DETERMINING THE CLINICAL AND ECONOMIC IMPACT OF INTENSIVE WEIGHT-LOSS MANAGEMENT IN ADULTS WITH SEVERE OBESITY USING A MARKOV MICROSIMULATION MODEL

by
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Abstract

Background: Obesity continues to remain a major public health concern. Designing appropriate policies and interventions to address this complex problem has been extraordinarily challenging, and could benefit from innovative means of modeling the likely impact of potential interventions. Because of the high morbidity, mortality, and cost from obesity and associated illness, policymakers and the public have been interested in understanding how these costs will change over time and how new policies may alter these trends in costs. The goal of the thesis is to develop a computational model that can be used to predict the health and economic consequences of obesity weight loss interventions.

Methods: In this proposal we will take a systematic, multi-factor approach to modeling obesity and obesity-related health outcomes by predicting progression across BMI and associated health states. We developed a Markov simulation model to determine the cost-benefits and cost-effectiveness for a severely obese adult getting bariatric surgery and Pharmacotherapy versus standard care (diet, physical activity, and behavioral modification) from the third-party payer, employers and societal perspective.

Findings: Gastric banding and gastric bypass are cost-effective options for weight loss in a severely obese patient across a broad range of health risk states. Qsymia based intensive weight loss plans are more cost effective over the life time than non-surgical

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management in all obese individuals. Age of patient and obesity-associated health risk at time of interventions had the largest impact on cost-effectiveness outcomes. Furthermore, both bariatric surgery and weight loss pharmacotherapy are cost-effective weight loss treatment options in patients with T2DM and help reduce overall complication over the lifetime.

Conclusion: As this has not previously been achieved the thesis work presents high gain potential, though, since achieving the proposed objectives could positively impact future means of intervening at the policy and/or clinical levels to prevent and control obesity, and thus its health, economic, and other consequences. Third-party payers and employers would benefit from assessing economic value from weight loss inteventions by incorporating savings from both immediate weight change after procedures and downstream obesity-associated health outcomes.

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Background and Significance

CAPTURING OBESITY BURDEN OVER TIME

The obesity epidemic is a growing global problem. In the US, where currently ~36% of adults are overweight or obese, with a continuing rising trend, it poses a considerable burden to individuals, society and third party payers [1]. The most common health consequences of obesity include cardiovascular diseases, type-2 diabetes, musculoskeletal disorders, and many cancers [2-4]. In addition to these health outcomes, there is a direct link between obesity and reduced Health-Related Quality of Life (QoL), and self-esteem [4,5]. The economic impact of overweight and obesity is staggering as well, notably from increased health-care costs and lost productivity. Finkelstein and colleagues have shown that obese patients incur 46% more in inpatient costs as compared with normal-weight individuals, including 27% more physician visits and and 80% more spending on medications [6,7]. These cost are further saddled by the cost obesity-associated illness; annual cost of diabetes in medical expenditures and lost productivity estimated at $174 billion in 2007 and direct and indirect cost of cardiovascular disease estimated to be $403.1 billion in 2006 [8-10]. National health-care costs attributable to obesity/overweight alone have been estimated to rise to 860.7–956.9 billion US dollars by 2030, accounting for 16–18% of total US health-care costs [11]. As the population ages and both government and businesses increase the amount they spend on healthcare,

obesity and obesity-associated illness will be an even larger economic burden on the private and public sectors [12,13].

Because of the high morbidity, mortality, and cost from obesity and associated illness, policymakers and the public have been interested in understanding how these costs will change over time and how new policies may alter these trends in costs. Policymakers already are also keenly interested in developing and pursuing policies that can prevent this expected rise in burden. While it is clear that there is evidence of the need for effective strategies to curb the adverse outcomes linked to being overweight and obese, there are numerous associated factors that affect the eventual sustainability of these strategies. Furthermore, there is gap in in capturing the varied health factors associated with obesity.

PLANNING WEIGHT CONTROL INTERVENTIONS

Lifestyle interventions based on a combination of diet and physical activity, accompanied by strategies to support behavioral changes, form the cornerstones of obesity treatment. Pharmacotherapy and surgery are further options in selected cases. Weight management has been shown to improve the cardiovascular risk factors linked to obesity [14,15], including reduction in blood pressure, improved glycemic control, improved health status and other obesity-related co-morbid conditions [16].

There is a shortage of evidence-based treatment guidelines for severe obesity. Pharmacotherapy based weight loss programs are broadly available to the general public, providing structured recommendations and these programs represent a multimillion dollar industry [17]. Even as studies are establishing effectiveness, it is important to capture the impact of varying diets and physical activity regimes on the long term progression of health state and costs associated with varying plans.

While bariatric surgery generally have shown to have large, sustained weight loss and can dramatically improve some comorbid conditions, notably diabetes, the long-term health effects are not fully understood [18]. Although evidence from randomized trials does not go beyond two years, a few rigorous observational studies have shown encouraging results, including improvement in long term survival[19,20]. Emerging data from observational studies also show that some procedures are associated with a greater long term risk and nutritional deficiencies [21].

Increased research that examines differences in long term outcomes across various therapies (drugs and surgery) in heterogeneous patient populations are needed. This will help identify those who are most likely to benefit from pharmacotherapy and surgical interventions. Given the uncertainties associted with the long term trade-offs between the risks and benefits of surgery, the decision for various weight-loss interventions would benefit greatly from a clinical decision planning model.

USING A SYSTEMS APPROACH TO ENHANCE EXISTING METHODOLOGY

It has been recommended integrating obesity-related severity of disease and the presence of co-morbidities to stratify patients based on risk, as well as aid in the identification and prioritization of patients who would most likely benefit from resource-intensive weight management interventions [22]. Unfortunately, these complex interactions surrounding the obesity problem are not accounted for adequately within our current prevention and treatment models. The ability to predict progression across obesity-related health states across the lifespan requires models that take into account the dynamically-changing populations that interact at both the macro (societal, environmental, physical activity exposure) and micro scales (within- and between-individuals). Retrospective and even prospective epidemiologic and clinical studies alone do not fully capture and characterize such complex interactions. Testing interventions without first forecasting their impact can be prohibitively expensive, waste valuable time and effort, and potentially result in unanticipated adverse consequences.

A 'systems approach' implies that the dynamics and behavior of the system are different, qualitatively, than the sum of its parts. Thus, a systems approach not only allows researchers and ultimately policy makers and practitioners to contextualize the issues at hand, but also to anticipate the consequences of potential modifications, and identify points of leverage. Comprehensive computational models can help identify for practitioners and policy makers' decision points linked to optimum strategies, as well as

help elucidate interventions' potential secondary effects, and unintended adverse consequences. For example, vigorous physical activity interventions could actually lead to overeating and weight gain when diet is not adequately controlled and healthful foods are not readily available. Similarly, potential decreases in energy intake (e.g. by specific dietary improvements, or changes in dietary energy density) tend to be compensated for in whole or in part by substitution of other food choices and/or increases in portion size.

INNOVATION

While studies [23] have attempted to capture obesity-associated economic costs , burden of disease, and cost of illness these studies don't:

(1) Capture the progressive change in obesity status and health risk over time dynamically;

(2) Prioritize of strategies for the prevention and treatment based on individual risk and;

(3) Assess the impact of changing in obesity risk states on survival, disease progression, associated complications, comorbidities, quality of life, and cost.

In this proposal we will take a systematic, multi-factor approach to modeling obesity and obesity-related health outcomes by predicting progression across BMI and associated health states. Currently, there is a dearth of tools for simulating progression of obesity risk states across the lifespan, and for simulating the impacts of different strategies at

varied stages in the progression of weight change across the lifespan [24,25]. As a result, interventions and management protocols are often designed and implemented without fully realizing their multi-level impacts.

We propose to construct a Markov simulation model of obesity progression to estimate the long-term clinical and cost effectiveness of intensive weight management techniques (bariatric surgery and pharmacotherapy) applied to obese US adults. We expect the results of our model to have a two-fold impact:

1. Help guide physicians and patients to make inferences about future economic, quality of life, and health outcomes linked to obesity.
2. Provide critical data for third-party payers and policymakers to make informed and effective decisions.

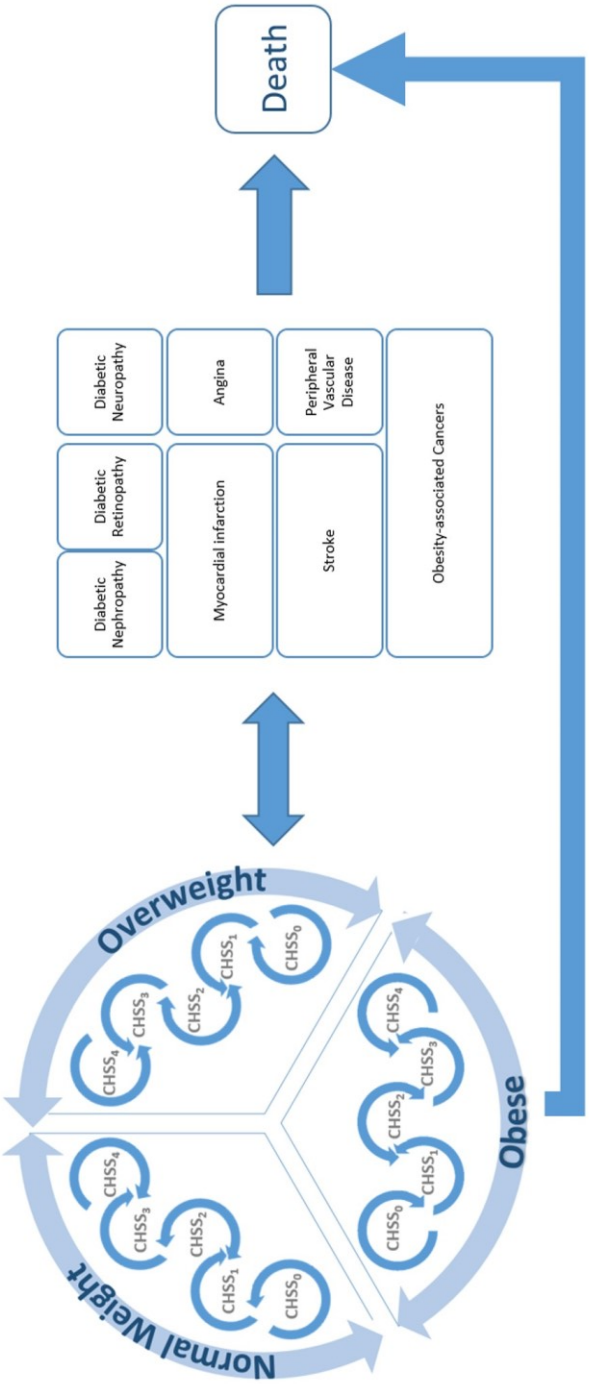
Specific Aims

Specific Aim 1 (SA1): Determine the cost-effectiveness of *bariatric surgery (BS)* on severely obese adults in the United States.

Specific Aim 2 (SA2): Determine the cost-effectiveness of *long-term pharmacotherapy* on severely obese adults in the United States.

Specific Aim 3 (SA3): Determine the clinical effectiveness and cost-effectiveness of intensive weight loss management (BS and pharmacotherapy) in severely obese adults with *significant baseline comorbidity (Type 2 diabetes)*

Concept Structure (Figure 1)



Experimental Design

OVERALL STRATEGY

The conceptual framework shown in Figure 1 describes the hypothesized obesity health trends. Obesity associated health states and complications (Boxes 1 and 3) are well reviewed in literature but the transitions between these elements (Box 2) and the feedback loops over time, altering health states and complications linked to Obesity, are poorly understood.

In this proposal, I will be laying the groundwork for the development and calibration of an individual level simulation model to evaluate and predict health burdens and the costs associated with obesity and associated diseases. This proposal will first establish the predictive simulation model to examine how obesity related costs will change over time (SA 1,2) and next test how new policies may alter these trends will be key to providing the information necessary to making individual0centeric, evidenced-based decisions (SA 3).

USING MARKOV MODELS

Conventional decision trees are unable to capture the complexity of obesity related health states and may require unrealistic simplifying assumptions. I believe the most appropriate approach is to create a state-transition or Markov model, a form of decision

analytic modeling used widely in health service research, and in economic evaluation in particular [26]. Markov models represent events that repeat over time. We allow for the time steps in the model to look at the varying probabilities and utilities to represent an accurate clinical setting that involve health factors [27,28]. By employing a Markov model structure to simulate obesity progression and using a Monte Carlo simulation of individual patients it extends beyond disease-oriented cohort models [29,30]. It also puts emphasis on obesity as well as obesity-associated risk states. Third, the Markov structure also allows the model to model interactions and dependencies between different progression paths that provide a richer description of obesity progression. To account for progression of disease, severity and comorbidity risk profiles we opted to use a Monte Carlo simulation to determine the prognoses of a large number of individual patients (instead of a hypothetical cohort of patients).

BEYOND ANTHROPOMETRIC MEASURES

Anthropometric classification of weight status (BMI, weight circumference) have been key in defining the progression of obesity and its link to population morbidity and mortality [31-33]. While obesity classification systems accurately capture weight changes, prior systems fail to capture the extent of co-morbid conditions, risk factors and health status at the individual level: data that is needed to make effective treatment decisions. The current anthropometric classification is also limited in estimating impairments in

QoL, and whether or not the patient's health would indeed improve with obesity treatment [22,34].

To accurately assess the health burden associated with obesogenic states over time we not only have to capture the health burden associated with the progression of obesity over time but also at the linked health risk states and outcomes. A simple obesity based model would not suffice. To this end, I have developed an innovative obesity risk staging system that look at functional states of obesity, their complications, risk factors and comorbidities as a series of discrete health states that represent the progression of severity of health risk. (FIGURE 2). Figure 1 describes a preliminary model of the staging system which we call "Chronic Health Staging System" (CHS).

Figure 2: Chronic Health Staging System (CHS)

TABLE 1	CHSS Stage 0	CHSS Stage 1	CHSS Stage 2	CHSS Stage 3	CHSS Stage 4
	Metabolic Healthy	(one or more of the following)	Prediabetes (AND) any one of CVD high risk factors	History of Diabetes (OR) one or more of CVD high risk factors	History of Di (Ctrl) one or more c factors
Fasting glucose (mmol/L)	< 100	100-126	100-126	>=126 or self-report of diabetes or self-report of treatment with insulin or antidiabetic agents	>=126 or self-report of diabetes or self-report of treatment with insulin or antidiabetic agents
Blood pressure (mm Hg)	BP < 130/85 with no self-report of hypertension or antihypertensive drug treatment.	SBP >=130 or DBP >=85	SBP >=130 or DBP >=85	(SBP >=140 or DBP >=90) OR Self-report of hypertension or treatment antihypertensive drugs.	(SBP >=140 or DBP >=90) OR Self-report of hypertension or treatment antihypertensive drugs.
HDL cholesterol (mg/dL)	>=60	< 40 mg/dL in men or < 50 mg/dL in women (or receiving drug therapy for reduced HDL-C)	< 40 mg/dL in men or < 50 mg/dL in women (or receiving drug therapy for reduced HDL-C)	< 40 mg/dL in men or < 50 mg/dL in women (or receiving drug therapy for reduced HDL-C)	< 40 mg/dL in men or < 50 mg/dL in women (or receiving drug therapy for reduced HDL-C)
Triglycerides (mg/dL)	<150	150-199	150-199	>=200	>=200
Total cholesterol (mg/dL)	<200	200 - 239	200 - 239	>240	>240
LDL cholesterol (mg/dL)	<130	130 - 159	130 - 159	>160	>160

This process is not new in the clinical space. Multiple other disease conditions record and communicate extent and severity of disease. Examples are the tumor, node, metastasis (TNM) classification system for cancer, and the New York Heart Association functional classification system for heart failure [35]. These systems provide a standardized framework to describe the extent and impact of disease, facilitating communication among health professionals, researchers and payers. Using a similar approach the CHS is formulated from the Edmonton Obesity Staging System (EOSS) and the Cardiometabolic Disease Staging System (CMDS) that have been proposed as functional and disease-related staging for obesity [22,36]. The CHS complements BMI classifications that serve as surrogate measures for the magnitude of body fat, its distribution and to assess progress in treatment and uses relevant parameters to formulate a simple disease-related and functional staging system that provides additional clinical information to guide and evaluate treatment [22,34,36,37]. While the EOSS incorporates assessment of both cardiometabolic disease complications, the CMDS factors in metabolic syndrome and pre-diabetes for a more granular stratification of risk. With the significant variation in risk among patients, both these staging systems have been integrated in CHS to provide a more detailed assessment of obesity's risk over time.

QUANTIFYING CHS RISK (FIGURE 2)

The CHS will derive health risk states scores as an ordinal risk-stratification system based on morbidity and health-risk profile. We will incorporate three obesity-related

comorbidity variables into creating the scores, notably diabetes, hypertension, dyslipidemia. Figure 2 gives an overview of the cutoffs for each of the comorbidity variables incorporated in the CHS. The cutoffs for each health risk factor are defined based on established guidelines and in reviews with experts [38]. Each comorbidity variable is scored separately based on the cutoffs (Appendix 1) resulting in different combinations scores for each CHS state. The CHS state is then assigned to the patent based on the combination of comorbidities they present with. Table A and B in Appendix 1 review the ordinal risk-stratification system and summarize the health states included at each CHS stage.

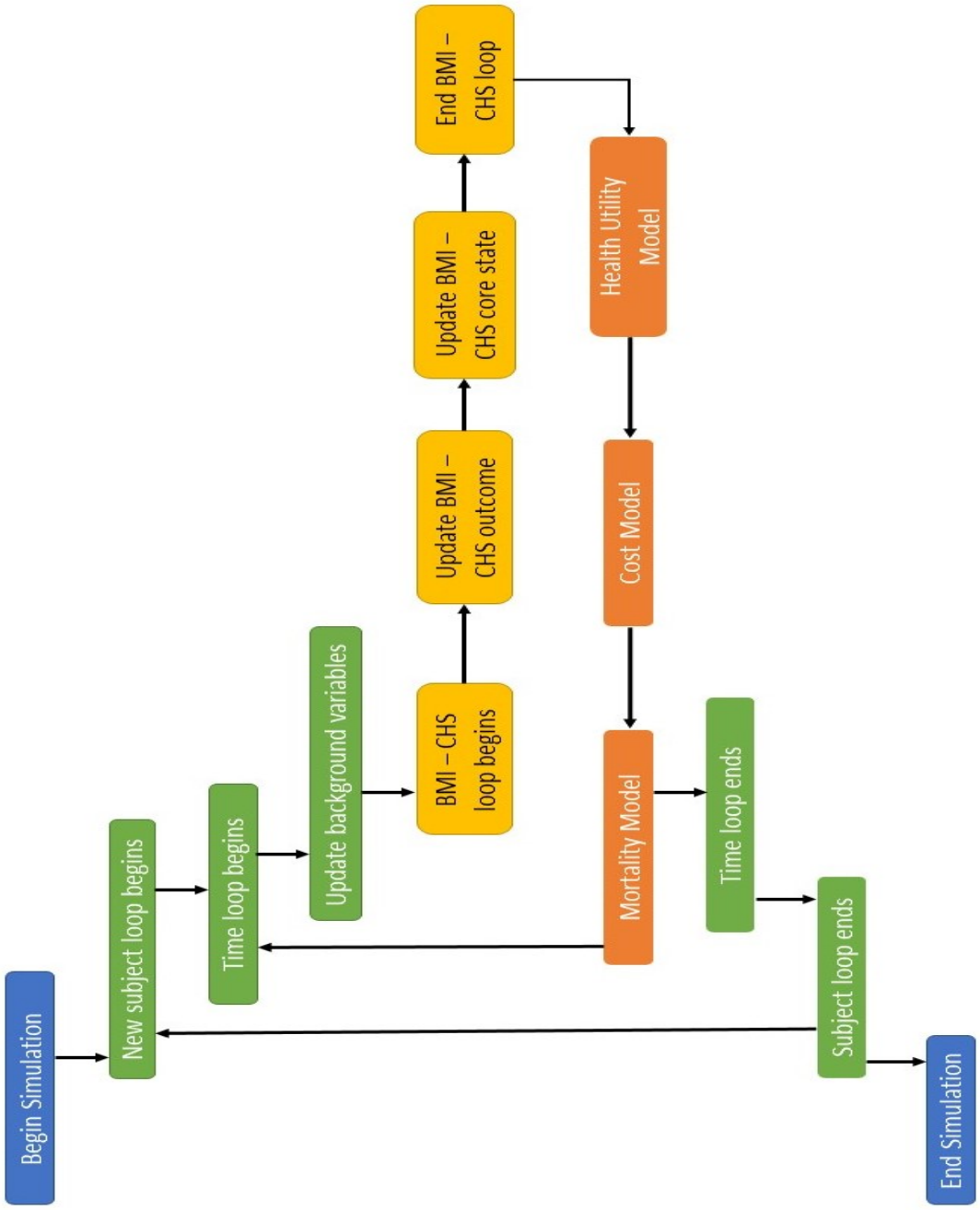
CHS COMPLICATIONS

As stated in the background and significance, an obesity progression model is incomplete without capturing the clinical outcomes resulting from being at obesity-associated risk states. While not looking to model all the outcomes, my proposed model will capture the four main outcomes (based on overall costs and death) associated with obesity, namely Coronary Heart Disease (CHD), stroke, Diabetes complications and Cancers. These individual "sub-models" are developed as standalone Markov models and integrated into the larger core model at each BMI-CHS state. At the start of every cycle, each individual that is alive will be assessed to have the probability of either developing one of the outcomes. If outcomes are present from previous cycle, the individual will remain in the "diseased-state" from a predefined period of time or till death. Costs and utilities will be

adjusted to reflect the burden of being of having these outcomes. Details on the structure of each outcome are elaborated in the following section.

