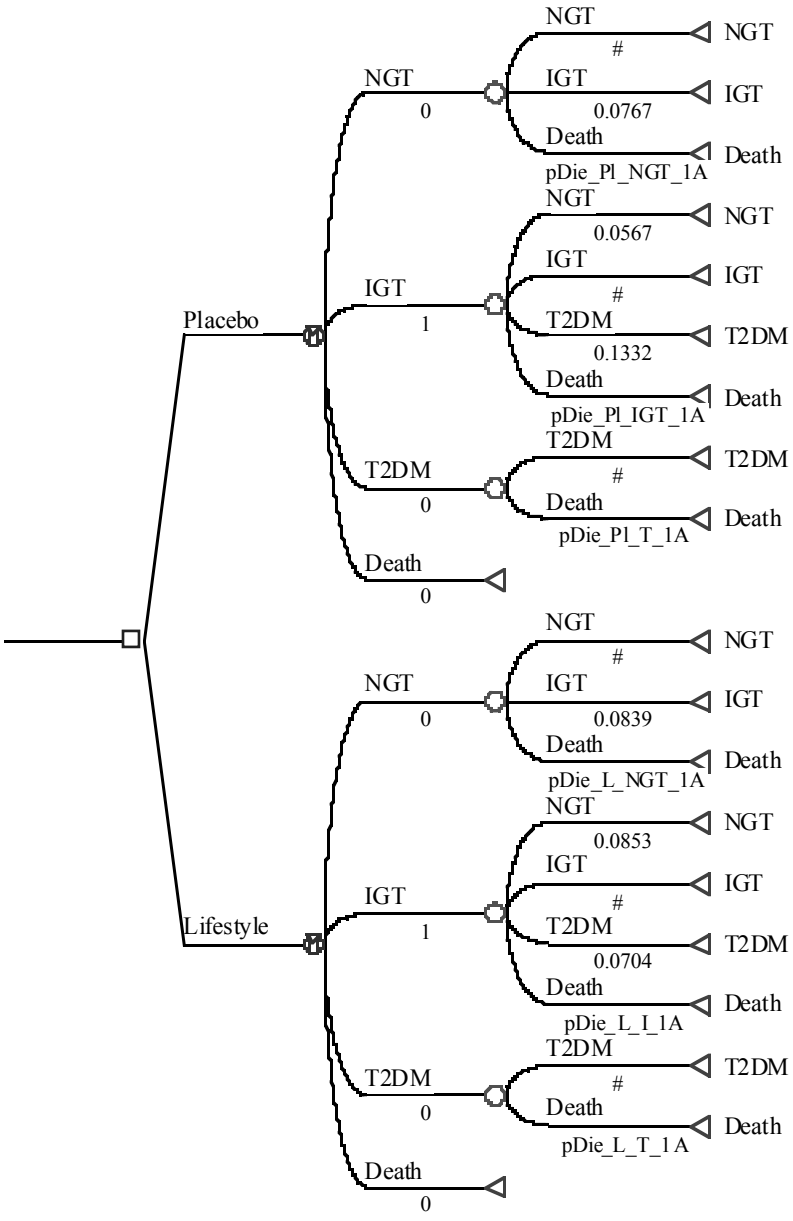
Sources:
a: Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.
b: Weyer C, Tataranni PA, Bogardus C, et al. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening glucose tolerance during each stage of type 2 diabetes development. *Diabetes Care*. 2001:24:89-94.

The reversion from IGT to NGT reflects a 39.4% decrease from the overall cohort. The Pima Indian Study progression from NGT to IGT was increased by this same value.

All other input variables remained the same for these models as Model 1A. The transition probabilities from NGT to IGT, IGT to NGT, and IGT to T2DM reverted back to placebo values for the model based on three-year duration effect as outlined in section 4.3.1.3.2.

Figure 4.12 illustrates the required model, and Appendix 2 contains a table with all required input data.

Figure 4.12 Submodel of 1A for BMI Subcategory ≥ 35 kg/m^2



Variable Definitions:
pDie_Pl_NGT_1A: The probability of a NGT subject in the placebo arm dying in Model 1A
pDie_Pl_IGT_1A: The probability of an IGT subject in the placebo arm dying in Model 1A
pDie_Pl_T_1A: The probability of a T2DM subject in the placebo arm dying in Model 1A
pDie_L_NGT_1A: The probability of a NGT subject in the lifestyle arm dying in 1A
pDie_L_IGT_1A: The probability of an IGT subject in the lifestyle arm dying in 1A
pDie_L_T_1A: The probability of a T2DM subject in the lifestyle arm dying in 1A

IGT, impaired glucose tolerance; NGT, normal glucose tolerance; p, probability; Pl, placebo; T2DM, type 2 diabetes mellitus

4.3.2 MODEL 1B: THE MODEL BASED ON THE DPP ADJUSTED FOR OBESITY

4.3.2.1 Changes in Adjustments to Direct Medical Care Cost Variables

The literature review suggests that the direct healthcare cost variable for obese subjects with NGT should be adjusted secondary to obesity. The Thompson et al. study reviewed in Section 3.5.4.3 suggests that a multiplier of 1.34 should be used to increase the cost of NGT in subjects who are obese (BMI ≥ 30 kg/m^2) and do not have abnormal glucose homeostasis, hypertension or hypercholesterolemia.[371] Therefore, the cost variable for NGT subjects was increased by a triangular distribution variable of 1.02, 1.34, and 1.74, with the most likely value being 1.34.

No further adjustments were made to the subjects in the IGT and T2DM states, and direct health care cost multipliers were the same as for Model 1A as listed in Table 4.4.

4.3.2.2 Changes to Hazard Ratios for Mortality

The second set of variables to be modified in Model 1B were the multipliers for mortality rates. The T2DM mortality hazard ratio were increased to 2.64 and used as a constant. This was based on the Rogers et al. study that incorporates BMI levels with calculations of hazard ratios secondary to T2DM (Section 3.6.3.1).[372]

As also noted in the literature review, mortality rates appear to increase secondary to obesity, but this increase occurs primarily in studies that exclude cardiovascular disease from their baseline cohort, such as the studies using data from the Nurses' Health Study, [373]

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371 Thompson D, Brown JB, Nichols GA, et al. Body mass index and future healthcare costs: a retrospective cohort study. *Obesity Research*. 2001;9:210-218.

372 Rogers RG, Hummer RA, Krueger PM. The effect of obesity on overall, circulatory disease, and diabetes-specific mortality. *Journal of Biosocial Science*. 2003;35:107-129.

373 Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women. *New England Journal of Medicine*. 1995;333:677-685.

Framingham Heart Study Data,[374] and subjects with no history of disease at baseline from the Cancer Prevention Study II.[375] Hazard ratio values for increased mortality for subjects with a BMI ≥ 30 kg/m^2 ranged from 1.3 to 2.05. As there were no specific studies on this topic for IGT subjects, the decision was made to adjust mortality rates by an increased hazard ratio of 1.7 for this subgroup. Subjects with NGT had an increased hazard ratio of 1.3. This was based on the assumption that IGT subjects may have a slightly higher mortality hazard ratio than those with NGT. A summary of the adjustments to mortality rates for the Markov Cycle years > 3 is given in Table 4.16.

Table 4.16 Adjustments to Hazard Ratios for Mortality for Model 1B

Markov State	Adjustments to Mortality Rates After Cycle Year 3	Source
T2DM	Use a Hazard Ratio Multiplier of 2.64	a
IGT	Use a Hazard Ratio Multiplier of 1.7	b,c,d
NGT	Use a Hazard Ratio Multiplier of 1.3	b,c,d

Source:
a: Rogers RG, Hummer RA, Krueger PM. The effect of obesity on overall, circulatory disease, and diabetes-specific mortality. *Journal of Biosocial Science*. 2003;35:107-129.
b: Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women. *New England Journal of Medicine*. 1995;333:677-685.
c: Peeters A, Barendregt JJ, Willekens F, et al. Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Annals of Internal Medicine*. 2003;138:24-32.
d: Calle EE, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of U.S. adults. *New England Journal of Medicine*. 1999;341:1097-1105.

4.3.2.3 Model Specifications

The Markov model for Model 1B is essentially the same as that illustrated in Figure 4.2 except for the required variable adjustments. The Model 1B variable box is illustrated in Figure 4.13, and definitions are given in Table 4.17. A complete input table is given in Appendix 2.

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374 Peeters A, Barendregt JJ, Willekens F, et al. Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Annals of Internal Medicine*. 2003;138:24-32.

375 Calle EE, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of U.S. adults. *New England Journal of Medicine*. 1999;341:1097-1105.

Figure 4.13 Variable Information for Model 1B

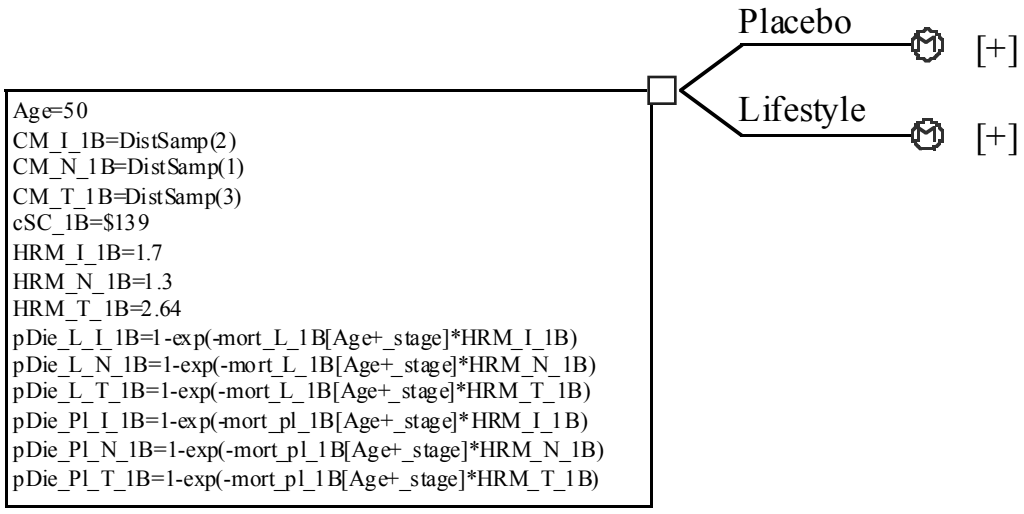

Table 4.17 Variable Information for Model 1B

Variable	Definition	Formula or Distribution
Age	50 years	
CM_N_1B	Cost Multiplier of NGT in 1B	Triangular distribution of 1.02, 1.34, and 1.74 (DistSamp 1)
CM_I_1B	Cost Multiplier of IGT in 1B	Triangular distribution of 1.35, 1.48, and 1.79 (DistSamp 2)
CM_T_1B	Cost Multiplier of T2DM in 1B	Triangular distribution of 2.03, 2.27, and 2.83 (DistSamp 3)
cSC_1B	Cost of Screening in 1B	$139
HRM_N_1B	Hazard ratio of mortality for NGT in 1B	1.3
HRM_I_1B	Hazard ratio of mortality for IGT in 1B	1.7
HRM_T_1B	Hazard ratio of mortality for T2DM in 1B	2.64
pDie_Pl_N_1B	Probability of death for a NGT subject in the placebo arm	1-exp(-mort_pl_1B[Age+_stage] *HRM_N_1B)
pDie_Pl_I_1B	Probability of death for an IGT subject in the placebo arm	1-exp(-mort_pl_1B[Age+_stage] *HRM_I_1B
pDie_Pl_T_1B	Probability of death for a T2DM subject in the placebo arm	1-exp(-mort_pl_1B[Age+_stage] *HRM_T_1B
pDie_L_N_1B	Probability of death for a NGT subject in the lifestyle arm	1-exp(-mort_L_1B[Age+_stage] *HRM_N_1B)
pDie_L_I_1B	Probability of death for an IGT subject in the lifestyle arm	1-exp(-mort_L_1B[Age+_stage] *HRM_I_1B
pDie_L_T_1B	Probability of death for a T2DM subject in the lifestyle arm	1-exp(-mort_L_1B[Age+_stage] *HRM_T_1B

(mort_pl_1B) refers to the mortality table for the placebo arm of 1B
(mort_L_1B) refers to the mortality table for the lifestyle arm of 1B
[Age+_stage] refers to the number of the cycle under evaluation in an imported table
DistSamp, distribution sample; exp, exponential

The mortality table for the placebo arm for 1B (mort_pl_1B) is the same as Table 4.6 (Mortality Rates for the Placebo Arm of Model 1A). The mortality table for the lifestyle arm for 1B (mort_L_1B) is the same as mort_Pl_1A that is described in section 4.3.1.3.1.

4.3.3 MODEL 2A AND 2B: MORE GENERALIZABLE MODELS

Modeling is one method that can be used to predict cost-effectiveness of clinical studies for populations that are more likely to be found in "real-world" situations. Two final models were planned to attempt to apply the DPP data to a more generalized, hypothetical cohort of subjects.

In both of these models, the assumption was made that the starting cohort of subjects does not have exclusion of other healthcare states at the beginning of the study. The most important assumption that must be made in these models is that there is no change in probabilities of moving from the Markov states of IGT to T2DM, IGT to NGT, or NGT to IGT for the placebo group and the lifestyle group (as detailed in Section 4.3). This assumption may not be a totally accurate assumption, but currently there are no data to refute it. Due to the uncertainty of these assumptions, extensive sensitivity analyses were conducted for these transition probabilities.

Mortality transition rates changed in Models 2A and 2B. The values derived for mortality by the DPP were no longer incorporated. Instead, U.S. Life Table values were used for all Markov cycles, with appropriate HR adjustments as specified.[376]

Another change that occurred in these models was that for control costs. In Models 2A and 2B the DPP control cost is no longer used for the first three years of the study. The assumption was made that control costs will be higher because subjects have other health conditions besides IGT. Two figures were used for the models. The first was the control

376 Arias E. *United States Life Tables, 2000.* Hyattsville, MD: National Center for Health Statistics; 2002. vol. 51;3.

cost figure generated by the Kaiser Permanent studies of $2,699.[377, 378] A second control cost value of $3,968 derived from the ADA 2002 data was also used as a sensitivity analysis.[379]

Utility values also changed in this model. The third-year value from each arm of the study was used for all Markov cycles. This was done with the assumption that with added healthcare abnormalities, utilities for each arm of the study more closely approximate the year-three value.

A sensitivity analysis was conducted for Model 2A and Model 2B based on the possibility that a newly diagnosed T2DM subject may revert to IGT for a short period due to caloric restriction (as discussed in section 2.1.2.3.5). These models included an additional arm off of the T2DM node that allowed for a transition from diabetes to IGT. The first cycle transition probability was 0.20, and all subsequent cycles were 0.00.

4.3.3.1 Additional Model 2A Adjustments

Model 2A allows for adjustments due to inclusion of additional healthcare abnormalities at baseline but does not include specific adjustments for obesity. Therefore the model used the adjustments for costs that were outlined for Model 1A in Table 4.4 and the mortality adjustments in Table 4.5.

4.3.3.1.1 Model Specifications

The variable information for Model 2A (lifetime duration of effect) is illustrated in

377 Brown JB, Nichols GA, Glauber HS, et al. Type 2 diabetes: incremental medical care costs during the first 8 years after diagnosis. *Diabetes Care*. 1999;22:1116-1124.

378 Nichols GA, Glauber HS, Brown JB. Type 2 diabetes: incremental medical care costs during the 8 years preceding diagnosis. *Diabetes Care*. 2000;23:1654-1659.

379 American Diabetes Association. Economic costs of diabetes in the U.S. in 2002. *Diabetes Care*. 2003;26:917-932.

Figure 4.14, and definitions are given in Table 4.18. A complete input table is given in Appendix 3.

Figure 4.14 Variable Information for Model 2A

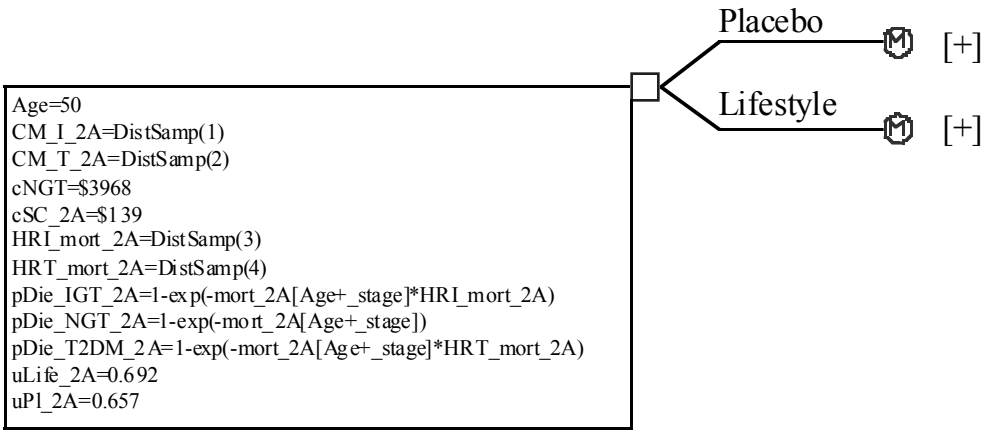

Table 4.18 Variable Information for Model 2A

Variable	Definition	Formula or Distribution
Age	50 years	
CM_I_2A	Cost multiplier of IGT in 2A	Triangular distribution of 1.35, 1.48 and 1.79
CM_T_2A	Cost multiplier of T2DM in 2A	Triangular distribution of 2.03, 2.27, and 2.83
cNGT	Cost of NGT	$2,688 or $3,966
cSC-2A	Cost of screening in 2A	$139
HRI_mort_2A	Hazard ratio of mortality for IGT in 2A	Triangular distribution of 0.8, 1.1, and 1.6 (DistSamp 3)
HRT_mort_2A	Hazard ratio of mortality for T2DM in 2A	Triangular distribution of 1.4, 1.9, and 2.5 (DistSamp 4)
pDie_NGT_2A	Probability of death for a NGT subject in the lifestyle and placebo arms	1-exp(-mort_2A[Age+_stage])
pDie_IGT_2A	Probability of death for an IGT subject in the lifestyle and placebo arms	1-exp(-mort_l2A[Age+_stage] *HRI_mort_2A)
pDie_T_2A	Probability of death for a T2DM subject in the lifestyle and placebo arms	1-exp(-mort_2A[Age+_stage] *HRT_mort_2A_
uLife_2A	Utility score in the lifestyle arm	0.692
uPl_2A	Utility score in the placebo arm	0.657

(mort_2A) refers to the mortality table for 2A
[Age+_stage] refers to the number of the cycle under evaluation in an imported table
DistSamp, distribution sample; exp, exponential

The mortality table for Model 2A (mort_2A) was taken from the U.S. Life Tables.[380] There was no need to have separate formulas for the probability of dying of NGT, IGT, and T2DM for each arm, as the mortality table was now the same for both the placebo and lifestyle arms. The difference in the arms depends on the intervention effect, duration of

380 Arias E. *United States Life Tables, 2000.* Hyattsville, MD: National Center for Health Statistics; 2002. vol. 51;3.

effect, and hazard ratio of mortality (in this case, an increase for the IGT and T2DM arms).

4.3.3.2 Adjustments Made to Model 2B

Model 2B allows for inclusion of additional healthcare states and also makes any potential adjustments necessary for obesity. The cost adjustment to NGT that was outlined in Section 4.3.2.1 used for Model 1B was applied to Model 2B. This adjustment was the use of a triangular distribution multiplier of 1.02, 1.34, and 1.74 to the NGT control cost.

The hazard ratios for mortality for NGT and IGT subjects remained those which were used in Model 1A, Table 4.5. Therefore, there was no increased hazard ratio for NGT, and a triangular distribution hazard ratio of 0.8, 1.1, and 1.6 was used for IGT subjects. The hazard ratio multiplier for T2DM was adjusted for obesity in this model. The previously used triangular distribution of 1.4, 1.9, and 2.5 was changed to 2.64. This change was made to reflect the increased hazard ratio found by Rogers et al. for increased levels of BMI in T2DM subjects (section 3.6.3.1).[381]

No adjustment was made to mortality for obese subjects with NGT because as noted in the literature review, there appears to be little effect on mortality secondary to obesity in subjects with normal glucose homeostasis in studies that have no exclusions for cardiovascular disease at baseline.[382]

The sensitivity analysis to incorporate the possibility of a reversion from T2DM to IGT was also conducted for this model.

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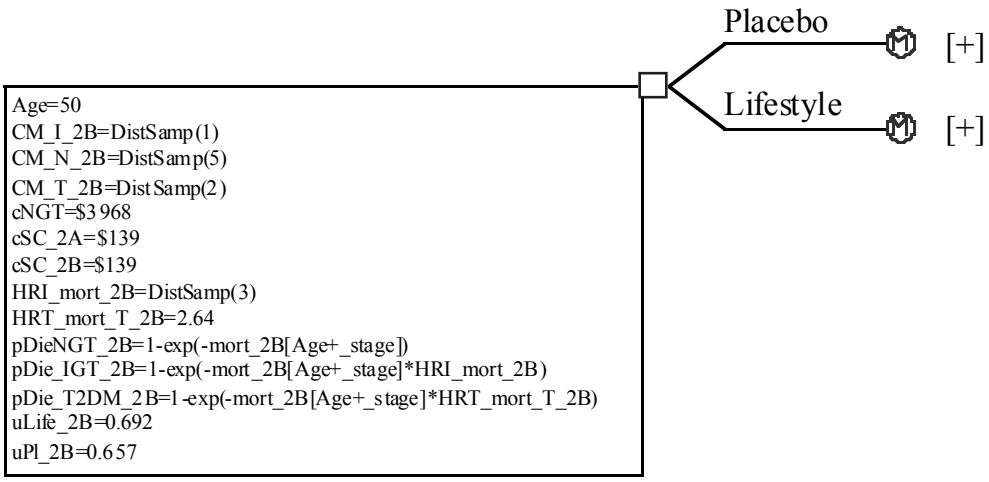
381 Rogers RG, Hummer RA, Krueger PM. The effect of obesity on overall, circulatory disease, and diabetes-specific mortality. *Journal of Biosocial Science*. 2003;35:107-129.

382 Calle EE, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of U.S. adults. *New England Journal of Medicine*. 1999;341:1097-1105.

4.3.3.2. Model Specifications

The variable information for Model 2B (lifetime duration of effect) is illustrated in Figure 4.15, and definitions are given in Table 4.19. A complete input table is given in Appendix 3. The mortality table for this model was taken directly from the year 2000 U.S. Life Table.[383]

Figure 4.15 Variable Information for Model 2B



383 Arias E. *United States Life Tables, 2000*. Hyattsville, MD: National Center for Health Statistics; 2002. vol. 51;3.

Table 4.19 Variable Information for Model 2B

Variable	Definition	Formula or Distribution
Age	50 years	
CM_N_2B	Cost multiplier of NGT in 2B	Triangular distributioin of1.02, 1.34, and 1.74 (DistSamp 5)
CM_I_2B	Cost multiplier of IGT in 2B	Triangular distribution of 1.35, 1.48 and 1.79 (DistSamp 1)
CM_T_2B	Cost multiplier of T2DM in 2B	Triangular distribution of 2.03, 2.27, and 2.83 (DistSamp 2)
cNGT	Cost of NGT	$2,688 or $3,966
cSC-2B	Cost of screening in 2B	$139
HRI_mort_2B	Hazard ratio of mortality for IGT in 2B	Triangular distribution of 0.8, 1.1, and 1.6 (DistSamp 3)
HRT_mort_2B	Hazard ratio of mortality for T2DM in 2B	2.64
pDie_NGT_2B	Probability of death for a NGT subject in the lifestyle and placebo arms	1-exp(-mort_2B[Age+_stage])
pDie_IGT_2B	Probability of death for an IGT subject in the lifestyle and placebo arms	1-exp(-mort_2B[Age+_stage] *HRI_mort_2B)
pDie_T_2B	Probability of death for a T2DM subject in the lifestyle and placebo arms	1-exp(-mort_2B[Age+_stage] *HRT_mort_2B
uLife_2B	Utility score in the lifestyle arm	0.692
uPl_2B	Utility score in the placebo arm	0.657

(mort_2B) refers to the mortality table for 2B
[Age+_stage] refers to the number of the cycle under evaluation in an imported table
DistSamp, distribution sample; exp, exponential

4.4 Data Analysis

A healthcare system perspective, using direct medical costs, was assumed for all models. The models were run using Data 4.0 software (TreeAge Software, Inc., Williamstown, Massachusetts).[384] A Markov process technique was utilized, which allows for varying transition probabilities with time. This technique is required due to

384 Suzuki H, Fukushima M, Usami M, et al. Factors responsible for development from normal glucose tolerance to isolated postchallenge hyperglycemia. *Diabetes Care*. 2003;26(4):1211-1215.

changes in mortality rates over the lifespan of the subjects calculated from the U.S. life tables.[385]

Half-cycle corrections were incorporated for costs and rewards. This correction allows for transitions to occur at the mid-point of a Markov cycle. Therefore, this correction was also used in both the cost per life-year and cost per QALY analyses.