Methods

CONCEPT MODEL STRCUTURE (FIGURE 3)



OVERALL MODEL STRCUTURE

The model will be built using TreeAge software (version Data Professional release 2015; TreeAge Software, Inc., Williamstown, MA) [26,39,40]. As we are building this model (Figure 3) as a Markov state transition model, each state in the model will be associated with obesity-related health-risk progression. Progression on CHS scores is modeled as transition between states; each transition can be assigned specific transition probabilities.

To explain the model in more detail, I have divided the model framework into:

1. Core model: This details the BMI-CHSS progression structure
2. Complications models: These define the sub-models for the four obesity-associated outcomes

CORE MODEL

Structure: In our Monte Carlo simulated Markov model a series of individuals' progress through the model. For our model we ensure the following characteristics at baseline:

- Age, 18 – 30 years
- Sex (male/female)
- Race/Ethnicity (non-Hispanic White, African-American)
- BMI (Normal/overweight/obese)
- Hypertension (normal/pre-hypertension/above normal)

- Cholesterol (normal/above normal)
- LDL
- HDL
- Diabetes (none/pre-diabetes/diabetes).

Given our BMI-CHS system there are 15 possible health states (3 BMI categories x 5 CHS states) an individual can progress aside from a death state. This is can be seen in Figure A in Appendix 2. All individuals entering the model are assumed to be in one of the BMI-CHS state. They are followed along the paths until they turn 85 years old, when they are assumed to die [41]. The transition to move between states at every cycle will also be functions of various factors like age, gender, race and model specific factors like cycle number and underlying risk factors associated with obesity and its co-morbidities.

The initialization characteristics are derived to match the background characteristics of the patient population from existing longitudinal data cohorts: (1) The Coronary Artery Risk Development in Young Adults (CARDIA) Study and (2) The Atherosclerosis Risk in Communities Study external disclaimer (ARIC) study [42,43]. In addition to the initialization characteristics, we will also use these databases to calculate the initial probabilities of starting at each of the derived BMI-CHS states and the yearly transition probabilities of moving between these states or dying.

CARDIA and ARIC are longitudinal studies for cardiovascular disease of men and women in the United States. These studies allow us to derive a continued surveillance database

for a nationally represented population from at ages of 18 years till death. Both provide data to investigate the etiology and natural history obesity (dietary and exercise patterns, behavioral and psychological variables, medical and family history), obesity associated risk factors (smoking, blood pressure and cholesterol), and Obesity associated outcomes (atherosclerotic diseases, diabetes, variation in cardiovascular risk factors).

Mortality: The mortality component assumes that an individual can die from one of four causes within each CHS state:

- CHD
- End stage renal disease (ESRD)
- Stroke
- Other Obesity-associated outcomes
- Non obesity-associated causes

To model causes of death, mortality risks will be calculated for each patient for each year of life in the model. Non-renal, non-stroke, and non-CHD mortality risk will be taken from age-, sex-, and race-specific mortality for the US [44]. Disease specific risks are detailed in the Outcome sub-models. Mortality rates of overweight and obese subjects in a normal health state are assumed to be equivalent to those observed in the general population. Since we are modeling mortality on multiple different disease paths simultaneously, we will take precautions to avoid overestimating total mortality

The first three causes of death are all related to outcomes specific paths. The final mode of death is the general, nonspecific population death rate from other causes. Patients who have ESRD face a higher mortality risk than patients without ESRD. Age-, sex-, and race-specific diabetes-ESRD mortality risks will be obtained from the US Renal Data System [45]. Patients with CHD can die from CA, MI, or sudden death. Once a patient has experienced a CHD event, they face a higher mortality risk than patients who have not had one. Patients experiencing stroke can die immediately; if they survive, they face higher mortality rates in subsequent periods. Mortality rates from ESRD are a function of the cohort's age, sex, and race/ethnicity as shown in. We assume that a person does not die during the period in which he or she develops ESRD. Mortality for CHD and stroke are derived from Framingham Risk Score (FRS) [46].

Utility Values (UVs): Uvs represent the strength of patient preferences for their own health on a scale from 0.0 (death) to 1.0 (perfect health). These are used to calculate quality-adjusted life years (QALYs) for patients who are alive. The progression of BMI-CHS staging and developing an outcomes will result in a decrease in the health utility scores. The minimum combination method was used such that an individual experiencing multiple complications at the same time was assigned the lowest quality-of-life value. We also used published sources of utilities (e.g., Tufts CEA registry) to incorporate utilities for overweight and obese people, utilities changes due to decreases in BMI, and utilities associated with the complications of obesity [47]. In some cases, we

used disutility weights to reflect the loss in health-related quality of life by having increases severity of a health state. We applied the mean utilities obtained in studies for the available outcomes which included cancer, ESRD, peripheral neuropathy, blindness, MI, and angina (details in Appendixes).

Cost: The cost values are associated with patient-level direct medical costs that account for demographic factors, treatments, complications, and comorbidities. The costs of obesity complications will be taken from published literature and adjusted to current prices using the consumer price index. Medical encounter and/or claims data will be obtained from AHRQ's Medical Expenditure Panel Survey (MEPS) to describe inpatient, outpatient, lab, and pharmacy utilization [48].

COMPLICATIONS MODEL

CHD sub-model

Cardiovascular risk associated with Obesity was captured as Coronary Heart Disease (CHD) that accounts for both Angina and Myocardial Infarction. This pooled risk was derived from the Framingham Risk Score (FRS). The FRS presents a simplified coronary prediction model, building on the blood pressure, cholesterol, and LDL-C [38]. The utility and accuracy of the FRS is well documented and matches closely to the CHS states we have conceptualized. As obesity risk was not included in the original FRS equation, we

added in a multiplicative factor based on literature based on the Framingham literature published at later years. This allowed us to quantify the FRS over age, gender, BMI, CHS state and smoking status adding extensive variability in the model.

To account for the age-varying costs in Angina and MI, we created weighted costs UVs for CHD in the model. The costs were attained through literature (Appendix 3). We further decided to allow individuals to remain in the permanent state of CHD lifelong after initial CHD episode and we modified the life expectancy associated with CHD by the risk of death given CHD. So unlike stroke were surviving in a stroke state for 10 years individuals would go back to their original cost and utility, CHD costs and UVs are permanent till they die.

Also captured in the model are the likely risks for "recurrent" CHD events (based on FRS equations) which modifies costs and death risks over time. Details for the model are listed in Appendix 3.

Stroke sub-model

We allow an individual to develop stroke based on age and sex dependent probabilities. There are derived from the literature and in consultation with experts. The risk also varies across the BMI-CHS states to allow variation by BMI categories and CHS states. We have allowed an individual to remain in a stroke state for 10 years following initial stroke. Death during this period is modelled to reflect death risk from post stroke states and

surviving 10 years in this states allows the individual to return to the respective BMI-CHS health state and age associated life expectancy. All costs and UV of a stroke and being in post-stroke state are captured in each cycle.

Similar to CHD, we have also captured in the model the likely risks for "second" stroke events (which modifies costs and death risks over time). After the second stroke happens we increase the life expectancy so that we impose the higher cost and lower utility for a longer period of time. However, since the chance of death increases, we expect that individuals die within that period. If individuals are still alive, their chance of death goes back to the normal situation (when there is no store). Details for the model are listed in Appendix 4.

Diabetic Complications sub-model

We have modelled three primary complication linked to Obesity and Diabetes.

1. Diabetic Nephropathy
2. Diabetic Retinopathy
3. Diabetic Neuropathy

Appendix 4 shows the Diabetic complications sub-model conceptually. As the number of years being diabetic influences the likelihood of developing any complication, we used data from literature to estimate age/gender dependent risk of diabetic complications

based on duration of diabetes [49-51]. Details on model variables and parameters are provided in the Appendix 4.

Cancer sub-model

Although obesity has long been recognized as an important cause of diabetes and cardiovascular diseases, the relationship between obesity and different types of cancer has received less attention than its cardiovascular effects. It has been estimated that 15–20% of all cancer deaths in the United States can be attributed to overweight and obesity [52,53]. Results from epidemiological studies indicate that adiposity contributes to the increased incidence and/or death from cancers of the colon, breast (in postmenopausal women), endometrium, kidney (renal cell), oesophagus (adenocarcinoma), gastric cardia, pancreas, gallbladder and liver, and possibly other cancers [54]. In our model we specifically focused on these eight cancers in women and six in men.

We allow to individual to enter into any of the above cancer states based on age and sex dependent probabilities. There are derived from the SEER database from NCI. The risk also varies across the BMI-CHS states to allow variation by BMI categories and CHS states.

While cancer-specific Markov models are common in literature they are varied depending on the type of cancer and the rate of progression across the TNM staging system. As our model is looking at obesity associated progression over time, the current

iteration of the model will take a simplistic assumption of allowing individuals to be in a Cancer state for a period of 10 years. During this period they can die from the cancer progression or survive and return to a cancer-free state. Costs and utility values are accounted for every year in this period and vary based on cancer type. Surviving cancer (10 years), allows the individuals to return to their original BMI-CHS state. Details on model variables and parameters are provided in the Appendix.

Validation, Verification, Model Consistency and Sensitivity analysis

VALIDATION AND VERFIFCATION

The model underwent a thorough process evaluation (using a series of trackers) during the development stages to ensure both the tree distributions were accurately captured and also the mathematical calculations were consistent.

Validation assures that the model represents the true mechanical behavior of the physical system with sufficient accuracy. Model accuracy was assessed using quantitative comparisons between computational predictions and outcomes from the longitudinal datasets at hand (CARDIA and ARIC studies) and expert opinions from researchers and physicians at Hopkins. The computational model and/or tree structure were revised if the model was determined to be inaccurate for the intended use.

MODEL CONSISTENCY

Both internal and external consistency will be assessed. To investigate internal consistency, different sensitivity analyses in terms of model parameters and modeling assumptions will be performed. External consistency will be investigated by comparing risk estimates from the model with estimates based on epidemiologic data and from other studies.

SENSITIVITY ANALYSIS

One-way sensitivity analysis will be carried out to investigate the robustness of the data input, including the baseline risks of transitioning to CHS-complications, intervention effects, the utility values, the costs of complications, and the costs of interventions. It is the most appropriate method for handling parameter uncertainty because it facilitates assessment of the joint effect of uncertainty over all parameters [40]. Distributional forms of the model parameters will be decided at the time of analysis. A predicated number of replications will be performed in order to examine the distribution of the resulting costs and effects. An acceptability curve will be then constructed from the incremental cost and QALYs between different strategies for all the simulations.

Specific Aim 1 (SA1): Economic Value of Bariatric Surgery in severely obese adults in the United States: a simulation model approach

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ABSTRACT

Background: Even though bariatric surgery has resulted in successful weight reduction many insurance plans still do not cover bariatric surgery for severely obese adults. Employers and insurers can benefit from a better understanding of the economic value of bariatric surgery.

Methods: We developed a Markov simulation model to determine the cost-benefits and cost-effectiveness for a severely obese adult getting bariatric surgery versus standard care (diet, physical activity, and behavioral modification) from the third-party payer, employers and societal perspective.

Findings: Gastric banding led to net savings of $15,098 per QALY (UI: $12,155/QALY - $18,443/QALY) in direct medical costs and $18,930 per QALY (UI: $3,834/QALY to $28,166/QALY) in productivity losses averted. Gastric bypass led to net savings of $14,550 per QALY (UI: $11,243/QALY - $17,882/QALY) in direct medical costs and $30,991 per QALY (UI: $15,004/QALY to $87,630/QALY) in productivity losses averted. A severely obese patient with two or more comorbidities saw approximately 46% higher direct medical cost savings and 95% lower productivity losses compared to a metabolically healthy obese patient.

Interpretation: Gastric banding and gastric bypass are cost-effective options for weight loss in a severely obese patient across a broad range of health risk states. Age of patient and obesity-associated health risk at time of bariatric surgery had the largest impact on cost-effectiveness outcomes. Third-party payers and employers would benefit from assessing economic value from bariatric surgery by incorporating savings from both immediate weight change after procedures and downstream obesity-associated health outcomes.

Funding: This work was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Office of Behavioral and Social Sciences Research (OBSSR) and the Global Obesity Prevention Center (GOPC) via grant U54HD070725, NICHD via grants U01 HD086861 and R01 HD08601301, the Agency for Healthcare Research and Quality (AHRQ) via grant R01HS023317, and a Pilot Grant awarded by the Mid-Atlantic NORC (Nutrition Obesity Research Center) funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript

BACKGROUND AND SIGNIFICANCE.

Bariatric surgery has been shown to be a successful treatment option for individuals with severe obesity[55-62], but many eligible patients still find it difficult to get the procedure covered by their health insurance[63,64]. Current studies underestimate the economic value of bariatric surgery as they evaluate savings within a short timespan post-surgical intervention (average 1 – 3 years)[65]. Furthermore, majority of the studies estimate savings based on reductions in body weight alone, without accounting for changes in obesity-associated health risks (ex. type 2 diabetes mellitus, hypertension, hyperlipidemia)[66-68] nor forecasting for downstream adverse clinical complications (coronary heart disease, stroke, type 2 diabetes complications)[66,67,69,70].

Capturing these likely effects of obesity progression and associated health risk require computational models that can incorporate the extent of co-morbid conditions, risk factors and health status at the individual level: data that are needed to make effective treatment decisions. In this study, we have developed a Markov simulation model to estimate the economic burden of obesity over the lifespan of individuals and use it to determine cost-benefits and cost-effectiveness of gastric bypass and gastric banding surgeries in comparison to lifestyle modification management alone. The results of our model will help guide insurers and employers make inferences about future impact and quality of life outcomes linked to the surgical management of severe obesity.

MODIFICATION OF CEOM

METHODS

Model Structure

We developed a Markov computer simulation model using TreeAge Pro 2016 (TreeAge Software, Williamstown, Massachusetts) to determine the cost-benefits and cost-effectiveness for a severely obese adult opting for gastric banding and gastric bypass versus standard care from a third-party payer, employer and societal perspective. A Markov model is an analytical methodology that is used commonly to predict future states based on current and past information. It is utilized in this model to predict future obesogenic states, associated health outcomes, and mortality[71]. Figure 1 provides an overview of our model, and Appendix 1 reports all the model parameters with values and sources.

A patient entering the model could receive one of the following treatment options:-

1. Lifestyle modification management: A regime of diet control, physical activity, and lifestyle counseling.
2. Gastric Banding procedure: Patient underwent gastric banding and followed-up with lifestyle management.
3. Gastric Bypass procedure: Patient underwent gastric bypass and followed-up with lifestyle management.

We defined 25 health states that correspond to a range of healthy to obese and to a clinical staging system. The Chronic Health State (CHS) system is built integrating the Edmonton Obesity Staging System (EOSS) and the Cardiometabolic Disease Staging System (CMDS)[34,36,72]. It derives health risk states scores as an ordinal risk-stratification system based on morbidity and health-risk profile incorporating six obesity-related comorbidity variables into creating the scores, notably diabetes, hypertension, and dyslipidemia. Figure 1 provides an overview these health states and Appendix 2 reviews the clinical staging system used in conjunction with BMI cut points to create our mutually exclusive health states. The patients entering the simulation model were in Class 2 (BMI 35 – 39.9) and Class 3 (BMI >40) of obesity as these are commonly used thresholds to assess eligibility for the surgical procedure. They are also assigned a health state. The model proceeds in one-year time intervals as it best reflects the likelihood of progressing between health states. Each year the individual has the probability of progressing between health states, developing associated clinical outcomes or moving to death states from either disease or age-related mortality. The transition probabilities between BMI and health states factor in age-related changes in weight status as well as gender and race variations. The likelihood of developing obesity-associated specific health outcomes: stroke, cancer, coronary heart disease (CHD), and type 2 diabetes mellitus (T2DM) complications are associated with each agent's age and health state.

In the first year of the each scenario, the intervention modifies the transitional health state probability based on successful weight loss post intervention. Patients undergoing bariatric surgery, have added risk of having a surgical failure, developing a surgical complication, or dying during the procedure. The probabilities vary based on type of bariatric surgery (Appendix 1). Surgical relapse, complications and re-surgery probabilities are captured for five years. All patients continue to be on lifestyle management until year 5 in the model. Post year five, all patients continued health state transitions, irrespective of intervention scenario. The patient will continue through the model until he or she reached the death state due to death from obesity-related illness, from other causes (i.e., overall mortality). Each simulated year, the model will accrue direct medical costs, productivity losses and health utility scores based on age-, health state- and health outcomes for each. Appendix 1 details all parameter models included.

Simulations and model outcomes

Simulation run consisted of a total 1,000,000 trials; 1,000 patients (age >=18 years) run 1,000 times. Each run we calculated incremental cost-effectiveness ratio (ICER):

$$(\text{Cost}_{\text{Treament Option A}} - \text{Cost}_{\text{Treatment Option B}}) / (\text{Effectiveness}_{\text{Treament Option A}} - \text{Effectiveness}_{\text{Treatment Option B}})$$

"A" reprsent either gatric banding or gastric bypass and "B" is lifestyle managgment. Costs are either direct medical costs, prodcutivity losses or both and Effectivenss is measures using

QALYs. ICERs of ≤$50 000 per QALY were considered to be cost-effective. A treatment option was considered to be dominant if it led cost savings and increased health benefits.

Data Inputs and sources

The 25 distinct health states, transition probabilities, and associated mortality probabilities are derived from the Coronary Artery Disease Risk Development in Young Adults (CARDIA) and the Atherosclerosis Risk in Communities (ARIC) studies. CARDIA and ARIC are ongoing prospective, longitudinal studies tracking adults over a variety of different health risk factors and outcomes, including BMI. Incidence rates, recurrence and death probabilities on the four obesity-associated specific health outcomes (stroke, cancer, CHD, and T2DM complication) are elaborated in Table 1. Mortality rates of overweight and obese subjects in a normal health state are assumed to be equivalent to those observed in the general population. Since we are modeling mortality on four different disease paths simultaneously, we will take precautions to avoid overestimating total mortality.

The third-party payer perspective considered costs from outpatient visits, hospitalization, emergency room visits, and medications. These were derived from the Medical Expenditure Panel Survey (MEPS) and published literature. The employer perspective considered costs from productivity losses. Productivity losses were derived from annual wages attenuated by utility weights for a given health condition served as a proxy for productivity losses. Annual

QALYs for each health state were calculated using age-specific healthy QALYs attenuated by a utility value associated with the health state and/or outcome an individual developed over the year. As the model allows for individuals to develop multiple clinical outcomes in each time step, we looked to attribute costs and health effects conservatively. Direct medical costs incorporated the highest cost amongst the multiple clinical outcomes and health effects used the lowest QALYs values. Table 1 details the cost and utility values sources. A 3% discount rate converted all past and future costs to 2017 U.S. dollars. The societal perspective looked at both direct medical costs and productivity loses.

Data for the bariatric surgery model were derived from the various sources in the literature and are detailed in Table 1. Surgical data from the Department of Bariatric Surgery at Johns Hopkins University Hospital and other large RCTs were used to derive the annual weight loss probabilities, surgical failures, probability of complications, and health risk parameters. Complications included short-term surgical risk of procedures themselves, immediate post-surgical risk from infection, and need for reversal surgery in cases of failures. We used multiple literature sources to estimate the effect of surgery on glycemic control, blood pressure, and cholesterol values. Costs of surgery are derived from and encompasses both the costs attributable to surgery (in-hospital surgery costs and any complication costs in the first year). Subsequent year costs post-surgery included costs of follow-up care hospital visits, nutritional supplements, long-term complications. Table 1 also lists these all surgical related

parameters by year after surgery. Health utility was captured as product of change in BMI status change associated with surgery and also captured temporary decrease in quality of life immediately post-surgery[73].

Sensitivity analyses

Sensitivity analysis varied key parameters in the model to determine their effect on the cost-effectiveness of bariatric procedures. The cost of gastric banding and gastric bypass was varied over a range from $7,000 - $55,000 for gastric bypass and $3,000 - $30,000 for gastric banding. The health utility values post-surgery were similarly varied from 0.55 – 0.88. We also look at the age of the patient at surgery and probability of perioperative mortality. Also, we simultaneously varied all parameters in Table 1 through their ranges in a probabilistic sensitivity analysis.

RESULTS

Third-party payer perspective: A patient at class 2 obesity (BMI 35 – 39.9 kg/m^2) undergoing bariatric procedure accrued, on average $84,205 (UI: $73,019 - $95,392) direct medical costs for gastric banding and $89,338 (UI: $77,329 - $101,347) direct medical costs for gastric bypass over his/her lifetime. Similarly, a class 3 obese patient (BMI >40 kg/m^2) undergoing bariatric procedure would accrue, on average $84,405 (UI:

$66,016 - $102,793) direct medical costs for gastric banding and $89,045 (UI: $59,973 - $118,117) direct medical costs for gastric bypass over the course of his/her lifetime.

Table 2 reports the net benefits in direct medical costs over the lifetime for a severely obese individual undergoing either gastric bypass or gastric banding versus lifestyle management. A severely obese patient without preexisting clinical comorbidities (CHS 0 – CHS 2) would accrue $23,224 (UI: $9,029 – $25,005) more in direct medical costs over his/her lifetime undergoing gastric banding management and $23,281 (UI: $11,498 – $31,840) more in direct medical costs undergoing gastric bypass. A patient with preexisting comorbidities (CHS-3 and CHS-4) showed a net-benefit of $23,478 (UI: $8,481 – $42,745) in direct medical costs undergoing gastric banding management and $28,296 (UI: $9,934 – $56,936) in direct medical costs undergoing gastric bypass. Patients with preexisting comorbidities undergoing gastric banding showed net-benefits in direct costs by over 44% as compared to metabolically healthy (CHS-0) obese individuals. Similarly, those undergoing bypass procedures saw an increase cost savings of 48% in direct medical costs.

Table 3 shows results from of incremental cost-effectiveness ratios (ICER) by surgery type. Gastric banding and gastric bypass procedures were an economically dominant weight-loss intervention option (i.e., saved costs and higher health effects) in a severely obese patient with two of more clinical comorbidities (CHS-4). Gastric banding led to $15,098 averted per QALY (UI: $12,155/QALY - $18,443/QALY) and gastric bypass led to

$14,550 (UI: $11,243/QALY - $17,882/QALY). In a severely obese patient in preclinical health state (CHS1 – CHS2) bariatric surgery was also cost-effective weight-loss intervention option but not dominant (i.e. higher costs per QALY gained). The ICERs for direct medical cost ranged between $20,194/QALY and $28,632/QALY for a patient in CHS-1 and $7,044/QALY and $7,309/QALY if in CHS-2. Bariatric surgery interventions was not a cost-effective weight loss options for severely obese patients at CHS-0 (metabolically healthy).

Figure 2 shows the impact in ICERs with varying model parameters. The figure highlights key results from sensitivity runs on a severely obese patient with two or more health risks at time of surgery (CHS4). We see that age of the patient at time of surgery had the largest impact on ICERs. In a patient of 20 years to 40 year of age, net savings in direct medical costs were higher by 34% (UI: 18% - 42%) per QALY gained (Figure 3). Surgical costs (that included both the costs of the procedures and the costs of likely complications and failure) and quality of life post-surgery also varied ICERs but not significantly.

Employer perspective: A patient in with class 2 obesity undergoing bariatric procedure would accrue, on average $127,578 (UI: $169,639 - $148,799) in productivity losses over their lifetime after gastric banding and $175,229 (UI: $152,493 - $197,964) in productivity losses for gastric bypass. Similarly, a patient in class 3 obesity opting for gastric banding would accrue on average $148,799 (UI: $127,624 - $169,974) in

productivity losses and $174,461 (UI: $151,770 - $197,152) in productivity losses when opting for gastric bypass.

Table 2 reports the productivity losses for a severely obese patient undergoing gastric bypass/gastric banding versus lifestyle management. Other than a metabolically healthy class 2 obese patient, all other simulated patient scenarios show net benefits in productivity opting bariatric surgery versus lifestyle management. Productivity loss savings from surgery are higher if an obese patient has additional health risk. A severely obese patient in CHS4 undergoing gastric banding would see a 105% reduction in productivity losses as compared to similar patient in CHS-0. Similarly, a patient undergoing gastric bypass at CHS-4 would see an 85% reduction in productivity losses over their lifetime.

In looking at net savings in productivity per QALY gained, bariatric surgery is an economically dominant weight loss option in a severely obese patient at any health risk state (CHS1 – CHS4). The ICERs in these health states average at - $18,930/QALY (Range: -$3,834/QALY to - $28,166/QALY) for gastric banding procedures and -$30,991/QALY (UI:-$15,004/QALY to - $87,630/QALY).

In looking at the impact of varying key model parameters, age of the patient at time of surgery the largest impact on ICERs in both gastric banding and gastric bypass. In a patient undergoing gastric banding, net savings in productivity were higher by 84% (UI:

14% - 202%) per QALY gained if the patient was 20 – 40 years of age. In a patient undergoing gastric bypass, net savings in productivity were higher by 25% (UI: 7% - 43%) per QALY gained if the patient was 20 – 30 years of age. Post-operative complications and quality of life post-surgery also varied ICERs but not significantly.

Societal perspective: A severely obese patient at CHS0 and CHS1 opting for bariatric surgery accrued incrementally higher total societal costs in comparison to lifestyle management. A patient undergoing gastric banding accrued on average $27,296 (UI: $16,709 - $35,377) in total costs and $13,195 (UI: $4,001 - $19,104) in total costs for gastric bypass. Net-savings in societal costs from bariatric surgery versus lifestyle management in an obese patient at CHS2 – CHS4 averaged $45,459 (UI: $11,336 - $86,405) when undergoing gastric banding and $86,048 (UI: $19,794 - $140,911) for gastric bypass.

Gastric banding and gastric bypass procedures were an economically dominant intervention option (i.e., saved total costs and QALYs) in a severely obese patient in health states CHS-2 to CHS-4. ICERs averaged -$25,866/QALY (UI: $8,118/QALY - $37,645/QALY) when opting for gastric banding and -$32,836 (UI: $13,794/QALY - $45,037/QALY) when undergoing gastric bypass. Surgical interventions were cost-effective in all other health states expect in severely obese patients at CHS-0 undergoing gastric banding.

DISCUSSION

In our study, at a willingness to pay threshold of $50,000 per QALY, we found that gastric bypass and gastric banding procedures are cost-effective options for weight loss in a severely obese patient across a broad range of health risk states. In a patient with clinical comorbidities, opting for either gastric banding or gastric bypass lead to net savings in direct medical costs and productivity losses over his/her lifetime in comparison to undergoing lifestyle management only. In an obese patient with any health risk, gastric banding management plan led to incrementally higher net savings in direct medical costs as compared to gastric bypass but was not significantly different. Net benefits were 45% higher for gastric bypass when assessing net savings in productivity losses over the lifetime between the two procedures.

Our study shows that cost savings from bariatric surgery did not vary significantly between BMI classes. Larger variation was seen when assessing added comorbid health state in addition to BMI obesity status. Surgical intervention for weight loss was between 45% - 103% more cost effective in a patient at CHS2 – CHS4. Using a simulation-based model to assess economic value of bariatric procedures allowed us incorporate both immediate impact from weight change after procedures but also project the downstream impact from obesity-associated health risks. By assessing both initial change in weight, associated health risk change and further projecting change over the lifetime, our study captures downstream costs and health impact from clinical health outcomes (CHD,

stroke, T2DM related microvascular and macrovascular complications) as well. The medical costs and health effects from obesity-associated chronic conditions outweigh the early surgical costs associated with bariatric procedures. In earlier CHS states, we don't see direct medical cost savings as the reduction in chronic health outcomes are more modest and cost are primarily driven by the cost and risk of the intervention itself. Third-party payers and employers would benefit from taking a lifetime approach in evaluating the cost-effectiveness of surgical weight loss interventions as cost savings can be underestimated in short-term costing studies. Studies have also shown that the improvement in weight status are negligible beyond first few years' post-surgery.

We also determined that the age at intervention varied the cost savings significantly as well. While bariatric surgery was seen to be cost-effective in a patient aged less than 60 years, opting for surgery at earlier ages (20 years to 40 years) led to the largest savings in both direct medical costs per QALY gained and productivity losses averted per QALY gained.

Limitations

As with all modeling studies, our model is a simplification of reality. Weight loss achieved through bariatric surgery has been widely reviewed in the literature, but there is limited data on long-term effects. Projecting lifetime health outcomes and costs were assessed under the assumption that beyond 5 years of study direct surgical benefits were not

maintained. Projections were carried based on natural trajectories at individual BMI-CHS states beyond year 5. Similarly, changes in health states associated with obesity came from limited resources and cross-sectional data. Our model can estimate varied possible trajectory scenarios based on health outcome probabilities at each time interval, allowing us to get more realistic estimates.

The challenge in tackling obesity arises as much of the consequences related to being in an obesogenic state occur in the future and much downstream to current obesity state. Without this comprehensive understanding various questions remain for the different stakeholders. Bariatric surgical coverage is varied by health insurers as population change health plans frequently, and long-term projections on economic benefits from weight loss and impact on overall health status are less clear. Our results, taking a lifetime approach, comprehensively capture the projected impact (both costs and productivity losses) associated with obesity and the savings from each surgical intervention. Our model further highlights the need to keep patients post-surgery within weight management plans to continue benefits of weight reduction and improvements in comorbidities. Overall, our analysis indicate that gastric bypass and gastric banding surgery provide a cost-effective weight loss option in obese adults with pre-existing health conditions. The costs are associated with weight reduction, as well as improvements in health status over time leading to fewer obesity-associated complications over the lifetime. Our model suggests that priority should be given to

treating obese individuals in CHS-3 and CHS-4 as the procedures to maximize benefits in the long-term. The medical costs saved and productivity losses averted over the lifetimes in this population significantly outweighs the surgical treatment costs.

FIGURES & TABLES

Figure 1: Individual-based BMI progression model structure

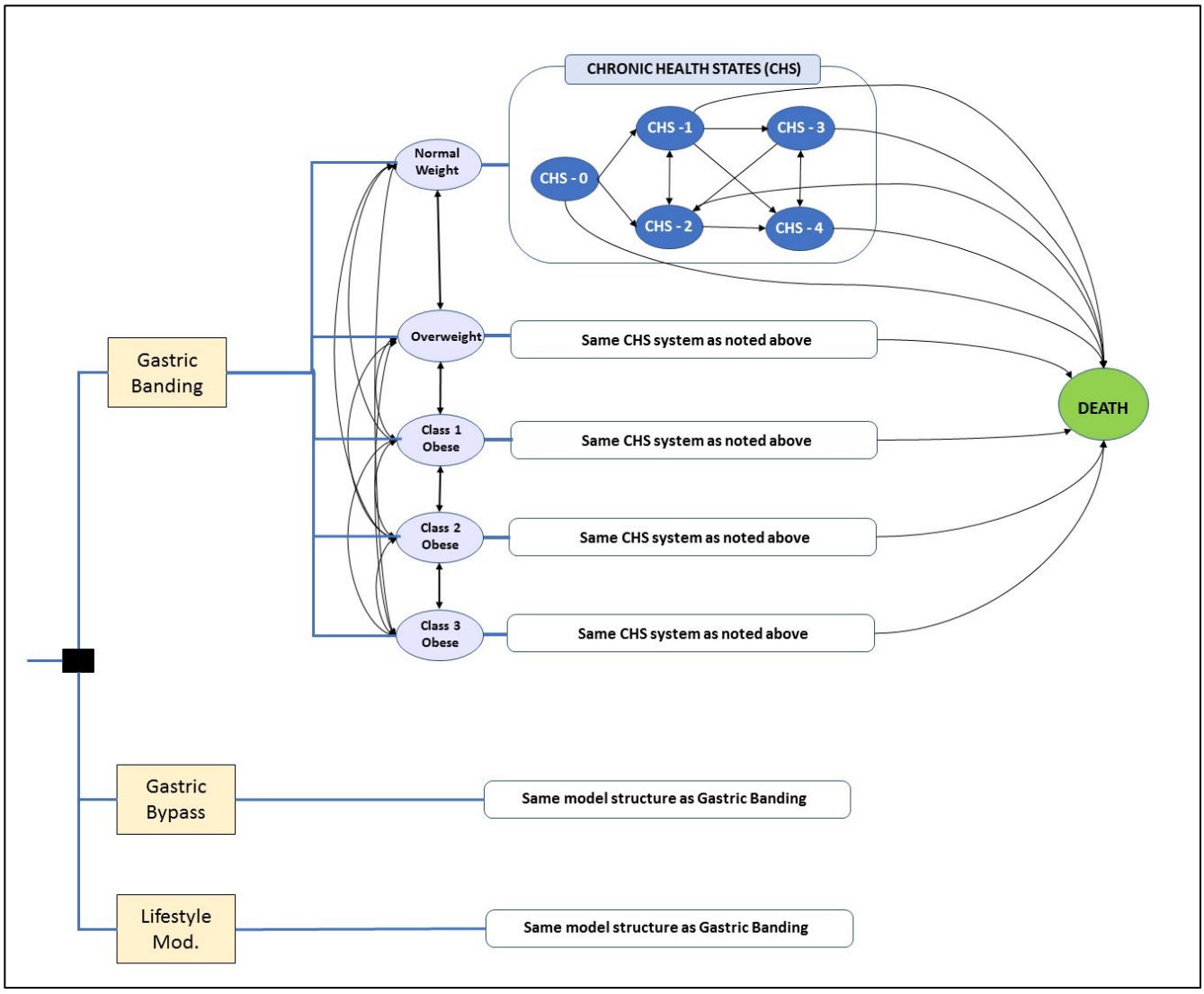


Table 2: Net benefits and QALYs by Obese status and CHS state

		Gastric Banding vs. Lifestyle Management				Gastric Bypass vs. Lifestyle Management			
		Class 2 Obesity		Class 3 Obesity		Class 2 Obesity		Class 3 Obesity	
	Health state	Net benefits	Net effects	Net benefits	Net effects	Net benefits	Net effects	Net benefits	Net effects
Third-party Perspective (Direct Medical Costs)	CHS 0	$ 32,235	0.487	$32,437	0.23	$31,840	1.024	$34,208	0.74
	CHS 1	$ 21,914	0.765	$25,005	0.85	$23,394	1.093	$25,784	1.28
	CHS 2	$ 18,721	1.160	$9,029	1.08	$12,960	1.435	$11,498	1.63
	CHS 3	$ 8,481	1.391	$(28,979)	1.42	$9,934	1.789	$(24,986)	2.38
	CHS 4	$ (30,674)	2.295	$(42,745)	2.54	$(41,197)	3.129	$(56,936)	3.57
Employer Perspective (Productivity losses)	CHS 0	$ 3,142	0.487	$2,911	0.229	$(15,361)	1.024	$(15,104)	0.735
	CHS 1	$ (5,205)	0.765	$(3,255)	0.849	$(24,596)	1.093	$(21,783)	1.277
	CHS 2	$ (19,817)	1.160	$(22,165)	1.075	$(32,754)	1.435	$(36,154)	1.632
	CHS 3	$ (30,016)	1.391	$(41,332)	1.421	$(68,302)	1.789	$(75,692)	2.377
	CHS 4	$ (55,731)	2.295	$(71,525)	2.539	$(89,714)	3.129	$(114,944)	3.574
Societal Perspective (total costs)	CHS 0	$35,377	0.487	$35,348	0.229	$16,479	1.024	$19,104	0.735
	CHS 1	$ 16,709	0.765	$21,750	0.849	$(1,202)	1.093	$4,001	1.277
	CHS 2	$ (11,336)	1.160	$(13,136)	1.075	$(19,794)	1.435	$(24,657)	1.632

	CHS 3	$ (11,295)	1.391	$(60,311)	1.421	$(58,369)	1.789	$(100,678)	2.377
	CHS 4	$ (86,405)	2.295	$(114,270)	2.539	$(140,911)	3.129	$(171,880)	3.574

Table 3: Incremental cost-effectiveness ratios by Obesity status and CHS state

		Gastric Banding vs. Lifestyle Management		Gastric Bypass vs. Lifestyle Management	
	Health state	Class 2 Obesity	Class 3 Obesity	Class 2 Obesity	Class 3 Obesity
ICER (Third-party Perspective)	CHS 0	$66,151	$141,822	$31,100	$46,516
	CHS 1	$28,632	$29,453	$21,406	$20,194
	CHS 2	$13,456	$8,398	$9,031	$7,044
	CHS 3	$7,309	$(20,395)	$5,553	$(10,511)
	CHS 4	$(13,364)	$(16,833)	$(13,167)	$(15,933)
	CHS 0	$6,448	$12,727	$(15,004)	$(20,539)

ICER (Employer Perspective)	CHS 1	$(6,801)	$(3,834)	$(22,506)	$(17,060)
	CHS 2	$(17,078)	$(20,616)	$(22,825)	$(22,151)
	CHS 3	$(21,574)	$(29,089)	$(38,184)	$(31,841)
	CHS 4	$(24,281)	$(28,166)	$(87,630)	$(32,165)
ICER (Societal Perspective)	CHS 0	$72,599	$154,549	$16,096	$25,977
	CHS 1	$21,831	$25,619	$(1,100)	$3,133
	CHS 2	$(9,769)	$(12,218)	$(13,794)	$(15,106)
	CHS 3	$(8,118)	$(42,446)	$(32,631)	$(42,352)
	CHS 4	$(37,645)	$(44,999)	$(45,037)	$(48,098)

Figure 2: Sensitivity analysis: (a) ICER for direct medical costs (b) ICERs for Productivity losses

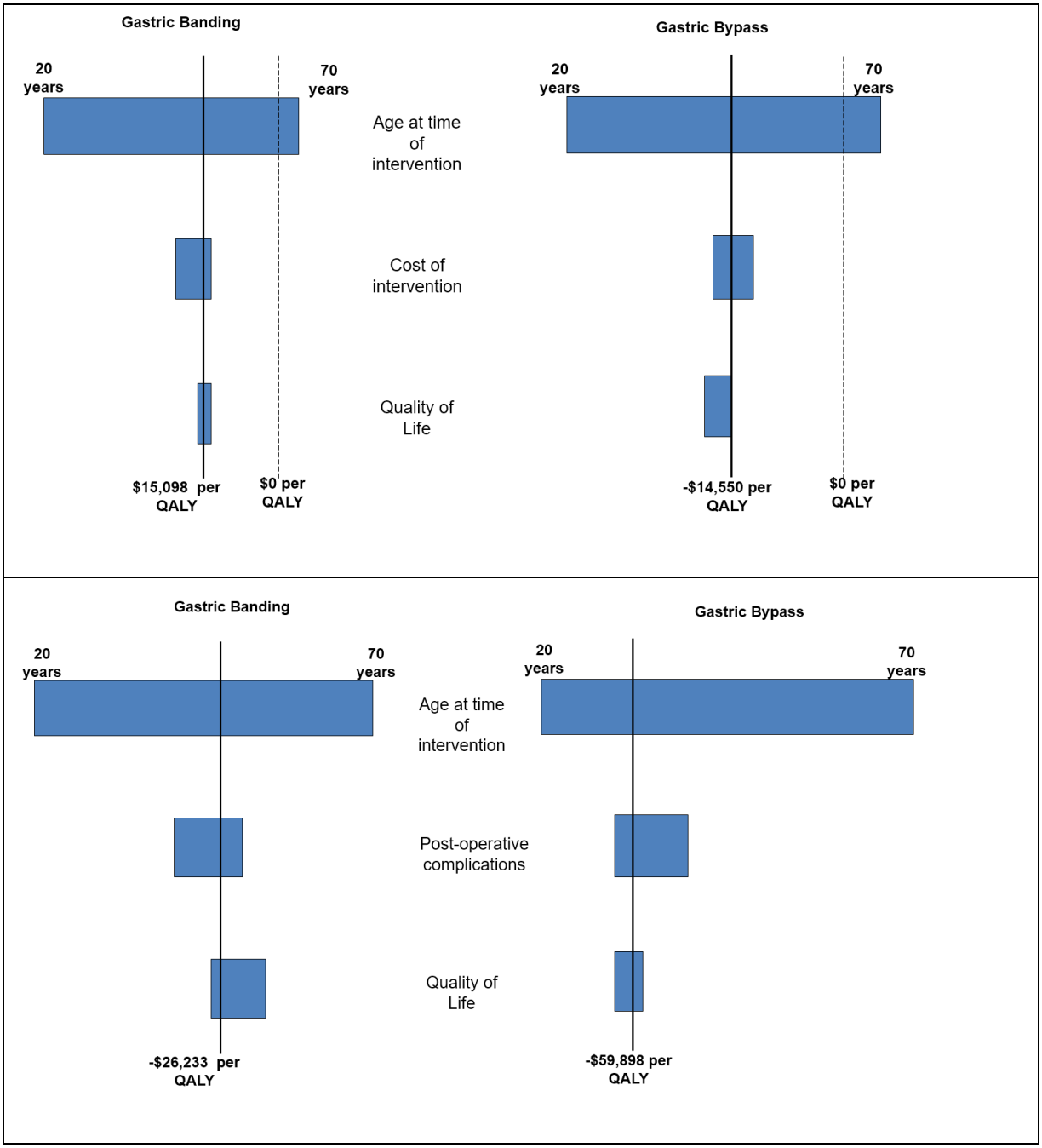
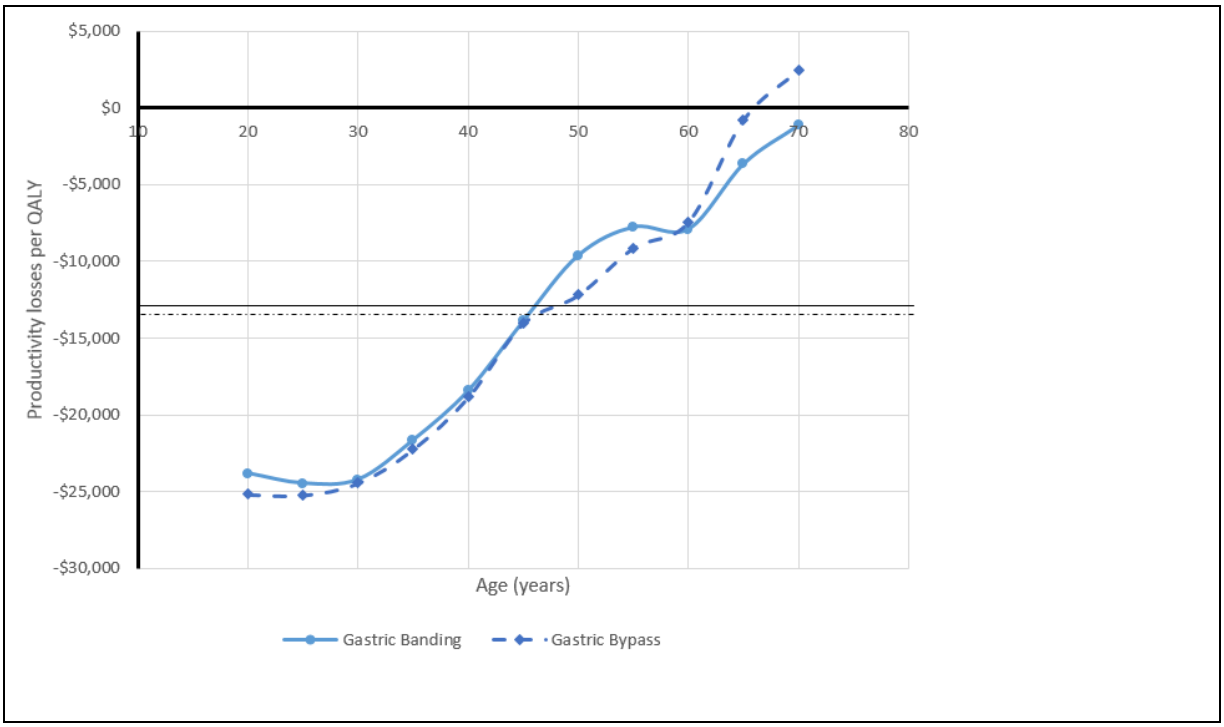
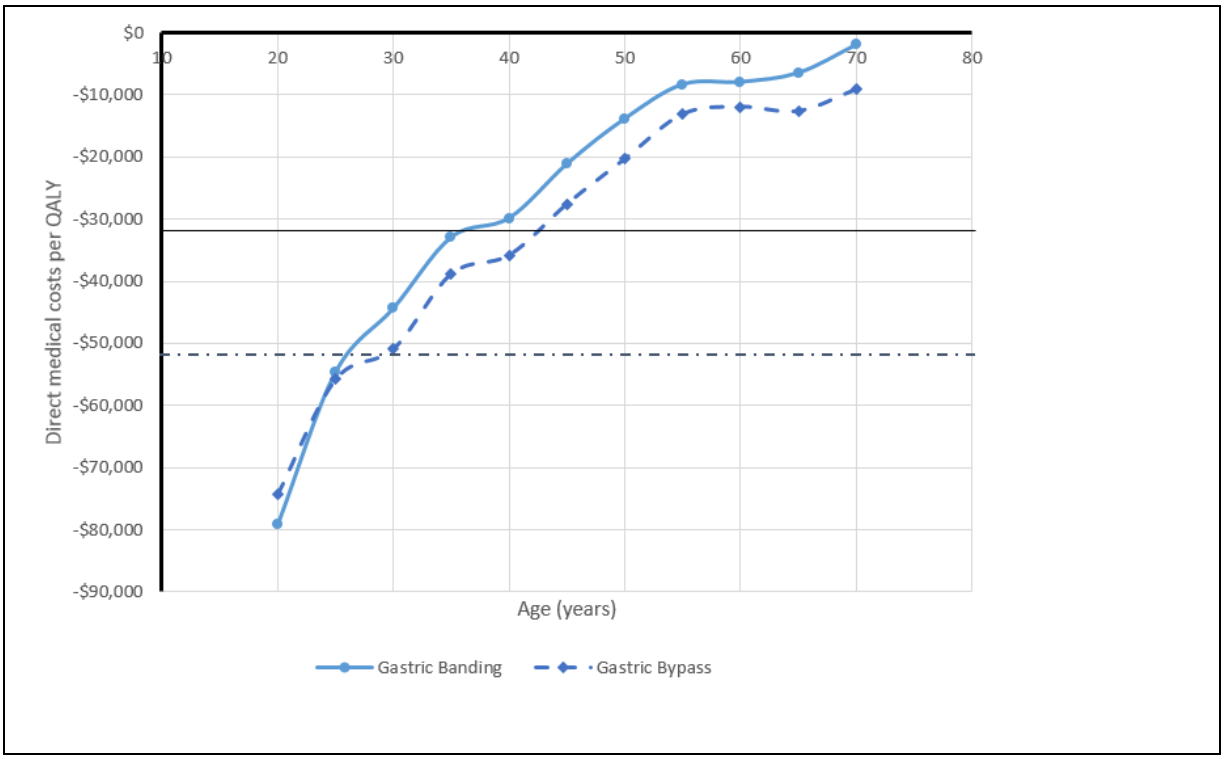