Monte Carlo simulation was used for the probabilistic sensitivity analyses. The simulation was run 10,000 times.

The following outcomes were assessed for each arm of the study: (1) number of years free of T2DM; (2) number of years free of both IGT and T2DM; (3) life expectancy; and (4) total costs. Incremental costs, utilities, and life expectancy were calculated in between-arm analyses. Finally, incremental cost-effectiveness ratios for costs per life-year gained and cost per QALY were calculated. These ratios were compared to the U.S. accepted standards for cost effectiveness given in section 3.3.

385 Arias E. *United States Life Tables, 2000*. Hyattsville, MD: National Center for Health Statistics; 2002. vol. 51;3.

CHAPTER 5 – RESULTS

The results of this dissertation are presented in four major sections, and then summarized. The first section directly addresses the three major questions of the research project: (1) What is the long-term cost-effectiveness of the use of intensive lifestyle intervention to prevent progression from IGT to T2DM? (2) What is the effect of obesity on this evaluation? and (3) How does the evaluation change if an attempt is made to make the analysis more generalizable using a hypothetical population that may be more representative of that which is currently found in the U.S. rather than the cohort studied by the DPP? This last question specifically relates to the baseline, exclusion criteria for the DPP study cohort.

A base-case result is presented for each of the proposed models (Model 1A, 1B, 2A, and 2B), and the submodels of Model 1A (those that address the different effects of the lifestyle intervention according to BMI subcategories). An overview of the models and hypotheses is given in Appendix 1. These models were analyzed as both a Monte Carlo simulation and a Markov analysis. The results are given for: (1) a three-year duration of effect of the intervention given a three-year duration of intervention; and (2) a lifetime duration of effect of the intervention given a three-year duration of the intervention.

As a reminder, Model 1A is the model most similar to the DPP cohort. In this model, DPP results were used for the morality, utility, and cost values for the first three cycles. The first submodel of 1A used DPP data to analyze cost-effectiveness for the BMI subcategory of 30 kg/m^2 to < 35 kg/m^2. The second submodel of 1A used DPP data to analyze cost-effectiveness for the BMI subcategory of ≥ 35 kg/m^2. Model 1B made adjustments for obesity by increasing the hazard ratio for mortality for NGT, IGT and T2DM subjects, and adding a cost-multiplier for obesity for NGT subjects. DPP data for

mortality, utility and costs were used for the first-three years for all of the models described above.

Model 2A is similar to Model 1A, but the DPP data for the first-three years were not used, and data that are potentially more representative of current U.S. values for mortality, utilities and costs were inserted. Model 2B attempted to adjust Model 2A for obesity by adding a cost-multiplier for NGT subjects and increasing the hazard ratio for mortality for T2DM subjects. As noted, the models and hypotheses are listed in table form in Appendix 1.

The results of analyses of determinates of the range of cost-effectiveness (as defined by incremental cost-effectiveness ratios) are then reported. These analyses include comparisons of the least and most cost-effective models. Additional analyses reported include the effect of "control cost of illness" (as defined as the direct medical costs of a non-obese, NGT subject) on incremental cost-effectiveness ratios, as well as the effect of varying the range of the cost of the intervention on this same output.

A comparison of the obesity-adjusted models to unadjusted models is then given. This entails comparing Model 1B to Model 1A, and Model 2B to Model 2A. The lifestyle and placebo arms of each of the obesity-adjusted models (the B Models) are compared to the unadjusted models (the A Models) in terms of total lifetime costs, total life-years, cost per life-year differences, QALYs, cost per QALY differences, and overallincremental cost-effectiveness ratio differences for both cost per life-year and cost per QALY.

The section concludes with a comparison of Model 1A and the submodels of 1A for a BMI subcategory of 30 kg/m^2 to < 35 kg/m^2 and a BMI subcategory of ≥ 35 kg/m^2. These models are also compared in terms of differences in total lifetime costs, total life-years, cost per life-year, QALYs, cost per QALY, and over-all incremental cost-effectiveness ratio differences for life-year and QALY outcomes.

A second major section addresses the maximum acceptable cost of the intervention for Models 1A and 1B and Models 2A and 2B for the following scenarios: (1) a three-year cost of treatment intervention with a three-year effect of the intervention; and (2) a three-year cost of the treatment intervention with a lifetime effect of the intervention. "Maximum acceptable cost of intervention" is defined as the maximum cost of the intervention that is allowed in order to maintain domination of the lifestyle intervention arm over the placebo arm in each of the models. As a sensitivity analysis for the scenario in which a lifetime effect is achieved from the intervention, results are presented examining cost-effectiveness if the treatment is continued for the lifetime of the subject. This section also examines the separate influences of the adjustments made for obesity and baseline exclusions in the DPP study cohort on maximum acceptable cost of intervention.

A maximum acceptable cost of intervention comparison is then reported for Model 1A and the submodels of 1A based on BMI subcategories. These models are run for: (1) a three-year cost of treatment intervention with a three-year effect of the intervention; (2) a three-year cost of treatment intervention with a lifetime effect; and (3) a lifetime cost of treatment intervention with a lifetime effect. A final discussion examines the effect of changing the control cost of illness of a non-obese NGT subject from $3,968 to $2,688 on the maximum acceptable cost of the intervention for Models 2A and 2B.

A third major section first gives the time free of T2DM for each model. The section also provides an analysis of the cost per Markov healthcare state using the same Markov cohort methodology.

The final section addresses the sensitivity analyses performed in this dissertation. The analyses examine the effect of the following changes on the incremental cost-effectiveness ratios for life-years:

(1) Altering the duration of effect of the three-year intervention (comparing a

three-year duration to a lifetime-duration);

(2) Changing the discount rate from 0% to both 3% and 5%;

(3) Decreasing the treatment effect by 20% (by increasing the progression from IGT to T2DM by 20% in the lifestyle arm and decreasing the rate of reversion from IGT to NGT by the same percentage in the same arm);

(4) Increasing the progression from NGT to IGT in both arms by 20%; and

(5) Inserting a possible reversion from T2DM to IGT in the intervention (in models 2A and 2B only).

All sensitivity analyses are performed on cost per life-year results only due to the uncertainty surrounding the QALY measurement in this dissertation.

5.1 Results and Comparisons of Models with Hypothesis Testing

The following section gives base-case results for each proposed model, followed by hypotheses testing. Comparisons of obesity-adjusted models (Model 1B and 2B) to non-adjusted models (1A and 1B) are first provided, followed by comparisons of Model 1A to the 1A submodels based on BMI subcategories (30 kg/m2 to < 35 kg/m^2 and ≥ 35 kg/m^2.

5.1.1 BASE-CASE RESULTS

The following tables give the base-case results for cost per life-year and cost per QALY for a three-year effect of the three-year intervention and a lifetime effect of the three-year intervention for each of the models and submodels of the dissertation:

Table 5.1 – Model 1A;

Table 5.2 – Submodel 1A (BMI 30 kg/m^2 to < 35 kg/m^2);

Table 5.3 – Submodel 1A (BMI ≥ 35 kg/m^2);

Table 5.4 – Model 1B;

Table 5.5 – Model 2A; and

Table 5.6 – Model 2B.

These results are given using the Monte Carlo simulation technique and the Markov process technique. All values for Models 2A and 2B are given with a direct medical control cost of illness of $3,968.

Table 5.1 Monte Carlo and Markov Results for Three-Year and Lifetime Effects of a Three-Year Intervention for Model 1A

	Costs	Life-Years	Cost-Effectiveness for Life-Years[a]	QALYs	Cost-Effectiveness for QALYs[a]
Monte Carlo Simulation[b]					
Pl	$121,979 ($7,246)	25.13 (0.58)	$4,853/LY ($251/LY)	16.54 (0.38)	$7,375/QALY ($386/QALY)
Three-Year Effect					
L	$119,308 ($6,283)	25.54 (0.58)	$4,668/LY ($214/LY)	17.69 (0.35)	$6,744/QALY ($312/QALY)
Incremental Cost-Effectiveness Ratio			***-$6,941/LY ($3,671/LY) Lifestyle Dominates***		***-$2,384/QALY ($985/QALY) Lifestyle Dominates***
Lifetime Effect					
L	$105,093 ($4,069)	26.52 (0.34)	$3,965/LY ($134/LY)	18.37 (0.23)	$5,726/QALY ($195/QALY)
Incremental Cost-Effectiveness Ratio			***-$12,815/LY ($4,860/LY) Lifestyle Dominates***		***-$9,336/QALY ($2,524/QALY) Lifestyle Dominates***
Markov Technique					
Pl	$121,728	25.10	$4,850/LY	16.52	$7,369/QALY
Three-Year Effect					
L	$119,074	25.52	$4,665/LY	17.67	$6,738/QALY
Incremental Cost-Effectiveness Ratio			***-$6,319/LY Lifestyle Dominates***		***-$2,308/QALY Lifestyle Dominates***
Lifetime Effect					
L	$105,084	26.51	$3,963/LY	18.36	$5,725/QALY
Incremental Cost-Effectiveness Ratio			***-$11,804/LY Lifestyle Dominates***		***-$9,045/QALY Lifestyle Dominates***

a: Cost-Effectiveness for Life-Years and QALYs for Monte Carlo simulation reflects program output variation
b: Monte Carlo results given in mean values with standard deviations in parenthesis
L, lifestyle; LY, life-year; Pl, placebo; QALY, quality-adjusted life-year

Table 5.2 Monte Carlo and Markov Results for Three-Year and Lifetime Effects of a Three-Year Intervention for Submodel 1A: BMI 30 kg/m^2 to < 35 kg/m^2

	Costs	Life-Years	Cost-Effectiveness for Life-Years [a]	QALYs	Cost-Effectiveness for QALYs [a]
Monte Carlo Simulation [b]					
Pl	$114,542 ($5,992)	25.63 (0.49)	$4,471/LY ($205/LY)	16.87 (0.28)	$6,789/QALY ($315/QALY)
Three-Year Effect					
L	$110,091 ($4,921)	26.15 (0.40)	$4,214/LY ($162/LY)	18.09 (0.35)	$6,085/QALY ($237/QALY)
Incremental Cost-Effectiveness Ratio			***-$9,070/LY ($3,893/LY) Lifestyle Dominates***		***-$3,590/QALY ($1,121/QALY) Lifestyle Dominates***
Lifetime Effect					
L	$96,803 ($2,830)	27.04 (0.25)	$3,578/LY ($95/LY)	18.72 (0.18)	$5,169/QALY ($136/QALY)
Incremental Cost-Effectiveness Ratio			***-$13,270/LY ($4,665/LY) Lifestyle Dominates***		***-$9,749/QALY ($2,487/QALY) Lifestyle Dominates***
Markov Technique					
Pl	$114,409	25.60	$4,468/LY	16.85	$6,788/QALY
Three-Year Effect					
L	$110,065	26.13	$4,213/LY	18.09	$6,085/QALY
Incremental Cost-Effectiveness Ratio			***-$8,196/LY Lifestyle Dominates***		***-$3,503/QALY Lifestyle Dominates***
Lifetime Effect					
L	$96,744	27.03	$3,579/LY	18.72	$5,169/QALY
Incremental Cost-Effectiveness Ratio			***-$12,353/LY Lifestyle Dominates***		***-$9,447/QALY Lifestyle Dominates***

a: Cost-Effectiveness for Life-Years and QALYs for Monte Carlo simulation reflects program output variation
b: Monte Carlo results given in mean values with standard deviations in parenthesis
L, lifestyle; LY, life-year; Pl, placebo; QALY, quality-adjusted life-year

Table 5.3 Monte Carlo and Markov Results for Three-Year and Lifetime Effects of A Three-Year Intervention for Submodel 1A: ≥ 35 kg/m^2

	Costs	Life-Years	Cost-Effectiveness for Life-Years[a]	QALYs	Cost-Effectiveness for QALYs[a]
Monte Carlo Simulation[b]					
Pl	$126,016 ($7,998)	24.82 (0.64)	$5,083/LY ($284/LY)	16.34 (0.42)	$7,716/QALY ($430/QALY)
Three-Year Effect					
L	$124,440 ($7,184)	25.16 (0.58)	$4,948/LY ($251/LY)	17.43 (0.40)	$7,143/QALY ($362/QALY)
Incremental Cost-Effectiveness Ratio			***-$5,110/LY ($3,479/LY) Lifestyle Dominates***		***-$1,502/QALY ($53/QALY) Lifestyle Dominates***
Lifetime Effect					
L	$113,883 ($5,374)	25.96 (0.44)	$4,386/LY ($181/LY)	17.84 (0.33)	$6,330/QALY ($264/QALY)
Incremental Cost-Effectiveness Ratio			***-$11,745/LY ($4,882/LY) Lifestyle Dominates***		***-$7,706/QALY ($2,249/QALY) Lifestyle Dominates***
Markov Technique					
Pl	$125,973	24.79	$5,083/LY	16.32	$7,721/QALY
Three-Year Effect					
L	$124,401	25.14	$4,948/LY	17.41	$7,147/QALY
Incremental Cost-Effectiveness Ratio			***-$4,491/LY Lifestyle Dominates***		***-$1,442/QALY Lifestyle Dominates***
Lifetime Effect					
L	$113,681	25.94	$4,383/LY	17.96	$6,331/QALY
Incremental Cost-Effectiveness Ratio			***-$10,688/LY Lifestyle Dominates***		***-$7,495/QALY Lifestyle Dominates***

a: Cost-Effectiveness for Life-Years and QALYs for Monte Carlo simulation reflects program output variation
b: Monte Carlo results given in mean values with standard deviations in parenthesis
L, lifestyle; LY, life-year; Pl, placebo; QALY, quality-adjusted life-year

Table 5.4 Monte Carlo and Markov Results for Three-Year and Lifetime Effects of a Three-Year Intervention for Model 1B

	Costs	Life-Years[a]	Cost-Effectiveness for Life-Years[b]	QALYs[a]	Cost-Effectiveness for QALYs[b]
Monte Carlo Simulation[c]					
Pl	$113,299 ($5,727)	22.87 (0.00)	$4,949/LY ($250/LY)	15.06 (0.00)	$7,502/QALY ($378/QALY)
Three-Year Effect					
L	$113,002 ($5,276)	23.35 (0.00)	$4,839/LY ($227/LY)	16.17 (0.00)	$6,986/QALY ($327/QALY)
Incremental Cost-Effectiveness Ratio			***-$573/LY ($2,198/LY) Lifestyle Dominates***		***-$245/QALY ($964/QALY) Lifestyle Dominates***
Lifetime Effect					
L	$106,500 ($5,255)	24.48 (0.00)	$4,394/LY ($216/LY)	16.95 (0.00)	$6,283/QALY ($310/QALY)
Incremental Cost-Effectiveness Ratio			***-$4,168/LY ($2,279/LY) Lifestyle Dominates***		***-$3,561/QALY ($1,959/QALY) Lifestyle Dominates***
Markov Technique					
Pl	$113,235	22.86	$4,953LY	15.06	$7,524/QALY
Three-Year Effect					
L	$112,965	23.35	$4,838/LY	16.17	$6,988/QALY
Incremental Cost-Effectiveness Ratio			***-$551/LY Lifestyle Dominates***		***-$243/QALY Lifestyle Dominates***
Lifetime Effect					
L	$106,541	24.48	$4,352/LY	16.95	$6,287/QALY
Incremental Cost-Effectiveness Ratio			***-$4,132/LY Lifestyle Dominates***		***-$3,541/QALY Lifestyle Dominates***

a: There is no variation in the model for life-years, so standard deviations are calculate as a zero value.
b: Cost-Effectiveness for Life-Years and QALYs for Monte Carlo simulation reflects program output variation
c: Monte Carlo results given in mean values with standard deviations in parenthesis
L, lifestyle; LY, life-year; Pl, placebo; QALY, quality-adjusted life-year

Table 5.5 Monte Carlo and Markov Results for Three-Year and Lifetime Effects of a Three-Year Intervention for Model 2A

	Costs	Life-Years	Cost-Effectiveness for Life-Years[a]	QALYs	Cost-Effectiveness for QALYs[a]
Monte Carlo Simulation[b]					
Pl	$187,256 ($10,765)	24.86 (0.58)	$7,531/LY ($381/LY)	16.34 (0.38)	$11,732/QALY ($680/QALY)
Three-Year Effect					
L	$181,273 ($9,315)	25.23 (0.52)	$7,184/LY ($324/LY)	17.46 (0.36)	$10,765/QALY ($489/QALY)
Incremental Cost-Effectiveness Ratio			***-$17,631/LY ($8,444/LY) Lifestyle Dominates***		***-$5,341/QALY ($1,574/QALY) Lifestyle Dominates***
Lifetime Effect					
L	$160,718 ($6,118)	26.20 (0.36)	$6,133/LY ($209/LY)	18.13 (0.25)	$8,702/QALY ($297/QALY)
Incremental Cost-Effectiveness Ratio			***-$21,093/LY ($8,053/LY) Lifestyle Dominates***		***-$12,548/QALY ($3,101/QALY) Lifestyle Dominates***
Markov Technique					
Pl	$186,897	24.83	$7,527LY	16.31	$11,457/QALY
Three-Year Effect					
L	$180,953	25.20	$7,180/LY	17.44	$10,375/QALY
Incremental Cost-Effectiveness Ratio			***-$16,064 /LY Lifestyle Dominates***		***-$5,260/QALY Lifestyle Dominates***
Lifetime Effect					
L	$160,578	26.18	$6,134/LY	18.12	$8,864/QALY
Incremental Cost Effectiveness Ratio			***-$19,496/LY Lifestyle Dominates***		***-$14,540/QALY Lifestyle Dominates***

a: Cost-Effectiveness for Life-Years and QALYs for Monte Carlo simulation reflects program output variation
b: Monte Carlo results given in mean values with standard deviations in parenthesis
L, lifestyle; LY, life-year; Pl, placebo; QALY, quality-adjusted life-year

Table 5.6 Monte Carlo and Markov Results for Three-Year and Lifetime Effects of a Three-Year Intervention for Model 2B

	Costs	Life-Years	Cost-Effectiveness for Life-Years[a]	QALYs	Cost-Effectiveness for QALYs[a]
Monte Carlo Simulation[b]					
Pl	$179,326 ($6,759)	23.31 (0.17)	$7,696/LY ($381/LY)	15.31 (0.11)	$11,732/QALY ($680/QALY)
Three-Year Effect					
L	$178,000 ($8,176)	23.90 (0.19)	$7,443/LY ($341/LY)	16.88 (0.13)	$10,549/QALY ($482/QALY)
Incremental Cost-Effectiveness Ratio			***-$2,231/LY ($2,845/LY) Lifestyle Dominates***		***-$862/QALY ($1,072/QALY) Lifestyle Dominates***
Lifetime Effect					
L	$170,171 ($8,642)	25.41 (0.21)	$6,704/LY ($334/LY)	17.93 (0.15)	$9,502QALY ($470/QALY)
Incremental Cost-Effectiveness Ratio			***-$4,307/LY ($2,752/LY) Lifestyle Dominates***		***-$3,416/QALY ($2,196/QALY) Lifestyle Dominates***
Markov Technique					
Pl	$179,297	23.30	$7,694/LY	15.31	$11,711/QALY
Three-Year Effect					
L	$177,953	23.89	$7,448/LY	16.88	$10,543/QALY
Incremental Cost-Effectiveness Ratio			***-$2,278/LY Lifestyle Dominates***		***-$856/QALY Lifestyle Dominates***
Lifetime Effect					
L	$170,307	25.40	$6,705/LY	17.92	$9,502/QALY
Incremental Cost-Effectiveness Ratio			***-$4,281/LY Lifestyle Dominates***		***-$3,444/QALY Lifestyle Dominates***

a: Cost-Effectiveness for Life-Years and QALYs for Monte Carlo simulation reflects program output variation
b: Monte Carlo results given in mean values with standard deviations in parenthesis
L, lifestyle; LY, life-year; Pl, placebo; QALY, quality-adjusted life-year

5.1.2 HYPOTHESES TESTING

Individual hypotheses were tested using the cost-effectiveness findings in Tables 5.1 through 5.6 (reported with Monte Carlo simulation values). Intensive lifestyle intervention dominated placebo for every model analyzed (both three-year effect and lifetime effect) as indicated by negative incremental cost-effectiveness ratios. The specific hypotheses and supporting results are now discussed.

H1: In a population similar to that studied by the DPP that is diagnosed with IGT and no other disease-state abnormalities, long-term intensive lifestyle intervention to prevent progression to T2DM is cost-effective.

This hypothesis was tested using Model 1A (Table 5.1), which is the model that most closely resembles that studied by the DPP. The incremental cost-effectiveness ratios using the Monte Carlo simulation results for the three-year effect of the three-year intervention are -$6,941/LY (S.D. $3,671/LY), and -$2,384/QALY (S.D. $985/QALY). The incremental cost-effectiveness ratios using the same methodology for the lifetime effect of the three-year intervention are -$12,815/LY (S.D. $4,860/LY) and -$9,336/QALY (S.D. $2,524/QALY). Therefore, lifestyle dominates placebo for all scenarios, and H1 is not rejected.

H2: In a population that is diagnosed with IGT and no other disease-state abnormalities that falls into a specific BMI classification of 30 kg/m^2 to < 35 kg/m^2, long-term intensive lifestyle intervention to prevent progression to T2DM is cost-effective.

This hypothesis was tested using the submodel of Model 1A that addresses the BMI subcategory of 30 kg/m^2 to < 35 kg/m^2 (Table 5.2), which is the model that most closely approximates the DPP cohort in this BMI subcategory. The incremental cost-effectiveness ratios using the Monte Carlo simulation results for the three-year effect of the three-year

intervention are -$9,070/LY (S.D. $3,893/LY), and -$3,590/QALY (S.D. $1,121/QALY). The incremental cost-effectiveness ratios using the same methodology for the lifetime effect of the three-year intervention are -$13,270/LY (S.D. $4,665/LY) and -$9,749/QALY (S.D. $2,487/QALY). Therefore, lifestyle dominates placebo for all scenarios, and H2 is not rejected.

H3: In a population that is diagnosed with IGT and no other disease-state abnormalities that falls into a BMI classification of > 35 kg/m^2, long-term intensive lifestyle intervention to prevent progression to T2DM is cost-effective.

This hypothesis was tested using the submodel of Model 1A that addresses the BMI subcategory of ≥ 35 kg/m^2 (Table 5.3), which is the model that most closely approximates the DPP cohort in this BMI subcategory. The incremental cost-effectiveness ratios using the Monte Carlo simulation results for the three-year effect of the three-year intervention are -$5,110/LY (S.D. $3,479/LY), and -$1,502/QALY (S.D. $53/QALY). The incremental cost-effectiveness ratios using the same methodology for the lifetime effect of the three-year intervention are -$11,745/LY (S.D. $4,882/LY) and -$7,706/QALY (S.D. $2,249/QALY). Therefore, lifestyle dominates placebo for all scenarios, and H3 is not rejected.

H4: If adjustments to mortality hazard rates and direct healthcare costs that are suggested by current literature are made for the *exclusion of baseline disease-state abnormalities as well as obesity* in an evaluation of a population similar to that studied by the DPP (average BMI classification of obese class I, and diagnosis of IGT), long-term intensive lifestyle intervention to prevent progression to T2DM is cost-effective.