Figure 3: Sensitivity analysis: Age at time of surgery impact on ICER (a) Direct medical costs (b) Productivity losses

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60
70
80
Direct medical costs per QALY
Age (years)
Gastric Banding
Gastric Bypass

Specific Aim (SA2): Economic Value of Qsymia in severely obese adults in the United States: a simulation model approach

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ABSTRACT

Background: Qsymia based weight loss intervention programs have been shown to be successful in weight reduction and cost effective in the short term. However, lack of long term economic benefits and mixed findings on costs savings have led to varied coverage about health insurance providers.

Methods: Our study uses an individual-level Markov model to determine cost effectiveness and cost savings from Qsymia based weight loss programs over the lifetime of severely obese individuals.

Our Markov model is built incorporating a BMI clinical staging system with associated clinical outcomes probabilities for stroke, cancer, coronary heart disease, and type 2 diabetes mellitus complications. Each simulated year, individuals transition BMI clinical states and have state-based risk of developed health outcomes. Qsymia or standard for care interventions are modelled as intervention scenarios that effect the transition probabilities, health outcomes risks, health risk remission and relapse and long-term mortality. The model accrues direct medical costs, losses from productivity and health effects. Incremental costs are compared between Qsymia and standard care at different health states to assess cost effectiveness and cost savings.

Results: Individuals on Qsymia accrue, on average, $67,825 (UI: $60,354 - $76,996) in direct medical costs, $176,840 (UI: $162,259 - $193,621) in productivity losses and additional 14.13 QALYS (UI: 13.23 - 14.98) over their lifetime. From a lifetime horizon, all obese individuals with any preexisting comorbidities at the time of procedures (CHS 1 – CHS 4) undergoing Qsymia based management accrue less direct medical costs and total societal costs than those undergoing on non-surgical interventions.

Conclusions: In our study, we find that Qsymia based intensive weight loss plans are more cost effective over the life time than non-surgical management in all obese individuals. The incremental cost savings for Qsymia led therapies are higher and more significant as obesity interventions are initiated in individuals with significant health risk states

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BACKGROUND AND SIGNIFICANCE.

With bariatric surgery having narrow eligibiligty criteria and costs of surgery still high, pharmacotherapy-driven weight loss interventions have become a popular option in severly obese adults in United States[17,74]. In the last decade, some drug combinations have shown success in randomized control trial settings from which Qsymia (phentermine plus topiramate extended-release) has been the most successful in maintaining weight loss without increasing associated health risk from medication side effects[75]. With newer drugs coming into the market third-party payers would benefit from studies that show potential cost savings and cost-effectiveness in patients opting for pharmacotherapy led interventions.

A few costing studies have looked at the cost-effectiveness of Qsymia and other medications, and while they have shown cost savings over the time of the trial, the results are limited in their generalizability[76-81]. The majority of the costing studies assess impact over a shorter time frame (3-5 years). Futhermore, these models don't capture the impact of weight reduction on chronic outcomes (ex. coronary heart disease, stroke, type 2 diabetes Complications) linked to obesity. Computer simulation models can not only project obesity changes over the lifetime of simulated individuals but also estimate the likely associated health risks and obesity-related clinical outcomes. In this study, we use a Markov simulation mode to detemine the lifetime economic impact in severely obese individuals from the recommended Qsymia based weight loss plan in comparison to lifestyle modifications. The

results of our model will help payers make inferences about future costs and quality of life outcomes linked to obesity and if pharmacotherapy based weight loss programs are cost-effective strategies.

METHODS

Model Structure

We developed am individual-level Markov model in TreeAge Pro Suite 2016 (TreeAge Software, Williamstown, MA) to determine the cost savings and cost-effectiveness of pharmacotherapy-led weight loss interventions from third-party payer, employer and societal perspective in severely obese individuals over their lifetime. The outline of our model is depicted in Figure 1. Model parameters and sources are in listed in Table 1.

The model looked at adults, 18 years and over, with either Class 2 or Class 2 BMI category for obesity. These are common eligibility criteria for intensive weight loss interventions. All simulated patients either received standard weight loss care that included a strict regime of diet control, physical activity, and lifestyle counseling or a Qsymia-led intervention plan. The Qsymia intervention included an extended two-year course of the controlled-release combination of phentermine plus topiramate with adjuvant diet control, physical activity, and lifestyle counseling.

The Markov model proceeded in one year cycles and consisted of 25 mutually exclusive obesity states representing every combination of 5 BMI categories [(normal (18.5 ≤ BMI ≤ 25), overweight (25 ≤ BMI ≤ 30), Class 1 obese (30 ≤ BMI ≤ 35), Class 2 obese (35 ≤ BMI ≤ 40), and Class 3 obese (40 ≤ BMI)] and 5 discrete Chronic Health Stages (CHS). The CHS was developed from a combination of the Edmonton Obesity Staging System and the Cardiometabolic Disease Staging System[34,36,72]. The CHS accounts for six clinical parameters (blood pressure, fasting blood glucose, total cholesterol, high density lipoprotein, low-density lipoprotein, and triglycerides) to derive the following five stages:

- CHS – 0: Metabolically healthy (Fasting Blood Glucose (FBG): <100 mg/L; Blood Pressure (BP): <130/85 mm Hg with no self-report of Hypertension or antihypertensive medication; HDL cholesterol (HDL): >=60 mg/dL; LDL Cholesterol (LDL):<130 mg/dL; Triglycerides (Trig): <150 mg/dL; Total Cholesterol (Tchol): <200 mg/dL)
- CHS – 1: Develop either Pre-Diabetes Mellitus (FBG: 100 – 126 mg/L) only; Pre-Hypertension only (BP: >130/85 mm Hg & <140/90 mmHg) ; Hypertension only (BP: >=140/90 mm Hg or self-report of Hypertension or antihypertensive medication); Hyperlipidemia only (HDL: <40 mg/dL in males and <50 mg/dL in females, LDL: 130-159 mg/dL, Trig: 150-199 mg/dL, Tchol: 200-239 mg/dL); Pre-Hypertension + Hyperlipidemia

- CHS – 2: Develop either Pre-Diabetes Mellitus (FBG: 100 – 126 mg/L) + Pre-Hypertension, Pre-Diabetes Mellitus + Hypertension, Pre-Diabetes Mellitus + Hyperlipidemia (HDL: <40 mg/dL in males and <50 mg/dL in females, LDL: 130-159 mg/dL, Trig: 150-199 mg/dL, Tchol: 200-239 mg/dL); Pre-Diabetes Mellitus + Pre-Hypertension + Hyperlipidemia; or Pre-Diabetes Mellitus + Hypertension + Hyperlipidemia
- CHS – 3: Develop either Diabetes Mellitus only (FBG: >= 126 mg/L or self-report of diabetes or self-report of medication); Hypertension + Hyperlipidemia (HDL: <40 mg/dL in males and <50 mg/dL in females, LDL: >160 mg/dL, Trig: >200 mg/dL, Tchol: >240 mg/dL)
- CHS – 4: Develop either Diabetes Mellitus + Hypertension; Diabetes Mellitus + Hyperlipidemia; or Diabetes Mellitus + Hypertension + Hyperlipidemia

Each year, simulated patients had an age- and state-specific probability of transitioning to a different health state. In addition, at each time step (year) and based on the age and health state, a patient can develop obesity related clinical outcome (stroke, cancer, coronary heart disease (CHD), and type 2 diabetes mellitus (T2DM) complications). The age of the individual, their obesity status, CHS status, smoking history and history of previous CHDs are used to calculate the risk of developing CHD (angina and myocardial infarction) and stroke. The risk calculations are based on the Framingham Risk Score[38,82]. Mortality risks for fatal CHD or

stroke are calculated based on the age, duration of illness, and obesity health state[83]. At each time step, the individual also has the risk of developing any of eight obesity-related cancers for females (Breast cancer, Cervix cancer, Colorectal cancer, Esophagus cancer, Kidney cancer, Pancreas cancer, Stomach cancer, and Uterus cancer) and six obesity-related cancers for males (Colorectal cancer, Esophagus cancer, Kidney cancer, Pancreas cancer, Prostate cancer, Stomach cancer). The risk is calculated based on the age of the individual, gender, and the obesity health state. Mortality risks from are also calculated based on the each cancer type, duration of cancer history, and age of individuals. We also captured the risk of developing diabetes (T2DM) complications for nephropathy, retinopathy, and neuropathy at each year. These were calculated based on the age of the individual, the obesity health state and the number of years they have had diabetes. We also allowed for agents who developed End Stage Renal Disease (ESRD) to have a higher mortality risk than diabetic individuals without ESRD. Mortality risks were estimated based on the age and duration of ESRD as well.

In the first year, a weight loss intervention modifies the transitional health state probability based on the likelihood of intervention success. In year two and three, transitional probabilities modification vary depending on the successful weight loss in first year and patients dropping out of the program (Table 1) Post year three, all patients continue with standard lifestyle management for weight control till year 5. Post year five, all patients continued health state transitions, irrespective of intervention scenario. Each simulated

patient continued to cycle in the model until he or she moved to a death state (which is an absorptive state) either from mortality from one of the specified health outcomes or reaching the end of that individual's life expectancy. At each time step, the model will accrue age- and state- specific direct medical costs, productivity losses, and QALYs. Table 1 details all parameter models included.

Simulations and model outcomes

Each scenario consisted of the 1,000 patients repeated 1,000 times (total 1,000,000 trials). At each run we determined the incremental cost-effectiveness ratio (ICER) based on the follow formula:

$$(\text{Cost}_{\text{Treament Qsymia}} - \text{Cost}_{\text{Treatment Standard care}}) / (\text{Effectiveness}_{\text{Treament Qsymia}} - \text{Effectiveness}_{\text{Treatment Standard care}})$$

Cost are captured as direct medical costs, productivity losses or both. Effectiveness is determined using QALYs.

Upon completion of the initial model run, we will accumulate statistics on background variables, health states, health utility scores, and direct medical costs. ICERs of ≤$50 000 per QALY were considered to be cost-effective . A treatment option was considered to be dominant if it led cost savings and increased health benefits.

Data Inputs and sources

We will provide estimates for our model using data from a variety of secondary sources detailed below.

As noted, three different health parameters to calculate CHS states; fasting blood glucose, systolic blood pressure, diastolic blood pressure, and lipid panel. The correlation between BMI and annual risk of being each CHS health state is calculated from the Coronary Artery Disease Risk Development in Young Adults (CARDIA) and the Atherosclerosis Risk in Communities (ARIC) studies. CARDIA and ARIC are ongoing prospective, longitudinal studies tracking adults over a variety of different health risk factors and outcomes, including BMI. The probabilities of transition between health states depend on background variables and the actual health state. The transition probabilities are based on the CHS state progression with age, gender, body mass index (BMI) and cycle number. To model causes of death, mortality risks for each patient for each year of life. Data from the US Renal Data System was used to derive age-, sex-, and race-specific diabetes-ESRD mortality risks. Framingham Heart Study was used to derive estimates of stroke and CHD mortality. General mortality rates will reflect age- and race-specific mortality for the US population. Since we are modeling mortality on four different disease paths simultaneously, we will take precautions to avoid overestimating total mortality. Table 1 details all parameter values and sources.

Third-party payer costs include direct medical costs calculated using costs from outpatient visits, hospitalization, emergency room visits, and medications for each health outcome they develop. All direct medical costs were estimated using a two-part model, a logistic regression model based on the probability of incurring individual medical costs and a generalized linear model with a gamma distribution and log link estimating annual medical costs incurring such costs. Productivity losses are used to determine Employer perspective costs. There are estimated by using morbidity costs and premature mortality costs for each health outcome. Work loss days were estimated using a negative binomial model estimated work loss days due to illness as a function on each clinical outcomes. An individual's clinical outcomes throughout the year may result in missed days of work (productivity losses) and lost years of quality life (QALYs). In each year, we estimate productivity losses by attenuating age-specific annual wages by utility weights for an individual's health condition. Utility weights represent the strength of individual's preferences for their health on a scale from 0.0 (death) to 1.0 (perfect health)[84]. The progression of health state and resulting clinical outcomes lead to a decrease in the health utility value at each year. The model calculated QALYs by using age-specific healthy QALYs attenuated by the utility weight associated with health state and/or outcome an individual developed in each year. Since individuals can develop multiple clinical outcomes in each time step, we looked to attribute costs and health effects conservatively. Direct medical costs incorporated the highest cost amongst the multiple clinical outcomes and health effects used the lowest QALYs values. A 3% discount rate converted all past and

future costs to 2017 U.S. dollars. The societal perspective looked at both direct medical costs and productivity loses. Table 2 details the direct, indirect costs and health utility scores included.

Qysmia, a combination of phentermine plus topiramate, was approved by the US FDA in 2012 for chronic weight management. In conjunction with diet and physical therapy, it has shown to have significant improvement in weight status as well as noted improvements in blood pressure, lipids, and glycemic parameters[85]. This study utilized effectiveness results from the multiple randomized controlled trials (EQUIP, CONQUER, and its follow-up SEQUEL). Complete descriptions of the individual trials are available elsewhere[77,86-88]. In brief, these studies were double blinded placebo-controlled trials looking at the effectiveness of the Qsymia for weight reduction and obesity-related comorbidities. The studies were used to derive annual weight loss percentages, failure rates, and changes in health status while on Qsymia. Costs of Qsymia were estimated from the direct costs of the medication itself and doctors' office visits. Cost per unit were obtained for 2016 Medi-Span's PriceRx database. Participants with no utilization at initiation and on stoppage were allocated a cost of zero dollars. Table 2 lists these Qysmia linked parameters.

Sensitivity analysis

Sensitivity analysis varied key parameters in the model to determine their effect on the cost-effectiveness of bariatric procedures. The cost of Qsymia was varied over a range from $1,000

- $1,800. The health utility values on medication were similarly varied from 0.7 – 0.88. We also look at the age of the patient at surgery. In addition, we simultaneously varied all parameters in Table 1 through their ranges in a probabilistic sensitivity analysis.

RESULTS

Third-party payer perspective: Class 2 obese individuals taking Qsymia accrue, on average $66,296 (UI: $61.386 - $71.207) in direct medical costs over their lifetimes. Similarly, Class 3 obese individuals taking Qsymia accrue, on average $69,353 (UI: $59,322 - $82,785) in direct medical costs.

Table 2 reports the direct medical costs savings over the lifetime for severely obese individuals on Qsymia versus lifestyle management. All severely obese individuals with preexisting comorbidities at the time of procedures (CHS 1 – CHS 4) on Qsymia accrue fewer direct medical costs than those undergoing on lifestyle management interventions. Class 2 obese patients saw average cost savings of $14,724 and Class 3 obese patients saw average cost savings of $18,956. Cost savings were significantly higher in patients with more severe health risks. Severely obese patients with two or more health comorbidities increased savings in direct costs by over 103% as compared to metabolically healthy (CHS-0) obese individuals.

Table 3 reports results from of incremental cost-effectiveness ratios (CER) by BMI class and health state. Qsymia led therapy is cost-effective in all severely obese patients. In

patients with added health risk (CHS1 – CHS4), Qsymia was economically dominant (i.e., saved costs and QALYs). ICERs for direct medical costs in these health state were on average -$18,977/QALY. ICERs for patients with predefined clinical comorbidities (CHS-3 & CHS-4) were 41% higher than similar patients with preclinical comorbidities (CHS-1 & CHS-2). Qsymia led therapies are still more cost effective than lifestyle management at a willingness to pay threshold of $50,000 per QALY in all these patients. Qsymia interventions in severely obese patients at CHS-0 is cost-effective compared to Lifestyle management but not economically dominant (more expensive while providing more health benefits).

Employer perspective: All severely obese patients on Qsymia accrue lower productivity losses than those on lifestyle modification therapy only. Individuals in Class 2 Obesity opting for Qsymia led therapies would save, on average $15,057 ($2,318 - $34,869) in productivity losses over the course of their lifetime. Similarly, Class 3 obese individuals would save on average $19,952 ($4,022 - $45,071) in productivity losses over the course of their lives (Table 2). Productivity loss savings are higher in patients with advanced health risk states with severely obese patients in CHS4 showing 98% reduction in productivity losses as compared to similar patients in CHS-0. As seen in Table 3, Qsymia based weight loss interventions are not only cost effective (at a willingness to pay threshold of $50,000 per QALY), they economically dominant in all severely obese individuals. The ICERs in these health states average at - $19,591/QALY (Range: -

$980/QALY to - $40,009/QALY) in Class 2 obese and -$19,939 (Range:-$2,417 to -$34,525).

Total costs: Total societal costs includes both the direct medical costs to the individual as well as the costs from loss of productivity. All severely obese patients opting for Qsymia had incrementally lower total societal costs as compared to individuals on lifestyle management. Average total societal savings is $26,771/QALY (UI: $4,618/QALY - $57,533/QALY) for Class 2 obese individuals and $34,891/QALY (UI: $6,260/QALY - $79,016/QALY) in Class 3 obese individuals. For obese populations in higher CHS states Qsymia leads to larger cost savings with largest savings being at CHS-4 (100% more total societal savings than CHS-0). Qsymia is both cost-effective and economically dominant in estimating total costs in comparison to lifestyle-based weight loss intervention plans.

Sensitivity analysis: Figure 2 shows the impact in ICERs with varying model parameters. The figures hihghlight key results from runs on metabolically healthy obese (CHS0) individuals and those with two or more health risks at time of surgery (CHS4). In all patients, age at time of which Qsymia led therapy was initiated had the largest impact on ICERs. Starting Qsymia in younger ages showed increased cost savings. In patients over 40 years, Qsymia was still cost-effective but not economically dominant (incremental cost savings were not seen).

DISCUSSION

Our results show that Qsymia-led (phentermine plus topiramate-ER) weight loss treatment plans is not only a cost-effective treatment option in all severely obese individuals but also show large cost savings in comparison to standard care. Cost savings were consistently seen at all perspectives. Severely obese individuals with clinical comorbidities at time of surgery (T2DM and/or Hypertension) on Qsymia show over 50% more savings per quality adjusted life years than similar individuals who are metabolically healthy. Qsymia in severely obese individuals that are metabolically healthy a cost-effective but doesn't show cost savings. The incremental cost savings for Qsymia led therapies are higher and more significant as obesity interventions are initiated in individuals at earlier ages and in those with existing health risk states.

Using a simulation model to assess cost-effectivenss allowed us to capture both the impact of weight loss on obesity assocatied medical costs and productivity losses and the downstream impact from changes in risks of obesity-asscіated health outcomes (CHD, stroke, T2DM complications and cancer). Our study shows that on Qsymia, incremental savings in productivity losses were between 20% - 45% higher than savings in direct medical costs. Third-party payers and employers evalauting the cost-effectiveness of weight loss medication would benefit from (1) continuing to cover indivudals on weight-loss medication beyond the immdediate course of the medication future cost savings

significatnly outweigh the risks and costs the medication itself, and (2) to include both direct and indirect cost savings into account.

Limitations

While weight loss treatment options through behavioral modalities and bariatric surgery result in weight reduction in long-term, we cannot extrapolate results in assessing the impact of pharmacotherapy. Long-term efficacy of drug-based treatment for weight loss is limited. More recent clinical trials are more stringent in their study design and approach to deal with missing data but don't look beyond a 2-year impact. We used data from a significant number of these trials in our model under the assumption that beyond three years of study, Qsymia benefits were not maintained and were driven primarily by lifestyle. Projections were carried based on natural trajectories at individual BMI-CHS states beyond year 5. Similarly, changes in health states associated with obesity came from limited resources and short-term follow-up.

In overall management of obesity, lifestyle modification through strict diet, physical activity and counseling has been the first line of management and had successfully sustained weight loss over the short term[89]. However, maintenance of weight loss over longer durations has shown poor efficacy in multiple study settings[70,90,91]. Bariatric surgery has proved to be effective in severely obese individuals, but high costs of procedures with mixed long-term efficacy findings have limited its use[18,73,92]. Until

recently pharmacotherapy for weight loss was limited. By projecting over the life span and capturing not only economic effects from weight loss but also the downstream changes in obesity-associated clinical outcomes, our model paints a clearer picture on the addressing the need for long-term impact. It should allow health insurers, especially Medicare to prioritize patients early in weight loss programs and look at cost savings from initiating a drug based protocol in applicable populations. Overall, our study indicates that pharmacotherapy-led weight loss interventions are cost-effective treatment options all in obese adults with pre-existing health conditions. The costs are associated with weight reduction as well improvements in health status over time leading to fewer obesity-associated complications over the lifetime. At all obese health states, ICERs for Qsymia are below the expected willingness to pay threshold for direct medical costs. The priority to treating obese individuals in CHS3 and CHS4 is important as the reductions medical costs and productivity losses linked to obesity incurred over the lifetimes in this population lead to far greater savings.

FIGURES & TABLES

Figure 1: Individual-based BMI progression model structure

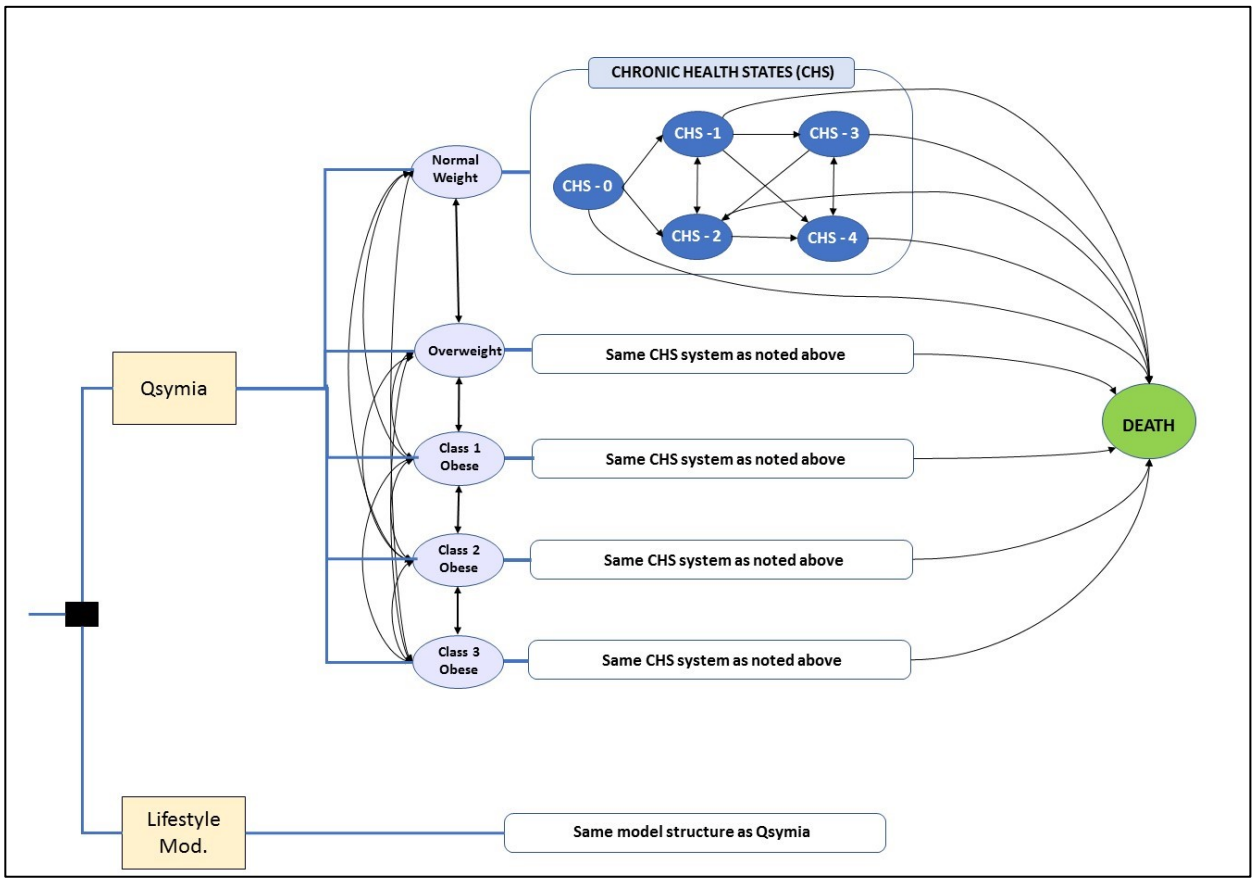


Table 2: Net costs and QALYs by obese status and CHS state

		Qsymia vs. Lifestyle Management			
		Class 2 Obesity		Class 3 Obesity	
	Health state	Net costs	Net effects	Net costs	Net effects
Third-party Perspective (Direct Medical Costs)	CHS 0	$323	0.507	$1,124	0.48
	CHS 1	$(2,300)	0.263	$(2,238)	0.21
	CHS 2	$(12,073)	0.639	$(16,037)	0.90
	CHS 3	$(21,860)	0.872	$(23,603)	1.27
	CHS 4	$(22,663)	0.872	$(33,946)	1.31
Employer Perspective (Productivity losses)	CHS 0	$(496)	0.507	$(1,148)	0.475
	CHS 1	$(2,318)	0.263	$(4,022)	0.209
	CHS 2	$(12,027)	0.639	$(14,074)	0.900
	CHS 3	$(25,574)	0.872	$(35,443)	1.270
	CHS 4	$(34,869)	0.872	$(45,071)	1.305
	CHS 0	$(173)	0.507	$(24)	0.475
	CHS 1	$(4,618)	0.263	$(6,260)	0.209

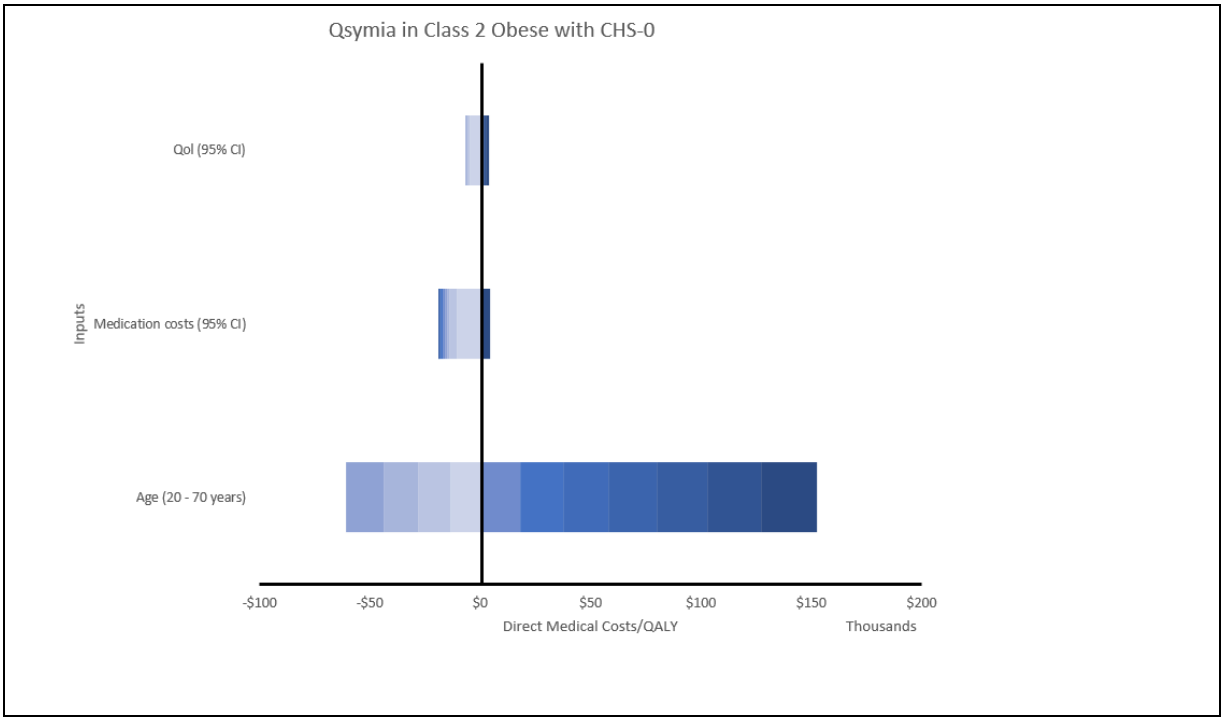
Societal Perspective (total costs)	CHS 2	$(24,100)	0.639	$(30,111)	0.900
	CHS 3	$(47,434)	0.872	$(59,045)	1.270
	CHS 4	$(57,533)	0.872	$(79,016)	1.305

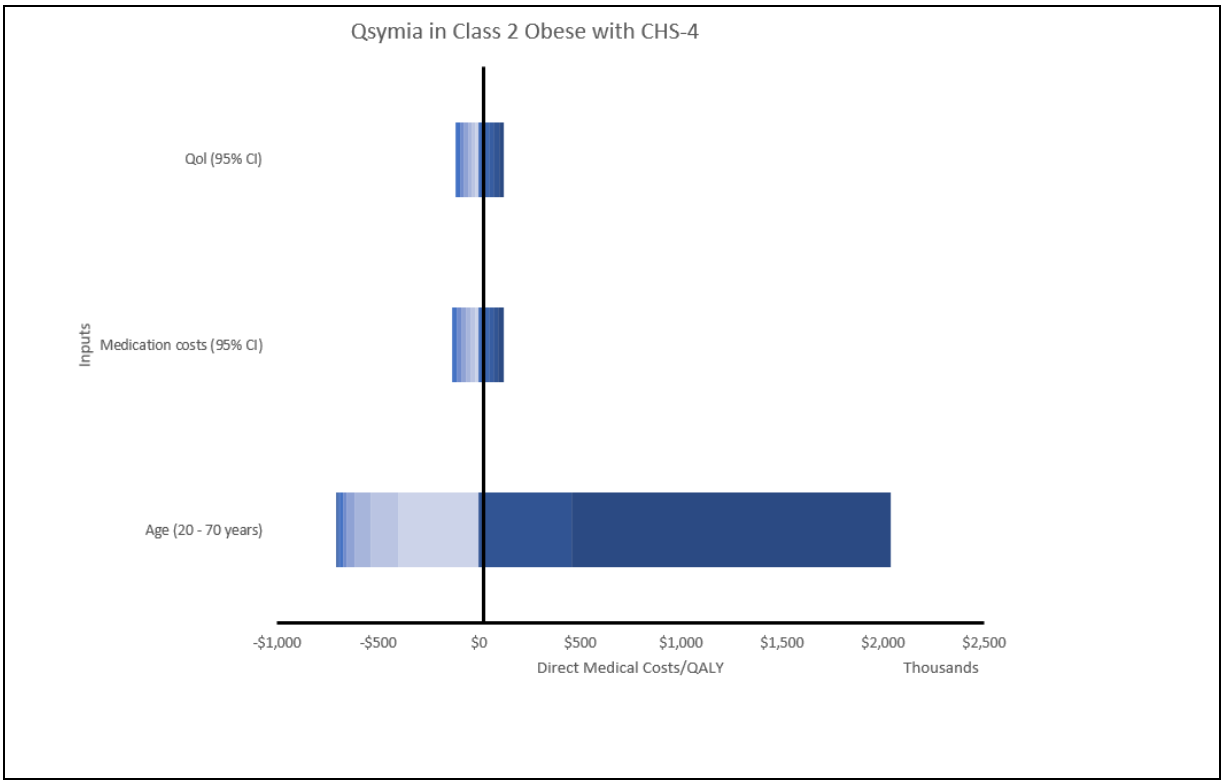
Table 3: Incremental cost-effectiveness ratios by Obesity status and CHS state

		Qsymia vs. Lifestyle Management	
	Health state	Class 2 Obesity	Class 3 Obesity
ICER (Third-party Perspective)	CHS 0	$638	$2,367
	CHS 1	$(8,735)	$(10,684)
	CHS 2	$(18,906)	$(17,819)
	CHS 3	$(25,074)	$(18,590)
	CHS 4	$(26,003)	$(26,004)
	CHS 0	$(980)	$(2,417)

ICER (Employer Perspective)	CHS 1	$(8,801)	$(19,202)
	CHS 2	$(18,833)	$(15,638)
	CHS 3	$(29,334)	$(27,914)
	CHS 4	$(40,009)	$(34,525)
ICER (Societal Perspective)	CHS 0	$(341)	$(51)
	CHS 1	$(17,536)	$(29,885)
	CHS 2	$(37,739)	$(33,457)
	CHS 3	$(54,409)	$(46,504)
	CHS 4	$(66,012)	$(60,529)

Figure 2: One-way sensitivity analysis




Qsymia in Class 2 Obese with CHS-4
QoI (95% CI)
Medication costs (95% CI)
Age (20 - 70 years)
Inputs
-$1,000
-$500
$0
$500
$1,000
$1,500
$2,000
$2,500
Direct Medical Costs/QALY
Thousands

Specific Aim 3 (SA3): Economic Value of intensive Weight loss Interventions on severely obese adults with Type 2 Diabetes Mellitus in the United States: a simulation model approach

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Keywords: Cost-effectiveness, Qsymia, Liraglutide, Gastric banding, Gastric bypass, healthcare cost, societal cost

BACKGROUND AND SIGNIFICANCE.

Type 2 diabetes (T2DM) has been not only been shown to be closely linked to increases in obesity but global numbers of T2DM are expected to be close to 440 billion by 2030[93]. Observational and randomized controlled trials have shown that management and treatment of obesity in T2DM patients using bariatric surgery or newer pharmacotherapy medications have led to diabetic remission and improvement in glycemic control, and improvments in other health consequences of obesity[61,74,94-97]. Additional improvements have also been shown in reducing cardiovascular risk and microvascular compilcations from T2DM[98-100].

Both modalities of treatment are not without their limitations. While surgical treatment has shown short term improvement in diabetic remission and glycemic control, long term effects on quality of life, impact on T2DM complications are less clear. Studies examining the cost-effectiveness of surgical interventions have found them to be cost effective or lead to cost savings under controlled trail settings[73,101,102]. But there is a paucity of information linked to the long-term health benefits and cost savings from multicomponent weight loss interventions in individuals with T2DM. As pharmacotherapy options are relatively newer and have similarly not been extensively studied for long term benefits[75], there is little or no information on extended impact of drug-based treatment modalities. Furthermore, these studies are limited in that: (1) use simplistic models of obesity and T2DM; (2) don't factor in progression of obesity health

status; (3) don't build in obesity-associated clinical outcomes and complication from T2DM; and (4) assess impact of interventions on newly diagnosed and established T2DM patients.

In this study, we used an individual-level cost-effectiveness model to examine the health benefits and cost savings from bariatric sugary (gastric banding and gastric bypass) and weight-loss pharmacotherapy (Qsymia and Liraglutide) in comparison to lifestyle modifications from a patient and payer perspective. We examined the cost savings and health benefits of each type intervention in Class 2 and 3 obese individuals with and without T2DM over their lifetime.

METHODS

Model Structure

We developed a Markov simulation model in TreeAge Pro Suite 2016 (TreeAge Software, Williamstown, MA) to determine the cost savings and cost-effectiveness of intensive weight management therapies from the third-party payer, employer and societal perspective in severely obese individuals with T2DM over their lifetime. The mode outline and input parameters, with sources, are detailed in Figure 1 and Table 1 respectively.

All simulated patients entering the model are at least 18 years of age in either Class 2 (35 ≤ BMI ≤ 40) or Class 3 (40 ≤ BMI) obesity with existing T2DM. They could receive one of the following treatment options:-

1. Lifestyle modification management: Patients were placed on a strict regime of diet control, physical activity, and lifestyle counseling.
2. Gastric Banding procedure: Patients underwent gastric banding and followed-up with lifestyle management.
3. Gastric Bypass procedure: Patients underwent gastric bypass and followed-up with lifestyle management.
4. Daily dosing of oral Qsymia (combination of phentermine plus topiramate) with adjuvant lifestyle management.
5. Daily subcutaneous injections of Liraglutide with adjuvant lifestyle management.

The Markov model transitions the simulated patients at one year time-steps. Each year they have the likelihood of transitions into 25 mutually exclusive health states. These chronic health states (CHS) represent combinations of 5 BMI categories [(normal (18.5 ≤ BMI ≤ 25), overweight (25 ≤ BMI ≤ 30), Class 1 obese (30 ≤ BMI ≤ 35), Class 2 obese (35 ≤ BMI ≤ 40), and Class 3 obese (40 ≤ BMI)] and six clinical parameters (blood pressure, fasting blood glucose, total cholesterol, high density lipoprotein, low-density lipoprotein, and triglycerides. The six clinical parameters are incorporated in 5 health states or increasing health risk:-

- CHS – 0: Metabolically healthy (Fasting Blood Glucose (FBG): <100 mg/L; Blood Pressure (BP): <130/85 mm Hg with no self-report of Hypertension or antihypertensive medication; HDL cholesterol (HDL): >=60 mg/dL; LDL Cholesterol (LDL):<130 mg/dL; Triglycerides (Trig): <150 mg/dL; Total Cholesterol (Tchol): <200 mg/dL)
- CHS – 1: Develop either Pre-Diabetes Mellitus (FBG: 100 – 126 mg/L) only; Pre-Hypertension only (BP: >130/85 mm Hg & <140/90 mmHg) ; Hypertension only (BP: >=140/90 mm Hg or self-report of Hypertension or antihypertensive medication); Hyperlipidemia only (HDL: <40 mg/dL in males and <50 mg/dL in females, LDL: 130-159 mg/dL, Trig: 150-199 mg/dL, Tchol: 200-239 mg/dL); Pre-Hypertension + Hyperlipidemia
- CHS – 2: Develop either Pre-Diabetes Mellitus (FBG: 100 – 126 mg/L) + Pre-Hypertension, Pre-Diabetes Mellitus + Hypertension, Pre-Diabetes Mellitus + Hyperlipidemia (HDL: <40 mg/dL in males and <50 mg/dL in females, LDL: 130-159 mg/dL, Trig: 150-199 mg/dL, Tchol: 200-239 mg/dL); Pre-Diabetes Mellitus + Pre-Hypertension + Hyperlipidemia; or Pre-Diabetes Mellitus + Hypertension + Hyperlipidemia
- CHS – 3: Develop either Diabetes Mellitus only (FBG: >= 126 mg/L or self-report of diabetes or self-report of medication); Hypertension + Hyperlipidemia (HDL: <40

mg/dL in males and <50 mg/dL in females, LDL: >160 mg/dL, Trig: >200 mg/dL, Tchol: >240 mg/dL)

- CHS – 4: Develop either Diabetes Mellitus + Hypertension; Diabetes Mellitus + Hyperlipidemia; or Diabetes Mellitus + Hypertension + Hyperlipidemia

Figure 1 provides an overview these health states. Transition between states are based on age, sex and multivariate risk-adjusted transition probabilities. Each year the individual has the probability of progressing between health states, developing associated clinical outcomes (stroke, cancer, coronary heart disease (CHD), and type 2 diabetes mellitus (T2DM) complications) or moving to death states from either disease or age-related mortality. The clinical health outcomes are based on BMI-health state the individual. The model also captured the likelihood of progressing through T2DM in both newly diagnosed (T2DM less than 5-years duration) and established T2DM individuals (T2DM over 10-years duration). The risk of developing T2DM complications for nephropathy, retinopathy, and neuropathy are each year are calculated based on the age of the individual, the BMI health state and the number of years they have had T2DM. We also allowed for individuals who developed End Stage Renal Disease (ESRD) to have a higher mortality risk than diabetic individuals without ESRD. Mortality risks were estimated based on the age and duration of ESRD for each individual. Based on the model assumptions, each intevention scenario leads to diabetes remission, and the share of patients in remission declines over time as patients relapse or die.