This hypothesis was tested using Model 1B (Table 5.4), which is the model that most closely resembles a population similar to that studied by the DPP that is adjusted for obe-

sity as it relates to baseline disease-state abnormalities. The incremental cost-effectiveness ratios using the Monte Carlo simulation results for the three-year effect of the three-year intervention are -$573/LY (S.D. $2,198/LY), and -$245/QALY (S.D. $964/QALY). The incremental cost-effectiveness ratios using the same methodology for the lifetime effect of the three-year intervention are -$4,168/LY (S.D. $2,279/LY) and -$3,561/QALY (S.D. $1,959/QALY). Therefore, lifestyle dominates placebo for all scenarios, and H4 is not rejected.

H5: In a population with IGT and an average BMI category of obese class I that is drawn from a hypothetical cohort that has no disease-state exclusions in the baseline study design criteria, and in which no adjustments are made for obesity, long-term intensive lifestyle intervention to prevent progression to T2DM is cost-effective.

This hypothesis was tested using Model 2A (Table 5.5), which is the model that attempts to apply the DPP study results to a more generalized population. The incremental cost-effectiveness ratios using the Monte Carlo simulation results for the three-year effect of the three-year intervention are -$17,631/LY (S.D. $8,444/LY), and -$5,341/QALY (S.D. $1,574/QALY). The incremental cost-effectiveness ratios using the same methodology for the lifetime effect of the three-year intervention are -$21,093/LY (S.D. $8,053/LY) and -$12,548/QALY (S.D. $3,101/QALY). Therefore, lifestyle dominates placebo for all scenarios, and H5 is not rejected.

H6: In a population with IGT and an average BMI category of obese class I that is drawn from a hypothetical cohort that has no disease-state exclusions in the baseline study design criteria, and in which adjustments are made for obesity, long-term intensive lifestyle intervention to prevent progression to T2DM is cost-effective.

This hypothesis was tested using Model 2B (Table 5.6), which is the obesity-adjusted model that attempts to apply the DPP results to a more generalized population. The incremental cost-effectiveness ratios using the Monte Carlo simulation results for the three-year effect of the three-year intervention are -$2,231/LY (S.D. $2,845/LY), and -$862/QALY (S.D. $1,072/QALY). The incremental cost-effectiveness ratios using the same methodology for the lifetime effect of the three-year intervention are -$4,307/LY (S.D. $2,752/LY) and -$3,416/QALY (S.D. $2,196/QALY). Therefore, lifestyle dominates placebo for all scenarios, and H6 is not rejected.

5.1.3 A COMPARISON OF THE LEAST AND MOST COST-EFFECTIVE MODELS

While all models generated an outcome of "lifestyle dominates," there are substantial differences in cost-effectiveness ratios across the scenarios presented. When comparing Models 1A, 1B, 2A, and 2B (using the values generated by the Markov technique due to consistency of numbers) the following ranges are found:

Three-Year Intervention with Three-Year Duration of Effect:

Life-Years: -$551/LY to -$16,064/LY

QALYs: -$243/QALY to -$5,260/QALY

Three-Year Intervention with Lifetime Duration of Effect:

Life-Years: -$4,132/LY to -$19,496/LY

QALYs: -$3,444/QALY to -$14,540/QALY

The lower values are generated in all cases by Model 1B, three-year intervention with three-year duration of effect, and the highest values are generated by Model 1A, three-year intervention, lifetime duration of effect. A comparison of the two models is illustrated in Table 5.7 (using the Markov technique values).

Table 5.7 A Comparison of Model 1B and Model 2A

		Model 1B: Three-Year Effect	Model 1B: Lifetime Effect	Model 2A: Three-Year Effect	Model 2A: Lifetime Effect
Lifetime Cost	*Pl*	\$113.2K		\$186.9K	
	L	\$112.9K	\$106.5K	\$180.9K	\$160.6K
Incremental Costs		*\$270*	*\$6,694*	*\$5,944*	*\$26,319*
Life-Years	*Pl*	22.86		24.83	
	L	23.35	24.48	25.20	26.18
Incremental Life-Years		*-0.49*	*-1.62*	*-0.37*	*-1.35*
Incremental C/E		**-\$551/LY**	**-\$4,132/LY**	**-\$16,064/LY**	**-\$19,496/LY**
Time Free of Diabetes	*Pl*	46.54%		44.35%	
	L	56.24%	75.20%	53.89%	73.24%

L, lifestyle; LY, life-year; Pl, placebo

5.1.4 THE EFFECT OF CONTROL COST OF ILLNESS

The incremental cost-effectiveness ratios of both Models 2A and 2B are lower than those found for Models 1A and 1B, making the more generalized models appear to be more cost-effective. One potential explanation is the higher control cost of illness found in the more generalized models (\$3,968 for Models 2A and 2B versus \$1,100 for the first-three Markov cycles, and then \$2,688 per cycle for Models 1A and 1B).

To examine this possibility more closely, the following analyses were performed using the Markov technique. Starting with Model 1A and 1B, control cost of illness was varied from \$2,000 to \$5,000. The results presented in Table 5.8 show that by increasing control cost of illness in each model (for each duration of effect) total incremental costs increase, and subsequently incremental cost-effectiveness ratios also increase. Table 5.9 shows the results of the same analysis performed on Models 2A and 2B.

Table 5.8 The Effect of Varying Control Cost of Illness on Model 1A and

Model	Incremental Costs	Incremental Effect (Life-Years)	Incremental C/E Ratio
1A: Three-Year			
$2,000	$1,535	-0.42	-$3.7K/LY
$3,500	$4,710		-$11.2K/LY
$5,000	$7,884		-$18.8K/LY
1A: Lifetime Duration of			
$2,000	$11,948	-1.41	-$8.5K/LY
$3,500	$22,932		-$16.3K/LY
$5,000	$33,916		-$24.1K/LY
1B: Three-Year			
$2,000	$312	-0.49	-$0.6K/LY
$3,500	$1,477		-$3.0K/LY
$5,000	$3,266		-$6.7K/LY
1B: Lifetime Duration of Effect			
$2,000	$4,491	-1.62	-$2.8K/LY
$3,500	$9,884		-$6.1K/LY
$5,000	$15,275		-$9.4K/LY

a: Calculated by subtracting lifestyle from placebo
C/E, cost-effectiveness; K, thousands; LY, life-year

Table 5.9 The Effect of Varying Control Cost of Illness on Model 2A and Model 2B[a]

Model	Incremental Costs	Incremental Effect (Life-Years)	Incremental C/E Ratio
2A: Three-Year			
$2,000	$1,662	-0.37	-$4.5K/LY
$3,500	$4,927		-$13.3K/LY
$5,000	$8,191		-$22.1K/LY
2A: Lifetime Duration of			
$2,000	$11,932	-1.35	-$8.8K/LY
$3,500	$22,899		-$16.9K/LY
$5,000	$33,866		-$25.1K/LY
2B: Three-Year			
$2,000	$660	-0.59	-$1.1K/LY
$3,500	$864		-$1.5K/LY
$5,000	$2,387		-$4.0K/LY
2B: Lifetime Duration of			
$2,000	$3,197	-2.1	-$1.5K/LY
$3,500	$7,614		-$3.6K/LY
$5,000	$12,000		-$5.7K/LY

a: Calculated by subtracting lifestyle from placebo
C/E, cost-effectiveness; K, thousands; LY, life-year

The results suggest that the one reason that the more generalized models appear more cost-effective is their higher control direct medical costs.

5.1.5 THE EFFECT OF INCREASING THE COST OF INTERVENTION

Using algebraic reasoning, incremental cost-effectiveness ratios will obviously increase with increasing incremental costs if the effect of the intervention is held constant. The other variable that is held constant in the analysis described in 5.1.4 is the cost of the intervention. The model that appears to be the most "cost-effective" (having the lowest incremental cost-effectiveness ratio) is Model 2A. Control cost of illness in Model 2A is

approximately 1.5 times higher ($3,968 vs. $2,698) than in Model 1B. The following analysis evaluates the effect of increasing the cost of intervention for both the placebo and lifestyle arms in Model 2A by 1.5 times, while holding all other variables constant to evaluate the effect of this change on incremental cost-effectiveness ratios. The results are given in Table 5.10.

Table 5.10 The Effect of Increasing the Cost of Intervention on Model 2A

Duration of Effect	Group	Costs	Life-Years	Incremental C/E
Three-Year Duration	*Pl*	$186.9K	24.83	-$12.4K/LY
	L	$182.3K	25.20	
Lifetime Duration	*Pl*	$186.9K	24.83	-$18.5K/LY
	L	$161.9K	26.18	

L, lifestyle; LY, life-year; Pl, placebo.

Increasing the cost of intervention increases total costs for the intervention arms, and therefore decreases the incremental cost difference (as compared to the results in Table 5.5). Life-years do not change; therefore, the incremental cost-effectiveness ratio decreases.

5.1.6 OBESITY- ADUSTED MODELS VS. UNADJUSTED MODELS

The following section compares the obesity-adjusted models versus the unadjusted models (Model 1B versus 1A, and Model 2B versus 2A). This comparison includes the following differences between the models: total lifetime costs; total life-years; cost per life-year; QALYs; cost per QALY; and the incremental cost-effectiveness ratios. The results are derived by subtracting the unadjusted model results (1A and 2A) from the obesity-adjusted models (1B and 2B). This section was designed to examine the influence of the obesity-adjusted modifications on cost-effectiveness.

Table 5.11 illustrates the differences between Model 1B (obesity-adjusted) and Model

1A (unadjusted) for life-years. Table 5.12 does the same for QALYs. Table 5.13 and Table 5.14 illustrate these results for Models 2B (obesity-adjusted) and 2A (unadjusted) for life-years and QALYs, respectively. All values used for these calculations are taken from the Markov Technique values found in Tables 5.1, 5.4, 5.5, and 5.6. A negative value in a column means that the obesity-adjusted model values (the B models) are lower than the unadjusted model values (the A models), and vice-versa for a positive value.

Table 5.11 Comparisons between Model 1B (Obesity-Adjusted) and Model 1A (Unadjusted) for Life-Years[a]

	Lifetime Cost Difference	Life-Years Difference	Cost/LY Difference	Incremental C/E Difference
3-Year Effect				
Placebo	-$8,493	-2.24	+$103/LY	***+$5,768/LY***
Lifestyle	-$6,109	-2.17	+$173/LY	
Lifetime Effect				
Placebo	- $8,493	-2.24	+ $103/LY	***+$7,672/LY***
Lifestyle	+ $1,457	- 2.03	+ $389/LY	

a: Calculated by subtracting the Model 1A values from the Model 1B values
Negative values indicate that Model 1B values are lower than those for Model 1A, and vice-versa for positive values.
C/E, cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year

Table 5.12 Comparisons between Model 1B (Obesity Adjusted) and Model 1A (Unadjusted) for QALY[sa]

	Lifetime Cost Difference	QALY Difference	Cost/QALY Difference	Incremental C/E Difference
3-Year Effect				
Placebo	-$8,493	-1.46	+$155/QALY	***+$2,065/QALY***
Lifestyle	-$6,109	-1.50	+$250/QALY	
Lifetime Effect				
Placebo	- $8,493	-1.46	+ $155/QALY	***+$5,504/QALY***
Lifestyle	+ $1,457	-1.41	+ $562/QALY	

a: Calculated by subtracting the Model 1A values from the Model 1B values
Negative values indicate that Model 1B values are lower than those for Model 1A, and vice-versa for positive values.
C/E, cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year

Table 5.13 Comparisons between Model 2B (Obesity-Adjusted) and Model 2A (Unadjusted) for Life-Years[a]

	Lifetime Cost Difference	Life-Years Difference	Cost/LY Difference	Incremental C/E Difference
3-Year Effect				
Placebo	-$7,600	-1.53	+$167/LY	***+$13,786/LY***
Lifestyle	-$3,000	-1.31	+$268/LY	
Lifetime Effect				
Placebo	- $7,600	-1.53	+ $167/LY	***+$15,215/LY***
Lifestyle	+ $9,729	- 0.78	+ $571/LY	

a: Calculated by subtracting the Model 2A values from the Model 2B values
Negative values indicate that Model 2B values are lower than those for Model 2A, and vice-versa for positive values.
C/E, cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year

Table 5.14 Comparisons between Model 2B (Obesity Adjusted) and Model 2A (Unadjusted) for QALYsa

	Lifetime Cost Difference	QALY Difference	Cost/QALY Difference	Incremental C/E Difference
3-Year Effect				
Placebo	-$7,600	-1.00	$254/QALY	***+$4,404/QALY***
Lifestyle	-$3,000	-0.56	$168/QALY	
Lifetime Effect				
Placebo	- $7,600	-1.00	+$254/QALY	***+$11,096/QALY***
Lifestyle	+ $9,729	-0.20	+$638/QALY	

a: Calculated by subtracting the Model 2A values from the Model 2B values
Negative values indicate that Model 2B values are lower than those for Model 2A, andvice-versa for positive values.
C/E, cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year

5.1.7 MODEL 1A COMPARED TO THE SUBMODELS

To complete the examination of the base-case results, the following section is presented to compare Model 1A to the submodels of BMI 30 to < 35 kg/m^2 and ≥ 35 kg/m^2. This comparison includes the following differences between the models: total lifetime costs; total life-years; cost per life-year; total QALYs; cost per QALY; and the incremental cost-effectiveness ratio differences. The results were derived by subtracting the Model 1A results from the individual submodel results. Negative values indicate that submodel values are lower than those for Model 1A, and vice-versa for positive values.

Table 5.15 illustrates the differences between Model 1A and the submodels for a three-year duration of intervention and a three-year effect of intervention for life-years. Table 5.16 does the same for QALYs. Table 5.17 gives the differences between Model 1A and the submodels for a three-year duration of intervention and a lifetime effect of intervention for life-years. Table 5.18 repeats this analysis for QALYs. All values are taken from

the Markov technique values given in Tables 5.1, 5.2, and 5.3.

Table 5.15 Comparison of Model 1A and the Submodels (Based on BMI subgroups) for a Three-Year Duration of Intervention and a Three-Year Effect for Cost per Life-Year[a]

	Lifetime Cost Difference	LY Difference	Cost/LY Difference	Incremental C/E Difference
BMI of 30 kg/m^2 to less than 35 kg/m^2				
Placebo	-$7,319	+0.50	-$382/LY	***-$1,877/LY***
Lifestyle	-$9,009	+0.61	-$452/LY	
BMI of greater than or equal 35 kg/m^2				
Placebo	+$4,245	-0.31	+$233/LY	***+$1,828/LY***
Lifestyle	+$5,327	-0.38	+$283/LY	

a: Calculated by subtracting Model 1A results from submodel results
Negative values indicate submodel values are lower than those for Model 1A, and vice-versa for positive values.
C/E, cost-effectiveness ratio; kg/m^2, kilogram per meters-squared; LY, life-year

Table 5.16 Comparison of Model 1A and the Submodels (Based on BMI subgroups) for a Three-Year Duration of Intervention and a Three-Year Effect for Cost per QALY[a]

	Lifetime Cost Difference	QALY Difference	Cost/QALY Difference	Incremental C/E Difference
BMI of 30 kg/m^2 to less than 35 kg/m^2				
Placebo	-$7,319	+0.33	-$581/QALY	***-$1,195/QALY***
Lifestyle	-$9,009	+0.42	-$653/QALY	
BMI of greater than or equal 35 kg/m^2				
Placebo	+$4,245	-0.20	+$352/QALY	***+$886/QALY***
Lifestyle	+$5,327	-0.26	+$409/QALY	

a: Calculated by subtracting Model 1A results from submodel results
Negative values indicate submodel values are lower than those for Model 1A, and vice-versa or positive values.
C/E, cost-effectiveness ratio; kg/m^2, kilogram per meters-squared; QALY, quality-adjusted life-year

Table 5.17 Comparison of Model 1A and the Submodels (Based on BMI subgroups) for a Three-Year Duration of Intervention and a Lifetime Effect for Cost per Life-Year[a]

	Lifetime Cost Difference	QALY Difference	Cost/QALY Difference	Incremental C/E Difference
BMI of 30 kg/m^2 to less than 35 kg/m^2				
Placebo	-$7,319	+0.50	-$382/LY	***-$549/LY***
Lifestyle	-$8,340	+0.52	-$384/LY	
BMI of greater than or equal 35 kg/m^2				
Placebo	+$4,245	-0.31	+$233/LY	***+$1,116/LY***
Lifestyle	+$8,597	-0.57	+$420/LY	

a: Calculated by subtracting Model 1A results from submodel results
Negative values indicate submodel values are lower than those for Model 1A, and vice-versa for positive values.
C/E, cost-effectiveness ratio; kg/m^2, kilogram per meters-squared; LY, life-year

Table 5.18 Comparison of Model 1A and the Submodels for a Three-Year Duration of Intervention and a Lifetime Effect for Cost per QALY[a]

	Lifetime Cost Difference	QALY Difference	Cost/QALY Difference	Incremental C/E Difference
BMI of 30 kg/m^2 to less than 35 kg/m^2				
Placebo	-$7,319	+0.33	-$581/QALY	***-$402/QALY***
Lifestyle	-$8,340	+0.36	-$556/QALY	
BMI of greater than or equal 35 kg/m^2				
Placebo	+$4,245	-0.20	+$352/QALY	***+$1,550/QALY***
Lifestyle	+$8,597	-0.40	+$606/QALY	

a: Calculated by subtracting Model 1A results from submodel results
Negative values indicate submodel values are lower than those for Model 1A, and vice-versa for positive values.
C/E, cost-effectiveness ratio; kg/m^2, kilogram per meters-squared; QALY, quality-adjusted life-year

5.2 The Maximum Acceptable Cost of Lifestyle Intervention

The following section examines the maximum acceptable cost of the lifestyle intervention for each of the models presented in the dissertation. "Maximum acceptable cost" is defined as the maximum cost of the intervention that still allows for lifestyle to dominate placebo. In particular, the effects of the modifications to the dissertation models for obesity (including those related to disease-state exclusions found in the DPP study cohort design) are examined. A final discussion reexamines the effect of varying control cost of illness on this analysis.

5.2.1 MODELS 1A, 1B, 2A, AND 2B

While all models presented generated an outcome of "lifestyle dominates" when analyses were run, there were substantial differences in cost-effective ratios across the scenarios presented as noted in Section 5.1.3. It also appears that this wide range of incremental cost-effectiveness ratios depends at least in part on control cost of illness, as well as the obesity-adjusted modifications. To test if the maximum acceptable cost of lifestyle intervention reflected the same wide range of incremental cost-effectiveness ratios, the following comparisons were performed.

Table 5.19 compares the maximum acceptable cost of lifestyle intervention as well as cost per life-year for Models 1A and 1B. The values are presented for a three-year intervention and a three-year effect, a three-year intervention and a lifetime effect, and a lifetime intervention and a lifetime effect. The final analysis is presented as a sensitivity analysis. Due to the uncertainty surrounding QALYs in the dissertation, the following comparisons are performed using the life-year outcome only. Table 5.20 gives the same comparison of Models 2A and 2B. All calculations are made using the Markov technique values from Tables 5.1, 5.4, 5.5, and 5.6.

Table 5.19 Comparison of Maximum Acceptable Cost of Intervention Per Year for Model 1A, the Unadjusted Model, to Model 1B, the Obesity-Adjusted Model[a]

		1A[a]	1B [a]	1B as a Percent of 1A
Three-Year Intervention with Three-Year Effect	**Maximum Acceptable Cost of Intervention**	$1,820	$1,020	56.04%
	Cost/LY	*$4,770/ LY*	*$4,851/ LY*	
Three-Year Intervention with Lifetime Effect	**Maximum Acceptable Cost of Intervention**	$6,500	$3,180	48.92%
	Cost/LY	*$4,593/ LY*	*$4,628/ LY*	
Lifetime Intervention and Lifetime Effect	**Maximum Acceptable Cost of Intervention**	$720	$390	54.17%
	Cost/LY	*$4,602/ LY*	*$4,637/ LY*	

a: Presented as maximum cost of intervention and cost per life-year over the duration of the model
The cost per life-year is calculated using the values given for maximum acceptable cost of intervention.
LY, life-year

Table 5.20 Comparison of Maximum Acceptable Cost of Intervention Per Year for Model 2A, the Unadjusted Model, to Model 2B, the Obesity-Adjusted Model[a]

		2A[a]	2B [a]	1B as a Percent of 1A
Three-Year Intervention with Three-Year Effect	**Maximum Acceptable Cost of Intervention**	$2,910	$1,380	47.42%
	Cost/LY	*$7,417/ LY*	*$7,504/ LY*	
Three-Year Intervention with Lifetime Effect	**Maximum Acceptable Cost of Intervention**	$9,750	$3,950	40.51%
	Cost/LY	*$7,139/ LY*	*$7,060/ LY*	
Lifetime Intervention and Lifetime Effect	**Maximum Acceptable Cost of Intervention**	$1,100	$470	42.73%
	Cost/LY	*$7,149/ LY*	*$7,075/ LY*	

a: Presented as maximum cost of intervention and cost per life-year over the duration of the model The cost per life-year is calculated using the values given for the maximum acceptable cost of intervention.
LY, life-year

5.2.2 THE INFLUENCE OF OBESITY-ADJUSTED VARIABLES

By examining comparisons made in Tables 5.11- 5.14, it is apparent that the obesity-adjusted models (Model 1B and 2B) have lower overall lifetime costs for the scenario that includes a three-year duration of effect However, as the duration of effect approaches life-time, overall costs becomes higher in the obesity-adjusted lifestyle arm than in the non-adjusted lifestyle arm. Overall life-expectancy is lower in the obesity adjusted models for both placebo and lifestyle intervention. Obesity-adjusted models cost more per life-year, and have a lower maximum acceptable cost of intervention than the unadjusted models

(Models 1A and 2A). The following analyses were run to evaluate the effect of the variables used for these "obesity" adjustments on the maximum acceptable cost of intervention.

5.2.2.1 The Influence of Obesity-Adjusted Variables on Model 1A and Model 1B

Table 5.21 illustrates the different maximum acceptable costs of intervention that occur by adding each set of the obesity-adjusted variables to Model 1A (the unadjusted model) both singly and in combinations for both the three-year and lifetime duration of effect of the three-year intervention. The results ultimately give the maximum acceptable cost of intervention for the total adjusted model, Model 1B.

For clarification, Model 1A has the following characteristics: no cost-multiplier for NGT; a triangular distribution for the hazard ratio for mortality for IGT (0.8, 1.1, and 1.6)[386] and a triangular distribution for the hazard ratio for mortality for T2DM (1.4, 1.9, and 2.5).[387, 388] The total adjusted model is Model 1B. This model includes an increased cost multiplier for NGT subjects (a triangular distribution of 1.02, 1.34, and 1.74),[389] and increased hazard ratios for mortality of 1.3 for NGT subjects and 1.7 for IGT subjects (addressing the issue of increased hazard ratio for mortality for obese subjects in study cohorts with multiple disease-state exclusion criteria).[390, 391, 392] An increased hazard ratio

386 Saydah SH, Miret M, Sung J, et al. Postchallenge hyperglycemia and mortality in a national sample of U.S. adults. *Diabetes Care*. 2001;24:1397-1402.

387 Saydah SH, Loria CM, Eberhardt MS, et al. Subclinical states of glucose intolerance and risk of death in the U.S. *Diabetes Care*. 2001;24:447-453.

388 Saydah SH, Eberhardt MS, Loria CM, et al. Age and the burden of death attributable to diabetes in the United States. *American Journal of Epidemiology*. 2002;156:714-719.

389 Thompson D, Brown JB, Nichols GA, et al. Body mass index and future healthcare costs: a retrospective cohort study. *Obesity Research*. 2001;9:210-218.

390 Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women. *New England Journal of Medicine*. 1995;333:677-685.

391 Peeters A, Barendregt JJ, Willekens F, et al. Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Annals of Internal Medicine*. 2003;138:24-32.

392 Calle EE, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of U.S. adults. *New England Journal of Medicine*. 1999;341:1097-1105.

for mortality for T2DM subjects of 2.64 is also added to address the possible increase in this ratio for T2DM subjects secondary to increasing BMI.[393]

The table itself is set up to report the maximum acceptable cost of intervention from the lowest derived value to the highest derived value. The order reported in the table is described below. The first analysis, which has the lowest maximum cost of intervention, includes the increased cost-multiplier for NGT subjects, no hazard ratio of mortality for NGT subjects, the triangular distribution found in Model 1A for IGT subjects, and a hazard ratio for mortality of 2.64 for T2DM subjects. The next highest value is given by Model 1B itself (includes a cost multiplier for NGT, and a hazard ratio for mortality of 1,3, 1.7 and 2.64 for NGT, IGT, and T2DM subjects).

The third highest maximum acceptable cost of intervention is derived when a cost-multiplier is included for NGT subjects, but the Model 1A values are used for the hazard ratios for mortality (no increase for NGT, and the triangular distribution for IGT and T2DM). The fourth highest value omits the increased cost-multiplier for NGT subjects, and includes the Model 1A hazard ratios for NGT and IGT (no multiplier for NGT, and triangular distribution for IGT), and includes the 2.64 hazard ratio for mortality value for T2DM subjects.

The fifth highest maximum acceptable cost of intervention scenario does not include an increased cost-multiplier for NGT subjects, but includes all of the increased hazard ratios for mortality in the adjusted model, Model 1B (NGT = 1.3, IGT = 1.7, and T2DM = 2.64). The sixth highest value is Model 1A, the unadjusted model. This model has no cost multiplier for NGT, no increased hazard ratio for mortality for NGT subjects, and lower triangular distributions for hazard ratios for mortality for IGT and T2DM.

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393 Rogers RG, Hummer RA, Krueger PM. The effect of obesity on overall, circulatory disease, and diabetes-specific mortality. *Journal of Biosocial Science*. 2003;35:107-129.

The highest maximum acceptable cost of intervention is derived from an analysis that includes no cost-multiplier for NGT subjects, the Model 1B values for NGT and IGT (1.3 and 1.7, respectively), and the Model 1A triangular distribution for T2DM (1.4, 1.9, and 2.5).

Table 5.21 The Variation in Maximum Acceptable Cost of Intervention Secondary to Changes in Obesity-Adjusted Variables to the Unadjusted Model (Model 1A)

	Three-Year Effect	Lifetime Effect
Increased CM-NGT, No HRM-NGT, Triangular IGT, HRM-T2DM = 2.64		
Maximum Acceptable Cost of Intervention	*$810*	*$2,600*
Increased CM-NGT, HRM-NGT = 1.3, HRM-IGT = 1.7, HRM-T2DM = 2.64 (Model 1B)		
Maximum Acceptable Cost of Intervention	*$1,020*	*$3,180*
Increased CM-NGT, No HRM-NGT, Triangular IGT, Triangular T2DM		
Maximum Acceptable Cost of Intervention	*$1,250*	*$4,180*
No CM-NGT, No HRM-NGT, Triangular IGT, HRM- T2DM = 2.64		
Maximum Acceptable Cost of Intervention	*$1,370*	*$4,910*
No CM-NGT, HRM-NGT = 1.3, HRM-IGT = 1.7, HRM-T2DM = 2.64		
Maximum Acceptable Cost of Intervention	*$1,560*	*$5,350*
No CM-NGT, No HRM-NGT, Triangular IGT, Triangular T2DM (Model 1A)		
Maximum Acceptable Cost of Intervention	*$1,820*	*$6,500*
No CM-NGT, HRM-NGT = 1.3, HRM-IGT = 1.7, Triangular T2DM		
Maximum Acceptable Cost of Intervention	*$2,000*	*$7,000*

The cost multiplier (CM) for NGT is 1.02, 1.34, and 1.74.
The triangular values for hazard ratio for mortality for IGT are 0.8, 1.1, and 1.6.
The triangular values for hazard ratio for mortality for T2DM are 1.4, 1.9, and 2.5.
CM, cost multiplier; HRM, hazard ratio of mortality; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T2DM, type 2 diabetes mellitus

Table 5.22 is presented to show that the maximum acceptable cost of intervention values for the above scenarios trend in the same direction as incremental cost-effectiveness ratios for the seven scenarios presented. This analysis is done to test for trending only, and is only performed on the results for the lifetime duration of effect.

Table 5.22 The Variation in Incremental Cost-Effectiveness Ratios Secondary to Changes in Obesity-Adjusted Variables to the Unadjusted Model (Model 1A)

	Incremental Costs	Incremental Effect (Life-Years)	Incremental C/E Ratio
Increased CM-NGT, No HRM-NGT, Triangular IGT, HRM-T2DM = 2.64	$4,828	-2.16	-$2.2KLY
Increased CM-NGT, HRM-NGT = 1.3, HRM-IGT = 1.7, HRM-T2DM = 2.64 (Model 1B)	$6,694	-1.62	-$4.1K/LY
Increased CM-NGT, No HRM-NGT, Triangular IGT, Triangular T2DM	$9,613	-1.41	-$6.8K/LY
No CM-NGT, No HRM-NGT, Triangular IGT, HRM- T2DM = 2.64	$11,886	-2.16	-$5.5K/LY
No CM-NGT, HRM-NGT = 1.3, HRM-IGT = 1.7, HRM-T2DM = 2.64	$13,164	-1.61	-$8.2K/LY
No CM-NGT, No HRM-NGT, Triangular IGT, Triangular T2DM (Model 1A)	$16,644	-1.41	-$11.8K/LY
No CM-NGT, HRM-NGT = 1.3, HRM-IGT = 1.7, Triangular T2DM	$17,872	-0.88	-$20.3K/LY

The cost multiplier (CM) for NGT is 1.02, 1.34, and 1.74.
The triangular values for hazard ratio for mortality for IGT are 0.8, 1.1, and 1.6.
The triangular values for hazard ratio for mortality for T2DM are 1.4, 1.9, and 2.5.
C/E, cost-effectiveness; CM, cost multiplier; HRM, hazard ratio for mortality; K, thousands; IGT, impaired glucose tolerance; LY, life-year; NGT, normal glucose tolerance; T2DM, type 2 diabetes mellitus

This analysis shows that, in general, the maximum acceptable cost of intervention trends upward with increasing incremental cost-effectiveness ratios, but adjustments made for mortality to each of the glucose homeostasis states will also have an effect on the analysis. This is in contrast to the findings in Section 5.1.5, which is understandable, in that life-years were held constant in that analysis (involving the effect of increasing the cost of intervention on incremental cost/effectiveness ratio for Model 2A).

5.2.2.2 The Influence of Obesity-Adjusted Variables on Model 2A and Model 2B

A similar analysis as that found in section 5.2.2.1 is performed in this section for Model 2A and Model 2B. These models are much more straight-forward, as there are only two adjustments due to obesity. This is because these are the "generalized" models, and using findings in current available literature, there appears to be no need to address obesity adjustments due to exclusion criteria found in the initial study design as were required in Model 1B. The adjustments found in Model 2B include an increased cost multiplier for NGT subjects (triangular distribution of 1.02, 1.34, and 1.74),[394] and an increased hazard ratio for mortality for T2DM subjects of 2.64[395] (versus the NHANES II based value of 1.4, 1.9, and 2.5).[396, 397]

Table 5.23 gives the results of this analysis. Once again, the table is presented from the lowest to the highest maximum acceptable cost intervention. The lowest value is obtained using Model 2B (the adjusted model). The next highest value is obtained when the cost multiplier for NGT is inserted, but the triangular distribution is used for T2DM

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394 Thompson D, Brown JB, Nichols GA, et al. Body mass index and future healthcare costs: a retrospective cohort study. *Obesity Research*. 2001;9:210-218.

395 Rogers RG, Hummer RA, Krueger PM. The effect of obesity on overall, circulatory disease, and diabetes-specific mortality. *Journal of Biosocial Science*. 2003;35:107-129.

396 Saydah SH, Loria CM, Eberhardt MS, et al. Subclinical states of glucose intolerance and risk of death in the U.S. *Diabetes Care*. 2001;24:447-453.

397 Saydah SH, Miret M, Sung J, et al. Postchallenge hyperglycemia and mortality in a national sample of U.S. adults. *Diabetes Care*. 2001;24:1397-1402.

(1.4, 1.9, and 2.5) instead of the 2.64 value. If the increased hazard ratio for mortality is inserted (2.64) for the T2DM subjects instead of the triangular distribution, and no cost multiplier is inserted for NGT subjects, the third highest value is obtained. The highest value is obtained for Model 2A (the unadjusted model), a model that has no cost multiplier for NGT and no increased hazard ratio for mortality for T2DM (the triangular distribution is used).

Table 5.23 The Variation in Maximum Acceptable Cost of Intervention Secondary to Changes in Obesity-Adjusted Variables in Model 2A

	Three-Year Effect	Lifetime Effect
Both increased CM-NGT and increased HRM for T2DM = 2.64 (Model 2B)		
Maximum Acceptable Cost of Intervention	*$1,380*	*$3,950*
CM for NGT but no increased HRM for T2DM (Triangular T2DM)		
Maximum Acceptable Cost of Intervention	*$2,060*	*$6,330*
Increased HRM for T2DM (2.64) but no increased CM for NGT		
Maximum Acceptable Cost of Intervention	*$2,230*	*$7,390*
No increased CM-NGT and Triangular T2DM (Model 2A)		
Maximum Acceptable Cost of Intervention	*$2,910*	*$9,750*

The cost multiplier (CM) of NGT is a triangular distribution of 1.02, 1.34, and 1.74.
The triangular values for hazard ratio for mortality for T2DM are 1.4, 1.9, and 2.5
CM, cost multiplier; HRM, hazard ratio of mortality; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T2DM, type 2 diabetes mellitus

Table 5.24 is presented to again to show the results of incremental cost-effectiveness ratio analysis for the above scenarios, and to test if maximum acceptable cost of intervention trends in the same fashion as the incremental cost-effectiveness ratios. Once again, this analysis is done to test for trending only, and is only performed on the result- for the lifetime duration of effect.

Table 5.24 The Variation in Incremental Cost-Effectiveness Ratios Secondary to Changes in Obesity-Adjusted Variables in the Unadjusted Model (Model 2A)

	Incremental Costs	Incremental Effect (Life-Years)	Incremental C/E Ratio
Both increased CM-NGT and increased HRM for T2DM = 2.64 (Model 2B)	$8,991	-2.10	-$4.3K/LY
CM for NGT but no increased HRM for T2DM (Triangular T2DM)	$16,054	-1.35	-$11.9K/LY
Increased HRM for T2DM (2.64) but no increased CM for NGT	$19,287	-2.10	-$9.2K/LY
No increased CM-NGT and Triangular T2DM (Model 2A)	$26,320	-1.35	-$19.5K/LY

The cost multiplier (CM) of NGT is a triangular distribution of 1.02, 1.34, and 1.74.
The triangular values for hazard ratio for mortality for T2DM are 1.4, 1.9, and 2.5
C/E, cost-effectiveness; CM, cost multiplier; HRM, hazard ratio of mortality; K, thousands; LY, life-year; IGT, impaired glucose tolerance; NGT, normal glucose tolerance;
T2DM, type 2 diabetes mellitus

This analysis again shows that, in general, maximum acceptable cost of intervention trends upward with increasing incremental cost-effectiveness ratios, but adjustments made for mortality to each of the glucose homeostasis states will also have an effect on the analysis.

5.2.3 THE EFFECT OF CONTROL COST OF ILLNESS ON MAXIMUM ACCEPTABLE INTERVENTION COST

As a sensitivity analysis, Model 2A and Model 2B were run using a control cost of illness of $2,688 as well as $3,968 (the value used in the above tables). Table 5.25 gives a comparison of the maximum acceptable cost of intervention for each of the control cost of illness values for Model 2A and Model 2B, and the percent difference between the two. In this analysis, maximum acceptable cost of intervention varies directly with increasing control cost of illness.

Table 5.25 Comparison of Maximum Acceptable Cost of Intervention Using Control Cost of Illness Values of $2,688 and $3,968

	Maximum Acceptable Cost of Intervention		MACI at $2,688 as a Percent of MACI at $3,968
	Control Cost of $2,688	Control Cost of $3,968	
Model 2A			
Three-Year Intervention with Three-Year Effect	$1,990	$2,910	**68.38%**
Three-Year Intervention with Lifetime Effect	$6,630	$9,750	**68.00%**
Lifetime Intervention and Lifetime Effect	$740	$1,100	**67.27%**
Model 2B			
Three-Year Intervention with Three-Year Effect	$950	$1,380	**68.84%**
Three-Year Intervention with Lifetime Effect	$2,690	$3,950	**68.10%**
Lifetime Intervention and Lifetime Effect	$320	$470	**68.09%**

MACI, maximum acceptable cost of intervention

5.2.4 THE SUBMODELS OF 1A

To complete the analysis of maximum acceptable cost of intervention, Table 5.26 compares the maximum acceptable cost of lifestyle intervention for Model 1A and the submodels of 30 to < 35 kg/m^2 and ≥ 35 kg/m^2. The values are presented for a three-year intervention and a three-year effect, a three-year intervention and a lifetime effect, and a lifetime intervention and a lifetime effect. The final analysis is presented as a sensitivity analysis. A comparison is made between the Model 1A maximum acceptable cost of intervention value compared to those of the submodels by dividing each separate submodel value by the Model 1A value, to derive values for the BMI 30 kg/m^2 to < 35 kg/m^2 and the ≥ 35 kg/m^2 subcategories. Due to the uncertainty surrounding QALYs in this analysis, the following comparisons are performed using the life-year outcome only.

Table 5.26 Comparison of Maximum Acceptable Cost of Intervention of Model 1A and Submodels Based on BMI Subcategory

		1A[a]	30 kg/m^2 to less than 35 kg/m^2 [a]	BMI Submodel as a Percent of 1A[b]	Greater than or equal 35 kg/m^2 [a]	BMI Submodel as a Percent of 1A[b]
Three-Year Intervention with Three-Year Effect	*Maximum Acceptable Cost of Intervention*	$1,820	$2,390	**131.3%**	$1,470	**80.8%**
	Cost/LY	*$4,770/ LY*	*$4,380/ LY*		*$5,304/ LY*	
Three-Year Intervention with Lifetime Effect	*Maximum Acceptable Cost of Intervention*	$6,500	$6,830	**105.1%**	$5,150	**79.2%**
	Cost/LY	*$4,593/ LY*	*$6,114/ LY*		*$7,035/ LY*	
Lifetime Intervention and Lifetime Effect	*Maximum Acceptable Cost of Intervention*	$720	$750	**104.2%**	$570	**79.2%**
	Cost/LY	*$4,602/ LY*	*$6,124/ LY*		*$7,030/ LY*	

a: Presented as maximum cost of intervention and cost per life-year over the duration of the model
b: Calculated by dividing maximum acceptable cost of intervention value of the BMI subcategories by the maximum acceptable cost values for Model 1A
kg/m^2, kilograms per meter-squared; LY, life-year

5.3 Time Free of Diabetes and Cost Breakdown by Markov State

This section of the results gives the analysis of the time free of diabetes for Models 1A, 1B, 2A and 2B. The Model 1A submodels are not analyzed because of uncertainty about input data.

Markov modeling allows for an analysis of time spent in each Markov state (NGT, IGT, T2DM, and death). This is accomplished through a Markov cohort analysis. Using the methodology recommended in the TreeAge training course, the half-cycle correction is removed from the IGT branches, which results in values for life-expectancy that are 0.5 years lower than the above-presented results.[398]

398 *TreeAge Software 2-Day Training Course*. Williamstown, Mass.: TreeAge Software, Inc; 2004.

Table 5.27 gives the results for the time free of diabetes for Model 1A and Model 1B for a three-year intervention and a three-year effect and a three-year intervention and a lifetime effect. Table 5.28 does the same for Models 2A and 2B.

Table 5.27 Years in Each Markov State and Years Free of T2DM for Model 1A and Model 1B (Three-Year and Lifetime Effect)

	Model 1A - Three-Year Effect	Model 1A - Lifetime Effect	Model 1B - Three-Year Effect	Model 1B - Lifetime Effect
Years in Each Markov Stage				
Placebo				
NGT	4.72		4.45	
IGT	6.19		5.96	
T2DM	13.70		11.95	
Total	*24.61*		*22.36*	
Years Free of T2DM [a]	***10.91 (44.33%)***		***10.41 (46.55%)***	
Years in Each Markov Stage				
Lifestyle				
NGT	6.51	11.87	6.16	11.06
IGT	6.97	7.17	6.69	7.35
T2DM	11.55	6.97	10.00	6.07
Total	*25.03*	*26.01*	*22.85*	*24.48*
Years Free of T2DM [a]	***13.48 (53.86%)***	***19.04 (73.20%)***	***12.85 (56.24%)***	***18.41 (75.20%)***

a: Years free of T2DM presented as actual years and percent of total life expectancy in parentheses.
IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T2DM, type 2 diabetes mellitus

Table 5.28 Years in Each Markov State and Years Free of T2DM for Model 2A and Model 2B (Three-Year and Lifetime Effect)

	Model 2A - Three-Year Effect	Model 2A - Lifetime Effect	Model 2B - Three-Year Effect	Model 2B - Lifetime Effect
Years in Each Markov Stage				
Placebo				
NGT	4.67		4.67	
IGT	6.12		6.12	
T2DM	13.54		12.01	
Total	*24.33*		*22.80*	
Years Free of T2DM [a]	***10.70 (44.35%)***		***10.79 (47.32%)***	
Years in Each Markov Stage				
Lifestyle				
NGT	6.43	11.72	6.43	11.72
IGT	6.88	7.08	6.88	7.08
T2DM	11.39	6.87	10.08	6.10
Total	*24.70*	*25.67*	*23.39*	*24.90*
Years Free of T2DM [a]	***13.31 (53.89%)***	***18.80 (73.24%)***	***13.31 (55.71%)***	***18.80 (75.50%)***

a: Years free of T2DM presented as actual years and percent of total life expectancy in parentheses.
IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T2DM, type 2 diabetes mellitus

Using the same methodology, the cost per Markov state was also calculated and is presented in Table 5.29 for Models 1A and 1B, and Table 5.30 for Models 2A and 2B.

Table 5.29 Total Cost in Each Markov State for Model 1A and Model 1B (Three-Year and Lifetime Effect)

	Model 1A - Three-Year Effect	Model 1A - Lifetime Effect	Model 1B - Three-Year Effect	Model 1B - Lifetime Effect
Total Cost in Each Markov State				
Placebo				
NGT	\$12,384		\$15,940	
IGT	\$22,983		\$22,033	
T2DM	\$86,360		\$75,263	
Total	*\$121,727*		*\$113,236*	
Total Cost in Each Markov State				
Lifestyle				
NGT	\$17,204	\$31,627	\$22,260	\$40,230
IGT	\$28,532	\$29,374	\$27,394	\$28,045
T2DM	\$75,315	\$44,056	\$63,390	\$38,312
Total	*\$121,051*	*\$105,057*	*\$113,044*	*\$106,587*

IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T2DM, type 2 diabetes mellitus

Table 5.30 Total Cost in Each Markov State for Model 2A and Model 2B (Three-Year and Lifetime Effect)

	Model 2A - Three-Year Effect	Model 2A - Lifetime Effect	Model 2B - Three-Year Effect	Model 2B - Lifetime Effect
Total Cost in Each Markov State				
Placebo				
NGT	$18,526		$25,318	
IGT	$40,669		$40,669	
T2DM	$127,704		$113,312	
Total	*$186,899*		*$179,299*	
Total Cost in Each Markov State				
Lifestyle				
NGT	$25,736	$46,738	$35,093	$63,796
IGT	$47,708	$48,920	$47,708	$43,920
T2DM	$107,510	$64,920	$95,159	$57,591
Total	*$180,954*	*$160,578*	*$177,960*	*$165,307*

IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T2DM, type 2 diabetes mellitus

5.4 Sensitivity Analyses

The sensitivity analyses listed in the introduction of this section will complete the results section. As a reminder, these analyses include:

(1) altering the duration of effect of the three-year intervention (from a three-year duration to a lifetime-duration);

(2) comparing the base-case results at discount rates of 0%, 3%, and 5%;

(3) decreasing the treatment effect by 20% (by increasing the progression from IGT to T2DM by 20% in the lifestyle arm and decreasing the rate of reversion from IGT to NGT by the same percentage in the same arm);

(4) increasing the progression from NGT to IGT in both arms by 20%;

(5) adding a possible reversion from T2DM to IGT due to the intervention (in Models 2A and 2B only)

A more in-depth description of each of these analyses will be provided with their results.

5.4.1 THE EFFECT OF DURATION ON INTERVENTION ON THE INCREMENTAL COST-EFFECTIVENESS RATIO

It is apparent from examining Tables 5.1-5.6 (the base-case results) that there is a large difference in incremental cost-effectiveness ratios between a three-year intervention with a three-year duration of effect, and a three-year intervention with a lifetime duration of effect. Table 5.31 has been constructed to illustrate the percentage difference in the ratio for each scenario (three-year and lifetime duration of effect) for each of the models presented in the dissertation. All values are taken from the Markov technique values given in Tables 5.1 -5.6. The cost per QALY results are not included due to the uncertainty surrounding these values in the analysis.

Duration of effect improves incremental cost-effectiveness ratios in all scenarios, but the values vary according to the model analyzed.

Table 5.31 The Effect of Duration of Effect of Intervention on the Incremental Cost-Effectiveness Ratio

Model	Duration of Effect	Incrmental C/E for Life-Years	Three-Year C/E as a Percent of Lifetime C/E
1A	*Three-Year*	-$6.3K/LY	53.5%
	Lifetime	-$11.8K/LY	
1A: 30 kg/m^2 to less than 35 kg/m^2	*Three-Year*	-$8.2K/LY	66.3%
	Lifetime	-$12.4K/LY	
1A: greater than or equal 35 kg/m^2	*Three-Year*	-$4.5K/LY	42.0%
	Lifetime	-$10.7K/LY	
1B	*Three-Year*	-$0.6K/LY	13.3%
	Lifetime	-$4.1K/LY	
2A	*Three-Year*	-$16.1K/LY	82.4%
	Lifetime	-$19.5K/LY	
2B	*Three-Year*	-$2.3K/LY	53.2%
	Lifetime	-$4.3K/LY	

a: Calculated by dividing the three-year duration of effect result by the lifetime duration of effect result
C/E, cost-effectiveness ratio; K, thousands; kg/m^2, kilogram per meter-squared;
LY, life-year

5.4.2 THE EFFECTS OF DISCOUNTING AT 3% AND 5%

Current literature suggests analyzing the results of a cost-effectiveness analysis using both a 3% and 5% rate.[399] Both costs and rewards are discounted in this model. Table 5.32 gives the results of discounting at these rates for Models 1A, 1B, 2A, and 2B. Table 5.33 gives the results for Model 1A and the submodels based on BMI subcategory. The analysis performed for cost per life-year. Cost per QALY analysis is not performed due to the

399 Drummond M, McGuire A. *Economic Evaluation in Health Care: Merging Theory With Practice*. Oxford: Oxford University Press; 2001.

uncertainty surrounding the input data.

All discount analyses result in lifestyle dominating placebo except for the three-year intervention results of Model 1B. At 3% and 5%, positive incremental cost-effectiveness ratio differences are obtained.