Inteventions also reduce the incidence of many diabetes-related complications. We used data from literature to estimate age/gender dependent risk of diabetic complications based on duration of diabetes[49,103,104]. Details on model variables and parameters are provided in the Table 1. Each simulated year, the model will accrue direct medical costs, productivity losses and health utility scores based on age-, health state- and health outcomes for each individual.

At the start of the model (Year 1), the interventions scenario determines the health state transition probability. Patients undergoing bariatric surgery, have added risk of having a surgical failure, developing a surgical complication, or dying during the procedure. In following years, all scenario will have patients undergoing lifestyle modification. Surgical relapse, complications, re-surgery probabilities, and adverse events from drugs are captured for five years. Post year five, all patients continued health state transitions, irrespective of intervention scenario. The patient will continue through the model until he or she reached the death state due to death from obesity-related illness, from other causes (i.e., overall mortality). At each time step, the model will accrue age- and state- specific direct medical costs, productivity losses, and QALYs. Table 1 details all parameter models included.

Simulations and model outcomes

Simulation run consisted of a total 1,000,000 trials; 1,000 patients (age >=18 years) run 1,000 times. Each run we calculated incremental cost-effectiveness ratio (ICER):

$$(\text{Cost}_{\text{Treament Option A}} - \text{Cost}_{\text{Treatment Option B}}) / (\text{Effectiveness}_{\text{Treament Option A}} - \text{Effectiveness}_{\text{Treatment Option B}})$$

"A" reprsent either gatric banding, gastric bypass, Qsymia or Liraglutide and "B" is lifestyle managgment. Costs are either direct medical costs, prodcutivity losses or both and Effectivenss is measures using QALYs. ICERs of ≤$50 000 per QALY were considered to be cost-effective. A treatment option was considered to be dominant if it led cost savings and increased health benefits.

Model parameters

The mutually exclusive BMI health states were derived from established prospective, longitudinal studies: Coronary Artery Disease Risk Development in Young Adults (CARDIA) and the Atherosclerosis Risk in Communities (ARIC) studies[42,105]. Incidence rates, recurrence and death probabilities on the four obesity-associated specific health outcomes (stroke, cancer, CHD, and T2DM complications) were derived from either large cohort studies (ex. Framingham Heart Study, North Manhattan Stroke Study) or extracted from literature. Appendix 2 details all transition probabilities and health outcome parameters, including data sources, in detail.

Direct medical costs were derived from the Medical Expenditure Panel Survey (MEPS) and published literature and included costs from outpatient visits, hospitalization, emergency room visits, and medications for each BMI health state and health outcome. All direct medical costs were estimated using a two-part model, a logistic regression model based on the probability of incurring individual medical costs and a generalized linear model with a gamma distribution and log link estimating annual medical costs incurring such costs. Productivity losses were estimated by using morbidity costs and pre-mature mortality costs were used to estimate productivity losses.

Work loss days were estimated using a negative binomial model estimated work loss days due to illness as a function on each health outcomes. Annual QALYs were estimated by using age-specific healthy QALYs attenuated by the utility weight associated with health state and/or outcome an individual developed in each year. Since individuals can develop multiple health outcomes in each time step, we looked to attribute costs and health effects conservatively. Direct medical costs incorporated the highest cost amongst the multiple health outcomes and health effects used the lowest QALYs values. When an individual transitions to a death state, we totaled the direct medical costs, productivity losses and QALYs that an individual accrues in each year of his/her lifetime. Table 1 details the direct, indirect costs and health utility scores included.

Data for the bariatric surgery model were derived from the Swedish Obesity Study and from data in at the Department of Bariatric Surgery at Johns Hopkins University Hospital. For perioperative mortality, we use separate rates for bypass and banding surgery[73,101,102]. We used multiple literature sources to estimate the effect of surgery on blood pressure and cholesterol values. Costs of surgery are derived from and encompasses both thee costs attributable to surgery, including the surgery costs and any complication costs in the first year. For costs in subsequent years, we included costs of follow-up care visits; nutritional supplements; long-term complications. Table 1 lists these costs by year after surgery. Health utility was captured as product of change in BMI status associated with surgery.

Qysmia, a combination of phentermine plus topiramate, is a 2012 US FDA approved drug for chronic weight management. In conjunction with diet and physical therapy, it has been shown to have significant improvement in weight status as well as noted improvements in blood pressure, lipids, and glycemic parameters[85]. The study utilized effectiveness results from the multiple randomized controlled trials (EQUIP, CONQUER, and its follow-up SEQUEL). Complete descriptions of the individual trials are available elsewhere[77,86-88]. In brief, these studies were double blinded placebo-controlled trials looking at the effectiveness of the Qsymia for weight reduction and obesity-related comorbidities. The studies were used to derive annual weight loss percentages, failure rates, and changes in health status while on Qsymia. Costs of Qsymia were estimated from the direct costs of the medication itself and doctors' office visits. Cost

per unit were obtained for 2016 Medi-Span's PriceRx database. Participants with no utilization at initiation and on stoppage were allocated a cost of zero dollars. Table 2 lists these Qysmia linked parameters.

Liraglutide, a glucagon-like peptide-1 analogue with and has been shown to be effective for the treatment of T2DM in addition to weight loss management. The study utilized results from the multiple studies reviewing effectiveness of the Liraglutide on severely obese individuals with T2DM. Complete descriptions of the individual trials are available elsewhere[78,106-111]. In brief, these studies were double blinded placebo controlled trials looking at the effectiveness of the Liraglutide for weight reduction and glycemic control. The studies were used to derive annual weight loss percentages, failure rates, and changes in health status while on Liraglutide. Costs of Liraglutide were estimated from the direct costs of the medication itself and doctors' office visits. Both direct medical costs and quality of life scores were extracted from literature.

RESULTS

Third-party payer perspective: Over their lifetime, obese individuals with T2DM would accrue $108,176 (UI: $73,445 - $131,942) in direct medical costs after Qsymia based therapy, $122,152 (UI: $89,741 - $151,308) in direct medical costs after Liraglutide based therapy, $111,830 (UI $104,901 - $117,097) in direct medical costs after laparoscopic

gastric banding procedures and accrue $116,498 (UI: $102,033 - $124,200) in direct medical costs after laparoscopic gastric bypass.

Table 2 shows the cost effectiveness ratios (CER) by payer perspective, intervention types and in different patient groups. Pharmacotherapy based interventions are cost-effective and economically dominant (i.e., saved costs and had larger health benefits) in all severely obese patients with T2DM. The cost-effectiveness ratio ranged between -$9,400/QALY and - $26,004/QALY. Gastric banding and gastric bypass procedures were economically dominant in all severely obese patients with T2DM and an added comorbidity (hypertension or hyperlipidemia). Bariatric procedures have a cost-effectiveness ratio between $5,795/QALY and $33,330/QALY. In newly diagnosed diabetics, Qsymia led cost savings of $23,918/QALY; and Liraglutide lead cost savings of $17,406. In established diabetes individuals the CERs were relatively the same as well. Gastric banding procedure has in T2DM obese individuals with single clinical health risk state (CHS3) did not show cost savings but CERs were well under the willingness to pay threshold. In new T2DM with multiple comorbidities, gastric banding led to cost savings of $18,780/QALY; and Gastric bypass led to cost savings of $11,626/QALY. In established diabetes individuals the ICERs were relatively the same as well.

<u>Employer Perspective:</u>

Over their lifetime, obese individuals with T2DM undergoing Qsymia based therapy would accrue $229,777 (UI: $184,897 - $259,467) in productivity losses, those on Liraglutide based therapy would accrue $241,293 (UI: $194,456 - $283,749) in productivity losses, those undergoing laparoscopic gastric banding procedures would accrue $215,331 (UI $174,193 - $236,852) in productivity losses; and those undergoing laparoscopic gastric bypass procedures would accrue $192,128 (UI: $176,784 - $198,112) in productivity losses.

All severely obese adults with T2DM accrue lower productivity losses than those on lifestyle modification therapy only on both surgical therapy and medication in comparison to standard care and are economically dominant. Average costs savings were highest for gastric banding procedures (-$47,883 per QALY) and Liraglutide (-$35,577 per QALY). There was not significant difference in cost savings between the procedures as compared to standard care.

Total costs: Total costs accrued over the lifetime includes both the direct medical costs to the individual as well as the costs from loss of productivity. Similar to direct medical costs and productivity losses, all interventions lead to large savings in total societal savings compared to standard care. While largest cost savings were seen with the surgical procedures, looking at cost saved per QALY, pharmacotherapy procedures were 24% more economically dominant than surgical therapies. Average CERs were for Qsymia (-

$56,864 per QALY), Liraglutide was (-$51,371 per QALY), gastric banding was (-$51,758 per QALY) and gastric bypass was (-$30,952 per QALY).

DISCUSSION

Our results show that both bariatric surgery and weight loss pharmacotherapy are cost-effective weight loss treatment options in patients with T2DM and help reduce overall complication over the lifetime. The cost-effectiveness ratios are all well below the commonly used diabetic intervention threshold of $50,000/QALY benchmark. Looking purely at medical costs, medical interventions are shown to be more cost-effective in individuals with higher obesity states and added additional health risk factors as compared to surgical interventions. But when including indirect costs, treatment on weight loss medication are equal if not more cost-effectiveness. Among medical interventions, Qysmia leads to 27% more in direct medical costs saved per QALY than Liraglutide in new T2DM patients and 41% more in direct medical costs saved per QALY in established T2DM patients. Overall, treatment in obese individuals with T2DM complicated by additional health risk states (CHS4) leads to more cost savings over time.

Qsymia and Liraglutide, while both used in T2DM patients have differing primary use scenarios. Qsymia is commonly used chronic weight management medication that shows improved glycemic control with improvements in weight status. Liraglutide is used in T2DM patients with severe obesity for glycemic control. Due to its appetite suppressant

actions, it also leads to weight loss. More recently, randomized control trials showed similar weight loss effects of Liraglutide in obese individuals with and without T2DM. In our study, we note that Liraglutide has lower ICER that Qsymia in obese patients with T2DM. We also see a lower number of T2DM related complications arising over the lifetime in patients taking Liraglutide. Achieving glycemic control and stability is a larger driver in the estimating lifetime costs than looking at purely obesity management.

There have been a few T2DM focused disease simulation models that assess clinical impact on changing health risk over time[49,103,104]. Hoerger et. al used cost-effectiveness T2DM model that included both T2DM complications and T2DM duration to estimate economic impact of bariatric surgery on obese patients with T2DM[102]. Our study further expands on these model by incorporating not only the progression of obesity over the lifetime but also incorporating (1) obesity associated health risk states as individual age; (2) clinical outcomes models linked to obesity-associated health states; and (3) a T2DM sub-model linked to obesity health state. This allows for a more realistic estimation on impact of interventions over long-term scenarios. But there are limitations in our model estimations as well. Weight loss achieved bariatric surgery has been widely reviewed in literature but there is limited data on long-term effects of bariatric surgery. Similarly, long-term efficacy of drug-based treatment for weight loss is limited. We used more recent clinical trials but most data most don't go beyond a 2-year impact. We also used data from a significant number of these trials in our model under the assumption that

beyond three years of study direct benefits from surgery or pharmacotherapy were not maintained. Similarly, changes in health states associated with obesity came from limited resources and cross-sectional data. Our model can estimate varied possible trajectory scenarios based on health outcome probabilities at each time interval, allowing us to get more realistic estimates.

FIGURES & TABLES

Figure 1: Individual-based BMI progression model structure

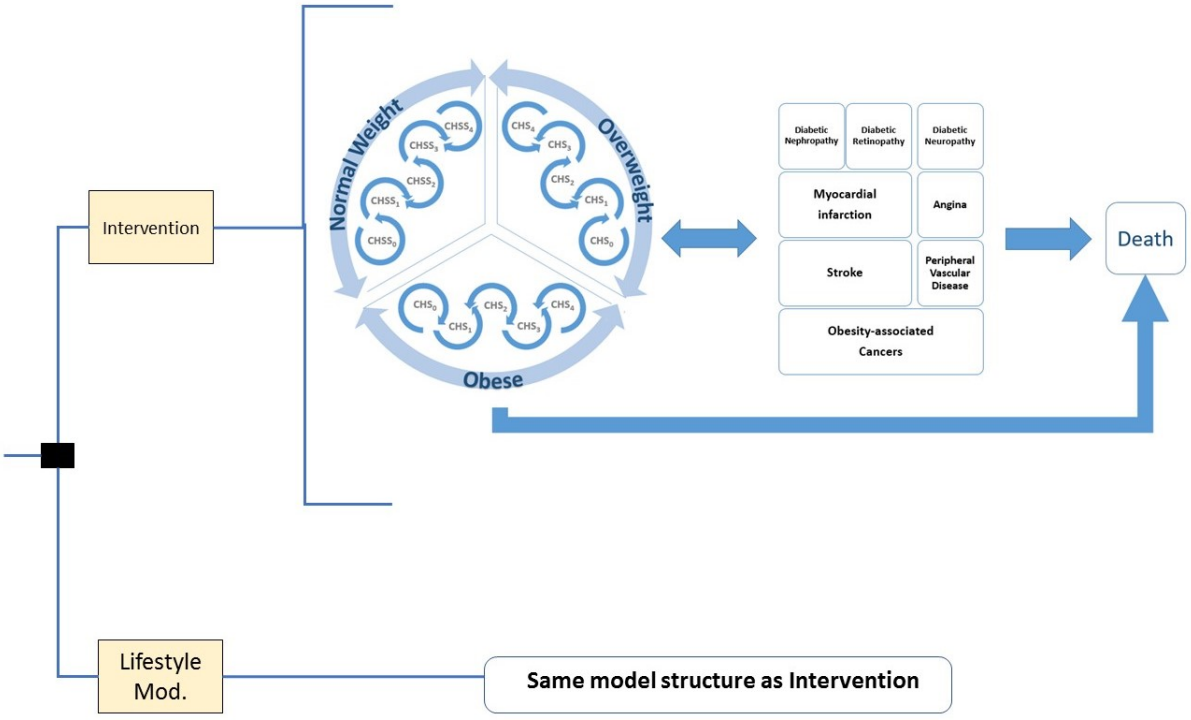


Table 2: Incremental cost-effectiveness ratios by Obesity status and CHS state

Dollars / QALY gained			QSYMIA	QSYMIA	LIRAGLUTIDE	LIRAGLUTIDE	BANDING	BANDING	BYPASS	BYPASS
			Class 2 Obesity	Class 3 Obesity	Class 2 Obesity	Class 3 Obesity	Class 2 Obesity	Class 3 Obesity	Class 2 Obesity	Class 3 Obesity
Third-party Perspective (Direct Medical Costs)	New T2DM	CHS 3	-$25,074	-$18,590	-$15,455	-$12,861	$19,535	-$5,099	$12,996	-$4,817
		CHS 4	-$26,003	-$26,004	-$17,924	-$23,386	-$16,286	-$21,274	-$10,535	-$12,718
	Established T2DM	CHS 3	-$25,074	-$18,590	-$13,596	-$10,546	$33,330	-$3,072	$18,768	-$5,795
		CHS 4	-$26,003	-$26,004	-$9,400	-$23,181	-$16,960	-$21,168	-$10,380	-$12,359
Employer Perspective (Productivity losses)	New T2DM	CHS 3	-$29,334	-$27,914	-$40,841	-$33,728	-$68,577	-$37,436	-$24,065	-$28,797
		CHS 4	-$40,009	-$34,525	-$30,424	-$29,802	-$41,933	-$42,904	-$30,558	-$26,413
	Established T2DM	CHS 3	-$29,334	-$27,914	-$60,865	-$29,882	-$64,636	-$40,737	-$22,802	-$26,473
		CHS 4	-$40,009	-$34,525	-$30,179	-$28,896	-$42,697	-$44,146	-$32,235	-$31,430
Societal Perspective (total costs)	New T2DM	CHS 3	-$54,409	-$46,504	-$56,297	-$46,589	-$49,042	-$42,535	-$11,070	-$33,614
		CHS 4	-$66,012	-$60,529	-$48,348	-$53,188	-$58,219	-$64,178	-$41,092	-$39,131
	Established T2DM	CHS 3	-$54,409	-$46,504	-$74,460	-$40,428	-$31,306	-$43,809	-$4,034	-$32,269
		CHS 4	-$66,012	-$60,529	-$39,579	-$52,077	-$59,657	-$65,313	-$42,615	-$43,789

Table 3: Health Benefits by Obesity status and CHS state

			LIESTYLE MOD.	LIESTYLE MOD.	QSYMIA	QSYMIA	LIRAGLUTIDE	LIRAGLUTIDE	BANDING	BANDING	BYPASS	BYPASS
			Class 2 Obesity	Class 3 Obesity	Class 2 Obesity	Class 3 Obesity	Class 2 Obesity	Class 3 Obesity	Class 2 Obesity	Class 3 Obesity	Class 2 Obesity	Class 3 Obesity
			%	%	%	%	%	%	%	%	%	%
CHD	New T2DM	CHS 3	43.42%	49.73%	30.45%	34.13%	33.36%	35.25%	33.14%	32.05%	28.98%	29.54%
		CHS 4	43.42%	49.73%	42.84%	39.94%	44.34%	43.48%	34.81%	35.06%	31.21%	30.91%
	Established T2DM	CHS 3	43.42%	49.73%	30.45%	34.13%	34.65%	36.38%	35.33%	35.02%	30.26%	30.68%
		CHS 4	43.42%	49.73%	42.84%	39.94%	45.43%	44.59%	35.15%	35.83%	31.66%	31.91%
STROKE	New T2DM	CHS 3	10.12%	11.13%	10.34%	9.81%	10.50%	9.95%	10.13%	9.70%	9.87%	29.54%
		CHS 4	10.12%	11.13%	10.93%	10.18%	10.90%	10.23%	10.15%	11.06%	10.07%	10.06%
	Established T2DM	CHS 3	10.12%	11.13%	10.34%	9.81%	10.72%	10.22%	10.47%	10.17%	10.15%	9.69%
		CHS 4	10.12%	11.13%	10.93%	10.18%	10.91%	10.09%	10.78%	10.56%	9.88%	10.28%
T2DM complications	New T2DM	CHS 3	66.25%	77.98%	31.67%	39.94%	33.68%	34.17%	44.36%	41.13%	35.45%	35.34%
		CHS 4	66.25%	77.98%	61.01%	61.69%	61.01%	68.92%	50.78%	49.67%	40.41%	39.84%
	Established T2DM	CHS 3	66.25%	77.98%	31.67%	39.94%	35.21%	39.12%	45.98%	47.01%	38.93%	37.52%
		CHS 4	66.25%	77.98%	61.01%	61.69%	63.83%	65.35%	46.80%	48.65%	41.61%	40.48%

Figure 2: Incremental cost-effectiveness ratios for Direct Medical Costs in (1) New T2DM and (2) Established T2DM