Table 5.32 The Effect of 3% and 5% Discounting on the Analysis (Models 1A, 1B, 2A, and 2B)

		Cost	Life-Years[a]	Incremental C/E Ratio	Cost	Life-Years[a]	Incremental C/E Ratio
		Three-Year Effect			Lifetime Effect		
1A							
0%	*Pl*	$121.7K	25.10	**-$6.3K/LY**	$121.7K	25.10	**-$11.8K/LY**
	L	$119.1K	25.52		$105.1K	26.51	
3%	*Pl*	$79.5K	17.10	**-$6.5K/LY**	$79.5K	17.10	**-$14.7K/LY**
	L	$77.9K	17.33		$69.4K	17.78	
5%	*Pl*	$62.3K	13.80	**-$5.8K/LY**	$62.3K	13.80	**-$16.5K/LY**
	L	$61.4K	13.96		$55.0K	14.24	
1B							
0%	*Pl*	$113.2K	22.86	**-$0.6K/LY**	$113.2K	22.86	**-$4.1K/LY**
	L	$112.9K	23.35		$106.5K	24.48	
3%	*Pl*	$75.90	15.96	***+$0.3K/LY***	$75.9K	15.96	**-$5.3K/LY**
	L	$76.0K	16.23		$71.6K	16.77	
5%	*Pl*	$60.4K	13.05	***+1.8K/LY***	$60.3K	13.05	**-$5.8K/LY**
	L	$60.7K	13.24		$57.2K	13,58	
2A							
0%	*Pl*	$186.9K	25.20	**-$16.1K/LY**	$186.9K	24.83	**-$19.5K/LY**
	L	$180.9K	24.83		$160.6K	26.18	
3%	*Pl*	$124.9K	16.92	**-$21.5K/LY**	$124.9K	16.92	**-$25.8K/LY**
	L	$120.8K	17.11		$108.4K	17.56	
5%	*Pl*	$99.6K	13.66	**-$24.3K/LY**	$99.6K	13.66	**-$30.2K/LY**
	L	$96.5K	13.79		$87.3K	14.07	
2B							
0%	*Pl*	$179.3K	23.30	**-$2.3K/LY**	$179.3K	23.30	**-$4.3K/LY**
	L	$177.9K	23.89		$170.3K	25.40	
3%	*Pl*	$122.3K	16.17	**-$3.7K/LY**	$122.3K	16.17	**-$6.7K/LY**
	L	$121.2K	16.48		$115.6K	17.18	
5%	*Pl*	$98.6K	13.17	**-$4.0K/LY**	$98.6K	13.17	**-$8.4K/LY**
	L	$97.7K	13.39		$93.2K	13.82	

a: Given in years
Slight inconsistencies in incremental cost-effectiveness ratio values are due to rounding
C/E, cost-effectiveness ratio; K, thousands; L, lifestyle; LY, life-year; Pl, placebo

Table 5.33 The Effect of 3% and 5% Discounting on the Analysis (Model 1A, and Submodels Based on BMI Subcategory)

		Cost	Life-Years[a]	Incremental C/E Ratio	Cost	Life-Years[a]	Incremental C/E Ratio
		Three-Year Effect			Lifetime Effect		
1A							
0%	*Pl*	$121.7K	25.10	**-$6.3K/LY**	$121.7K	25.10	**-$11.8K/LY**
	L	$119.1K	25.52		$105.1K	26.51	
3%	*Pl*	$79.5K	17.10	**-$6.5K/LY**	$79.5K	17.10	**-$14.7K/LY**
	L	$77.9K	17.33		$69.4K	17.78	
5%	*Pl*	$62.3K	13.80	**-$5.8K/LY**	$62.3K	13.80	**-$16.5K/LY**
	L	$61.4K	13.96		$55.0K	14.24	
1A: 30 kg/m^2 to < 35 kg/m^2							
0%	*Pl*	$114.4K	25.60	**-$8.2K/LY**	$114.4K	25.60	**-$12.4K/LY**
	L	$110.1K	26.13		$96.7K	27.03	
3%	*Pl*	$74.6K	17.34	**-$9.7K/LY**	$74.6K	17.34	**-$15.4K/LY**
	L	$71.9K	17.61		$63.9K	18.03	
5%	*Pl*	$58.5K	13.95	**-$9.4K/LY**	$58.5K	13.95	**-$17.2K/LY**
	L	$56.7K	14.14		$50.7K	14.40	
1A: Greater than or equal 35 kg/m^2							
0%	*Pl*	$126.0K	24.79	**-$4.4K/LY**	$126.0K	24.79	**-$10.6K/LY**
	L	$124.4K	25.14		$113.7K	25.94	
3%	*Pl*	$82.5K	16.94	**-$3.7K/LY**	$82.5K	16.94	**-$13.1K/LY**
	L	$81.7K	17.14		$75.0K	17.51	
5%	*Pl*	$64.7K	13.70	**-$2.3K/LY**	$59.4K	13.70	**-$14.5K/LY**
	L	$64.4K	13.84		$64.7K	14.07	

a: Given in years
Slight inconsistencies in incremental cost-effectiveness ratios are secondary to rounding.
C/E, cost-effectiveness ratio; K, thousands; L, lifestyle; LY, life-year; Pl, placebo

5.4.3 A 20% REDUCTION IN THE EFFECT OF THE LIFESTYLE INTERVENTION

In the DPP presentation of within trial cost-effectiveness of the study, a sensitivity analysis was run lowering the effectiveness of the lifestyle intervention[400] For this dissertation, the effect of lowering the effectiveness of the intervention by 20% on the intermittent cost effectiveness ratio was evaluated. This analysis was run by lowering the rate of

400 Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518-2523.

reversion from IGT to T2DM by 20% and raising the rate of progression from IGT to T2DM by 20%. The results are presented for a three-year effect of the three-year intervention in Table 5.34, and a lifetime effect of the three-year intervention in Table 5.35. The 20% decrease in the effect of the intervention results has one value for which lifestyle does not dominate placebo, and this is for Model 1B (obesity-adjusted) given a three-year intervention with a three-year effect (see Table 5.34). The results are given for cost per life-year. Cost per QALY values are not given due to uncertainty surrounding QALY values for the dissertation. The results are only given for Models 1A, 1B, 2A, and 2B. The Model 1A submodels are not analyzed due to uncertainty surrounding input data.

Table 5.34 The Effect of a 20% Decrease in the Effect of the Lifestyle Intervention Given a Three-Year Intervention and a Three-Year Effect[a]

		Lifetime Cost	Life-Years[b]	Incremental C/E Ratio	Lifetime Cost	Life-Years[b]	Incremental C/E Ratio
		Base-Case			Intervention Effect Decreased by 20%		
1A	*Pl*	\$121.7K	25.10	**-\$6.3K/LY**	\$121.7K	25.10	**-\$2.9K/LY**
	L	\$119.0K	25.52		\$120.8K	25.41	
1B	*Pl*	\$113.2K	22.86	**-\$0.6K/LY**	\$113.2K	22.86	***+\$1.9K/LY***
	L	\$112.9K	23.35		\$113.9K	23.22	
2A	*Pl*	\$186.9K	24.83	**-\$16.1K/LY**	\$186.9K	24.83	**-\$15.2K/LY**
	L	\$181.0K	25.20		\$181.9K	25.16	
2B	*Pl*	\$179.3K	23.30	**-\$2.3K/LY**	\$179.3K	23.30	**-\$0.5K/LY**
	L	\$178.0K	23.89		\$179.1K	23.73	

a: Calculated by increasing the rate of progression of conversion form IGT to T2DM by 20% and decreasing the rate of reversion from IGT to NGT by 20% in the lifestyle arm
b: Given in years.
Slight inconsistencies in incremental cost-effectiveness ratios are secondary to rounding.
C/E, cost-effectiveness; K, thousands; L, lifestyle; LY, life-year; Pl, placebo

Table 5.35 The Effect of a 20% Decrease in the Effect of the Lifestyle Intervention Given a Three-Year Intervention and a Lifetime Effect[a]

		Lifetime Cost	Life-Years[b]	Incremental C/E Ratio	Lifetime Cost	Life-Years[b]	Incremental C/E Ratio
		Base-Case			Intervention Effect Decreased by 20%		
1A	*Pl*	\$121.7K	25.10	**-\$11.8K/LY**	\$121.7K	25.10	**-\$10.7K/LY**
	L	\$105.1K	26.51		\$110K	26.17	
1B	*Pl*	\$113.2K	22.86	**-\$4.1K/LY**	\$113.2K	22.86	**-\$3.5K/LY**
	L	\$106.5K	24.48		\$108.8K	24.10	
2A	*Pl*	\$186.9K	24.83	**-\$19.5K/LY**	\$186.9K	25.84	**-\$18.5K/LY**
	L	\$160.6K	26.18		\$168.2K	24.83	
2B	*Pl*	\$179.3K	23.30	**-\$4.3K/LY**	\$179.3K	23.30	**-\$3.8K/LY**
	L	\$170.3K	25.40		\$173.3K	24.88	

a: Calculated by increasing the rate of progression of conversion form IGT to T2DM by 20% and decreasing the rate of reversion from IGT to NGT by 20% in the lifestyle arm
b: Given in years.
Slight inconsistencies in incremental cost-effectiveness ratios are secondary to rounding.
C/E, cost-effectiveness; K, thousands; L, lifestyle; LY, life-year; Pl, placebo

5.4.4 A 20% INCREASE IN THE PROGRESSION FROM NGT TO IGT

Due to the uncertainty of the values derived for progression from NGT to IGT in both arms of the study (neither value is given in the DPP results), a sensitivity analysis was conducted increasing the rate of progression from NGT to IGT in both the placebo and lifestyle arms of the analysis. This was done, in part, secondary to the finding that the rate of progression in the placebo arm from IGT to T2DM (0.1075) was higher than what was predicted in the initial study design (0.0065). It is possible that progression from NGT to IGT could mimic this elevated progression.

The results of this sensitivity analysis are given in Table 5.36 for the three-year duration of effect given a three-year duration of intervention, and in Table 5.37 for a lifetime

401 Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.

402 Diabetes Prevention Program Research Group. The Diabetes Prevention Program: design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care*. 1999;22:623-634.

duration of effect given a three-year duration of intervention. In the three-year effect table (Table 5.36), the analysis as performed with the following methodology: (1) increase the rate of progression of NGT to IGT in the placebo arm from 0.0767 to 0.0920; (2) increase the rate of progression of NGT to IGT in the lifestyle arm by 0.0406 to 0.0487 in the first-three cycles, and then to 0.0920 for the duration of the model.

In the lifetime-effect table (Table 5.37), the analysis was run by: (1) increasing the rate of progression from NGT to IGT in the placebo arm from 0.0767 to 0.0920; and (2) increasing the rate of progression from NGT to IGT in the lifestyle arm by 0.0406 to 0.0487.

All incremental cost–effectiveness ratio values derived in this analysis are higher, and therefore less cost-effective (although very similar) than those found in the base-case analysis. This analysis also results in one value in which no strategy dominates (model 1B, three-year effect of intervention).

Table 5.36 The Effect of Increasing the Rate of Progression of NGT to IGT by 20% in Both Arms of the Study for a Three-Year Effect of the Intervention[a]

		Lifetime Cost	Life-Years[b]	Incremental C/E Ratio	Lifetime Cost	Life-Years[b]	Incremental C/E Ratio
		Base-Case			Rate of Progression from NGT to IGT Increased by 20% in Both Arms		
1A	*Pl*	\$121.7K	25.10	**-\$6.3K/LY**	\$122.7K	25.04	**-\$5.8K/LY**
	L	\$119.0K	25.52		\$120.3K	25.44	
1B	*Pl*	\$113.2K	22.86	**-\$0.6K/LY**	\$113.6K	22.79	***+\$0.3K/LY***
	L	\$112.9K	23.35		\$113.4K	23.25	
2A	*Pl*	\$186.9K	24.83	**-\$16.0K/LY**	\$188.2K	24.77	**-\$15.2K/LY**
	L	\$181.0K	25.20		\$182.8K	25.13	
2B	*Pl*	\$179.3K	23.30	**-\$2.3K/LY**	\$179.8K	23.22	**-\$2.1K/LY**
	L	\$178.0K	23.89		\$178.60	23.78	

a: Analysis performed by increased the progression of NGT to IGT in the placebo arm from 0.0767 to 0.0920, and increasing the rate of progression of NGT to IGT in the lifestyle are from 0.0406 to 0.0487 in the first –three cycles, and then to 0.0920 for the duration of the model.
b; Given in years.
Slight inconsistencies in incremental cost-effectiveness ratios are secondary to rounding.
C/E, cost-effectiveness; K, thousands; L, lifestyle; LY, life-year; Pl, placebo

Table 5.37 The Effect of Increasing the Rate of Progression of NGT to IGT by 20% in Both Arms of the Study for a Lifetime Effect of the Intervention[a]

		Lifetime Costs	Life-Years[b]	Incremental C/E Ratio	Lifetime Costs	Life-Years[b]	Incremental C/E Ratio
		Base-Case			Rate of Progression From NGT to IGT Increased by 20% in Both Arms		
1A	*Pl*	$121.7K	25.10	**-$11.8K/LY**	$122.6K	25.04	**-$11.7K/LY**
	L	$105.1K	26.51		$106.0K	26.46	
1B	*Pl*	$113.2K	22.86	**-$4.1K/LY**	$113.6K	22.79	**-$4.1K/LY**
	L	$106.5K	24.48		$106.9K	24.43	
2A	*Pl*	$186.9K	24.83	**-$19.5K/LY**	$188.3K	24.77	**-$19.3K/LY**
	L	$160.6K	26.18		$162.1K	26.13	
2B	*Pl*	$179.3K	23.30	**-$4.3K/LY**	$179.80	23.33	**-$4.3K/LY**
	L	$170.3K	25.40		$170.7K	25.33	

a: Analysis performed by increasing the rate of progression from NGT to IGT in the placebo arm from 0.0767 to 0.0920, and increasing the rate of progression from NGT to IGT in the lifestyle arm by 0.0406 to 0.0487.
b; Given in years.
Slight inconsistencies in incremental cost-effectiveness ratios are secondary to rounding.
C/E, cost-effectiveness; K, thousands; L, lifestyle; LY, life-year; Pl, placebo

5.4.5 THE POSSIBILITY OF REVERTING FROM T2DM TO IGT

Section 2.1.2.3.5 suggests that there is a possibility of reverting from T2DM to IGT secondary to intensive lifestyle intervention. The current literature suggests that this is a short-lived state (approximately one year), and is most probably secondary to a negative caloric balance rather than stable weight loss maintenance.[403]

A sensitivity analysis was performed on Models 2A and 2B to include a possibility of T2DM subjects reverting to IGT in the first Markov cycle by a transition probability of 0.20. This change is only reflected in this cycle, as this is the time of the most intensive

403 Turner RC, Cull CA, Firghi V, et al. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus. *JAMA*. 1999;281:2005-2012.

lifestyle intervention, and therefore, the cycle at which this event is most likely to occur. In addition, this analysis is not performed in Models 1A and 1B as these models are those that most closely approximated the DPP, and the assumption is made that subjects with T2DM are removed from the analysis upon diagnosis.

The results of this analysis give almost identical answers to those derived in the base case for Models 2A and 2B (for both three-year duration of effect and lifetime duration of effect). Therefore, no tables have been constructed for this analysis.

5.5 Summary of Results

It is apparent that lifestyle dominates placebo in all of the models presented in this dissertation, but there is a vast range of values for the incremental cost-effectiveness ratios generated by the analyses. In addition, maximum acceptable cost of intervention has a wide range of values, which seems in part to depend on the wide range of incremental cost-effectiveness values. Chapter 6 presents a discussion of these results and their potential implications for health policy.

CHAPTER 6 – DISCUSSION

While there have been few studies in the literature to date assessing the cost-effectiveness of long-term, intensive lifestyle intervention for the prevention of T2DM, those that are available suggest that this treatment plan is generally cost effective.[404, 405, 406, 407] The DPP reports that the cost per case of diabetes prevented over the three-year duration of the study is $15,655 (using a "health system" perspective). These numbers were obtained by multiplying the incremental cost between the placebo arm and the lifestyle intervention arm by the number needed to treat to prevent one case of diabetes (6.9 participants).[408] The DPP researchers did not choose to calculate a cost per LY gained, which may be secondary to the low mortality rates that were found in the study, or the limited time frame (three years). This makes direct comparisons of the results of the DPP study and the dissertation difficult.

A cost per QALY of $31,512 was obtained by the DPP by dividing incremental cost ($2,269) by incremental QALYs gained (0.072).[409] When the dissertation model is run for a three-year period (taking out the half-cycle correction), a similar result is obtained (cost

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404 Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518-2523.

405 Palmer AJ, Roze S, Valentine WJ, et al. Intensive lifestyle changes or metformin in patients with impaired glucose tolerance: modeling the long-term health economic implications of the Diabetes Prevention Program in Australia, France, Germany, Switzerland, and the United Kingdom. *Clinical Therapeutics*. 2004;26:304-321.

406 Palmer AJ, Roze S, Cabrieres L, et al. Long-term projection of the costs of the Diabetes Prevention Program in the USA using the CORE diabetes prevention model: intensive lifestyle changes and metformin are both cost-effective. Paper presented at: 18th International Diabetes Federation Congress, 2003; Paris.

407 Segal L, Dalton A, Richardson J. Cost-effectiveness of the primary prevention of non-insulin dependent diabetes mellitus. *Health Promotion International*. 1998;13:197-209.

408 Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care*.. 2003;26:2518-2523.

409 Ibid.

per QALY = $33,726, with slight inconsistencies due to assumptions about cost of illness values and cost multipliers used in the dissertation model). Unfortunately, the incomplete information regarding QALYs for the long-term analysis required for this dissertation limit the use of this outcome.

The Palmer et al. studies are also not directly compatible to the results generated in this dissertation due to differences in the Markov models used for the respective analyses. The most substantial difference between the two basic models is that the Palmer et al. model does not include transitioning back to the NGT state from IGT. The international evaluation performed by these authors suggests that in four of the five countries examined (Australia, France, Germany, and Switzerland), lifestyle dominates placebo, and that in the U.K., the incremental cost-effectiveness ratio is £6,381/life-year gained (approximately US$11,700).[410] In the similar analysis that the authors have performed on implementing a DPP-like program in the U.S., findings suggest that the cost per life-year gained for the lifestyle intervention is $11,518.[411] These results were found to be sensitive to the duration of the intervention and the costs of the intervention program, as were the results of this dissertation.

The Segal et al. study also found that an intensive diet and behavioral modification program using a model that included transitioning from IGT to NGT was highly cost effective, with a "gross cost of life-year saved" of $4,300, and a "net cost of life-year saved" of $1,900.[412] The reduction in incidence of progression from IGT to T2DM in this

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410 Palmer AJ, Roze S, Valentine WJ, et al. Intensive lifestyle changes or metformin in patients with impaired glucose tolerance: modeling the long-term health economic implications of the Diabetes Prevention Program in Australia, France, Germany, Switzerland, and the United Kingdom. *Clinical Therapeutics*. 2004;26:304-321.

411 Palmer AJ, Roze S, Cabrieres L, et al. Long-term projection of the costs of the Diabetes Prevention Program in the USA using the CORE diabetes prevention model: intensive lifestyle changes and metformin are both cost-effective. Paper presented at: 18th International Diabetes Federation Congress, 2003; Paris.

412 Segal L, Dalton A, Richardson J. Cost-effectiveness of the primary prevention of non-insulin dependent diabetes mellitus. *Health Promotion International*. 1998;13:197-209.

model was from 70% to 30% (a 57% reduction).

How do the results of this dissertation, which can be classified as a "what if" analysis in that much of the input data were derived from multiple studies (in other words, the model is not based on actual trial data), add to the above results? It is apparent that intensive lifestyle intervention to prevent progression from IGT to T2DM appears to be "highly cost-effective." The results generated by this dissertation may help to address the problems that policy makers may encounter as they attempt to decide how best to implement this treatment option on a global scale in the U.S.

The first problem the results suggest that policy makers may encounter is that while all scenarios proposed by the dissertation models give a result of lifestyle dominating placebo, there are a large range of values for the incremental cost-effectiveness ratios, and these values depend on the model proposed. Therefore, input data included in the model, as well as the actual model itself, will affect the outcome generated. One important area that appears to affect the model substantially is the potential effect of obesity on transition probabilities and Markov rewards. Another appears to be the effect of exclusion criteria in the study design of the DPP. This becomes important as DPP results are used as the primary data for the dissertation models. The most important result of these DPP "exclusion criteria" may be that the subjects of the DPP may not be particularly representative of the U.S. population. A final important variable that emerges as the results are examined appears to be the underlying direct medical costs included in the model.

A second important problem that policy makers may face is "What is the upper limit of the maximum acceptable cost of the intensive lifestyle intervention?" In other words, "What is the most I can spend on the lifestyle intervention and still have it dominate placebo in a cost-effectiveness analysis?" The results suggest that the maximum cost value appears to vary according to the model, and with no surprise, seems to be influenced by

both the incremental cost difference range and the incremental reward (life-years in the case of the analyses performed). These values, in turn, are influenced by all of the above mentioned variables.

This discussion section of this dissertation attempts to address these problems. The chapter is divided into four sections. The first examines the individual results derived form the dissertation. The second section attempts to summarize these individual results to present an overall picture that may be helpful to policy makers dealing with the problem of implementing intensive lifestyle interventions for preventing T2DM. Section three addresses the limitations of the study, and section four discusses potential areas for further research on this topic.

6.1 Discussion of Specific Results

The specific results of the dissertation as outlined in Chapter 5 are now discussed. The section first gives an analysis of the base-case results and comparisons for Models 1A and 1B, and Models 2A and 2B. A similar analysis is also given for Model 1A and the submodels of 1A based on BMI subcategory. In particular, this section of the analysis describes in greater detail the large range of values generated for incremental cost-effectiveness ratios, and sets the stage for a discussion of maximum acceptable cost of intervention.

6.1.1 THE BASE-CASE RESULTS AND COMPARISONS

As noted in the results section, all base-case models for Models 1A, 1B, 2A and 2B used in this dissertation generated a result of lifestyle dominating placebo (Tables 5.1, 5.4, 5.5, and 5.6). In addition, all proposed hypotheses are not rejected based on these base-case findings.

The first thing to note is the large difference in values for incremental cost-effectiveness ratios. As noted in 5.1.3 and specifically in Table 5.7, the range of values for a three-year intervention for a three-year duration of effect for life-years is -$551/LY to -$16,064/LY, and for a three-year intervention with a lifetime duration of effect is -$4,132/LY to -$19,496/LY (using the values derived from the Markov technique methodology). The model with the lowest incremental cost-effectiveness ratio, and therefore, the model that is potentially the most cost-effective is Model 2A (lifetime duration of effect). The model with the highest incremental cost-effectiveness ratio, and therefore, the model that is the least cost-effective is Model 1B (three-year duration of effect). The following section attempts to address the role of cost inputs in the models as an explanation for the differences found in the incremental cost-effectiveness ratios.

6.1.1.1 The Differences Between the Upper and Lower Range Models

As noted above, the model with the highest cost-effectiveness ratio is Model 2A (lifetime effect of duration), and the model with the lowest cost-effectiveness ratio is Model 1B (three-year effect of duration). There are several important factors that differentiate these models that can potentially explain this large range of incremental cost-effectiveness ratios. To someone investigating the possibility of implementing long-term, intensive lifestyle intervention for T2DM prevention, the questions become, "What makes Model 1B appear to be less cost-effective?" and, "What makes Model 2A appear to be more cost-effective?"

Referring to the data input references in Appendices 2 and 3, the following differences may be ascertained. The first is that Model 1B is an obesity-adjusted model that uses DPP data for transition probabilities and Markov cost rewards, while Model 2A is an obesity-unadjusted model that attempts to address a more generalized population than that stud-

ied by the DPP. The Markov transition probabilities differ between the models, in that a lower overall mortality is used in Model 1B than in Model 2A for the first-three Markov cycles, reflecting the mortality rates of the DPP study. On the other hand, the hazard ratios for mortality are larger for all three stages of glucose homeostasis for Model 1B than Model 2A. The end result is that life-expectancy is longer in the placebo arm and lifestyle arm for Model 2A for both durations of effect.

It is also important to note that while life expectancy is longer in Model 2A, time free of T2DM is very similar in both models. One may see upon examining Tables 5.27 and 5.28 that the Model 2A subjects live in a similar range or slightly longer range in the NGT and IGT stages than those subjects in Model 1B. On the other hand, Model 2A subjects live approximately 14% longer in the T2DM stage than those subjects in Model 1B. These results are found for placebo and lifestyle, regardless of duration of effect. This can be explained in part by the increased hazard ratio for mortality for T2DM subjects in Model 1B (2.64)[413] versus that found in Model 2A (a triangular distribution of 1.4, 1.9, and 2.5).[414, 415] As a summary, Model 2A subjects live longer, and in particular, live longer in the T2DM state. The end result adds to the increased total lifetime cost found in the model because subjects live longer, and in particular, live longer in a more expensive state (T2DM).

The other major difference in the models involves the direct medical control cost of illness for all stages of glucose homeostasis. The total cost differences between the models, outlined in Table 5.7, show that overall, total lifetime costs in Model 2A are greater

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413 Rogers RG, Hummer RA, Krueger PM. The effect of obesity on overall, circulatory disease, and diabetes-specific mortality. *Journal of Biosocial Science*. 2003;35:107-129.

414 Saydah SH, Loria CM, Eberhardt MS, et al. Subclinical states of glucose intolerance and risk of death in the U.S. *Diabetes Care*. 2001;24:447-453.

415 Saydah SH, Eberhardt MS, Loria CM, et al. Age and the burden of death attributable to diabetes in the United States. *American Journal of Epidemiology*. 2002;156:714-719.

than in Model 1B, at least in part because the control cost of illness is greater ($3,968 for model 2A[416] vs. $2,688 for Markov cycles three and greater for Model 1B[417, 418]). On the other hand, Model 1B does include a cost-multiplier for NGT subjects (adjusting for obesity) using a triangular distribution of 1.02, 1.34, and 1.74, which is not included in Model 2A.[419] This cost-multiplier does not offset the increased costs found in Model 2A.

6.1.1.1.1 The Incremental Cost and Life-Year Differences between the Two Models

Model 2A has higher lifetime costs for subjects in the placebo and lifestyle arm, but the model has a lower (more negative) incremental cost-effectiveness ratio, making it appear to be more cost-effective. In addition, Model 2A subjects live longer than Model 1B subjects. Continuing the process, incremental differences between overall costs and total life-years between the two models must be examined. The following results are derived when comparing the incremental cost values for Model 2A as a percent of Model 1B, (calculated by taking the total incremental cost of Model 2A and dividing by that of Model 1B from Table 5.7):

Model 2A (three-year effect) vs. Model 1B (three-year effect):

Model 2A incremental cost is 2,202% of that of Model 1B ($5,944/ $270);

Model 2A (lifetime effect) vs. Model 1B (lifetime effect):

Model 2A incremental cost is 393% of that of Model 1B ($26,319/ $6,694).

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416 American Diabetes Association. Economic costs of diabetes in the U.S. in 2002. *Diabetes Care*. 2003;26:917-932.

417 Brown JB, Nichols GA, Glauber HS, et al. Type 2 diabetes: incremental medical care costs during the first 8 years after diagnosis. *Diabetes Care*. 1999;22:1116-1124.

418 Nichols GA, Glauber HS, Brown JB. Type 2 diabetes: incremental medical care costs during the 8 years preceding diagnosis. *Diabetes Care*. 2000;23:1654-1659.

419 Thompson D, Brown JB, Nichols GA, et al. Body mass index and future healthcare costs: a retrospective cohort study. *Obesity Research*. 2001;9:210-218.

The incremental life-year values for the two models are compared below (see Table 5.7):

Model 2A (three-year effect) vs. Model 1B (three-year effect):

Model 2A incremental life-years are 76% of that of Model 1B (-0.37 / -0.49);

Model 2A (lifetime effect) vs. Model 1B (lifetime effect):

Model 2A incremental life-years are 83% of that of Model 1B (-1.35 / -1.62).

Therefore, it is no surprise that Model 2A appears more cost-effective than Model 1B based on the above numbers. The total life-year results are very similar for the two models, but when these values are divided into the total incremental costs, very large incremental cost-effectiveness ratio ranges result.

One key to this analysis then is the answer to the following question, "What makes Model 2A total costs so much greater than those in Model 1B?" An obvious answer is the increased control cost of illness found in this model ($3,968) vs. that found in model 1B ($1,100 for the first-three cycles, and then $2,689 for the duration). It therefore appears that in this analysis, the control cost of illness used in the model will have a very large effect on the incremental cost-effectiveness ratio output.

6.1.1.1.2 The Actual Incremental Cost between Placebo and Lifestyle

Additional questions that must be addressed are, "What is the actual incremental cost between placebo and lifestyle in Model 1B and Model 2A?" and "How do these values compare between models?" The answers may be found by comparing the placebo and lifestyle arms for the two scenarios of Model 1B and Model 2A. The results, found in Table 5.7, are the following (derived by dividing the placebo values of each model by the lifestyle model). For the three-year effect scenarios, the placebo arm incremental cost value is 100.24% of that of the lifestyle arm of Model 1B. For the same scenario of Model

2A, the placebo arm incremental cost value is 103.28% of that of the lifestyle arm of Model 2A. For the lifetime-effect values, the placebo arm incremental cost value is 106.28% of that of the lifestyle arm of Model 1B, and in Model 2A, the placebo arm incremental cost value is 116.39% of that of the lifestyle arm.

Summarizing the above analysis, it again becomes apparent that a great deal of the large difference between the two models (2A vs. 1B) results from the greater incremental cost value for 2A than that found in 1B. The actual total cost value should be emphasized here because when percentage comparisons are made between placebo and lifestyle arms of the two models, these values are very similar.

The above findings may be summarized in the following way:

(1) Model 2A total costs are greater than Model 1B total costs.

(2) The value calculated dividing the total costs of the placebo arm by the lifestyle arm of Model 2A and this same value calculated for Model 1B is very similar. The value calculated dividing the total life-years using the same methodology for both models is also very similar.

(3) The actual numerical value for incremental cost difference is much higher for Model 2A than 1B (which is most probably secondary to the higher control cost of illness of Model 2A). On the other hand, the value for incremental life-years for Model 2A is very similar to the same value for Model 1B.

(4) In Model 2A, a lower incremental cost-effectiveness ratio is obtained when these higher incremental cost values are divided by incremental life-years, giving the appearance of greater cost-effectiveness.

Further analysis of the effect of control cost of illness as well as cost of intervention is now given.

6.1.1.1.3 The Effect of Control Cost of Illness on Incremental Cost-effectiveness Ratios

The summary above implies that increasing the control cost of illness in the model appears to make incremental costs greater, and therefore, increases the incremental cost-effectiveness ratio (holding all other variables constant). Tables 5.8 and 5.9 test this hypothesis and show that incremental costs increase with increased control cost of illness, and while holding incremental reward constant, incremental cost-effectiveness ratios also increase. Therefore, at least part of the cost-effectiveness found in Model 2A is potentially a result of the approximately 1.5 times higher control cost of illness of the model compared to Model 1B.

The influence of total incremental costs on the analysis is consistent with the findings presented in Table 5.22 and Table 5.24. The results presented in these tables, which compared trends of maximum acceptable cost of intervention to incremental cost-effectiveness ratio, found that maximum acceptable cost of intervention was most likely to trend with total incremental costs than incremental cost-effectiveness ratios. This finding appears to be secondary to adjustments made to mortality in the model.

6.1.1.1.4 The Effect of Increasing the Intervention Cost on Model 2A

One other way to evaluate the etiology of why Model 1B appears to be more cost-effective than Model 2A involves evaluating the cost of the intensive lifestyle intervention in the models. The direct medical cost of Model 2A is approximately 1.5 times higher than that found in Model 1B, but the intervention cost has been held constant at the same value used in the DPP study. The results of the effect of increasing the intervention cost by 1.5 times, to approximate the increase in control cost of illness are presented in Table 5.10 It is apparent that increasing the intervention cost in Model 2A (the most cost-effective model) does decrease incremental cost differences, and also decreases incremental

cost-effectiveness ratios. Cost of intervention in this analysis, in relationship to direct medical control cost, also plays a role in the ultimate incremental cost-effectiveness ratio result of any given model.

6.1.1.1.5 Summary

Evaluating the base-case results reveals that lifestyle dominates placebo in all models of the dissertation. The results also show that there is a large range of incremental cost-effectiveness ratios that are derived from the dissertation models, with the most "cost-effective" model being Model 2A, and the "least cost-effective" model being 1B. Some factors contributing to these ‘cost-effectiveness" differences, as defined by incremental cost-effectiveness ratio, are evaluated in the above discussion. It becomes apparent that the control cost of illness and the cost of intervention (as it relates proportionately to this cost of illness) are important variables that must be considered when modeling diabetes prevention as these variables have the ability to greatly affect the final cost-effectiveness ratio of any analysis.

It is also apparent that the control cost of illness and intervention costs are not the only explanations of why Model 2A appears to be more cost-effective than Model 1B. The "A" models are referred to throughout this dissertation as the ‘unadjusted" models, and the "B" models are referred to as the "obesity-adjusted" models. The influence of the obesity-adjusted variables on cost-effectiveness is now presented.

6.1.1.2 The Obesity-Adjusted Versus Unadjusted Models

Cost input in the dissertation models explains part of the differences in the range of incremental cost-effectiveness ratios, but it is apparent that the variables adjusting the models for obesity also contribute to this range. Comparing Models 1B to 1A and Models

2B to 2A allows for an examination of the effect of the specific obesity-adjusted variables on each of these models (both the DPP specific model, and a more generalized model). These comparisons are found in Tables 5.11- 5.14, and are described in further detail in the following sections.

6.1.1.2.1 A Comparison of Model 1A to Model 1B

The comparison of these two models begins by examining total lifetime costs (see Table 5.11 and 5.12). This value is less for the obesity-adjusted model (Model 1B) than the unadjusted model (Model 1A) for the scenario of a three-year duration of effect for both the placebo arm and the lifestyle arm. While this trend holds true for total lifetime costs for the placebo arm in the scenario with a lifetime duration of effect, the results show that lifetime total costs are actually greater in the lifestyle arm for the obesity-adjusted models (Model 1B and Model 2B). The apparent reasoning for the lower costs for the placebo and lifestyle arm of the three-year effect and the placebo arm of the lifetime effect (Model 1B vs. Model 1A) appears to be the increased hazard ratio for mortality for all three states of glucose homeostasis in Model 1B. Subjects in these scenarios of the model do not live as long, and the result is lower total lifetime costs.

The difficulty comes in explaining the lifetime effect scenario of the lifestyle arm comparing Model 1B to Model 1A. In this comparison, Model 1B costs are higher than those found in Model 1A, in spite of the fact that subjects continue to live longer in Model 1A than in Model 1B. The answer lies in looking at Table 5.29. This table, which breaks down the costs per stage per model, allows for a comparison of Model 1A with a lifetime effect to Model 1B with a lifetime effect. The results show that while subjects do live longer in the NGT state in Model 1A, this NGT state is more expensive in Model 1B ($40,230 for Model 1B vs. $31,627 for Model 1A). This appears to result from the addi-

tion of the cost-multiplier to adjust for obesity for NGT subjects in Model 1B. Therefore, this adjustment for obesity has a substantial effect on total costs in this model.

It has already been noted that subjects live longer in Model 1A than in Model 1B, and this most likely results from the increased hazard ratios for mortality for all three glucose homeostasis states in Model 1B (see Table 5.27). This effect is more pronounced in the three-year effect scenario than the lifetime scenario. While in the lifetime scenario, subjects live longer in Model 1A in the NGT and T2DM states, but they actually live for less time in the IGT state (Model 1B subjects live 0.48 years longer in IGT than Model 1A subjects). A possible explanation is the longer duration of effect of the intervention with the possibility of more subjects moving into the NGT state.

The obesity-adjusted model (Model 1B) has a higher cost-effectiveness ratio for both durations of effect, making it less cost-effective than the unadjusted model (Model 1A). This follows the rationale presented in the above discussion about the effect of costs on the model results. Model 1A total costs are greater than Model 1B, but the life-years are similar. When the reward (the life-years) is divided into these greater costs, which in this case appear to be heavily influenced by the greater total life-years in the unadjusted models (resulting from the increased hazard ratios for mortality for all three glucose homeostasis states), lower cost-effectiveness ratios are produced, and the unadjusted model (Model 1A) appears more cost-effective. This effect become more pronounced in the comparison of Model 1B vs. Model 1A for the lifetime effect secondary to the added influence of the cost-multiplier for NGT subjects in Model 1B.

6.1.1.2.2 A Comparison of Model 2A to Model 2B

Examining Tables 5.13 and 5.14, it is evident that once again total lifetime costs follow a similar pattern to that found in the comparison of Model 1A to Model 1B. Lifetime

costs are lower for the three-year duration of effect for both the placebo and lifestyle arms. This is most likely due to the decreased life-years found in the obesity-adjusted model (Model 2B). Subjects die earlier in Model 2B due to increased hazard ratios for mortality, but in this model there is no increased hazard ratio for mortality for NGT subjects, and the IGT subjects share the same hazard ratio for both Model 2A and Model 2B because no obesity adjustments are made for mortality in these states due to the generalized nature of the models (i.e., there are no exclusion criteria for health states for the starting cohort). On the other hand, there continues to be an increased hazard ratio for mortality for T2DM subjects to adjust for increasing BMI (see Appendix 3).[420]

Evaluating the lifetime duration scenario for these two models, the results again indicate that the total lifetime costs for the lifestyle arm of the lifetime effect duration scenario for Model 2B (the obesity-adjusted model) are again greater than those found in the unadjusted model (Model 2A). By referring to Tables 5.28 and 5.30, the reasons for the increased costs become evident. Comparing the NGT state for the lifestyle arm for both Model 2A and Model 2B, one notes that subjects live for the exact same length of time (11.72 years). On the other hand, the cost for this state is greater ($63,796 for Model 2B and $46,738 for Model 2A). This increased cost can be attributed to the increased cost-multiplier for NGT subjects included to adjust for obesity in Model 2B.

As noted above, subjects live longer in Model 2A than in Model 2B, and this effect is again more pronounced in the three-year effect scenario than the lifetime scenario. The etiology of this difference appears to be due to the duration of effect of the intervention with more subjects in the NGT and IGT states.

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420 Rogers RG, Hummer RA, Krueger PM. The effect of obesity on overall, circulatory disease, and diabetes-specific mortality. *Journal of Biosocial Science*. 2003;35:107-129.

6.1.1.2.3 Summary: The Explanation of the Range of Incremental C/E Ratios

The above comparisons of the obesity-adjusted (Models 1B and 2B) to unadjusted (Models 1A and 2A) models indicate that in addition to the influence of cost input (such as control cost of illness and cost of intervention) on the model, the obesity adjustments made to the models have substantial impact. These adjustments include increases in hazard ratios for mortality as well as increased cost of illness for NGT subjects. The reasoning behind the large range of incremental cost-effectiveness ratio ranges, and particularly between Model 1B and Model 2A (the least and most cost-effective models) is two-pronged: (1) the increased cost-input variables in Model 2A ultimately increases the incremental total costs, which results in increased incremental cost-effectiveness ratios compared to Model 1B; and (2) the obesity-adjusted corrections to Model 1B, which include increases in hazard ratio of mortality and an increased cost-multiplier for NGT, subjects make further adjustments to both incremental costs and incremental rewards and result in further increases to the incremental cost-effectiveness ratio.

6.1.1.3 Model 1A and the BMI –Specific Submodels

This section of the discussion concludes with a discussion of the base-case results of Model 1A and the submodels based on BMI subcategory presented in Tables 5.1-5.3. The most important finding is that regardless of the BMI subcategory, lifestyle dominates placebo for all of these models, including the subcategory of ≥ 35 kg/m^2.

Comparisons of these models are given in Tables 5.15-5.18. The results are consistent with the DPP study findings.[421] Incremental cost-effectiveness ratios are lower for the BMI subgroup of 30 kg/m^2 to < 35 kg/m^2 than the overall DPP study cohort, or the BMI subgroup with a BMI ≥ 35 kg/m^2 for the three-year and lifetime scenarios of all three

421 Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.

models. Total costs are higher for the BMI ≥ 35 kg/m^2 subgroup, and this group also has lower total life-years.

6.1.1.4 The Use of QALYs in the Analysis

As noted in the introduction to this discussion, the main addition of the use of QALYs in this analysis enabled a check of the accuracy of the dissertation model compared to that of the DPP (comparing the dissertation results after three cycles to the DPP results). The use of QALYs for the long-term analysis remains limited due to the lack of standardized values for the different glucose homeostasis states, as well as the effect of obesity on quality of life. As this information becomes more available with future research, the accuracy of the cost per QALY values derived in the dissertation may be verified.

6.1.2 THE MAXIMUM ACCEPTABLE COST OF LIFESTYLE INTERVENTION

Finding that all models result in lifestyle dominating placebo in this dissertation is useful, but it might also be helpful if policy makers had a proposed maximum acceptable cost of intervention to use when beginning to design intensive lifestyle intervention programs. The problem is that just as there is a large range of cost-effectiveness ratios among the models, there is an equally large range of values derived for maximum acceptable cost of intervention.

With no surprise, when comparing Models 1A, 1B, 2A and 2B for three-year and lifetime duration of effect (using Tables 5.19 and 5.20), the lowest maximum acceptable cost of intervention is that found for Model 1B, three-year duration of effect ($1,020 per year for each of the three-years of the intervention), and the highest value is that found for Model 2A, lifetime duration of effect ($9,750 per year for each of the three-years of the intervention).

Once again, examining Tables 5.19 and 5.20, the reader may see that the obesity-adjusted models (Model 1B and Model 2B) all have lower maximum acceptable costs of intervention than those found in the unadjusted models. These results generally trended with the results of the incremental cost-effectiveness ratios found for these same models, but were actually more likely to trend with the incremental costs (see Table 5.22 and 5.24). Therefore, it appears that the cost input variables that influence incremental costs as well as incremental cost-effectiveness ratios have very similar influences on the maximum acceptable costs of intervention, depending on mortality adjustments made to a given model. Of great importance is the trend that models with a higher control cost of illness (such as Models 2A and 2B) have a higher maximum acceptable cost of intervention.
The emphasis of the following discussion deals with the effect of the obesity-adjusted variables added to the models, and how their addition to the models influences the maximum acceptable control cost of intervention.

6.1.2.1 The Effect of Obesity-Adjusted Variables on Model 1A

Table 5.21 allows the reader to examine the effects of adding separately, and in combination, the obesity-adjusted variables found in Model 1B to Model 1A. These effects include the following:

(1) The increased hazard ratio for mortality for NGT and IGT subjects to adjust for obesity relating to the findings of these increased hazard ratios in situations with multiple health care exclusions in study design. (Model 1A has no hazard ratio for mortality for NGT, and a triangular distribution of 0.8, 1.1, and 1.6 for IGT.[422] Model 1B has a hazard ratio of mortality of 1.3 for NGT subjects,

422 Saydah SH, Miret M, Sung J, et al. Postchallenge hyperglycemia and mortality in a national sample of U.S. adults. *Diabetes Care*. 2001;24:1397-1402.

and 1.7 for IGT subjects.[423, 424, 425])

(2) The increased hazard ratio for mortality for the T2DM subjects in Models 1B to adjust for increased hazard ratios with increased BMI (Model 1A has a triangular distribution of 1.4, 1.9, and 2.5.[426, 427] Model 1B has a value of 2.64.[428])

(3) A cost-multiplier for NGT subjects (triangular distribution of 1.02, 1.34, and 1.74)[429] to adjust for added costs due to obesity versus none in Model 1A.

Table 5.22 shows that maximum acceptable cost of intervention is most likely to trend with incremental costs in this model. Maximum acceptable cost of intervention generally trends with incremental cost-effectiveness ratios, but is affected by adjustments made to the models for mortality. The other important trend is that the scenarios with the lowest maximum acceptable cost of intervention, and therefore, the lowest incremental cost-effectiveness ratios all include the cost-multiplier for NGT subjects. Probably of most importance is that there are at least seven ways to model this analysis, and each gives a different result depending on which obesity-adjusted variable is added.

6.1.2.2 The Effect of Obesity-Adjusted Variables on Model 2A

A similar analysis of Model 2A is easier to interpret, as the obesity-adjustments to the

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423 Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women. *New England Journal of Medicine*. 1995;333:677-685.

424 Peeters A, Barendregt JJ, Willekens F, et al. Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Annals of Internal Medicine*. 2003;138:24-32.

425 Calle EE, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of U.S. adults. *New England Journal of Medicine*. 1999;341:1097-1105.

426 Saydah SH, Loria CM, Eberhardt MS, et al. Subclinical states of glucose intolerance and risk of death in the U.S. *Diabetes Care*. 2001;24:447-453.

427 Saydah SH, Eberhardt MS, Loria CM, et al. Age and the burden of death attributable to diabetes in the United States. *American Journal of Epidemiology*. 2002;156:714-719.

428 Rogers RG, Hummer RA, Krueger PM. The effect of obesity on overall, circulatory disease, and diabetes-specific mortality. *Journal of Biosocial Science*. 2003;35:107-129.

429 Thompson D, Brown JB, Nichols GA, et al. Body mass index and future healthcare costs: a retrospective cohort study. *Obesity Research*. 2001;9:210-218.

hazard ratio for mortality for NGT and IGT (#1 above in section 6.1.2.1) are not required because this is the generalized model, and the assumption is made that there are no exclusions made for healthcare states in the cohort.

In this more straightforward example, illustrated in Table 5.23, one may see that the addition of both adjustments for obesity (both the increased cost-multiplier for NGT subjects and the increased hazard ratio for mortality for T2DM subjects) to yield the lowest maximum acceptable cost of intervention. Adding each of the adjustments separately changes the maximum acceptable cost of intervention to an intermediate level. As in the above analysis, scenarios including the cost-multiplier for NGT give the lower maximum cost of intervention values. In addition, Table 5.24 again shows that maximum cost of intervention in this model is more likely to trend with incremental costs than incremental cost-effectiveness ratios due to the adjustments for mortality made to the models.

6.1.2.3 Summary of the Obesity Adjustments

A discussion of the maximum acceptable cost of intervention is important in several ways. The analysis verifies that maximum cost of intervention in this analysis appears to depend on the incremental cost. The maximum cost of intervention also depends on the incremental cost-effectiveness ratio to a lesser extent, and this appears to depend on the adjustments made to the model for mortality. The analysis also shows that the lowest values for maximum cost are found for both sets of models when the increased cost multiplier for NGT and the increased hazard ratio for mortality for T2DM subjects are both included. If only one of these adjustments is added to this set of models, the increased cost-multiplier for NGT seems to have a greater effect on lowering both the incremental costs and the cost-effectiveness ratios, and therefore, the maximum acceptable cost of intervention.

6.1.2.4 A Test of the Effect of Direct Medical Costs

As with the analysis of incremental cost-effectiveness ratios, the analysis of the maximum acceptable cost of intervention reveals (as shown in Table 5.24) that increasing direct medical costs in this model increases the maximum cost of intervention. Once again, this seems to directly trend with the increase in incremental cost-effectiveness ratio.

6.1.2.5 The Submodels of 1A

For completeness, this section includes an analysis of maximum acceptable cost of intervention for the submodels of 1A based on BMI subcategories as found in Table 5.26. These values are found to be highest in the model with a BMI of 30 kg/m^2 to < 35 kg/m^2. The values for the model with a BMI of ≥ 35 kg/m^2 are about 80% of those found for the overall DPP study cohort.

6.1.3 TIME FREE OF DIABETES AND COST BREAKDOWN BY STATE

The discussion section has made liberal use of the data found in Tables 5.27 and 5.28, which illustrate the years free of diabetes for the models, and Tables 5.29 and 5.30, the cost breakdown by Markov healthcare state. It is important to note the value of the ability to run a Markov cohort analysis, which is the methodology used for these tables, in order to more closely evaluate specific models, and in particular, their input variables.

6.1.4 SENSITIVITY ANALYSES

The discussion of the specific results concludes with examining the sensitivity analyses described in section 5.4.

6.1.4.1 Duration of Effect

With no surprise, incremental cost-effectiveness ratios increased with increased duration of effect. Duration of effect also appears to have effects on total costs in the lifetime scenarios of the obesity adjusted value by being part of the etiology that makes these values higher than the non-adjusted model values (see Tables 5.11-5.14, and the discussion in Sections 6.1.1.2.1 and 6.1.1.2.2).

6.1.4.2 The Effects of Discounting

For the lifetime effect of all models, discounting at 3% and 5% improved incremental cost-effectiveness ratios (see Tables 5.32 and 5.33). This did not hold true for Models 1A (including submodels) and 1B for a three-year duration of effect. In Model 1A, the incremental cost-effectiveness ratio, while still showing lifestyle dominating placebo, increased at the 5% discount rate. In the obesity-adjusted model (Model 1B), discounting at both 3% and 5% resulted in no strategy dominating another (versus lifestyle dominating placebo), with values of ($0.3/LY AND $1.8K/LY, respectively. The overall increase in incremental cost-effectiveness when discounting is incorporated in the models with increased range of duration of effect is of even greater encouragement for the use of intensive lifestyle intervention to prevent T2DM.

6.1.4.3 Changes in Effect and Transition Probabilities

The effect of changes in transition probabilities will complete the discussion of the results. The first change, that of decreasing the effect of the intervention by 20%, was also performed by the DPP in their within cost analysis.[430] The results show that in Model 1B,

430 Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518-2523.

with a three-year duration of effect, no strategy dominates (incremental cost-effectiveness ratio of +$1.9K/LY). In all other scenarios for Models 1A, 1B, 2A, and 2B, lifestyle dominates placebo.