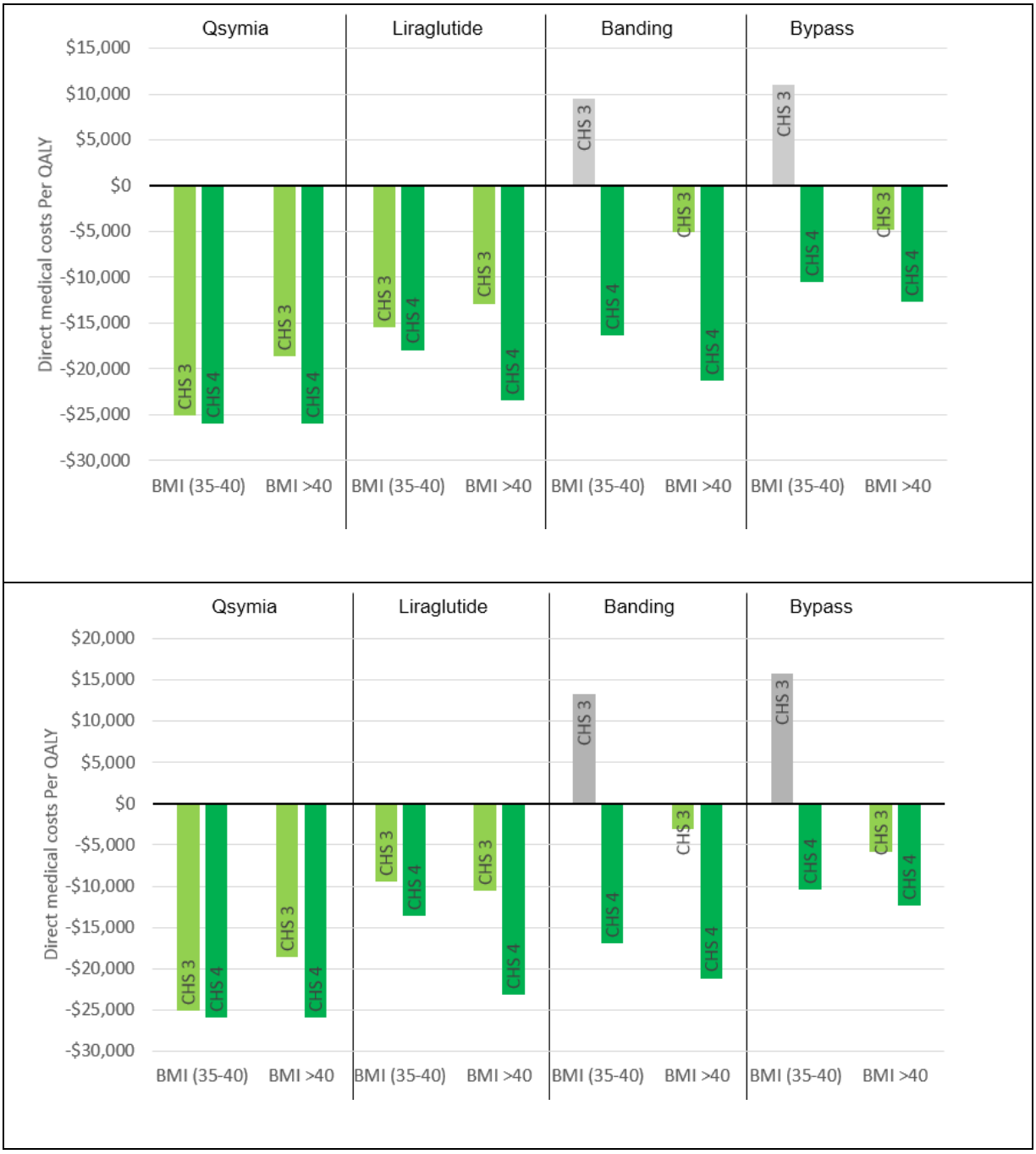
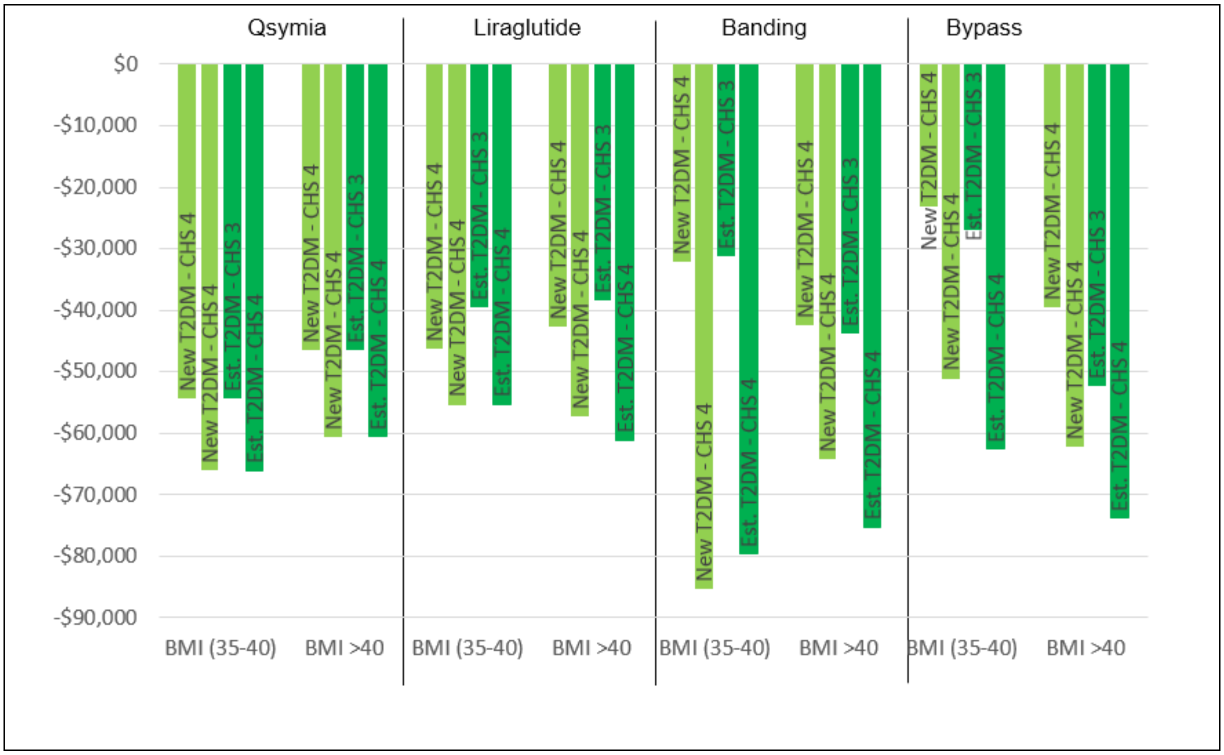


Figure 3: Incremental cost-effectiveness ratios for Total Costs



Limitations of overall simulation model

Our model analyzes lifetime obesity risks linked to CHS staging. A shortcoming of this system is the lack of inclusion of BMI level (a person who is obese level 3 is at higher risk than someone who is overweight). To address this, we have followed guidelines set by the authors of the EOSS system to incorporate BMI levels into the modeling framework [34,37].

Another limitation is that initially we assess all co-morbid conditions in developing CHS states equally without assigning weights based on their burden of illness. As is the first iteration of the model, it is not yet clear whether certain comorbidities should receive a higher weighting. Future revisions will add these varying burdens.

A limitation of the modeling structure itself is that some diseases for which obesity is a risk factor (hypertension, diabetes, dyslipidemias) are themselves risk factors for CHD and stroke. Because of the complexity of the interrelationships, we opted to make the simplifying assumption that those diseases for which obesity is a risk factor will not be counted as an additive effect on lifetime health and costs in the model. Therefore, the current model will provide a conservative estimate of risks and costs.

In integrating the four outcomes models into the core model we had to assume individual outcomes be independent of each other. This results in outcome processes affecting the

progression or rates of each other. This will be modified in the future iterations of the model over time.

In the overall conceptual framework we do not take in to account mental and physical functioning losses/burdens, both at the individual and societal level in the model. Also, population dynamics in the model do not include immigration and emigration were not stated in the base population generation. This being an individual-based simulation model, larger cohort effects are not considered. In future iterations of the model we look to incorporate both indirect costs from obesity and socio-economic variability.

Appendix 1: CHS states

Table A

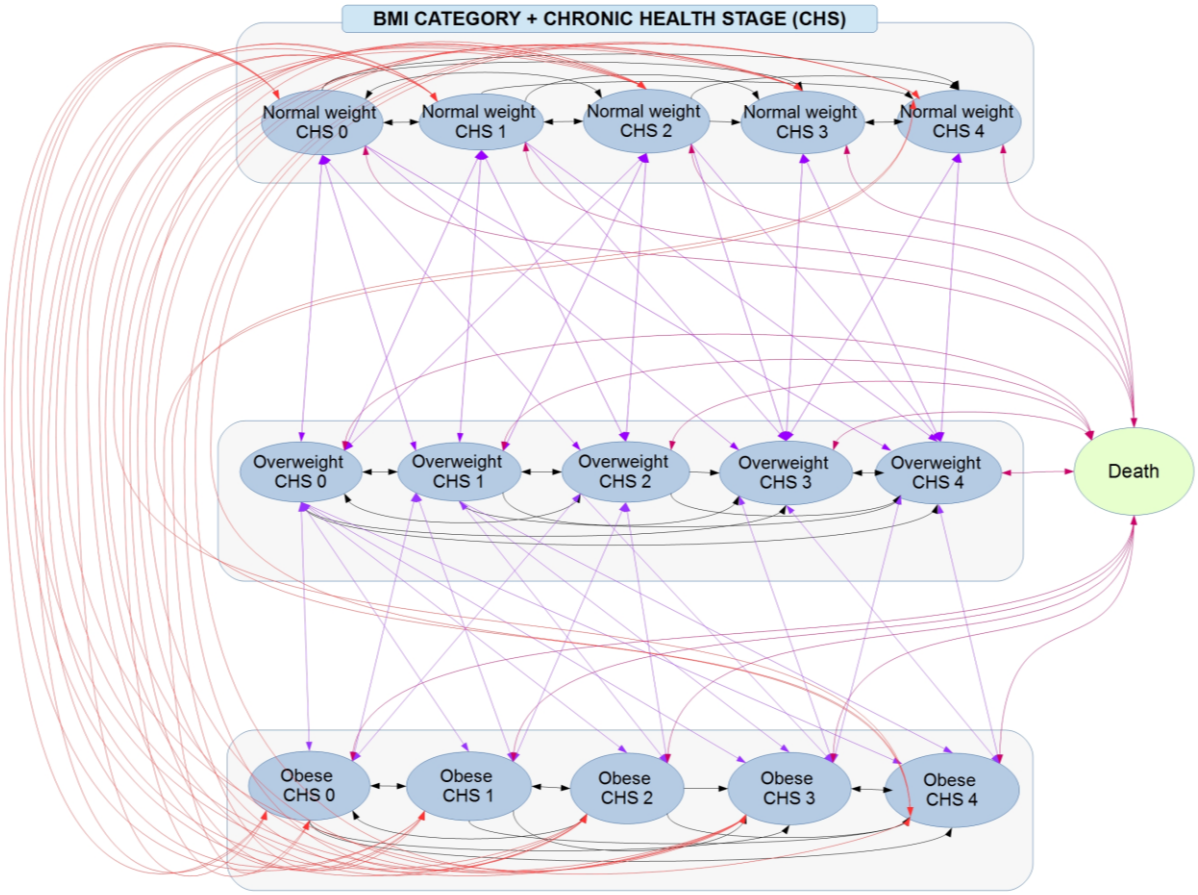
TABLE 2	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	Metabolic Healthy	(one or more of the following)	Prediabetes (AND) any one of CVD high risk factors	History of Diabetes (OR) one or more of CVD high risk factors	History of Diabetes (AND) one or more of CVD high risk factors
Fasting glucose (mmol/L)	1	2	2	3	3
Blood pressure (mm Hg)	1	2,3	2,3	3	3
HDL cholesterol (mg/dL)	1	2	2	2	2
Triglycerides (mg/dL)	1	2	2	3	3
Total cholesterol (mg/dL)	1	2	2	3	3
LDL cholesterol (mg/dL)	1	2	2	3	3

Table B

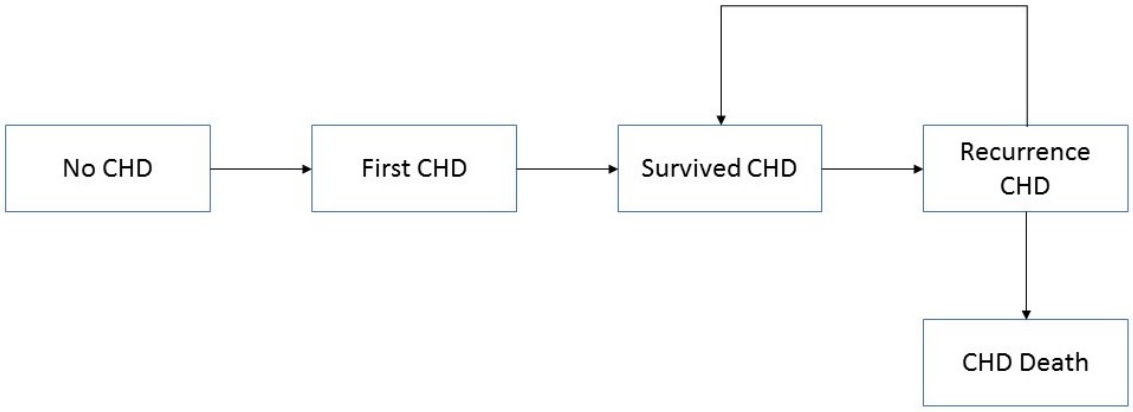
Stage 1	Stage 2	Stage 3	Stage 4
PreDiab only	PreDiab + PreHTN	Diab only	Diab + HTN
PreHTN only	PreDiab + HTN	HTN + HyperLip	Diab + HyperLip
HTN only	PreDiab + HyerLip		Diab + HTN + HyperLip
HyperLip only	PreDiab + PreHTN + HyperLip		
PreHTN + HyperLip	PreDiab + HTN + HyperLip		

Appendix 2: BMI – CHS transitions

Figure A



Appendix 3: CHD sub-model

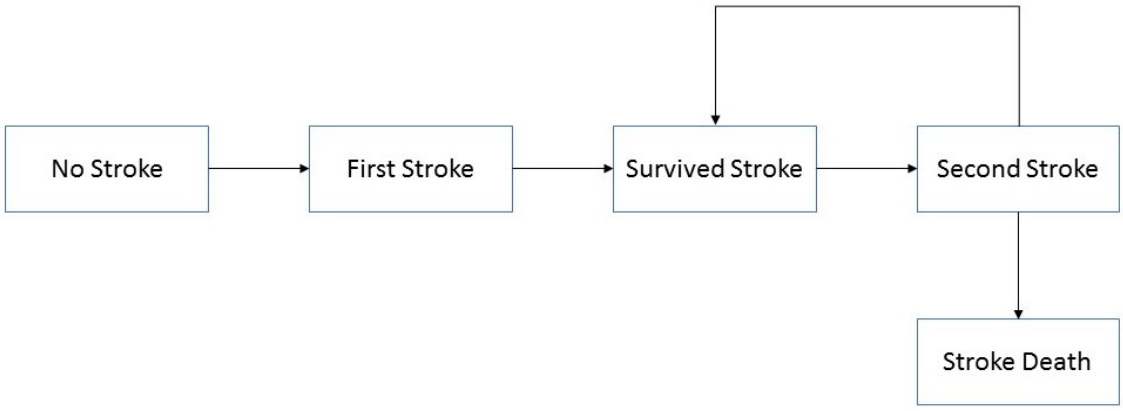


How are we modelling CHD	CHD is broken up into Angina and MI. As we are using data from Framingham Risk Score (FRS) and it doesn't separate out Angina and MI, we will taking a weighted average for both as we look at CHD as a whole	https://www.framinghamheartstudy.org/risk-functions/coronary-heart-disease/10-year-risk.php
How long does a person stay with CHD costs and UV in the mode?	Life time	On consultation with Dr. Cheskin

Initial prob of CHD	Formula from Framingham Risk Score (by gender, smoking status, age, and CHS stage)	Wilson, D'Agostino, Levy et al. 'Prediction of Coronary Heart Disease using Risk Factor Categories', Circulation 1998 https://www.framinghamheartstudy.org/risk-functions/coronary-heart-disease/10-year-risk.php
Death risk from CHD	Formula from Framingham Risk Score (by gender, smoking status, age, and CHS stage)	
Prob. Of recurrence of CHD	Formula from Framingham Risk Score (by gender, smoking status, age, and CHS stage)	
Bmi multiplier for risk (men)	Normal: 1	Wilson, P. W., D'Agostino, R. B., Sullivan, L., Parise, H., & Kannel, W. B. (2002). Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. Archives of internal medicine, 162(16), 1867-1872.
	Overweight: 1.4	
	Obese: 1.58	
Bmi multiplier for risk women)	Normal: 1	
	Overweight: 1.22	
	Obese: 1.54	
Bmi multiplier for death risk (men)	Normal: 1	
	Overweight: 1.37	
	Obese: 1.45	
Bmi multiplier for death risk (women)	Normal: 1	
	Overweight: 0.93	
	Obese: 1.3	

Angina and MI prevalence distribution	Distribution by age	https://www.heart.org/idc/groups/heart-public/@wcm/@sop/@smd/documents/downloadable/ ucm_449846.pdf Amsterdam, E. A., Lee, G., Mathews, E. A., & Mason, D. T. (1978). Relationship of myocardial infarction to presence of angina pectoris in patients with coronary heart disease: lack of abolition of angina by infarction. Clinical cardiology, 1(1), 31-34.
Cost of CHD	For Initial year after diagnosis, and Continuing after, (by gender and a weighted average of angina and MI)	Geisler, B. P., Egan, B. M., Cohen, J. T., Garner, A. M., Akehurst, R. L., Esler, M. D., & Pietzsch, J. B. (2012). Cost-effectiveness and clinical effectiveness of catheter-based renal denervation for resistant hypertension. Journal of the American College of Cardiology, 60(14), 1271-1277.
Utility values	For Initial year after diagnosis, and Continuing after, (by gender, age and a weighted average of angina and MI)	

Appendix 4: Stroke sub-model

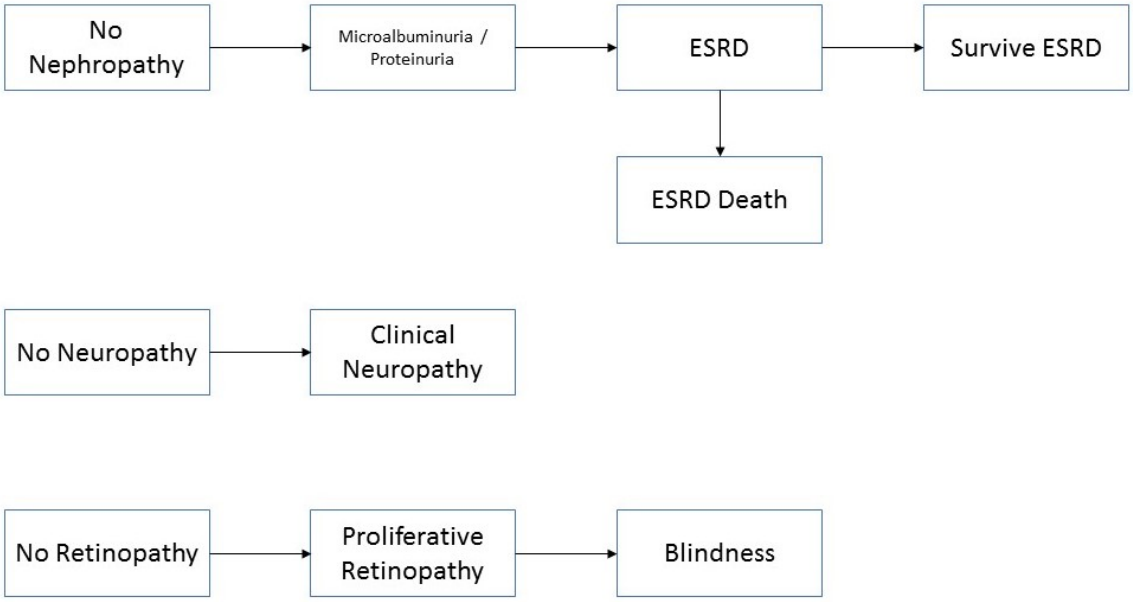


What is the length of stroke impact after 1st event?	10 years	Lee, W. C., Christensen, M. C., Joshi, A. V., & Pashos, C. L. (2007). Long-term cost of stroke subtypes among Medicare beneficiaries. Cerebrovascular Diseases, 23(1), 57-65. Demaerschalk, B. M., Hwang, H. M., & Leung, G. (2010). US cost burden of ischemic stroke: a systematic literature review. The American journal of managed care, 16(7), 525-533. ** On consultation with Dr. Larry Cheskin

Chance of recurrent stroke	CHS0 – 2 (1st year): 0.0924 CHS0 – 2 (after): 0.0318 CHS3-4 (1st year): 0.165 CHS3-4 (after): 0.0567	Sacco, R. L., Shi, T., Zamanillo, M. C., & Kargman, D. E. (1994). Predictors of mortality and recurrence after hospitalized cerebral infarction in an urban community The Northern Manhattan Stroke Study. Neurology, 44(4), 626-626. Chicago
Initial prob of stroke	Formula from Framingham Risk Score (by gender and smoking status)	Wolf, P. A., D'Agostino, R. B., Belanger, A. J., & Kannel, W. B. (1991). Probability of stroke: a risk profile from the Framingham Study. Stroke, 22(3), 312-318.
Bmi multiplier for risk (men)	Normal: 1	Hu, G., Tuomilehto, J., Silventoinen, K., Sarti, C., Männistö, S., & Jousilahti, P. (2007). Body mass index, waist circumference, and waist-hip ratio on the risk of total and type-specific stroke. Archives of internal medicine, 167(13), 1420-1427.
	Overweight: 1.17	
	Obese: 1.42	
Bmi multiplier for risk women)	Normal: 1	
	Overweight: 1.06	
	Obese: 1.23	
Gender multiple for death (1st year)	female x 1.14	Lloyd-Jones, D., Adams, R. J., Brown, T. M., Carnethon, M., Dai, S., De Simone, G., ... & Wylie-Rosett, J. (2010). Heart disease and stroke statistics—2010 update A report from the American Heart Association. Circulation, 121(7), e46-e215.
Gender multiple for death (within 5 year)	female x 1.09	
	0.241 for diabetics	

Stroke to Stroke Death (1st year)	0.135 for IGT	Sacco RL, Shi T, Zamanillo MC, Kargman DE: Predictors of mortality and recurrence after hospitalized cerebral infarction in an urban community: the Northern Manhattan Stroke Study. Neurology 44:626–634, 1994
Stroke to Stroke Death (after 1st year)	Diabetics: 0.1064 for subsequent years	
	IGT: 0.0596 for subsequent years	

Appendix 5: Diabetes Complications sub-model



Transition states	Probability	Ref.
No Nephropathy to Micro-Albuminuria	0.0509	Ref 18 (Gall 1997) - number for 5 year progression in key messages p.787 is 0.23. Adjusted for 1 year from 5 years. ~ 1-(1-0.23)**(1/5)
Micro-Albuminuria to Proteinuria	0.1032	Ref 20 (Ravid 1993) (the risk for developing this degree of proteinuria within 5 years of follow-up was 19/45 (42%) in the placebo group. Number adjusted for 1 year from 5 years: 0.1032 ~ 1-(1-0.42)**(1/5)

Proteinuria to ESRD Dialysis	0.0082	Ref A38 (Humphrey 1989): page 791, page 791, after 5 year, 7.0% , 8.4% developed it by 10 years and 11.6% by 15 years, the 15 year number was selected. Number adjusted for 1 year from 15 years: 0.0082 ~ 1-(1-0.116)**(1/15)
ESRD Dialysis to ESRD Transplant	0.006 to 0.084	*** depends on gender, age, race, Hypertension (adjusted by other death causes) Saran R, Li Y, Robinson B, et al. US Renal Data System 2014 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis 2015;66(1) (suppl 1):S1-S306. Table H.4.1 in Section H
ESRD Dialysis to ESRD Death	0.0434 to 0.5472	
ESRD Transplant to ESRD Death	0.0081 to 0.245	

States	Cost (2014 dollars)	Ref.	
	Event	Ongoing	
Microalbuminuria	437	437	Charbonnel B, Schernthaner G, Brunetti P, Matthews DR, Urquhart R, Tan MH, Hanefeld M. Long-term
Proteinuria	748	748	

			efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabete. Diabetologia. 2005; 48(6):1093-104
End-stage renal disease with hemodialysis	99046	99046	Chaitman BR, Hardison RM, Adler D, Gebhart S, Grogan M, Ocampo S, Sopko G, Ramires JA, Schneider D, Frye RL; Bypass Angioplasty Revascularization Investigation 2
End-stage renal disease with renal transplant	138071	44331	

			Diabetes (BARI 2D) Study Group. The bypass angioplasty revascularization investigation 2 diabetes randomized trial of different treatment strategies in Type 2 diabetes mellitus with stable ischemic heart disease. Circulation 2009; 120: 2529-2540

States	Utility Weights (penalty)	Ref.
No nephropathy	Ref	1. Coffey JT, Brandle M, Zhou H, Marriott D, Burke R, Tabaei BP, Engelgau MM, Kaplan RM, Herman WH: Valuing health-related quality of life in diabetes. Diabetes Care 25:2238–2243, 2002
Microalbuminuria	-0.011	
Proteinuria	-0.011	
End-stage renal disease with hemodialysis	-0.078	

End-stage renal disease with renal transplant	-0.078	2. Zhang P, Brown MB, Bilik D, Ackermann RT, Li R, Herman WH. Health Utility Scores for People With Type 2 Diabetes in U.S. Managed Care Health Plans. Diabetes Care 35:2250– 2256, 2012

Transition states	Probability	Ref.
No Neuropathy to Clinical Neuropathy	0.0518	Sands ML, Shetterly SM, Franklin GM, Hamman RF: Incidence of distal symmetric (sensory) neuropathy in NIDDM. The San Luis Valley Diabetes Study. Diabetes Care 20:322-329, 1997. 23
Clinical Neuropathy to Amputation	0.0113	Adler AI, Boyko EJ, Ahroni JH, Smith DG: Lower-extremity amputation in diabetes. The independent effects of peripheral vascular disease, sensory neuropathy, and foot ulcers. Diabetes Care 22:1029-1035, 1999.