Due to the uncertainty found for the transition probability from NGT to IGT, this value was increased by 20% in Models 1A, 1B, 2A, and 2B. This increase also resulted in no strategy dominating for Model 1B with a three-year duration of effect (+0.3K/LY). In all other scenarios, lifestyle dominated placebo.

Using the current clinical literature as a guide, adding a transition of T2DM subjects to IGT had little to no effect on the results of the model. The literature on this transition probability was not as robust as that for the transition from IGT to NGT, and this remains an area of the model where further refinement is needed.

6.2 Conclusion: How the Results May Apply to Policy Related to Prevention of T2DM

Current literature related to the cost-effectiveness of preventive services generally brings up several points that are very important for healthcare financing: (1) Monetary resources are scarce; (2) Limitless spending cannot be the result of placing a high value on health; and (3) Limitless spending cannot occur because an intervention is successful.[431] Bonneux and Birnie state these points this way: "If resources are scarce, trade offs have to be made between investing in the cure of existing disease and in the prevention of future disease."[432]

The U.S. Preventive Services Task Force made the following recommendation in December 2003: "The USPSTF recommends that clinicians screen all adult patients for

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431 Probstfield JL. How cost-effective are new preventive strategies for cardiovascular disease? *The American Journal of Cardiology*. 2003;22:22-27.

432 Bonneux L, Birnie E. The discount rate in the economic evaluation of prevention: a thought experiment. *Journal of Epidemiology and Community Health*. 2001;55:123-125.

obesity and offer intensive counseling and behavioral interventions to promote sustained weight loss for obese adults."[433] The DPP study was one reference used to support this recommendation.

Cost-effectiveness analysis is not a requirement for recommendations by the Task Force[434] though the following is suggested, "Evidence of effectiveness should be supplemented when possible by information on cost-effectiveness in any decision-making context in which available resources can be used for multiple purposes."[435] They also state, "Cost-effectiveness analysis raises important questions about opportunity costs of alternative choices that decision-makers should consider."[436]

Therefore, this dissertation is a starting point to look at the ultimate cost of implementing the above recommendation on a long-term basis, or to answer the first of the three-main questions asked in this dissertation, "What is the long-term cost-effectiveness of intensive lifestyle intervention to prevent T2DM from the state of IGT?"

The analysis is very encouraging in that all four of the basic models (Models 1A, 1B, 2A, and 2B) of the dissertation result in lifestyle dominating placebo at a discount rate of 0%. The importance of this is that these varied models attempt to address the impact of obesity on the evaluation as well as attempt to project the DPP findings onto a more generalized population, the second and third goals of this study. The positive results allow the reader to determine that while there is a varied range of results of incremental cost-effectiveness ratios that are produced in the analyses, overall, long-term diabetes preven-

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433 U.S. Preventive Services Task Force. Screening for Obesity in Adults: Recommendations and Rationale. Agency for Healthcare Research and Quality. Available at: http://www.ahrq.gov/clinic/3rduspstf/obesity/. Accessed October 2004.

434 U.S. Preventive Services Task Force. Guide to Clinical Preventive Services, 2nd Edition. Washington, D.C.: U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion; 1996.

435 Ibid.

436 Ibid.

tion by intensive lifestyle intervention dominates placebo.

Discounting is very important for cost-effectiveness analyses of preventive services, and the dissertation results are encouraging in that only one model (the obesity-adjusted model that is most like the DPP study cohort with a three-year duration of effect (Model 1B)) results in a scenario where there is no dominate strategy at discount rates of both 3% and 5%. The Model 1B results are still encouraging as the values generated are very close to the break-even level ($0.3K/LY and $1.8K/LY, respectively).

In addition, it is also very encouraging that lifestyle dominates placebo in the BMI subcategory of ≥ 35 kg/m^2. While the effect of the intervention in this subcategory is less than found for the overall cohort, it appears that intensive lifestyle intervention in this subcategory of patients should not be discouraged by clinicians based on cost-effectiveness. The range of incremental cost-effectiveness ratios points out the great importance of input variables in any model of diabetes prevention. Above all, the model must be as transparent as possible. The current ISPOR Best Practice Guidelines stress transparency as a requirement.[437] As further cost-effectiveness studies are published on diabetes prevention, it will be important to examine variables that are included in the models presented. From this dissertation, the input data that appear to have the most substantial influence on the model include: (1) direct medical control cost of illness; (2) cost of intervention; (3) duration of intervention effect; (4) adjustments to control cost of illness for obese non-diabetic subjects; and (5) adjustments to mortality rates for all subjects, regardless of glucose homeostasis level. Additionally, future models should carefully examine the actual transitions that are present in the DPP study, and should attempt to include a transition from IGT to NGT.

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437 Weinstein MC, O'Brien B, Hornberger J, et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices - Modeling Studies. *Value in Health*. 2003;6:9-17.

The maximum acceptable cost of intervention results generated in the model are also an important starting point for policy makers. It is one thing to state that intensive lifestyle intervention for T2DM prevention from an IGT state appears cost-effective, but it is another to begin to determine how much the healthcare community may spend on the intervention. This range of intervention costs also varied widely, as did the wide range of incremental cost-effectiveness ratios that resulted in the study.

An example of how the large range of maximum cost of interventions might affect policy is the following. If the only value generated was that found in the scenario of Model 2A (an annual expenditure of $9,750 in a generalized, unadjusted model with a three-year intervention and a lifetime effect), policy makers might begin to think that a very viable suggestion for diabetes prevention might be invasive intervention such as gastric bypass surgery. The rationale might be the following; (1) The model projects that the healthcare system has approximately $30K to spend over a three-year period; (2) A gastric bypass procedure might be the most effective way to maintain weight loss, which appears to influence the effect of the intervention; and (3) the surgical procedure costs approximately $30K. Adjustments to the models show this is just one maximum acceptable cost value that may be projected for cost-effectiveness of diabetes prevention. The example shows the importance to modeling of data input, sensitivity analyses, and transparency.

The prevailing cost of illness in a community appears to have a great influence on the incremental cost-effectiveness ratios and maximum acceptable cost of intervention values found in this dissertation. This may be because of the model design that uses this value as a starting point from which additional multipliers are used to increase cost of illness for the different Markov healthcare states. Another reason for the importance of this variable may be the limited effect of the intervention of life expectancy as projected in this model

(as well as those used by Palmer et al.),[438, 439] which tends to hold the denominator of the cost-effectiveness ratio fairly constant. For other modelers that use this technique, the potential influence of the control cost of illness must be recognized.

6.3 Directions for Future Research

Out of this dissertation research arise several areas where future research is needed. The first involves the fact that the study is performed on a cohort that is not particularly representative of the U.S. population (due to healthcare exclusion criteria in the study design), and we have no evidence that the results obtained by the DPP will be similar in a more generalized population. Clinical research is suggested in this area to determine the effect of intensive lifestyle intervention on a more generalized population of subjects with IGT to prevent T2DM.

Further research is required to establish the effect of obesity on non-diabetic subjects. This is important because it appears that much of the cost of illness of obese diabetics is related to their diabetes. If one is basing cost of illness of obese subjects on a population that includes diabetics and non-diabetics, it is possible that inaccuracies might occur in cost values.

The effect of obesity on mortality rates in non-diabetics also remains controversial. As noted in the dissertation, there are two schools of thought on this subject. For this dissertation, the assumption was made that mortality rates appear to increase in studies based on baseline cohorts that do not have broad healthcare exclusions in their study design. The

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438 Palmer AJ, Roze S, Cabrieres L, et al. Long-term projection of the costs of the Diabetes Prevention Program in the USA using the CORE diabetes prevention model: intensive lifestyle changes and metformin are both cost-effective. Paper presented at: 18th International Diabetes Federation Congress, 2003; Paris.

439 Palmer AJ, Roze S, Valentine WJ, et al. Intensive lifestyle changes or metformin in patients with impaired glucose tolerance: modeling the long-term health economic implications of the Diabetes Prevention Program in Australia, France, Germany, Switzerland, and the United Kingdom. *Clinical Therapeutics*. 2004;26:304-321.

reason for this discrepancy also requires further analysis.

Further clinical research is required to determine the potential duration of effect of diabetes prevention based on weight loss and physical activity. The results of this dissertation are encouraging in that lifestyle dominates placebo for all models even in the least optimistic scenario in which the effect of duration is only three-years (at a discount rate of 0%).

6.4 Limitations

One major limitation of this study is that DPP study data were not available. While having the data is important, the fact that it may have limited generalizability to the U.S. population must also be considered. The possibility that the effect from the lifestyle intervention found in the DPP study might not reflect that which would be found if intensive lifestyle intervention was implemented in a population without exclusions of healthcare states, and in particular, exclusion of cardiovascular disease (an early, macrovascular complication) is a great limitation.

The large number of assumptions required for the model (see Appendix 4) adds to the limitations of this study. At least part of this is secondary to the paucity of data about the effect of obesity on the Markov transition probabilities and rewards found in the models. This limitation is addressed in part by the four scenarios presented for the models and the extensive sensitivity analyses performed. It is clear that further adjustments will be required in future research on diabetes prevention, obesity, and the role of weight loss on these areas.

An additional limitation to the study is the inability to capture the effect of weight loss on other medical conditions that appear to be causally linked to obesity. This limitation potentially underestimates the cost-effectiveness of the analysis. The fact that a 7%

weight loss still placed the average intervention subject in a category of obese class I (as defined by the WHO)[440] somewhat tempers this limitation.

6.5 Conclusion

Intensive lifestyle intervention to prevent T2DM appears to be cost-effective on a long-term basis based on the results found in this dissertation. Until further clinical research is completed examining the actual long-term results of lifestyle intervention on diabetes prevention, modeling must be employed. In light of the fact that the DPP study is not particularly generalizable to the current U.S. population, the need for modeling in any diabetes prevention analysis is also emphasized.

This dissertation becomes a starting point for other researchers in the field of diabetes prevention to evaluate the effect of the variables included in cost-effectiveness models. The dissertation also hopefully helps to start introducing values for maximum acceptable cost of lifestyle intervention for diabetes prevention as the December 2003 recommendation by the U.S. Preventive Service Task Force for "intensive counseling and behavioral interventions to promote weight loss for obese adults" begins to be implemented.

440 World Health Organization. *Obesity: Preventing and Managing the Global Epidemic. Report of the WHO Consultation on Obesity.* Geneva: World Health Organization; 2000.

APPENDIX 1: Hypotheses and Models

Appendix 1

Hypotheses and Models

Hypothesis and Models	Similar to the DPP Cohort	Specific BMI Subcategories	Disease-State Exclusions	Adjustments for Obesity	Adjustments for Exclusions	Adjustiments for Generalization
H1 Model 1A	+	30kg/m2 to 35 kg/m2	+		Mortality, utility and cost Values from the DPP will be used for the first three years	
H2 Model 1A Submodel	+	30 kg/m^2 to 35 kg/m^2	+		Mortality, utility and cost Values from the DPP will be used for the first three years	
H3 Model 1A Submodel	+	Greater than or equal 35 kg/m^2	+		Mortality, utility and cost Values from the DPP will be used for the first three years	
H4 Model 1B	+	30kg/m2 to 35 kg/m2	+	Increaed HR for mortality for NGT and IGT subjects		
				Multiplier added for costs of NGT subjects Increased HR for mortality for T2DM subjects	Mortality, utility and cost Values from the DPP will be used for the first three years	
H5 Model 2A		30kg/m2 to 35 kg/m2				Increased control costs and increased mortality rates over DPP values Last DPP Utility value used
H6 Model 2B		30kg/m2 to 35 kg/m2		Multiplier added for costs of NGT subjects Increased HR for mortality for T2DM subjects		Increased control costs and increased mortality rates over DPP values Last DPP Utility value used

APPENDIX 2

Model 1A Data Input (Including Equations for Lifetime and Three-Year Effect)

Variable with Description (Specific Variable Names are in Bold Font)	Value	Reference
Age: start age of cohort	50 years	a
Progression from IGT to T2DM in placebo arm	0.1075	a
Reversion from IGT to NGT in placebo arm	0.0678	a
Progression from NGT to IGT in placebo arm	0.0767	b,c,d
Progression from IGT to T2DM in lifestyle arm	0.0505	a
Progression from IGT to NGT in lifestyle arm	0.1121	a
Progression from NGT to IGT in lifestyle arm	0.0406	b,c,d
pIGT_T_Life_1A[Age+_stage]: probability of progression from IGT to T2DM for the lifestyle arm (three-year duration of effect)	0.0505 for the first-three cycles, and then 0.1075	-
pIGT_N_Life_1A[Age+_stage]: probability of progression from IGT to NGT for the lifestyle arm (three-year duration of effect)	0.1121 for the first-three cycles, and then 0.0678	-
pNGT_IGT_L_1A[Age+_stage]: probability of progressing from NGT to IGT for the lifestyle arm (three-year duration of effect)	0.0406 for the first-three cycles, and then 0.0767	-
Hazard ratio of mortality for NGT	none	-
HRI_mort_1A: hazard ratio of mortality for IGT	Triangular distribution of 0.8, 1.1, and 1.6	e
HRT_mort_1A: hazard ratio of mortality for T2DM	Triangular distribution of 1.4, 1.9, and 2.5	f,g

mort_Pl_1A[Age+_stage]: mortality rates for the placebo arm	0.0017 for the first-three cycles, and then reverts to U.S. Life Tables	h,i
mort_L_1A[Age+_stage]: mortality rates for the lifestyle arm	0.0010 for the first-three cycles, and then reverts to the U.S. Life Tables	h,i
pDie_Pl_NGT_1A: probability of death for a NGT subject in the placebo arm	1-exp(-mort_Pl_1A [Age+_stage])	-
pDie_Pl_IGT_1A: probability of death for an IGT subject in the placebo arm	1-exp(-mort_Pl_1A [Age+_stage]*HR_I_mort_1A)	-
pDie_Pl_T_1A: probability of death for a T2DM subject in the placebo arm	1-exp(-mort_Pl_1A [Age+_stage]*HR_T_mort_1A	-
pDie_L_NGT_1A: probability of death for a NGT subject in the lifestyle arm	1-exp(-mort_L_1A [Age+_stage])	-
pDie_L_I_1A: probability of death for an IGT subject in the lifestyle arm	1-exp(-mort_L_1A [Age+_stage]*HR_I_mort_1A)	-
pDie_L_T_1A: probability of death for a T2DM subject in the lifestyle arm	1-exp(-mort_L_1A [Age+_stage]*HR_T_mort_1A)	-
cSC_1A: Cost of screening	$139	j
cINT_pl-1A[Age+_stage]: cost of intervention for placebo arm	Values for first-three cycles: $43, $18, $18, and the $0	j
cINT_L_1A:[Age+_stage] cost of intervention for lifestyle arm	Values for first-three cycles: $1,399, $679, and $702, and then $0	j
cNGT_1A[Age+_stage]: direct medical costs (cost for a subject with NGT)	$1,100 for the first-three cycles, and then $2,688	j,k,l
CM_I_1A: cost multiplier of IGT in 1A	Triangular distribution of 1.35, 1.48, and 1.79	k
CM_T_1A: cost multiplier of T2DM in 1A	Triangular distribution of 2.03, 2.27, and 2.83	l,m,n
uPl_1A[Age+_stage]; the cycle dependent utilites required for the placebo arm	0.686, 0.675, and 0.657 for the first-three cycles, and then 0.657	h
uLife_1A[Age+_stage]	0.703, 0.695, and 0.692, and then 0.692	h

Sources:
a:, Knowler WC, Barrett-Conner E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.
b: Weyer C, Tataranni PA, Bogardus C, et al. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening glucose tolerance during each stage of type 2 diabetes development. *Diabetes Care*.2001:24:89-94.
c: Edelstein SI, Knowler WC, Bain RP, et al. Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. *Diabetes*. 1997;46:701-710.
d: Meigs, JB, Mueller DC, Nathan DM, et al. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of the Aging. *Diabetes*. 2003;52:1475-1484.
e: Saydah SH, Miret M, Sung J, et al. Postchallenge hyperglycemia and mortality in a national sample of U.S. adults. *Diabetes Care*. 2001;24:1397-1402.
f: Saydah SH, Loria CM, Eberhardt MS, et al. Subclinical states of glucose intolerance and risk of death in the U.S. *Diabetes Care*. 2001;24:447-453.
g: Saydah SH, Eberhardt MS, Loria CM, et al. Age and the burdens of death attributable to diabetes in the United States. *American Journal of Epidemiology*. 2002;156:714-719.
h:The Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or Metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518-2523.
i: Arias E. *United States Life Tables, 2000*. Hyattsville, MD: National Center for Health Statistics, 2002. vol.51,3.
j: Diabetes Prevention Program Research Group. Costs associated with the primary prevention of type 2 diabetes mellitus in the Diabetes Prevention Program. *Diabetes Care*. 2003;26:36-47.
k: Nichols GA, Glauber HS, Brown JB. Type 2 diabetes: incremental medical care costs during the 8 years preceding diagnosis. *Diabetes Care*. 2000;23:1654-1659.
l: Brown JB, Nichols GA, Glauber HS, et al. Type 2 diabetes: incremental medical care costs during the first eight years after diagnosis. *Diabetes Care*. 1999;22:1116-1124.
m: American Diabetes Association. Economic costs of diabetes in the US. In 2002. *Diabetes Care*. 2003;26:917-932.
n: Ramsey S, Summers K, Leong SA, et al. Productivity and medical costs of diabetes in a large employer population. *Diabetes Care*. 2002;25:23-29.

Model 1A Submodel Input Data for BMI Subcategory of 30 kg/m^2 to < 35 kg/m^2 (Including Equations for Lifetime and Three-Year Effect)

Variable with Description (Specific Variable Names are in Bold Font)	Value	Reference
Age: start age of cohort	50 years	a
Progression from IGT to T2DM in placebo arm	0.0851	a
Reversion from IGT to NGT in placebo arm	0.0885	a
Progression from NGT to IGT in placebo arm	0.0602	b
Progression from IGT to T2DM in lifestyle arm	0.0363	a
Progression from IGT to NGT in lifestyle arm	0.1653	a
Progression from NGT to IGT in lifestyle arm	0.0433	b
pIGT_T_Life_1A[Age+_stage]: probability of progression from IGT to T2DM for the lifestyle arm (three-year duration of effect)	0.0363 for the first-three cycles, and then 0.0851	-
pIGT_N_Life_1A[Age+_stage]: probability of progression from IGT to NGT for the lifestyle arm (three-year duration of effect)	0.1653 for the first-three cycles, and then 0.0885	-
pNGT_IGT_L_1A[Age+_stage]: probability of progressing from NGT to IGT for the lifestyle arm (three-year duration of effect)	0.0433 for the first-three cycles, and then 0.0602	-
Hazard ratio of mortality for NGT	none	-
HRI_mort_1A: hazard ratio of mortality for IGT	Triangular distribution of 0.8, 1.1, and 1.6	c
HRT_mort_1A: hazard ratio of mortality for T2DM	Triangular distribution of 1.4, 1.9, and 2.5	d,e

mort_Pl_1A[Age+_stage]: mortality rates for the placebo arm	0.0017 for the first-three cycles, and then reverts to U.S. Life Tables	-
mort_L_1A[Age+_stage]: mortality rates for the lifestyle arm	0.0010 for the first-three cycles, and then reverts to the U.S. Life Tables	-
pDie_Pl_NGT_1A: probability of death for a NGT subject in the placebo arm	1-exp(-mort_Pl_1A [Age+_stage])	-
pDie_Pl_IGT_1A: probability of death for an IGT subject in the placebo arm	1-exp(-mort_Pl_1A [Age+_stage]*HR_I_mort_1A)	-
pDie_Pl_T_1A: probability of death for a T2DM subject in the placebo arm	1-exp(-mort_Pl_1A [Age+_stage]*HR_T_mort_1A	-
pDie_L_NGT_1A: probability of death for a NGT subject in the lifestyle arm	1-exp(-mort_L_1A [Age+_stage])	-
pDie_L_I_1A: probability of death for an IGT subject in the lifestyle arm	1-exp(-mort_L_1A [Age+_stage]*HR_I_mort_1A)	-
pDie_L_T_1A: probability of death for a T2DM subject in the lifestyle arm	1-exp(-mort_L_1A [Age+_stage]*HR_T_mort_1A)	-
cSC_1A: Cost of screening	$139	f
cINT_pl-1A[Age+_stage]: cost of intervention for placebo arm	Values for first-three cycles: $43, $18, $18, and the $0	f
cINT_L_1A:[Age+_stage] cost of intervention for lifestyle arm	Values for first-three cycles: $1,399, $679, and $702, and then $0	f
cNGT_1A[Age+_stage]: direct medical costs (cost for a subject with NGT)	$1,100 for the first-three cycles, and then $2,688	g,h
CM_I_1A: cost multiplier of IGT in 1A	Triangular distribution of 1.35, 1.48, and 1.79	g
CM_T_1A: cost multiplier of T2DM in 1A	Triangular distribution of 2.03, 2.27, and 2.83	h,I,j
uPl_1A[Age+_stage]; the cycle dependent utilites required for the placebo arm	0.686, 0.675, and 0.657 for the first-three cycles, and then 0.657	k
uLife_1A[Age+_stage]	0.703, 0.695, and 0.692, and then 0.692	k

Sources:
a: Knowler WC, Barrett-Conner E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.
b: Miegs JB, Muller DC, Nathan DM, et al. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of the Aging. *Diabetes*. 2003;52:1475-1484.
c: Saydah SH, Miret M, Sung J, et al. Postchallenge hyperglycemia and mortality in a national sample of U.S. adults. *Diabetes Care*. 2001;24:1397-1402.
d: Saydah SH, Loria CM, Eberhardt MS, et al. Subclinical states of glucose intolerance and risk of death in the U.S. *Diabetes Care*. 2001;24:447-453.
e: Saydah SH, Eberhardt MS, Loria CM, et al. Age and the burdens of death attributable to diabetes in the United States. *American Journal of Epidemiology*. 2002;156:714-719.
f: k: The Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or Metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518-2523
g: Arias E. *United States Life Tables, 2000*. Hyattsville, MD: National Center for Health Statistics, 2002. vol.51,3.
h: Diabetes Prevention Program Research Group. Costs associated with the primary prevention of type 2 diabetes mellitus in the Diabetes Prevention Program. *Diabetes Care*. 2003;26:36-47.
i: Nichols GA, Glauber HS, Brown JB. Type 2 diabetes: incremental medical care costs during the 8 years preceding diagnosis. *Diabetes Care*. 2000;23:1654-1659.
j: Brown JB, Nichols GA, Glauber HS, et al. Type 2 diabetes: incremental medical care costs during the first eight years after diagnosis. *Diabetes Care*. 1999;22:1116-1124.
k: American Diabetes Association. Economic costs of diabetes in the US. In 2002. *Diabetes Care*. 2003;26:917-932.
l: Ramsey S, Summers K, Leong SA, et al. Productivity and medical costs of diabetes in a large employer population. *Diabetes Care*. 2002;25:23-29.

Model 1A Submodel Input Data for BMI Subcategory of ≥ 35 kg/m^2 (Including Equations for Lifetime and Three-Year Effect)

Variable with Description (Specific Variable Names are in Bold Font)	Value	Reference
Age: start age of cohort	50 years	a
Progression from IGT to T2DM in placebo arm	0.1332	a
Reversion from IGT to NGT in placebo arm	0.0567	a
Progression from NGT to IGT in placebo arm	0.0767	b
Progression from IGT to T2DM in lifestyle arm	0.0704	a
Progression from IGT to NGT in lifestyle arm	0.0853	a
Progression from NGT to IGT in lifestyle arm	0.0465	b
pIGT_T_Life_1A[Age+_stage]: probability of progression from IGT to T2DM for the lifestyle arm (three-year duration of effect)	0.0704 for the first-three cycles, and then 0.1332	-
pIGT_N_Life_1A[Age+_stage]: probability of progression from IGT to NGT for the lifestyle arm (three-year duration of effect)	0.0853 for the first-three cycles, and then 0.0567	-
pNGT_IGT_L_1A[Age+_stage]: probability of progressing from NGT to IGT for the lifestyle arm (three-year duration of effect)	0.0465 for the first-three cycles, and then 0.0767	-
Hazard ratio of mortality for NGT	none	-
HR_I_mort_1A: hazard ratio of mortality for IGT	Triangular distribution of 0.8, 1.1, and 1.6	c
HR_T_mort_1A: hazard ratio of mortality for T2DM	Triangular distribution of 1.4, 1.9, and 2.5	d,e

mort_Pl_1A[Age+_stage]: mortality rates for the placebo arm	0.0017 for the first-three cycles, and then reverts to U.S. Life Tables	-
mort_L_1A[Age+_stage]: mortality rates for the lifestyle arm	0.0010 for the first-three cycles, and then reverts to the U.S. Life Tables	-
pDie_Pl_NGT_1A: probability of death for a NGT subject in the placebo arm	1-exp(-mort_Pl_1A [Age+_stage])	-
pDie_Pl_IGT_1A: probability of death for an IGT subject in the placebo arm	1-exp(-mort_Pl_1A [Age+_stage]*HR_I_mort_1A)	-
pDie_Pl_T_1A: probability of death for a T2DM subject in the placebo arm	1-exp(-mort_Pl_1A [Age+_stage]*HR_T_mort_1A	-
pDie_L_NGT_1A: probability of death for a NGT subject in the lifestyle arm	1-exp(-mort_L_1A [Age+_stage])	-
pDie_L_I_1A: probability of death for an IGT subject in the lifestyle arm	1-exp(-mort_L_1A [Age+_stage]*HR_I_mort_1A)	-
pDie_L_T_1A: probability of death for a T2DM subject in the lifestyle arm	1-exp(-mort_L_1A [Age+_stage]*HR_T_mort_1A)	-
cSC_1A: Cost of screening	$139	f
cINT_pl-1A[Age+_stage]: cost of intervention for placebo arm	Values for first-three cycles: $43, $18, $18, and the $0	f
cINT_L_1A:[Age+_stage] cost of intervention for lifestyle arm	Values for first-three cycles: $1,399, $679, and $702, and then $0	f
cNGT_1A[Age+_stage]: direct medical costs (cost for a subject with NGT)	$1,100 for the first-three cycles, and then $2,688	g,h
CM_I_1A: cost multiplier of IGT in 1A	Triangular distribution of 1.35, 1.48, and 1.79	g
CM_T_1A: cost multiplier of T2DM in 1A	Triangular distribution of 2.03, 2.27, and 2.83	h,I,j
uPl_1A[Age+_stage]; the cycle dependent utilites required for the placebo arm	0.686, 0.675, and 0.657 for the first-three cycles, and then 0.657	k
uLife_1A[Age+_stage]	0.703, 0.695, and 0.692, and then 0.692	k

Sources:
a: Knowler WC, Barrett-Conner E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.
b: Miegs JB, Muller DC, Nathan DM, et al. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of the Aging. *Diabetes*. 2003;52:1475-1484.
c: Saydah SH, Miret M, Sung J, et al. Postchallenge hyperglycemia and mortality in a national sample of U.S. adults. *Diabetes Care*. 2001;24:1397-1402.
d: Saydah SH, Loria CM, Eberhardt MS, et al. Subclinical states of glucose intolerance and risk of death in the U.S. *Diabetes Care*. 2001;24:447-453.
e: Saydah SH, Eberhardt MS, Loria CM, et al. Age and the burdens of death attributable to diabetes in the United States. *American Journal of Epidemiology*. 2002;156:714-719.
f: k: The Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or Metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518-2523
g: Arias E. *United States Life Tables, 2000*. Hyattsville, MD: National Center for Health Statistics, 2002. vol.51,3.
h: Diabetes Prevention Program Research Group. Costs associated with the primary prevention of type 2 diabetes mellitus in the Diabetes Prevention Program. *Diabetes Care*. 2003;26:36-47.
i: Nichols GA, Glauber HS, Brown JB. Type 2 diabetes: incremental medical care costs during the 8 years preceding diagnosis. *Diabetes Care*. 2000;23:1654-1659.
j: Brown JB, Nichols GA, Glauber HS, et al. Type 2 diabetes: incremental medical care costs during the first eight years after diagnosis. *Diabetes Care*. 1999;22:1116-1124.
k: American Diabetes Association. Economic costs of diabetes in the US. In 2002. *Diabetes Care*. 2003;26:917-932.
l: Ramsey S, Summers K, Leong SA, et al. Productivity and medical costs of diabetes in a large employer population. *Diabetes Care*. 2002;25:23-29.

Model 1B Data Input (Including Equations for Lifetime and Three-Year Effect)

Variable with Description (Specific Variable Names are in Bold Font)	Value	Reference
Age: start age of cohort	50 years	a
Progression from IGT to T2DM in placebo arm	0.1075	a
Reversion from IGT to NGT in placebo arm	0.0678	a
Progression from NGT to IGT in placebo arm	0.0767	b,c,d
Progression from IGT to T2DM in lifestyle arm	0.0505	a
Progression from IGT to NGT in lifestyle arm	0.1121	a
Progression from NGT to IGT in lifestyle arm	0.0406	b,c,d
pIGT_T_Life_1B[Age+_stage]: probability of progression from IGT to T2DM for the lifestyle arm (three-year duration of effect)	0.0505 for the first-three cycles, and then 0.1075	-
pIGT_N_Life_1B[Age+_stage]: probability of progression from IGT to NGT for the lifestyle arm (three-year duration of effect)	0.1121 for the first-three cycles, and then 0.0678	-
pNGT_IGT_L_1B[Age+_stage]: probability of progressing from NGT to IGT for the lifestyle arm (three-year duration of effect)	0.0406 for the first-three cycles, and then 0.0767	-
HRM_T_1B: hazard ratio of mortality for NGT	2.64	e
HRM_I_1B: hazard ratio of mortality for IGT	1.7	f,g,h
HRM_N_1B: hazard ratio of mortality for T2DM	1.3	f,g,h
mort_pl_1B[Age+_stage]: mortality rates for the placebo arm	0.0017 for the first-three cycles, and then reverts to U.S. Life Tables	i,j

mort_L_1B[Age+_stage]: mortality rates for the lifestyle arm	0.0010 for the first-three cycles, and then reverts to the U.S. Life Tables	i,j
pDie_Pl_N_1B: probability of death for a NGT subject in the placebo arm	1-exp(-mort_pl_1B [Age+_stage]*HRM_N_1B)	-
pDie_Pl_I_1B: probability of death for an IGT subject in the placebo arm	1-exp(-mort_pl_1B [Age+_stage]*HRM_I_1B)	-
pDie_Pl_T_1B: probability of death for a T2DM subject in the placebo arm	1-exp(-mort_pl_1B [Age+ stage]*HRM T 1B)	-
pDie_L_N_1B: probability of death for a NGT subject in the lifestyle arm	1-exp(-mort_L_1B [Age+_stage]*HMR_N_1B)	-
pDie_L_I_1B: probability of death for an IGT subject in the lifestyle arm	1-exp(-mort_L_1B [Age+_stage]*HRM_I_1B)	-
pDie_L_T_1B: probability of death for a T2DM subject in the lifestyle arm	1-exp(-mort_L_1B [Age+_stage]*HRM_T_1B)	-
cSC_1B: Cost of screening	$139	g
cINT_pl-1B[Age+_stage]: cost of intervention for placebo arm	Values for first-three cycles: $43, $18, $18, and the $0	g
cINT_L_1B:[Age+_stage] cost of intervention for lifestyle arm	Values for first-three cycles: $1,399, $679, and $702, and then $0	g
cNGT_1B[Age+_stage]: direct medical costs (cost for a subject with NGT)	$1,100 for the first-three cycles, and then $2,688	h,i
CM_N_1B: cost multiplier of NGT in 1B	Triangular distribution of 1.02, 1.34, and 1.74	j
CM_I_1B: cost multiplier of IGT in 1B	Triangular distribution of 1.35, 1.48, and 1.79	h
CM_T_1A: cost multiplier of T2DM in 1B	Triangular distribution of 2.03, 2.27, and 2.83	i,k,l
uPl_1A[Age+_stage]; the cycle dependent utilities required for the placebo arm	0.686, 0.675, and 0.657 for the first-three cycles, and then 0.657	m
uLife_1A[Age+_stage]	0.703, 0.695, and 0.692, and then 0.692	m

Sources:
a: Knowler WC, Barrett-Conner E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.
b: Weyer C, Tataranni PA, Bogardus C, et al. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening glucose tolerance during each stage of type 2 diabetes development. *Diabetes Care*.2001;24:89-94.
c: Edelstein SI, Knowler WC, Bain RP, et al. Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. *Diabetes*. 1997;46:701-710.
d: Meigs, JB, Mueller DC, Nathan DM, et al. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of the Aging. *Diabetes*. 2003;52:1475-1484.
e: Rogers RG, Hummer RA, Krueger PM. The effect of obesity on overall, circulatory disease, and diabetes-specific mortality. *Journal of Biosocial Science*. 2003;35:107-129.
f: Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women. *New England Journal of Medicine*. 1995;333:677-685.
g: Peeters A, Barendregt JJ, Willekens F, et al. Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Annals of Internal Medicine*. 2003;138:24-32.
h: Calle EE, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of U.S. adults. *New England Journal of Medicine*. 1999;341:1097-1105.
i: The Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or Metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518-2523.
j: Arias E. *United States Life Tables, 2000*. Hyattsville, MD: National Center for Health Statistics, 2002. vol.51,3.
k: Diabetes Prevention Program Research Group. Costs associated with the primary prevention of type 2 diabetes mellitus in the Diabetes Prevention Program. *Diabetes Care*. 2003;26:36-47.
l: Nichols GA, Glauber HS, Brown JB. Type 2 diabetes: incremental medical care costs during the 8 years preceding diagnosis. *Diabetes Care*. 2000;23:1654-1659.
m: Brown JB, Nichols GA, Glauber HS, et al. Type 2 diabetes: incremental medical care costs during the first eight years after diagnosis. *Diabetes Care*. 1999;22:1116-1124.
n: Thompson D, Brown JB, Nichols GA, et al. Body mass index and future healthcare costs: a retrospective cohort study. *Obesity Research*.2001;9:210-218.
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: Ramsey S, Summers K, Leong SA, et al. Productivity and medical costs of diabetes in a large employer population. *Diabetes Care*. 2002;25:23-29.

APPENDIX 3

Model 2A Data Input (Including Equations for Lifetime and Three-Year Effect)

Variable with Description (Specific Variable Names are in Bold Font)	Value	Reference
Age: start age of cohort	50 years	a
Progression from IGT to T2DM in placebo arm	0.1075	a
Reversion from IGT to NGT in placebo arm	0.0678	a
Progression from NGT to IGT in placebo arm	0.0767	b,c,d
Progression from IGT to T2DM in lifestyle arm	0.0505	a
Progression from IGT to NGT in lifestyle arm	0.1121	a
Progression from NGT to IGT in lifestyle arm	0.0406	b,c,d
pIGT_T_Life_2A[Age+_stage]: probability of progression from IGT to T2DM for the lifestyle arm (three-year duration of effect)	0.0505 for the first-three cycles, and then 0.1075	-
pIGT_N_Life_2A[Age+_stage]: probability of progression from IGT to NGT for the lifestyle arm (three-year duration of effect)	0.1121 for the first-three cycles, and then 0.0678	-
pNGT_IGT_L_1A[Age+_stage]: probability of progressing from NGT to IGT for the lifestyle arm (three-year duration of effect)	0.0406 for the first-three cycles, and then 0.0767	-
Hazard ratio of mortality for NGT	none	-
HRI_mort_2A: hazard ratio of mortality for IGT	Triangular distribution of 0.8, 1.1, and 1.6	e
HRT_mort_2A: hazard ratio of mortality for T2DM	Triangular distribution of 1.4, 1.9, and 2.5	f,g

mort_2A[Age+_stage]: mortality rates for the placebo arm	U.S. Life Table Values for the year 2000	f
pDie_NGT_2A: probability of death for a NGT subject in the placebo and the lifestyle arms	1-exp(-mort_2A [Age+_stage])	-
pDie_IGT_2A: probability of death for an IGT subject in the placebo arm	1-exp(-mort_2A [Age+_stage]*HRI_mort_2A)	-
pDie_T2DM_2A: probability of death for a T2DM subject in the placebo and lifestyle arms	1-exp(-mort_Pl_1A [Age+_stage]*HR_T_mort_1A	-
cSC_1A: Cost of screening	$139	f
cINT_pl-1A[Age+_stage]: cost of intervention for placebo arm	Values for first-three cycles: $43, $18, $18, and the $0	f
cINT_L_1A:[Age+_stage] cost of intervention for lifestyle arm	Values for first-three cycles: $1,399, $679, and $702, and then $0	f
cNGT: direct medical costs (cost for a subject with NGT)	$2,688 or $3,968	g,h,i
CM_I_2A: cost multiplier of IGT in 2A	Triangular distribution of 1.35, 1.48, and 1.79	g
CM_T_2A: cost multiplier of T2DM in 2A	Triangular distribution of 2.03, 2.27, and 2.83	h,i,j
uLife_2A	0.692	k
uPl_2A	0.657	k
pT2DM_IGT[Age+_stage]:probability of reversion from T2DM to IGT	0.20 for the first cycle, and then 0.00	l,m

Sources:

a:Knowler WC, Barrett-Conner E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.
b: Weyer C, Tataranni PA, Bogardus C, et al. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening glucose tolerance during each stage of type 2 diabetes development. *Diabetes Care*. 2001;24:89-94.
c: Edelstein SI, Knowler WC, Bain RP, et al. Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. *Diabetes*. 1997;46:701-710.
d: Meigs, JB, Mueller DC, Nathan DM, et al. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of the Aging. *Diabetes*. 2003;52:1475-1484.
e: Saydah SH, Miret M, Sung J, et al. Postchallenge hyperglycemia and mortality in a national sample of U.S. adults. *Diabetes Care*. 2001;24:1397-1402.
f: Saydah SH, Loria CM, Eberhardt MS, et al. Subclinical states of glucose intolerance and risk of death in the U.S. *Diabetes Care*. 2001;24:447-453.
g: Saydah SH, Eberhardt MS, Loria CM, et al. Age and the burdens of death attributable to diabetes in the United States. *American Journal of Epidemiology*. 2002;156:714-719.

f: Arias E. *United States Life Tables,2000*.Hyattsville, MD: National Center for Health Statistics; 2002. vol. 51;3.
h: The Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or Metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518-2523.
i: Arias E. *United States Life Tables, 2000*. Hyattsville, MD: National Center for Health Statistics, 2002. vol.51,3.
j: Diabetes Prevention Program Research Group. Costs associated with the primary prevention of type 2 diabetes mellitus in the Diabetes Prevention Program. *Diabetes Care*. 2003;26:36-47.
k: Nichols GA, Glauber HS, Brown JB. Type 2 diabetes: incremental medical care costs during the 8 years preceding diagnosis. *Diabetes Care*. 2000;23:1654-1659.
l: Brown JB, Nichols GA, Glauber HS, et al. Type 2 diabetes: incremental medical care costs during the first eight years after diagnosis. *Diabetes Care*. 1999;22:1116-1124.
m: American Diabetes Association. Economic costs of diabetes in the US. in 2002. *Diabetes Care*. 2003;26:917-932.
n: Ramsey S, Summers K, Leong SA, et al. Productivity and medical costs of diabetes in a large employer population. *Diabetes Care*. 2002;25:23-29.
o: Pascale RW, Wing RR, Butler BA, et al. Effects of a behavioral weight loss program stressing calorie restrictions versus calorie restriction versus calorie plus fat restriction in obese individuals with NIDDM or a family history of diabetes. *Diabetes Care*. 1995;18:1241-1248.
p: Wing RR, Koeske R, Epstein LH, et al. Long-term effects of modest weight loss on type II diabetic patients. *Archives of Internal Medicine*. 147:1749-1753.

Model 2B Data Input (Including Equations for Lifetime and Three-Year Effect)

Variable with Description (Specific Variable Names are in Bold Font)	Value	Reference
Age: start age of cohort	50 years	a
Progression from IGT to T2DM in placebo arm	0.1075	a
Reversion from IGT to NGT in placebo arm	0.0678	a
Progression from NGT to IGT in placebo arm	0.0767	b,c,d
Progression from IGT to T2DM in lifestyle arm	0.0505	a
Progression from IGT to NGT in lifestyle arm	0.1121	a
Progression from NGT to IGT in lifestyle arm	0.0406	b,c,d
pIGT_T_Life_2B[Age+_stage]: probability of progression from IGT to T2DM for the lifestyle arm (three-year duration of effect)	0.0505 for the first-three cycles, and then 0.1075	-
pIGT_N_Life_2B[Age+_stage]: probability of progression from IGT to NGT for the lifestyle arm (three-year duration of effect)	0.1121 for the first-three cycles, and then 0.0678	-
pNGT_IGT_L_1B[Age+_stage]: probability of progressing from NGT to IGT for the lifestyle arm (three-year duration of effect)	0.0406 for the first-three cycles, and then 0.0767	-
Hazard ratio of mortality for NGT	none	-
HRI_mort_2B: hazard ratio of mortality for IGT	Triangular distribution of 0.8, 1.1, and 1.6	e
HRT_mort_2B: hazard ratio of mortality for T2DM	2.64	f

mort_2B[Age+_stage]: mortality rates for the placebo arm	U.S. Life Table Values for the year 2000	e
pDie_NGT_2B: probability of death for a NGT subject in the placebo and the lifestyle arms	1-exp(-mort_2B [Age+_stage])	-
pDie_IGT_2B: probability of death for an IGT subject in the placebo arm	1-exp(-mort_2B [Age+_stage]*HRI_mort_2B)	-
pDie_T2DM_2B: probability of death for a T2DM subject in the placebo and lifestyle arms	1-exp(-mort_Pl_1B [Age+_stage]*HR_T_mort_1B	-
cSC_1A: Cost of screening	$139	f
cINT_pl-1B[Age+_stage]: cost of intervention for placebo arm	Values for first-three cycles: $43, $18, $18, and the $0	f
cINT_L_1A:[Age+_stage] cost of intervention for lifestyle arm	Values for first-three cycles: $1,399, $679, and $702, and then $0	f
cNGT: direct medical costs (cost for a subject with NGT)	$2,688 or $3,968	g,h,i
CM_N_2B	1.02, 1.34, and 1.74	j
CM_I_2B: cost multiplier of IGT in 2B	Triangular distribution of 1.35, 1.48, and 1.79	g
CM_T_2B: cost multiplier of T2DM in 2B	Triangular distribution of 2.03, 2.27, and 2.83	h,i,k
uLife_2B	0.692	l
uPl_2B	0.657	l
pT2DM_IGT[Age+_stage]:probability of reversion from T2DM to IGT	0.20 for the first cycle, and then 0.00	m,n

a: Knowler WC, Barrett-Conner E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;346:393-403.
b: Weyer C, Tataranni PA, Bogardus C, et al. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening glucose tolerance during each stage of type 2 diabetes development. *Diabetes Care*. 2001;24:89-94.
c: Edelstein SI, Knowler WC, Bain RP, et al. Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. *Diabetes*. 1997;46:701-710.
d: Meigs, JB, Mueller DC, Nathan DM, et al. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of the Aging. *Diabetes*. 2003;52:1475-1484.
e: Saydah SH, Miret M, Sung J, et al. Postchallenge hyperglycemia and mortality in a national sample of U.S. adults. *Diabetes Care*. 2001;24:1397-1402.
f: Rogers RG, Hummer RA, Krueger PM. The effect of obesity on overall, circulatory disease, and diabetes-specific mortality. *Journal of Biosocial Science*. 2003;35:107-129.
g: Arias E. *United States Life Tables, 2000*. Hyattsville, MD: National Center for Health Statistics, 2002. vol.51,3.
h: Diabetes Prevention Program Research Group. Costs associated with the primary prevention of type 2 diabetes mellitus in the Diabetes Prevention Program. *Diabetes Care*. 2003;26:36-47.

i: Nichols GA, Glauber HS, Brown JB. Type 2 diabetes: incremental medical care costs during the 8 years preceding diagnosis. *Diabetes Care*. 2000;23:1654-1659.
j: Brown JB, Nichols GA, Glauber HS, et al. Type 2 diabetes: incremental medical care costs during the first eight years after diagnosis. *Diabetes Care*. 1999;22:1116-1124.
k: American Diabetes Association. Economic costs of diabetes in the US. In 2002. *Diabetes Care*. 2003;26:917-932.
l: Thompson D, Brown JB, Nichols GA, et al. Body mass index and future healthcare costs: a retrospective cohort study. *Obesity Research*. 2001;9:210-218.
l: Ramsey S, Summers K, Leong SA, et al. Productivity and medical costs of diabetes in a large employer population. *Diabetes Care*. 2002;25:23-29.
m: The Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or Metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518-2523.
n: Pascale RW, Wing RR, Butler BA, et al. Effects of a behavioral weight loss program stressing calorie restrictions versus calorie restriction versus calorie plus fat restriction in obese individuals with NIDDM or a family history of diabetes. *Diabetes Care*. 1995;18:1241-1248.
o: Wing RR, Koeske R, Epstein LH, et al. Long-term effects of modest weight loss on type II diabetic patients. *Archives of Internal Medicine*. 147:1749-1753.

APPENDIX 4:
Explicit Assumptions Made in the Dissertation Analysis Over and Above Those Noted in Appendix 2 and Appendix 3

1) A subject does not progress from NGT to T2DM in any of the Markov models.
2) A subject does not revert from T2DM to IGT in any of the Markov models. A sensitivity analysis is performed inserting this reversion probability into Model 2A and Model 2B (see Section 5.4.5).
3) The upper and lower ranges of the intervention effect are a three-year and lifetime duration.
4) Progression from NGT to IGT is assumed to be similar to that found in the Pima Indian Study in all models but the Model 1A submodel based on a BMI subcategory of 30 kg/m^2 to < 35 kg/m^2 (see Section 4.3).
5) A lower transition probability from NGT to IGT (0.0602) based on Meigs et al. data is used for the submodel of Model 1A based on a BMI subcategory of 30 kg/m^2 to < 35 kg/m^2. [442]
6) The control cost of illness for Model 1A and Model 1B is assumed to be $2,688 based on Kaiser Permanente research (see Section 4.3.1.1.1).).[443, 444]
7) The transition from IGT to NGT in the Model 1A submodels based on BMI subcategory was based on the percentage difference in rate of progression from IGT to T2DM for the overall cohort versus that of the specific subcategory (the value of the percent-

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442 Weyer C, Tataranni P, Bogardus C, et al. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of type 2 diabetes development. *Diabetes Care*. 2001;24(1):89-94.

443 Meigs JB, Muller DC, Nathan DM, et al. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of the Aging. *Diabetes*. 2003;52:1475-1484.

445 Nichols GA, Glauber HS, Brown JB. Type 2 diabetes: incremental medical care costs during the 8 years preceding diagnosis. *Diabetes Care*. 2000;23:1654-1659.

age change is applied to the original value for the DPP cohort: see Section 4.3.1.4.1).

8) The transition from NGT to IGT in the Model 1A submodels based on BMI subcategory was also altered in the models using the above methodology (see Section 4.3.1.4.1).

9) The treatment effect of the intervention in Model 2A and 2B, the more "generalized" models is assumed to be the same as that found in the DPP. The concern is that there were multiple healthcare exclusions found in the study design of the DPP, and the intervention may not have the same effect in subjects without these exclusions.

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Vita

Suzanne Novak is a native Houstonian. After graduating from Rice University with a B.A. in Biology, she went on to San Antonio, where she graduated with a M.D. degree from the University of Texas Health Science Center at San Antonio Medical School. She continued her training there, completing an Internal Medicine Internship and an Anesthesia Residency. She is Board Certified in Anesthesiology.

After practicing medicine for ten years in Central Texas, she spent several years raising her "blended family." This time period also involved intensive volunteer work for fine arts groups in the Austin area. In 1999 she returned to school, where she entered the Option II MBA program at the University of Texas at Austin. After completing one year in this program, she transferred into the Pharmacy Administration program in order to complete her Ph.D. degree.

Dr. Novak's future plans involve applying the knowledge gained by completing this dissertation to aid in building diabetes prevention programs in the Central Texas area.

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