States	Cost (2014 dollars)		Ref.	
	Event		Ongoing	

Clinical neuropathy	511	511	Avogaro A, Giorda C, Maggini M, Mannucci E, Raschetti R, Lombardo F, Spila-Alegiani S, Turco S, Velussi M, Ferrannini E; Diabetes and Informatics Study Group, Association of Clinical Diabetologists, Istituto Superiore di Sanità. Incidence of coronary heart disease in type 2 diabetic men and women: impact of microvascular complications, treatment, and geographic location. Diabetes Care 2007; 30: 1241-1247
Amputation	42929	1500	

States	Utility Weights (penalty)	Ref.

Clinical neuropathy	-0.065	1. Coffey JT, Brandle M, Zhou H, Marriott D, Burke R, Tabaei BP, Engelgau MM, Kaplan RM, Herman WH: Valuing health-related quality of life in diabetes. Diabetes Care 25:2238–2243, 2002 2. Zhang P, Brown MB, Bilik D, Ackermann RT, Li R, Herman WH. Health Utility Scores for People With Type 2 Diabetes in U.S. Managed Care Health Plans. Diabetes Care 35:2250–2256, 2012
Amputation	-0.105	

Transition states	Probability	Ref.
No Retinopathy to Non Proliferative	0.1140 with Insulin 0.0653 otherwise	Klein R, Klein BE, Moss SE, Cruickshanks KJ: The Wisconsin Epidemiologic Study of diabetic retinopathy. XIV. Ten-year incidence and progression of diabetic retinopathy. Arch Ophthalmol 112:1217-1228, 1994.
Non Proliferative to Proliferative	0.0390 with Insulin 0.0233 otherwise	
Non Proliferative to Blindness	0.0308	
Non Proliferative to Blindness	0.0141 with Insulin 0.0166 otherwise	
Proliferative to Macular edema	0.0248	

Proliferative to Blindness	0.0148 with Insulin 0.0166 otherwise	

States	Cost (2014 dollars)		Ref.
	Event	Ongoing	
NonProliferative Retinopathy	103	103	Avogaro A, Giorda C, Maggini M, Mannucci E, Raschetti R, Lombardo F, Spila-Alegiani S, Turco S, Velussi M, Ferrannini E; Diabetes and Informatics Study Group, Association of Clinical Diabetologists, Istituto Superiore di Sanità. Incidence of coronary heart disease in type 2 diabetic men and women: impact of microvascular complications, treatment, and geographic location. Diabetes Care 2007; 30: 1241-1247
Macular edema or proliferative retinopathy	1101	103	
Blindness	2951	2951	Bretzel RG, Nuber U, Landgraf W, Owens DR, Bradley C, Linn T. Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open

			randomised controlledtrial. Lancet. 2008 Mar 29;371(9618):1073-84.

States	Utility Weights (penalty)	Ref.
No blindness in both eyes	Ref.	1. Coffey JT, Brandle M, Zhou H, Marriott D, Burke R, Tabaei BP, Engelgau MM, Kaplan RM, Herman WH: Valuing health-related quality of life in diabetes. Diabetes Care 25:2238–2243, 2002 2. Zhang P, Brown MB, Bilik D, Ackermann RT, Li R, Herman WH. Health Utility Scores for People With Type 2 Diabetes in U.S. Managed Care Health Plans. Diabetes Care 35:2250– 2256, 2012
NonProliferative Retinopathy	no change	
Macular edema or proliferative retinopathy	no change	
Blind in one eye	-0.043	
Blind in both eyes	-0.17	

Appendix 6: Model Parameters

Variable		Distribution type	Mean	Range or standard deviation	Source
Utility Values					
Utility Values	Stroke	Beta	0.6	0.09	112-157
	CHD	Beta	0.73	0.1	
	Diabetic nephropathy	Beta	0.74	0.09	
	Diabetic neuropathy	Beta	0.65	0.04	
	Diabetic retinopathy	Beta	0.78	0.04	
	ESRD	Beta	0.63	0.03	
	Blindness	Beta	0.52	0.06	
	Renal Cancer	Beta	0.7	0.06	
	Cervical Cancer	Beta	0.63	0.11	
	Pancreatic Cancer	Beta	0.66	0.08	
	Gastric Cancer	Beta	0.52	0.08	
	Hypertension	Beta	0.97	0.01	
	Prostate	Beta	0.71	0.16	
	DM2	Beta	0.85	0.08	
	- First year	Beta	0.66	0.06	

Utility Values (Breast Cancer)	- After First year	Beta	0.77	0.06	
	- Last year	Beta	0.23	0.001	
Utility Values (Colon Cancer)	- First year	Beta	0.52	0.12	
	- After First year	Beta	0.83	0.05	
	- Last year	Beta	0.3	0.001	
Utility Values (Esophageal Cancer)	- Early years	Beta	0.71	0.22	
	- Last year	Beta	0.34	0.001	
Utility Values (Uterine Cancer)	- Early years	Beta	0.69	0.15	
	- Last year	Beta	0.79	0.11	
Cost values					
Cost ($U.S.)	Stage 1 (CHS-1)		$497		158
	Stage 2 (CHS-2)		$1,123		
	Normal Weight Stage 3 (CHS-3)		$1,680		
	Overweight CHS-3		$2,055		
	Obese CHS-3		$3,930		
	Normal Weight Stage 4 (CHS-4)		$2,906		
	Overweight CHS-4		$3,656		
	Obese CHS-4		$7,406		
Cost ($U.S.): CHD	In first year				

	- Age 18-44 years	Gamma	$19,933	$24,824	158
	- Age 44- 65 years	Gamma	$17,244	$11,109	
	- Age > 65 years	Gamma	$13,724	$9,324	
	After first year				
	- Age 18-44 years	Gamma	$5,178	$14,673	158
	- Age 44- 65 years	Gamma	$6,926	$18,766	
	- Age > 65 years	Gamma	$4,100	$11,576	
Cost ($U.S.): DM2	- Age 18-44 years	Gamma	$11,706	$17,764	158
	- Age 44- 65 years	Gamma	$8,109	$22,031	
	- Age > 65 years	Gamma	$1,332	$3,409	
	- Age 18-44 years	Gamma	$672	$3,373	158
	- Age 44- 65 years	Gamma	$867	$3,895	
	- Age > 65 years	Gamma	$1,050	$3,901	
Cost ($U.S.): Diabetic Nephropathy	Diabetic Nephropathy	Gamma	$593	$220	159
	ESRD-Initial year	Gamma	$95,130	$31,396	160
	ESRD-After Initial year	Gamma	$62,578	$15,802	
Cost ($U.S.): Diabetic Neuropathy		Gamma	$456	$323	158
	Diabetic Retinopathy	Gamma	$650	$363	

Cost ($U.S.): Diabetic Retinopathy	Blindness	Gamma	$2,872	$75	
Cost ($U.S.): Stroke	- Age 18-44 years	Gamma	$11,034	$16,744	158
	- Age 44- 65 years	Gamma	$7,643	$20,766	
	- Age > 65 years	Gamma	$7,098	$13,860	
Cost ($U.S.): Cancer (female)	Breast cancer				161
	- First year		$25,386		
	- After First year		$2,207		
	- Last year		$78,570		
	Cervical cancer				
	- First year		$49,692		
	- After First year		$1,425		
	- Last year		$98,192		
	Colorectal cancer				
	- First year		$56,460		
	- After First year		$3,159		
	- Last year		$105,649		
	Esophageal cancer				
	- First year		$87,486		
	- After First year		$6,853		
	- Last year		$130,348		

	Renal cancer				
	- First year		$42,237		
	- After First year		$6,255		
	- Last year		$92,304		
	Pancreatic cancer				
	- First year		$102,808		
	- After First year		$8,672		
	- Last year		$137,426		
	Stomach cancer				
	- First year		$78,184		
	- After First year		$3,977		
	- Last year		$129,697		
	Uterine cancer				
	- First year		$29,452		
	- After First year		$1,535		
	- Last year		$87,719		
Cost ($U.S.): Cancer (male)	Colorectal cancer				161
	- First year		$25,386		
	- After First year		$2,207		
	- Last year		$78,570		

Esophageal cancer			
- First year		$49,692	
- After First year		$1,425	
- Last year		$98,192	
Renal cancer			
- First year		$56,460	
- After First year		$3,159	
- Last year		$105,649	
Pancreatic cancer			
- First year		$87,486	
- After First year		$6,853	
- Last year		$130,348	
Prostate cancer			
- First year		$42,237	
- After First year		$6,255	
- Last year		$92,304	
Stomach cancer			
- First year		$102,808	
- After First year		$8,672	
- Last year		$137,426	
Risk of developing health complications			

CHD	Risk of developing CHD (by age)				
	at CHS-2	Triangular	0.01023	0-0.04	[46,162]
	at CHS-3	Triangular	0.01193	0-0.047	
	at CHS-4	Triangular	0.01813	0-0.063	
	multiplier for increased risk due to being overweight	Triangular	1.31	1.22-1.4	[162]
	multiplier for increased risk due to being obese	Triangular	1.56	1.54-1.58	
	Risk of recurring of CHD (by age)				
	at CHS-2	Triangular	0.04275	0-0.1	[163]
	at CHS-3	Triangular	0.0347	0-0.057	
	at CHS-4	Triangular	0.0397	0-0.074	
	Mortality risk due to CHD (by age)				
	at CHS-2	Triangular	0.01023	0-0.04	[46,162]
	at CHS-3	Triangular	0.01193	0-0.047	
	at CHS-4	Triangular	0.037	0.0007-0.113	
	multiplier for increased mortality	Triangular	1.175	0.98-1.37	

	risk due to being overweight				
	multiplier for increased mortality risk due to being obese	Triangular	1.375	1.3-1.45	
Stroke	Risk of developing Stroke (by age)				
	at CHS-0	Uniform		0-0.012	46,162,164
	at CHS-1	Uniform		0-0.015	
	at CHS-2	Uniform		0-0.017	
	at CHS-3	Uniform		0-0.015	
	at CHS-4	Uniform		0-0.028	
	multiplier for increased risk due to being overweight	Uniform		1.06-1.17	165,166
	multiplier for increased risk due to being obese	Uniform		1.23-1.42	
	Risk of recurring of Stroke				
	- First year	Uniform		0.0924-0.165	167

	- After First year	Uniform		0.0318-0.0567	
	Mortality risk (by age)				
	- First year	Uniform		0.135-0.241	[167]
	- After First year	Uniform		0.0596-0.1064	
Diabetic nephropathy	Risk by years of having T2DM	Uniform		0-0.28	[168]
	Probability of developing ESRD	Uniform			[169]
	Mortality risk from ESRD (by age)	Uniform		0.081-0.239	[170]
Diabetic neuropathy	Risk by years of having T2DM	Uniform		0-0.72	[168]
Diabetic neuropathy	Risk by years of having T2DM	Uniform		0	[168]
	Probability of developing blindness	Uniform		0-0.8	[171,172]
Cancer	Risk of developing Cancer (female)				
	Breast	Uniform		0-0.0191	
	Cervical	Uniform		0-0.0007	
	Colorectal	Uniform		0-0.0066	
	Esophageal	Uniform		0-0.0004	

	Renal	Uniform		0-0.0018	[173,174]
	Pancreatic	Uniform		0-0.0025	
	Stomach	Uniform		0-0.001	
	Uterine	Uniform		0-0.0044	
	Risk of developing Cancer (male)				
	Colorectal	Uniform		0-0.0071	[173,174]
	Esophageal	Uniform		0-0.0013	
	Renal	Uniform		0-0.0031	
	Pancreatic	Uniform		0-0.0025	
	Prostate	Uniform		0-0.0284	
	Stomach	Uniform		0-0.0017	
	Risk of death from Cancer (female)				
	Breast	Uniform		0.008-0.06	[174]
	Cervical	Uniform		0.006-0.083	
	Colorectal	Uniform		0.027-0.105	
	Esophageal	Uniform		0.035-0.426	
	Renal	Uniform		0.011-0.057	

	Pancreatic	Uniform		0.033-0.289	
	Stomach	Uniform		0.03-0.314	
	Uterine	Uniform		0.007-0.048	
	Risk of death from Cancer (male)				
	Colorectal	Uniform		0.016-0.162	174
	Esophageal	Uniform		0.018-0.409	
	Renal	Uniform		0.008-0.069	
	Pancreatic	Uniform		0.018-0.335	
	Prostate	Uniform		0.015-0.051	
	Stomach	Uniform		0.015-0.264	
Annual wages		Triangular	$48,320	$37,286-$94,873	175

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Bio sketch

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EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YYYY	FIELD OF STUDY
Johns Hopkins Bloomberg School of Public Health (JHSPH), USA	PhD (c)	2017	Public Health (Health Systems)
Manipal University, India	MBBS	2006	Medicine

Personal Statement

I am PhD candidate in Health Systems at the Bloomberg School of Public Health at Johns Hopkins, graduating early 2017. I am currently a Fellow with the Global Obesity Prevention Center (GOPC) and the Center on Aging and Health (COAH) at Hopkins. My work at the COAH revolves on utilizing **geographic information systems (GIS)** to understand spatio-temporal variations in social and lifestyle patterns at the community level in the elderly. I am building on this work to integrate **wearable sensor data and spatial modeling techniques** to understand associations of activity spaces and walkability assessments in the elderly communities. My work with the GOPC (http://www.globalobesity.org/) uses **systems science models and GIS** to understand adverse health outcomes and health disparities linked to individual variability within the population. My PhD work explores clinical models on understanding obesity to chronic disease progression and building an **individual-based computational model** to evaluate the potential clinical and economic impact of obesity interventions through the lifespan.

Positions and Employment (most recent)

2015 – Curent	**Research Fellow,** *Johns Hopkins Aramco Healthcare Collaborative (JHAH), JHU*
2013 – Current	**Predoctotal Fellow & Senior Analyst,** *Johns Hopkins Global Obesity Prevention Center, JHSPH*
2013 – Current	**Research Fellow,** *Center on Aging and Health, JHSPH*
2012 – Current	**Research Assistant,** *Dr. Michelle Carlson, Carlson Lab, Center of Aging and Health, JHSPH*
2012 – 2013	**Research Assistant,** *Dr. Youfa Wang, Department of International Health, JHSPH*
2012 – 2013	**Research Assistant,** *Dr. Asad Latif, Anesthesiology and Critical Care Medicine, Johns Hopkins Hospital*
2012 – 2013	**Research Assistant,** *Dr. Alexander Vu, Department of International Health, JHSPH*
2012 – 2013	**Research Assistant,** *Dr. Eileen McGurty, Environmental Sciences & Policy, JHU*

Positions and Employment (most recent)

2015 – Curent	**Research Fellow,** *Johns Hopkins Aramco Healthcare Collaborative (JHAH), JHU*
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2012 – 2013	**Research Assistant,** *Dr. Eileen McGurty, Environmental Sciences & Policy, JHU*

Selected Publications (most recent)

1. Nau, C., Kumanyika, S., Gittelsohn, J., ***Adam, A.***, Lee, B. (2016) Identifying financially sustainable pricing interventions to promote healthier beverage purchases in small neighborhood stores. Preventing Chronic Disease (under review)
2. Lee, B., Ferguson, M., Hertenstein, D., ***Adam, A.***, Zenkov, E., Mui, Y., Brown, S. (2016) Simulating the Impact of Sugar-Sweetened Beverage Warning Labels in Baltimore, San Francisco and Philadelphia. American journal of Public Health (under review)
3. Fallah-Fini, S. ***Adam, A.***, Cheskin, L., Lee., B. Projecting clinical and economic burden of obesity in United States: A computational model (2016), Obesity (under review)
4. Lee, B., ***Adam, A.***, Zenkov, E., Ferguson, M., Hertenstein, D., Mui, Y., Brown, S. Identifying the impact of organized sports among youth on national healthcare costs from obesity: Simulation model from Project Play (2016). Health Affairs (under review)
5. Carlson MC, Varma VR, ***Adam A***, Harris GC, Zipunnikov V, Crainiceanu C. Mobile technology to measure activities related to cognitive health in older adults. Submitted (2016)
6. ***Adam A***, Varma VR, Harris GC, Carlson MC. Using Digital Tools to Link Cognitive Aging and Neighborhood Factors. Submitted (2016)
7. ***Adam A***, Varma VR, Carlson MC, Zipunnikov V, Crainiceanu C. Move beyond life spaces: Translating GPS data to characterize mobility patterns and trends at the individual and population-level. (Manuscript in prep.)
8. ***Adam, A.***, Fallah-Fini, S., Cheskin, L., Lee., B. Determining the clinical effectiveness and cost-effectiveness of Bariatric Surgery on Class 1, 2 and 3 obese adults in the United States. (Manuscript in prep.)
9. ***Adam, A.***, Fallah-Fini, S., Cheskin, L., Lee., B. Determine the impact of diet and physical activity on the BMI variability in the USA using individual based Markov models. (Manuscript in prep.)
10. Gittelsohn, J., Mui, Y., ***Adam, A.***, Lin, S., Kharmats, A., Igusa, T., & Lee, B. Y. (2015). Incorporating systems science principles into the development of obesity prevention interventions: Principles, benefits, and challenges. Current obesity reports, 4(2), 174-181.
11. Mui, Y., Lee, B. Y., ***Adam, A.***, Kharmats, A. Y., Budd, N., Nau, C., & Gittelsohn, J. (2015). Healthy versus Unhealthy Suppliers in Food Desert Neighborhoods: A Network Analysis of Corner Stores' Food Supplier Networks. International journal of environmental research and public health, 12(12), 15058-15074.
12. ***Adam, A.***, Wirtz, A., Pham, K., Leonard Rubenstein, J. D., Glass, N., & Singh, S. (2014). The prevalence of sexual violence among female refugees in complex humanitarian emergencies: a systematic review and meta-analysis.

Awards and Research Support

2015 – Curent	**Johns Hopkins Aramco Healthcare Collaborative Research Fellowship,** *Johns Hopkins Medical Institution, JHU*
2014 - 2015	**Mid Atlantic Nutrition Obesity Research Center (NORC) Pilot/Feasibility Grants** *Using computational modeling to evaluate the potential clinical and economic impact of obesity interventions through the lifespan: a tool for prevention and treatment* *Role:*
2013 – 2016	**Doctoral Fellowship in Systems Science,** *Johns Hopkins Global Obesity Prevention Center, JHSPH*
2013	**Wireless Health Doctoral Award,** *Wireless Health Conference, NSF*

Software Skills

Quantitative analysis: R, Stata, StatsDirect, Epi Info, SaTScan,
Agent based modelling: Netlogo, AnyLogic
Systems Dynamic modelling: Vensim,
Economic modelling: TreeAge
Social network Analysis: UCINet
Qualitative analysis: NVivo, HyperRESEARCH, Atlas.ti
GIS Tools: ArcGIS, ArcGIS Server, Google Earth, MapInfo
Web Mapping: MapServer, Google Maps API, ArcExplorer
Image Processing: Photoshop, Irfanview, Gimp

Coding, Publishing, Web: Adobe Acrobat Professional, Tableau Public, Visual Basic, RefWorks, Endnote, Dreamweaver, Illustrator, InDesign, Microsoft Office Tools,

Language and Experience Abroad

Fluent in English and Hindi. Basic in Arabic and Kanada.
Dual residence between India and United Arab Emirates for over 20 years.
Work experience as a health care professional in India, United Kingdom and United Arab Emirates.
Travel experience in Africa, Middle East, America, Europe and Asia.

References

Available on request